4-ACYLISOXAZOLES AS ACRYLATE SYNTHONS FOR ASYMMETRIC SYNTHESIS OF 2-ISOXAZOLINES

A thesis submitted in fulfillment of the
requirements for admission to the degree of:

Doctor of Philosophy (Organic Chemistry)

By

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January 2002

VOLUME I

DECLARATION

This is to declare that the work presented herein represents original work that I have carried out during the period of 1998-2002. To the best of my knowledge this thesis does not contain material that has been accepted for the award of any other degree or diploma in any university or other tertiary institution. Established results and methodologies published or written by another person are acknowledged by citation of the original work.

I give consent to this copy of my thesis, when deposited in the University library, being available for loan or photocopying.

Connie Kwok Yee LEE
(B.Sc. Hons., First Class, University of Sydney)

January, 2002

ACKNOWLEDGMENTS

I am most fortunate to have been given the opportunity to work under the supervision of Professor Christopher Easton. Chris' professionalism, dedication and enthusiasm for chemistry are to be aspired to. Many thanks for his unfailing support and faith in me.

Thank you to all present and past members of the Easton group who have made my experience here enjoyable and memorable. Thanks to James Kelly for his technical assistance and email funnies, Hideki Onagi for his friendship, round-the-clock assistance with computer matters and great cooking, Ian Walker for driving me up the wall and Leonie Chow for her humour and infamous laboratory push-up demos!

For technical and general assistance, I am indebted to Dr. Anthony Willis for solving the numerous X-ray crystallographic structures, Professor Leo Radom and Dr. Anthony Scott for the work on the theoretical calculations, and Chris Blake for his help with the NMR experiments.

Most of all, I would like to thank my parents Anthony and Margaret, sister Clara and my pet Yorkie "Peanut" for their unwavering love, care and faith. Without their unconditional support and love, this thesis would not have been possible. Lastly, many thanks to Dave for being there over these past few years.

Connie Kwok Yee Lee

THESIS ORGANIZATION

This thesis is comprised of two sections. The first section, incorporating Chapters 1 to 7 (Volume I) and Appendices 1 and 2 (Volume II), involves work carried out on acrylate chemistry of 4-acylisoxazoles. The second part, comprising Appendix 3 (Volume II), is concerned with the synthesis of potential muscarinic agonists for treatment of Alzheimer's disease. This work was carried out during the course of study, though it is not directly related to the general scope of the other research described in the thesis.

Corrigendum

p. ix:	nuclear Overhauser effect
p. 7:	for entries d and e of Table 2, the ratio of compounds **12** and **13** should read as 66:34 and 31:69, respectively
p. 21:	Scheme 13, the central resonance form of the radical anion is missing atom X
p.31:	lines 3 and 5, replace "unit cell" with "asymmetric unit"
p. 55:	line 4 should read as "...bond differing in length in the two molecules in the asymmetric unit..."
p. 90:	line 16 should read as "...discernible..."
p. 102:	line 7 and 8 should read as "...The amide **139** is likely to have formed from hydrolysis of the nitrile **128** during work-up of the reaction..."
page 120:	line 4 should read as "...β-amino carbonyl compounds **165**..."
page 122	line 2 should read as "...the orientation between..."
page 193:	line 27 should read as "...L-Selectride®..."
page 211:	line 2 should read as "...with high..."
page 215:	line 12 should read as "...Inova 500 spectrometer..."
reference 96:	there should be no full-stop after "*Synlett*"
references 117, 119c, 148:	should read as "*Synth. Commun.*"
Appendix 3, p. 314	line 11 should read as "...quaternary..."

ABSTRACT

Chapter 1 introduces the general chemistry of isoxazoles and 2-isoxazolines. Synthesis of these heterocycles, and the regio- and stereo-chemistry of cycloadditions of nitrile oxides with alkynes and alkynes is described. A brief summary of ring-opening reactions of isoxazoles and 2-isoxazolines is presented. The peculiar substituent effects observed in baker's yeast-catalysed and electrochemical ring-opening reactions of isoxazoles are discussed.

Chapter 2 describes the investigation of substituent effects observed for hydrogenolytic, baker's yeast-catalysed and electrochemical ring-opening reactions of 4- and 5-acyl-, cyano- and phenyl-substituted isoxazoles. The substituent effects were examined through X-ray crystallographic and theoretically determined bond lengths and π-electron distribution calculations. The role of intermediate isoxazole radical anions was also examined through theoretical calculations of bond lengths, π-electron distribution and electron affinities. These studies indicate that the polarization of acyl- and cyano-substituted isoxazoles accounts for the substituent effects observed in electron-transfer based ring-opening reactions. The π-electron density calculations also indicate that 4-acylisoxazoles are electronically similar to acrylates.

The work described in the subsequent Chapters 3 to 5 encompasses experimental verification of the predicted acrylate-chemistry of 4-acylisoxazoles. In Chapter 3, 4-acylisoxazoles are shown to behave as Michael acceptors in reactions with borohydride to give 2-isoxazolines. The reaction is applicable to 4-alkoxycarbonyl- and 4-amido-substituted isoxazoles with alkyl- or aryl-substituents at the 3- and 5-positions of the isoxazole ring. Control of relative stereochemistry is attainable with the appropriate borohydride reagent in reductions of 5-substituted 4-alkoxycarbonyl- and 4-amido-substituted isoxazoles. The Michael acceptor-type chemistry of 4-acylisoxazoles is further demonstrated in reactions with alkyl halides in the presence of a zinc-copper(I) iodide couple, described in Chapter 4. Under aqueous sonochemical conditions, 5-unsubstituted 4-acylisoxazoles alkylate at the 5-position to give 2-isoxazolines. Reaction

occurs with alkoxycarbonyl- and amido-substituents at C4, and irrespective of the alkyl- or aryl-substituents at C3. The zinc-copper(I) iodide-mediated alkylation of 4-acylisoxazoles proceeds under mild conditions with high diastereoselectivity. The borohydride reduction and zinc-copper(I) iodide-mediated alkylation of 4-acylisoxazoles can be used for the diastereoselective synthesis of 2-isoxazolines. Prior to this work, synthesis of 2-isoxazolines with control of relative stereochemistry was generally accomplished *via* cycloadditions of nitrile oxides with 1,2-disubstituted alkenes where the relative configuration of the 2-isoxazoline is predetermined by the geometry of the olefinic dipolarophile.

As an extension to the work carried out in Chapters 3 and 4, Chapter 5 describes the development of an asymmetric methodology for synthesis of 2-isoxazolines *via* reductions and alkylations of chiral 4-acylisoxazoles, coupled with the readily available chiral auxiliaries, (-)-(1*R*,2*S*)-2-phenyl-1-cyclohexanol **236**, (-)-8-phenylmenthol **237** and (+)-dicyclohexylsulfamoyl-L-isoborneol **238**. Whilst borohydride reductions of chiral 4-acylisoxazoles gave low optical yields (10% *d.e.*), the complementary zinc-copper(I) iodide-mediated alkylations were highly stereoselective, affording 2-isoxazolines with control of both relative and absolute stereochemistry, in optical yields greater than 90% *d.e.* and as high as greater than or equal to 98% *d.e.*

The Conclusion and Future Directions Section, and the Experimental Section for the work described in Chapters 2 to 5 form Chapters 6 and 7. Appendices 1 and 2 comprise the X-ray crystallographic structural reports and results from the theoretical calculations.

Described in Appendix 3 is the synthesis of 3,3'-quinuclidine-[5,5']-spiroisoxazolines **12a-d** as potential muscarinic agonists for treatment of Alzheimer's disease. Compounds **12a-d** were synthesized from cycloaddition of 3-methylenequinuclidine **14** with alkyl- and aryl-nitrile oxides. Preliminary bioassays indicate that **12a-d** are not acetylcholinesterase inhibitors. Their muscarinic activity is currently under investigation.

PUBLICATION AND PRESENTATIONS BASED ON WORK CARRIED OUT DURING THE PERIOD OF Ph.D. CANDIDATURE

Publication:

Electrochemical and Yeast-catalysed Ring-opening of Isoxazoles in the Synthesis of Analogues of the Herbicide Grasp®.
C. J. Easton, G. A. Heath, C. M. M. Hughes, C. K. Y. Lee, G. P. Savage, G. W. Simpson, E. R. T. Tiekink, G. J. Vuckovic and R. D. Webster, *J. Chem. Soc., Perkin Trans. 1*, 2001, 1168.

Presentations:

4-Acylisoxazoles as Masked Acrylate Synthons for Stereocontrolled Reduction and Alkylation.
Poster Presentation given at the 38th IUPAC World Chemistry Congress,
Brisbane, Queensland, Australia,
1st-6th July, 2001.

4-Acylisoxazoles – Unique Chemical Behaviour and Applications in Synthesis.
Poster Presentation given at Pacifichem 2000,
Waikiki, Hawaii, USA,
14th-19th December, 2000.

4-Acylisoxazoles – Unique Chemical Behaviour and Applications in Synthesis.
Poster Presentation given at the 11th Royal Australian Chemical Institute Convention,
Canberra, ACT, Australia.
6th-11th February, 2000.

ABBREVIATIONS

The following abbreviations have been used throughout this thesis:

AcOH	acetic acid
app	apparent
APT	attached proton test
aq.	aqueous
atm	atmosphere
br	broad
bp	boiling point
Bu	butyl
n-BuLi	normal butyllithium
c	concentration (g/100 mL)
ca.	circa (approximately)
cat.	catalyst
conc.	concentrated
δ	chemical shift
DCC	1,3-dicyclohexylcarbodiimide
d.e.	diastereomeric excess
DMAP	4-*N*,*N*-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide

DMSO	dimethyl sulfoxide
e.e.	enantiomeric excess
EI	electron impact
ES	electrospray
Et_2O	diethyl ether
EtOAc	ethyl acetate
equiv.	equivalents
Et	ethyl
et al.	*et alia*
eV	electron volt
h	hour(s)
GCMS	gas chromatography mass spectrometry
HRMS	high resolution mass spectrometry
Hz	Hertz
IR	infrared
J	coupling constant (Hz)
LRMS	low resolution mass spectrometry
L-Selectride®	lithium tri-*sec*-butylborohydride
$M^{\bullet+}$	molecular ion (mass spectra)
Me	methyl
Mesityl	2,4,6-trimethylphenyl
min	minutes
mp	melting point (°C)

m/z	mass-to-charge ratio
n	normal
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NMR	nuclear magnetic resonance
NOE	nuclear overhauser effect
ν_{max}	infrared absorption maximum (cm^{-1})
ORTEP	Oak Ridge Thermal Ellipsoid Plot
Ph	phenyl
rt	room temperature
THF	tetrahydrofuran
TLC	thin layer chromatography
v	volume
wt	weight
<	less than
>	greater than
≥	greater than or equal to

TABLE OF CONTENTS

VOLUME I

CHAPTER 1

INTRODUCTION

1.1. Synthesis of Isoxazoles and 2-Isoxazolines *via* Nitrile Oxide Cycloadditions

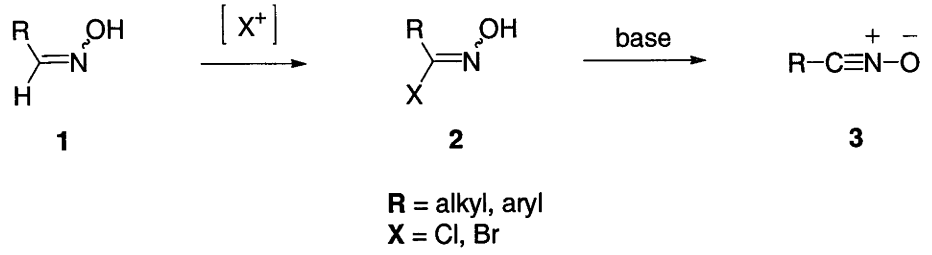
Isoxazole chemistry dates back to 1888 with the correct assignment of the heterocyclic structure by Ludwig Claisen.[1] Much of the early effort was devoted to synthesis of isoxazoles and the related dihydro-derivative Δ^2-isoxazolines, which are also commonly referred to as 2-isoxazolines or 4,5-dihydroisoxazoles.

There are two main methods for synthesis of isoxazoles and 2-isoxazolines. One involves oximation of carbonyl-containing three carbon components such as 1,3-dicarbonyl compounds[2] and α,β-unsaturated ketones.[3] The other is through 1,3-dipolar cycloadditions of nitrile oxides with unsaturated hydrocarbons[4] and is currently the dominant method as it allows for versatile and straightforward construction of a multitude of isoxazoles and 2-isoxazolines with efficient atom economy. From a synthetic viewpoint, nitrile oxides and their precursors are generally prepared with relative ease. Another advantage of the method is that it allows for stereochemically controlled synthesis of 2-isoxazolines through retention of the relative geometry of olefinic dipolarophiles.[5]

The syntheses of isoxazoles and 2-isoxazolines described in this thesis all involve nitrile oxide cycloadditions with alkynes and alkenes. In particular, they are concerned with preparation of acylisoxazoles, and thus the following sections are devoted to discussion of the regiochemistry and reactivity aspects of nitrile oxide cycloadditions with alkynoates and alkenoates.

1.1.1. Nitrile Oxide Synthesis

The two most general methods for the preparation of nitrile oxides involve oxidation of aldoximes[6-10] and dehydration of nitro compounds.[11] For the former method, aldehydes serve as the starting materials for preparation of oximes **1**. Oximes **1** are usually halogenated to give the hydroximinoyl halides **2**, followed by dehydrohalogenation with a base to afford the nitrile oxides **3** (Scheme 1).

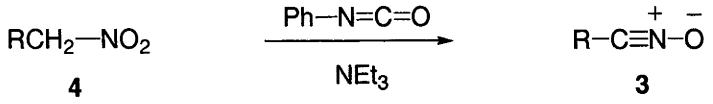


Scheme 1

Halogenation of oximes **1** can be accomplished by either chlorination or bromination,[6] although the former is more commonly utilised. Chlorination of oximes **1** may be achieved by direct halogenation with molecular chlorine,[7] or more commonly with the use of either aqueous sodium hypochlorite[8] or *N*-chlorosuccinimide (NCS).[9] With aromatic aldoximes, chlorination on the aromatic ring may also occur. In these cases, nitrosyl chloride has been shown to be selective as an oxime chlorinating agent.[10]

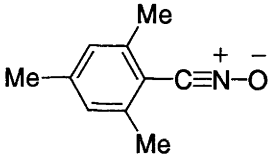
Nitrile oxides **3** are generated from hydroximinoyl halides **2** by treatment with aqueous bases[12] or triethylamine.[13] Most nitrile oxides **3** are generated *in situ* by slow addition of triethylamine to a solution of the hydroximinoyl chloride **2** and excess dipolarophile. The slow addition of base ensures a low concentration of the nitrile oxide **3** in the reaction mixture at any given time, and with excess dipolarophile present, nitrile oxide cycloaddition with alkynes and alkenes is encouraged over the competing dimerization process.[13]

Dehydration of primary nitroalkanes **4** for the preparation of nitrile oxides **3** is known as the Mukaiyama method.[11] The most commonly employed dehydrating agent is phenyl isocyanate, and it is usually used in the presence of a catalytic amount of triethylamine (Scheme 2).[11] Other dehydrating agents include phosphorus oxychloride,[14] diketene,[15] acetyl chloride[16] and acetic anhydride.[17] Arylnitromethanes may be utilized in this general method.[18]



Scheme 2

Most nitrile oxides **3** are short-lived, reactive species. In the absence of suitable reactants such as alkenes and alkynes, nitrile oxides **3** dimerize to furoxans and 1,2,5-oxadiazole 2-oxides, and rearrange to isocyanates or polymerize.[19] The half-lives of aliphatic nitrile oxides can be seconds to minutes whilst those of aromatic nitrile oxides can be minutes to days.[19,20] Ortho substitution of the phenyl ring with bulky groups enhances the stability of aryl nitrile oxides and some are indefinitely stable (for example, mesitonitrile oxide or 2,4,6-trimethylbenzonitrile oxide **5**).[19]



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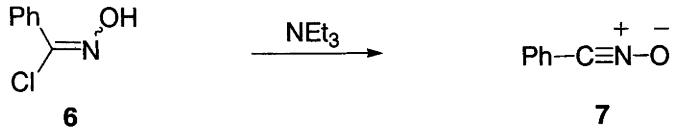
1.1.2. Nitrile Oxide Cycloadditions with Monosubstituted Alkynes

Conceptually, the most direct route to isoxazoles is *via* 1,3-dipolar cycloaddition of nitrile oxides to alkynes. With monosubstituted alkynes with electron-rich substituents such as alkyl or aryl groups, 5-substituted isoxazoles are afforded. This is exemplified by the work of Huigsen and coworkers[21] in their study of cycloadditions of benzonitrile oxide **7** with 1-hexyne **8a** and phenylacetylene **8b**, where the 5-substituted isoxazoles **10a,b** were furnished in good yields and none of the regioisomers **9a,b** was produced (Table 1). Benzonitrile oxide **7** was generated *in situ* by the action of triethylamine on benzohydroximinoyl chloride **6** (Scheme 3).



6 7

Scheme 3

Table 1. Cycloaddition of benzonitrile oxide **7** with monosubstituted acetylenes[21]

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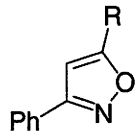


10

	R	Yield of 10 (%)*
a	*n*-Bu	98
b	Ph	79

Reagents and conditions:* **10a: **6** (1 equiv.), **8a** (10 equiv.), NEt_3 (1.5 equiv.), Et_2O, rt, 2 h; **10b**: **6** (1 equiv.), **8b** (10 equiv.), NEt_3 (1.5 equiv.), Et_2O, rt, 2 h.

The complete regioselectivity of the cycloadditions may be attributed to steric effects, where interactions between substituents on the dipole **7** and the dipolarophiles **8a,b** are minimized by union of the dipole oxygen with the substituted terminus of each alkyne.

The regioselectivity may also be explained in terms of frontier molecular orbital (FMO) energies.[21] The largest LUMO coefficient resides on the dipole carbon whilst the unsubstituted acetylenic carbon on the dipolarophile assumes the largest HOMO coefficient.[21] The LUMO (dipole) - HOMO (dipolarophile) interaction results in carbon-carbon bond formation across the dipole carbon and the unsubstituted acetylenic terminus of the dipolarophile, thus giving rise to the 5-substituted isoxazole.

For electron-deficient monosubstituted alkynes, nitrile oxide cycloadditions usually give rise to mixtures of the two possible regioisomers.[22-24] This is due to a combination of polar and steric effects. Polarization of the dipolarophile by conjugation with an electron-withdrawing group increases the electrophilicity at the carbon *beta* to the electron-withdrawing substituent. The β-carbon on the acetylene therefore becomes susceptible to attack by the dipole oxygen, thereby furnishing the 4-substituted adduct. To rationalize the polar effect in terms of FMO energies, the electron-withdrawing group lowers the HOMO and LUMO energies of the dipolarophile. The HOMO (dipole) - LUMO (dipolarophile) interaction then results in union of the nucleophilic oxygen of the nitrile oxide and the β-carbon of the electron-deficient alkyne, thereby leading to formation of the 4-substituted product.[25]

The regioselectivity of nitrile oxide cycloadditions with methyl propiolate **11** was examined by Huigsen *et al.*[22-24] The nitrile oxides **3a-c** were generated *in situ* by dehydrohalogenation of hydroximinoyl halides **2a-c** with triethylamine, whilst nitrile oxides **3d** and **5** were pregenerated prior to use (Scheme 4).[22-24]

2a. R = Me_3C, X = Cl
b. R = H, X = I
c. R = Me, X = Cl
d. R = 2,3,5,6-Me_4Ph, X = Cl
e. R = 2,4,6-Me_3Ph, X = Cl

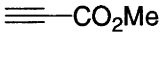
3a. R = Me_3C
b. R = H
c. R = Me
d. R = 2,3,5,6-Me_4Ph
5 R = 2,4,6-Me_3Ph

Scheme 4

The steric and polar influences on nitrile oxide cycloadditions with methyl propiolate **11** are illustrated in Table 2.[22-24] Steric effects are apparent from the product ratios of the 4- and 5-acylisoxazoles derived from the cycloadditions of dipolarophile **11** with pivalonitrile oxide **3a** and acetonitrile oxide **3c**. With the sterically more hindered dipole **3a**, more of the 5-acylisoxazole **13a** was afforded relative to that observed for the

5-acyladduct **13d**, formed from the cycloaddition of dipolarophile **11** with acetonitrile oxide **3c**.[24]

Table 2. Cycloaddition of nitrile oxides **3a-d**, **5** and **7** with methyl propiolate **11**[22-24]



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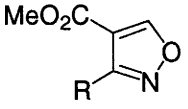

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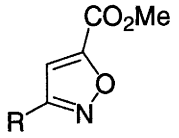


13

	R	Ratio of 12:13	Yield of 12 and 13 (%)*
a	Me_3C	9:91	95
b	H	16:84	52
c	Ph	28:72	98
d	Me	3:69	90
e	2,3,5,6-Me_4Ph	6:34	100
f	2,4,6-Me_3Ph	72:28	96

Reagents and conditions*: **12a and **13a**: **2a** (1 equiv.), **11** (8.3 equiv.), NEt_3 (1 equiv.), Et_2O, rt, 1 h; **12b** and **13b**: **2b** (1 equiv.), **11** (2.6 equiv.), NEt_3 (1 equiv.), Et_2O, rt, 2 h; **12c** and **13c**: **6** (1 equiv.), **11** (8.3 equiv.), NEt_3 (1 equiv.), Et_2O, rt, 1 h; **12d** and **13d**: **2c** (1 equiv.), **11** (2.5 equiv.), NEt_3 (1 equiv.), Et_2O, rt, 1 h; **12e** and **13e**: **3d** (1 equiv.), **11** (3.7 equiv.), Et_2O, rt, 24 h; **12f** and **13f**: **5** (1 equiv.), **11** (3.7 equiv.), Et_2O, rt, 24 h.

The influence of polar effects is exemplified by the cycloadditions of methyl propiolate **11** with acetonitrile oxide **3c** and formonitrile oxide **3b** (Table 2), where the more electron-rich nitrile oxide **3c** afforded more of the 4-acylisoxazole **12d** than that observed for the 4-acyladduct **12b**, derived from the cycloaddition of formonitrile oxide **3b** with alkyne **11** (Table 2).[23]

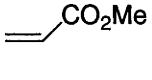
Dominant polar effects are also evident from the cycloadditions of methyl propiolate **11** with the aryl nitrile oxides, tetramethylbenzonitrile oxide **3d**, mesitonitrile oxide **5** and benzonitrile oxide **7** (Table 2). Cycloadditions of alkyne **11** with the more electron-rich aryl nitrile oxides **3d** and **5** favored the formation of the 4-acylisoxazoles

12e and **12f** over the 5-acyladducts **13e** and **13f**,[24] whilst with the less electron-rich benzonitrile oxide **7**, the 5-acylisoxazole **13c** was obtained as the major product.[22]

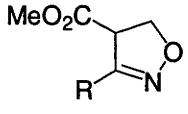
1.1.3. Nitrile Oxide Cycloadditions with Monosubstituted Alkenes

Cycloadditions of nitrile oxides with alkenes yield 2-isoxazolines. With monosubstituted alkenes, the regiochemistry of the cycloadditions is mainly determined by steric effects. This is illustrated by cycloadditions of methyl acrylate **14** with nitrile oxides **3a-c**, **5** and **7**, where the 5-acylisoxazolines **16a-e** were afforded as the predominant products over the 4-acyladducts **15a-e** (Table 3).[22,24] The predominant cycloadducts **16a-e** result from bonding of the oxygen of the nitrile oxides **3a-c**, **5** and **7** with the most substituted olefinic carbon of the dipolarophile **14**.

Table 3. Cycloaddition of nitrile oxides **3a-c**, **5** and **7** with methyl acrylate **14**[22,24]



14



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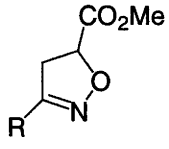


16

	R	Ratio of 15:16	Yield of 15 and 16 (%)*
a	Me_3C	< 1:99	95
b	H	< 1:99	94
c	Ph	3.6:96.4	98
d	Me	5.1:94.9	86
e	2,4,6-Me_3Ph	6.6:93.4	99

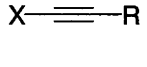
Reagents and conditions*: **15a and **16a**: **2a** (1 equiv.), **14** (8 equiv.), NEt_3 (1.5 equiv.), Et_2O, rt, 1 h; **15b** and **16b**: **2b** (1 equiv.), **14** (23 equiv.), NEt_3 (1 equiv.), neat, rt, 2 h; **15c** and **16c**: **6** (1 equiv.), **14** (6 equiv.), NEt_3 (1.4 equiv.), Et_2O, rt, 1 h; **15d** and **16d**: $EtNO_2$ (1 equiv.), PhNCO (2 equiv.), NEt_3 (0.2 equiv.), neat, 60 °C, 1 h; **15e** and **16e**: **5** (1 equiv.), **14** (5.5 equiv.), neat, rt, 2 h.

1.1.4. Nitrile Oxide Cycloadditions with 1,2-Disubstituted Alkynes

Nitrile oxide cycloadditions with unsymmetrically 1,2-disubstituted alkynes furnish regioisomeric 4,5-disubstituted isoxazoles. With 1,2-disubstituted electron-deficient alkynes, the regiochemistry of the nitrile oxide cycloadditions is strongly determined by polar effects. This is exemplified by the cycloadditions of alkynes **17a-d** with benzonitrile oxide **7**, where the 4-acylisoxazoles **18a-d** were furnished as the prevailing products over the 5-acyladducts **19a-d** (Table 4).[22,26]

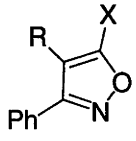
The dominance of the 4-acylisoxazoles **18a-d** over the 5-acyl-substituted isomers **19a-d** may be attributed to the polarization of the 1,2-disubstituted alkynes **17a-d**, which is induced by the electron-withdrawing carbonyl groups. As a result, the β-carbons on the dipolarophiles **17a-d** are activated towards bond formation with the dipole oxygen. The high regioselectivity of the cycloadditions may also be ascribed to secondary orbital interactions between the dipole **7** and the 1,2-disubstituted alkynes **17a-d**,[26] as well as dominant LUMO (dipolarophile) – HOMO (dipole) interactions.[26]

Table 4. Cycloaddition of benzonitrile oxide **7** with 1,2-disubstituted alkynes **17a-d**[22,26]



17

18



19

	R	X	Ratio of 18:19	Yield of 18 and 19 (%)*
a	Me	CO_2Me	99:1	83
b	Me	COPh	99:<1	80
c	Ph	CO_2Me	99:1	94
d	Ph	CO_2Et	99:<1	87

* *Reagents and conditions*: **18a** and **19a**: **6** (1 equiv.), **17a** (5 equiv.), NEt_3 (1.4 equiv.), Et_2O, rt, 1 h; **18b** and **19b**: **6** (1 equiv.), **17b** (1 equiv.), NEt_3 (1 equiv.), Et_2O, rt, 1 h; **18c** and **19c**: **6** (1 equiv.), **17c** (5 equiv.), NEt_3 (1.5 equiv.), Et_2O, rt, 1 h; **18d** and **19d**: **6** (1 equiv.), **17d** (12 equiv.), NEt_3 (1.2 equiv.), neat, rt, 20 min.

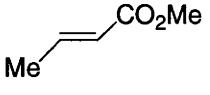
1.1.5. Nitrile Oxide Cycloadditions with 1,2-Disubstituted Alkenes

Nitrile oxide cycloadditions with unsymmetrical 1,2-disubstituted olefins furnish regioisomeric 4,5-disubstituted 2-isoxazolines.[4] The regiochemical outcome of these nitrile oxide cycloadditions is attributed to a combination of polar and steric effects.

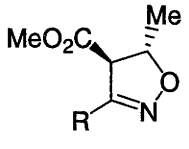
Dominant steric effects are exemplified by the cycloaddition of formonitrile oxide **3b** with methyl crotonate **20**, where the 5-acylisoxazoline **22a** was furnished as the major product (Table 5),[23] resulting from bonding between the oxygen of the dipole **3b** and the more sterically hindered olefinic carbon on dipolarophile **20**.

The cycloadditions of dipolarophile **20** with the aryl dipoles, benzonitrile oxide **7** and mesitonitrile oxide **5** illustrate dominant polar effects, as the 4-acylisoxazolines **21b** and **21c** were obtained in preference to the 5-acyladducts **22b** and **22c** (Table 5).[24] The 4-acyladducts **21b** and **21c** were formed by the union of the dipole oxygen with the β-carbon of dipolarophile **20**. This results from polarization of the dipolarophile **20** by the electron-withdrawing carbonyl group, which renders the β-carbon of the dipolarophile **20** more susceptible to attack by the oxygen of the dipoles **7** and **5**.

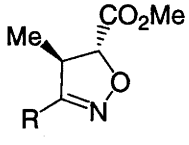
Table 5. Cycloaddition of nitrile oxides **3b**, **5** and **7**, with methyl crotonate **20**[23,24]



20



21
rac.



22
rac.

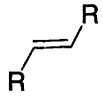
	R	Ratio of 21:22	Yield of 21 and 22 (%)*
a	H	38:62	36
b	Ph	66:34	84
c	2,4,6-Me_3Ph	73:27	90

Reagents and conditions*: **21a and **22a**: **2b** (1 equiv.), **20** (12.6 equiv.), NEt_3 (1 equiv.), Et_2O, rt, 1 h; **21b** and **22b**: **6** (1 equiv.), **20** (12.6 equiv.), NEt_3 (1 equiv.), Et_2O, rt, 1 h; **21c** and **22c**: **5** (1 equiv.), **20** (1 equiv.), neat, rt, 5 h.

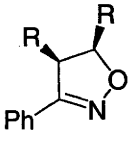
Also illustrated above by the *trans*-configuration of the dipolarophile **20**, and the cycloadducts **21a-c** and **22a-c**, nitrile oxide cycloadditions with 1,2-disubstituted olefins give rise to 4,5-disubstituted 2-isoxazolines where the configuration of the olefins is always retained in the products. This is further illustrated by the cycloadditions of benzonitrile oxide **7** with stilbenes **23a** and **24a**, and 2-butenes **23b** and **24b** (Table 6),[21] where the relative configuration of the products **25a**, **26a**, **25b** and **26b** reflects the geometry of the dipolarophiles **23a**, **24a**, **23b** and **24b**, respectively.[21] Currently, this is the primary method for synthesis of 4,5-disubstituted-2-isoxazolines with control of relative stereochemistry.[5]

Table 6. Cycloaddition of benzonitrile oxide **7** with stilbenes **23a** and **24a**, and 2-butenes **23b** and **24b**[21]

23



24



rac.
25

rac.
26

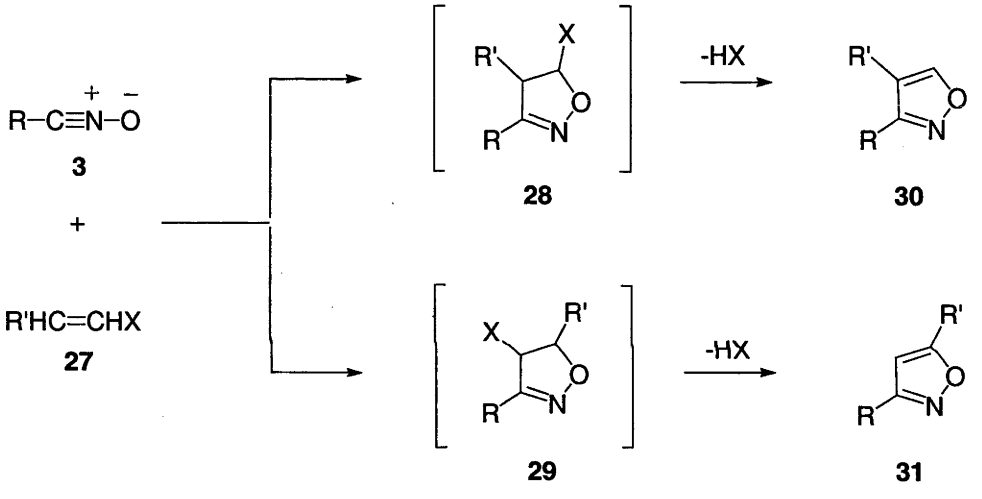
a. R = Ph
b. R = Me

Dipolarophile	Ratio of 25:26	Yield of 25 and 26 (%)*
23a	99:<1	66
24a	<1:99	75
23b	99:<1	48
24b	<1:99	36

Reagents and conditions*: **25a: **6** (1 equiv.), **23a** (16 equiv.), NEt_3 (1.5 equiv.), Et_2O, rt, 2 h; **26a**: **6** (1 equiv.), **24a** (8 equiv.), NEt_3 (1 equiv.), Et_2O, rt, 1 h; **25b**: **6** (1 equiv.), **23b** (13 equiv.), NEt_3 (1.2 equiv.), Et_2O, rt, 1 h; **26b**: **6** (1 equiv.), **24b** (8.9 equiv.), NEt_3 (1.2 equiv.), Et_2O, rt, 1 h.

1.1.6. Synthesis of Isoxazoles from 2-Isoxazolines

Isoxazoles can also be accessed from nitrile oxide cycloadditions with olefins **27** containing suitable leaving groups. These cycloadditions give rise to intermediate 2-isoxazolines **28** and **29** which then undergo elimination reactions to afford isoxazoles **30** and **31**. Some of the commonly used leaving groups include hydroxyl,[27] alkoxyl,[28] acetyloxy,[29] halo,[30] nitro[31] and amino[32] groups (Scheme 5). The steric and electronic influences of these auxiliaries are used to manipulate the regiochemistry of nitrile oxide cycloadditions.[33]



X = OH, OMe, OCOMe, halogens, NO_2, NH_2, NR_2

Scheme 5

Isoxazoles are also attainable by dehydrogenation of 2-isoxazolines, with aromatisation providing the driving force for the transformation. Oxidizing agents are used to effect the conversion, and they include Chloranil,[34] 2,3-dichloro-5,5-dicyanobenzoquinone,[35] nickel peroxide,[36] γ-activated manganese dioxide[37] and potassium permanganate.[38]

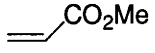
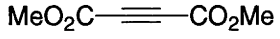
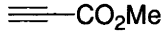
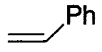
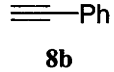
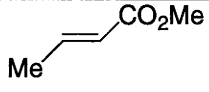
1.2. Dipolarophile Reactivity in Nitrile Oxide Cycloadditions

The rates of nitrile oxide cycloadditions are influenced by the dipolarophilicity of the alkynes and alkenes. The relative reactivity of a range of alkynes and alkenes in cycloadditions with benzonitrile oxide **7** was studied by Huisgen and coworkers.[39] The results of the study indicate that carbon-carbon triple bonds are weaker dipolarophiles than the corresponding carbon-carbon double bonds. This is exemplified by the reduced reactivity of the alkynes, **8b**, **11**, **17a** and **35**, relative to the respective alkenes **33**, **14**, **20** and **34** (Table 7).[39]

The reactivity of alkynes as dipolarophiles is improved by substitution with electron-withdrawing groups. This is illustrated by the relative reactivity of dimethyl acetylenedicarboxylate **32**, methyl propiolate **11** and acetylene **35** for cycloadditions with **7** (Table 7), where the diacyl-substituted alkyne **32** is more reactive than the monoacyl-substituted alkyne **11**,[39] which is in turn more reactive than the unsubstituted dipolarophile, acetylene **35**.[39] Enhanced reactivity of the alkynoates **32** and **11** relative to the alkyne **35** is attributed to the electron-withdrawing carbonyl substituent which lowers the LUMO energies of the alkynoates **32** and **11** relative to those of the alkyne **35**.

The reactivity of a dipolarophile can be reduced by steric effects. This is exemplified by the reduced reactivity of methyl tetrolate **17a** relative to methyl propiolate **11**,[39] resulting from the steric hindrance of the methyl-substituent at the β-carbon of the dipolarophile **17a**. Similarly, reduced dipolarophilicity of phenylacetylene **8b** relative to acetylene **35** is due to the steric hindrance of the phenyl-substituent on dipolarophile **8b** (Table 7).[39]

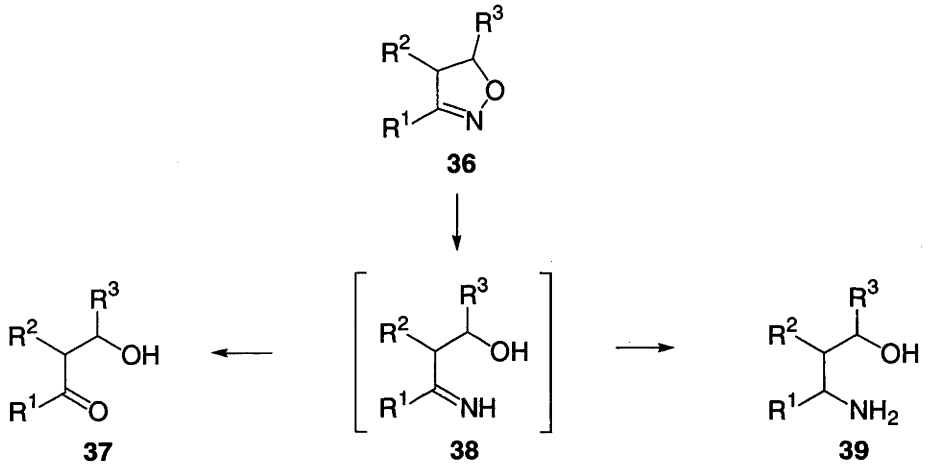
Table 7. Relative reactivity of dipolarophiles **8b**, **11**, **14**, **17a**, **20** and **32-35** in cycloadditions with benzonitrile oxide **7**[39]

Dipolarophile	k_{rel} ($k_{ethylene}$ = 1.00)*
 **14**	8.3
 **32**	3.1
 **11**	1.24
 **33**	1.15
34	1.00
35	0.40
 **8b**	0.112
 **20**	0.082
17a	0.030

Reagents and conditions*: **6 (1 equiv.), **34** (1 equiv.), dipolarophile (1 equiv.) listed above, NEt_3 (1.5 equiv.), Et_2O, rt, 1h.

1.3. Ring-opening of 2-Isoxazolines

2-Isoxazolines **36** are often synthesized for their utility as versatile synthons, and their synthetic potential is realized upon cleavage of the weak N-O bond, as shown in Scheme 6. 2-Isoxazolines **36** are more widely used than isoxazoles as key intermediates in synthesis since they are generally more accessible than isoxazoles, as alkenes are more reactive dipolarophiles than alkynes (see Section 1.2.).

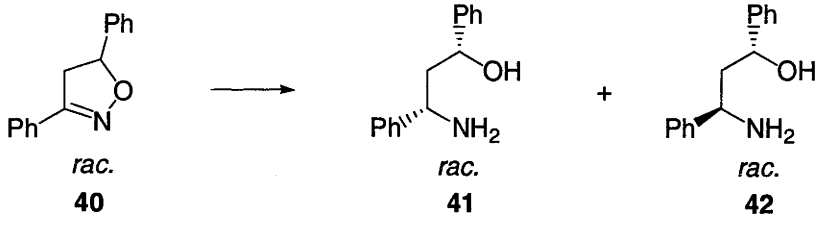


Scheme 6

Catalytic hydrogenation of 2-isoxazolines **36** gives rise to β-hydroxyketones **37** and γ-amino alcohols **39**. Use of palladium on carbon[40] and platinum[41] usually affords the γ-amino alcohols **39** *via* reduction of the intermediate β-hydroxyketimines **38**. With Raney nickel,[42] β-hydroxyketones **37** are furnished *via* hydrolysis of the labile intermediate imino alcohols **38** (Scheme 6).

Apart from through the hydrogenation methods, reductive cleavage of 2-isoxazolines **36** to γ-amino alcohols **39** can also be effected by sodium/ethanol,[43] sodium/mercury amalgam,[43] borane complexes[43] and lithium aluminium hydride.[43] The

latter reagent was used for the stereoselective ring-opening of 3,5-diphenylisoxazoline **40** where the *erythro*- and *threo*-1,3-amino alcohols **41** and **42** were furnished in a ratio of 95:5 (Scheme 7).[43] By contrast with sodium/mercury amalgam, the γ-amino alcohols **41** and **42** were obtained in a ratio of 42:58.[43] The highly diastereoselective lithium aluminium hydride reduction of **40** may be attributed to steric control during hydride attack. The steric influence of the phenyl group at the 5-position of the 2-isoxazoline **40** directs the trajectory of the incoming hydride *anti* to the phenyl group at the 5-position.

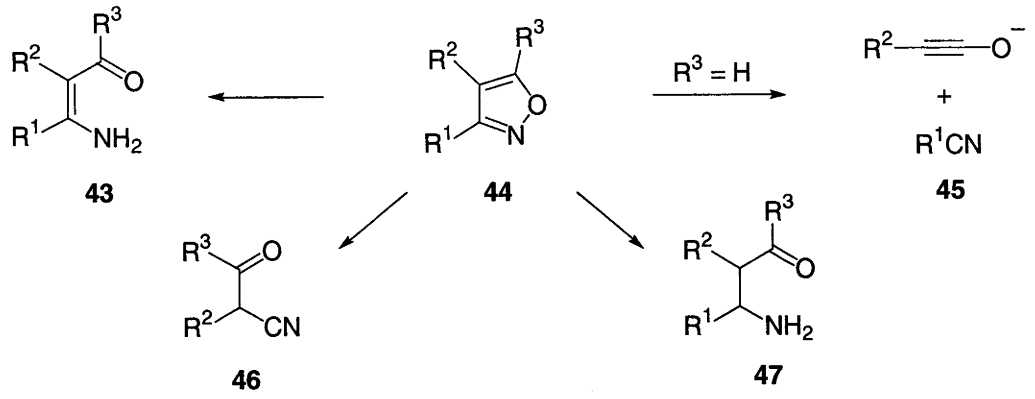


Scheme 7

The synthetic utility of 2-isoxazolines **36** as key intermediates has been demonstrated in the synthesis of sugars,[44] amino acids,[45] and the macrolactone antibiotic, (±)-vermiculine,[46] and the β-lactam antibiotic, thienamycin.[47]

1.4. Ring-opening of Isoxazoles

The latent functionality of isoxazoles **44** is also realized upon cleavage of the labile N-O bond, thereby giving rise to various synthetically useful building blocks **43** and **45-47** (Scheme 8).



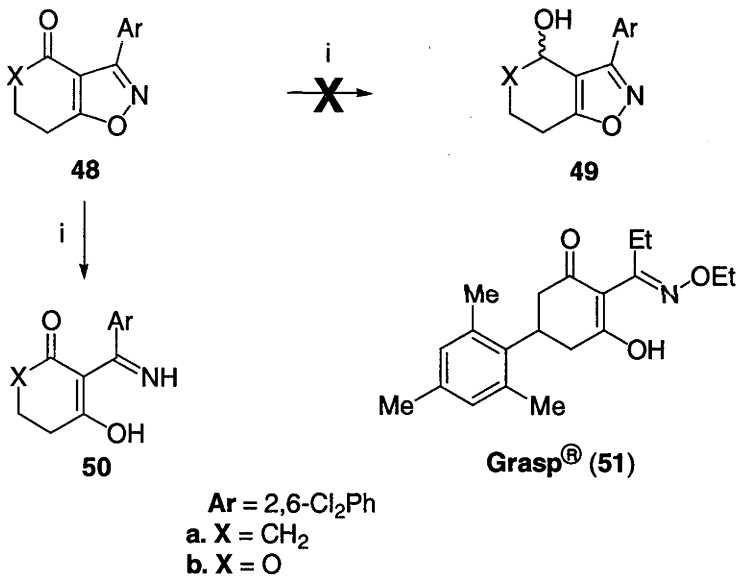
Scheme 8

Anionic cleavage of isoxazoles **44** usually leads to α-cyano ketones **46**. Some of the bases used to achieve this transformation include lithium diisopropylamide[48] and sodium amide.[49] Most often, the ring-cleavage of isoxazoles **44** is accomplished by hydrogenolysis, whereby β-enamino ketones **43** are furnished. Some of the commonly used catalysts for this transformation include palladium on carbon,[50] platinum black[51] and Raney nickel.[52] Other reagents that are also known to effect ring-cleavage include samarium iodide,[53] molybdenum hexacarbonyl,[54] iron pentacarbonyl[55] and phenylmagnesium bromide.[56] β-Amino ketones **47** are obtained from metal-ammonia[57] reductions of isoxazoles **44** whilst anionic fragmentation of 5-unsubstituted isoxazoles **44** with sodium ethoxide affords nitriles **45**.[58]

The utility of isoxazoles as versatile synthons is demonstrated in Stork's synthesis of progesterone,[59] where hydrogenolytic opening of the isoxazole ring unmasked the latent carbonyl functionality which was incorporated in the construction of the A/B rings of the steroidal framework, *via* annelation methodology. The use of isoxazoles as synthons is also illustrated in Steven's synthesis of the macrocyclic ligands, corphins and corrins.[60]

1.5. Baker's Yeast-catalysed and Electrochemical Ring-opening of Isoxazoles

More recently, a novel method for effecting the ring-cleavage of isoxazoles was reported by Easton *et al.*[61] Initially, the intention was to reduce the carbonyl groups on the isoxazoles **48a,b**, in the synthesis of analogues of the herbicide Grasp® (**51**) (Scheme 9). Instead of obtaining the desired products **49a,b**, incubation of the isoxazoles **48a,b** with baker's yeast (*Saccharomyces cerevisiae*) gave rise to the imines **50a,b** (Scheme 9). This is an anomalous result as reports in the literature indicate that the action of yeast on other acylisoxazoles is restricted to the carbonyl groups, and does not occur on the heterocyclic rings.[62]

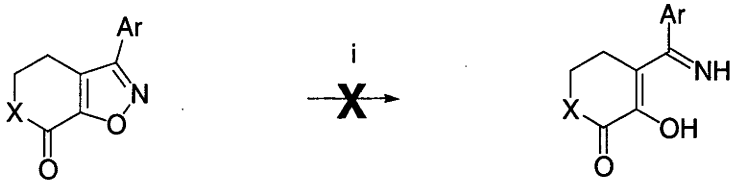


Reagents and conditions: i. **48**, baker's yeast, H_2O, 37 °C, 1 h.

Scheme 9

The ring-opening of the 4-carbonyl-substituted isoxazoles **48a,b** is the first example of a yeast-catalysed reductive cleavage of either an aromatic ring or a single

bond.[61] Incubation of the 5-acylisoxazoles **52a,b** with baker's yeast did not yield the ring-cleaved products **53a,b** (Scheme 10).



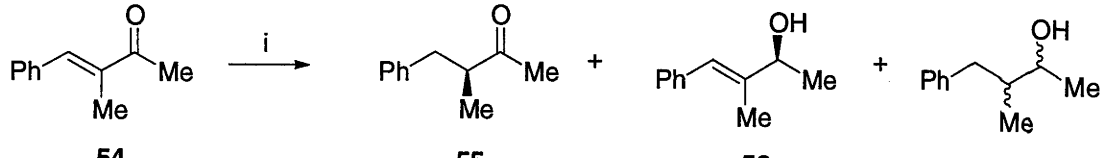
52 **53**

Ar = 2,6-Cl_2Ph
a. X = CH_2
b. X = O

Reagents and conditions: i. **52**, baker's yeast, H_2O, 37 °C, 1 h.

Scheme 10

The ring-cleavage of the bicyclic 4-acylisoxazoles **48a,b** was proposed to involve an electron-transfer process, analogous to the mechanism for the yeast-catalysed reductions of enones.[63,64] The work of Kawai *et al.*[64] showed that enone **54** was reduced asymmetrically with baker's yeast, to give the ketone **55**, the allyl alcohol **56** and the alcohol **57** (Scheme 11).

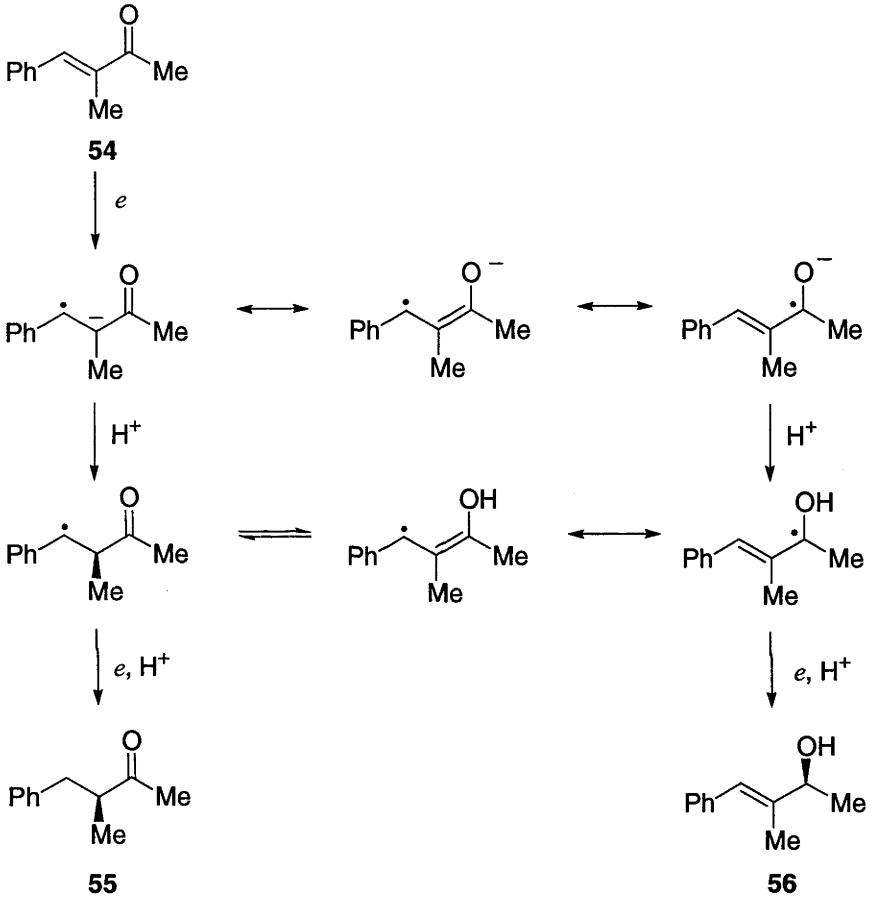


54 **55** **56** **57**

Reagents and conditions: i. **54**, baker's yeast, H_2O, 35 °C, 50 h.

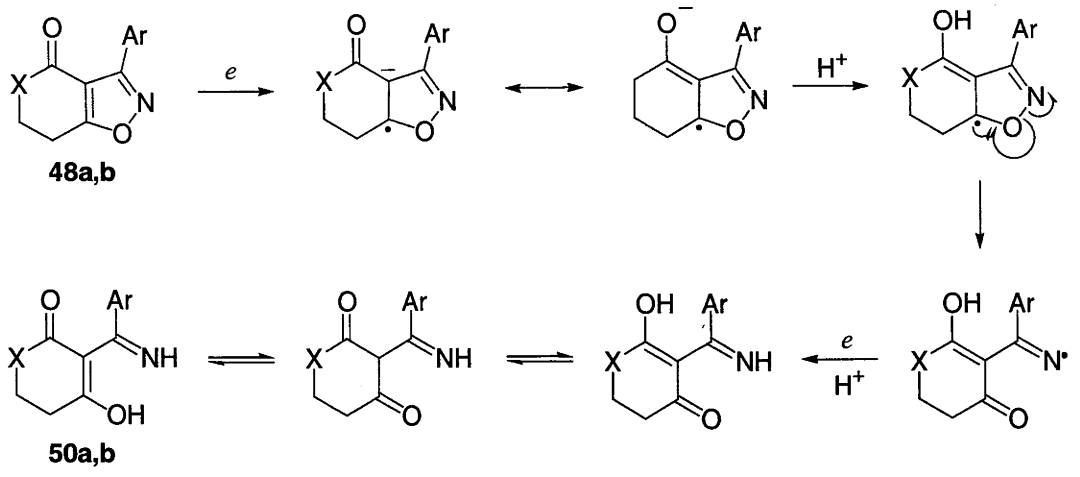
Scheme 11

The mechanism for the formation of the ketone **55** and the allylic alcohol **56** involves electron-transfer to the enone **54** (Scheme 12). The saturated alcohol **57** is formed through more complete reduction of the ketone **55**.



Scheme 12

Based on the electron-transfer pathway invoked for the conjugate reduction of the enone **54** to the ketone **55**, it was suggested that the mechanism of the yeast-catalysed cleavage of the 4-acylisoxazoles **48a,b** could be a diversion from an analogous pathway. It was thought that ring-cleavage of the isoxazoles **48a,b** could be initiated by electron-transfer, as shown in Scheme 13.



Scheme 13

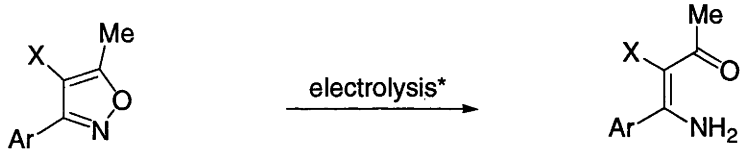
The validity of the electron-transfer mechanism was verified by the electrolysis of **48a,b** and **52a,b**.[65] Ring-opening of **48a,b** was reproduced electrochemically to afford imines **50a,b**, as effected by baker's yeast-catalysis.[61] The 5-acylisoxazoles **52a,b** which failed to produce the ring-opened products **53a,b** with baker's yeast,[61] gave rise to complex mixtures upon electrolysis.[65]

The generality of the electrochemical behaviour of isoxazoles **48a,b** and **52a,b** was examined by the electrolysis of other isoxazoles, namely, the 4- and 5-acyl- and cyano-substituted isoxazoles **58a,b** and **60a,b**, and the 4- and 5-phenylisoxazoles **61a,b**. The isoxazoles **58a** and **60a** were chosen so that their reactivities could be compared with those of the more rigid fused bicyclic isoxazoles **48a,b** and **52a,b**. Upon electrochemical reduction, the 4-acylisoxazole **58a** underwent ring-cleavage to give the imine **59a** (Scheme 14) whilst with the 5-acylisoxazole **60a**, a complex product mixture resulted.

Clean ring-opening was not limited to the 4-acylisoxazoles **48a,b** and **58a**, as demonstrated by the facile electrochemical ring-cleavage of the 4-cyanoisoxazole **58b**

(Scheme 14). By contrast, electrolysis of the 5-cyanoisoxazole **60b** gave rise to a complex mixture. From these results, it was inferred that substitution with electron-withdrawing groups at the 4-position on the isoxazole facilitates clean ring-cleavage, whilst substitution of electron-withdrawing groups at the 5-position leads to complex product mixtures.

These substituent effects were discerned with acyl and cyano groups but not with phenyl substituents as neither of the 4- and 5-phenylisoxazoles **61a,b** afforded clean ring-cleaved species upon electrolysis.

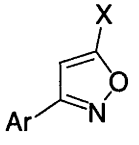


58 **59**

Ar = 2,6-Cl_2Ph
a. X = CO_2Me
b. X = CN

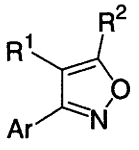
* At rt in AcCN (0.1 mol dm^{-3} tetrabutylammonium hexafluorophosphate) under Ar, using a 1 mm planar Hg coated Pt working electrode and a Pt auxiliary electrode, in conjunction with a Ag/AgCl reference electrode.

Scheme 14



60

Ar = 2,6-Cl_2Ph
a. X = CO_2Me
b. X = CN



61

Ar = 2,6-Cl_2Ph
a. R^1 = Ph, R^2 = H
b. R^1 = H, R^2 = Ph

On the basis of this work, it was apparent that the reactivity of isoxazoles to baker's yeast-catalysed and electrochemical ring-opening is strongly influenced by the electronic nature of substituents, and their position on the isoxazole ring. From the experiments, it was inferred that substitution of conjugating and electron-withdrawing groups, such as acyl or cyano groups, at the 4-position of an isoxazole makes the ring susceptible to cleavage, whilst substitution of these groups at the 5-position does not lead to formation of clean ring-opened products. Also, irrespective of its substitution at the 4- or 5-position on the isoxazole ring, the conjugating but not electron-withdrawing phenyl group does not activate the heterocycle to ring-opening.[65]

The initial aim of the work described in this thesis was to investigate the basis of these substituent effects by examining other ring-opening reactions (Chapter 2). Also the possibility of inherent structural differences was explored through X-ray crystallography and by considering theoretical calculations of bond distances and π-electron distribution. These studies are described in the following chapter of this thesis.

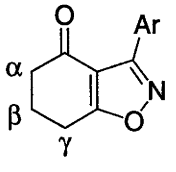
CHAPTER 2

INVESTIGATION INTO THE BASIS OF SUBSTITUENT EFFECTS ON RING-OPENING OF ISOXAZOLES

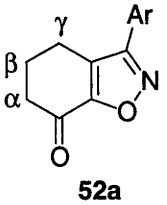
2.1. Hydrogenolytic Ring-opening of 4- and 5-Acylisoxazoles

In the previous chapter, contrasting reactivities of the 4- and 5-acylisoxazoles **48a,b** and **52a,b** towards ring-opening *via* electron-transfer processes, namely through baker's yeast catalysis[61] and electrolysis,[65] were discussed. To examine whether these substituent effects are also observed in reactions that involve direct cleavage of the N-O bond as opposed to electron-transfer processes where ring-cleavage occurs at a subsequent stage, hydrogenation of the isoxazoles **48a** and **52a** was investigated. The isoxazoles **48a** and **52a** were available from previous work within the group.[33,66] Of the two, hydrogenation of **48a** was previously studied and the structure of the ring-opened product **50a** was assigned.[66] In the present study, hydrogenation of the isoxazole **52a** was examined and using palladium on carbon as a catalyst (10% by wt), the ring-opened species **53a** was afforded. The chemical shifts of the methylene protons of the isoxazoles **48a** and **52a**, and the imines **50a** and **53a** are shown in Table 8.

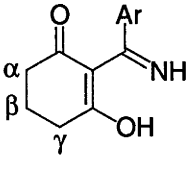
Table 8. Chemical shifts (ppm) of methylene proton resonances of isoxazoles **48a** and **52a**, and imines **50a** and **53a**



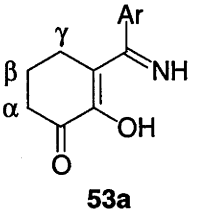
48a



52a



50a



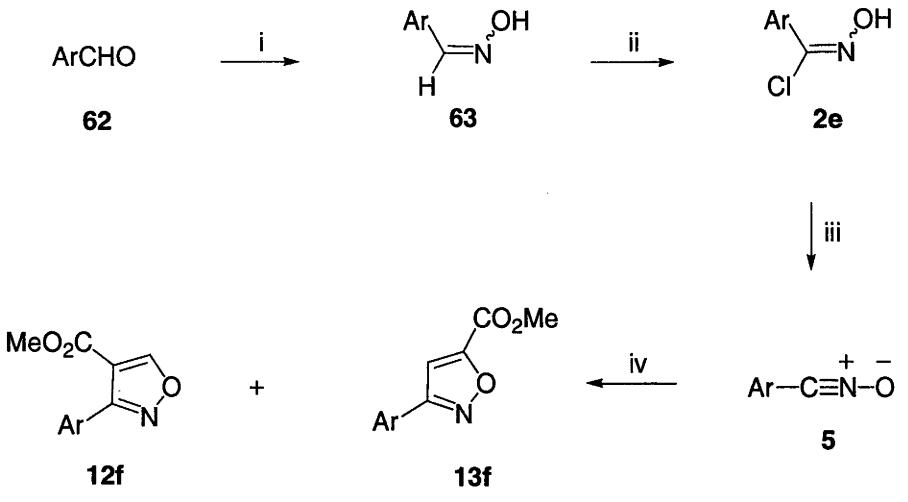
53a

Ar = 2,6-Cl_2Ph

Compound	C_α	C_β	C_γ
48a	2.54 (t, J = 6 Hz)	2.29 (p, J = 6 Hz)	3.12 (t, J = 6 Hz)
52a	2.63 (t, J = 6 Hz)	2.24 (p, J = 6 Hz)	2.73 (t, J = 6 Hz)
50a	2.43 (t, J = 6.5 Hz)	1.97 (p, J = 6.5 Hz)	2.65 (t, J = 6.5 Hz)
53a	2.46 (t, J = 6 Hz)	2.24 (p, J = 6 Hz)	2.98 (t, J = 6 Hz)

Hydrogenation of equimolar quantities of isoxazoles **48a** and **52a** with palladium on carbon as the catalyst afforded a mixture of starting materials and ring-opened species **48a**, **50a**, **52a** and **53a** in a ratio of 1:6:5:2 as determined from integration of the methylene proton signals (Table 8) in the ^{1}H NMR spectrum of the crude reaction mixture. The rate of formation of the imine **50a** was thus observed to be approximately three times faster than that of the imine **53a**. This implies that the N-O bond of the 4-acylisoxazole **48a** is weaker than that of the 5-carbonyl-substituted isomer **52a**, since the strengths of bonds are usually reflected by their ease of cleavage. The fact that **48a** is more prone to ring-opening than **52a** *via* a range of mechanistically different reaction pathways, as shown by the baker's yeast-catalysed, electrochemical and hydrogenolytic ring-opening reactions, indicates a common trend for the substituent effects.

The generality of hydrogenolytic ring-cleavage of acylisoxazoles was examined through the competitive hydrogenation of the alkoxycarbonyl-substituted isoxazoles **12f** and **13f**. These isoxazoles were studied because of their conformational flexibility between the carbonyl group and the isoxazole ring, by comparison to the fused bicyclic isoxazoles **48a,b** and **52a,b** which are conformationally fixed. The isoxazoles **12f** and **13f** were prepared using Huigsen's method,[24] from the cycloaddition of mesitonitrile oxide **5** with methyl propiolate **11**, as shown in Scheme 15. Mesitonitrile oxide **5** was chosen as the 1,3-dipole because it is inert towards dimerization.[19] Preparation of the nitrile oxide **5** began with synthesis of the oxime **63** which was prepared from condensation of the aldehyde **62** with hydroxylamine hydrochloride. The oxime **63** was then converted to the hydroximinoyl chloride **2e** using the chlorinating agent, NCS. Due to the electron-rich methyl substituents, the aromatic ring of the oxime **63** is particularly prone to chlorination. This was circumvented by using a stoichiometric amount of NCS, and maintaining the internal temperature of the reaction mixture between 20-25 °C, since chlorination of the aromatic ring is initiated above 30 °C.[9] Although nitrosyl chloride is the best reagent for selective chlorination of aromatic oximes **2**,[10] NCS was used instead because of its availability. The dipole **5** was afforded *via* dehydrohalogenation of **2e** through the use of triethylamine as the base (Scheme 15).



Ar = 2,4,6-Me_3Ph

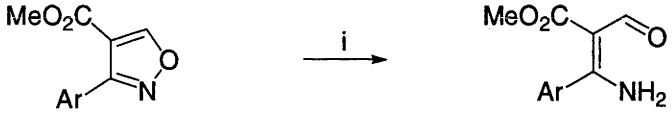
Reagents and conditions: i. **62** (1.0 equiv.), $NH_2OH.HCl$ (1.1 equiv.), 50% wt/v NaOH (1.1 equiv.), 30% aq. EtOH, 18 °C, 3 h; ii. **63** (1.0 equiv.), NCS (1.0 equiv.), DMF, 20-25 °C, 3.5 h; iii. **2e** (1.0 equiv.), NEt_3 (1.2 equiv.), Et_2O, 18 °C, 2 h; iv. **5** (1.0 equiv.), **11** (1.0 equiv.), THF, reflux, 2 days.

Scheme 15

Having prepared the dipole **5**, it was then treated with the dipolarophile **11** to afford a mixture of 4- and 5-alkoxycarbonylisoxazoles **12f** and **13f**, in a ratio of *ca.* 2.6:1 and in a combined yield of 97% (Scheme 15). The structures of the isoxazoles **12f** and **13f** were deduced using EI mass spectrometric methods, where accurate mass measurement of the parent ions at *m/z* 245 indicated the molecular composition of $C_{14}H_{15}NO_3$. The structures of the regioisomeric pair **12f** and **13f** were assigned according to the chemical shifts of the ^1H NMR resonances of the C4- and C5-isoxazole protons. In general, the chemical shift of a C4 proton is in the region of δ 6-7 ppm whilst for the C5 proton, it is usually observed further downfield at δ 8-9.5 ppm.[67] Thus the isoxazole **12f** was determined to be the 4-acyl-substituted isomer, based on the one proton singlet at δ 9.06 ppm, ascribed to the C5 proton. Similarly, the structure of the 5-substituted regioisomer **13f** was established by the one proton singlet at δ 6.90 ppm, with the characteristic chemical shift of the C4 proton. In the infrared spectra, the carbonyl stretching vibrations of the isoxazoles **12f** and **13f** were discerned as intense

absorption bands at 1724 cm^{-1} and 1749 cm^{-1}, respectively. The energy of the carbonyl stretching vibration of **12f** is higher than that of **13f**. This may be attributed to more extensive conjugation of the carbonyl group and the isoxazole ring in **12f**.[68] Based on the structural assignments of the regioisomeric cycloadducts **12f** and **13f**, the isoxazole **12f** was determined to be the major product. Its dominance over the 5-methoxycarbonyl-substituted isomer **13f** is due to polar effects in the cycloaddition of dipole **5** with the electron-deficient alkyne, methyl propiolate **11** (see Chapter 1, Section 1.1.2.).[24]

With the isoxazoles **12f** and **13f** in hand, independent hydrogenations of these compounds were carried out (Schemes 16 and 17) for the purpose of assigning the structures of the ring-cleaved products **64** and **65**.

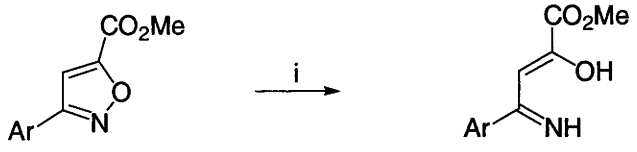


12f **64**

Ar = 2,4,6-Me_3Ph

Reagents and conditions: i. **12f**, H_2, Pd/C (10% by wt), MeOH, 18 °C, 24 h.

Scheme 16



13f **65**

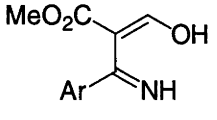
Ar = 2,4,6-Me_3Ph

Reagents and conditions: i. **13f**, H_2, Pd/C (10% by wt), MeOH, 18 °C, 10 days.

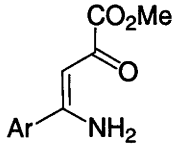
Scheme 17

The structures of the ring-opened products **64** and **65** were deduced from their EI mass spectrometric and ^{1}H NMR spectroscopic data. For both compounds **64** and **65**, accurate mass measurement of the parent ions at *m/z* 247 indicated the molecular composition of $C_{14}H_{17}NO_3$. From the ^{1}H NMR spectrum (in $CDCl_3$) of the ring-cleaved product resulting from hydrogenation of the isoxazole **12f**, the β-keto enamine **64** was determined to be the sole product as indicated by the one proton singlet at δ 10.2 ppm, ascribed to the aldehydic proton. From the ^{1}H NMR spectral data, there was no evidence for the enol imine tautomeric form **66** as its presence would be indicated by a singlet resonance in the olefinic region. The complete dominance of the keto-form **64** over the enol-form **66** is attributed to keto-enol tautomerisation where the carbonyl compounds are usually the preferred form.

The ring-cleaved product resulting from hydrogenation of the 5-acylisoxazole **13f** was rationalized to be the enol imine **65**, rather than the keto enamine **67**. Preference for the enol imine tautomer **65** is attributed to unfavorable electronic effects in the keto enamine **67**, arising from the adjacent positioning of the electropositive carbon centres of the alkoxycarbonyl and the ketone carbonyl groups. The olefinic proton of the enol imine **65** is indicated by a singlet resonance in the olefinic region at δ 5.90 ppm.



66

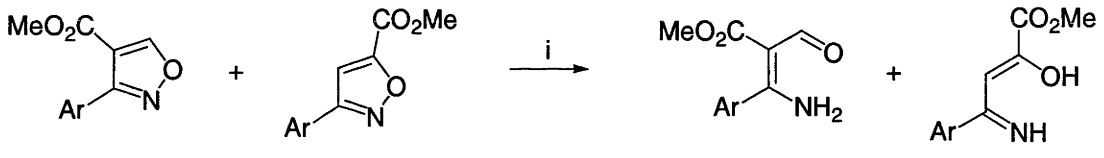


67

Ar = 2,4,6-Me_3Ph

The hydrogenolytic cleavage of the 4-acylisoxazole **12f** was observed to proceed at a markedly faster rate than for the 5-acyl-substituted isomer **13f**; whilst hydrogenation of **12f** was complete within 24 hours (Scheme 16), a reaction time of 10 days was required for the complete conversion of the 5-substituted isomer **13f** to the enol imine **65**

(Scheme 17). To quantify these findings, stoichiometric amounts of the isoxazoles **12f** and **13f** were hydrogenated (Scheme 18). After a reaction period of two days, a product mixture consisting of the isoxazole and the ring-opened species **64**, **13f** and **65** in a ratio of 11:10:1 was obtained, with none of the isoxazole **12f** detected (Scheme 18). It follows that the rate of ring-cleavage of the 4-acylisoxazole **12f** is at least an order of magnitude greater than that of the 5-acyl-substituted isomer **13f**. This implies that the N-O bond of the isoxazole **12f** is much weaker than that of the 5-acylisoxazole **13f**. Compared to that observed with the fused bicyclic isoxazoles **48a** and **52a**, an even greater substituent effect is seen for the more flexible systems **12f** and **13f**, though the reasons for this are not immediately apparent.



12f **13f** **64** **65**

Ar = 2,4,6-Me_3Ph

Reagents and conditions: i. **12f** (1.0 equiv.), **13f** (1.0 equiv.), H_2, Pd/C (10% by wt), MeOH, 18 °C, 2 days.

Scheme 18

From the above results, substituent effects were discerned for baker's yeast-catalysed, electrochemical and hydrogenolytic reactions of 4- and 5-acylisoxazoles. These reactions are mediated *via* electron-transfer in the cases of the baker's yeast and the electrochemical processes, or direct N-O bond cleavage through hydrogenation of the acylisoxazoles. The results suggest that structural factors inherent in the isoxazoles influence their reactivities to reductive ring-opening.

2.2. X-Ray Crystallography of Solid State Structures of Isoxazoles

The putative structural effects were examined through X-ray crystallography of the isoxazoles **48a,b** and **52a,b**. The X-ray crystallographic structures of these had been solved previously.[66] In the solid state, two molecules are found in the unit cells of the isoxazoles **52a,b**, arising from the effects of intermolecular interactions. For **48a,b**, only one molecule was observed in the unit cell of the solid state structure. Selected bond lengths from the X-ray crystallographic analyses of the isoxazoles **48a,b** and **52a,b** are listed in Table 9. Large standard errors are discerned for the data, especially so for the isoxazoles **52a,b**.

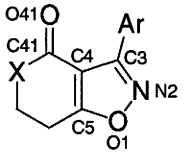
While the error limits are large and caution must therefore be taken in interpreting the data, the N-O bonds of the 4-acylisoxazoles **48a,b** generally appear to be longer than those of the 5-acylisoxazoles **52a,b**. This indicates that the 4-acylisoxazoles **48a,b** have weaker N-O bonds than those of the 5-acyl-substituted isomers **52a,b**, since the strength of a covalent bond is generally inversely proportional to its length. This is reflected in the competitive hydrogenation of **48a** and **52a** where the 4-acylisoxazole **48a** ring-cleaved more readily than the 5-acyl-substituted isomer **52a**.

Apart from studying the N-O bonds, the C5-O1, C4-C5, C4-C41, C5-C51, C41-O41 and C51-O51 bonds were examined for conjugation based on the baker's yeast and electrochemical ring-opening of the isoxazoles **48a,b**. As indirect ring-opening of the isoxazole occurs subsequent to electron-transfer to the carbonyl group (see Chapter 1, Section 1.5.), it therefore appears that ring cleavage results from interaction of the N-O bond with the carbonyl group, possibly through conjugative effects *via* the series of bonds which connect the carbonyl group and N-O bond.

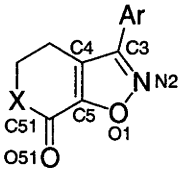
Despite the large standard errors, the data indicate that the C5-O1 bonds of the 4-acylisoxazoles **48a,b** are mostly shorter than those of the 5-acylisoxazoles **52a,b**. Lengthening of the C4-C5 bonds of the 4-acylisoxazoles **48a,b** in comparison to those of the 5-acyl-substituted isomers **52a,b** is also discerned. These results suggest conjugation of the ring oxygen to the carbonyl group at the 4-position of isoxazoles **48a,b**. Shortening of the C4-C41 bonds relative to the C5-C51 bonds, and lengthening of the C41-O41 bonds relative to the C51-O51 bonds might also be expected as a result of

conjugation in the 4-acylisoxazoles **48a,b**. However such effects are not seen, possibly due to the large standard errors for these bond lengths.

Table 9. Selected bond lengths (Å) from the X-ray crystallographic data of isoxazoles **48a,b** and **52a,b**



48



52

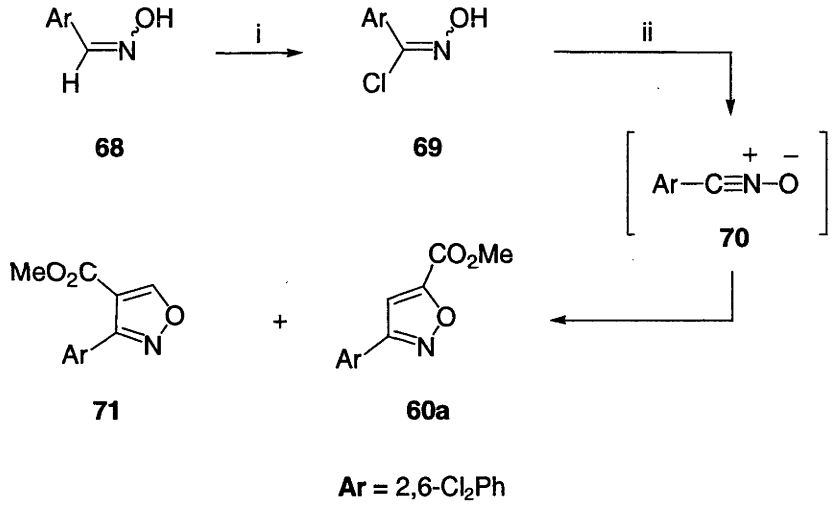
Ar = 2,6-Cl_2Ph
a. X = CH_2
b. X = O

Compound	O1-N2	C5-O1	C4-C5	C4-C41	C41-O41	C5-C51	C51-O51
48a	1.411(3)	1.324(4)	1.340(4)	1.445(4)	1.207(4)	-	-
48b	1.426(2)	1.320(3)	1.330(3)	1.438(3)	1.188(3)	-	-
52a	1.407(7)	1.349(8)	1.326(8)	-	-	1.45(1)	1.209(8)
	1.397(7)	1.329(8)	1.326(8)	-	-	1.461(9)	1.188(7)
52b	1.391(7)	1.322(9)	1.32(1)	-	-	1.44(1)	1.19(3)
	1.398(7)	1.329(9)	1.32(1)	-	-	1.48(1)	1.18(1)

For the fused bicyclic isoxazoles **48a,b** and **52a,b**, the reliability of the X-ray crystallographic data is limited by very large standard errors. In an attempt to obtain data with lower standard errors, which would therefore be more reliable, the X-ray crystallographic structures of other acylisoxazoles were also examined. Isoxazoles **12f** and **13f** were available as a regioisomeric pair but could not be used because isoxazole **13f** is not crystalline. Therefore the X-ray crystallographic structures of the isoxazoles **71** and **60a** were examined instead. The isoxazoles **71** and **60a** were also studied because they are conformationally more flexible about the isoxazole ring and the carbonyl group,

in comparison to the fused bicyclic isoxazoles **48a,b** and **52a,b** where their bridged frameworks restrict such conformational mobility. Thus the influences of conformational mobility as well as substituent effects on the structures of isoxazoles were examined.

The synthesis of isoxazoles **71** and **60a** involved preparation of 2,6-dichlorobenzonitrile oxide **70**. Starting with commercially available oxime **68**, it was chlorinated with a stoichiometric amount of NCS to give the hydroximinoyl chloride **69**.[9] The dipole **70** which was generated *in situ* by treatment of hydroximinoyl chloride **69** with triethylamine, underwent cycloaddition with methyl propiolate **11** to afford the regioisomeric isoxazoles **71** and **60a** (Scheme 19).



Reagents and conditions: i. **68** (1.0 equiv.), NCS (1.0 equiv.), DMF, 20-25 °C, 3.5 h; ii. **69** (1.0 equiv.), **11** (1.2 equiv.), NEt_3 (1.1 equiv.), THF, reflux, 2 days.

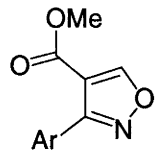
Scheme 19

The structures of the cycloadducts **71** and **60a** were deduced from mass spectrometric and ^1H NMR spectroscopic data. For the isoxazole **71**, although the parent ions were not detected by EI mass spectrometry, the $[M^{\bullet+}-^{37}Cl]$ and $[M^{\bullet+}-^{35}Cl]$ fragments of *m/z* 238 and *m/z* 236 were observed. Accurate mass measurement of these indicated the composition of $C_{11}H_7ClNO_3$. For isoxazole **60a**, the molecular ions were detected at

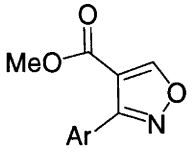
m/z 277, *m/z* 275 and *m/z* 273. As discussed above for isoxazoles **12f** and **13f**, the 4- and 5-methoxycarbonylisoxazoles **71** and **60a** are also differentiated by the chemical shifts of the ^{1}H NMR resonances of the C4- and C5-isoxazole protons. For the 4-acylisoxazole **71**, the C5 proton is observed as a one proton singlet at δ 9.08 ppm, whilst the C4 proton of isomer **60a** resonates further upfield at δ 7.08 ppm.[65] In the infrared spectra, the carbonyl stretching vibrations of the isoxazoles **71** and **60a** were discerned as intense absorption bands at 1732 cm^{-1} and 1736 cm^{-1}. There is little difference between the two vibrational stretching frequencies so any conjugation in the 4-acylisoxazole **71** is not apparent, though this could be due to other differences in the structures of **71** and **60a**.

The 5- and 4-acylisoxazoles **60a** and **71** formed from the cycloaddition of dipole **70** and dipolarophile **11** in a ratio of 3:1, with a combined yield of 76%. The regioselectivity of the reaction is dominated by steric effects. Thus, formation of the 5-acylisoxazole **60a** is favoured, whereby the oxygen of the dipole **70** is bonded to the most substituted alkynyl carbon of the dipolarophile **11**. Polar effects are less important. Thus the 4-acylisoxazole **71** resulting from bonding between the electron-rich dipole oxygen and the electropositive β-carbon of the dipolarophile **11** is only the minor adduct.

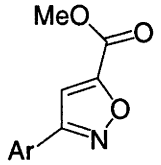
The X-ray crystallographic structure of the 5-acylisoxazole **60a** had been solved previously within the group.[69] The 4-acylisoxazole **71** was crystallized from a mixture of hexanes and ether at 18 °C and the X-ray crystallographic structure of the material was recorded (Figures 2-5). There are two possible planar conformations for the 4- and 5-methoxycarbonyl-substituted isoxazoles **71** and **60a** as shown below. When the carbon-oxygen double bond is on the same side as the C4-C5 double bond, the isoxazole is said to be in a *cis*-conformation. When the carbonyl group is opposite to the C4-C5 double bond, the *trans*-conformer results.



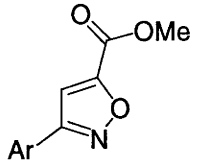
71 (*trans*)



71 (*cis*)



60a (*trans*)

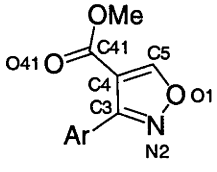


60a (*cis*)

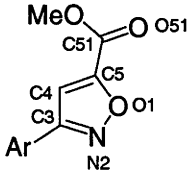
Ar = 2,6-Cl_2Ph

In the solid state, the unit cell consists of four molecules of **71**, all in the *trans*-conformation which is also the conformation of the bridged 4-acylisoxazoles **48a,b**. For isoxazole **60a**, there is only one molecule in the unit cell. As shown in the ORTEP diagram of **60a** (Figure 1), the molecule is of *trans*-configuration which is also the conformation of **52a,b**. The bond length data of the isomeric isoxazoles **71** and **60a** are listed in Table 10.

Table 10. Selected bond lengths (Å) from the X-ray crystallographic data of acylisoxazoles **71** and **60a**



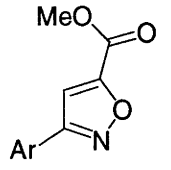
71



60a

Ar = 2,6-Cl_2Ph

Compound	O1-N2	C5-O1	C4-C5	C4-C41	C41-O41	C5-C51	C51-O51
71	1.422(5)	1.337(6)	1.345(7)	1.472(7)	1.196(5)	-	-
	1.422(5)	1.339(6)	1.354(7)	1.462(7)	1.211(5)	-	-
	1.423(5)	1.324(6)	1.350(7)	1.464(7)	1.198(6)	-	-
	1.419(5)	1.340(6)	1.338(7)	1.482(7)	1.204(5)	-	-
60a	1.400(2)	1.349(2)	1.337(3)	-	-	1.477(3)	1.203(2)



60a

Ar = 2,6-Cl_2Ph

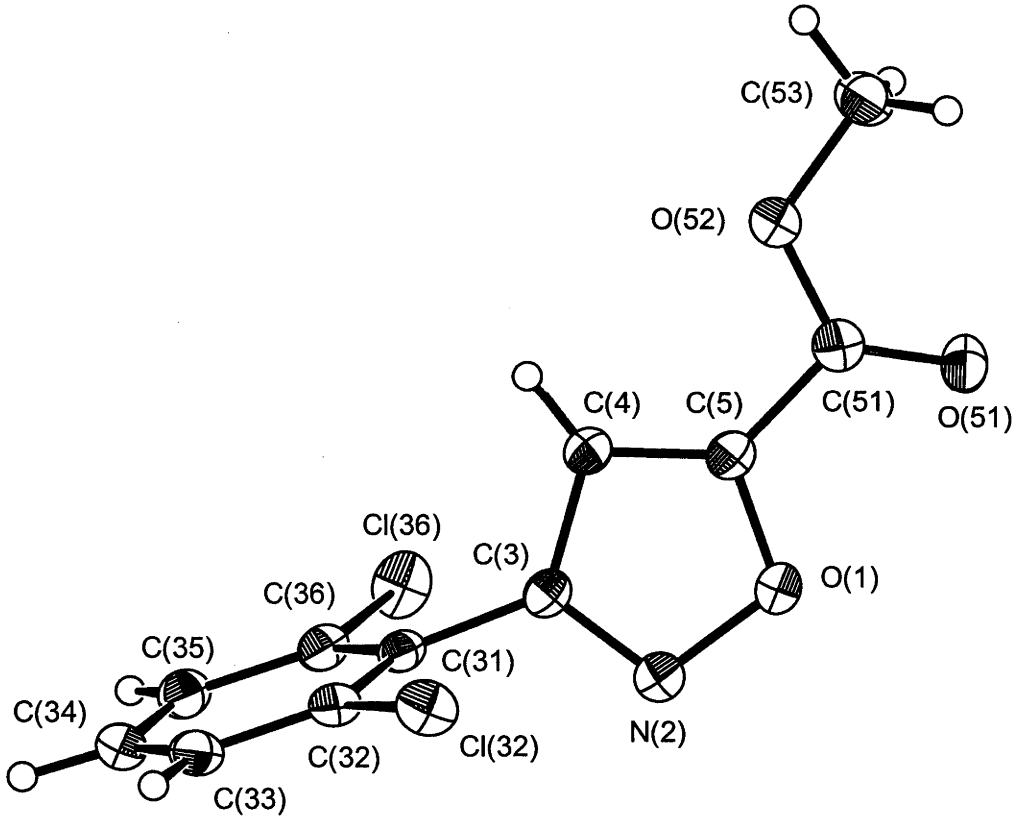
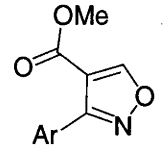


Figure 1. ORTEP derived from single crystal X-ray analysis of compound **60a**.



71

Ar = 2,6-Cl_2Ph

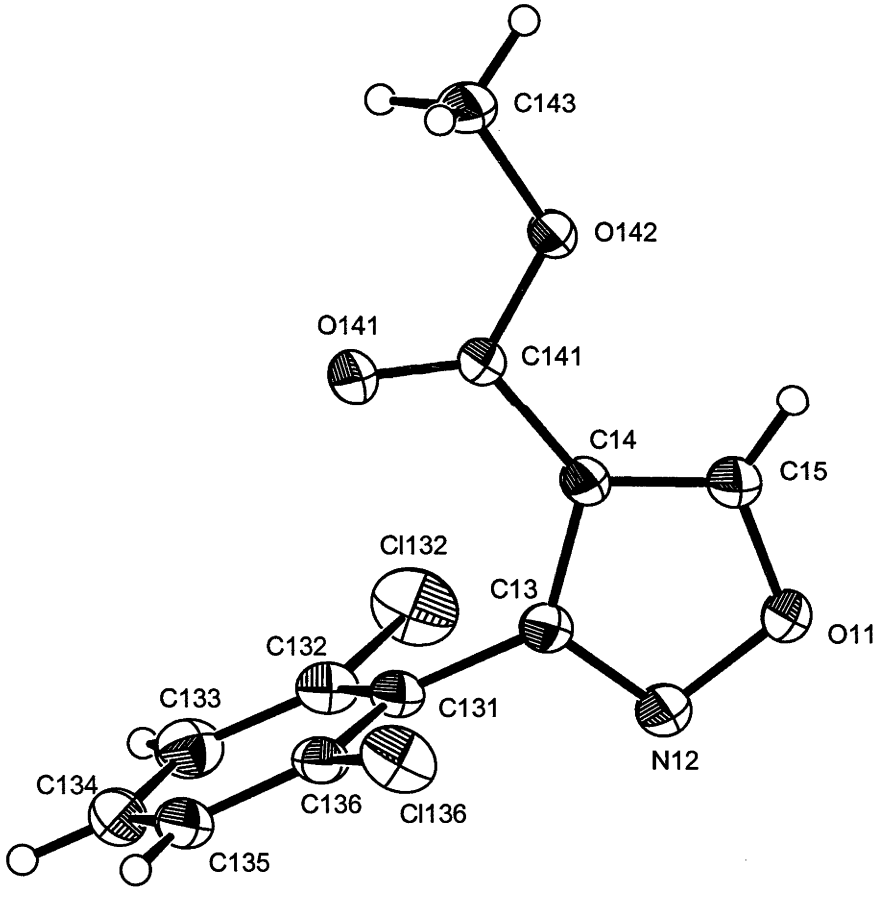
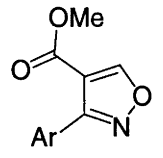


Figure 2. ORTEP derived from single crystal X-ray analysis of compound **71**, conformer 1.



71

Ar = 2,6-Cl_2Ph

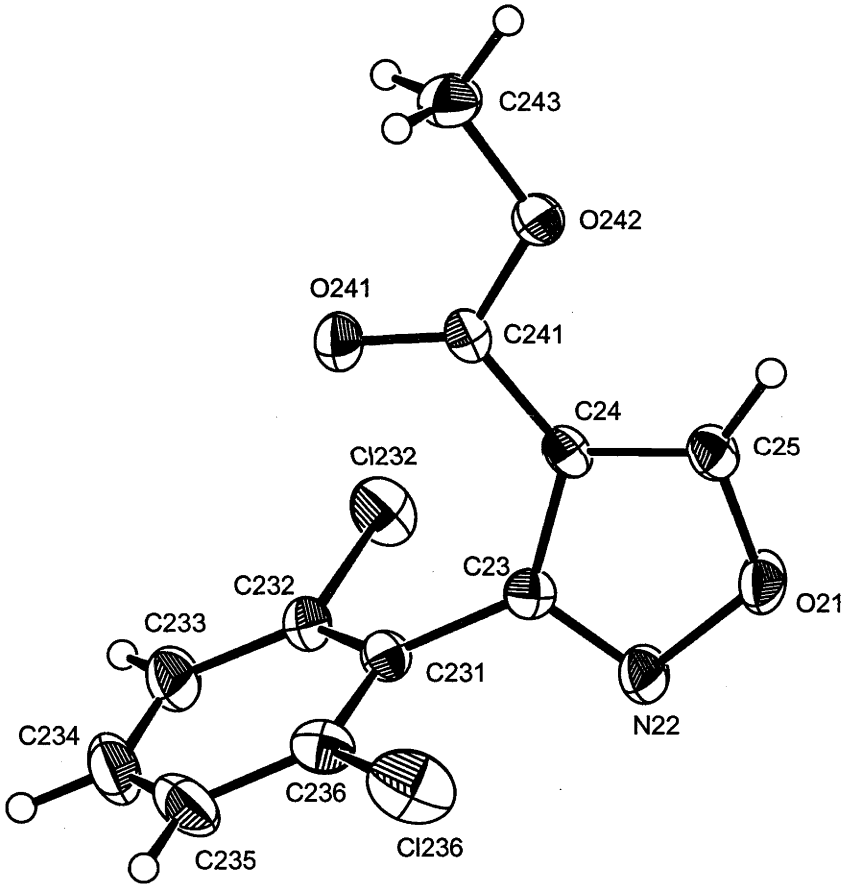
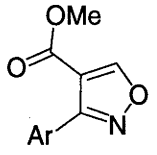


Figure 3. ORTEP derived from single crystal X-ray analysis of compound **71**, conformer 2.



71

Ar = 2,6-Cl_2Ph

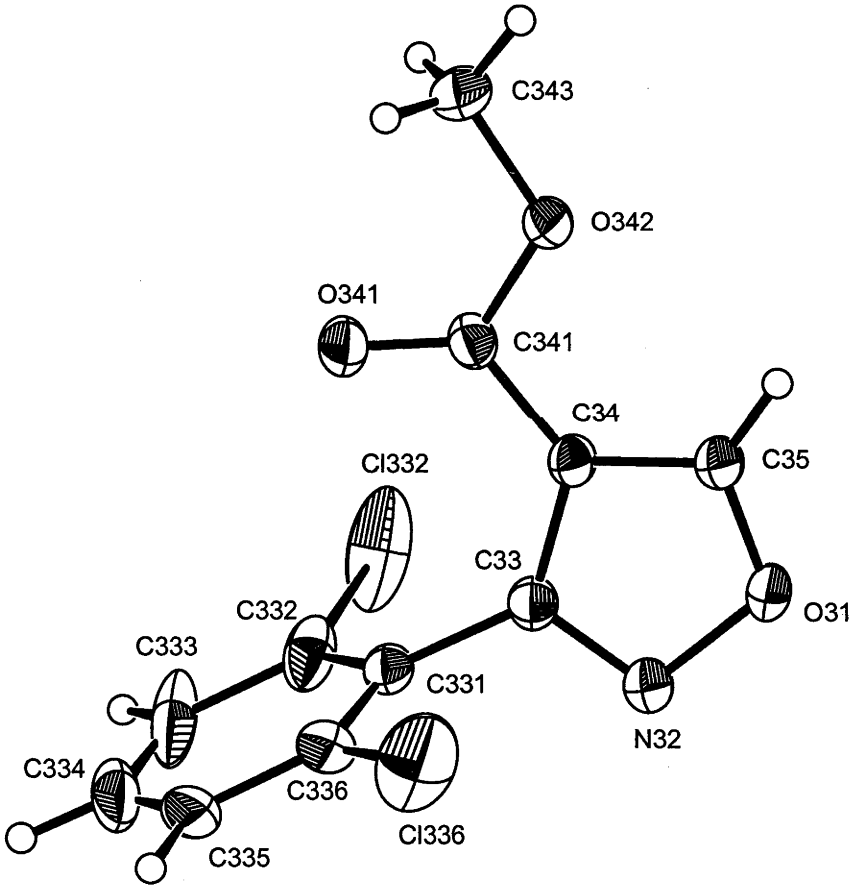
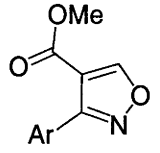


Figure 4. ORTEP derived from single crystal X-ray analysis of compound **71**, conformer 3.



71

Ar = 2,6-Cl_2Ph

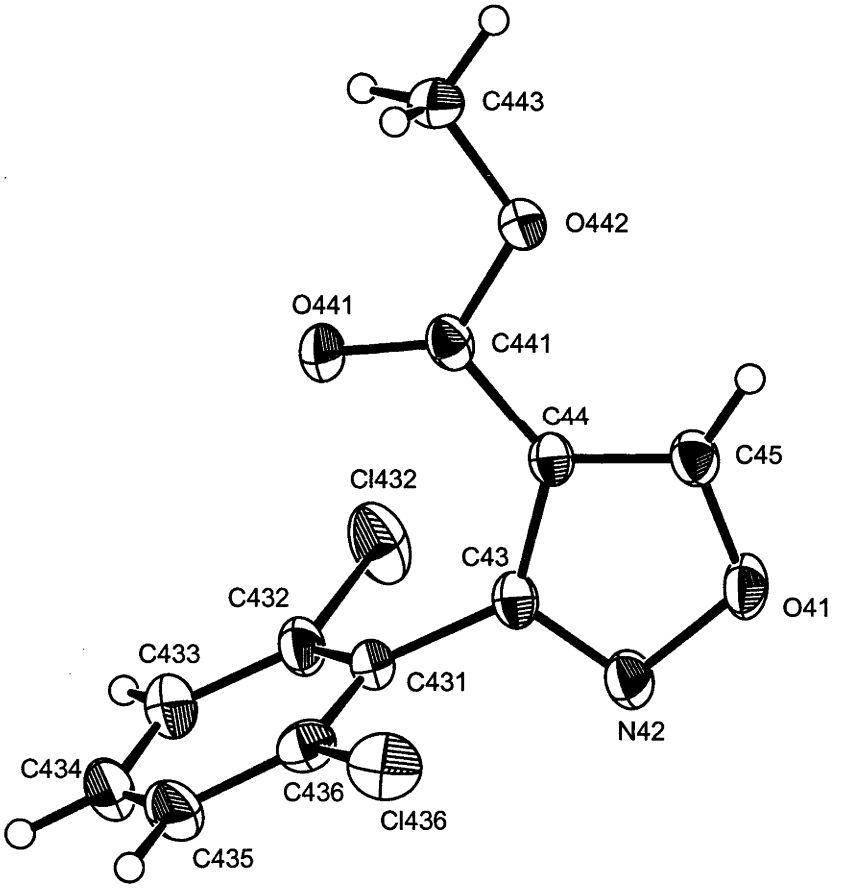


Figure 5. ORTEP derived from single crystal X-ray analysis of compound **71**, conformer 4.

Compared to the standard errors for the bond lengths of the X-ray crystallographic structures of the fused bicyclic isoxazoles **48a,b** and **52a,b**, those of the conformationally flexible systems **71** and **60a** are lesser in magnitude. The data more clearly show lengthening of the O1-N2 bonds of the four conformers of the 4-acylisoxazole **71** relative to that of the 5-acyl-substituted isoxazole **60a**, than indicated earlier for the isoxazoles **48a,b** and **52a,b**.

For the C5-O1 and C4-C5 bonds, the standard errors are larger and the bond lengths less reliable than those of the O1-N2 bonds. Nevertheless, indications of conjugation are also discerned for the isoxazoles **71** and **60a**. The C5-O1 bonds of the conformers of **71** appear shortened relative to that of **60a**. The C4-C5 bonds also appear to be lengthened in **71** relative to that of **60a**.

From the data listed in Table 10, the lengths of the C4-C41 and C41-O41 bonds do not appear to be significantly different to those of the C5-C51 and C51-O51 bonds, respectively, but the large standard errors undermine the reliability of the data.

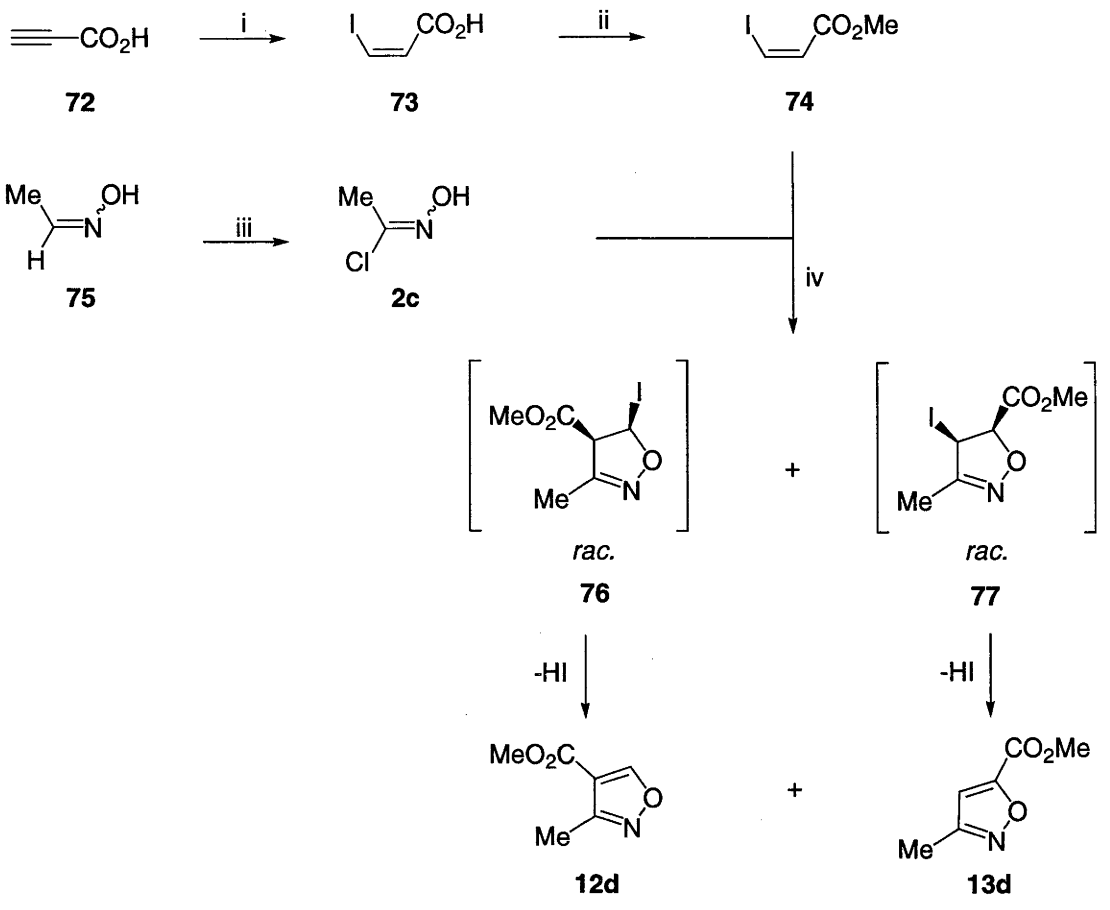
Although the structural trends concerning the O1-N2 and C5-O1 bonds of the isoxazoles **71** and **60a** are more clear than those of the isoxazoles **48a,b** and **52a,b**, the standard errors are still of considerable magnitude. In a further attempt to obtain more reliable data, isoxazoles **12d** and **13d** were synthesized and their X-ray crystallographic structures were recorded. The 3-methylisoxazoles **12d** and **13d** were initially prepared according to Huisgen *et al.*'s method.[24] In contrast to the combined yield of 90% for the cycloadducts **12d** and **13d** in a ratio of *ca.*1:2.2 as reported by these authors for the cycloaddition of acetonitrile oxide **3c** with a 2.5-fold excess of methyl propiolate **11**, the best yield in the present work was 55% due to competing nitrile oxide dimerization. Since purification of the isomers **12d** and **13d** was complicated by the presence of the by-product furoxan, formed from this dimerization of the nitrile oxide **3c**, an alternative method that produces less of the contaminant was sought.

As alkenes are generally more reactive than alkynes as dipolarophiles (see Chapter 1, Section 1.2.),[39] isoxazoles **12d** and **13d** were synthesized from the olefin **74** instead of the alkyne **11**. The dipolarophile **74** was prepared through hydroiodination of propiolic acid **72**,[70] followed by acid-catalysed esterification of the acrylic acid **73** with methanol.[70]

The hydroximinoyl chloride **2c** was prepared from chlorination of the oxime **75** with NCS (Scheme 20).[71] In order to maximize the yield of the cycloaddition, acetonitrile oxide **3c** was generated *in situ* through treatment of the hydroximinoyl chloride **2c** with triethylamine, in an excess of the dipolarophile **74** in order to suppress competing dimerization of the nitrile oxide **3c**. The combined yield of the cycloadducts **12d** and **13d** using the acrylate **74** as the dipolarophile was 75%, which is a substantial improvement on 55%, obtained from the cycloaddition of methyl propiolate **11** with dipole **3c**.

As discussed earlier for the isoxazoles **71**, **60a**, **12f** and **13f**, structural assignments of the isoxazoles **12d** and **13d** were based on the chemical shifts of their C4 and C5 isoxazole proton resonances. In the ^{1}H NMR spectrum of **12d**, the one proton singlet at δ 8.84 ppm was assigned to the C5 proton. For isoxazole **13d**, the singlet at δ 6.80 ppm was ascribed to the C4 proton. In the infrared spectra, the carbonyl stretching vibrations of **12d** and **13d** do not fit the trends observed for the 3-arylisoxazoles **12f**, **13f**, **71** and **60a**. For the isoxazole **12d**, the carbonyl stretching vibration was observed at 1734 cm^{-1} whilst for its regioisomer **13d** it was discerned at 1731 cm^{-1}. Conjugation of the carbonyl group with the isoxazole ring of the 4-acylisoxazole **12d** is therefore not apparent from the infrared data, although this may be masked by other structural effects. Due to the volatility of the isoxazole **12d**, attempts to measure the parent ion peak with EI, GCMS and ES methods were unsuccessful. Nevertheless, the mass spectral data of compound **13d** are consistent with the literature values,[24] with accurate mass analysis of the molecular ion at *m/z* 141 for the structural composition of $C_6H_7NO_3$.

The adducts **12d** and **13d** were furnished in a ratio of *ca.* 1:2.6 from the cycloaddition of dipole **3c** with dipolarophile **74** presumably *via* elimination of hydrogen iodide from the intermediate 2-isoxazolines **76** and **77** (Scheme 20). As the methoxycarbonyl and the iodine groups are both electron-withdrawing and sterically demanding, the regioselectivity of the cycloaddition is therefore influenced by a balance of steric and polar effects.



Reagents and conditions: i. **72** (1.0 equiv.), NaI (1.5 equiv.), AcOH, 115 °C, 90 min; ii. **73**, H_2SO_4 (cat.), MeOH, reflux, 36 h; iii. **75** (1.0 equiv.), NCS (1.0 equiv.), DMF, 20-25 °C, 3.5 h; iv. **2c** (1.0 equiv.), **74** (8.0 equiv.), NEt_3 (1.1 equiv.) added over 16 h, Et_2O, 18 °C, 24 h.

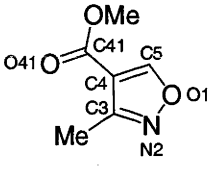
Scheme 20

Crystallization of the isoxazoles **12d** and **13d** was effected from a mixture of hexanes and ether at 0 °C as both cycloadducts readily sublime at atmospheric pressure and room temperature (18 °C). The X-ray crystallographic structures of the isoxazoles **12d** and **13d** were recorded and their ORTEP diagrams are shown in Figures 6 and 7, respectively. The unit cells of **12d** and **13d** each consist of one conformer. Similar to the configuration of the 4-acylisoxazole **71**, isoxazole **12d** is in the *trans*-conformation. However for **13d**, it is in the *cis*-conformation, which is the reverse to that observed for **60a**. Clearly 5-acylisoxazoles may adopt *cis*- and *trans*-configurations in the solid state,

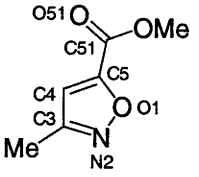
and the preference for one over the other may be influenced by intermolecular interactions.

The data for the lengths of the O1-N2, C5-O1, C4-C5, C4-C41, C5-C51, C41-O41 and C51-O51 bonds of the isomeric isoxazoles **12d** and **13d** are listed in Table 11. Overall, the standard errors are considerably lower than those of **71** and **60a** and because of this the data are much more reliable.

Table 11. Selected bond lengths (Å) from the X-ray crystallographic data of acylisoxazoles **12d** and **13d**

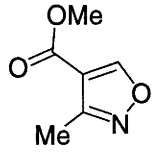


12d



13d

Compound	O1-N2	C5-O1	C4-C5	C4-C41	C41-O41	C5-C51	C51-O51
12d	1.427(2)	1.331(2)	1.345(2)	1.459(2)	1.211(2)	-	-
13d	1.416(2)	1.349(2)	1.347(2)	-	-	1.479(2)	1.203(2)



12d

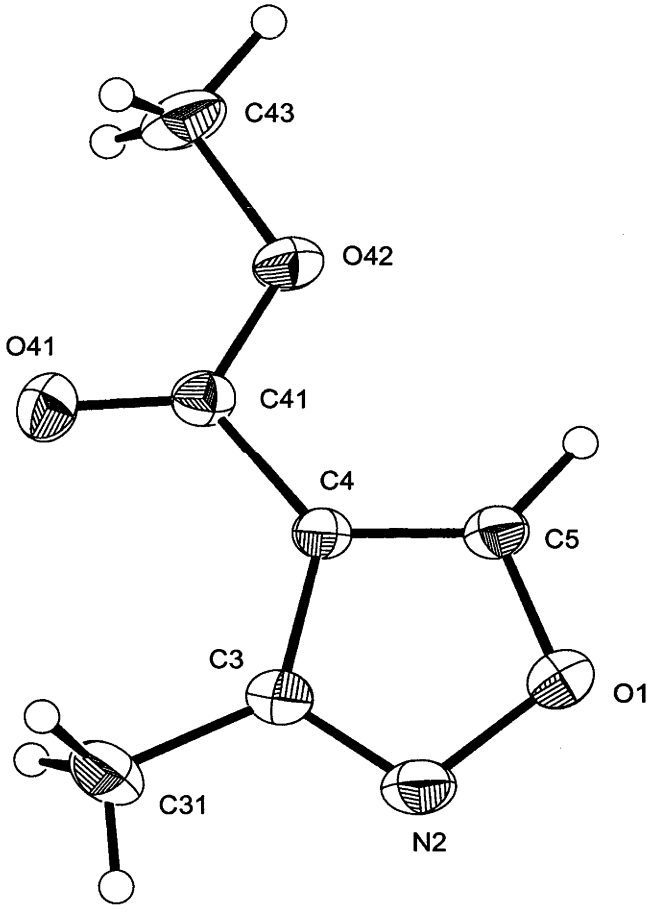
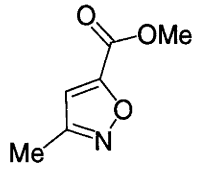


Figure 6. ORTEP derived from single crystal X-ray analysis of compound **12d**.



13d

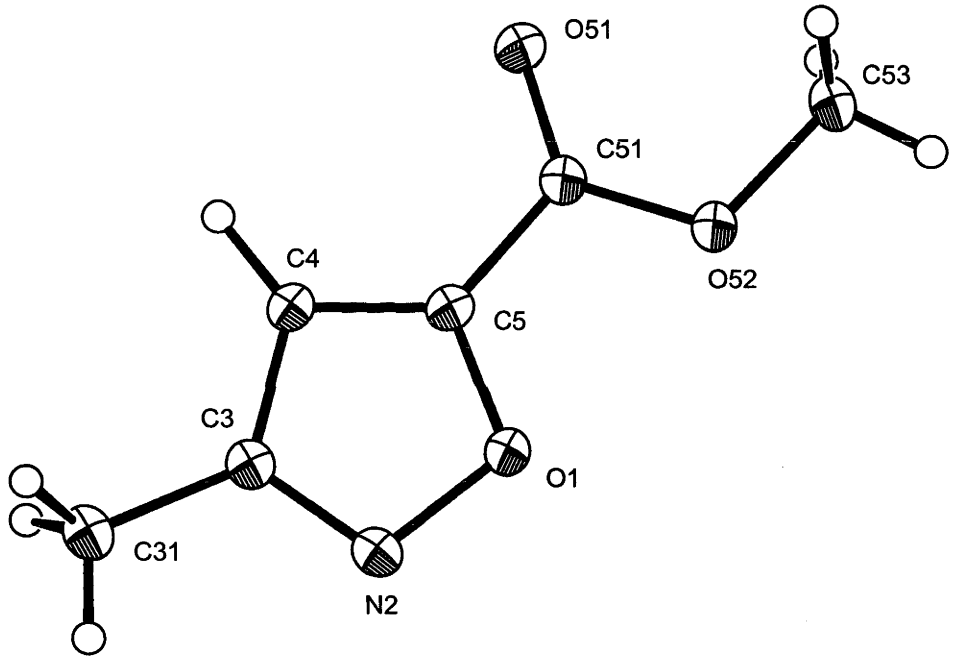


Figure 7. ORTEP derived from single crystal X-ray analysis of compound **13d**.

The X-ray crystallographic data show that the O1-N2 bond of the 4-acylisoxazole **12d** is lengthened relative to that of **13d**. This implies that the O1-N2 bond of the 4-acylisoxazole **12d** is inherently weaker than that of the 5-acyl-substituted isomer **13d**.

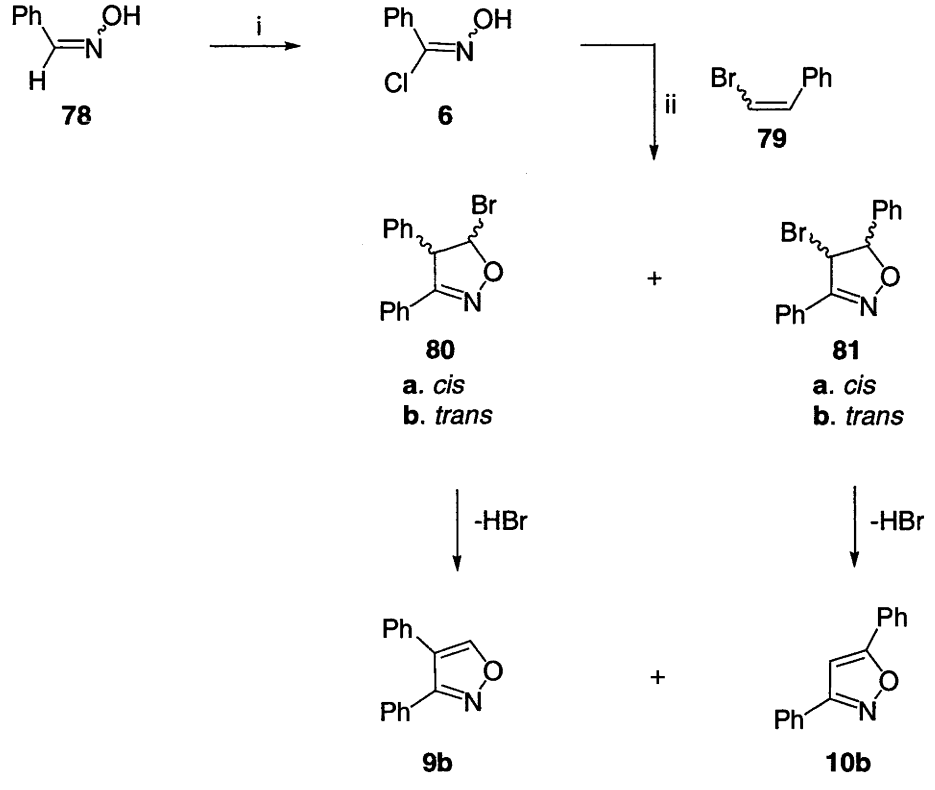
Conjugation in the 4-acylisoxazole **12d** is evident from comparison of the C5-O1, C4-C41/C5-C51 and C41-O41/C51-O51 bonds of **12d** and **13d**. The C5-O1 bond of the 4-acylisoxazole **12d** is clearly shorter than that of the 5-acylisoxazole **13d**, indicating the ring oxygen is conjugated to the carbonyl group at the 4-position of the isoxazole ring. The data also show that the C4-C41 single bond of **12d** is shorter than the C5-C51 bond of **13d**, whilst the C41-O41 double bond of **12d** is lengthened relative to the C51-O51 bond of **13d**. This is characteristic of a conjugated system where single bonds are usually shortened whilst multiple bonds are lengthened, resulting from resonance stabilization.

The X-ray crystallographic analyses show that 4- and 5-acylisoxazoles are inherently different in their structures. The N-O bond of a 4-acylisoxazole is weaker than that of the 5-substituted isomer, as indicated by lengthening of the N-O bond. This structural effect is reflected in the competitive hydrogenation of isomeric isoxazoles. Conjugation between the ring oxygen and the carbonyl group of 4-acylisoxazoles is also apparent from the bond lengths. This is probably reflected in the electron-transfer based ring-opening reactions.

As shown by the electrochemical reactions[65] of isoxazoles, ring-opening was observed for isoxazoles substituted with conjugating electron-withdrawing acyl- and cyano-substituents at the 4-position of the ring whilst 5-acyl- and cyano-substituted isoxazoles did not give rise to clean ring-opened species. By contrast these substituent effects were not discerned for the conjugating but not electron-withdrawing phenyl group, as reflected by the complex product mixtures resulting from electrolysis of 4- and 5-phenylisoxazoles **61a,b**. Therefore phenylisoxazoles were examined for inherent structural effects that may account for the resistance of **61a,b** to ring-open cleanly upon electrolysis. As the phenylisoxazoles **61a,b** used for the electrochemical study are not crystalline, isoxazoles **9b** and **10b** were studied instead.

The synthesis of the isoxazoles **9b** and **10b** commenced with preparation of benzonitrile oxide **7** (Scheme 21). Benzohydroximinoyl chloride **6** was furnished from

controlled chlorination of benzaldoxime **78** with NCS.[9] The dipole **7**, generated *in situ* through treatment of **6** with triethylamine, underwent cycloaddition with the 1,2-disubstituted olefin, β-bromostyrene **79**. Dipolarophile **79** was chosen because it was expected to give rise to **80a,b** and hence **9b**, which is otherwise inaccessible from phenylacetylene **8b** as a result of dominant steric effects for the cycloaddition of dipole **7** and dipolarophile **8b** (see Chapter 1, Section 1.1.2.).[21] After 7 days at room temperature, the crude reaction mixture consisted of the cycloadducts **81b**, **9b** and **10b** (Scheme 21).



Reagents and conditions: i. **78** (1.0 equiv.), NCS (1.0 equiv.), DMF, 20-25 °C, 3.5 h; ii. **6** (1.0 equiv.), **79** (2.5 equiv.), NEt_3 (2.0 equiv.) added over 3 days, Et_2O, 18 °C, 4 days.

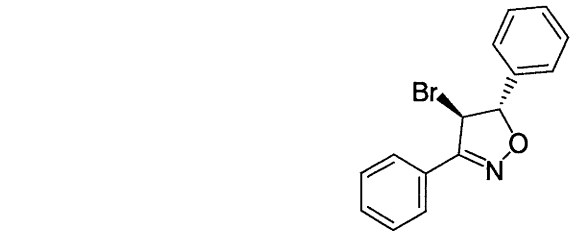
Scheme 21

Compounds **81b**, **9b** and **10b** were isolated by chromatography and characterized. For the 2-isoxazoline **81b**, molecular ions were detected at *m/z* 301 and *m/z* 303. Accurate mass measurement of the molecular ion at *m/z* 301 indicated the structural composition of $C_{15}H_{12}BrNO$. The structure was confirmed from the ^1H NMR data, where the resonances of the C4- and C5-isoxazoline protons are observed as doublets at δ 5.38 ppm and δ 6.06 ppm respectively. The C4 proton was deduced to be *anti* to the C5 proton, based on the magnitude of the coupling constant, $J_{4,5}$ = 2.0 Hz, which is characteristic of the *trans*-configuration ($J_{4,5}$ = 1.5-8 Hz), as opposed to those of *cis*-isoxazolines ($J_{4,5}$ = 8-12 Hz).[21,23,24,72] Crystals of **81b** were obtained from a boiling hexane solution upon cooling, and the melting point of the crystalline material is consistent with the literature value.[73] X-Ray crystallographic analysis of **81b** showed substitution of the bromine at the 4-position and the phenyl group at the 5-position, in an *anti* relationship (Figure 8).

The structure of the 4-phenylisoxazole **9b** was deduced from mass spectral and ^1H NMR spectroscopic data. Accurate mass measurement for the molecular composition of $C_{15}H_{11}NO$ was based on the molecular ion *m/z* 221, which was detected through the EI method. In the ^1H NMR spectrum, the signal of the C5 isoxazole proton resonance is observed as a singlet at δ 8.52 ppm, comparable to the reported value of δ 8.73 ppm.[74] Crystallization of **9b** was effected from boiling hexanes upon cooling. The X-ray crystallographic structure of **9b** was recorded, and two conformers were detected in the unit cell. The ORTEP diagrams of these conformers are shown in Figures 9 and 10.

The physical and spectral properties of the isomeric 5-phenylisoxazole **10b** are in full accord with literature values. In the ^1H NMR spectrum, the signal of the C4 proton is distinguished as a singlet at δ 6.82 ppm,[75] and the melting point of the material is consistent with that reported.[76] The X-ray crystallographic structure of **10b** had been solved previously.[77]

Presumably, cycloaddition of nitrile oxide **7** with β-bromostyrene **79** (which comprised a mixture of *cis*- and *trans*-isomers in a ratio of *ca.* 1:6) gave rise to the intermediate *cis*- and *trans*-2-isoxazolines **80a,b** and **81a,b**. These adducts underwent elimination of hydrogen bromide to afford the isoxazoles **9b** and **10b**.



rac.
81b

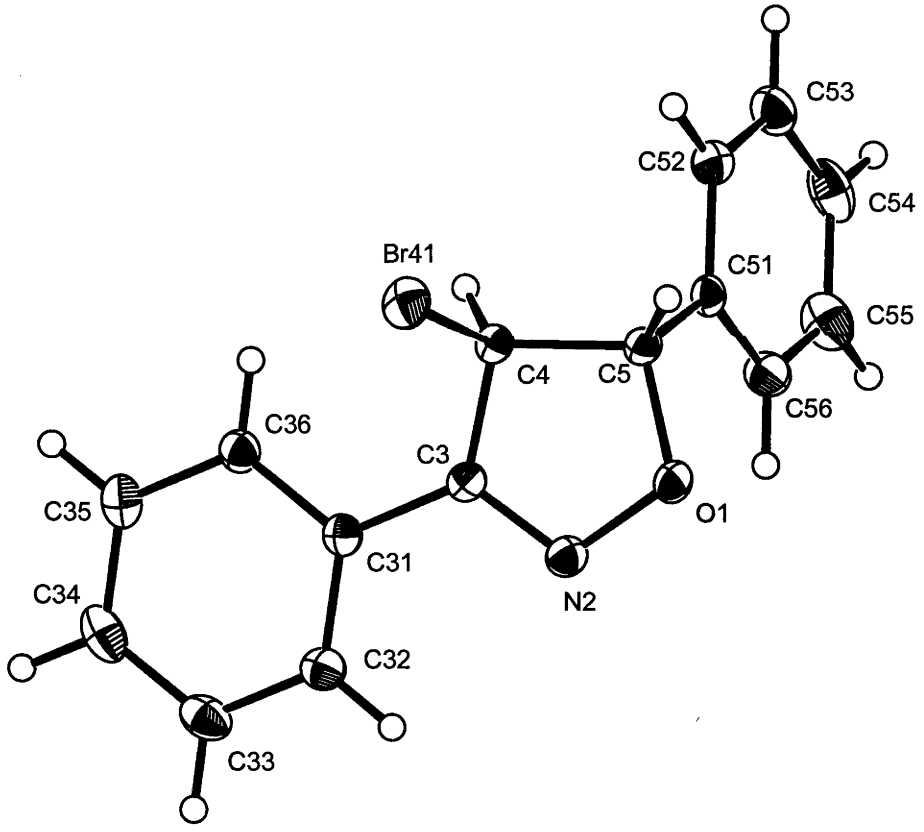
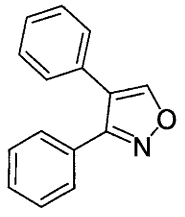


Figure 8. ORTEP derived from single crystal X-ray analysis of compound **81b**.



9b

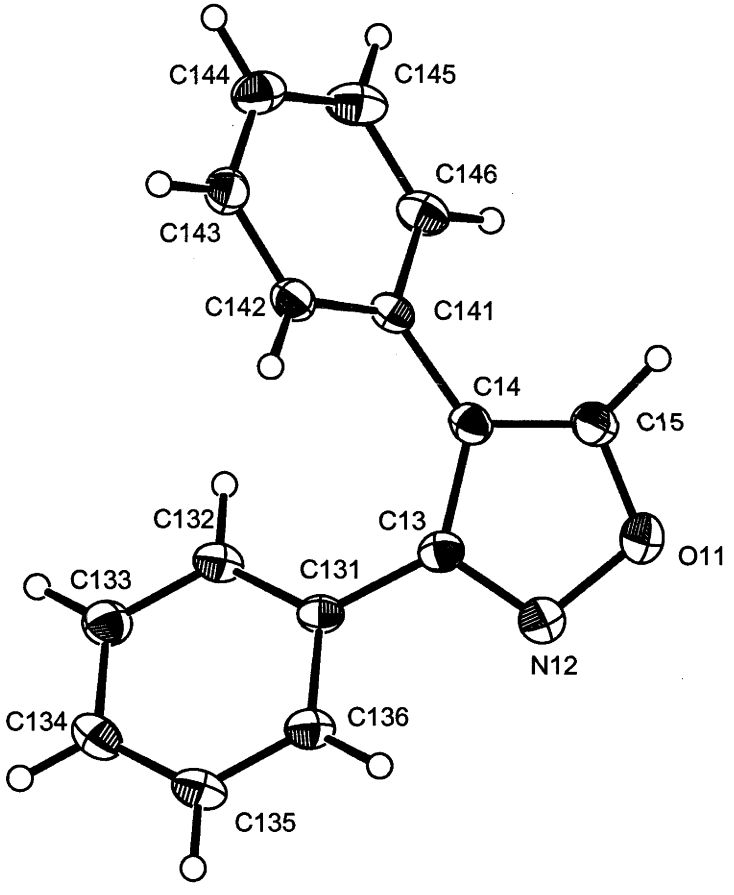
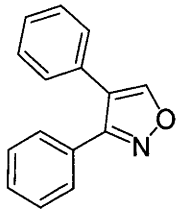


Figure 9. ORTEP derived from single crystal X-ray analysis of compound **9b**, conformer 1.



9b

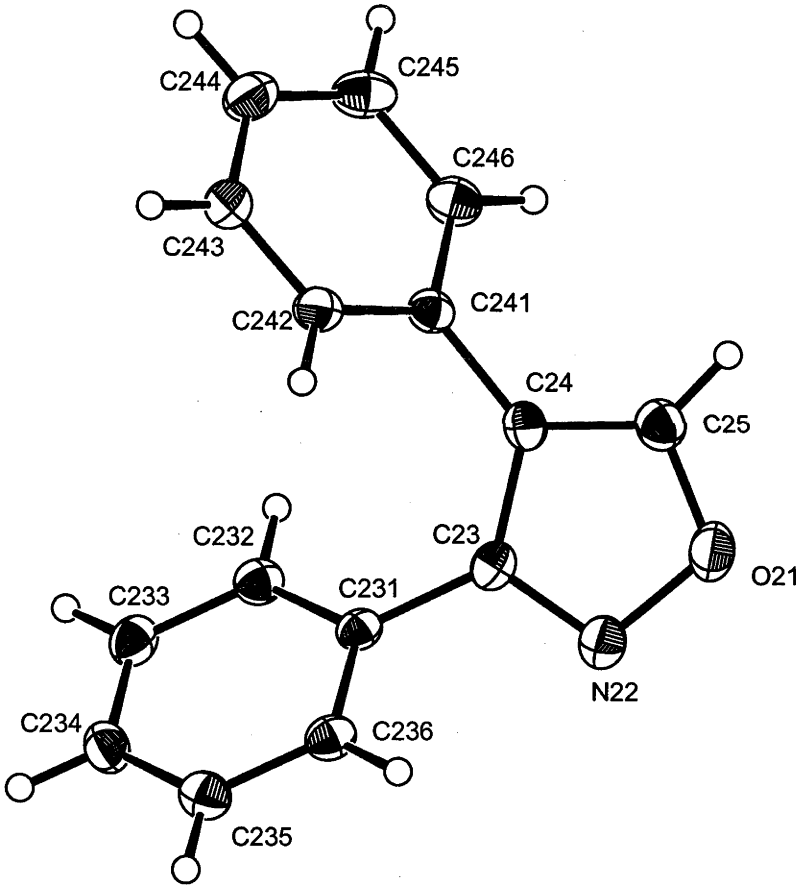
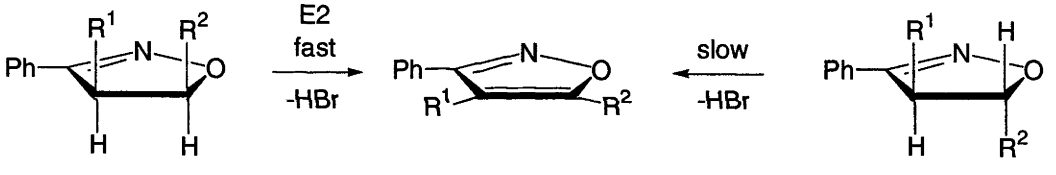


Figure 10. ORTEP derived from single crystal X-ray analysis of compound **9b**, conformer 2.

2-Isoxazoline **81b**, and isoxazoles **9b** and **10b**, were furnished in the ratio of *ca.* 6:1:0.1. The product ratio shows that the combined yield of the 5-phenyl-substituted species **10b** and **81b** exceeds that of the 4-phenyl-substituted product **9b**. Presumably this reflects polar effects which favour bonding between the dipole oxygen and the olefinic carbon *beta* to the inductively electron-withdrawing bromine. The 5-phenylisoxazole **10b** was presumably formed through elimination of hydrogen bromide from either or both of the 2-isoxazolines **81a,b**. The 4-phenylisoxazole **9b** was presumably formed *via* elimination of hydrogen bromide from either or both of the 2-isoxazolines **80a,b**.

The *cis*-2-isoxazolines **80a** and **81a** were not detected in the reaction mixture. Assuming that they were formed, they must eliminate hydrogen bromide efficiently. This can occur *via* a facile E2-elimination pathway which is facilitated by the *anti*-disposition of the bromine and the vicinal hydrogen (Scheme 22).



80a. R^1 = Ph, R^2 = Br
81a. R^1 = Br, R^2 = Ph

9b. R^1 = Ph, R^2 = H
10b. R^1 = H, R^2 = Ph

80b. R^1 = Ph, R^2 = Br
81b. R^1 = Br, R^2 = Ph

Scheme 22

Of the two possible *trans*-2-isoxazolines **80b** and **81b**, only the latter was observed in the product mixture. Presumably, the resistance of **81b** to loss of hydrogen bromide is a consequence of the *syn*-alignment of the bromine and the vicinal hydrogen, which does not allow E2-elimination to occur. Any of the 2-isoxazoline **80b** which formed must have reacted by loss of hydrogen bromide. It is possible that this occurs *via* an $E1_{cb}$ mechanism due to the acidity of the isoxazoline C4 proton.

The X-ray crystallographic structure of the 5-phenylisoxazole **10b** is unusual due to its *C2/c* space group assignment,[77] thereby implying a plane of symmetry through H4 and C4 and perpendicular to the plane of the isoxazole, such that the nitrogen and oxygen become indistinguishable (Figure 11).[77] Thus the oxygen and nitrogen are treated as statistically interchangeable with an occupancy factor of 0.5 at the two positions and, consequently, the C3 and C5 centres are also considered as interchangeable. Under these symmetry considerations, it is impossible to distinguish the N2-C3 bond from the O1-C5 bond, and likewise, the C4-C5 bond from the C3-C4 bond. As the O1-N2 bond is the only isoxazole ring bond that is unaffected, it was therefore the only one used for comparative purposes with **9b**. Selected X-ray crystallographic data of phenylisoxazoles **9b** and **10b** are listed in Table 12.

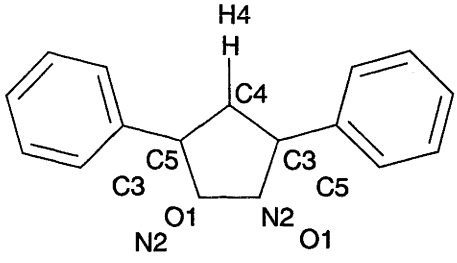
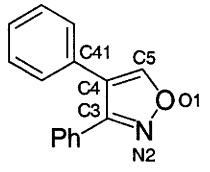


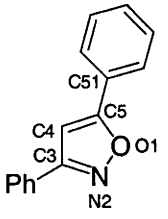
Figure 11

The data show that the N-O bond lengths of the phenylisoxazoles **9b** and **10b** are not statistically different. The N-O bonds of the phenylisoxazoles **9b** and **10b** are markedly shorter than those of the 4-acylisoxazoles **71** and **12d**, and in fact, they are closer in length to those of the 5-acylisoxazoles **60a** and **13d**. This indicates that the N-O bond strengths of the 4- and 5-phenyl-substituted isoxazoles are similar to those of 5-acylisoxazoles. This trend parallels the contrasting reactivities of isoxazoles **58a**, **60a** and **61a,b** in the electrochemical reactions, where the 4-acylisoxazole **58a** was reduced more easily than the 5-acylisoxazole **60a** and the 4- and 5-phenyl-substituted isoxazoles **61a,b**.

Table 12. Selected bond lengths (Å) from the X-ray crystallographic data of phenylisoxazoles **9b** and **10b**



9b



10b

Compound	O1-N2	C5-O1	C4-C5	C4-C41
9b	1.409(2)	1.351(2)	1.340(2)	1.472(2)
	1.415(2)	1.362(2)	1.340(2)	1.472(2)
10b	1.407(4)	-	-	-

2.3. Theoretical Calculations of Gas Phase Structures of Isoxazoles

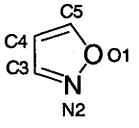
Although the X-ray crystallographic data indicate inherent structural differences between the O1-N2 bonds and the C5-O1 bonds of the 4- and 5-acylisoxazoles, the reliability of the data is limited by large standard errors. Intermolecular interactions also distort the data, as is illustrated by a given bond differing in length amongst conformers of the same molecule. In some instances, the difference is large, as shown for example by the C5-O1 bond lengths of 1.351(2) Å and 1.362(2) Å for the two conformers of **9b** (Table 12). A theoretical study was therefore carried out in an attempt to obtain data that are independent of the intermolecular distortions present in the solid state. This involved modelling calculations on gas matrices.

In order to study substituent effects of gas phase isoxazoles, formyl-, cyano- and vinyl-substituted derivatives were examined, along with the unsubstituted isoxazole **82** as the basis for comparison. Whilst the formyl group serves as a model for the keto and

ester groups, the vinyl group was used as a substitute for the phenyl group. The formyl and vinyl groups were used to simplify the basis sets. The theoretical calculations of the minimum energy conformations were carried out because they are the statistically most populated species. From the calculations of the minimum energy conformations, molecular dimensions and geometries such as bond lengths and conformational preferences, as well as electronic parameters such as π-electron densities were extracted. The theoretical calculations also provide information about the polarization of these heterocycles, which is not directly apparent from the X-ray crystallographic data.

2.3.1. Isoxazole

Bond lengths of isoxazole **82** have previously been estimated using a variety of semiempirical, molecular orbital and *ab initio* methods. Some of the methods used include VESCF,[78] LCAO-SCF-MO,[79] improved LCAO,[80] CNDO-CI,[81] *ab initio*,[82] MNDO SCF-MO[83] and STO-3G.[84] The results of these studies are summarized in Table 13. The data clearly show marked inconsistencies across these studies, especially for the C5-O1 bond which varies in length from 1.31 Å to 1.380 Å.



82

In an attempt to obtain more accurate data, more recent theories were evaluated to identify the most suitable method for calculating the bond lengths of isoxazole **82** and variously substituted isoxazoles. The theoretical methods surveyed in the present study were B3-LYP/6-31G*, B3-LYP/6-31+G*, B3-LYP/6-311+G(3df,2p), MP2/6-31G* and CCSD/6-31G*. The bond lengths of isoxazole **82** measured from the calculated minimum energy planar conformation were then compared to experimental values in order to determine the optimum method. The experimental data were obtained from

rotation spectra of isotopic forms of isoxazole **82**, in their natural abundance, by Stark effect-modulated (SEM)[85] and double-resonance-modulated (DRM) microwave spectroscopy.[86] DRM spectroscopy is considered an improvement over the SEM method.[86] The theoretical and experimental bond lengths data are summarized in Table 13.

Table 13. Bond lengths (Å) of isoxazole **82**

Method	O1-N2	N2-C3	C3-C4	C4-C5	C5-O1
VESCF	1.38	1.30	1.43	1.36	1.36
LCAO-SCF-MO	1.36	1.34	1.33	1.41	1.31
improved LCAO	1.38	1.30	1.44	1.35	1.36
CNDO-CI	1.39	1.33	1.42	1.37	1.39
ab initio	1.391	1.316	1.438	1.335	1.380
MNDO SCF-MO	1.301	1.351	1.449	1.387	1.373
STO-3G	1.383	1.316	1.436	1.349	1.372
B3-LYP/6-31G*	1.400	1.313	1.424	1.360	1.345
B3-LYP/6-31+G*	1.401	1.313	1.425	1.362	1.345
B3-LYP/6-311+G(3df,2p)	1.394	1.305	1.420	1.354	1.339
MP2/6-31G*	1.392	1.328	1.414	1.364	1.354
CCSD/6-31G*	1.396	1.311	1.427	1.355	1.349
SEM microwave spectroscopy	1.398	1.314	1.427	1.358	1.346
DRM microwave spectroscopy	1.399	1.309	1.425	1.356	1.344

Of the theories examined in the present study, the data derived from the MP2/6-31G* and B3-LYP/6-311+G(3df,2p) methods show the largest disparity from the experimental values especially for the O1-N2, N2-C3 and C5-O1 bonds, with a difference of 0.019 Å being observed between the MP2/6-31G* determined and the DRM microwave spectroscopically-derived N2-C3 bond length. The B3-LYP/6-31+G* and CCSD/6-31G* data are in good agreement with the experimental values, and the largest deviation of the theoretical values from the optimized experimental values was 0.006 Å. The data obtained using the B3-LYP/6-31G* theory showed the best

correlation with the DRM microwave spectroscopically-derived values. As the calculated bond lengths are theoretical entities, there are no standard errors associated with them. Instead, the accuracy of the calculations may be gauged from the absolute deviation from the experimental values. For the unsubstituted isoxazole **82**, the largest discrepancy between the optimized theoretically and experimentally determined bond lengths is 0.004 Å.

Having determined the bond lengths of the isoxazole **82** using the B3-LYP/6-31G* theory, the π-electron distribution of **82** was determined using the same method. In the past four decades, the π-electron distribution of the isoxazole **82** has been evaluated using various molecular orbital methods, namely the HMO,[87] MO-LCAO,[88] PPP-SCF-CI,[89] improved LCAO[80] and CNDO-CI[81] methods. The results of these studies are listed in Table 14.

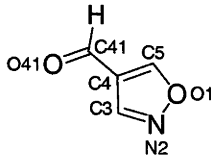
Table 14. Calculated π-electron densities of isoxazole **82**

Method	O1	N2	C3	C4	C5
HMO	1.85	1.28	0.87	0.99	1.02
MO-LCAO	1.719	1.189	1.019	1.104	0.968
PPP-SCF-CI	1.686	1.357	0.907	1.063	0.986
improved LCAO	1.91	1.13	0.96	1.05	0.95
CNDO-CI	1.784	1.256	0.903	1.096	0.962
B3-LYP/6-31G*	1.68	1.23	0.99	1.09	1.00

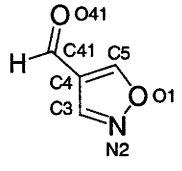
As anticipated, these studies show that high π-electron densities reside on the oxygen and nitrogen since these heteroatoms are more electronegative than carbon. The data show considerable variation in the π-electron density across these studies. It is reasonable to assume that the B3-LYP/6-31G* data are more reliable than those obtained using the outdated methods. The B3-LYP/6-31G* calculations also indicate that the C4-C5 bond is polarized, with the C4 centre being electron-rich.

2.3.2. 4- and 5-Formylisoxazoles

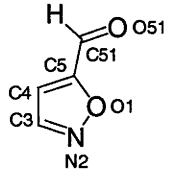
Once the optimum method was established to be B3-LYP/6-31G*, it was used to calculate the minimum energy conformations of formylisoxazoles. Two minimum energy conformations were found for each of the 4- and 5-formylisoxazoles **83** and **84**. These are illustrated below. These minimum energy conformations have the formyl group and the isoxazole ring coplanar due to conjugation between the two. This allows maximum overlap of the π-orbitals.



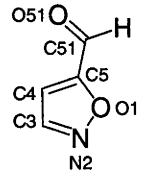
83a (*trans*)



83b (*cis*)



84a (*trans*)



84b (*cis*)

Conformational analysis of 4-formylisoxazole **83** using the EHT and Dewar σ-π methods had been reported by Sheinker *et al.* two decades ago.[90] Their study indicated that the *cis*-conformer **83b** is more stable than the *trans*-conformer **83a** by 0.8 kJ mol^{-1}. However this level of theory is outdated, and thus the B3-LYP/6-31G* method was used in the present study to re-determine the conformational stabilities. This showed that the *trans*-conformer **83a** is more stable than the *cis*-conformer **83b** by 1.9 kJ mol^{-1}. Either way, the energy difference between the *cis*- and *trans*-conformers of the 4-formylisoxazole **83** is small.

For 5-formylisoxazole **84**, the energy difference between the conformers **84a** and **84b** calculated using the B3-LYP/6-31G* method is 7.1 kJ mol^{-1} in favor of the *cis*-isomer **84b**. The preference for **84b** may be attributed to minimization of repulsion between the ring oxygen O1 and the carbonyl oxygen O51. Interestingly the isoxazole **60a** exists as the *trans*-conformer in the solid state (Figure 1), but in this case there would be unfavorable electrostatic interactions between the ring oxygen and an oxygen of the methoxycarbonyl group in either conformer, and presumably the conformational preference is therefore determined by intermolecular interactions.

Having determined the minimum energy conformations of the 4- and 5-formylisoxazoles **83** and **84**, the bond lengths in these conformers were then measured. The results are listed in Table 15. The observed trends reinforce those seen in the solid state irrespective of the *cis*- or *trans*-conformation.

The most salient difference of bond lengths between the 4- and 5-formylisoxazoles **83** and **84** is seen with the O1-N2 bonds. Weakening of the O1-N2 bond of 4-formylisoxazole **83** relative to that of the 5-formyl-substituted isomer **84** is clear. This is indicated by lengthening of the O1-N2 bonds of the conformers of 4-formylisoxazole **83** relative to those of the 5-formyl-substituted isomer **84**.

Conjugation is also apparent in the gas phase structures of 4-formylisoxazole **83** from a comparison of bond lengths with those of the 5-substituted isomer **84**. Shortening of the C5-O1 bonds of the conformers of the 4-formylisoxazole **83** relative to those of the 5-formylisoxazole **84** is pronounced. Some shortening of the C4-C41 bonds relative to the C5-C51 bonds, and lengthening of the C41-O41 bonds relative to the C51-O51 bonds is also observed.

Table 15. Selected bond lengths (Å) of 4-and 5-formylisoxazoles **83** and **84**, determined using the B3-LYP/6-31G* method

Compound	O1-N2	C5-O1	C4-C5	C4-C41	C41-O41	C5-C51	C51-O51
83a	1.415	1.334	1.369	1.464	1.217	-	-
83b	1.412	1.332	1.371	1.466	1.217	-	-
84a	1.386	1.351	1.369	-	-	1.472	1.212
84b	1.387	1.355	1.368	-	-	1.471	1.215
82	1.400	1.345	1.360	-	-	-	-

The theoretical calculations present an opportunity for comparing the bond lengths of the 4- and 5-formylisoxazoles **83** and **84** with those of the unsubstituted isoxazole **82**. Relative to the O1-N2 bond of the unsubstituted isoxazole **82**, those of the conformers of 4-formylisoxazole **83** are elongated whilst the opposite effect is observed

for 5-formylisoxazole **84**. Lengthening of the C5-O1 bonds of the conformers of **84** relative to that of the unsubstituted isoxazole **82** is discerned. By contrast, attachment of a formyl group at the 4-position is associated with shortening of the C5-O1 bond relative to that of the unsubstituted isoxazole **82**. Lengthening of the C4-C5 bonds is observed for the conformers of the 4- and 5-formylisoxazoles **83** and **84**, relative to that of **82**.

Comparison of the bond length data of the O1-N2, C5-O1 and C4-C5 bonds of formylisoxazoles **83** and **84** to those of the unsubstituted isoxazole **82** indicates that the observed trends are due to conjugation. In the 4-formylisoxazole **83**, conjugation of the ring oxygen to the formyl group leads to shortening of the C5-O1 bond and lengthening of the C4-C5 bond. Consequently, the O1-N2 bond is also elongated. However in the 5-formylisoxazole **84**, conjugation of the C4-C5 bond to the ring oxygen is disrupted by conjugation of the former to the formyl group. The C5-O1 bond and the C4-C5 bond are therefore lengthened, and consequently, the O1-N2 bond is shortened in the cross-conjugated system **84**, with respect to those of **82**.

The extent of polarization of the formylisoxazoles **83** and **84** was determined by measuring their π-electron distributions (Table 16). As discussed previously, the C4-C5 bond of the unsubstituted isoxazole **82** is polarized, where C5 is more electropositive than C4. Comparison of the π-electron densities at C4 and C5 of the formylisoxazoles **83** and **84** with those of the unsubstituted isoxazole **82** indicates that a formyl group at the 4-position accentuates polarization of the C4-C5 double bond through conjugation. By contrast, polarization across the C4-C5 bonds of the conformers of 5-formylisoxazole **84** is diminished relative to that seen in **82**. This is due to conjugation of the C4-C5 bond to the formyl group.

The data show that polarization across the C5, C4, C41 and O41 centres of the 4-formylisoxazole **83** resembles that of an acrylate where the β-carbon (C5) is more electropositive than the α-carbon centre (C4). However for the 5-formylisoxazole **84**, absence of such acrylate-type polarization is clear as the β-carbon (C4) is indicated to be more electronegative than the α-carbon (C5). This acrylate-type polarization of 4-acylisoxazoles accounts for their observed electron-transfer mediated processes, such as

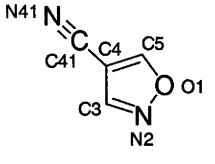
the baker's yeast-catalysed and electrochemical reactions, and for the less facile reactions of the corresponding 5-acylisoxazoles.

Table 16. π-Electron densities of 4- and 5-formylisoxazoles **83** and **84**, determined using the B3-LYP/6-31G* method

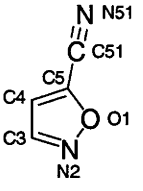
Compound	O1	N2	C3	C4	C5	C41	O41	C51	O51
83a	1.68	1.22	0.95	1.09	0.96	0.79	1.31	-	-
83b	1.66	1.23	0.97	1.10	0.94	0.79	1.32	-	-
84a	1.67	1.19	0.99	1.05	1.01	-	-	0.80	1.29
84b	1.68	1.20	0.99	1.03	1.02	-	-	0.79	1.30
82	1.68	1.23	0.99	1.09	1.00	-	-	-	-

2.3.3. 4- and 5-Cyanoisoxazoles

Like the formyl group, the cyano substituent is a conjugating electron-withdrawing group, though it is less electron-deficient. The effects of the cyano group on bond lengths and π-electron distributions of 4- and 5-cyanoisoxazoles **85** and **86** were also investigated, using the B3-LYP/6-31G* method. The calculations indicate there is only one minimum energy conformation for each of the 4- and 5-cyanoisoxazoles **85** and **86**. The minimum energy conformations of **85** and **86** are illustrated below. They are planar and this allows conjugation of the isoxazole ring with the cyano group.



85



86

The calculated bond lengths of **85** and **86** are tabulated in Table 17. Similar to the general trends observed for the formylisoxazoles **83** and **84**, shortening of the C5-O1 bond and lengthening of the C4-C5 and O1-N2 bonds are seen in 4-cyanoisoxazole **85**, attributed to conjugation of the oxygen to the C4-C5 bond. By contrast, shortening of the O1-N2 bond and lengthening of the C5-O1 and C4-C5 bonds are observed for the 5-cyanoisoxazole **86**. This is attributed to effects of cross-conjugation where overlap of the π-orbitals of the C51-N51 and C4-C5 bonds disrupts conjugation of the latter bond to the ring oxygen, as seen in the unsubstituted isoxazole **82**.

Table 17. Selected bond lengths (Å) of 4- and 5-cyanoisoxazoles **85** and **86**, determined using the B3-LYP/6-31G* method

Compound	O1-N2	C5-O1	C4-C5	C4-C41	C41-N41	C5-C51	C51-N51
85	1.405	1.334	1.370	1.419	1.163	-	-
86	1.387	1.356	1.367	-	-	1.419	1.163
82	1.400	1.345	1.360	-	-	-	-

The π-electron densities as shown in Table 18 indicate that the polarization of the cyanoisoxazoles **85** and **86** is similar to the general trends seen with the formylisoxazoles **83** and **84**. Polarization across the C4-C5 bond of the unsubstituted isoxazole **82** is reinforced by the cyano group at the 4-position, whilst the effect is nullified by substitution at the 5-position. An acrylonitrile-type polarization is thus discerned for the 4-cyanoisoxazole **85**, where the β-carbon or C5 is more electropositive than the α-carbon or C4. For the 5-cyanoisoxazole **86**, there is no indication of acrylonitrile-type polarization.

Table 18. π-Electron densities of and 4- and 5-cyanoisoxazoles **85** and **86**, determined using the B3-LYP/6-31G* method

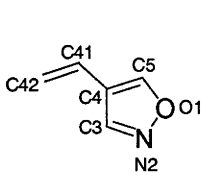
Compound	O1	N2	C3	C4	C5	C41	N41	C51	N51
85	1.66	1.22	0.97	1.13	0.97	0.96	1.09	-	-
86	1.68	1.20	0.98	1.05	1.05	-	-	0.96	1.08
82	1.68	1.23	0.99	1.09	1.00	-	-	-	-

Substituent effects on theoretical bond lengths and π-electron distributions of cyanoisoxazoles were found to be similar to those observed for formylisoxazoles and this is attributed to the conjugating and electron-withdrawing properties of both the formyl and cyano groups. The magnitude of these substituent effects was however observed to be less pronounced for the cyano group, relative to that discerned for the formyl group. This is consistent with the cyano group being less electron-attracting than the formyl group. The theoretically determined bond lengths and π-electron distributions of the model systems **85** and **86** imply an acrylonitrile-type structure of 4-cyanoisoxazoles which is likely to contribute to their observed electrochemical ring-opening, by contrast to the less facile electrochemistry of 5-cyanoisoxazoles where the polarization is absent.

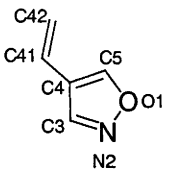
2.3.4. 4- and 5-Vinylisoxazoles

With the conjugating electron-withdrawing formyl and cyano groups examined, the effect of a conjugating but not electron-withdrawing group, namely the vinyl group, on the π-electron distribution and molecular dimensions of isoxazole **82** was investigated. The minimum energy conformations of 4- and 5-vinylisoxazoles **87** and **88** were calculated using the B3-LYP/6-31G* method. In the minimum energy conformations, the vinyl groups and the isoxazole rings are coplanar, with the vinyl groups in a *cis* or *trans* orientation to the C4-C5 double bonds. The planar geometries

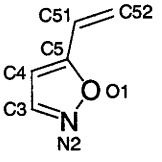
enable conjugation of the vinyl groups and the isoxazole rings through overlap of the π-orbitals. The *cis*- and *trans*-conformers of the 4- and 5-vinylisoxazoles **87** and **88** are shown below.



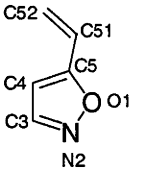
87a (*trans*)



87b (*cis*)



88a (*trans*)



88b (*cis*)

For the 4- and 5-vinylisoxazoles **87** and **88**, the calculations indicate that the *trans*-isomers **87a** and **88a** are favoured over the *cis*-forms **87b** and **88b** by 3.9 kJ mol^{-1} and 3.7 kJ mol^{-1}, respectively. The energy difference for the *trans-cis* conformational equilibrium of the 5-vinylisoxazole **88** is markedly less than that observed for the 5-formylisoxazole **84**, with the preferred conformation of **88** being opposite to that discerned for **84**. As the vinyl substituent does not experience electrostatic repulsion with the ring oxygen, the energy difference between the *cis*- and *trans*-conformers of **88** is therefore small by comparison to **84**, where relief of unfavorable electrostatic field effects is realized only in the *cis*-conformation **84b**.

With the minimum energy conformations of the 4- and 5-vinylisoxazoles **87** and **88** calculated, the bond lengths were then measured. These are listed in Table 19. The theoretical calculations show that the vinyl group has little effect on the O1-N2 bond lengths of the isomeric vinylisoxazoles **87** and **88**, compared to the effects of the formyl and cyano groups on the isoxazoles **83-86**. The trends are similar to those discerned from X-ray crystallographic data.

The data in Table 19 show lengthening of the C4-C5 bond of **87** and **88** relative to that of **82**, indicating conjugation is present in the vinylisoxazoles **87** and **88**. Relative to the C5-O1 bond of **82**, those of the conformers of **87** are shortened whilst lengthening is observed for those of the conformers of **88**. This indicates that the oxygen is conjugated to the C4-C5 bond in the 4-vinylisoxazole **87**, whilst cross conjugation is apparent for the 5-vinylisoxazole **88**.

Table 19. Selected bond lengths (Å) of 4- and 5-vinylisoxazoles **87** and **88**, determined using the B3-LYP/6-31G* method

Compound	O1-N2	C5-O1	C4-C5	C4-C41	C41-C42	C5-C51	C51-C52
87a	1.402	1.343	1.368	1.457	1.339	-	-
87b	1.401	1.341	1.370	1.460	1.339	-	-
88a	1.398	1.354	1.371	-	-	1.451	1.339
88b	1.394	1.356	1.372	-	-	1.453	1.339
82	1.400	1.345	1.360	-	-	-	-

The π-electron density data of the conformers of the 4- and 5-vinylisoxazoles **87** and **88** are shown in Table 20. These indicate that there is little polarization of **87** and **88** by the vinyl substituent. The vinylisoxazoles **87** and **88** therefore do not resemble Michael acceptors, as seen for the 4-formylisoxazole **83** and 4-cyanoisoxazole **85**. Since the vinyl group is used here as a surrogate for the phenyl group, it seems likely that phenylisoxazoles are not polarized and this may account for their failure to ring-open smoothly on electrolysis.

Table 20. π-Electron densities of 4- and 5-vinylisoxazoles **87** and **88**, determined using the B3-LYP/6-31G* method

Compound	O1	N2	C3	C4	C5	C41	C42	C51	C52
87a	1.68	1.22	0.99	1.06	1.02	1.00	1.02	-	-
87b	1.67	1.23	1.00	1.07	1.01	1.00	1.02	-	-
88a	1.70	1.23	0.99	1.10	0.99	-	-	1.02	0.97
88b	1.69	1.23	0.99	1.10	0.99	-	-	1.00	0.99
82	1.68	1.23	0.99	1.09	1.00	-	-	-	-

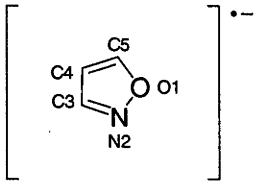
2.4. Activation Energy for Electron-transfer to Isoxazoles

The rates of electron-transfer mediated ring-opening of isoxazoles are determined by the activation energies ($\Delta G^{\ddagger}$) associated with the reductions. These are reflected by the magnitudes of the reduction potentials. The earlier work in this area[65] showed that ring-opening of 4-acyl- and 4-cyano-isoxazoles **48a,b** and **58a,b** is more facile than the corresponding reactions of 5-acyl- and 5-cyano-isoxazoles **52a,b** and **60a,b**. The reduction potentials[65] reflect the reactivities of these isoxazoles **48a,b**, **52a,b**, **58a,b** and **60a,b** in electrochemical ring-opening reactions. The reduction potentials of the 4-acylisoxazoles **48a,b** (-2.2 V, -2.1 V) and **58a** (-2.3 V) are lower than those of the corresponding 5-acyl-substituted isoxazoles **52a,b** (-2.5 V, -2.5 V) and **60a** (-2.4 V), indicating that electron-transfer to **48a,b** and **58a** is more facile than that observed for **52a,b** and **60a**. A similar trend is observed for the cyanoisoxazoles **58b** and **60b**, where the reduction potential of the 4-cyanoisoxazole **58b** (-1.4 V) is measured to be lower than that of the 5-cyanoisoxazole **60b** (-1.7 V). This indicates that reduction occurs more readily when the isoxazole ring is substituted with a conjugating electron-withdrawing group at the 4-position, rather than at the 5-position. These substituent effects may be attributed to the polarization described earlier in this Chapter which facilitates electron-transfer to the 4-acyl- and 4-cyano-substituted isoxazoles **48a,b** and **58a,b** by lowering the activation energy for this process. By contrast, the lack of polarization accounts for the less facile reductions of **52a,b** and **60a,b**.

2.5. Theoretical Calculations of Gas Phase Structures of Isoxazole Radical Anions

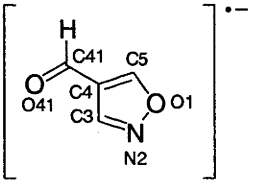
Structural studies of isoxazoles helped identify factors contributing to substituent effects seen in reactions of these species. The initial products of the electrochemical reactions of the isoxazoles are the radical anions, so to determine if structural studies of these species might provide further information, the minimum energy structures of the isoxazole, formylisoxazole, cyanoisoxazole and vinylisoxazole radical anions were

determined using the B3-LYP/6-31G* method. In the minimum energy conformations, the 5-formyl-, cyano- and vinyl-isoxazole radical anions **91**, **93** and **95** are all planar. On the other hand, the minimum energy conformations of the unsubstituted, 4-formyl-, cyano- and vinyl-isoxazole radical anions **89a**, **90a,c**, **92a** and **94a,c** are non-planar. To enable comparisons with the planar 5-substituted radical anions **91**, **93** and **95**, the minimum energy planar conformations of **89**, **90**, **92** and **94** were also examined. These are indicated to be less stable than the non-planar conformers **89a**, **90a,c**, **92a** and **94a,c** by 14.8 kJ mol^{-1}, 1.65 kJ mol^{-1}, 1.00 kJ mol^{-1}, 14.7 kJ mol^{-1}, 7.53 kJ mol^{-1} and 5.62 kJ mol^{-1}. The structures of the isoxazole radical anions are shown below. Their measured bond lengths and π-electron densities are listed in Tables 21 and 22. The corresponding electron affinity values, calculated using the G3(MP2)/B3-LYP method, are listed in Table 23. The accuracy of the G3(MP2)/B3-LYP method was assessed by Baboul *et al.*[91] through comparison of theoretical electron affinity values with those derived experimentally. The average absolute deviation of the theoretical values from the experimentally derived values was found to be 0.06 eV.[91] This value indicates the reliability of electron affinity data derived for the present work.



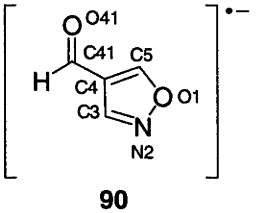
89

a. non-planar
b. planar



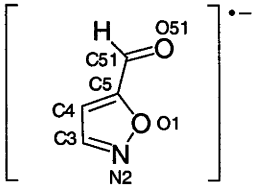
90

a. non-planar (*trans*)
b. planar (*trans*)



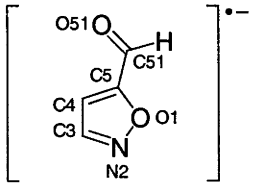
90

c. non-planar (*cis*)
d. planar (*cis*)



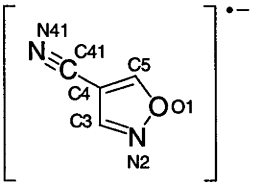
91

a. planar (*trans*)



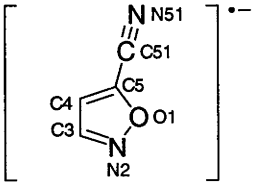
91

b. planar (*cis*)



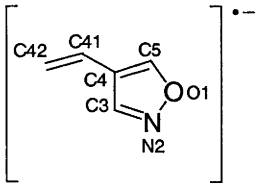
92

a. non-planar
b. planar

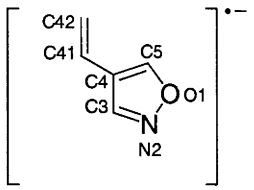


93

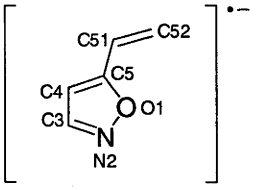
a. planar



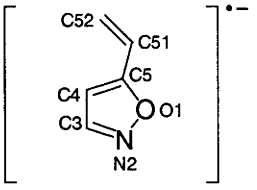
94
a. non-planar (*trans*)
b. planar (*trans*)



94
c. non-planar (*cis*)
d. planar (*cis*)



95
a. planar (*trans*)



95
b. planar (*cis*)

Table 21. Selected bond lengths (Å) of isoxazole radical anions **89-95**, determined using the B3-LYP/6-31G* method

Compound	O1-N2	C5-O1	C4-C5	C4-C41	C5-C51	C41-O41 C41-N41 C41-C42	C51-O51 C51-N51 C51-C52
89a	1.470	1.422	1.432	-	-	-	-
89b	1.491	1.407	1.400	-	-	-	-
90a	1.420	1.406	1.426	1.420	-	1.265	-
90b	1.416	1.398	1.413	1.423	-	1.272	-
90c	1.421	1.404	1.420	1.421	-	1.262	-
90d	1.418	1.397	1.412	1.423	-	1.266	-
91a	1.434	1.385	1.413	-	1.415	-	1.264
91b	1.434	1.390	1.408	-	1.414	-	1.270
92a	1.442	1.415	1.453	1.396	-	1.179	-
92b	1.445	1.409	1.436	1.395	-	1.182	-
93a	1.445	1.408	1.419	-	1.382	-	1.189
94a	1.427	1.417	1.442	1.424	-	1.378	-
94b	1.418	1.404	1.423	1.423	-	1.392	-
94c	1.431	1.414	1.432	1.423	-	1.376	-
94d	1.426	1.404	1.416	1.423	-	1.384	-
95a	1.448	1.390	1.416	-	1.403	-	1.395
95b	1.444	1.396	1.416	-	1.402	-	1.399

Table 22. π-Electron densities of isoxazole radical anions **89-95**, determined using the B3-LYP/6-31G* method

Compound	O1	N2	C3	C4	C5	C41	C51	O41	O51	N41	N51	C42	C52
89b	1.81	1.49	1.18	1.20	1.32	-	-	-	-	-	-	-	-
90b	1.77	1.28	0.99	1.11	1.27	1.05	-	1.53	-	-	-	-	-
90d	1.77	1.29	1.02	1.11	1.25	1.05	-	1.51	-	-	-	-	-
91a	1.75	1.35	1.06	1.22	1.07	-	1.05	-	1.49	-	-	-	-
91b	1.76	1.36	1.05	1.20	1.07	-	1.05	-	1.50	-	-	-	-
92b	1.80	1.34	1.03	1.23	1.22	1.00	-	-	-	1.28	-	-	-
93a	1.79	1.39	1.07	1.22	1.20	-	1.03	-	-	-	1.30	-	-
94b	1.78	1.30	1.02	1.12	1.32	1.12	-	-	-	-	-	1.34	-
94d	1.78	1.32	1.05	1.11	1.28	1.11	-	-	-	-	-	1.31	-
95a	1.78	1.39	1.06	1.25	1.06	-	1.16	-	-	-	-	-	1.29
95b	1.78	1.39	1.05	1.25	1.07	-	1.15	-	-	-	-	-	1.31

Table 23. Electron affinities (eV) of isoxazoles **82-88**, determined using the G3(MP2)/B3-LYP method

Compound	Electron Affinity (eV)
82	-1.02
83a	0.15
83b	0.35
84a	0.74
84b	0.75
85	0.10
86	0.41
87a	-0.55
87b	-0.28
88a	-0.02
88b	-0.02

Comparison of the O1-N2 bonds of isoxazole radical anions **90-95** with those of the conformers of unsubstituted isoxazole radical anion **89** indicates those of **90-95** are shorter, implying that cleavage of the O1-N2 bond is easier for **89**. Lengthening and hence weakening of the O1-N2 bonds of the conformers of the 5-formyl radical anion **91** relative to those of the conformers of the 4-substituted isoxazole radical anion **90** is also seen. This is inconsistent with the observed reactivities of 4- and 5-acylisoxazoles in the electrochemical and baker's yeast-mediated ring-opening reactions.[61,65]

Conjugation in the 4- and 5-substituted isoxazole radical anions **90b,d**, **91a,b**, **92b**, **93a**, **94b,d** and **95a,b** is indicated by lengthening of their C4-C5 bonds relative to that of the unsubstituted isoxazole radical anion **89b**. Within the isomeric pairs, conjugation is more pronounced in the 5-substituted isoxazole radical anions **91a,b**, **93a** and **95a,b** than with the 4-substituted isomers **90b,d**, **92b** and **94b,d**. This is indicated by shortening of the C5-C51 bonds of 5-substituted radical anions **91a,b**, **93a** and **95a,b** relative to the C4-C41 bonds of the 4-substituted isomers **90b,d**, **92b** and **94b,d**. These trends are the reverse of that seen experimentally, as 4-acyl- and cyano-substituted isoxazoles are observed to undergo more facile electrochemical ring-cleavage than 5-substituted acyl- and cyano-isoxazoles.

Little difference is seen for the π-electron densities of the exocyclic multiple bonds between the regioisomers of the formyl-, cyano- and vinyl-substituted isoxazole radical anions **90-95** (Table 22). The data show that the formyl group has the largest π-electron density, followed by the vinyl group, and then the cyano group. This is expected based on the polarization and bonding of these substituents.

Conjugative effects of the exocyclic multiple bonds are also reflected in the electron affinities of **82-88** (Table 23). The electron affinities of the formyl-, cyano- and vinyl-substituted isoxazoles **83-88** are all greater than that of the unsubstituted isoxazole **82**. This is because unlike the substituted isoxazoles **83-88**, the unsubstituted isoxazole **82** does not have any conjugating and/or electron-withdrawing exocyclic group to delocalize the unpaired spin density of the corresponding radical anion.

Polarization effects of the exocyclic multiple bonds are indicated by the magnitudes of the electron affinities of formylisoxazoles **83** and **84**, cyanoisoxazoles **85** and **86**, vinylisoxazoles **87** and **88** and isoxazole **82**, which decrease in the order

specified. This trend shows that the ease of radical anion formation is greatest for the formylisoxazoles **83** and **84**, followed by the cyanoisoxazoles **85** and **86**, the vinylisoxazoles **87** and **88**, and the unsubstituted isoxazole **82**. The magnitudes of the electron affinities reflect the efficiency of the exocyclic substituents to delocalize the charge of the isoxazole radical anions, and the electron affinities therefore correlate with the electronegativity of the exocyclic groups.

Comparison of the electron affinities to form the regioisomeric radical anions **90** and **91**, **92** and **93**, and **94** and **95** shows that the 5-substituted radical anions **91**, **93** and **95** are more stable and easily formed than the corresponding 4-substituted species **90**, **92** and **94**. The electron affinity calculations imply that electron-transfer mediated ring-opening reactions should therefore be more facile for 5-acyl- and cyano-substituted isoxazoles than with the corresponding 4-substituted isomers. This is opposite to that observed in the ring-opening reactions of 4- and 5-acyl- and cyano-substituted isoxazoles in baker's yeast-catalysed and electrochemical reactions.

The calculations on the unsubstituted isoxazole, formyl-, cyano- and vinyl-isoxazole radical anions **89-95** thus indicate that the observed substituent effects in the ring-opening reactions of isoxazoles are not related to the stability of the radical anions, but are instead associated with the polarization of the reactant isoxazoles, as implied from the X-ray crystallographic and theoretical structural analyses. For the hydrogenolytic ring-opening reactions where direct cleavage of the N-O bonds is effected, the observed substituent effects are related to the intrinsic weakness of the N-O bonds in 4-acylisoxazoles, as opposed to those of 5-acylisoxazoles. For the electron-transfer based ring-opening reactions where N-O bond cleavage occurs indirectly, polarization accounts for the more facile ring-opening of 4-acylisoxazoles relative to the 5-substituted isomers.

CHAPTER 3

REDUCTIONS OF ACYLISOXAZOLES

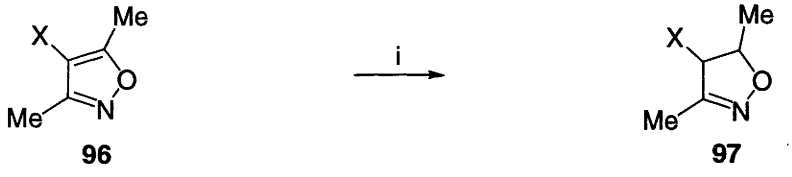
3.1. Reductions of 4- and 5-Alkoxycarbonylisoxazoles

As discussed in the previous chapter, 4-acylisoxazoles have acrylate-like structures as indicated from the X-ray crystallographic and theoretically determined bond lengths and π-electron distribution. Since they are structurally similar to acrylates, it seemed likely that they might undergo Michael reactions or 1,4-addition with nucleophiles, which is characteristic of the chemistry of acrylates. Conjugate addition occurs because the electron-withdrawing carbonyl group induces polarization of the acrylate such that the β-carbon is electropositive, and therefore susceptible to attack by nucleophiles. Methodologies for 1,4-additions of hydride to acrylates are well developed. Hydride delivery at the β-position of an α,β-unsaturated carbonyl system is effected by a wide range of reagents, including homogeneous and complex aluminium hydrides[92] and borohydrides,[93,94] silicon hydrides,[95] tributyltin hydride,[96] hydrogen in the presence of a suitable catalyst,[97] samarium iodide,[98] magnesium in methanol[99] and sodium in ammonia.[100] Unfortunately, the majority of these reagents are incompatible with the isoxazole framework. Dissolving metal reductions,[57] hydrogenation[50-52] and samarium iodide[53] have all been implicated in ring-cleavage of isoxazoles.

A survey of the literature uncovered one report of conjugate reduction of isoxazoles. Alberola *et al.*[101] showed that isoxazoles **96** functionalized with electron-deficient nitro, cyano, alkyl- and aryl-sulfonato and sulfonamido groups at the 4-position underwent reduction with sodium borohydride or lithium aluminium hydride to afford 2-isoxazolines **97** (Scheme 23). Sodium borohydride and lithium aluminium hydride reductions of 4-acylisoxazoles **99a,b** were also studied by Alberola *et al.*[101] Contrary to the reactions of the other isoxazoles examined, the authors observed formation of the isoxazoles **100a,b**, with none of the 2-isoxazolines **98a,b** produced. The isoxazoles **100a,b** were formed by reduction of the acetyl and alkoxycarbonyl groups of **99a,b** (Scheme 24).[101]

Nevertheless, since the theoretical calculations and the X-ray crystallographic data strongly indicate that 4-acylisoxazoles are polarized like Michael acceptors, reaction of 4-acylisoxazole **12f** with sodium borohydride was pursued and reaction

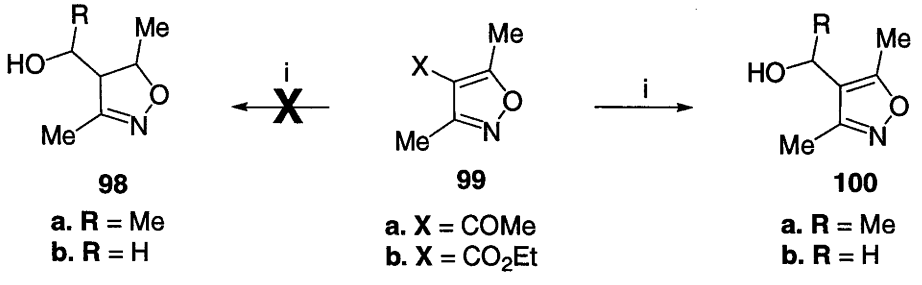
conditions to effect reduction of the isoxazole ring were explored. The synthesis and structural assignment of isoxazole **12f** were discussed in Chapter 2, Section 2.1. Crystals of **12f** were grown at 18 °C, from vapour diffusion of hexanes and ether. The X-ray crystallographic structure of the material was recorded and the ORTEP diagram is shown in Figure 12. Coplanarity of the C4-C5 double bond and the carbonyl group is apparent in the solid state, with a torsion angle of –176.3(4)°. This is important for conjugation and acrylate-type polarization of the 4-acylisoxazole **12f**. Conjugation of the carbonyl group and the C4-C5 double bond was examined through the X-ray crystallographic structure of **12f**. The data indicate that conjugation is present in **12f**, as its C5-O1 and C4-C41 bonds are shorter than those of the other 4-acylisoxazoles **71** and **12d**.



X = NO_2, CN, SO_3Et, SO_3Ph, SO_2NHPh

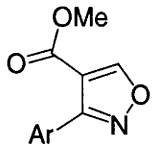
Reagents and conditions: i. **96** (1.0 equiv.), $NaBH_4$ or $LiAlH_4$ (2.0 equiv.), Et_2O, 0 °C, 4-8 h.

Scheme 23



Reagents and conditions: i. **99** (1.0 equiv.), $NaBH_4$ or $LiAlH_4$ (2.0 equiv.), Et_2O, 0 °C, 4 h.

Scheme 24



12f

Ar = 2,4,6-Me_3Ph

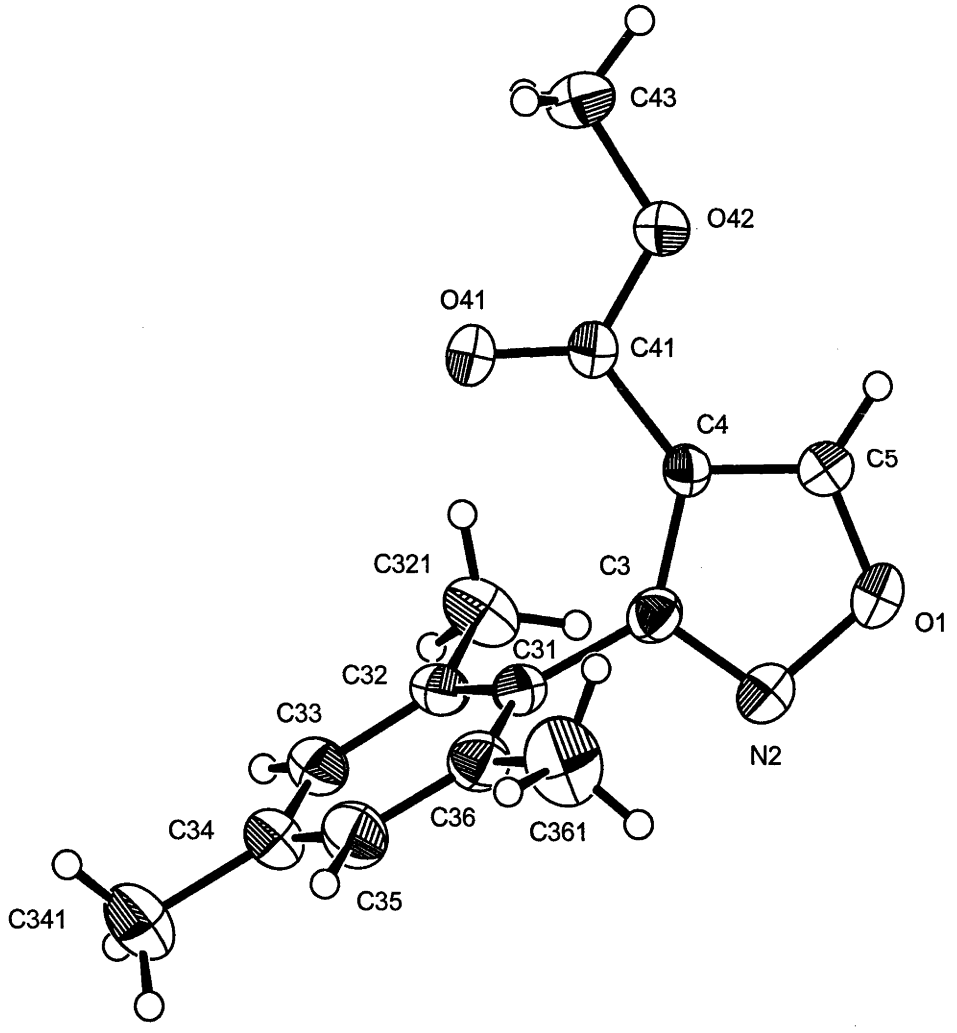
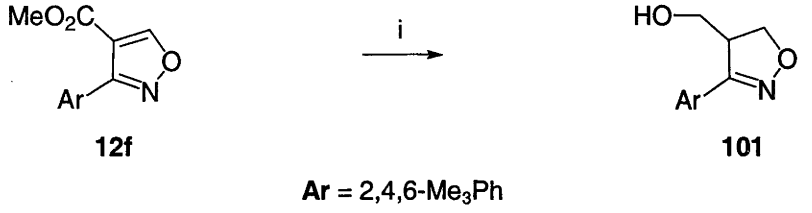


Figure 12. ORTEP derived from single crystal X-ray analysis of compound **12f**.

The isoxazole **12f** was treated with excess sodium borohydride and contrary to Alberola *et al.*'s findings,[101] conjugate reduction occurred. The product was the 2-isoxazoline **101** obtained in a yield of 91%, formed *via* reduction of the isoxazole ring and the methoxycarbonyl group, presumably in that order (Scheme 25).



12f **101**

Ar = 2,4,6-Me_3Ph

Reagents and conditions: i. **12f** (1.0 equiv.), $NaBH_4$ (15.0 equiv.), EtOH, reflux, 24 h.

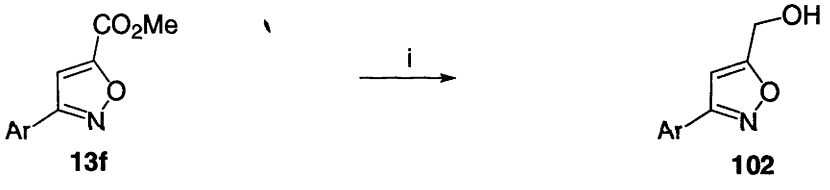
Scheme 25

The structure of 2-isoxazoline **101** was established using EI mass spectrometric and ^1H NMR spectroscopic methods. The composition of the molecular ion at *m/z* 219 was analyzed as $C_{13}H_{17}NO_2$ through accurate mass measurement. Signals of isoxazoline C4 and C5 protons are usually observed between δ 3-5 ppm. For **101**, a one proton multiplet at δ 3.75 ppm was assigned to the C4 proton, whilst a multiplet at δ 4.50 ppm was assigned to the two geminal C5 protons. The proton resonances of the other methylene group were seen as a two proton multiplet at δ 3.69 ppm. The signal of the hydroxyl proton was seen as a broad singlet at δ 1.55 ppm. In the infrared spectrum, the hydroxyl stretching vibration gave rise to a broad absorption band at 3369 cm^{-1}. The physical and spectral data are in accord with those reported in the literature.[102]

The reduction of the isoxazole ring in this procedure may be attributed to the use of excess sodium borohydride. Brown and Rapoport[103] had previously shown that reductions of unsaturated esters to saturated alcohols are dependent on the stoichiometry of the hydride reagent and the substrates, with the optimum yield for the saturated alcohol being obtained when at least a 10-fold excess of sodium borohydride is used. Thus the failure of Alberola *et al.*[101] to reduce isoxazoles **99a,b** to 2-isoxazolines **98a,b**

is a consequence of their using insufficient amounts of hydride. Conjugate reduction of the 4-alkoxycarbonylisoxazole **12f** to 2-isoxazoline **101** shows acrylate behaviour. The reaction confirms the implications of the X-ray crystallographic studies and the theoretical calculations, based on the conjugation and polarization apparent in the bond lengths and π-electron densities.

Reduction of 5-acylisoxazole **13f** was next investigated. The synthesis and characterization of **13f** were discussed in Chapter 2, Section 2.1. Based on the X-ray crystallographic data and theoretical studies of 5-acylisoxazoles, it was anticipated that **13f** would not undergo reduction to give the corresponding 2-isoxazoline. This was confirmed experimentally, where treatment of **13f** with 15 equivalents of sodium borohydride gave rise to the isoxazole **102** in 93% yield, with none of the corresponding 2-isoxazoline detected in the product mixture (Scheme 26).



Ar = 2,4,6-Me_3Ph

Reagents and conditions: i. **13f** (1.0 equiv.), $NaBH_4$ (15.0 equiv.), EtOH, reflux, 24 h.

Scheme 26

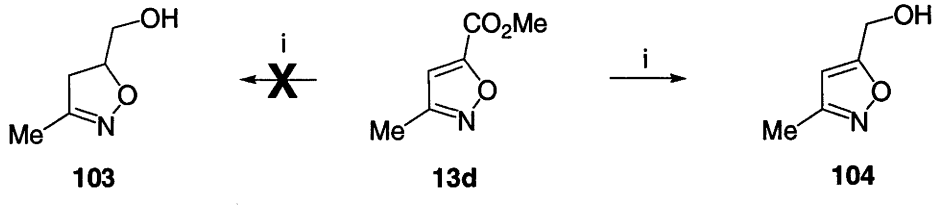
All physical and spectroscopic data obtained for **102** are in full accord with the assigned structure. Accurate EI mass measurement of the molecular ion at *m/z* 217 indicated the molecular composition of $C_{13}H_{15}NO_2$. In the ^1H NMR spectrum, the signal of the C4 isoxazole proton was seen as a one proton singlet at δ 6.21 ppm. The singlet at δ 4.87 ppm, integrating to two protons, was assigned to the methylene group. The signal of the hydroxyl proton was observed as a broad singlet at δ 1.20 ppm. In the infrared

spectrum, an intense absorption band at 3382 cm^{-1} was ascribed to the hydroxyl stretching vibration.

3.2. Effect of the C3-Substituent on Reductions of Alkoxycarbonylisoxazoles

The contrasting reactions of the 4- and 5-acylisoxazoles **12f** and **13f** with sodium borohydride are consistent with the polarization of related species observed in the X-ray crystallographic and theoretical studies. However, for **13f**, there was also a possibility that steric crowding at C4 by the large mesityl group at C3 might be limiting conjugate reduction. For **12f**, steric effects at C5 would be less severe.

In an attempt to investigate any steric effects of the C3-substituent, the methyl group was chosen as a more compact alternative to the mesityl group. The compounds chosen for study were therefore the 3-methylisoxazoles **12d** and **13d**. Their synthesis was discussed in Chapter 2, Section 2.2. Reaction of the 5-acylisoxazole **13d** with sodium borohydride afforded 5-hydroxymethylisoxazole **104** in 80% yield, with none of the 2-isoxazoline **103** being detected in the product mixture (Scheme 27).



103 **13d** **104**

Reagents and conditions: i. **13d** (1.0 equiv.), $NaBH_4$ (15.0 equiv.), EtOH, reflux, 24 h.

Scheme 27

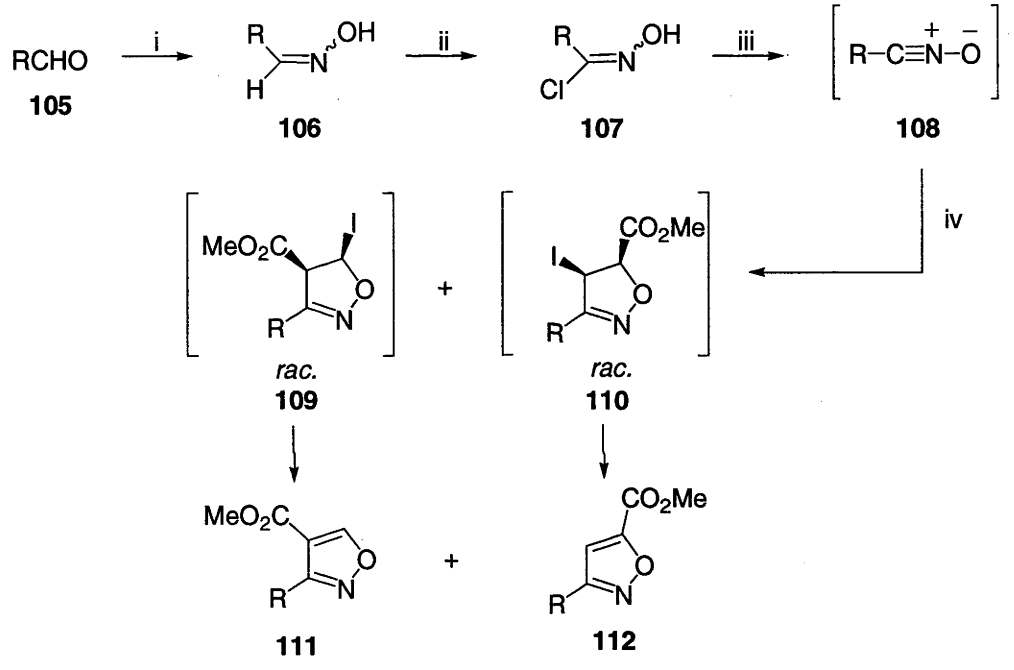
The structure of isoxazole **104** was deduced from ^1H NMR spectroscopy. The signal of the C4 isoxazole proton was clearly observed as a one proton singlet at δ 6.11 ppm. The methylene protons resonated as a singlet integrating for two protons, at

δ 4.76 ppm. The physical data of isoxazole **104** are in agreement with literature values.[104] The exclusive formation of isoxazole **104** through reduction of **13d** indicates that the resistance of 5-acylisoxazoles to reduction of the isoxazole ring is not a consequence of steric factors.

Reaction of the 4-acyl-substituted isoxazole **12d** with sodium borohydride was also examined. However isolation of any products from this reaction proved problematic due to their volatility. To investigate and compare reactions of C3-alkyl-substituted 4- and 5-alkoxycarbonylisoxazoles with borohydride, and circumvent the problem of volatility, compounds **111** and **112** were used instead. 3-Nonylisoxazoles **111** and **112** were synthesized *via* 1,3-dipolar cycloaddition of decylnitrile oxide **108** with methyl (*Z*)-3-iodopropenoate **74**. The synthesis of dipolarophile **74** was described in Chapter 2, Section 2.2. As discussed for the synthesis of **12d** and **13d**, methyl (*Z*)-3-iodopropenoate **74** was chosen over methyl propiolate **11** because the alkene **74** is a more reactive dipolarophile than the alkyne **11**. The synthesis began with preparation of the precursors of nitrile oxide **108**. Condensation of the decyl aldehyde **105** with hydroxylamine hydrochloride afforded decylaldoxime **106**.[105] Chlorination of the oxime **106** with NCS then furnished decylhydroximinoyl chloride **107**. Given that the aliphatic nitrile oxide **108** is prone to dimerization, the yield of the isoxazoles **111** and **112** was maximized through *in situ* generation of the dipole **108** in an excess of the alkene **74** *via* dehydrohalogenation of hydroximinoyl chloride **107** using triethylamine (Scheme 28).

The isoxazoles **111** and **112** were isolated by chromatography and their structures deduced through EI mass spectrometric and ^{1}H NMR spectroscopic methods. The molecular ions of **111** and **112** were detected at *m/z* 253 and both compounds analyzed for the molecular composition of $C_{14}H_{23}NO_3$ through accurate mass measurements. As discussed for isoxazoles **12f** and **13f** (see Chapter 2, Section 2.1.), the structures of the isomeric isoxazoles **111** and **112** were distinguished by the chemical shifts of the signals of their C4- and C5-isoxazole protons. The C5 proton of **111** gave rise to a one proton singlet at δ 8.85 ppm. By comparison, the C4 proton of **112** resonated further upfield, at δ 6.81 ppm.

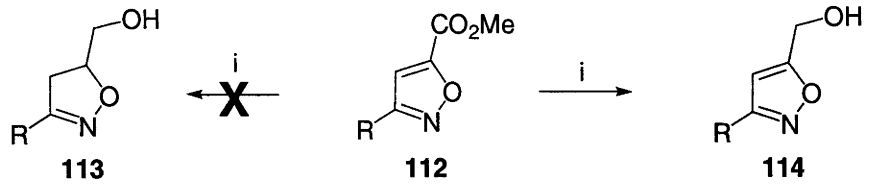
The isoxazoles **111** and **112** were afforded in yields of 17% and 43%, respectively. Presumably, they were formed from elimination of hydrogen iodide from the corresponding 2-isoxazolines **109** and **110**. As discussed earlier for the synthesis of isoxazoles **12d** and **13d** (Chapter 2, Section 2.2.), the regiochemical outcome of the cycloaddition is determined by a counterbalance of polar and steric effects, due to the electron-withdrawing and sterically demanding alkoxycarbonyl and iodine groups.



Reagents and conditions: i. **105** (1.0 equiv.), $NH_2OH.HCl$ (1.2 equiv.), $NaHCO_3$ (3.2 equiv.), H_2O, 0 °C, 15 min; ii. **106** (1.0 equiv.), NCS (1.0 equiv.), DMF, 20-25 °C, 3 h; iii. **107** (1.0 equiv.), **74** (8.0 equiv.), NEt_3 (1.1 equiv.) added over 18 h, Et_2O, 18 °C, 24 h.

Scheme 28

With the 3-nonylisoxazoles **111** and **112** in hand, reactions with sodium borohydride were examined. The 5-acylisoxazole **112** did not give rise to the 2-isoxazoline **113**. Instead the isoxazole **114** was obtained in 92% yield (Scheme 29).



R = $(CH_2)_8CH_3$

Reagents and conditions: i. **112** (1.0 equiv.), $NaBH_4$ (15.0 equiv.), EtOH, reflux, 24 h.

Scheme 29

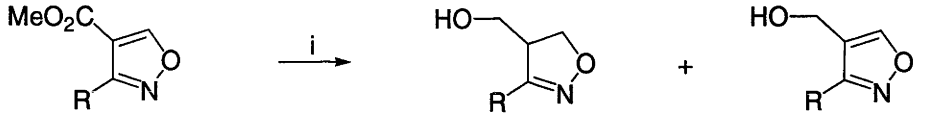
All physical and spectral data of isoxazole **114** are in full agreement with the assigned structure. Using the EI method, the molecular ion of *m/z* 225 was analyzed for the molecular composition of $C_{13}H_{23}NO_2$ through accurate mass measurement. In the ^1H NMR spectrum, the signal of the hydroxymethylene group is seen as a two proton singlet at δ 4.76 ppm. A one proton singlet at δ 6.11 ppm was assigned to the C4 isoxazole proton. In the infrared spectrum, the hydroxyl stretching vibration gave rise to an intense absorption band at 3368 cm^{-1}. The reaction of 5-acylisoxazole **112** with sodium borohydride to give **114** provides further evidence that the resistance of 5-acylisoxazoles to reduction of the isoxazole ring is not due to steric effects of C3-substituents.

By contrast to the 5-acylisoxazole **112**, the 4-acylisoxazole **111** reduced to the 2-isoxazoline **115** and the isoxazole **116** when treated with sodium borohydride (Scheme 30). 2-Isoxazoline **115** and isoxazole **116** were afforded in yields of 73% and 18%, respectively.

The physical and spectroscopic data acquired for 2-isoxazoline **115** are fully consistent with the assigned structure. In the EI mass spectrum, the parent ion was detected at *m/z* 227 for which accurate mass measurement indicated the molecular composition of $C_{13}H_{25}NO_2$. In the ^1H NMR spectrum, the C4 isoxazoline proton signal was discerned as a multiplet at δ 3.39 ppm. The signals of the two C5 isoxazoline protons appeared further downfield as a multiplet at δ 4.26 ppm. The hydroxymethylene

protons resonated as a multiplet at δ 3.78 ppm. In the infrared spectrum, the broad absorption band at 3400 cm^{-1} was ascribed to the hydroxyl stretching vibration.

For the isoxazole **116**, accurate mass measurement of the molecular ion at *m/z* 225 indicated a molecular composition of $C_{13}H_{23}NO_2$. In the ^1H NMR spectrum, a one proton singlet at δ 8.30 ppm was assigned to the C5 isoxazole proton. The signal of the hydroxymethylene protons was observed as a singlet at δ 4.58 ppm, integrating for two protons. In the infrared spectrum, a broad band at 3400 cm^{-1} was assigned to the hydroxyl stretching vibration.



111 **115** **116**

R = $(CH_2)_8CH_3$

Reagents and conditions: i. **111** (1.0 equiv.), $NaBH_4$ (15.0 equiv.), EtOH, reflux, 24 h.

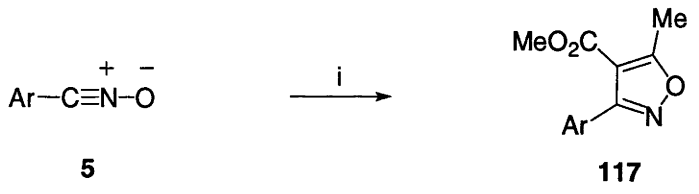
Scheme 30

2-Isoxazoline **115** and isoxazole **116** were formed in a ratio of 4:1. The dominant product resulted from reduction of the C4-C5 double bond and the methoxycarbonyl group of the 4-acylisoxazole **111**. The isoxazole **116** was formed from reduction of only the ester group.

The reactions of acylisoxazoles with sodium borohydride follow the predictions based on structural analyses. The lack of acrylate-type polarization in 5-acylisoxazoles as seen in the π-electron density calculations is reflected in the reductions, where the C4-C5 bonds are unreactive towards hydride. By contrast, the 4-acylisoxazoles react as Michael acceptors and through reduction of the C4-C5 double bonds, 2-isoxazolines are afforded. The trend is unaffected by alkyl- or aryl-substituents at the 3-position of the isoxazole ring.

3.3. Diastereoselective Reductions of 4-Alkoxycarbonylisoxazoles

Having developed a method for reducing 4-acylisoxazoles to 2-isoxazolines, the stereoselectivity of the reaction was explored using isoxazoles also substituted at the 5-position. The substituent at C5 can be conveniently incorporated into isoxazoles *via* cycloaddition of nitrile oxides with 1,2-disubstituted dipolarophiles. Isoxazole **117**, synthesized through cycloaddition of mesitonitrile oxide **5** with methyl tetrolate **17a**, was obtained in a yield of 98% (Scheme 31).



5 **117**

Ar = 2,4,6-Me_3Ph

Reagents and conditions: i. **5** (1.0 equiv.), **17a** (1.0 equiv.), THF, reflux, 4 days.

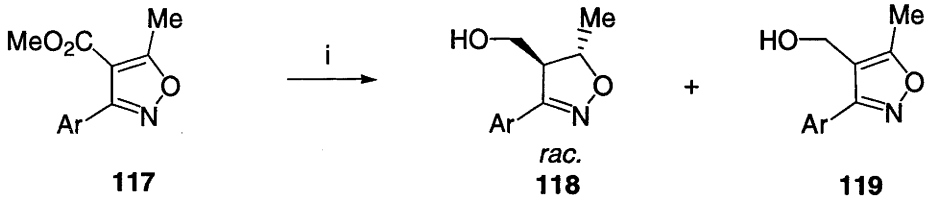
Scheme 31

The molecular ion of the 4-acylisoxazole **117** was observed at *m/z* 259 for which accurate mass analysis indicated the molecular composition of $C_{15}H_{17}NO_3$. In the ^1H NMR spectrum, the signal of the methoxy ester group was seen as a three proton singlet at δ 3.67 ppm and that of the methyl group at C5 was observed as a three proton singlet at δ 2.77 ppm. In the infrared spectrum, the carbonyl stretching vibration was seen at 1730 cm^{-1} as an intense absorption band.

The cycloaddition was completely regioselective. The 4-acylisoxazole **117** was obtained as the sole adduct, resulting from prevailing polar effects (see Chapter 1, Section 1.1.4.). Treatment of isoxazole **117** with sodium borohydride under reflux afforded two reduction products, the 2-isoxazoline **118** and isoxazole **119** (Scheme 32).

The molecular ion of the 2-isoxazoline **118** at *m/z* 233 analyzed for the molecular composition of $C_{14}H_{19}NO_2$ through accurate mass measurement using the EI method. In the ^1H NMR spectrum, the signals of the C4- and C5-isoxazoline protons were seen at

δ 3.34 ppm and δ 4.72 ppm, respectively. The C4 proton signal was a doublet of doublets of doublets (J = 7.2, 6.5, 5.6 Hz) whilst that of the C5 proton was a doublet of quartets (J = 7.2, 6.3 Hz). The magnitude of the coupling constant $J_{4,5}$ = 7.2 Hz indicates that the 2-isoxazoline **118** is of *trans*-configuration (the *cis*-isomer **137** with $J_{4,5}$ = 8.6 Hz is presented in page 100). The signal of the methylene protons adjacent to the hydroxyl group was observed as a multiplet, integrating for two protons, at δ 3.67 ppm. In the infrared spectrum, the hydroxyl stretching vibration gave rise to a broad absorption band at 3400 cm^{-1}. The physical and spectroscopic data are consistent with literature values.[102]



117 **118** **119**

Ar = 2,4,6-Me_3Ph

Reagents and conditions: i. **117** (1.0 equiv.), $NaBH_4$ (15.0 equiv.), EtOH, reflux, 24 h.

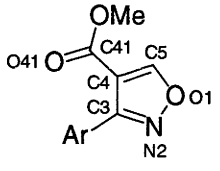
Scheme 32

In the ^1H NMR spectrum of the isoxazole **119**, the signal of the methylene protons was seen at δ 4.28 ppm, as a singlet integrating for two protons. The mass spectral data supported the structural assignment. The parent ion was detected at *m/z* 231 for which the molecular composition was determined to be $C_{14}H_{17}NO_2$ through accurate mass measurement using the EI method. In the infrared spectrum, the hydroxyl stretching vibration was observed as a broad absorption band at 3392 cm^{-1}. All physical and spectroscopic data are in agreement with reported values.[102]

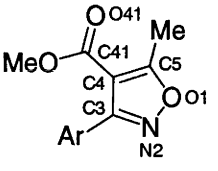
The 2-isoxazoline **118** and the isoxazole **119** were produced in yields of 61% and 30%, respectively. The 2-isoxazoline **118** is formed *via* hydride reduction of the C4-C5 double bond and the methoxycarbonyl group of **117**, presumably in that order. The isoxazole **119** is furnished through reduction of only the methoxycarbonyl group. Comparison of the product ratios obtained from reduction of **117** and **12f** indicates that

the acrylate behaviour of the 5-methyl-4-acylisoxazole **117** is less marked than that of the 4-acylisoxazole **12f**. In an attempt to rationalize the diminished conjugate reduction of **117**, crystals were grown from vapour diffusion of hexanes and ether at 18 °C. The X-ray crystallographic structure of **117** was recorded and the ORTEP diagram is shown in Figure 13. These data were compared to those of **12f**. The bond lengths of isoxazoles **12f** and **117** are listed in Table 24.

Table 24. Selected bond lengths (Å) from the X-ray crystallographic data of isoxazoles **12f** and **117**



12f



117

Ar = 2,4,6-Me_3Ph

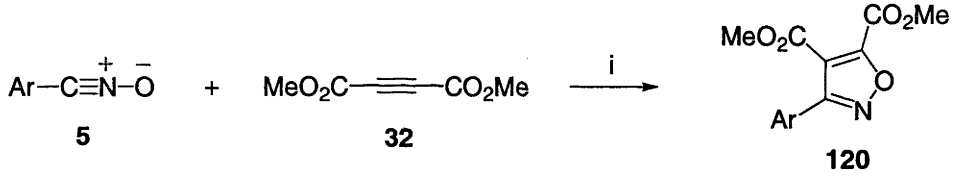
Compound	O1-N2	C5-O1	C4-C5	C4-C41	C41-O41
12f	1.429(4)	1.314(4)	1.347(4)	1.455(4)	1.197(4)
117	1.429(3)	1.344(3)	1.361(4)	1.467(4)	1.198(3)

The most significant differences are seen for the C5-O1, C4-C5 and C4-C41 bonds. The lengths of these are affected by the extent of conjugation of the ring oxygens to the carbonyl groups through the C4-C5 bonds. The X-ray crystallographic data indicate that the extent of this is less in the 5-methylisoxazole **117** than that seen with the isoxazole **12f**. This may be attributed to steric interactions between the methoxycarbonyl group and the methyl-substituent at C5 in **117**, which cause the former group to twist out of the plane of the isoxazole ring. This is indicated by a torsion angle of –12.3(4)° along O41-C41-C4-C5 of the 5-methylisoxazole **117**, which clearly shows a greater distortion from coplanarity than that observed for the isoxazole **12f**, where the

corresponding torsion angle is –176.3(4)°. The orientation of the C4-C5 bond to the carbonyl bond of **117** is *cis*, so that steric interactions between the methoxy group and the C5-methyl group are minimized.

Despite the diminished acrylate behaviour of isoxazole **117** relative to **12f**, the 2-isoxazoline **118** was obtained completely diastereoselectively, as the *trans*-isomer **118**. The temperature dependence of the stereoselectivity of the borohydride reduction of **117** was also investigated. From 78 °C (refluxing ethanol) to 0 °C, the stereochemical outcome of the reduction was not altered, with the *trans*-2-isoxazoline **118** being obtained without any of the corresponding *cis*-isomer being detected.

The effect on the diastereoselectivity of an acyl group at the 5-position was also examined. To do this, isoxazole **120** was synthesized in 97% yield, through cycloaddition of mesitonitrile oxide **5** and dimethyl acetylenedicarboxylate **32** (Scheme 33).

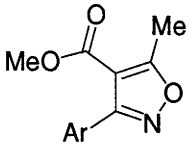


Ar = 2,4,6-Me_3Ph

Reagents and conditions: i. **5** (1.0 equiv.), **32** (1.0 equiv.), THF, reflux, 2 days.

Scheme 33

The structure of the isoxazole **120** was deduced using EI mass spectrometry and ^1H NMR spectroscopy. The molecular ion was detected at *m/z* 303 for which accurate mass measurement indicated the molecular composition of $C_{16}H_{17}NO_5$. In the ^1H NMR spectrum, the signals of the methoxy groups were seen as three proton singlets at δ 3.74 ppm and δ 4.05 ppm. In the infrared spectrum, the stretching vibrations of the two carbonyl groups were observed as an intense absorption band at 1739 cm^{-1}. The physical and spectral data of isoxazole **120** are in accord with literature values.[106]



117

Ar = 2,4,6-Me_3Ph

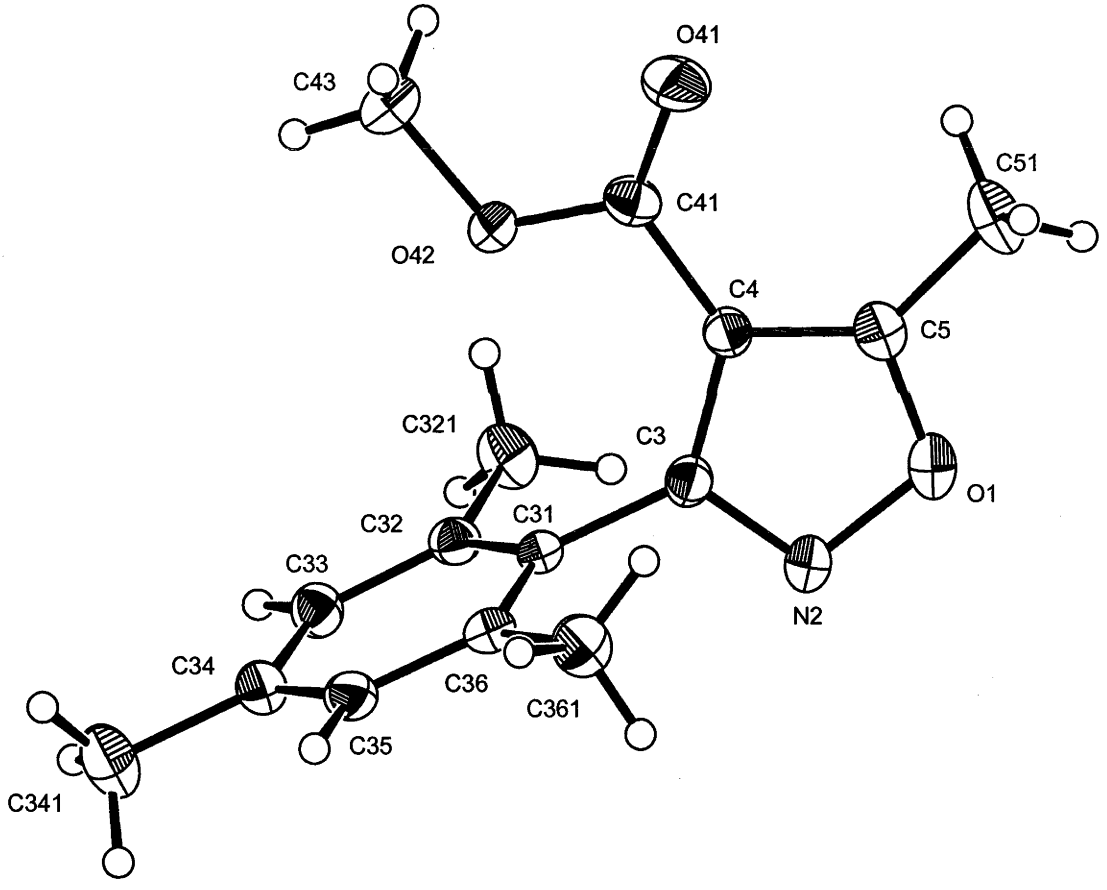
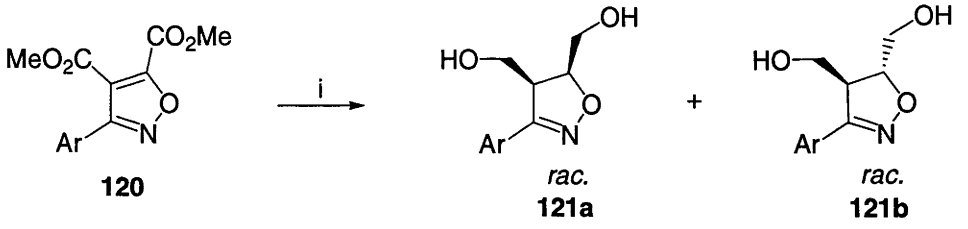


Figure 13. ORTEP derived from single crystal X-ray analysis of compound **117**.

Treatment of isoxazole **120** with excess sodium borohydride in refluxing ethanol afforded stereoisomeric 2-isoxazolines **121a,b** in a ratio of 3.5:1, with a combined yield of 90% (Scheme 34).



Ar = 2,4,6-Me_3Ph

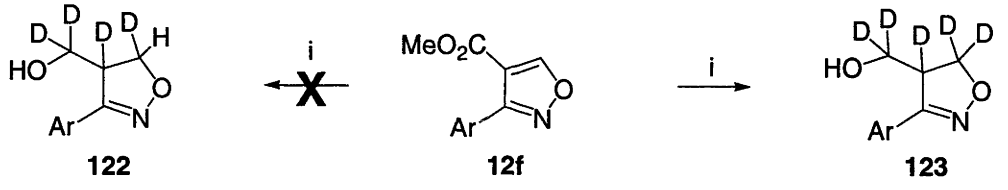
Reagents and conditions: i. **120** (1.0 equiv.), $NaBH_4$ (15.0 equiv.), EtOH, reflux, 24 h.

Scheme 34

The 2-isoxazoline stereoisomers **121a,b** were separated by chromatography and characterized. Their molecular ions were detected at *m/z* 249 and subsequent accurate mass measurements determined the structural composition to be $C_{14}H_{19}NO_3$ in each case. The relative configurations of the isomeric 2-isoxazolines **121a,b** were assigned based on the magnitudes of the $J_{4,5}$ coupling constants. As the $J_{4,5}$ coupling constant of a *cis*-isomer is always larger than that of a *trans*-isomer,[21,23,24,72] the major isomer was assigned as being *cis* ($J_{4,5}$ = 10.0 Hz) and the minor isomer was therefore deduced to be *trans* ($J_{4,5}$ = 7.5 Hz). For the *cis*-isomer **121a**, the C4 isoxazoline proton signal was observed as a multiplet at δ 3.65 ppm whilst the C5 isoxazoline proton resonated as a doublet of doublets of doublets at δ 4.89 ppm (J = 10.0, 6.0, 3.5 Hz). For **121b**, the C4 isoxazoline proton signal was observed at δ 3.62-3.77 ppm as part of a three proton multiplet with the resonance of two methylene protons adjacent to one of the hydroxyl groups. The C5 isoxazoline proton signal was seen as a doublet of triplets at δ 4.72 ppm (J = 7.5, 3.5 Hz). In the infrared spectra, the hydroxyl stretching vibrations were indicated by strong and broadened absorption bands at 3332 cm^{-1} and 3369 cm^{-1} for the *cis*- and *trans*-isomers **121a,b**, respectively. The 2-isoxazoline stereoisomers

121a,b are formed *via* reduction of the C4-C5 bonds and the 4- and 5-methoxycarbonyl groups of **120**. The effect of temperature on the diastereoselectivity of the reaction was examined. However changing the temperature from 78 °C to 0 °C did not alter the diastereoselectivity observed.

It was also planned to examine the diastereoselectivity of the reductions of 4-acylisoxazoles through treatment of **12f** with sodium borodeuteride in deuterated ethanol. It was anticipated that the deuterium incorporated at C5 of the resulting 2-isoxazoline **122** would be either *cis* or *trans* to the substituent at C4, and hence the diastereoselectivity of the reduction could be determined. However, instead of obtaining the expected product **122**, the reaction furnished the deuterium-enriched product **123** whereby two deuteriums were incorporated at C5 instead of one (Scheme 35).



Ar = 2,4,6-Me_3Ph

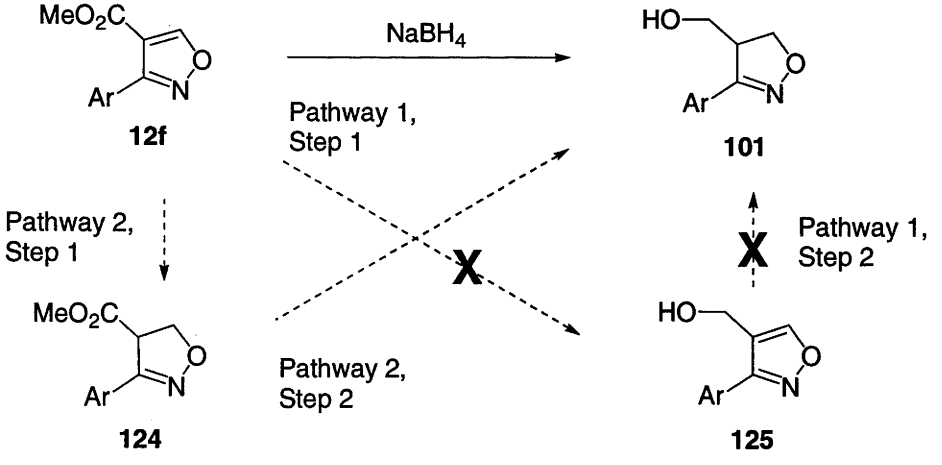
Reagents and conditions: i. **12f** (1.0 equiv.), $NaBD_4$ (15.0 equiv.), EtOD, reflux, 24 h.

Scheme 35

All physical and spectroscopic data obtained for the deuterium-enriched product **123** are in full accord with the assigned structure. By the use of EI mass spectrometry, accurate mass analysis of the parent ion at *m/z* 224 indicated the molecular composition of $C_{13}H_{12}D_5NO_2$. In the ^1H NMR spectrum, the diagnostic region for isoxazoline proton resonances (δ 3.5-4.7 ppm) was void of signals. The only discernable proton signals were attributed to the three methyl groups and the two aromatic protons on the mesityl ring, and the hydroxyl group.

3.4. Mechanism of Borohydride Reductions of 4-Alkoxycarbonylisoxazoles

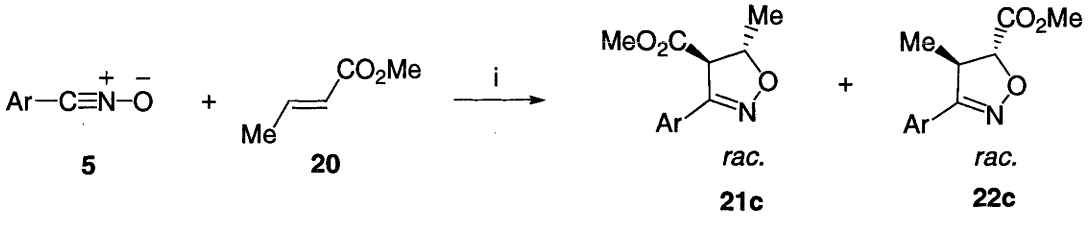
The unexpected deuterium exchange observed in the reduction of **12f** with sodium borodeuteride implied that proton exchange at C5 was also occurring for the borohydride reductions of 4-acylisoxazoles. This has obvious implications for the stereoselectivity of the reductions since the absolute configuration at C5 is therefore not fixed. To explore this, possible reaction pathways for reduction of 4-acylisoxazole **12f** to the 2-isoxazoline **101** were considered (Scheme 36). Two two step pathways may be conceived but pathway 1 is unlikely to be viable because the intermediate **125** would be expected to be inert towards reduction of the C4-C5 double bond, since it lacks the electron-withdrawing carbonyl group. Therefore reaction is considered to take place *via* pathway 2, with exchange of hydrogen or deuterium occurring prior to or after formation of ester **124**. 4-Acyl-2-isoxazoline **21c** was synthesized as an analogue of **124** in an attempt to determine whether hydrogen or deuterium exchange occurred during the second step of this pathway.



Ar = 2,4,6-Me_3Ph

Scheme 36

4-Acyl-2-isoxazoline **21c** was synthesized *via* cycloaddition of mesitonitrile oxide **5** and *trans*-methyl crotonate **20** (Scheme 37). Methyl crotonate **20** was used as the dipolarophile as polar effects favour bonding between the dipole oxygen and the electropositive β-carbon of the dipolarophile **20**, thereby giving rise to the 4-acyl-2-isoxazoline **21c** as the major product. The 2-isoxazoline **21c** was prepared instead of **124** because the latter is only accessible in very small quantities from reaction of mesitonitrile oxide **5** with methyl acrylate **14** (see Chapter 1, Section 1.1.3.).[24] There, steric effects by far dominate polar effects in cycloadditions with nitrile oxides, whereby 5-acyl-substituted 2-isoxazolines are the predominant products.



Ar = 2,4,6-Me_3Ph

Reagents and conditions: i. **5** (1.0 equiv.), **20** (1.0 equiv.), THF, reflux, 24 h.

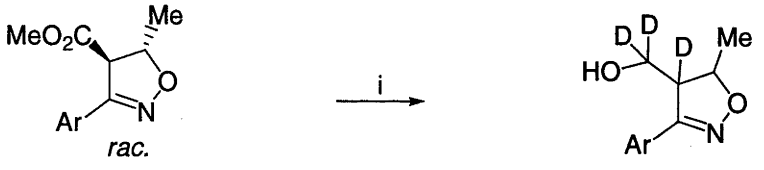
Scheme 37

The isomeric 2-isoxazolines **21c** and **22c** were separated by chromatography and their structures assigned. Using the EI method, their molecular ions were detected at *m/z* 261 for which accurate mass analyses were obtained for the structural composition of $C_{15}H_{19}NO_3$. In the ^1H NMR spectra, the 2-isoxazolines **21c** and **22c** were differentiated by the chemical shifts and multiplicity of the signals for the C4- and C5-isoxazoline protons. For the 2-isoxazoline **21c**, the C4 proton signal was observed as a doublet at δ 4.02 ppm (J = 8.7 Hz), whilst the C5 proton resonated as a doublet of quartets at δ 5.19 ppm (J = 8.7, 6.2 Hz). For the 2-isoxazoline **22c**, the C4 proton signal was seen as a multiplet at δ 3.80 ppm, whilst the C5 proton resonated

as a doublet at δ 4.76 ppm (J = 6.1 Hz). The spectral data for 2-isoxazolines **21c** and **22c** are consistent with literature values.[24]

The *trans*-configuration of the dipolarophile **20** was conserved in the nitrile oxide cycloadditions, as indicated by the magnitude of the $J_{4,5}$ coupling constant for the 2-isoxazolines **21c** and **22c**.[72] The regioisomeric 2-isoxazolines **21c** and **22c** were produced in a ratio of *ca.* 2.7:1, in a combined yield of 97%.

With the 4-acylisoxazoline **21c** in hand, it was treated with sodium borodeuteride in deuterated ethanol (Scheme 38). The 2-isoxazoline **126** was isolated as the sole product, in 87% yield. Its structure was deduced from mass spectrometric and ^{1}H NMR spectroscopic data. Accurate mass measurement of the molecular ion at *m/z* 236 using the EI method indicated the molecular composition of $C_{14}H_{16}D_3NO_2$. In the ^{1}H NMR spectrum, a one proton quartet at δ 4.72 ppm (J = 6.3 Hz) was seen and assigned to the C5 isoxazoline proton. The relative configuration of the 2-isoxazoline **126** could not be assigned since the proton at C5 is not coupled to the deuterium at C4. The lack of other proton signals in the region δ 3-5 ppm indicates deuteration had occurred at C4 and C41. Deuterium exchange at C4 had presumably occurred prior to reduction of the methoxycarbonyl group, owing to the acidity of the C4 proton *alpha* to the methoxycarbonyl group in **21c**.



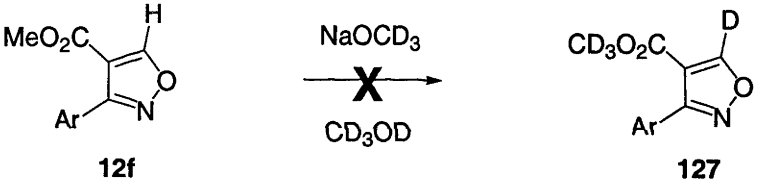
Ar = 2,4,6-Me_3Ph

Reagents and conditions: i. **21c** (1.0 equiv.), $NaBD_4$ (15.0 equiv.), EtOD, reflux, 24 h.

Scheme 38

The fact that deuterium exchange at C5 did not occur during reduction of **21c** indicates that hydrogen or deuterium exchange must occur during step 1 of the reaction of **12f** with sodium borodeuteride, before the ester intermediate **124** is formed. Since the reduction is carried out under basic conditions, hydrogen and deuterium exchange could conceivably involve base abstraction of the acidic C5-proton of 4-acylisoxazole **12f**, thereby affording the C5-deuterated isoxazole **127**.

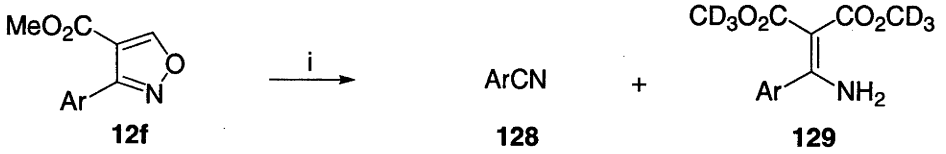
To examine if deuterium exchange occurred *via* this mechanism, reaction of **12f** with d_3-sodium methoxide was initially carried out at –78 °C for 12 hours (Scheme 39), but under these conditions, the isoxazole **12f** appeared unchanged. Likewise, when isoxazole **12f** was heated at reflux with d_3-sodium methoxide for 24 hours, only starting material was recovered. When the reaction was eventually carried out at 18 °C, products **128** and **129** were detected (Scheme 40).



12f **127**

Ar = 2,4,6-Me_3Ph

Scheme 39



12f **128** **129**

Ar = 2,4,6-Me_3Ph

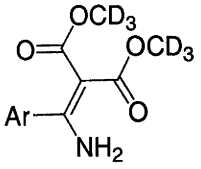
Reagents and conditions: i. **12f** (1.0 equiv.), Na metal (1.5 equiv.), CD_3OD, 18 ° C, 16 h.

Scheme 40

The major product which formed in 63% yield was identified as mesitonitrile **128** from EI mass spectrometry and ^{1}H NMR spectroscopy. Accurate mass measurement of the molecular ion at *m/z* 145 indicated the structural composition of $C_{10}H_{11}N$. In the ^{1}H NMR spectrum of the nitrile **128**, three singlets were observed at δ 2.24 ppm, δ 2.50 ppm and δ 6.95 ppm, integrating for three, six and two protons, respectively. The former two signals were assigned to the *p*-methyl and the *o,o'*-methyl groups on the mesityl ring, whilst the latter was ascribed to the mesityl ring protons. The mass spectrometric and ^{1}H NMR spectroscopic data are in accord with literature values.[107]

The minor product **129** was obtained in 31% yield. In the ^{1}H NMR spectrum, three singlets were seen at δ 2.25 ppm, δ 2.26 ppm and δ 6.84 ppm, integrating for six, three and two protons, were assigned to the *o,o'*-methyl, *p*-methyl and mesityl ring protons, respectively. Two broadened singlets at δ 4.95 ppm and δ 8.98 ppm were ascribed to the protons on the amino group. The molecular ion was detected at *m/z* 283 for which accurate mass measurement using the EI method was obtained for $C_{15}H_{13}D_6NO_4$. The mass spectrometric data indicated incorporation of two d_3-methoxy groups in the structure. Crystals of **129** were grown from vapour diffusion of hexanes and ether at 18 °C. The X-ray crystallographic structure was recorded and the ORTEP diagram is shown in Figure 14. The ORTEP diagram clearly shows incorporation of a d_3-methoxy group at the carbon centre that was C5 in the isoxazole **12f**. This indicates that methoxide was added to **12f** in a 1,4-sense.

Subsequently, the fully protonated β-alkoxycarbonylenamine **133** was prepared by treatment of isoxazole **12f** with sodium methoxide in methanol under the conditions described for the synthesis of the deuterated species **129**. The ^{1}H NMR signals of the two methoxy groups of **133** were observed as singlets at δ 3.33 ppm and δ 3.78 ppm, each integrating to three protons. The molecular ion was detected at *m/z* 277 and accurate mass analysis indicated the molecular composition of $C_{15}H_{19}NO_4$.



129

Ar = 2,4,6-Me_3Ph

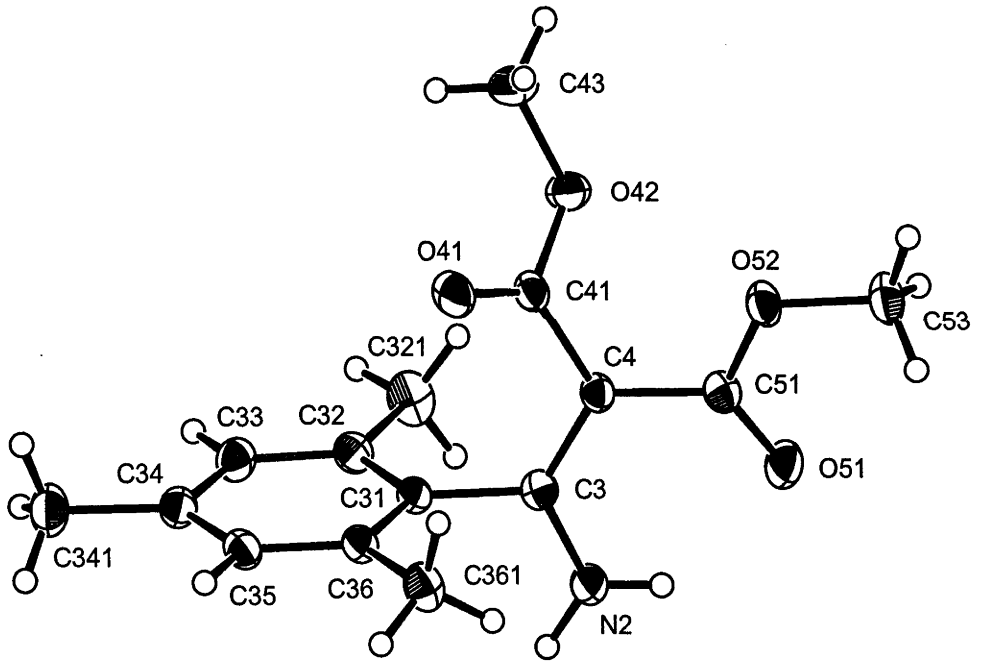
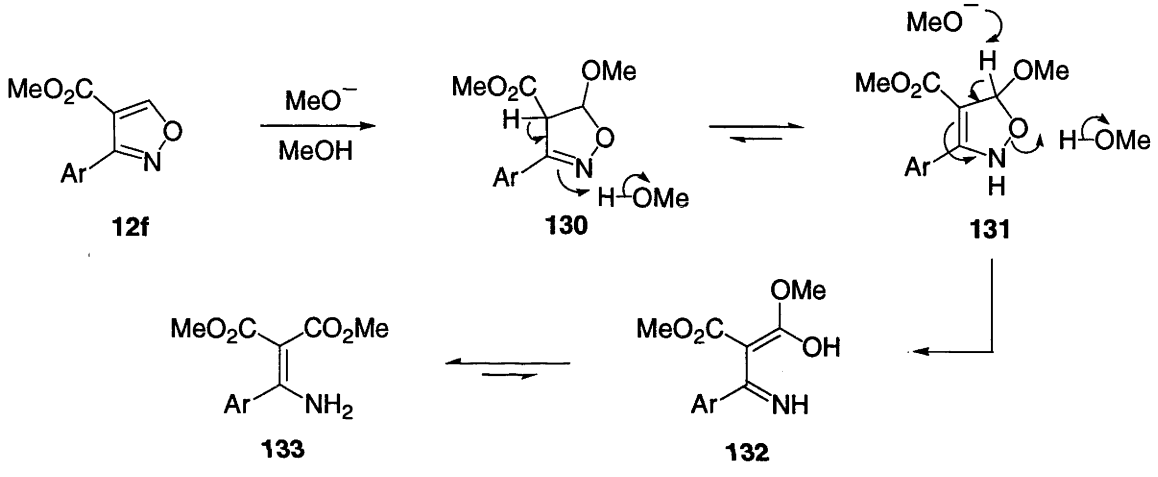


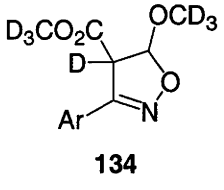
Figure 14. ORTEP derived from single crystal X-ray analysis of compound **129**.

Presumably, the first step in the formation of enamine **133** involves addition of methoxide at the 5-position of the isoxazole **12f**. This is followed by base-mediated tautomerization of the adduct **130**, thereby furnishing 3-isoxazoline **131**. Deprotonation at C5 and ring-cleavage then gives rise to the ring-opened species **132** which undergoes enol-keto tautomerization to afford the more stable keto-form **133** (Scheme 41). Thus, the formation of enamine **133** indicates 4-acylisoxazoles are susceptible to 1,4-addition with alkoxides.



Scheme 41

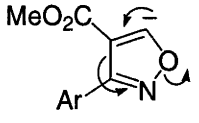
Why **129** forms at 18 °C but not at higher or lower temperatures is unclear. It may be that no reaction occurs at –78 °C whereas when the reaction is carried out at reflux, rapid elimination of d_4-methanol from the adduct **134** takes place.



134

Ar = 2,4,6-Me_3Ph

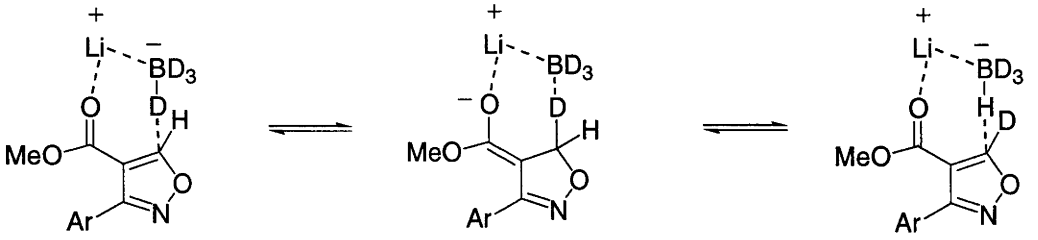
The nitrile **128** probably results from fragmentation of the isoxazole anion **135**. Base-induced fragmentations of 5-unsubstituted isoxazoles are known processes (see Chapter 1, Section 1.4.).[58] Formation of the nitrile **128** provides indirect support for the hypothesis of a deprotonation-protonation mechanism for the deuteration at C5 during the borodeuteride reduction of **12f**, however, it is by no means conclusive. The C5-deuterated isoxazole **127** was not detected.



135

Ar = 2,4,6-Me_3Ph

In an attempt to obtain direct evidence for formation of the C5-deuterated 4-acylisoxazole **127**, the 4-acylisoxazole **12f** was treated with sodium borodeuteride in deuterated ethanol and the reaction was quenched when it was 80% complete, as determined using ^{1}H NMR analysis. Based on the proposed deprotonation-protonation mechanism, deuterium exchange at the 5-position of **12f** was expected at this stage of the reaction. However, the ^{1}H NMR spectrum of the crude product indicated otherwise, as the integration of the C5 proton signal remained unchanged relative to those of the mesityl protons in the isoxazole **12f**. It therefore seems likely that deuterium exchange occurs *via* an isoxazole-borodeuteride complex **136**, as shown in Scheme 42, and that the exchanged species is reduced before dissociating from the complex. Further evidence is required to substantiate this hypothesis. In any event, the lability of the C5-hydrogen could potentially present problems for control of stereochemistry.



136

Ar = 2,4,6-Me_3Ph

Scheme 42

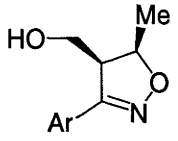
3.5. Scope of Hydride Reagents for Reductions of 4-Alkoxycarbonylisoxazoles

3.5.1. Effect of Counter Cations on Borohydride Reductions of 4-Acylisoxazoles

The effects of counter cations on the diastereoselectivity and yields of the borohydride reductions of 4-alkoxycarbonylisoxazoles were examined. Initially this involved treatment of **12f** with lithium and potassium borohydrides. Like sodium borohydride, lithium borohydride was effective in reducing the 4-acylisoxazole **12f** to the 2-isoxazoline **101**. The reaction was carried out in THF because lithium borohydride decomposes in ethanol after 2-4 hours at 0 °C.[108] When **12f** and a 15-fold excess of lithium borohydride in THF was heated at reflux for 24 hours, **101** was obtained in a yield of 90%. This is consistent with literature indicating that lithium borohydride is a useful reagent for 1,4-reductions of enones.[109]

No reaction was observed when a mixture of **12f** and a 15-fold excess of potassium borohydride was heated at reflux in ethanol for 24 hours. The effect of the counter cation was further examined through the use of cation traps, such as crown ethers. Isoxazole **12f** was unreactive on treatment with either sodium borohydride/ 15-crown-5 (15 equivalents) or lithium borohydride/12-crown-4 (15 equivalents) in refluxing ethanol for 24 hours.

Having established that lithium borohydride reduces **12f** to 2-isoxazoline **101**, the diastereoselectivity of the reaction of 5-methyl-4-acylisoxazole **117** was examined. The reaction gave rise to *trans*- and *cis*-2-isoxazolines **118** and **137**, and the isoxazole **119**, in a ratio of 4:2:1. The *trans*-2-isoxazoline **118** and the isoxazole **119** had already been obtained from sodium borohydride reduction of isoxazole **117**, and their ^{1}H NMR spectroscopic assignments are reported in Section 3.3. For the *cis*-2-isoxazoline **137**, the signal of the C5 isoxazoline proton was observed as a one proton doublet of quartets at δ 4.90 ppm (J = 8.6, 6.2 Hz) in the ^{1}H NMR spectrum of the product mixture.



rac.

137

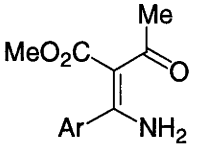
Ar = 2,4,6-Me_3Ph

These experiments show that borohydride reductions of 4-acylisoxazoles are promoted by sodium and lithium cations. Sodium borohydride appears to be a better reagent than lithium borohydride for diastereoselective reductions of 4-acylisoxazoles.

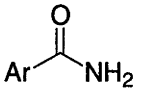
3.5.2. Effect of Hydride Sources on Reductions of 4-Acylisoxazoles

Alternative hydride sources were observed to have important effects on these reductions. Reaction with sodium cyanoborohydride was investigated as Gribble *et al.*[110] reported that indoles are reduced to indolines with this reagent in acetic acid, through a similar chemical transformation to the reduction of isoxazoles to 2-isoxazolines. However the isoxazole **117** was found to be unreactive under the conditions described by Gribble *et al.*[110]

Catecholborane was then examined as a potential reducing agent, based on Evans *et al.*'s[111] reported use of the reagent in combination with chlorotris(triphenylphosphine)rhodium(I), also known as Wilkinson's catalyst, for conjugate reductions of enoates and enones. Treatment of **117** with catecholborane and Wilkinson's catalyst (2 mol%) in THF at –20 °C for 24 hours however did not effect reduction of the C4-C5 double bond. Instead, the enamine **138**, amide **139** and nitrile **128** were produced in yields of 46%, 23% and 13%, respectively.



138



139

Ar = 2,4,6-Me_3Ph

All physical and spectroscopic data of the ring-cleaved product **138** are in full accord with the assigned structure. Using the EI method, accurate mass measurement of the parent ion at *m/z* 261 indicated the structural composition of $C_{15}H_{19}NO_3$. In the ^1H NMR spectrum, signals of the labile amine protons were seen as broad singlets, each integrating for one proton, at δ 5.40 ppm and δ 11.1 ppm. The signal of the methoxy protons was observed as a three proton singlet at δ 3.31 ppm. In the infrared spectrum, a broad intense absorption band at 1704 cm^{-1} was assigned to carbonyl stretching vibrations, whilst the amino stretching vibration was seen as a broad band at 3334 cm^{-1}. Instead of effecting conjugate reduction of the 4-acylisoxazole **117**, use of catecholborane led to cleavage of the N-O bond.

The spectral data of the nitrile **128** obtained from reaction of **117** with catecholborane are identical in every respect to those of the sample derived from methoxide-assisted cleavage of **12f**. Presumably, nitrile **128** was formed *via* fragmentation of isoxazole **117** or the ring-cleaved species **138**.

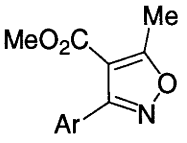
The structure of amide **139** was deduced from EI mass spectrometry and ^{1}H NMR spectroscopy. The molecular ion was detected at *m/z* 163 for which accurate mass measurement indicated the molecular composition of $C_{10}H_{13}NO$. In the ^{1}H NMR spectrum, the amide protons resonated as broad singlets at δ 5.63 ppm and δ 5.87 ppm. In the infrared spectrum, the amide carbonyl stretching vibration was seen as an intense absorption band at 1637 cm^{-1}.[112] The amide **139** is likely to have formed from hydrolysis or oxidation of the nitrile **128** during work-up of the reaction, which involved decomposition of borane by-products using hydrogen peroxide and potassium hydroxide.

The failure of catecholborane to effect conjugate reduction of the 4-acylisoxazole **117** led to an examination of another borohydride-based reagent. Lithium tri(*sec*-butyl)borohydride, otherwise known as L-Selectride®, was investigated as a potential reducing agent for 4-acylisoxazoles since it has been widely used for Michael reductions of α,β-unsaturated carbonyl compounds,[113] with good stereoselectivity observed for chiral substrates.[114]

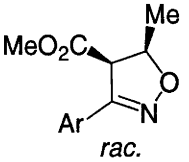
Reactions of **117** with L-Selectride® were investigated, and the results are shown in Table 25. In all cases, mixtures of *cis*- and *trans*-diastereomers **140** and **21c** were obtained except from reaction at -78 °C for 3 days, where only the *trans*-2-isoxazoline **21c** along with unreacted **117** were detected by ^{1}H NMR spectroscopy. Despite excellent diastereoselectivity, reduction of **117** at –78 °C was impractically slow.

The rate of reduction improved when the temperature was increased from –78 °C to 0 °C, however, this was accompanied with loss of diastereoselectivity and both the *cis*- and *trans*-2-isoxazolines **140** and **21c** were detected by ^{1}H NMR spectroscopy. The signal of the C4 isoxazoline proton of the *cis*-2-isoxazoline **140** was a doublet at δ 4.41 ppm ($J_{4,5}$ = 10.4 Hz) whilst the C5 isoxazoline proton gave rise to a doublet of quartets at δ 5.05 ppm ($J_{4,5}$ = 10.4, 6.4 Hz). Poor diastereoselectivity was also observed at 18 °C. Longer reaction times and use of excess L-Selectride® resulted in decomposition of the 2-isoxazolines **21c** and **140**.

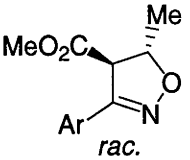
Table 25. L-Selectride® reduction of 4-acylisoxazole **117**



117



rac.
140



rac.
21c

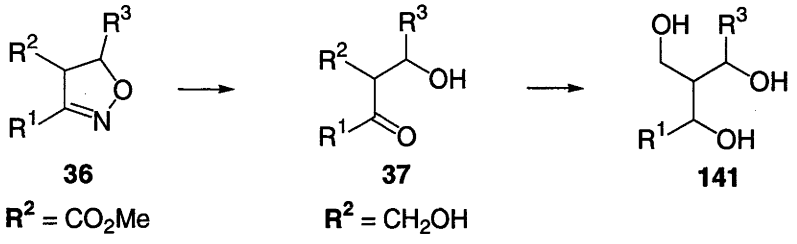
Ar = 2,4,6-Me_3Ph

Reagents (equiv.)	Conditions	140:21c:117
117 (1.0), L-Selectride® (1.0)	Et_2O, - 78 °C, 3 days	<0.1:0.24:1
117 (1.0), L-Selectride® (1.0)	Et_2O, 0 °C, 10 min	5:6.5:1
117 (1.0), L-Selectride® (1.0)	Et_2O, 0 °C, 70 min	2:2.6:1
117 (1.0), L-Selectride® (1.0)	Et_2O, 0 °C, 24 h	<0.1:<0.1:1
117 (1.0), L-Selectride® (1.0)	Et_2O, 18 °C, 10 min	10:12:1
117 (1.0), L-Selectride® (4.0)	Et_2O, 18 °C, 15 min	5:7.5:1
117 (1.0), L-Selectride® (4.0)	Et_2O, 18 °C, 3 h	decomposition products

The results indicate that sodium borohydride is a superior reagent to lithium borohydride and L-Selectride® for diastereoselective reductions of 4-alkoxycarbonylisoxazoles. The highly diastereoselective reaction is potentially useful for stereoselective synthesis of polyfunctional molecules derived from ring-opening of 2-isoxazolines.

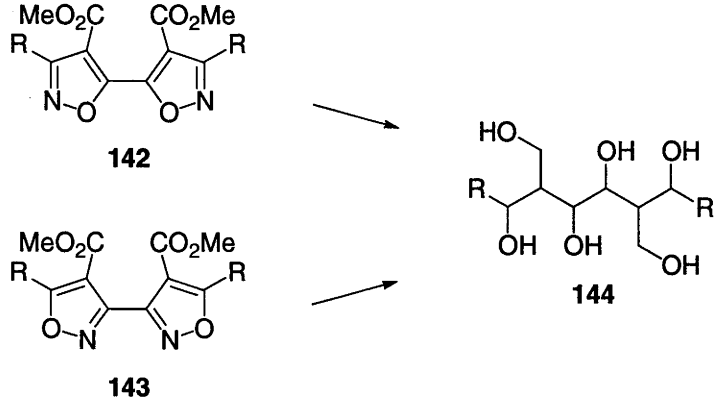
3.6. Reductions of 4,4'-Dialkoxycarbonyldiisoxazoles

The work described in the previous sections establishes that monomeric 4-alkoxycarbonylisoxazoles behave as Michael acceptors and are reduced to 2-isoxazolines with various borohydride reagents. Functional molecules, such as triols **141**, can be accessed through reduction of β-hydroxyketones **37**, obtained from ring opening of 2-isoxazolines **36** (Scheme 43).[115]



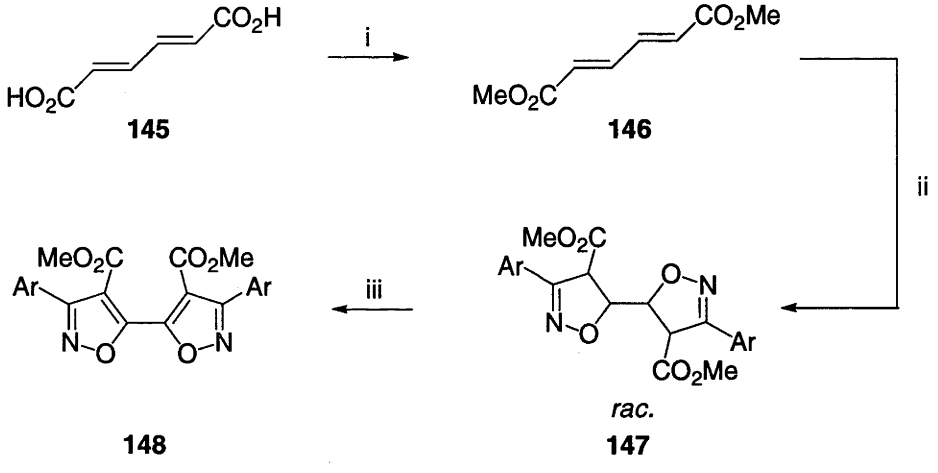
Scheme 43

By analogy, stereoselective reductions of polyisoxazoles potentially provide a method for synthesizing polyols with control of stereochemistry. With this aim, the reactions of diisoxazoles **142** and **143** with sodium borohydride were examined as potential routes to hexaols **144** (Scheme 44).



Scheme 44

Initial efforts involved synthesis of 5,5'-diisoxazole **148** due to the commercial availability of the dipolarophile precursor, *trans,trans*-muconic acid **145**. The *bis*-dipolarophile **146** was synthesized through acid-catalysed esterification of the dicarboxylic acid **145** with methanol. All physical and spectral data of the *bis*-dipolarophile **146** are in full accord with literature values.[116] Treatment of the *bis*-dipolarophile **146** with mesitonitrile oxide **5** afforded 5,5'-diisoxazoline **147** in 84% yield (Scheme 45).



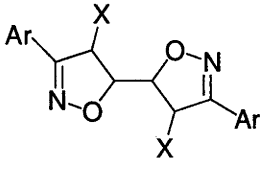
Reagents and conditions: i. **145**, H_2SO_4 (cat.), MeOH, reflux, 24 h; ii. **146** (1.0 equiv.), **5** (2.0 equiv.), THF, reflux, 4 days; iii. **147** (1.0 equiv.), γ-activated MnO_2 (5.0 equiv.), toluene, reflux, 36 h.

Scheme 45

Four possible stereoisomers of **147**, all with the *trans*-configuration at the isoxazoline rings, result from the addition of dipole **5** and diene **146**. The four stereoisomers are comprised of two sets of enantiomers, which differ by the geometry across the isoxazoline ring junctions. Of the two sets of enantiomers of **147**, only one is detected by ^{1}H NMR spectroscopy. In the ^{1}H NMR spectrum, doublets at δ 4.45 ppm (J = 4.7 Hz) and at δ 5.27 ppm (J = 4.7 Hz) were observed. The former signal was

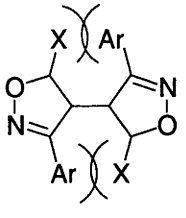
assigned to the C4- and C4'-isoxazoline protons, and the latter to the C5- and C5'-isoxazoline protons. A singlet at δ 3.61 ppm was assigned to the methoxy protons. The *trans*-configuration of the *bis*-dipolarophile **146** was conserved in the product 5,5'-diisoxazoline **147**, as indicated by the magnitude of the coupling constant $J_{4,5}$ = 4.7 Hz, which is characteristic.[74] The structure of the 5,5'-diisoxazoline **147** was also deduced from EI mass spectrometry. The molecular ion was detected at *m/z* 492 for which accurate mass measurement of the structural composition of $C_{28}H_{32}N_2O_6$ was obtained. In the infrared spectrum, an intense absorption band at 1743 cm^{-1} was assigned to the carbonyl stretching vibration.

The cycloaddition was also completely regioselective; the 5,5'-diisoxazoline **147** was produced with none of the 4,4'- and 4,5'-diisoxazolines **149** and **150** being formed. Presumably, formation of the diisoxazolines **149** and **150** is disfavored due to steric repulsion. By contrast, unfavorable steric interactions are less for the 5,5'-diisoxazoline **147**, as the mesityl groups are situated at the opposite ends of this material. Exclusive formation of the 5,5'-diisoxazoline **147** is also consistent with dominant polar effects, with addition of the oxygen of the nitrile oxide **5** to the electropositive β- and β'-carbon centres of the *bis*-acrylate **146**.



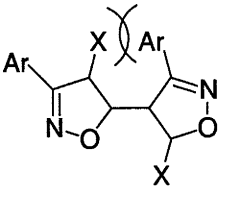
rac.
147
5,5'-diisoxazoline

steric repulsion



rac.
149
4,4'-diisoxazoline

steric repulsion



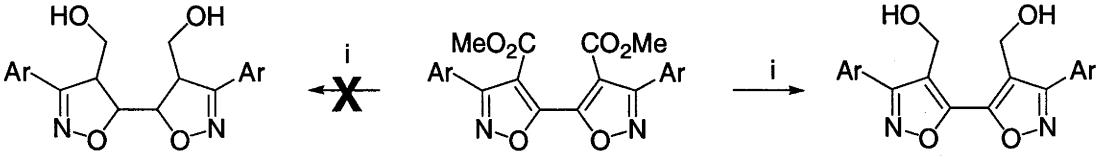
rac.
150
4,5'-diisoxazoline

Ar = 2,4,6-Me_3Ph
X = CO_2Me

Several reagents were investigated for the oxidation of the 5,5'-diisoxazoline **147** to the 5,5'-diisoxazole **148**. Aqueous potassium permanganate[38] and Chloranil[34] failed to dehydrogenate **147**. Success was finally realized through the use of γ-activated manganese dioxide[37] and the 5,5'-diisoxazole **148** was produced in 83% yield (Scheme 45).

The structure of the 5,5'-diisoxazole **148** was assigned as follows. The molecular composition of $C_{28}H_{28}N_2O_6$ was obtained from accurate mass measurement of the molecular ion at *m/z* 488 using the EI method. In the ^1H NMR spectrum, the proton signal of the methoxycarbonyl groups was observed as a singlet at δ 3.61 ppm. In the infrared spectrum, the carbonyl stretching vibrations were seen as intense absorption bands at 1736 cm^{-1} and 1723 cm^{-1}. Recrystallization of compound **148** from a mixture of hexanes and ether at 18 °C gave rise to a sample from which the X-ray crystallographic structure was recorded. The ORTEP diagram of the solid state structure of the 5,5'-diisoxazole **148** is shown in Figure 15.

Having successfully synthesized the 5,5'-diisoxazole **148**, it was treated with a 30-fold excess of sodium borohydride in refluxing ethanol for 24 hours (Scheme 46). Instead of affording the desired 5,5'-diisoxazoline **151**, the 5,5'-diisoxazole **152** was obtained in 90% yield.

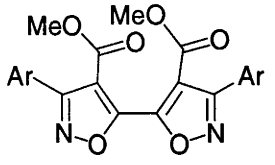


151 **148** **152**

Ar = 2,4,6-Me_3Ph

Reagents and conditions: i. **148** (1.0 equiv.), $NaBH_4$ (30.0 equiv.), EtOH, reflux, 24 h.

Scheme 46



148

Ar = 2,4,6-Me_3Ph

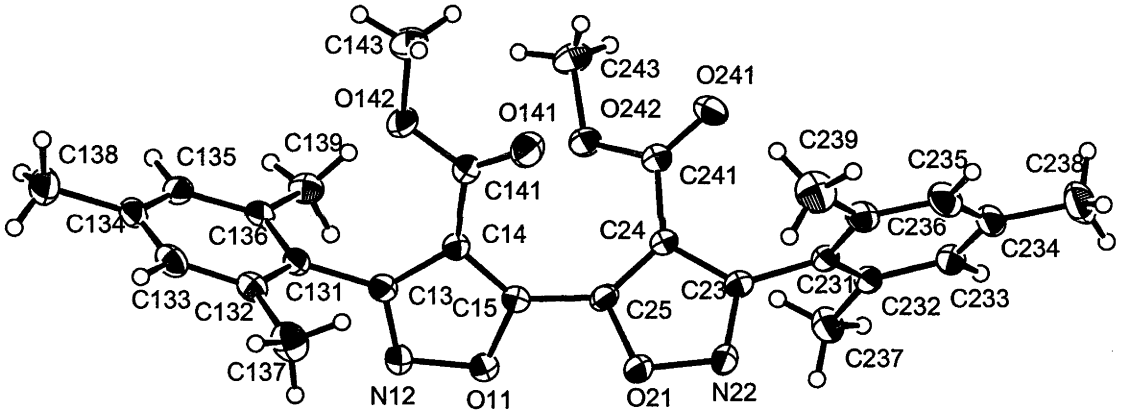


Figure 15. ORTEP derived from single crystal X-ray analysis of compound **148**.

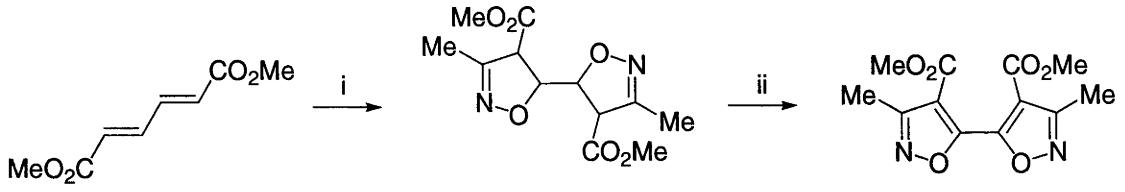
The structure of the 5,5'-diisoxazole **152** was deduced from mass spectral and ^{1}H NMR spectroscopic data. Using the EI method, accurate mass measurement of the molecular ion at *m/z* 432 indicated the molecular composition of $C_{26}H_{28}N_2O_4$. In the ^{1}H NMR spectrum, the methylene protons were observed as a singlet resonance at δ 4.65 ppm. In the infrared spectrum, the hydroxyl stretching vibration was seen as an broad intense absorption band at 3400 cm^{-1}.

Attempts were also made to effect conjugate reduction of 5,5'-diisoxazole **148** through use of other reducing agents. Reactions of **148** with sodium borohydride in combination with Lewis acids such as bismuth(III) chloride,[117] cobalt(II) chloride[94] and nickel(II) chloride[94] were examined. Disappointingly, these did not result in conjugate reduction of **148**, and in each case only the 5,5'-diisoxazole **152** was detected as the reaction product.

Use of the sodium borohydride-pyridine complex[118] was also examined. Although it has been reported as an effective agent for reducing sterically hindered activated alkenes, only unreacted 5,5'-diisoxazole **148** was recovered. A possible explanation for the lack of reaction is the sterically hindered nature of the borohydride-pyridine complex. Reactions with L-Selectride®[113] and lithium aluminium hydride[92] were also examined. No reaction was observed with L-Selectride® whilst lithium aluminium hydride gave rise to a complex product mixture.

It seemed likely that the resistance of the 5,5'-diisoxazole **148** to undergo reduction of the isoxazole rings might have resulted from unfavorable steric interactions. Conceivably, the sterically demanding mesityl groups might have caused the methoxycarbonyl groups to crowd over C5 and C5', thus rendering them inaccessible to hydride.

To examine this and in an attempt to relieve the steric crowding around C5 and C5', the mesityl groups were replaced by the more compact methyl groups. The synthesis of the sterically less congested 5,5'-diisoxazole **154** is shown below (Scheme 47).



146 *rac.* **153** **154**

Reagents and conditions: i. **2c** (1.0 equiv.), **146** (10.0 equiv.), NEt_3 (1.1 equiv.) added over 24 h, Et_2O, 18 °C, 24 h; ii. **153** (1.0 equiv.), γ-activated MnO_2 (5.0 equiv.), toluene, reflux, 48 h.

Scheme 47

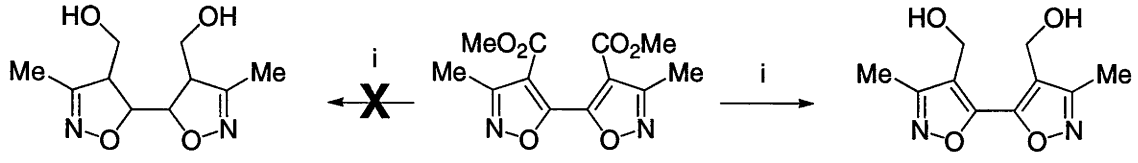
Acetonitrile oxide **3c** was generated *in situ* by dehydrohalogenation of acetohydroximinoyl chloride **2c** (for the synthesis of **2c**, refer to Chapter 2, Section 2.2.). To suppress the competing nitrile oxide dimerization whilst maximizing the nitrile oxide cycloaddition, triethylamine was added slowly to a mixture of the hydroximinoyl chloride **2c** and an excess of the *bis*-dipolarophile **146**. This afforded the 5,5'-diisoxazoline **153** in 72% yield.

As seen for the 5,5'-diisoxazoline **147**, only one of the two possible sets of the enantiomers of the *trans,trans*-5,5'-diisoxazoline **153** was detected by ^1H NMR spectroscopy, and the relative geometry across the junction of the isoxazoline rings is undetermined. In the ^1H NMR spectrum, the signals of the C4- and C4'-, and C5- and C5'-isoxazoline protons were observed as doublets at δ 3.98 ppm (J = 4.0 Hz) and δ 4.86 ppm (J = 4.0 Hz), respectively. The small vicinal coupling of $J_{4,5}$ = 4.0 Hz indicates a *trans*-configuration across the C4-C5 and C4'-C5' bonds. A singlet at δ 3.83 ppm was assigned to the methoxy groups. The molecular ion at *m/z* 285 was not detected by EI mass spectrometry. Instead, the fragment ion at *m/z* 253 was seen. Accurate mass measurement determined the structural composition of the fragment ion as $C_{11}H_{13}N_2O_5$, indicating loss of a methoxy group from the molecular ion. In the infrared spectrum, the carbonyl stretching vibration was seen as an intense absorption band at 1726 cm^{-1}.

The 5,5'-diisoxazoline **153** was obtained as the sole product. This completely regioselective cycloaddition is attributed to dominant polar effects, also seen for the cycloaddition of dipole **5** with *bis*-dipolarophile **146**.

The final step in the synthesis of 5,5'-diisoxazole **154** involved dehydrogenation of the 5,5'-diisoxazoline **153**. This was accomplished through the use of γ-activated manganese dioxide and in 83% yield. The physical and spectral data of **154** are in full accord with the assigned structure. Using the EI method, accurate mass measurement of the molecular ion at *m/z* 280 indicated the molecular composition of $C_{12}H_{12}N_2O_6$. In the ^1H NMR spectrum, two singlet resonances at δ 2.57 ppm and δ 3.78 ppm were seen. The former signal was assigned to the C3- and C3'-methyl protons whilst the latter was ascribed to the methoxy protons. In the infrared spectrum, the carbonyl stretching vibration was observed as an intense absorption band at 1736 cm^{-1}. The 5,5'-diisoxazole **154** was recrystallized from a mixture of hexanes and ether. The X-ray crystallographic structure of the material was recorded and the ORTEP diagram is shown in Figure 16.

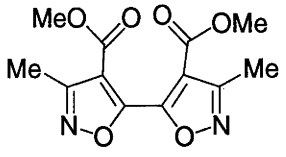
With the 5,5'-diisoxazole **154** in hand, it was examined for acrylate-type reactivity by treatment with sodium borohydride in refluxing ethanol. Disappointingly, the 5,5'-diisoxazoline **155** was not detected in the product mixture and instead, only 5,5'-diisoxazole **156** was obtained in 88% yield (Scheme 48).



155 **154** **156**

Reagents and conditions: i. **154** (1.0 equiv.), $NaBH_4$ (30.0 equiv.), EtOH, reflux, 24 h.

Scheme 48



154

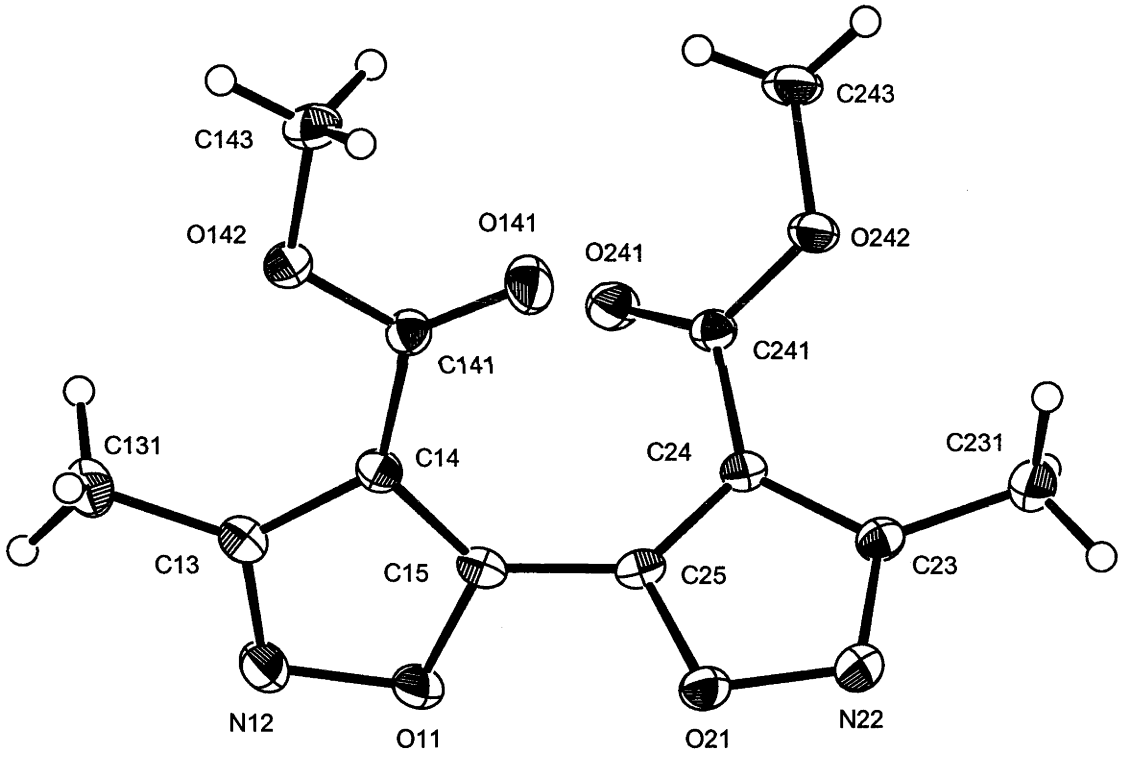


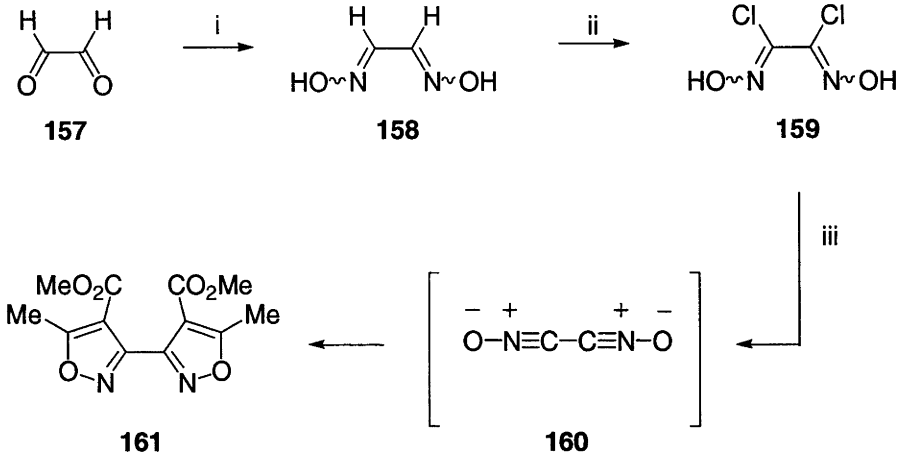
Figure 16. ORTEP derived from single crystal X-ray analysis of compound **154**.

All physical and spectroscopic data of 5,5'-diisoxazole **156** are consistent with the assigned structure. Using the EI method, the molecular ion was detected at *m/z* 224 for which accurate mass measurement indicated the structural composition of $C_{10}H_{12}N_2O_4$. In the ^1H NMR spectrum, only two singlets were observed, at δ 2.43 ppm and δ 4.81 ppm. The former signal was ascribed to the methyl protons and the latter to the methylene protons. In the infrared spectrum, the hydroxyl stretching vibration was seen as an intense absorption band at 3406 cm^{-1}.

The observed resistance of 5,5'-diisoxazole **148** and the less sterically hindered 5,5'-diisoxazole **154** to reduction of the isoxazole rings indicates that the source of steric congestion at C5 and C5' (or the β- and β'-carbons) is not due to the bulk of the C3- and C3'-substituents, but to the steric effects of the adjoining isoxazole units. In an attempt to decrease these steric interactions, the 3,3'-diisoxazole **161** was synthesized and reaction with sodium borohydride was studied. It was reasoned that steric congestion at C5 and C5' is less in 3,3'-diisoxazole **161** than in 5,5'-isoxazoles **148** and **154**. This is because these centres are located at the opposite ends of the 3,3'-diisoxazole structure, thereby making them more accessible to hydride than those of 5,5'-diisoxazoles.

The synthesis of 3,3'-diisoxazole **161** was accomplished by cycloaddition of oxalobisnitrile oxide **160** with methyl tetrolate **17a** (Scheme 49). The first step of the synthesis involved preparation of glyoxime **158**. Glyoxal **157** was condensed with hydroxylamine hydrochloride to afford the *bis*-oxime **158** in 91% yield. Chlorination of the *bis*-oxime **158** with NCS furnished dichloroglyoxime **159** in 93% yield. All physical and spectral data of *bis*-oxime **158**[119] and *bis*-hydroximinoyl chloride **159**[120] are in full agreement with literature values.

Since the *bis*-nitrile oxide **160** is prone to inter- and intra-molecular dimerization, it was generated *in situ* from gradual addition of triethylamine to the hydroximinoyl chloride **159**. The optimum yield of the 3,3'-diisoxazole **161** was realized with addition of triethylamine to the *bis*-hydroximinoyl chloride **159** over 48 hours in a 10-fold excess of the dipolarophile **17a**. This afforded **161** in a yield of 66%.

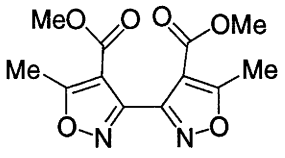


Reagents and conditions: i. **157** (1.0 equiv.), $NH_2OH.HCl$ (2.2 equiv.), 50% wt/v NaOH (2.2 equiv.), 30% aq. EtOH, 18 °C, 4 h; ii. **158** (1.0 equiv.), NCS (2.0 equiv.), DMF, 20-25 °C, 3 h; iii. **159** (1.0 equiv.), NEt_3 (2.0 equiv.) added over 48 h, **17a** (10.0 equiv.), THF, 18 °C, 32 h.

Scheme 49

The structure of **161** was deduced from EI mass spectrometry and ^1H NMR spectroscopy. The molecular composition of $C_{12}H_{12}N_2O_6$ was determined from accurate mass measurement of the molecular ion at *m/z* 280. In the ^1H NMR spectrum, two singlets were observed at δ 2.78 ppm and δ 3.74 ppm. The former signal was assigned to the isoxazole C5- and C5'-methyl protons whilst the latter was ascribed to the methoxy protons. In the infrared spectrum, an intense absorption band at 1728 cm^{-1} was assigned to carbonyl stretching vibrations of the two methoxycarbonyl groups. Crystals of the 3,3'-diisoxazole **161** were grown from a mixture of hexanes and ether *via* vapour diffusion at 18 °C. The X-ray crystallographic structure of the material was obtained and the ORTEP diagram is shown in Figure 17. The cycloaddition of the *bis*-nitrile oxide **160** with dipolarophile **17a** was completely regioselective and is attributed to dominant polar effects.

Having obtained 3,3'-diisoxazole **161**, it was treated with excess sodium borohydride in refluxing ethanol. This gave rise to a 3:1 mixture of the 3,3'-diisoxazole **162** and 3,3'-isoxazole-isoxazoline product **163**, but none of the desired 3,3'-diisoxazoline **164** (Scheme 50).



161

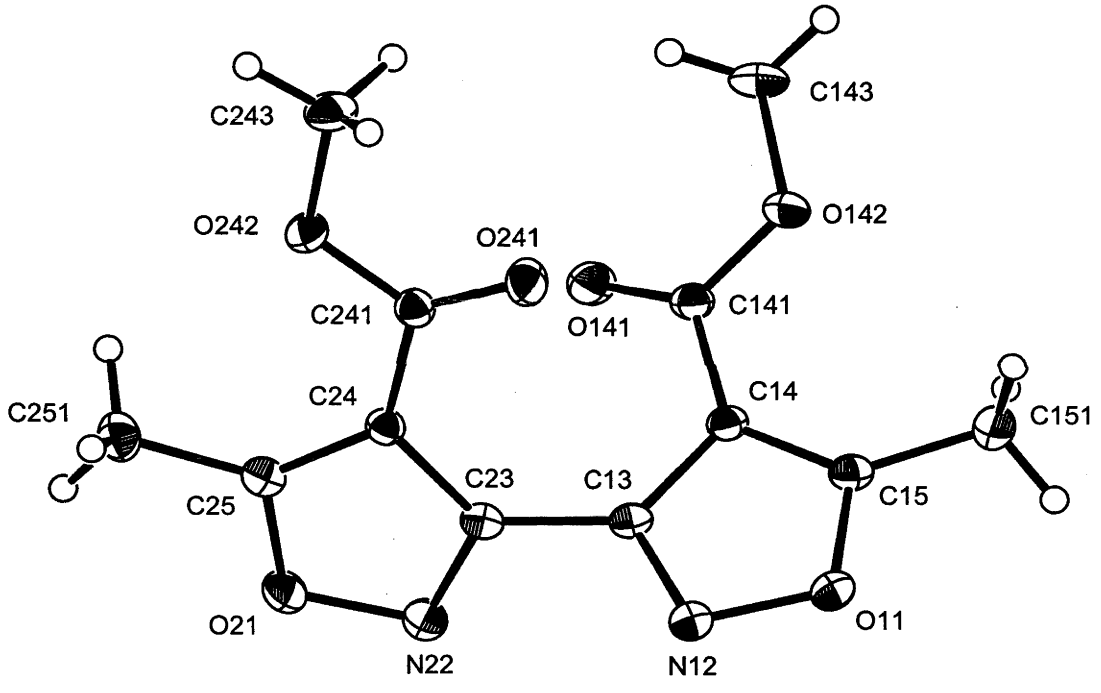
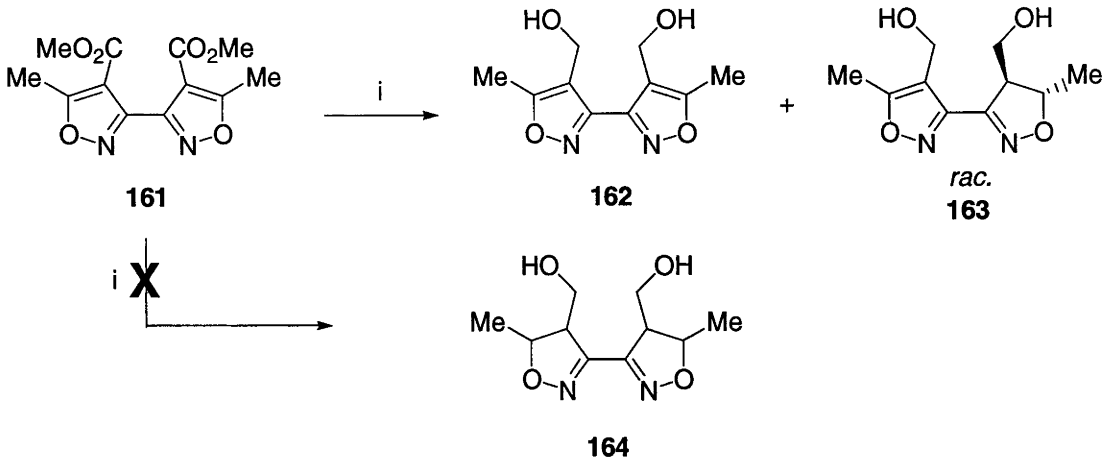


Figure 17. ORTEP derived from single crystal X-ray analysis of compound **161**.



Reagents and conditions: i. **161** (1.0 equiv.), $NaBH_4$ (30.0 equiv.), EtOH, reflux, 24 h.

Scheme 50

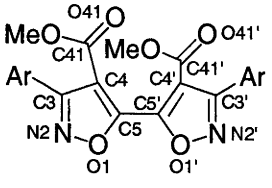
Compounds **162** and **163** were identified from the ^1H NMR spectrum of the crude product mixture. The structure of the 3,3'-diisoxazole **162** was assigned as follows; a singlet at δ 1.51 ppm was ascribed to the methyl protons whilst a singlet further downfield at δ 4.61 ppm was assigned to the methylene protons. The multiplicities of the proton signals of the 3,3'-isoxazole-isoxazoline **163** were relatively more complex than that of 3,3'-diisoxazole **162** due to the lack of molecular symmetry of the former compound. For the isoxazoline part of the molecule, the signal of the methyl protons was observed as a three proton doublet at δ 1.49 ppm (J = 6.3 Hz). The C5 isoxazoline proton resonated as a multiplet at δ 4.65 ppm whilst the signal of the C4 isoxazoline proton was seen as a doublet of doublets of doublets at δ 3.48 ppm (J = 8.5, 6.5, 4.5 Hz). The magnitude of the vicinal coupling constant $J_{4,5}$ = 8.5 Hz indicates the relative configuration of the isoxazoline is likely to be *trans*. The signal of the methylene protons were seen as a two proton multiplet at δ 3.91 ppm. For the isoxazole part of the structure, the signal of the methyl protons was seen as a three proton singlet at δ 2.46 ppm, and that of the methylene protons was observed as a two proton singlet at δ 4.61 ppm.

By contrast to the reactions of 5,5'-diisoxazoles **148** and **154** with sodium borohydride where 2-isoxazolines were not produced, reduction of 3,3'-diisoxazole **161** was observed but only at one of the isoxazole rings of the dimeric structure. Furthermore the 3,3'-isoxazole-isoxazoline was formed as a minor product. The reduced acrylate reactivity of diisoxazoles **148**, **154** and **161** was unexpected given that analogous monomeric 4-acylisoxazoles readily reduced to 2-isoxazolines under similar conditions. In order to understand this, the solid state structures of **148**, **154** and **161** were compared to those of the acylisoxazoles **12f**, **12d** and **13d** (Table 26). The diisoxazoles **148**, **154** and **161** are not symmetrical in the solid state. The X-ray crystallographic data show that the O1-N2 bonds of the diisoxazoles **148**, **154** and **161** are significantly shorter than those of the corresponding monomeric 4-acylisoxazoles **12f** and **12d**. Lengthening of the C5-O1 and C4-C41 bonds of **148**, **154** and **161** relative to those of the monomeric isoxazoles **12f** and **12d** was also seen. This indicates that the diisoxazoles **148, 154** and **161** are structurally different to the corresponding monomeric 4-acylisoxazoles **12f** and **12d**.

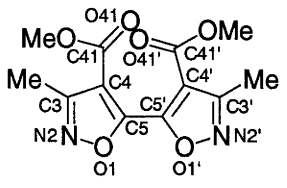
By contrast, the bond lengths of the diisoxazoles **154** and **161** compare closely to those of the 5-acylisoxazole **13d**. In fact, the O1-N2 and C5-O1 bond lengths of the diisoxazoles **154** and **161** are not statistically different to those of the 5-acylisoxazole **13d**. Likewise, the lengths of the C41-O41 bonds of diisoxazoles **154** and **161** are mostly statistically indifferent to that of the C51-O51 bond of 5-acylisoxazole **13d**, thereby implying that conjugation is disrupted in the diisoxazoles **148**, **154** and **161**.

The lack of conjugation is also reflected in the O41-C41-C4-C5 torsion angles of the diisoxazoles **148**, **154** and **161** (Table 27). By contrast to those of the monomeric 4-acylisoxazoles **12d** and **12f**, significant deviation from coplanarity between the O41-C41 and C4-C5 bonds is observed for **148**, **154** and **161**. This indicates that the O41-C41 and C4-C5 bonds are not conjugated in **148**, **154** and **161**, and hence these compounds do not behave as acrylates.

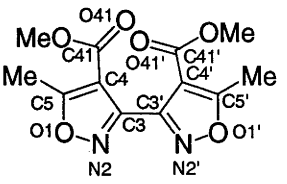
Table 26. Selected bond lengths (Å) from the X-ray crystallographic data of diisoxazoles **148**, **154** and **161**, and monomeric isoxazoles **12f**, **12d** and **13d**



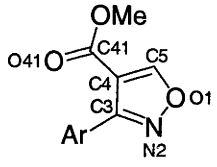
148



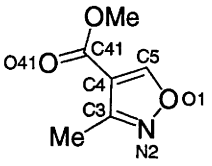
154



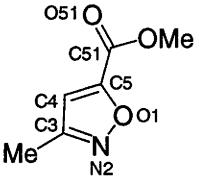
161



12f



12d



13d

Ar = 2,4,6-Me_3Ph

Compound	O1-N2/ O1'-N2'	C5-O1/ C5'-O1'	C4-C5/ C4'-C5'	C4-C41/ C4'-C41'	C41-O41/ C41'-O41'	C5-C51	C51-O51
148	1.420(2)/ 1.410(2)	1.350(2)/ 1.351(2)	1.360(3)/ 1.357(2)	1.472(2)/ 1.474(3)	1.199(2)/ 1.189(2)	-	-
154	1.418(2)/ 1.415(2)	1.344(2)/ 1.348(2)	1.363(2)/ 1.355(2)	1.472(2)/ 1.474(2)	1.199(2)/ 1.202(2)	-	-
161	1.415(2)/ 1.414(2)	1.352(2)/ 1.350(2)	1.358(2)/ 1.359(3)	1.463(3)/ 1.468(3)	1.208(2)/ 1.203(2)	-	-
12f	1.429(4)	1.314(4)	1.347(4)	1.455(4)	1.197(4)	-	-
12d	1.427(2)	1.331(2)	1.345(2)	1.459(2)	1.211(2)	-	-
13d	1.416(2)	1.349(2)	1.347(2)	-	-	1.479(2)	1.203(2)

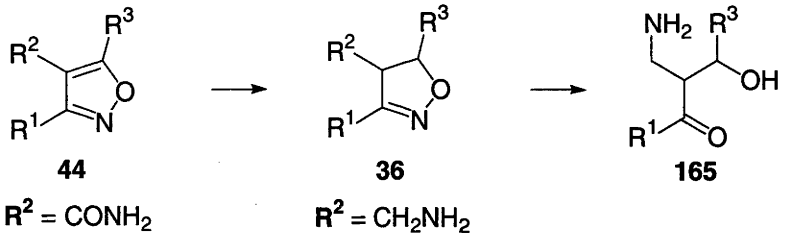
Table 27. Torsion angles (degrees) from the X-ray crystallographic data of diisoxazoles **148**, **154** and **161**, and monomeric isoxazoles **12d** and **12f**

Compound	O41-C41-C4-C5	O41'-C41'-C4'-C5'
148	-15.4(3)	162.3(2)
154	5.7(2)	-33.5(2)
161	153.3(2)	170.9(2)
12f	-176.3(4)	-
12d	-178.2(2)	-

Non-coplanarity of the C4-C5 and O41-C41 bonds is likely to be a consequence of intramolecular steric and electronic repulsion between the methoxycarbonyl groups of the diisoxazoles **148**, **154** and **161**, as is apparent from the ORTEP diagrams (Figures 15-17). Although the results indicate that directly attached diisoxazoles are unsuitable as synthons for polyols, it may be that polyisoxazoles linked by alkyl chains might be viable alternatives for the synthesis of polyols since intramolecular interactions between the acyl groups would be minimized. However, this work was not pursued further. Instead other aspects of the scope of reductions of 4-carbonyl-substituted isoxazoles were investigated.

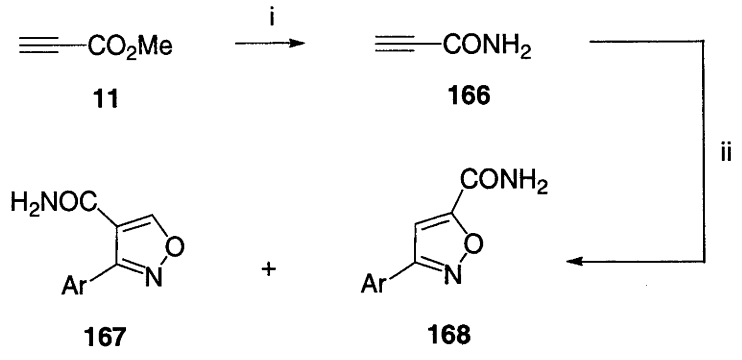
3.7. Reductions of Amidoisoxazoles

The acrylate behaviour of 4-methoxycarbonylisoxazoles had been demonstrated through borohydride reductions. The substituent effect of an amido group was next examined since reactions of amidoisoxazoles with borohydride offered a potential route to γ-amino carbonyl compounds **165** (Scheme 51)[121] and related species.



Scheme 51

The amidoisoxazoles used in this work were conveniently accessed from nitrile oxide cycloadditions of amido-substituted dipolarophiles, which were prepared from the available alkynoates. Initial efforts focussed on synthesis of the 4- and 5-amidoisoxazoles **167** and **168**. For reasons discussed above in relation to the synthesis of the methoxycarbonylisoxazoles **12f** and **13f** (see Chapter 2, Section 2.1.), mesitonitrile oxide **5** was chosen as the dipole because it is unreactive towards dimerization. The dipolarophile, propiolamide **166** was prepared through amidation of methyl propiolate **11** with liquid ammonia. All physical and spectroscopic data of dipolarophile **166** are in agreement with literature values.[122] Subsequent cycloaddition of **166** with mesitonitrile oxide **5** afforded the regioisomeric isoxazoles **167** and **168** (Scheme 52).



Ar = 2,4,6-Me_3Ph

Reagents and conditions: i. **11**, liquid NH_3, -78 °C, 24 h; ii. **166** (1.0 equiv.), **5** (1.0 equiv.), THF, reflux, 3 days.

Scheme 52

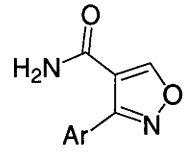
The 4- and 5-amidoisoxazoles **167** and **168** were separated by chromatography and their structures were established as follows. Using the EI method, accurate mass analysis of the molecular ion of each adduct at *m/z* 230 indicated the structural composition of $C_{13}H_{14}N_2O_2$. The regioisomers **167** and **168** were distinguished based on the chemical shifts of the isoxazole protons. For the 4-amidoisoxazole **167**, the signal of the C5 isoxazole proton was observed as a singlet at δ 9.16 ppm whilst that of the C4 isoxazole proton of the 5-substituted regioisomer **168** was seen at δ 6.91 ppm as a singlet. Signals of the labile amide protons were discerned as broad singlets, at δ 5.28 ppm and δ 5.44 ppm for **167**, and at δ 5.27 ppm and δ 6.55 ppm for **168**. In the infrared spectra, intense absorption bands at 1662 cm^{-1} and 1672 cm^{-1} were assigned to the amide carbonyl stretching vibrations for **167** and **168**, respectively. The energy of the carbonyl stretching vibration for the 4-amidoisoxazole **167** is lower than that of the 5-substituted isomer **168**. Conjugation of the carbonyl group to the isoxazole ring is therefore implied in the 4-amidoisoxazole **167**. The amidoisoxazoles **167** and **168** were recrystallized from a mixture of hexanes and acetone at 18 °C. Their X-ray crystallographic structures were subsequently recorded, and the ORTEP diagrams are shown in Figures 18-21. There is only one conformer of the 4-amidoisoxazole **167** in the

unit cell and the orientation of between the C4-C5 and C41-O41 bonds is *cis*. Due to the effects of intermolecular interactions, three distinct molecules of the 5-amidoisoxazole **168** occupy the unit cell. These are all in the *cis* conformation, possibly to minimize electrostatic repulsion between the ring oxygen and the carbonyl oxygen.

The regioisomeric isoxazoles **167** and **168** were obtained in a ratio of 1:2, with a combined yield of 96%. The regiochemistry of the cycloaddition is controlled by steric effects, which favour formation of the 5-amidoisoxazole **168** *via* bonding between the dipole oxygen and the most substituted olefinic carbon of the dipolarophile **166**. These dominate polar effects which favour formation of the 4-amidoisoxazole **167**, where the electropositive carbon *beta* to the dipolarophile amido group becomes bonded to the electronegative oxygen of the dipole **5**.

Using the procedure developed for the reduction of 4-alkoxycarbonylisoxazoles, the 4-amidoisoxazole **167** was treated with excess sodium borohydride. However, the amide **167** was resistant to reduction in refluxing ethanol for 24 hours. This may be attributed to the amido group being less electron-withdrawing than the alkoxycarbonyl group, thereby rendering C5 of **167** less electropositive than that of **12f**.

In attempts to effect reduction of **167**, more reactive reducing reagents were used. Lithium aluminium hydride was considered, as it reduces activated olefins in a 1,4-sense[92] as well as amide groups. However treatment of **167** with lithium aluminium hydride in refluxing THF for 24 hours gave rise only to a complex mixture, possibly due to cleavage of the isoxazole ring.[43]



167

Ar = 2,4,6-Me_3Ph

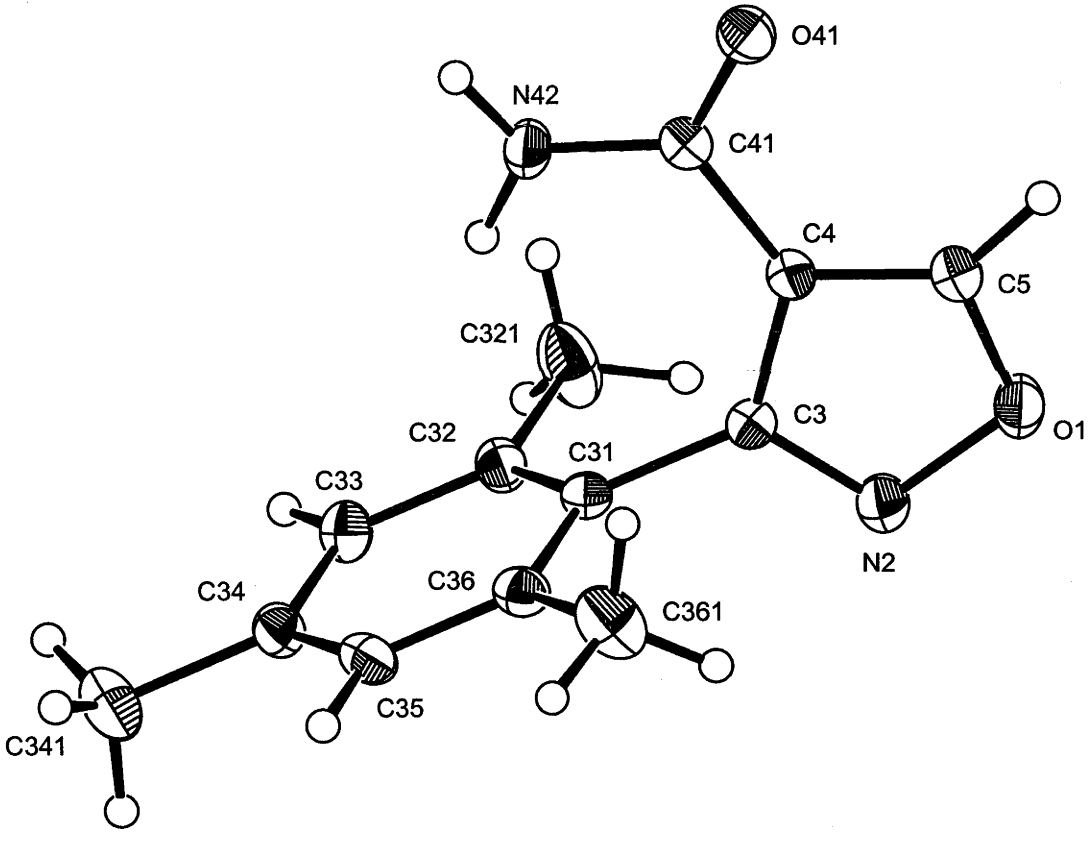
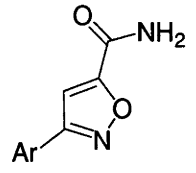


Figure 18. ORTEP derived from single crystal X-ray analysis of compound **167**.



168

Ar = 2,4,6-Me_3Ph

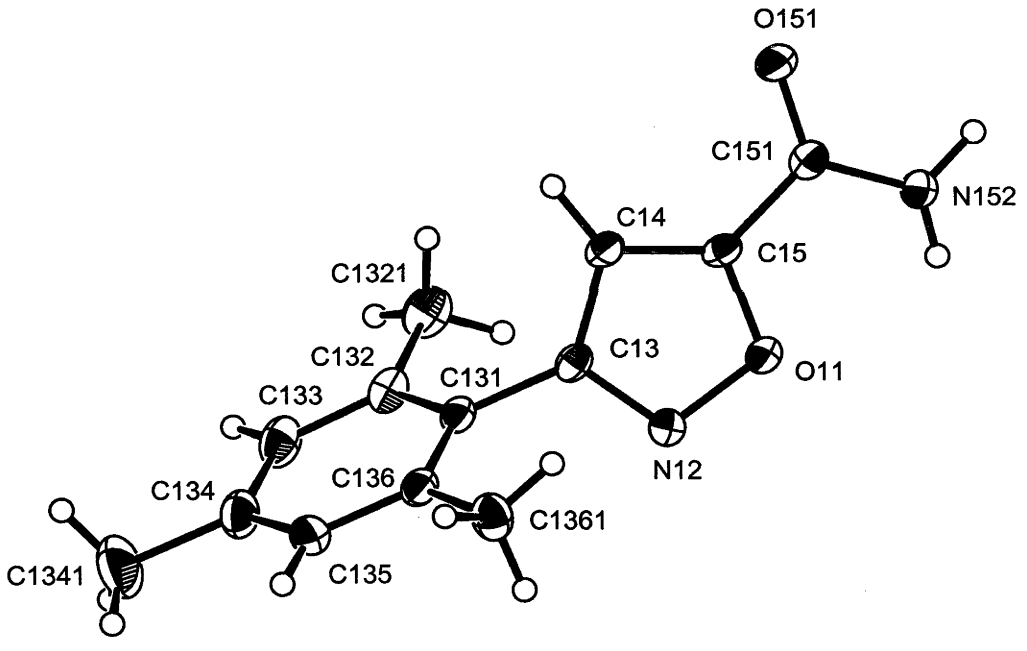
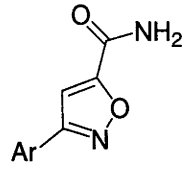


Figure 19. ORTEP derived from single crystal X-ray analysis of compound **168**, conformer 1.



168

Ar = 2,4,6-Me_3Ph

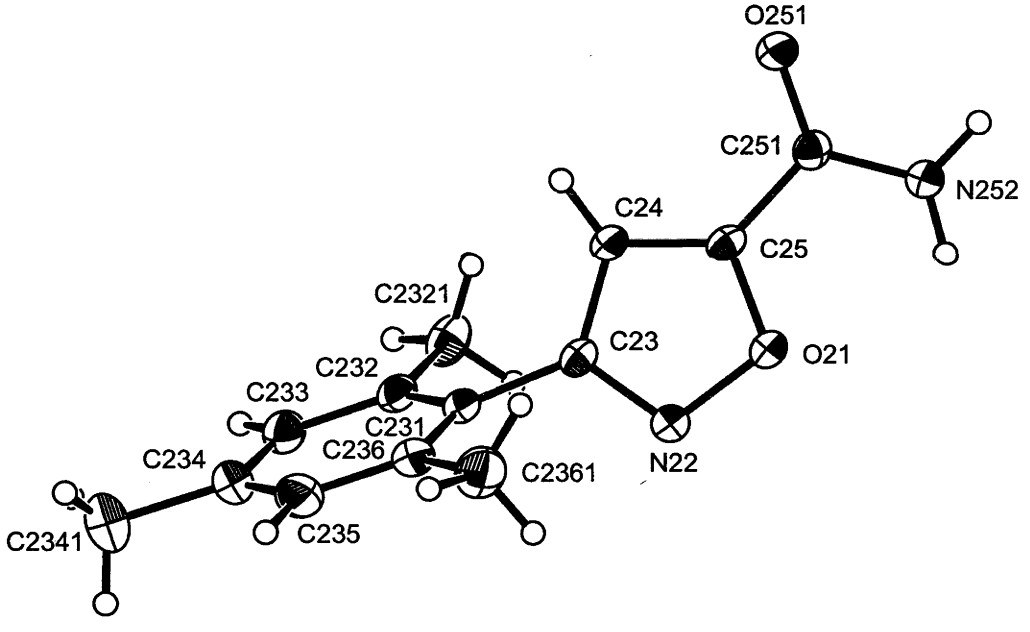
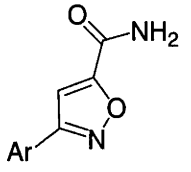


Figure 20. ORTEP derived from single crystal X-ray analysis of compound **168**, conformer 2.



168

Ar = 2,4,6-Me_3Ph

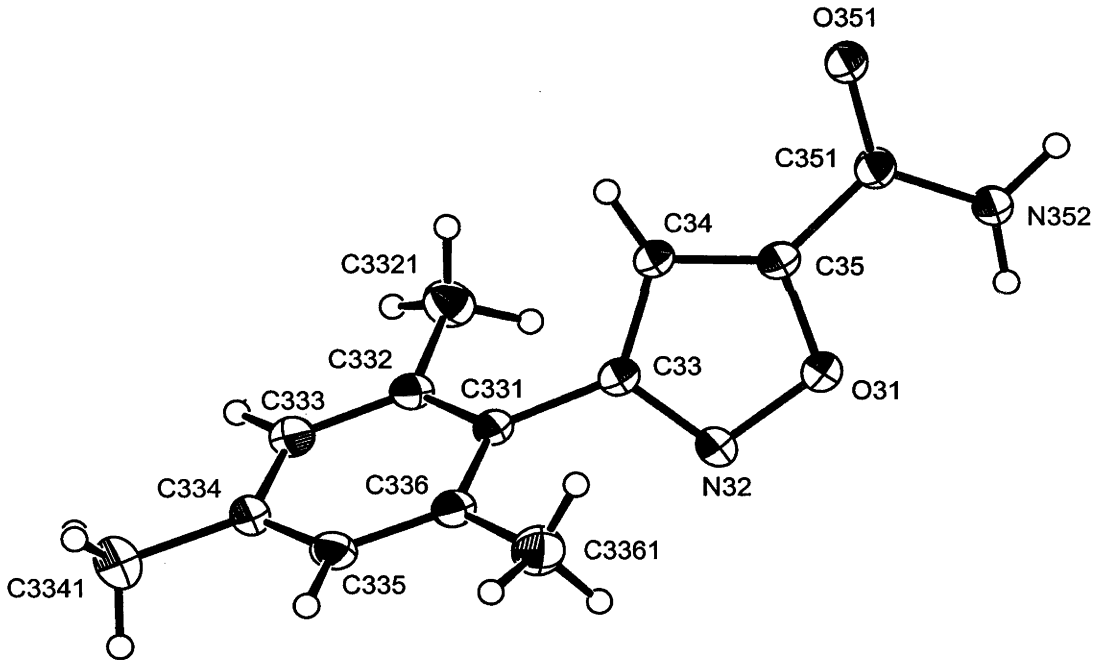
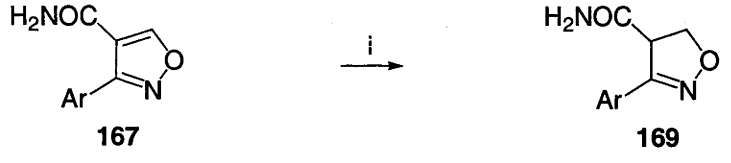


Figure 21. ORTEP derived from single crystal X-ray analysis of compound **168**, conformer 3.

4-Amidoisoxazole **167** was also treated with sodium borohydride in combination with bismuth(III) chloride as the reagent was recently reported for reductions of acrylamides.[123] Disappointing, only starting material **167** was recovered using a 15-fold excess of sodium borohydride and bismuth(III) chloride (0.1 equivalent) in refluxing ethanol for 48 hours.

Success was eventually realized with sodium trifluoroacetoxyborohydride, which is normally used in reductions of amides.[124] The borohydride was prepared *in situ* by reaction of trifluoroacetic acid and sodium borohydride. The 4-amido-2-isoxazoline **169** was furnished in 92% yield (Scheme 53).



167 **169**

Ar = 2,4,6-Me_3Ph

Reagents and conditions: **167** (1.0 equiv.), $NaBH_4$ (15.0 equiv.), CF_3CO_2H (15.0 equiv.), THF, 18 °C, 30 h.

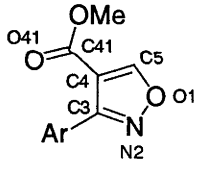
Scheme 53

The structure of the 4-amido-2-isoxazoline **169** was deduced using EI mass spectrometry and ^1H NMR spectroscopy. Accurate mass measurement of the molecular ion at *m/z* 232 was used to determine the molecular composition of $C_{13}H_{16}N_2O_2$. In the ^1H NMR spectrum, the C4 isoxazoline proton signal was seen as a doublet of doublets at δ 4.25 ppm (J = 10.8, 8.2 Hz). Signals of the C5 isoxazoline protons were observed further downfield as two multiplets, integrating for one proton each, at δ 4.64 ppm and δ 5.01 ppm. The amide protons resonated as two broad singlets, integrating for one proton each, at δ 5.10 ppm and δ 5.29 ppm. In the infrared spectrum, an intense absorption band at 1677 cm^{-1} was assigned to the amide carbonyl stretching vibration.

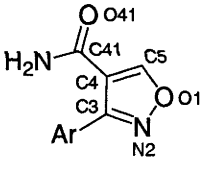
Acrylamide reactivity of 4-amidoisoxazole **167** had therefore been demonstrated through the sodium trifluoroacetoxyborohydride reduction. The effect of the location of the amido group on the isoxazole ring was also examined through the treatment of **168** with sodium trifluoroacetoxyborohydride. No reaction was observed, thereby indicating that like 5-alkoxycarbonylisoxazoles, 5-amidoisoxazoles do not behave as Michael acceptors.

As shown in the previous chapter, the contrasting reactivities of 4- and 5-methoxycarbonylisoxazoles are reflected in their bond lengths. The contrasting reactivities of the isomeric amidoisoxazoles **167** and **168** were therefore considered in relation to their X-ray crystallographic data (Table 28).

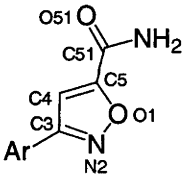
Table 28. Selected bond lengths (Å) from the X-ray crystallographic data of amidoisoxazoles **167** and **168**, and 4-methoxycarbonylisoxazole **12f**



12f



167



168

Ar = 2,4,6-Me_3Ph

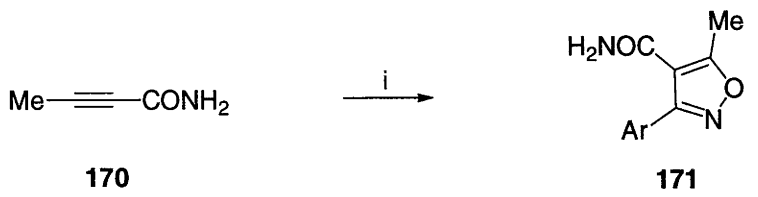
Compound	O1-N2	C5-O1	C4-C5	C4-C41	C41-O41	C5-C51	C51-O51
167	1.428(3)	1.339(3)	1.342(4)	1.481(4)	1.229(3)	-	-
168	1.409(2)	1.354(2)	1.337(3)	-	-	1.469(3)	1.231(3)
	1.422(2)	1.354(3)	1.335(3)	-	-	1.474(3)	1.239(3)
	1.408(2)	1.355(3)	1.337(3)	-	-	1.475(4)	1.238(3)
12f	1.429(4)	1.314(4)	1.347(4)	1.455(4)	1.197(4)	-	-

Differences between the 4- and 5-amidoisoxazoles **167** and **168** for the C4-C5, C4-C41/C5-C51 and C41-O41/C51-O51 bonds are either very small or insignificant, and this may be attributed to the large standard errors associated with these bonds. For the O1-N2 and C5-O1 bonds where their standard errors are smaller, the data indicate that the O1-N2 bond of **167** is significantly longer than those of two of the three conformers of **168**. Significant shortening in the C5-O1 bond of **167** relative to those of the conformers of **168** is also observed. This trend is associated with the Michael acceptor-like structure of 4-acylisoxazoles, as indicated by X-ray crystallographic and theoretical bond lengths of other carbonyl-substituted isoxazoles.

The reduced Michael acceptor-type reactivity of the 4-amidoisoxazole **167** relative to that of the 4-methoxycarbonylisoxazole **12f** is also indicated from the X-ray crystallographic data (Table 28). The C5-O1 and C4-C41 bonds of **167** are significantly longer than those of **12f**, implying that the 4-amidoisoxazole **167** is less conjugated than the 4-alkoxycarbonylisoxazole **12f**. This is a consequence of the reduced polarization of the amido group relative to that of the alkoxycarbonyl group.

3.7.1. Diastereoselective Reductions of 4-Amidoisoxazoles

Having established that amidoisoxazoles could be reduced to 2-isoxazolines, the diastereoselectivity of reduction was examined with 5-substituted-4-amidoisoxazoles **171** and **174**. Isoxazoles **171** and **174** were synthesized through cycloaddition of mesitonitrile oxide **5** with tetrolamide **170** and 3-phenylpropynamide **173**, respectively (Schemes 54 and 55). Mesitonitrile oxide **5** was the dipole of choice because it is inert towards dimerization and hence the efficiency of the nitrile oxide cycloaddition is maximized. Dipolarophile **170** was obtained commercially whilst **173**[125] was prepared through amidation of ethyl phenylpropynoate **172** (Scheme 55).

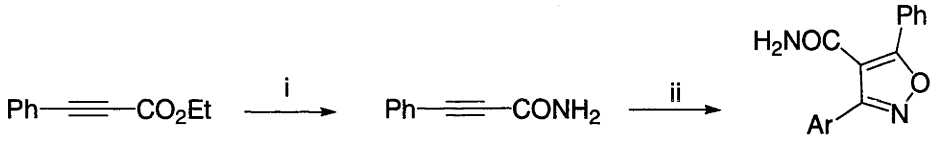


170 **171**

Ar = 2,4,6-Me_3Ph

Reagents and conditions: i. **170** (1.0 equiv.), **5** (1.0 equiv.), THF, reflux, 6 days.

Scheme 54



172 **173** **174**

Ar = 2,4,6-Me_3Ph

Reagents and conditions: i. **172**, liquid NH_3, -78 °C, 24 h; ii. **173** (1.0 equiv.), **5** (1.0 equiv.), THF, reflux, 6 days.

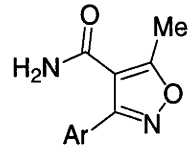
Scheme 55

The structure of the 4-amidoisoxazole **171** was assigned as follows. Accurate mass measurement of the molecular ion at *m/z* 244 using the EI method determined the structural composition of $C_{14}H_{16}N_2O_2$. In the ^1H NMR spectrum, a three proton singlet at δ 2.83 ppm was assigned to the methyl group at C5. The signals of the amide protons were seen as broad singlets, integrating for one proton each, at δ 5.02 ppm and δ 5.21 ppm. In the infrared spectrum, the amide carbonyl stretching vibration was observed at 1683 cm^{-1}, whilst the broad absorption band at 3439 cm^{-1} was ascribed to the N-H stretching vibration. Crystals of **171** were obtained from a mixture of hexanes and acetone at 18 °C. The X-ray crystallographic structure of the material was recorded and the ORTEP diagram is shown in Figure 22.

The structure of the isoxazole **174** was determined by EI mass spectrometry and ^{1}H NMR spectroscopy. Structural composition of $C_{19}H_{18}N_2O_2$ was determined from accurate mass measurement of the molecular ion at *m/z* 306. In the ^{1}H NMR spectrum, two multiplets at δ 7.51-7.56 ppm and δ 8.10-8.14 ppm, integrating for three protons and two protons, were assigned to the phenyl group. Two broad singlets at δ 5.15 ppm and δ 5.35 ppm, each integrating for one proton, were assigned to the labile N-H protons. In the infrared spectrum, the amide carbonyl stretching vibration was seen as an intense absorption band at 1677 cm^{-1}, whilst the N-H stretching vibrations were observed as a broadened band at 3304 cm^{-1}. Crystals were grown from a mixture of hexanes and acetone at 18 °C from which an X-ray crystallographic structure was recorded. The ORTEP diagram of the 4-amidoisoxazole **174** is shown in Figure 23.

The cycloadditions of mesitonitrile oxide **5** with dipolarophiles **170** and **173** were completely regioselective and the 4-amidoisoxazoles **171** and **174** were obtained in yields of 95% and 93%, with none of the isomeric 5-amidoisoxazoles being formed. The regioselectivity may be attributed to prevailing polar effects, whereby the electron-rich dipole oxygen becomes bonded to the electropositive *beta* carbon of each alkyne.

With **171** and **174** in hand, both were treated with sodium trifluoroacetoxyborohydride according to the procedure developed for the reduction of 4-amidoisoxazole **167**. Reduction proceeded smoothly to afford the 2-isoxazolines **175** and **176** in 90% and 92% yield, respectively (Scheme 56). Reduction of **174** proceeded at a slower rate than that observed for **171**, presumably due to the steric hindrance of the phenyl group at C5.



171

Ar = 2,4,6-Me_3Ph

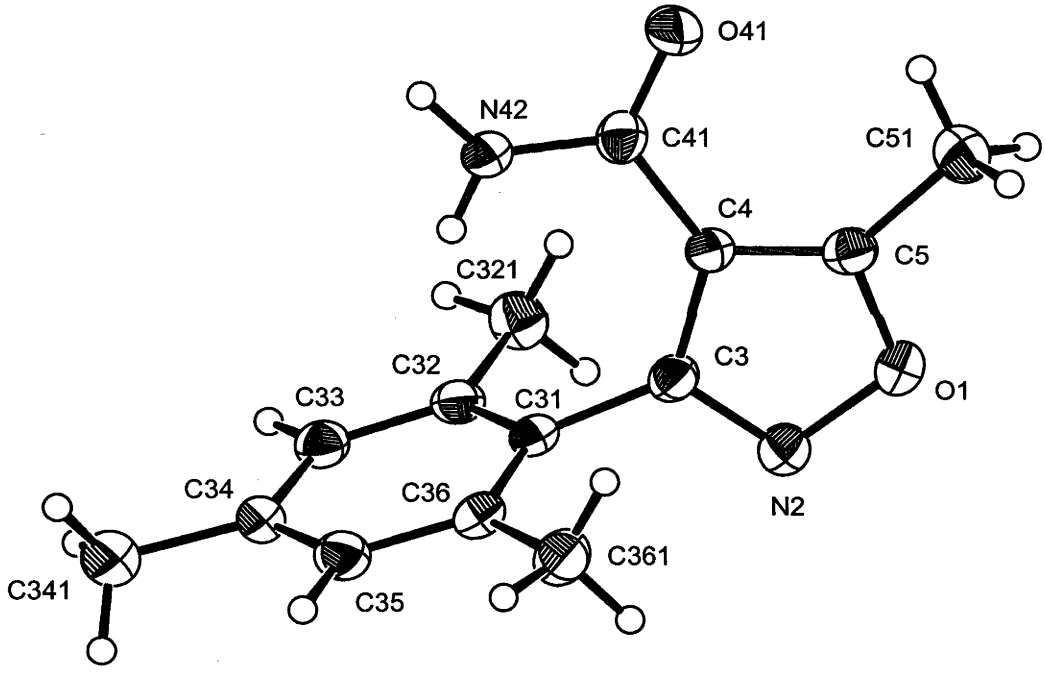
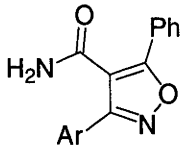


Figure 22. ORTEP derived from single crystal X-ray analysis of compound **171**.



174

Ar = 2,4,6-Me_3Ph

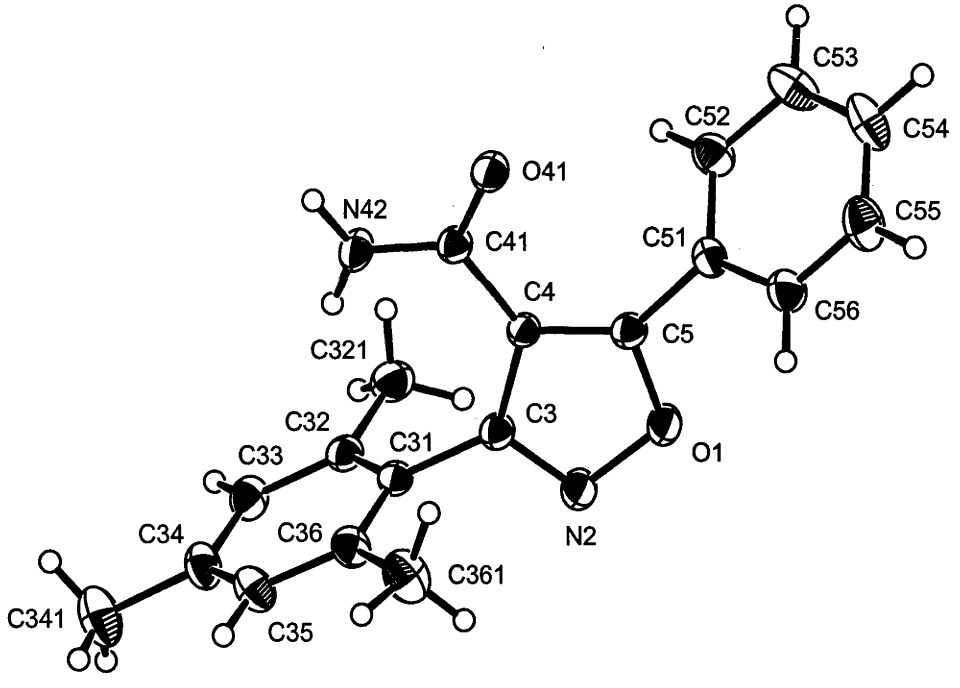
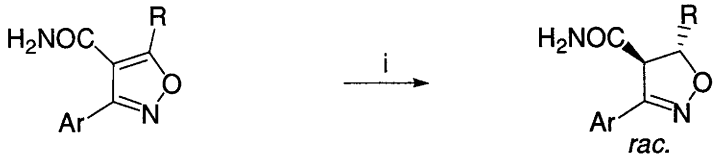


Figure 23. ORTEP derived from single crystal X-ray analysis of compound **174**.



171. R = Me
174. R = Ph

175. R = Me
176. R = Ph

Ar = 2,4,6-Me_3Ph

Reagents and conditions: for **175**: i. **171** (1.0 equiv.), $NaBH_4$ (15.0 equiv.), CF_3CO_2H (15.0 equiv.), THF, 18 °C, 5 days; for **176**: **174** (1.0 equiv.), $NaBH_4$ (15.0 equiv.), CF_3CO_2H (15.0 equiv.), THF, 18 °C, 8 days.

Scheme 56

Structural assignment of the 2-isoxazoline **175** was based on mass spectrometric and ^1H NMR spectroscopic data. Using the EI method, accurate mass measurement of the molecular ion at *m/z* 246 indicated the structural composition of $C_{14}H_{18}N_2O_2$. In the ^1H NMR spectrum, a doublet at δ 3.82 ppm (J = 8.0 Hz), integrating for one proton, was assigned to the C4 isoxazoline proton, whilst a doublet of quartets at δ 5.29 ppm (J = 8.0, 6.3 Hz), integrating for one proton, was ascribed to the C5 isoxazoline proton. Based on the magnitude of the vicinal coupling constant $J_{4,5}$ = 8.0 Hz which falls within the range for *trans*-coupling,[72] the relative configuration of the 2-isoxazoline **175** was deduced. A broad singlet, integrating for two protons at δ 5.06 ppm was assigned to the amide protons. In the infrared spectrum, the N-H and carbonyl stretching vibrations gave rise to intense absorption bands at 3326 cm^{-1} and 1678 cm^{-1}, respectively. The physical and spectroscopic data of the 2-isoxazoline **175** are in agreement with literature values.[126]

For the 2-isoxazoline **176**, its structure was assigned as follows. The molecular ion was detected at *m/z* 308 for which accurate mass measurment using the EI method indicated the structural composition of $C_{19}H_{20}N_2O_2$. In the ^1H NMR spectrum, the C4- and C5-isoxazoline proton signals were observed as doublets at δ 4.14 ppm (J = 8.2 Hz) and δ 6.27 ppm (J = 8.2 Hz), each integrating for one proton. The relative configuration of the 2-isoxazoline **176** was also assigned as *trans*, based on the

magnitude of the vicinal coupling constant $J_{4,5}$ = 8.2 Hz.[72] Signals of the amide protons were seen as two broad singlets at δ 4.98 ppm and δ 5.21 ppm, each integrating for one proton. In the infrared spectrum, the intense absorption band at 1650 cm^{-1} was assigned to the amide carbonyl stretching vibration, whilst the broad bands at 3434 cm^{-1} and 3180 cm^{-1} were ascribed to amide N-H stretching vibrations. The physical and spectroscopic data of the 2-isoxazoline **176** are in agreement with reported values.[126]

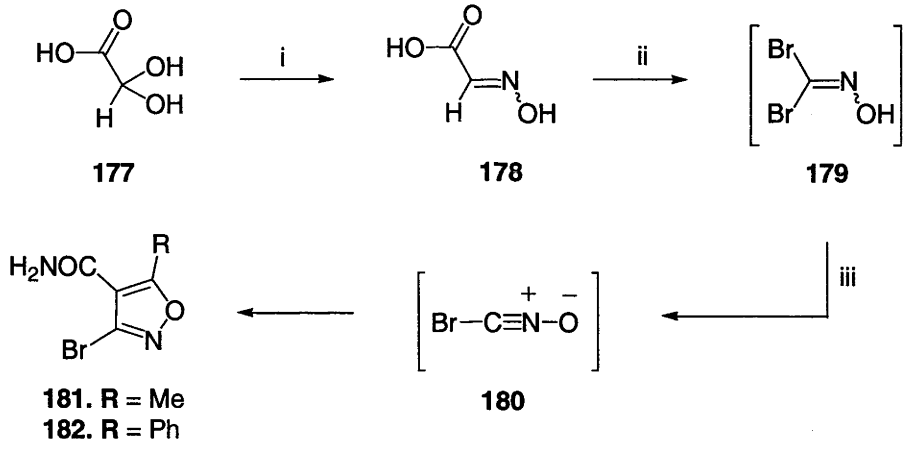
These reactions of 4-amidoisoxazoles with sodium trifluoroacetoxyborohydride show that reduction to 2-isoxazolines is possible, with control of relative stereochemistry at C4 and C5. This is a potentially useful method for stereoselective synthesis of trisubstituted 2-isoxazolines. Previously, the only method for diastereoselective synthesis of 2-isoxazolines had been *via* nitrile oxide cycloaddition where the relative configuration of the 2-isoxazolines at C4 and C5 was predetermined by the geometry of the 1,2-disubstituted alkenes used as dipolarophiles.

3.7.2. Effect of the C3-Substituent on Reductions of 4-Amidoisoxazoles

The reactions of 4-amidoisoxazoles with sodium trifluoroacetoxyborohydride examined in the preceeding sections all involved the mesityl group as the C3-substituent. However, the mesityl group is of limited use for synthetic applications. Consequently, the synthesis of 4-amidoisoxazoles with a labile C3-substituent was investigated, anticipating that a C3-substituent which could be manipulated would greatly increase the synthetic potential of this methodology. A survey of the literature indicated that only a few leaving groups are compatible with the isoxazole ring; these include the nitro,[127] sulphonyl[128] and halo groups.[129] Of these, the halo group is the most synthetically versatile as it enables nucleophilic substitution as well as metallation, which could potentially faciliate alkylation, acylation and arylation.

3-Bromo-4-amidoisoxazoles **181** and **182** were therefore identified as targets for study. Bromine was chosen as the halo-substituent since the methodology for nitrile

oxide cycloadditions of bromonitrile oxide **180** is well established. Compared to chloronitrile oxide, the bromo-substituted dipole **180** is less affected by dimerization and hence gives comparatively higher yields of the 3-halo-substituted cycloadducts.[130] Synthesis of **181** and **182** commenced with preparation of bromonitrile oxide **180**. Condensation of glyoxylic acid monohydrate **177** with hydroxylamine hydrochloride gave rise to the oxime **178**[131] which was brominated with *N*-bromosuccinimide (NBS) to give dibromoformoxime **179**.[131] The hydroximinoyl bromide **179** was not isolated, and was dehydrohalogenated with potassium hydrogencarbonate to afford the bromonitrile oxide **180** *in situ*. Reaction of the dipole **180** with the dipolarophiles **170** and **173** gave rise to the cycloadducts **181** and **182**, both in yields of 67% (Scheme 57).



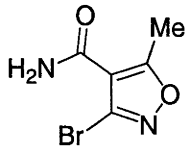
Reagents and conditions: i. **177** (1.0 equiv.), $NH_2OH.HCl$ (1.0 equiv.), $NaHCO_3$ (1.0 equiv.), H_2O, 18 °C, 24 h; ii. **178** (1.0 equiv.), NBS (2.0 equiv.), DME-H_2O, 18 °C, 40 min; iii. for **181**: **179** (1.0 equiv.), **170** (10.0 equiv.), $KHCO_3$ (2.0 equiv.), DME-H_2O, 18 °C, 12 days; for **182**: **179** (1.0 equiv.), **173** (10.0 equiv.), $KHCO_3$ (2.0 equiv.), DME-H_2O, 18 °C, 12 days.

Scheme 57

All physical and spectroscopic data obtained for the 5-methylisoxazole **181** are in full accord with the assigned structure. Using the EI method, the molecular ions were detected at *m/z* 204 and *m/z* 206 for which accurate mass measurement of these indicated

the structural composition of $C_5H_5BrN_2O_2$. In the ^1H NMR spectrum, a three proton singlet at δ 2.76 ppm was assigned to the methyl group. Two broad singlets at δ 6.39 ppm and δ 6.48 ppm, integrating for one proton each, were ascribed to the amide protons. In the infrared spectrum, intense broad absorption bands at 3421 cm^{-1} and 3208 cm^{-1} were assigned to the N-H stretching vibrations. The amide carbonyl stretching vibration was observed as an intense absorption band at 1667 cm^{-1}. 4-Amidoisoxazole **181** was recrystallized from a mixture of hexanes and acetone at 18 °C and the X-ray crystallographic structure was recorded. The unit cell is occupied by four distinct molecules, comprising two *trans*- and two *cis*-conformers. The ORTEP diagrams of the conformers of **181** are shown in Figures 24-27.

The structure of the 5-phenylisoxazole **182** was assigned as follows. Molecular ions at *m/z* 266 and *m/z* 268 were detected using the EI method. Accurate mass measurement of *m/z* 266 indicated the structural composition of $C_{10}H_7BrN_2O_2$. In the ^1H NMR spectrum, signals of the phenyl protons were seen as two multiplets at δ 7.48-7.60 ppm and δ 7.87-7.90 ppm, integrating for three and two protons, respectively. The amide protons resonated as broad singlets, integrating for one proton each, at δ 5.80 ppm and δ 6.00 ppm. In the infrared spectrum, an intense absorption band at 1649 cm^{-1} was assigned to the amide carbonyl stretching vibration. Two broad absorption bands at 3367 and 3175 cm^{-1} were ascribed to the N-H stretching vibrations. Recrystallization of the material was effected from a mixture of hexanes and acetone at 18 °C. The X-ray crystallographic structure was recorded and the ORTEP diagram is shown in Figure 28. There is only one conformer of **182** in the unit cell and it is of *cis*-conformation.



181

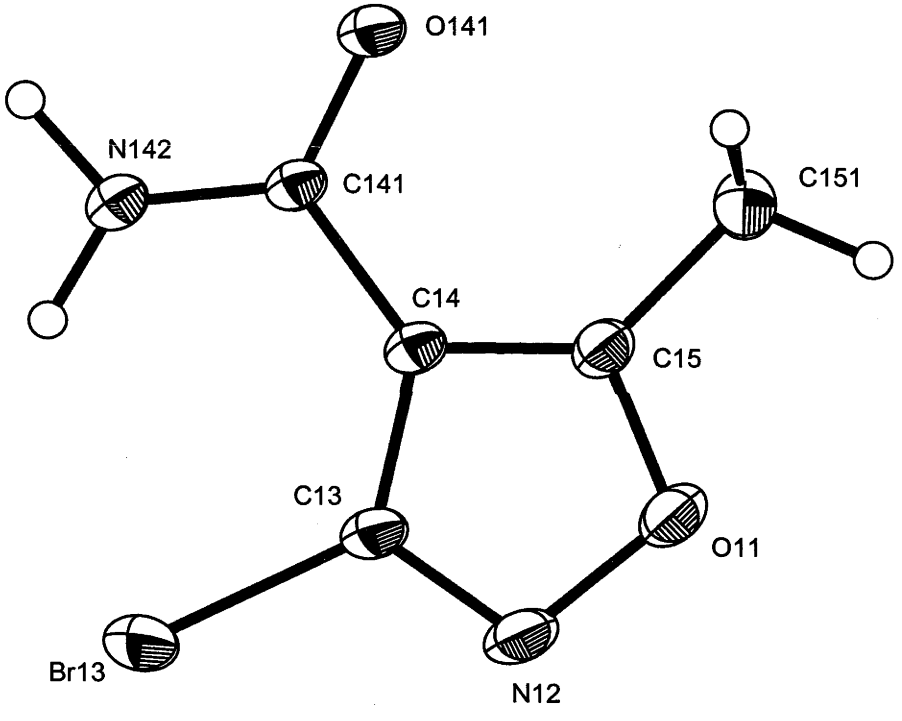
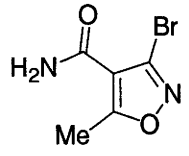


Figure 24. ORTEP derived from single crystal X-ray analysis of compound **181**, conformer 1.



181

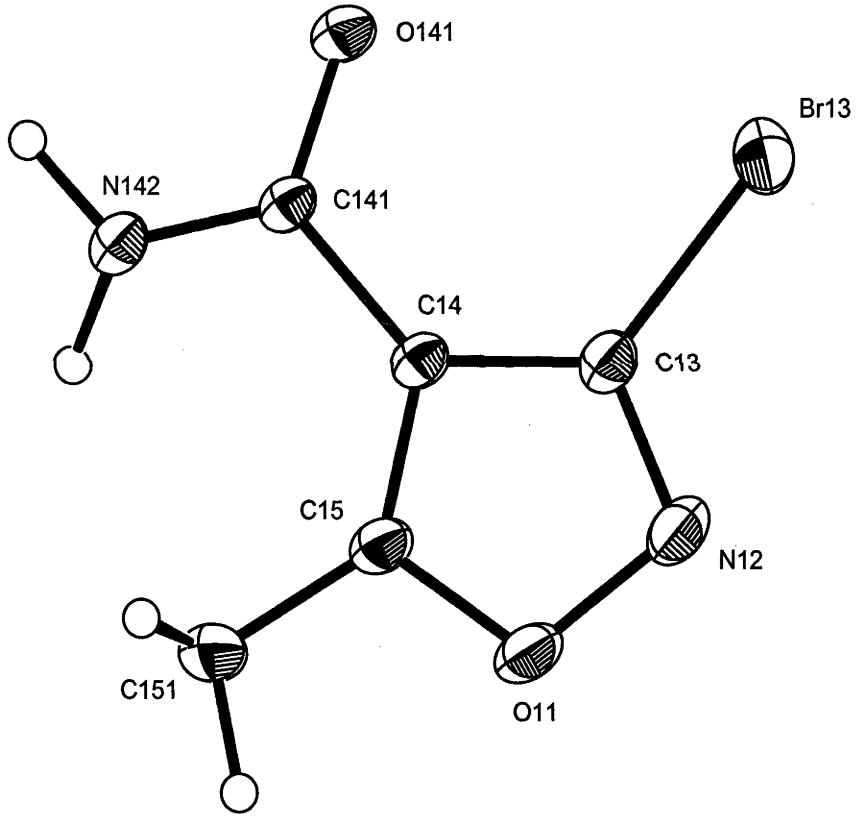
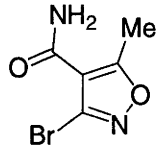


Figure 25. ORTEP derived from single crystal X-ray analysis of compound **181**, conformer 2.



181

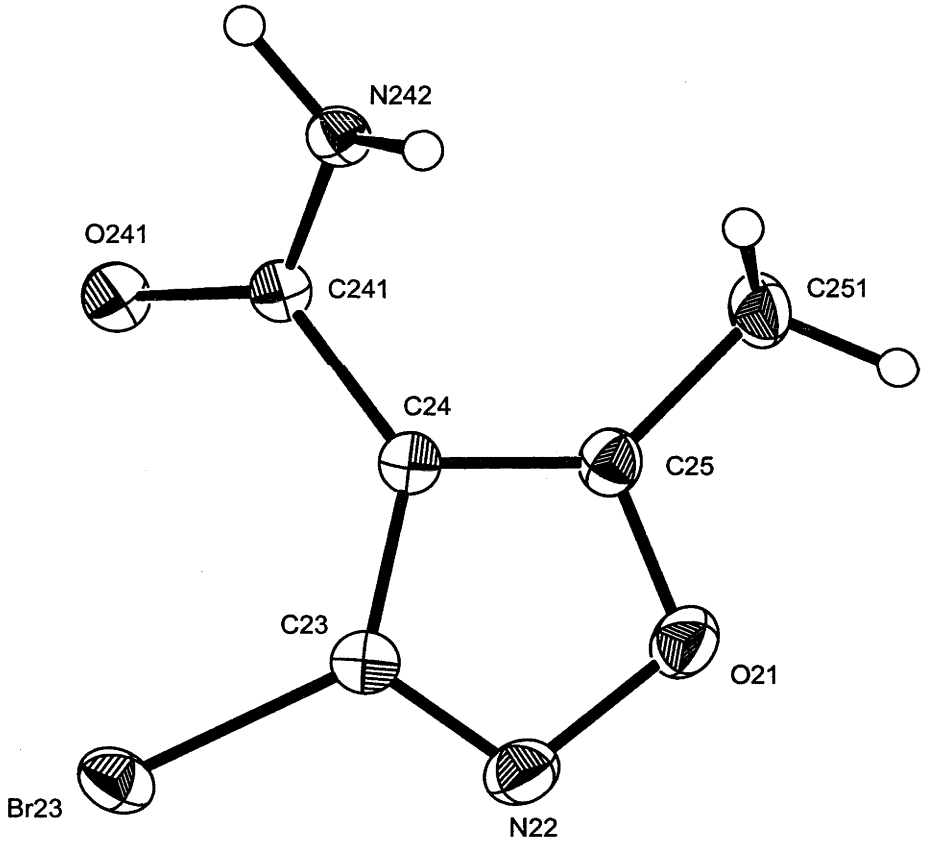


Figure 26. ORTEP derived from single crystal X-ray analysis of compound **181**, conformer 3.

181

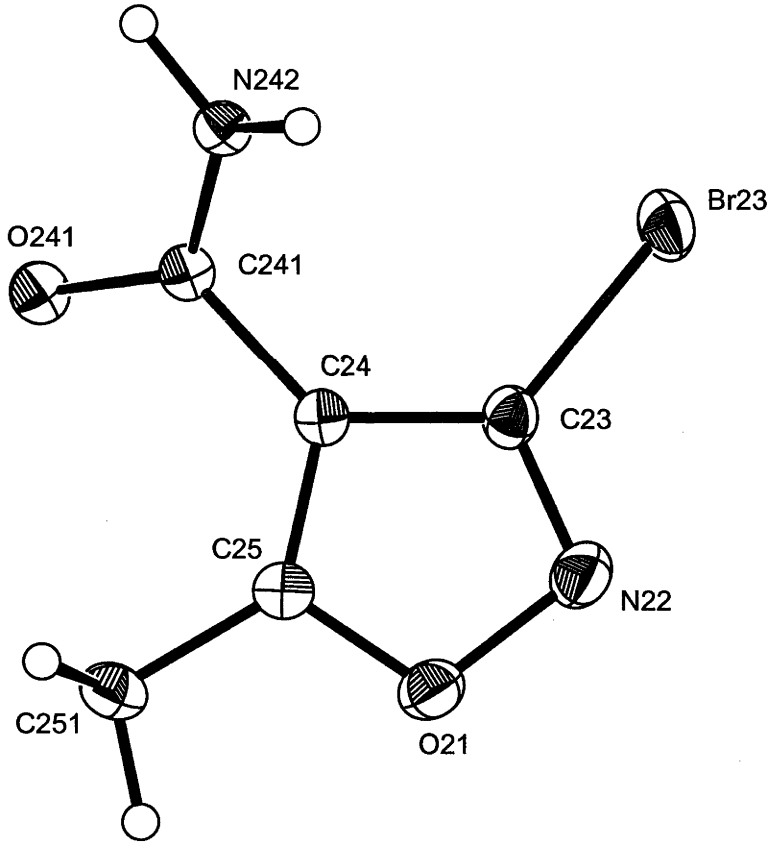
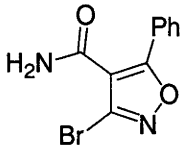


Figure 27. ORTEP derived from single crystal X-ray analysis of compound **181**, conformer 4 .



182

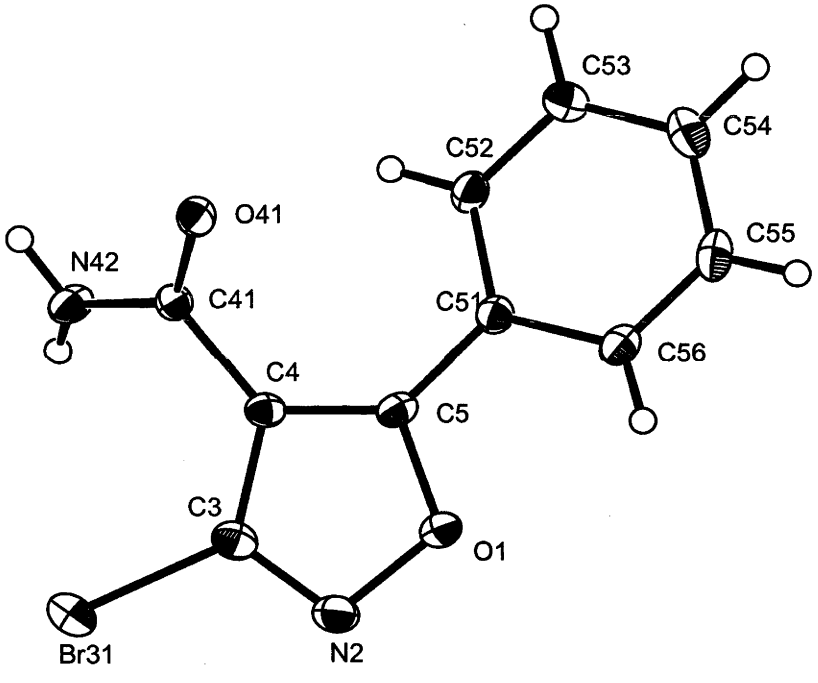
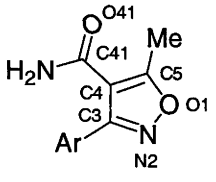


Figure 28. ORTEP derived from single crystal X-ray analysis of compound **182**.

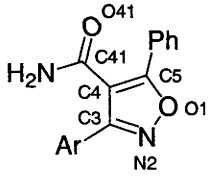
The cycloadditions of bromonitrile oxide **180** and the alkynes **170** and **173** were completely regioselective, and the 4-amidoisoxazoles **181** and **182** were obtained exclusively (Scheme 57). The observed regioselectivity is consistent with dominant polar effects which were also observed for analogous cycloadditions of mesitonitrile oxide **5** with **170** and **173** (discussed above).

In contrast to the 3-mesitylisoxazoles **171** and **174**, the 3-bromo-substituted analogues **181** and **182** did not react with sodium trifluoroacetoxyborohydride at 18 °C. When heated at reflux for 24 hours, they gave rise to complex mixtures from which isolation of any discrete species was impractical. To rationalize this, the X-ray crystallographic data of **181** and **182** were examined against those of **171** and **174**. Selected bond lengths of **171**, **174**, **181** and **182** are listed below (Table 29).

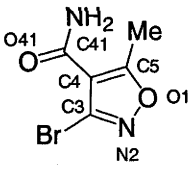
Table 29. Selected bond lengths (Å) from the X-ray crystallographic data of isoxazoles **171**, **174**, **181** and **182**



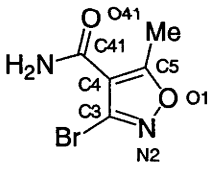
171



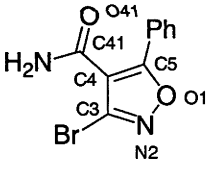
174



181a



181b



182

Ar = 2,4,6-Me_3Ph

Compound	O1-N2	C5-O1	C4-C5	C4-C41	C41-O41
171	1.419(4)	1.353(4)	1.343(5)	1.471(5)	1.235(5)
174	1.416(2)	1.351(2)	1.358(3)	1.482(3)	1.229(2)
181a	1.410(6)	1.337(7)	1.340(8)	1.480(6)	1.268(4)
	1.410(5)	1.337(7)	1.340(8)	1.480(6)	1.268(4)
181b	1.410(6)	1.337(7)	1.340(8)	1.480(6)	1.268(4)
	1.410(6)	1.337(7)	1.340(8)	1.480(6)	1.268(4)
182	1.418(3)	1.357(3)	1.368(4)	1.488(4)	1.240(4)

Due to the large standard errors, the differences in the bond lengths between **171** **174**, **181a,b**, and **182** are either very small or statistically insignificant. In an attempt to understand the lack of acrylamide reactivity observed for the 3-bromoisoxazoles **181** and **182**, the O41-C41-C4-C5 torsion angles of the isoxazoles **171**, **174**, **181a,b** and **182** were therefore examined (Table 30).

Table 30. Torsion angles (degrees) from the X-ray crystallographic data of 4-amidoisoxazoles **171**, **174**, **181** and **182**

Compound	O41-C41-C4-C5
171	2.0(6)
174	-9.6(3)
181a	-173.0(2) 145.5(7)
181b	-8.6(8) -35.0(2)
182	-41.8(5)

For the 3-mesityl-substituted isoxazoles **171** and **174** which reduce to 2-isoxazolines, their carbonyl groups and C4-C5 bonds are coplanar and hence conjugated, as indicated by their O41-C41-C4-C5 torsion angles which measured less than 10 degrees from the plane of coplanarity. By contrast, the torsion angles of two of the conformers of 3-bromoisoxazole **181** deviate from coplanarity by *ca.* 35 degrees, whilst the torsion angles of the other two conformers of **181** are only distorted by less than 10 degrees. For the 5-phenyl-substituted 3-bromoisoxazole **182**, the torsion angle is even larger than those of the conformers of **181**. The data indicate that conjugation of the carbonyl group and the C4-C5 bond is markedly reduced in the 3-bromoisoxazoles **181** and **182** relative to that of the 3-mesitylisoxazoles **171** and **174**, which may account for the resistance of **181** and **182** to reduction of the isoxazole rings. At this stage, there

is no clear explanation for the disrupted conjugation in 3-bromoisoxazoles **181** and **182**, although it is likely to be due to the electronic effects of the C3-bromo group.

The results indicate that 3-halo-4-amidoisoxazoles are not synthetically useful as they lack acrylamide reactivity. This problem might be overcome by use of ether groups as substituents at C3. Like the mesityl and alkyl groups, ethers are also electron-rich and are thus expected to be more compatible with reduction of the isoxazole ring than the electron-withdrawing halo groups.

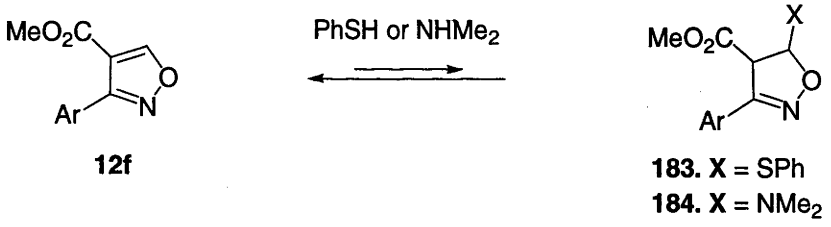
In summary, the work described in this chapter demonstrates the predicted Michael acceptor behaviour of 4-acylisoxazoles through reactions with borohydride reagents. This reaction provides an alternative route to the conventional nitrile oxide cycloaddition for synthesis of *trans*-2-isoxazolines with control of relative stereochemistry at the C4 and C5 centres. This may be useful in cases where the *trans*-dipolarophile is not readily accessible and hence the corresponding *trans*-2-isoxazoline could not be easily accessed from the nitrile oxide cycloaddition strategy.

CHAPTER 4

ALKYLATION OF 4-ACYLISOXAZOLES

4.1. Attempted Additions of Heteronucleophiles to 4-Acylisoxazole 12f

In the previous chapter, the predicted acrylate behaviour of 4-acylisoxazoles was realized through reactions with hydride to give 2-isoxazolines, and was also implied in the reaction of isoxazole **12f** with sodium methoxide. As a logical continuation, Michael additions with other nucleophiles were explored. Initially, the use of heteronucleophiles was examined for 1,4-additions to 4-acylisoxazole **12f**. Heteroanions such as amines and thiols are strongly nucleophilic. Reaction conditions from the literature were followed, however conjugate adducts **183** and **184** were not detected from treatment of **12f** with thiophenol[132] and dimethylamine.[133] As both amino- and thiyl-substituents are good leaving groups, the conjugate adducts **183** and **184** possibly convert back to the isoxazole **12f** through facile elimination of dimethylamine and thiophenol (Scheme 58). This is not unexpected since elimination of labile leaving groups from 2-isoxazolines is one of the methods for synthesis of isoxazoles (see Chapter 1, Section 1.1.6.).



12f

183. X = SPh
184. X = NMe_2

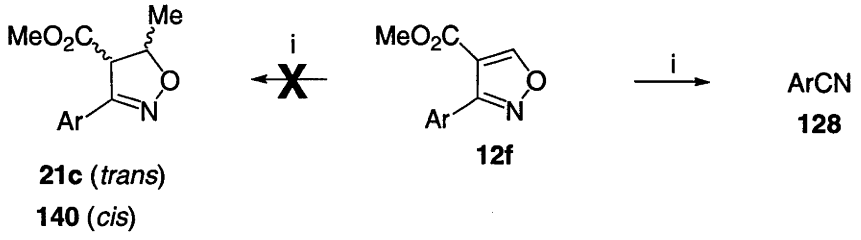
Ar = 2,4,6-Me_3Ph

Scheme 58

4.2. Attempted Alkylations of 4-Alkoxycarbonylisoxazoles

In an attempt to avoid this putative elimination, the use of carbon-centred nucleophiles was investigated. This is of particular interest as, currently, there is no satisfactory method in the literature for carbon-carbon bond formation at the 5-position of 2-isoxazolines. Nucleophilic substitution is usually effected at C3,[134] and lithiation reactions only allow for alkylation at C3, C4 and the *alpha* carbon on side chains connected to these centres.[135] The only reported method for incorporating a substituent at C5 of a 2-isoxazoline ring is *via* nitrile oxide cycloaddition to a 1,2-disubstituted alkene.

One of the most common methods for alkylating enones and enoates is through the use of lithium cuprates. The use of Gilman's reagent[136] or lithium dimethylcopper as an alkylating agent was explored. Isoxazole **12f** was treated with lithium dimethylcopper, generated *in situ* by reaction of copper(I) iodide and two equivalents of methyllithium. However, this did not yield either of the conjugate adducts **21c** or **140** (Scheme 59). Instead the decomposition product mesitonitrile **128** was obtained. The mass spectrometric and ^{1}H NMR spectral data of **128** are identical in every respect to those previously reported.[107] Formation of the nitrile **128** probably involved an anionic cleavage mechanism (Chapter 3, Section 3.4.).



21c (*trans*)
140 (*cis*)

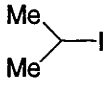
Ar = 2,4,6-Me_3Ph

Reagents and conditions: i. **12f** (1.0 equiv.), MeLi (2.0 equiv.), CuI (1.0 equiv.), Et_2O, -78 °C, 1 h.

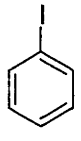
Scheme 59

Conjugate additions with the nitroethane anions were also attempted.[137] However, treatment of **12f** with nitroethane and two equivalents of triethylamine, and later, *n*-butyllithium did not give rise to reaction.

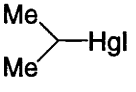
Unsuccessful in effecting alkylation of **12f** using Gilman's reagent and nitroethane anions, the use of free radical methodologies for carbon-carbon bond formation was investigated. Giese's organotin hydride method[138] was initially explored as it is particularly useful for alkylation of acrylates.[139] Thus 4-acylisoxazole **12f** was heated in refluxing toluene with isopropyl iodide **185** and tributyltin hydride for 24 hours, activated by 2,2'-azobisisobutyronitrile (AIBN) or ultraviolet light. However, only the starting material **12f** was recovered in both reactions. Arylation of **12f** with iodobenzene **186** was also attempted with AIBN and ultraviolet light activation but again, only unreacted starting material **12f** was detected.



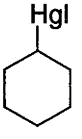
185



186



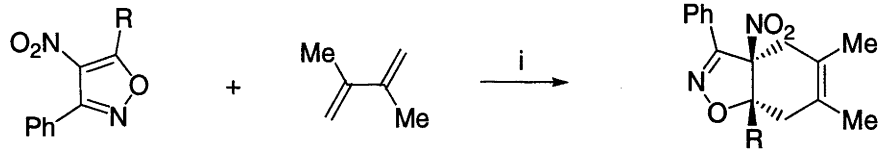
187



188

The use of the organomercuric hydride method was also examined.[140] This method is particularly useful for carbon-carbon bond formation in radical chain reactions as it involves mild reaction conditions (room temperature) and very short reaction times (usually in the order of minutes).[140] Alkylations of **12f** with isopropylmercuric iodide **187** and cyclohexylmercuric iodide **188** were attempted. Disappointingly, no reaction was observed in both instances, when **12f** was treated with a 2-fold excess of the alkylmercuric iodide and a 20-fold excess of sodium borohydride in dichloromethane at room temperature for 18 hours.

As the π-electron density calculations discussed in Chapter 2 showed that 4-acylisoxazoles are polarized like acrylates, and polarized systems of this type are prone to cycloadditions, Diels-Alder reactions were attempted. A survey of the literature established that Nesi *et al.*[141] had found that 4-nitro-5-acylisoxazoles **189** underwent cycloaddition with 2,3-dimethylbuta-1,3-diene **190** to give cycloadducts **191** (Scheme 60), whilst reaction with 2-methylbuta-1,3-diene **192** furnished **193** and **194** (Scheme 61).

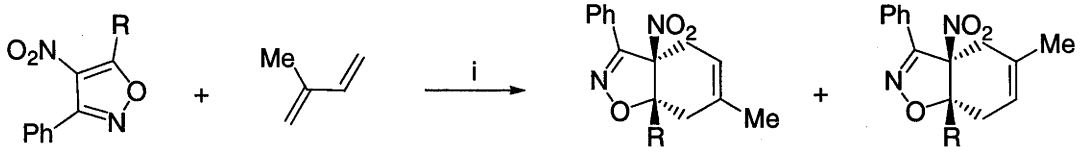


189 **190** *rac.* **191**

a. R = CO_2Et
b. R = COPh

Reagents and conditions: i. **189** (1.0 equiv.), **190** (5.0 equiv.), toluene, 110-115 °C, 48 h.

Scheme 60



189 **192** *rac.* **193** *rac.* **194**

a. R = CO_2Et
b. R = COPh

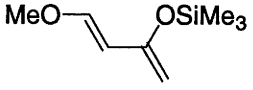
Reagents and conditions: i. **189** (1.0 equiv.), **192** (5.0 equiv.), toluene, 110-115 °C, 48 h.

Scheme 61

Noticing that the nitro group and the acyl group are both electron-withdrawing, the reactivity of 4-acylisoxazoles as dienophiles in Diels-Alder reactions was examined. Success of the reactions would allow for stereocontrolled preparation of fused bicyclic isoxazoles. However, treatment of the 4-acylisoxazole **12f** with cyclopentadiene **195** in refluxing toluene, and later, also with the Lewis acid catalyst tin(IV) chloride, did not result in reaction. In an attempt to encourage [4+2]-cycloaddition, the more reactive diene, *trans*-1-methoxy-3-(trimethylsilyloxy)-1,3-butadiene **196**,[142] or more commonly known as Danishefsky's diene, was used. Disappointingly, **12f** was unreactive when treated with Danishefsky's diene **196** in refluxing toluene, and under tin(IV) chloride catalysis at –40 °C.

In a further attempt to encourage [4+2]-cycloaddition, the 4,5-diacylisoxazole **120** was examined as a potential dienophile. The diacylisoxazole **120** was reasoned to be a more reactive dienophile than the monoacyl isoxazole **12f** as the C4-C5 bond of **120** is more electron-deficient, due to the second acyl-substituent. The synthesis of the isoxazole **120** was described in Chapter 3, Section 3.3. However, no reaction of **120** was observed even after prolonged heating in neat Danishefsky's diene **196**, and with tin(IV) chloride catalysis.

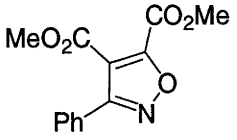
195



196

Subsequent further survey of the literature indicated that 4-acylisoxazoles do not undergo Diels-Alder cycloadditions. In an earlier communication, Nesi *et al.*[143] reported an attempted [4+2]-cycloaddition of 4-acylisoxazole **197** with 2,3-dimethylbuta-1,3-diene **190**. The diacylisoxazole **197** was heated at 115 °C with a 5-fold excess of diene **190** in xylene, however the authors only recovered unreacted starting material **197**. The

observed resistance of acylisoxazoles **12f** and **120** to react with dienes is therefore consistent with Nesi *et al.*'s[143] findings.



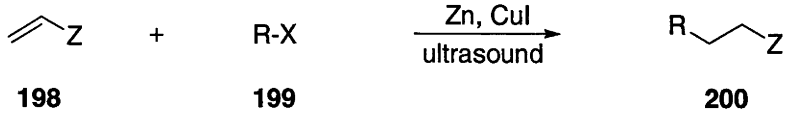
197

The Diels-Alder cycloadditions of 4-nitro-5-acylisoxazole **189** reported by Nesi *et al.*[141] appear to be a particular case as the literature indicates that isoxazoles generally do not undergo Diels-Alder reactions. The unreactive nature of isoxazoles as dienophiles was addressed using theoretical methods by Houk *et al.*[144] Their calculations indicate that [4+2]-cycloaddition is disfavored due to high activation energies and the endothermicity of such processes. The lack of reactivity shown by 4-acylisoxazoles **12f** and **120** as opposed to the 4-nitro-substituted system **189** may be due to the nitro group being more electron-withdrawing than the alkoxycarbonyl group. The nitro group therefore lowers the LUMO of the isoxazole more so than the alkoxycarbonyl group does, and hence [4+2]-cycloadditions involving 4-nitroisoxazoles occurs more readily than with 4-alkoxycarbonylisoxazoles.

4.3. Diastereoselective Zinc-copper(I) Iodide-mediated Alkylations of 4-Acylisoxazoles

The methodology developed by Luche *et al.*[145-148] for alkylation of electron-deficient olefins **198** (Scheme 62) was next examined for alkylations of 4-acylisoxazoles. Luche *et al.*'s[145-148] alkylations involved a zinc-copper(I) halide couple with ultrasound irradiation. Zinc powder is first activated with a copper(I) halide through

sonication in aqueous alcohol. This is followed by addition of electron-deficient olefins **198** and the alkyl halides **199**, and formation of conjugate adducts **200** is then promoted by ultrasound in an aqueous medium.



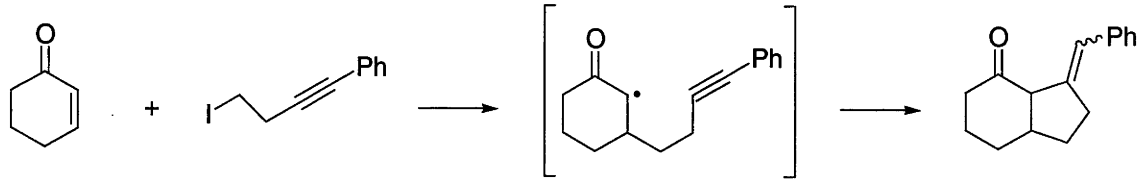
198 **199** **200**

X = Br, I

Z = CHO, COR, CO_2R, $CONH_2$, CN

Scheme 62

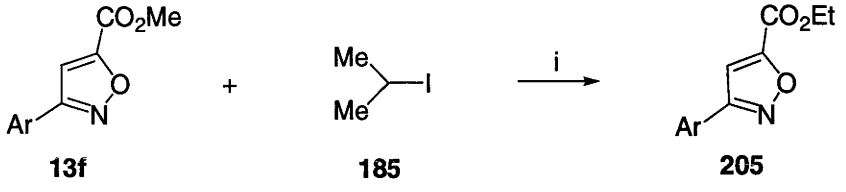
Luche *et al.*[145] found that the reactivities of alkyl halides **199** reflect the relative ease of halide abstraction, with decreasing order of reactivity for tertiary, secondary and primary iodides. While chlorides are found to be inert, bromides are reactive but at comparatively slower rates than those of the alkyl iodides. This pattern of reactivity for the alkyl halides **199** provides strong indications of a radical pathway. Further support for a free radical mechanism was indicated by the reaction of cyclohexenone **201** with 4-iodo-1-phenyl-1-butyne **202** which gave rise to the cyclized product **204**.[146] Formation of **204** presumably occurred *via endo*-cyclization of the intermediate alkynyl radical **203** (Scheme 63).



201 **202** **203** **204**

Scheme 63

Using the procedure described by Luche *et al.*,[147] 5-acylisoxazole **13f** was sonicated with isopropyl iodide **185** in 65% aqueous ethanol in the presence of the zinc-copper couple (Scheme 64). The solvent mixture of 65% aqueous ethanol was used because the authors[147] found that it gave the highest yield of conjugate adducts. Even with prolonged sonication, conjugate addition of **13f** was not effected. Instead the isoxazole **205** was produced in 24% yield (Scheme 64). The resistance to conjugate alkylation is consistent with the lack of acrylate-type polarization in 5-acylisoxazoles.



13f **185** **205**

Ar = 2,4,6-Me_3Ph

Reagents and conditions: i. **13f** (1.0 equiv.), **185** (3 equiv.), Zn (2.7 equiv.), CuI (0.8 equiv.), 65% aq. EtOH, ultrasound, 10-15 °C, 2 days.

Scheme 64

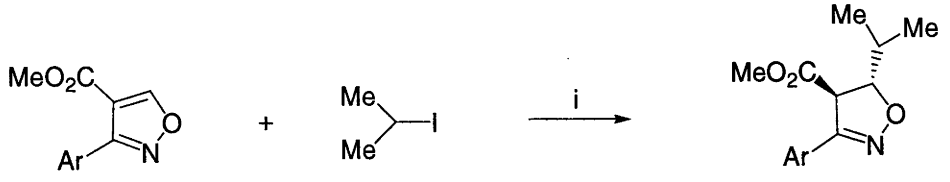
The structure of isoxazole **205** was deduced from EI mass spectroscopy and ^{1}H NMR spectroscopy. Using the EI method, accurate mass analysis of the molecular ion at *m/z* 259 indicated the molecular composition of $C_{15}H_{17}NO_3$. In the ^{1}H NMR spectrum, a three proton triplet resonance at δ 1.45 ppm (J = 7.1 Hz) and a two proton quartet at δ 4.48 ppm (J = 7.1 Hz) were assigned to the methyl and the methylene protons of the ethoxy group. The C4 isoxazole proton was observed as a one proton singlet at δ 6.91 ppm. Presumably, isoxazole **205** was formed *via* transesterification of 5-acylisoxazole **13f** with the solvent ethanol.

Reaction of the 4-acylisoxazole **12f** with alkyl iodide **185** was then investigated. Initially, the reaction mixture was sonicated for 75 minutes, which was reported as the

typical duration required for complete alkylation of enones and enoates.[145-148] Analysis of the reaction mixture using ^{1}H NMR spectroscopy indicated formation of the adduct **206**. In the ^{1}H NMR spectrum of the crude product mixture, a one proton doublet at δ 4.16 ppm (J = 10.0 Hz) and a one proton doublet of doublets at δ 4.86 ppm (J = 10.0, 7.1 Hz) were observed. The chemical shifts and multiplicities of these signals are consistent with those characteristic of the C4- and C5-isoxazoline protons. The ^{1}H NMR data also indicated that the alkylation of **12f** with **185** was diastereoselective. The rate of conjugate addition for the 4-acylisoxazole **12f** was clearly much slower than that observed by Luche *et al.*[145-148] for other activated olefins, as the ratio of the adduct 2-isoxazoline **206** to the isoxazole **12f** was *ca.* 9:91.

The yield of the 2-isoxazoline **206** was optimized through prolonged exposure of the reaction mixture to ultrasound irradiation. In order to maintain the bath water at a constant temperature during extended periods of sonication, chilled water was circulated in the sonic bath. Methanol was substituted for ethanol as a co-solvent to circumvent any problem of transesterification. Further to this, alkyl halides are reduced with the zinc-copper(I) iodide complex couple and the metallic couple decomposes over time. Zinc powder, copper(I) iodide and isopropyl iodide **185** were therefore added to the sonicating mixture at 8 h intervals. Under these conditions, the 4-acylisoxazole **12f** underwent addition with isopropyl iodide **185** to give adduct **206** as a single diastereomer in 82% yield (Scheme 65).

The structure of the 2-isoxazoline **206** was confirmed using mass spectrometry and ^{1}H NMR spectroscopy. Accurate mass measurement of the molecular ion at *m/z* 289 using the EI method indicated the molecular composition of $C_{17}H_{23}NO_3$. In the ^{1}H NMR spectrum, in addition to the signals of the C4- and C5-isoxazoline protons, two doublets at δ 1.00 ppm (J = 6.7 Hz) and δ 1.09 ppm (J = 6.7 Hz), and a multiplet at δ 2.05 ppm, integrating for three, three and one protons, were assigned to the methyl and the methine protons of the isopropyl group. The signal of the methoxy protons was seen as a three proton singlet at δ 3.56 ppm. In the infrared spectrum, an intense absorption band at 1742 cm^{-1} was assigned to the carbonyl stretching vibration.



Ar = 2,4,6-Me_3Ph

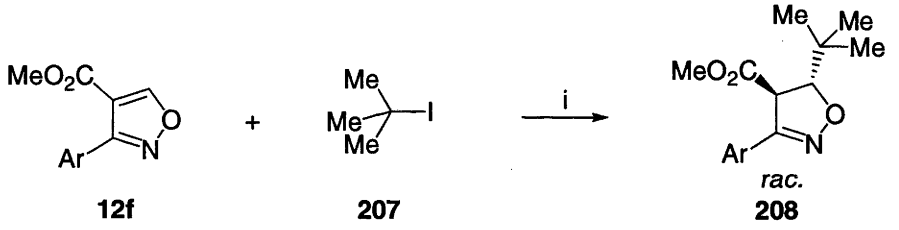
Reagents and conditions: **12f** (1.0 equiv.), **185** (7 × 3.0 equiv.), Zn (7 × 2.7 equiv.), CuI (7 × 0.8 equiv.), 65% aq. MeOH, ultrasound, 5 °C, 2.5 days.

Scheme 65

The relative configuration of the 2-isoxazoline **206** was deduced as *trans* from ^{1}H NMR experiments. In the 1D NOE spectrum, weak NOE interactions between the C4- and C5-isoxazoline protons suggested that they are likely to be *trans*. The spectral assignment was further supported by laboratory experiments. Alberola *et al.*[101] had previously reported that *cis*-2-isoxazolines substituted with electron-withdrawing groups at the 4-position can be converted to the corresponding *trans*-isomers by the heating at 80 °C with 5% aqueous sodium hydroxide. As reaction of **12f** with aqueous sodium hydroxide would lead to hydrolysis of the methoxycarbonyl group, the adduct **206** was instead treated with sodium methoxide for 24 hours. However, no reaction was observed. This led to the assignment of *trans*-relative configuration for the adduct **206**. The $J_{4,5}$ coupling constant of 10.0 Hz is uncharacteristically high for *trans*-coupling as vicinal coupling constants for *trans*-2-isoxazolines usually range from $J_{4,5}$ = 1.5-8 Hz.[21,23,24,72] The unusually high $J_{4,5}$ coupling constant observed for 2-isoxazoline **206** is probably due to the steric bulk of the C5-substituent.

The success of the diastereoselective reaction of **12f** with isopropyl iodide **185** prompted investigation into the scope and stereoselectivity of the zinc and copper(I) iodide-mediated alkylation of 4-acylisoxazoles. The reaction of isoxazole **12f** with *tert*-butyl iodide **207** afforded the 2-isoxazoline **208** in an excellent yield of 96% (Scheme 66).

The structure of 2-isoxazoline **208** was deduced from EI mass spectrometry and ^{1}H NMR spectroscopy. Accurate mass measurement of the molecular ion at *m/z* 303 using EI spectrometry indicated the molecular composition of $C_{18}H_{25}NO_3$. In the ^{1}H NMR spectrum, two doublets, integrating for one proton each, at δ 4.20 ppm (J = 10.7 Hz) and δ 4.85 ppm (J = 10.7 Hz) were assigned to the C4- and C5-isoxazoline protons. The signal of the methyl protons of the *tert*-butyl group was observed upfield at δ 1.02 ppm, as a singlet integrating for nine protons. The signal of the methoxy protons was a three proton singlet at δ 3.54 ppm. In the infrared spectrum, an intense absorption band at 1743 cm^{-1} was assigned to the carbonyl stretching vibration. The 2-isoxazoline **208** was deduced to be the *trans*-stereoisomer based on the results of 1D NOE experiments and its inert behaviour upon treatment with sodium methoxide.



12f **207** **208**

Ar = 2,4,6-Me_3Ph

Reagents and conditions: i. **12f** (1.0 equiv.), **207** (3.0 equiv.), Zn (2.7 equiv.), CuI (0.8 equiv.), 65% aq. MeOH, ultrasound, 5 °C, 9 h.

Scheme 66

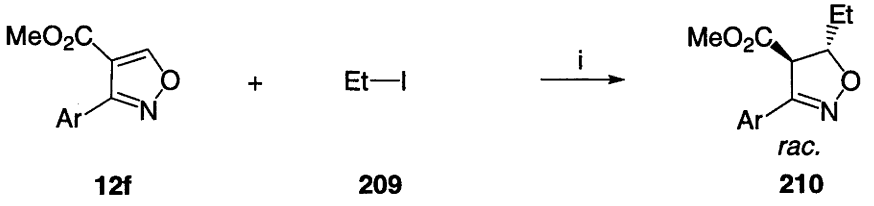
The reaction of **12f** with the tertiary alkyl halide **207** was markedly more facile than that with the secondary alkyl halide **185**. The heightened reactivity of the tertiary halide **207** supports the proposed free radical mechanism associated with the zinc-copper(I) iodide-mediated alkylations.

Having examined alkylations of **12f** with tertiary and secondary alkyl halides **207** and **185**, reaction with the primary alkyl iodide, iodoethane **209** was investigated.

Initially, isoxazole **12f** was sonicated with a 3-fold excess of **209**, zinc powder (2.7 equiv.) and copper(I) iodide (0.8 equiv.) for 2.5 days. ^{1}H NMR analysis of the crude product mixture indicated an *ca.* 8-10% yield of the adduct **210**, as a single diastereomer.

Attempts to improve the yield of **210** involved the use of water, and water-pyridine (1:4)[145] as alternative solvent systems, and ammonium chloride[148] as a substitute to copper(I) iodide. However, none were successful in improving the yield of **210** beyond 10%. The use sodium iodide[148] to promote reaction was also investigated. However, this also made little difference to the yield of **210**.

The best yield for 2-isoxazoline **210** was obtained by reaction of isoxazole **12f** with the primary iodide **209** for 8 days. Zinc powder, copper(I) iodide and iodoethane **209** were added at 8 hour intervals as the activated zinc-copper (I) complex appears to deteriorate over time and the primary alkyl halide **209** is prone to reduction. This procedure improved the yield of 2-isoxazoline **210** to 32%, and the unreacted isoxazole **12f** was recovered in 63% yield (Scheme 67).



12f **209** **210**

Ar = 2,4,6-Me_3Ph

Reagents and conditions: i. **12f** (1.0 equiv.), **209** (24 × 3.0 equiv.), Zn (24 × 2.7 equiv.), CuI (24 × 0.8 equiv.), 65% aq. MeOH, ultrasound, 5 °C, 8 days.

Scheme 67

The EI mass spectrometric and ^{1}H NMR spectroscopic data of **210** are in full accord with the assigned structure. Accurate mass measurement of the molecular ion at *m/z* 275 indicated for the molecular composition of $C_{16}H_{21}NO_3$. In the ^{1}H NMR

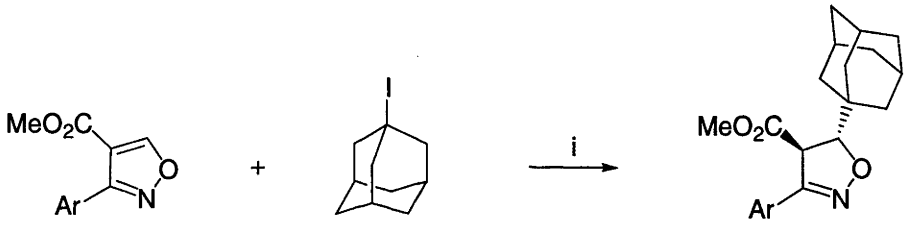
spectrum, the signal of the C4 isoxazoline proton was a doublet at δ 4.08 ppm (J = 8.9 Hz) whilst that of the C5 isoxazoline proton was a doublet of triplets at δ 5.02 ppm (J = 8.9, 6.5 Hz). Further upfield, a three proton triplet at δ 1.08 ppm (J = 7.4 Hz) was assigned to the methyl protons of the ethyl group at C5, whilst two multiplets integrating for one proton each, at δ 1.79 ppm and δ 1.92 ppm, were ascribed to the methylene protons. The signal of the methoxy protons was seen as a three proton singlet at δ 3.58 ppm. In the infrared spectrum, an intense absorption band at 1741 cm^{-1} was assigned to the carbonyl stretching vibration. The adduct **210** was obtained as a single diastereomer of *trans*-configuration, as indicated by weak NOE interactions between the C4- and C5-isoxazoline protons.

Having demonstrated that 4-acylisoxazole **12f** reacts with tertiary, secondary and primary alkyl halides **207**, **185** and **209** to give 2-isoxazolines **208**, **206** and **210**, respectively, alkylation with iodomethane was then attempted. The isoxazole **12f** was treated with iodomethane, with zinc powder and copper(I) iodide added at 8 hour intervals over 4 days. However ^{1}H NMR analysis of the crude product mixture indicated only unreacted starting material **12f**. The lack of reactivity of iodomethane as an alkylating agent was not unexpected since the methyl radical is particularly unstable. Alkylation of **12f** is likely to be impeded by facile reduction of the highly reactive methyl radical to methane. The rate of methyl radical reduction is likely to be markedly faster than that of the 1,4-alkylation of **12f**.

With the general methodology established, alkylations of 4-acylisoxazole **12f** with sterically demanding alkyl halides were examined. Alkylation of **12f** with the cyclic tertiary halide, 1-iodoadamantane **211** proceeded smoothly under sonochemical conditions, thereby furnishing the 2-isoxazoline **212** as a single diastereomer in an excellent yield of 95% (Scheme 68).

The structure of 2-isoxazoline **212** was deduced from EI mass spectrometry and ^{1}H NMR spectroscopy. Accurate mass measurement of the molecular ion at *m/z* 381 analyzed for the molecular composition of $C_{24}H_{31}NO_3$. In the ^{1}H NMR spectrum, the signals of the C4- and C5-isoxazoline protons were observed as one proton doublets at δ 4.27 ppm (J = 11.1 Hz) and δ 4.69 ppm (J = 11.1 Hz). Three multiplets at δ 1.18-1.37

ppm, δ 1.51-1.62 ppm and δ 2.00-2.09 ppm, integrating for six, six and three protons, respectively, were assigned to the adamantyl protons. The methoxy protons resonated as a three proton singlet at δ 3.53 ppm. In the infrared spectrum, a strong absorption band at 1743 cm^{-1} was assigned to the carbonyl stretching vibration. In an attempt to determine the relative configuration of **212** and therefore confirm that of the other adducts **206**, **208** and **210**, crystals of **212** were grown from vapour diffusion of hexanes and ether at 18 °C. The X-ray crystallographic structure of the material was recorded. As indicated by the ORTEP diagram (Figure 29), the relative configuration of the single diastereomer is *trans*.



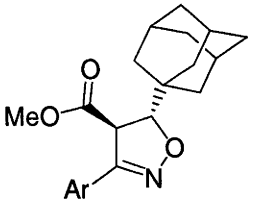
12f **211** *rac.* **212**

Ar = 2,4,6-Me_3Ph

Reagents and conditions: i. **12f** (1.0 equiv.), **211** (2 × 3.0 equiv.), Zn (2 × 2.7 equiv.), CuI (2 × 0.8 equiv.), 65% aq. MeOH, ultrasound, 5 °C, 14 h.

Scheme 68

Encouraged by these results, alkylation of isoxazole **12f** with the cyclic secondary halide cyclohexyl iodide **213** was examined. Unlike the previous examples, the reaction with **213** gave the adduct **214**, as a mixture of *cis*- and *trans*-diastereomers in a ratio of *ca.* 1:1.3 (Scheme 69).



rac.

212

Ar = 2,4,6-Me_3Ph

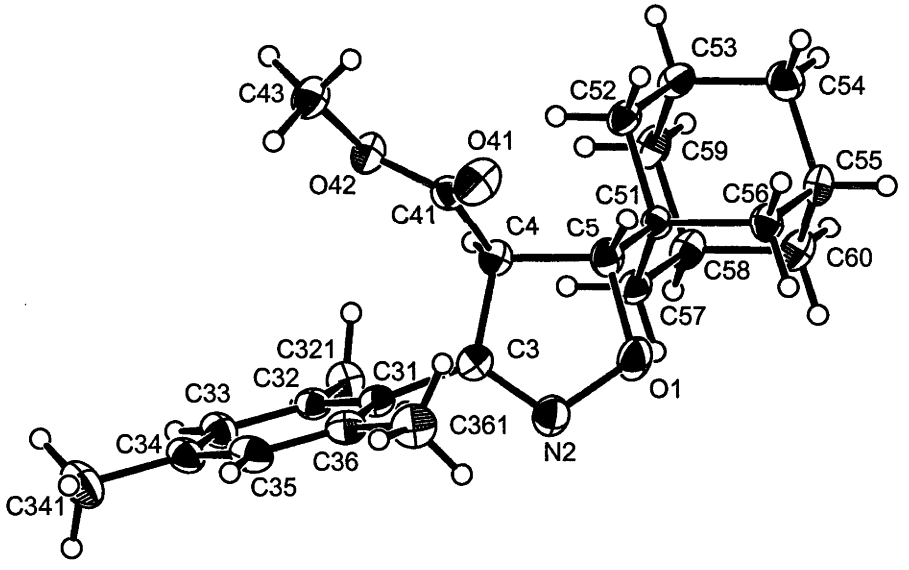
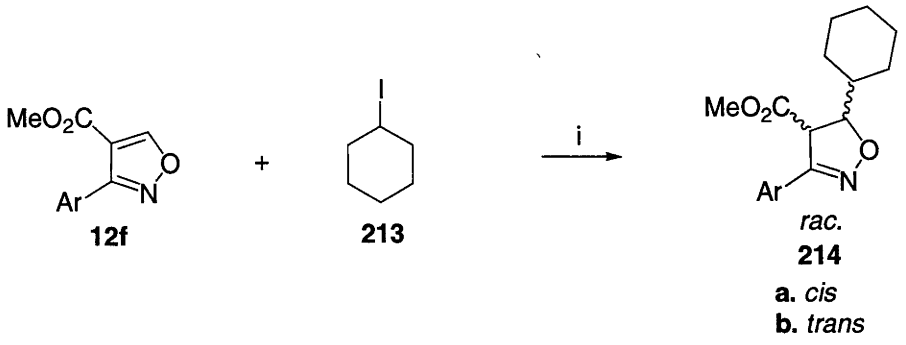


Figure 29. ORTEP derived from single crystal X-ray analysis of compound **212**.



Ar = 2,4,6-Me_3Ph

Reagents and conditions: i. **12f** (1.0 equiv.), **213** (3.0 equiv.), Zn (18.0 × 2.7 equiv.), CuI (18 × 0.8 equiv.), 65% aq. MeOH, ultrasound, 5 °C, 6 days.

Scheme 69

The stereoisomers of 2-isoxazoline **214** were separated by chromatography and characterized. Accurate mass measurement of the molecular ions of each of the stereoisomers of **214** at *m/z* 329 analyzed for the molecular composition of $C_{20}H_{27}NO_3$. In the ^1H NMR spectrum of the *cis*-isomer **214a**, the signal of the C4 isoxazoline proton was seen as a one proton doublet at δ 4.18 ppm (J = 10.5 Hz) whilst that of the C5 isoxazoline proton was observed as a doublet of doublets, integrating for one proton, at δ 4.83 ppm (J = 10.5, 7.3 Hz). A three proton singlet at δ 3.53 ppm was assigned to the methoxy group. The signals of the protons of the cyclohexyl group were seen as three multiplets at δ 1.00-1.50 ppm, δ 1.60-1.94 ppm and δ 1.97-2.09 ppm, integrating for six, four and one protons, respectively. For the *trans*-isomer **214b**, the chemical shifts of the signals of the C4- and C5-isoxazoline protons are upfield. A doublet at δ 4.15 ppm (J = 9.5 Hz) was assigned to the C4 proton whilst an apparent triplet at δ 4.43 ppm (J = 9.5 Hz) was ascribed to the C5 proton. A three proton singlet at δ 3.64 ppm was assigned to the methoxy group. The signals of the cyclohexyl protons were seen upfield, as multiplets at δ 1.00-1.40 ppm, δ 1.58-1.87 ppm and δ 1.88-2.09 ppm, integrating for six, four and one protons, respectively. In the infrared spectra, the carbonyl stretching

vibrations of the *cis*- and *trans*-stereoisomers **214a,b** were observed as strong absorption bands at 1742 cm^{-1} and 1740 cm^{-1}, respectively.

The reason for the less diastereoselective alkylation of **12f** with cyclohexyl iodide **213** compared to that with isopropyl iodide **185** is not clear, but is probably related to conformational flexibility of the cyclohexyl system.

Alkylations of 4-acylisoxazole **12f** with halides giving rise to stabilized carbon-centred radicals such as benzylic and allylic radicals were also attempted. However, benzyl bromide failed to alkylate isoxazole **12f**. ^{1}H NMR analysis of the crude product mixture indicated unreacted starting material **12f** and formation of toluene as a by-product. Presumably, toluene was formed from reduction of benzyl bromide. Treatment of **12f** with allyl iodide also led to recovery of starting material **12f**, presumably due to reduction of allyl iodide to propene.

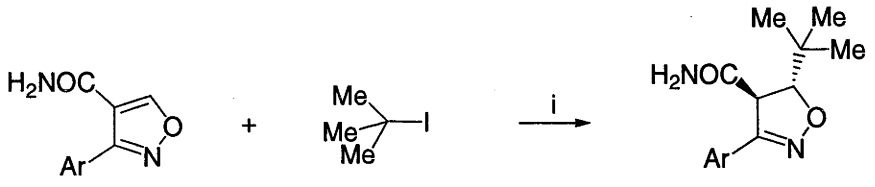
Arylation of **12f** with iodobenzene **186** was also attempted under zinc-copper(I) iodide-mediated sonochemical conditions. However, ^{1}H NMR analysis of the product mixture indicated unreacted **12f** and biphenyl. Biphenyl was presumably formed from Würtz coupling of **186**, since homocoupling of bromobenzene is known to occur readily under ultrasonic conditions.[149]

Arylation of isoxazole **12f** with other metallic catalysts was also attempted. However use of tetrakis(triphenylphosphine)palladium[150] and bis(triphenylphosphine)palladium diacetate[151] did not effect arylation of **12f** with aryl iodide **186**. In both cases, ^{1}H NMR analysis of the product mixture indicated only unreacted starting material **12f**.

4.4. Effects of C3- and C4-Substituents on Zinc-copper(I) Iodide-mediated Alkylations of 4-Acylisoxazoles

Having established that substitution of an alkoxycarbonyl group at the 4-position activates an isoxazole ring towards alkylation, the effect of an amido group was

examined. The 4-amidoisoxazole **167** was used in the study and its synthesis was discussed in Chapter 3, Section 3.7. Reaction of 4-amidoisoxazole **167** with the tertiary halide **207** in the presence of the zinc-copper(I) iodide couple gave rise to the 2-isoxazoline **215** in an excellent yield of 97%, and as a single diastereoisomer of *trans*-configuration (Scheme 70).



167 **207** *rac.* **215**

Ar = 2,4,6-Me_3Ph

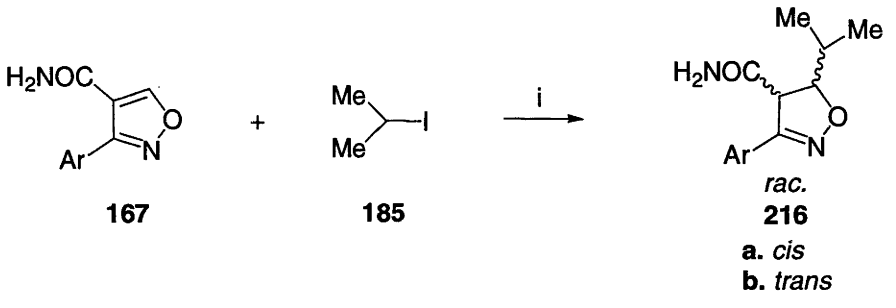
Reagents and conditions: i. **167** (1.0 equiv.), **207** (6 × 3.0 equiv.), Zn (6 × 2.7 equiv.), CuI (6 × 0.8 equiv.), 65% aq. MeOH, ultrasound, 5 °C, 48 h.

Scheme 70

The structure of the 2-isoxazoline **215** was deduced using EI mass spectrometry and ^{1}H NMR spectroscopy. Accurate mass measurement of the parent ion detected at *m/z* 288 indicated the molecular composition of $C_{17}H_{24}N_2O_2$. In the ^{1}H NMR spectrum, the signals of the C4- and C5-isoxazoline protons were observed as one proton doublets at δ 3.96 ppm and δ 5.02 ppm with a geminal coupling constant J = 10.1 Hz. 1D NOE experiments showed weak interactions between the C4- and C5-isoxazoline protons, thereby indicating the relative configuration of **215** is *trans*. The amide protons were seen as broad singlets at δ 4.20 ppm and δ 6.00 ppm. A singlet at δ 1.02 ppm, integrating for nine protons, was assigned to the methyl protons of the *tert*-butyl group. In the infrared spectrum, an intense absorption band at 1693 cm^{-1} was assigned to the amide carbonyl stretching vibration.

The reaction of *tert*-butyl iodide **207** with 4-amidoisoxazole **167** proceeded approximately five times slower than that with the 4-methoxycarbonylisoxazole **12f**. This is likely to be due to amido group being less electron-withdrawing than the alkoxycarbonyl group. This reactivity trend was also observed in the reductions of 4-alkoxycarbonylisoxazoles and 4-amidoisoxazoles (see Chapter 3).

Alkylation of 4-amidoisoxazole **167** with isopropyl iodide **185** was also examined. The diastereoselectivity of the reaction was observed to be less than that seen in the reaction of **12f** with **185**. Sonication of the amidoisoxazole **167** with the secondary alkyl halide **185** for 12 days gave rise to 2-isoxazoline **216** as an inseparable mixture of *cis*:*trans*-diastereomers in a ratio of 1:2, with a combined yield of 75% (Scheme 71).



167 **185** *rac.* **216**

a. *cis*
b. *trans*

Ar = 2,4,6-Me_3Ph

Reagents and conditions: i. **167** (1.0 equiv.), **185** (24 × 3.0 equiv.), Zn (24 × 2.7 equiv.), CuI (24 × 0.8 equiv.), 65% aq. MeOH, ultrasound, 5 °C, 12 days.

Scheme 71

The structures of the stereoisomers of **216** were determined from the ^{1}H NMR data. The relative stereochemistry of the adducts **216a,b** was assigned according to the magnitude of the geminal coupling constant $J_{4,5}$ as those for *cis*-2-isoxazolines are always larger than those of the *trans*-isomers.[72] For the *cis*-isomer **216a**, the signal of the C4 isoxazoline proton was seen as a one proton doublet at δ 3.88 ppm (J = 10.4 Hz) whilst that of the C5 isoxazoline proton was observed as a doublet of doublets at

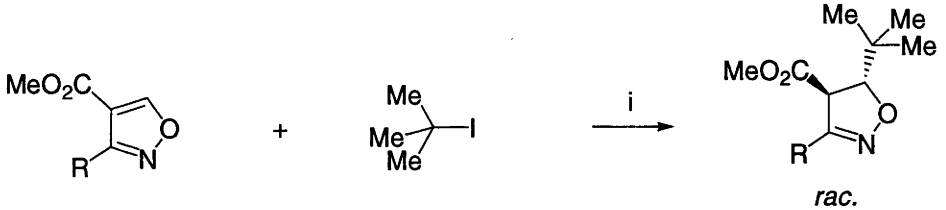
δ 4.35 ppm (J = 10.4, 8.1 Hz). Two broad singlets at δ 5.57 ppm and δ 5.77 ppm, integrating for one proton each, were assigned to the labile amide protons. The protons of the isopropyl group were observed upfield. Two three proton doublets at δ 1.04 ppm (J = 6.6 Hz) and δ 1.20 ppm (J = 6.6 Hz) were assigned to the methyl protons whilst a one proton multiplet at δ 2.28 ppm was ascribed to the methine proton. For the *trans*-isomer **216b**, the signal of the C4 isoxazoline proton was observed as a one proton doublet at δ 3.92 ppm (J = 9.0 Hz) whilst that of the C5 isoxazoline proton was seen as a one proton doublet of doublets, at δ 5.01 ppm (J = 9.0 Hz, 6.9 Hz). The amide protons resonated as broad one proton singlets at δ 5.02 ppm and δ 5.27 ppm. The signals of the isopropyl protons were observed upfield. Two doublets at δ 1.00 ppm (J = 6.7 Hz) and δ 1.08 ppm (J = 6.7 Hz), each integrating for three protons, were assigned to the methyl protons, whilst a one proton multiplet at δ 2.03 ppm was ascribed to the methine proton.

Alkylation of the 5-amidoisoxazole **168** was also examined by treatment with the reactive tertiary alkyl halide *tert*-butyl iodide **207** in the presence of a zinc-copper(I) iodide couple. Sonication at 5 °C in 65% aqueous methanol however did not result in any reaction. The contrasting reactivities of the 4- and 5-amidoisoxazoles **167** and **168** in the alkylation experiments parallel those observed for the borohydride reductions of these compounds, and are consistent with the theoretical and X-ray crystallographic data for the lack of polarization in 5-acylisoxazoles.

The effects of an alkyl group at C3 were next investigated through alkylations of 3-nonyl-substituted isoxazoles **111** and **112**. The synthesis of **111** and **112** was described in Chapter 3, Section 3.2. The 4-acylisoxazole **111** was treated with *tert*-butyl iodide **207** in the presence of a zinc-copper(I) iodide couple. The reaction gave rise to the 2-isoxazoline **217** as a single stereoisomer in an excellent yield of 95% (Scheme 72).

The structure of the *trans*-2-isoxazoline **217** was deduced from EI mass spectrometry and ^{1}H NMR spectroscopy. Accurate mass analysis of the molecular ion at *m/z* 311 established the structural composition of $C_{18}H_{33}NO_3$. In the ^{1}H NMR spectrum, two doublets at δ 3.77 ppm (J = 8.4 Hz) and δ 4.54 ppm (J = 8.4 Hz), each integrating for one proton, were assigned to the C4- and C5-isoxazoline protons, respectively. The

relative configuration of the adduct was deduced as *trans* from 1D NOE experiments, which showed only weak interactions between the C4- and C5-isoxazoline protons. The signal of the methoxy protons was observed as a three proton singlet at δ 3.76 ppm whilst that of the methyl protons from the *tert*-butyl group was seen as a nine proton singlet at δ 0.91 ppm. In the infrared spectrum, an intense absorption band at 1743 cm^{-1} was assigned to the carbonyl stretching vibration.



111 **207** *rac.* **217**

R = $(CH_2)_8CH_3$

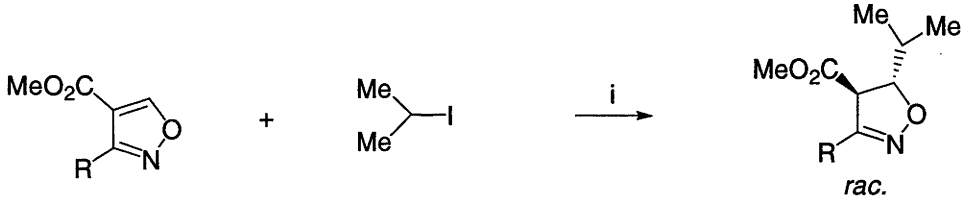
Reagents and conditions: i. **111** (1.0 equiv.), **207** (3.0 equiv.), Zn (2.7 equiv.), CuI (0.8 equiv.), 65% aq. MeOH, ultrasound, 5 °C, 9 h.

Scheme 72

Reaction of the 3-nonylisoxazole **111** with the secondary alkyl halide **185** was also examined. Treatment of isoxazole **111** with **185** in the presence of a zinc-copper(I) iodide couple gave rise to the 2-isoxazoline **218** in 74%, exclusively as the *trans*-diastereomer (Scheme 73).

The mass spectrometric and ^1H NMR spectroscopic data of 2-isoxazoline **218** are in full accord with the assigned structure. The molecular ion was detected at *m/z* 297 for which accurate mass measurement indicated the molecular composition of $C_{17}H_{31}NO_3$. In the ^1H NMR spectrum, the signal of the C4 isoxazoline proton was observed as a one proton doublet at δ 3.74 ppm (J = 8.2 Hz), whilst that of the C5 isoxazoline proton was seen as a one proton doublet of doublets at δ 4.59 ppm (J = 8.2, 6.6 Hz). Weak NOE

interactions between the C4- and C5-isoxazoline protons indicated that the relative configuration of the 2-isoxazoline **218** is *trans*. A singlet, integrating for three protons at δ 3.77 ppm, was assigned to the methoxy protons. The signals of the isopropyl methyl protons were observed upfield as two doublets, each integrating for three protons, at δ 0.91 ppm (J = 6.8 Hz) and δ 0.97 ppm (J = 6.8 Hz). A one proton multiplet at δ 1.87 ppm was ascribed to the isopropyl methine proton.



111 **185** **218**

R = $(CH_2)_8CH_3$

Reagents and conditions: i. **111** (1.0 equiv.), **185** (7 × 3.0 equiv.), Zn (7 × 2.7 equiv.), CuI (7 × 0.8 equiv.), 65% aq. MeOH, ultrasound, 5 °C, 2.5 days.

Scheme 73

The factors contributing to the highly diastereoselective alkylations of 4-methoxycarbonyl- and amido-substituted isoxazoles **12f**, **111** and **167** are not obvious, though complexation between the metal catalyst and the 4-acylisoxazole may be effecting stereochemical control.

The effect of the C3-alkyl substituent was also investigated through treatment of 5-acylisoxazole **112** with *tert*-butyl iodide **207**. However, sonication in the presence of a zinc-copper(I) iodide couple for 2 days did not result in alkylation and only isoxazole **112** was detected in the mixture by ^{1}H NMR spectroscopy. This confirmed the expected lack of acrylate reactivity of 5-acylisoxazoles, predicted from X-ray crystallographic and theoretically determined bond lengths and π-electron densities.

In summary, as an extension to the borohydride reductions of 4-acylisoxazoles, their acrylate behaviour was also demonstrated through the zinc-copper(I) iodide-mediated alkylations of 4-alkoxycarbonyl- and 4-amido-substituted isoxazoles. These 1,4-additions occur readily with both alkyl- and aryl-substituents at C3. The alkylations are generally diastereoselective and much more so than for conventional free radical alkylations of electron-deficient olefins where carbon-carbon bond formation usually occurs with little stereoselectivity.[152] The acrylate behaviour of 4-acylisoxazoles can therefore be exploited for diastereoselective synthesis of C5-substituted 2-isoxazolines *via* zinc-copper(I) iodide-mediated alkylations of 5-unsubstituted 4-acylisoxazoles or complementary borohydride reductions of 5-substituted 4-acylisoxazoles.

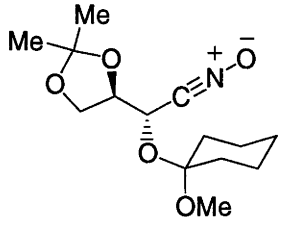
CHAPTER 5

ASYMMETRIC SYNTHESIS OF 2-ISOXAZOLINES

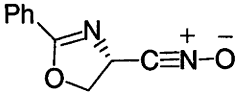
5.1. Stereoselective Synthesis of 2-Isoxazolines *via* Asymmetric Nitrile Oxide Cycloadditions

In the previous chapters, methodologies for diastereoselective synthesis of 2-isoxazolines *via* reduction and alkylation of 4-acylisoxazoles were developed. The possibility of developing variants of these methodologies for control of absolute and relative stereochemistry was the aim of the work described herein.

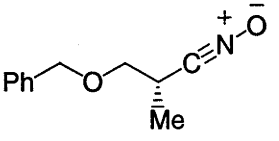
Asymmetric synthesis of 2-isoxazolines has been extensively researched for the past few decades.[153-176] Much of the impetus for the work stemmed from the synthetic utility of 2-isoxazolines, where for example β-hydroxycarbonyl structures may be accessed upon ring-opening (see Chapter 1, Section 1.3.). Currently, the main strategy for the enantioselective synthesis of 2-isoxazolines is through nitrile oxide cycloadditions. Studies[153] of cycloadditions of optically active nitrile oxides with alkenes are scarce and the asymmetric induction observed is typically poor. This is exemplified in the reactions of chiral nitrile oxides **219**,[154] **220**[155] and **221**[156] with alkenes, which gave rise to 2-isoxazolines in only 50-60% *d.e.*



219



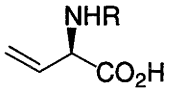
220



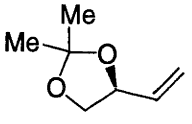
221

Contrary to the small number of publications dealing with 1,3-dipolar additions of chiral nitrile oxides with alkenes, chiral alkenes are more commonly used in asymmetric synthesis of 2-isoxazolines.[157-172] The chiral alkenes employed in these studies may be divided into two types: (i) those with the chiral centre located vicinal to the olefinic bond, such as allylic alcohols and ethers,[156-158] allylic amines,[159] allyl

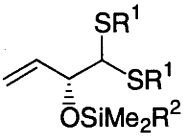
silanes,[160,161] vinyl sulfoxides[162] and vinyl phosphine oxides;[163] and (ii) those with the chiral centre located two or more bonds away from the double bond, such as vinyl ethers,[164] metal complexes,[165] acrylates[166-169] and acrylamides.[170] The use of chiral vinyl and allylic alcohols, and allylic amines in asymmetric nitrile oxide additions has met with mixed success. The stereoselectivities varied widely, but they generally ranged from low (32-40% *d.e.* for the allylic amine **222**[159]) to modest (60% *d.e.* for the glyceraldehyde-derived alkene **223**[156]). Only a few cases have demonstrated useful levels of asymmetric induction, such as reactions of the protected allylic alcohol **224**.[161]



222



223



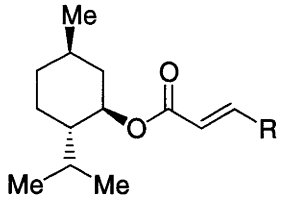
224

R[1] = Ph, *tert*-Bu
R[2] = *tert*-Bu

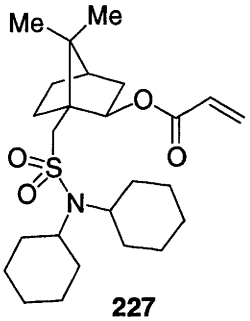
Nitrile oxide cycloadditions with alkenes attached to chiral auxiliaries *via* ester or amide linkages have been the subject of many studies. Reactions of acrylate and crotonate esters of L-menthol **225** and **226** with nitrile oxides produced 2-isoxazolines with very poor diastereoselectivity (*ca.* 4% *d.e.*).[166,167] Low selectivity (56% *d.e.*) was observed for cycloaddition of benzonitrile oxide **7** and the acrylate of Oppolzer's chiral sulfonamide **227**,[166] whilst moderate selectivity (78% *d.e.*) was observed for cycloaddition of acetonitrile oxide **3c** with the bornyl acrylates **228** and crotonates **229**.[168]

The literature indicates that nitrile oxide cycloadditions with chiral α,β-unsaturated amides are among the most effective methods for enantioselective synthesis of 2-isoxazolines. This is exemplified by reactions of nitrile oxides with the acrylamide of Oppolzer's chiral sultam **230** where 62-90% *d.e.* was observed.[170] More recently,

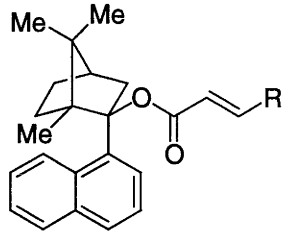
Chen *et al.*[171] showed that nitrile oxide cycloadditions with the novel camphor derived acryloyl hydrazide **231** occur with exceptionally high diastereoselectivity, up to 98% *d.e.* The acrylamide of the chiral auxiliary derived from Kemp's triacid **232** also provided excellent selectivity (98% *d.e.*) in cycloaddition with benzonitrile oxide **7**.[172] Although nitrile oxide cycloadditions with **231** and **232** are highly diastereoselective, limited availability of the chiral auxiliaries discourages their use in synthesis.



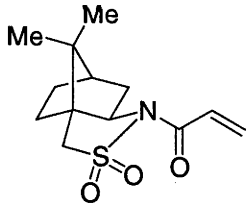
225. R = H
226. R = Me



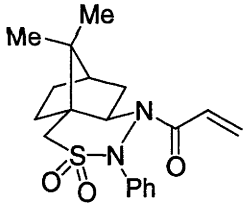
227



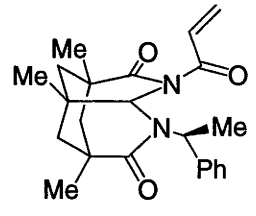
228. R = H
229. R = Me



230



231

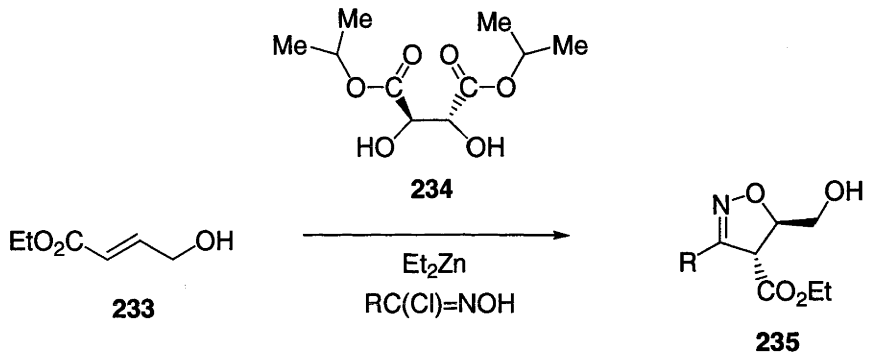


232

The use of enzymes and chiral hosts was explored in one study. The use of baker's yeast in cycloadditions of aryl nitrile oxides with 4-vinylpyridine however produced 2-isoxazolines with low stereoselectivity (<25% *e.e.*). Enhancement of selectivity using cyclodextrins increased the optical purity to 64% *e.e.*[173]

Lewis acids have been the subject of numerous studies involving nitrile oxide cycloadditions with allylic alcohols.[174-176] Recently, Ukaji and Inomata[175] reported a

procedure for the synthesis of enantioenriched 2-isoxazolines *via* diethyl zinc-catalysed nitrile oxide cycloadditions with γ-substituted allylic alcohol **233**. In the study, stereoselectivity was induced by the chiral ligand (*R,R*)-tartrate **234** and 2-isoxazolines **235** were obtained with optical yields in the range of 91-96% *e.e.* (Scheme 74).



Scheme 74

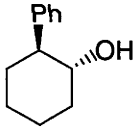
The highly enantioselective reactions are attributed to chelation of zinc with the oxygens of tartrate **234**, the nitrile oxides and allylic alcohol **233**.[174,175] The hydroxyl functionality at the allylic position of **233** is thus likely to be important for asymmetric induction. This therefore limits the methodology to the synthesis of 5-hydroxymethyl-2-isoxazolines.

5.2. Chiral 4-Acylisoxazoles as Masked Acrylates for the Synthesis of 2-Isoxazolines with Control of Relative and Absolute Stereochemistry

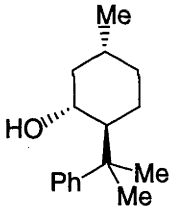
The challenge in this work was to develop a complementary methodology for the asymmetric synthesis of 2-isoxazolines of more diverse structure. The use of 4-alkoxycarbonylisoxazoles as acrylate synthons with chiral auxiliaries attached as esters

was proposed. The ester linkage allows for easy incorporation and removal of the chiral auxiliary. Low stereoselectivity is often observed with acyclic systems due to their conformational mobility,[176] and it was expected that geometric constraints associated with the cyclic framework of the 4-acylisoxazoles would facilitate stereochemical control.

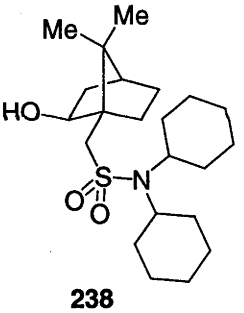
Considerable efforts have been devoted to the development of stereoselective methods for 1,4-additions to chiral electron-deficient alkenes. Cyclohexyl auxiliaries[177] and camphor-based auxiliaries[178] have proven to be effective chiral inducing agents in organozinc and cuprate-mediated conjugate alkylations and reductions. For these reasons, (-)-(1*R*,2*S*)-*trans*-2-phenyl-1-cyclohexanol **236**, (-)-8-phenylmenthol **237** and (+)-10-dicyclohexylsulfamoyl-L-isoborneol **238** were used in the present study, with the added advantage that these auxiliaries are accessible through commercial sources.



236



237

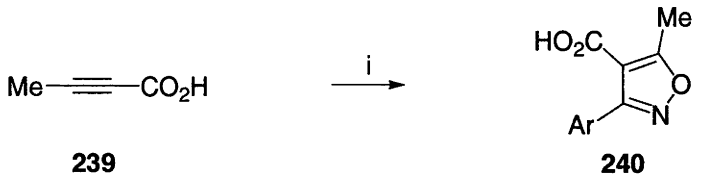


238

5.2.1. Synthesis of Chiral Trisubstituted Isoxazoles for Borohydride Reductions

In order to investigate the borohydride reduction of chiral 4-acylisoxazoles, the trisubstituted 4-acylisoxazoles **241**, **245** and **247** were synthesized. The synthesis commenced with the preparation of 4-acylisoxazole **240** as a general template from which the chiral isoxazoles **241**, **245** and **247** were to be prepared through conventional

ester coupling reactions. The isoxazole **240** was produced in 97% yield from cycloaddition of 2-butynoic acid **239** with mesitonitrile oxide **5** (Scheme 75).



239 **240**

Ar = 2,4,6-Me_3Ph

Reagents and conditions: i. **239** (1.0 equiv.), **5** (1.0 equiv.), THF, reflux, 2 days.

Scheme 75

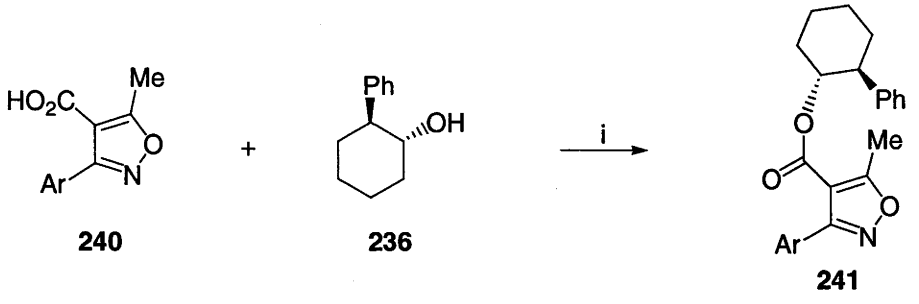
The structure of the cycloadduct **240** was deduced from mass spectrometry and ^{1}H NMR spectroscopy. Using the EI method, accurate mass measurement of the parent ion at *m/z* 245 indicated the molecular composition of $C_{14}H_{15}NO_3$. In the ^{1}H NMR spectrum, a three proton singlet at δ 2.80 ppm was assigned to the C5-methyl group, whilst two singlets at δ 2.08 ppm and δ 2.34 ppm, integrating for six and three protons respectively, were assigned to the *o,o'*-methyl and the *p*-methyl groups of the mesityl ring. A two proton singlet at δ 6.91 ppm was assigned to the mesityl ring protons whilst a broad one proton singlet at δ 2.02 ppm was ascribed to the acidic OH proton. In the infrared spectrum, an intense absorption band at 1688 cm^{-1} was ascribed to the carbonyl stretching vibration.

The cycloaddition of dipole **5** with alkyne **239** was highly regioselective, giving rise to the 4-acylisoxazole **240** as the exclusive product. This is attributed to dominant polar effects, where the electron-rich dipole oxygen becomes bonded to the electron-positive β-carbon of the 1,2-disubstituted alkyne **239** (see Chapter 1, Section 1.1.4.).

With the achiral isoxazole template **240** prepared, esterification with the chiral auxiliaries was investigated. Isoxazole **240** was smoothly esterified with the cyclohexyl

auxiliary **236** with the use of dicyclohexylcarbodiimide/*N*,*N*-dimethylamino-4-pyridine (DCC/DMAP).[179] The chiral 4-acylisoxazole **241** was furnished in 87% yield (Scheme 76).

The EI mass spectrometric and ^{1}H NMR spectroscopic data of compound **241** are in full accord with the assigned structure. The parent ion was detected at *m/z* 403 from which the molecular formula was determined as $C_{26}H_{29}NO_3$ from accurate mass measurement. In the ^{1}H NMR spectrum, the signal of the C1 proton of the chiral auxiliary was observed as a triplet of doublets at δ 5.05 ppm (J = 10.6, 4.6 Hz). Restricted rotation due to π-stacking of the phenyl and mesityl rings was indicated by the number and uncharacteristic upfield shifts of the signals of the mesityl methyl groups. The mesityl methyl groups resonated as three singlets at δ 1.73 ppm, δ 1.95 ppm and δ 2.37 ppm, each integrating for three protons. The signal of the isoxazole methyl group at C5 was observed at δ 2.59 ppm as a three proton singlet. In the infrared spectrum, an intense absorption band at 1716 cm^{-1} was assigned to the carbonyl stretching vibration.

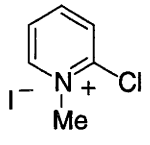


Ar = 2,4,6-Me_3Ph

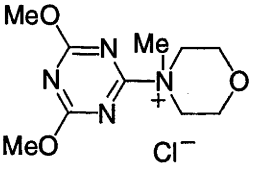
Reagents and conditions: i. **240** (1.0 equiv.), **236** (1.1 equiv.), DCC (1.1 equiv.), DMAP (0.1 equiv.), Et_2O, 18 °C, 2 days.

Scheme 76

Having successfully attached the sterically least encumbered auxiliary **236** to the isoxazole **240**, coupling of the more sterically demanding menthyl-based auxiliary **237** was attempted. However, treatment of isoxazolecarboxylic acid **240** with the chiral alcohol **237** in the presence of the DCC/DMAP coupling reagent was unsuccessful, even after prolonged reflux in THF. Use of *N*-methyl-2-chloropyridinium iodide (Mukaiyama's reagent)[180] **242** and 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMTMM)[181] **243** as alternative coupling reagents did not effect esterification. Lewis acid-catalysed transesterification was also attempted. However, treatment of the 4-methoxycarbonylisoxazole **117** with the chiral alcohol **237** in the presence of trimethylaluminium[182] gave no reaction, even with prolonged heating in refluxing toluene.

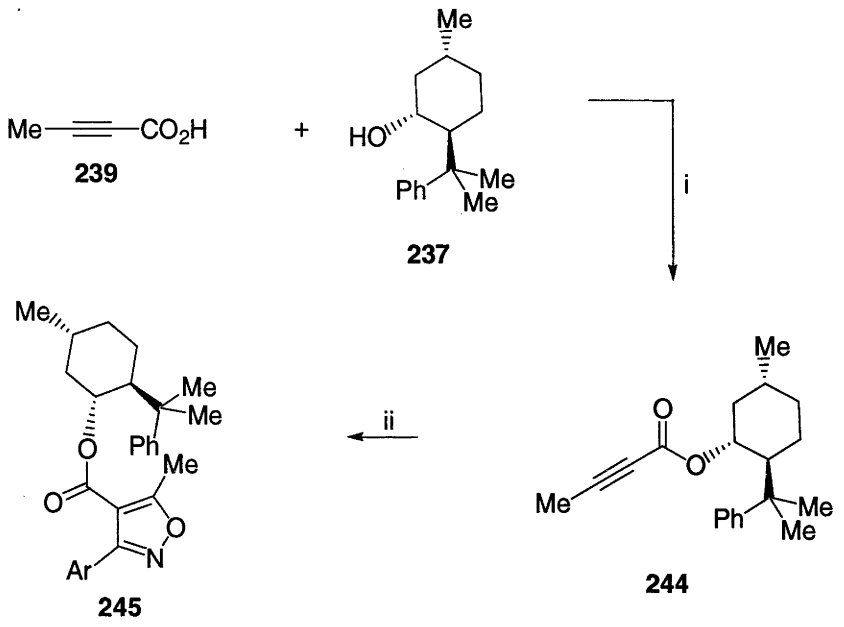


242



243

The failure to react the isoxazoles **240** and **117** with the chiral alcohol **237** indicates that the bulk of the isoxazole C3-mesityl and C5-methyl groups probably hinders these processes. In order to overcome the problem of steric crowding, the chiral isoxazole **245** was synthesized from cycloaddition of the chiral dipolarophile **244** with mesitonitrile oxide **5**. The chiral dipolarophile **244** was prepared in 86% yield from DCC/DMAP-mediated esterification of 2-butynoic acid **239** with the chiral alcohol **237** (Scheme 77). The ^{1}H NMR spectral data, melting point and optical rotation of alkyne **244** are in agreement with literature values.[183]



Ar = 2,4,6-Me_3Ph

Reagents and conditions: i. **239** (1.0 equiv.), **237** (1.1 equiv.), DCC (1.1 equiv.), DMAP (0.1 equiv.), Et_2O, 18 °C, 48 h; ii. **244** (1.0 equiv.), **5** (1.0 equiv.), THF, reflux, 5 days.

Scheme 77

Only the 4-acylisoxazole **245** was isolated from the reaction of dipole **5** with alkyne **244**. Lack of NOE interactions between the *o,o'*-mesityl methyl and the isoxazole C5-methyl groups indicated that the acyl group was substituted at the 4-position of the trisubstituted isoxazole **245**. Using the EI method, accurate mass measurement of the parent ion at *m/z* 459 indicated the molecular composition of $C_{30}H_{37}NO_3$. In the ^1H NMR spectrum, conformational restriction was indicated by the signals of the mesityl methyl groups, which were seen as three distinct singlets at δ 2.04 ppm, δ 2.11 ppm and δ 2.36 ppm, each integrating for three protons. The signal of the isoxazole C5-methyl group was observed as a three proton singlet at δ 2.43 ppm whilst that of the C1 proton of the chiral auxiliary resonated as a triplet of doublets at δ 4.98 ppm (J = 10.7, 4.1 Hz), integrating for one proton. In the infrared spectrum, the carbonyl stretching vibration

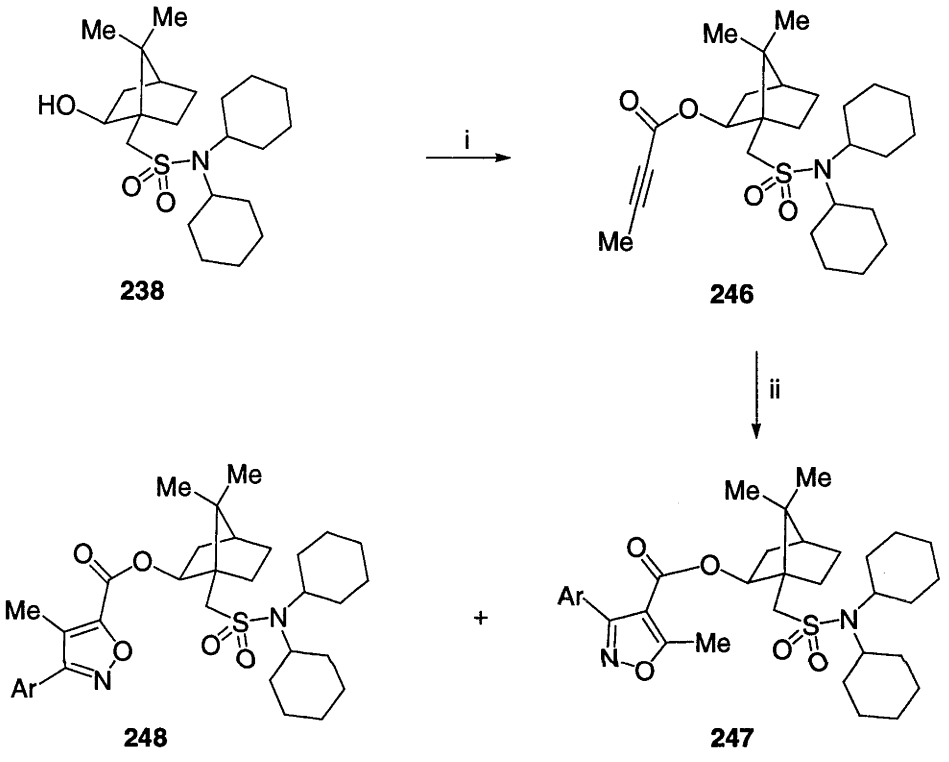
was seen as an intense absorption band at 1712 cm^{-1}. Chiral isoxazole **245** was produced in 93% yield.

Given that the camphor-based alcohol **238** is even more sterically hindered than the (-)-8-phenylmenthol auxiliary **237**, synthesis of the chiral isoxazole **247** was therefore undertaken *via* cycloaddition of dipole **5** with chiral alkyne **246**. Initially, synthesis of the chiral alkyne **246** was attempted *via* DCC/DMAP coupling of the sterically demanding alcohol **238** with 2-butynoic acid **239**. However, this was unsuccessful, probably due to the steric bulk of the chiral auxiliary **238**. Low yields of esters have been observed for esterifications of tertiary and other sterically demanding alcohols using DCC/DMAP as the coupling reagents,[184] probably caused by hindered attack on the intermediate *O*-acylureas by bulky tertiary or chiral alcohols. As reactions using Mukaiyama's reagent **242** and DMTMM **243** also involve bulky acyl-intermediates, coupling of chiral alcohol **238** and carboxylic acid **240** with these reagents was not attempted. Instead, the chiral dipolarophile **246** was synthesized in 95% yield from trimethylaluminium-catalysed transesterification of methyl tetrolate **17a** with alcohol **238** (Scheme 78).

The EI mass spectrometric and ^1H NMR spectrocopic data of the 1,2-disubstituted acetylene **246** are fully consistent with the assigned structure. The molecular ion was detected at *m/z* 463, for which accurate mass analysis indicated the structural composition of $C_{26}H_{41}NO_4S$. In the ^1H NMR spectrum, the signal of the C1 proton of the chiral auxiliary was observed as a one proton doublet of doublets at δ 5.04 ppm (J = 7.9, 3.0 Hz). The methyl group attached to the alkynyl carbon *beta* to the ester carbonyl group resonated as a three proton singlet at δ 1.92 ppm. In the infrared region, the carbonyl stretching vibration was seen as an intense absorption band at 1708 cm^{-1}.

With the dipolarophile **246** in hand, it was treated with mesitonitrile oxide **5** (Scheme 78). The isoxazoles **247** and **248**, produced in a combined yield of 94%, were separated by chromatography and their structures were assigned with the aid of NOE experiments. For the 4-acylisoxazole **247**, lack of NOE interactions between the mesityl *o,o'*-methyl and the isoxazole C5-methyl groups was observed, whilst for the

5-acylisoxazole **248**, strong NOE interactions were seen for the mesityl *o,o'*-methyl and the isoxazole C4-methyl groups.



Ar = 2,4,6-Me_3Ph

Reagents and conditions: i. **238** (1.1 equiv.), **17a** (1.0 equiv.), $AlMe_3$ (1.2 equiv.), toluene, reflux, 3 days; ii. **246** (1.0 equiv.), **5** (1.5 equiv.), THF, reflux, 10 days.

Scheme 78

Using the EI method, accurate mass measurement of the parent ion of each of the isoxazoles **247** and **248** at *m/z* 624 indicated the molecular composition of $C_{36}H_{52}N_2O_5S$. In the ^1H NMR spectra, the signals of the C1 proton of the chiral auxiliary for **247** and **248** were observed as one proton doublet of doublets at δ 5.27 ppm (J = 7.8, 3.0 Hz) and δ 5.22 ppm (J = 8.0, 3.6 Hz), respectively. Conformational restriction is also implicated

from the ^{1}H NMR data. For the 4-acylisoxazole **247**, the signals of the mesityl methyl groups were seen as three singlets at δ 2.01 ppm, δ 2.03 ppm and δ 2.08 ppm, each integrating for three protons. Those of the 5-acylisoxazole **248** were also observed as three proton singlets, at δ 2.04 ppm, δ 2.12 ppm and δ 2.29 ppm. The isoxazole C5-methyl group of **247** and the isoxazole C4-methyl group of **248** resonated as singlets, integrating for three protons each, at δ 2.33 ppm and δ 2.74 ppm, respectively. In the infrared spectra, the carbonyl stretching vibrations of **247** and **248** were observed as intense absorption bands at 1723 cm^{-1} and 1725 cm^{-1}, respectively.

The regioisomeric isoxazoles **247** and **248** were furnished in a ratio of 1:6.2. The polar effects that would favour formation of the 4-acylisoxazole **247** are dominated by steric effects as interactions between the chiral auxiliary and the mesityl group are minimized in the transition state leading to the 5-acylisoxazole **248**.

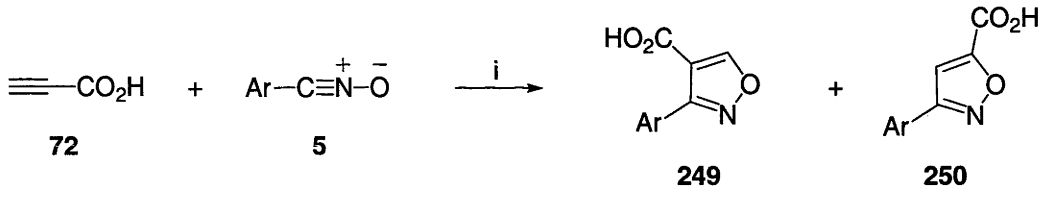
5.2.2. Synthesis of Chiral Disubstituted Isoxazoles for Zinc-copper(I) Iodide-mediated Alkylations

The demethylated analogues **251**, **253** and **256** of the trisubstituted isoxazoles **241**, **245** and **247** were also prepared, for use in alkylation studies. Trimethylaluminium-catalysed transesterification of isoxazole **12f** with the least hindered chiral alcohol **236** was first attempted. Disappointingly, a complex mixture resulted from reaction at reflux in toluene for 16 hours.

Unable to prepare the chiral isoxazole **251** *via* transesterification of **12f**, **251** was instead synthesized from esterification of the isoxazole-4-carboxylic acid **249** with the chiral alcohol **236** (Scheme 80). The isoxazole-4-carboxylic acid **249** was produced with the 5-substituted regioisomer **250**, from the reaction of mesitonitrile oxide **5** with propiolic acid **72** (Scheme 79). Unfortunately, the products were inseparable by chromatography. Accurate mass measurement of their parent ions at *m/z* 231 analyzed for the molecular compositions of $C_{13}H_{13}NO_3$. In the ^{1}H NMR spectrum of the mixture,

the signal of the C5 isoxazole proton of the 4-acylisoxazole **249** was seen at δ 9.16 ppm as a one proton singlet, whilst that of the C4 isoxazole proton of the 5-substituted regioisomer **250** was seen as a one proton singlet at δ 6.98 ppm. In the infrared spectrum, the carbonyl stretching vibrations of both regioisomers were observed as an intense absorption band at 1700 cm^{-1}.

The isoxazolecarboxylic acids **249** and **250** were obtained in a ratio of 1.3:1, in a combined yield of 97%. The product ratio indicates that the polar and steric effects are counterbalanced in the cycloaddition of dipole **5** with alkyne **72**.



72 **5** **249** **250**

Ar = 2,4,6-Me_3Ph

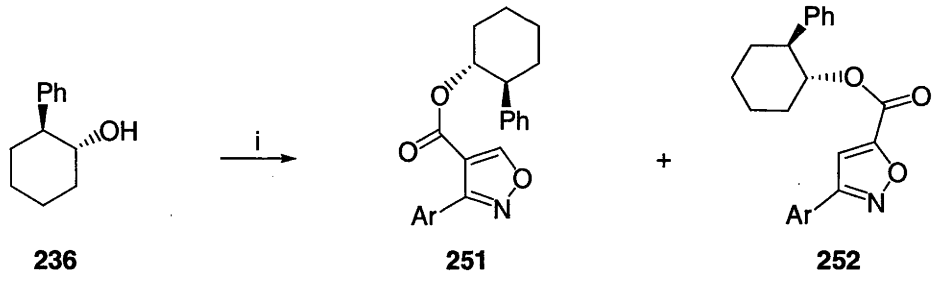
Reagents and conditions: i. **72** (1.0 equiv.), **5** (1.0 equiv.), THF, reflux, 2 days.

Scheme 79

The inseparable mixture of **249** and **250** was treated with DCC/DMAP and the cyclohexyl-based alcohol **236**. This gave rise to regioisomeric isoxazoles **251** and **252** in a ratio of 1.3:1 with a combined yield of 88% (Scheme 80).

The chiral isoxazoles **251** and **252** were separated by chromatography and characterized. Their structures were deduced from EI mass spectrometry and ^1H NMR spectroscopy. Accurate mass measurement of the parent ion of each of the isoxazoles **251** and **252** at *m/z* 389 indicated a molecular composition of $C_{25}H_{27}NO_3$. In the ^1H NMR spectrum of the 4-acylisoxazole **251**, the signal of the C1 proton of the chiral auxiliary was observed as a triplet of doublets at δ 5.06 ppm (J = 10.6, 4.4 Hz), integrating for one proton. The signal of the C5 isoxazole proton resonated at δ 8.87 ppm, as a one proton singlet. The mesityl methyl protons were observed as three

uncharacteristically upfield singlets at δ 1.80 ppm, δ 1.91 ppm and δ 2.37 ppm, integrating for three protons each. This indicates π-stacking as well as restricted motion of the mesityl group, possibly due to interaction with the phenyl ring of the chiral auxiliary. In the infrared spectrum, an intense absorption band at 1717 cm^{-1} was assigned to the carbonyl stretching vibration. Crystals of the 4-acylisoxazole **251** were obtained from recrystallization from a mixture of hexanes and ether at 0 °C. The material was analyzed by X-ray crystallography and the ORTEP diagram is shown in Figure 30. The ^1H NMR spectrum of the 5-substituted isoxazole **252** showed no indication of π-stacking or restricted motion. The C4 isoxazole proton was seen as a one proton singlet at δ 6.63 ppm, whilst the *o,o'*-methyl and *p*-methyl groups of the mesityl ring were observed as two singlets at δ 2.07 ppm and δ 2.31 ppm, integrating for six and three protons, respectively. The signal of the C1 proton of the chiral auxiliary resonated as a triplet of doublets at δ 5.20 ppm (J = 10.6, 4.0 Hz), integrating for one proton. In the infrared spectrum, the carbonyl stretching vibration was seen as a strong absorption band at 1739 cm^{-1}.

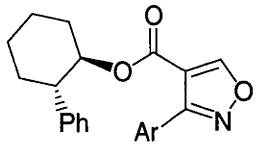


236 **251** **252**

Ar = 2,4,6-Me_3Ph

Reagents and conditions: i. **249** and **250** (1.0 equiv.), **236** (1.1 equiv.), DCC (1.1 equiv.), DMAP (0.1 equiv.), Et_2O, 18 °C, 2 days.

Scheme 80



251

Ar = 2,4,6-Me_3Ph

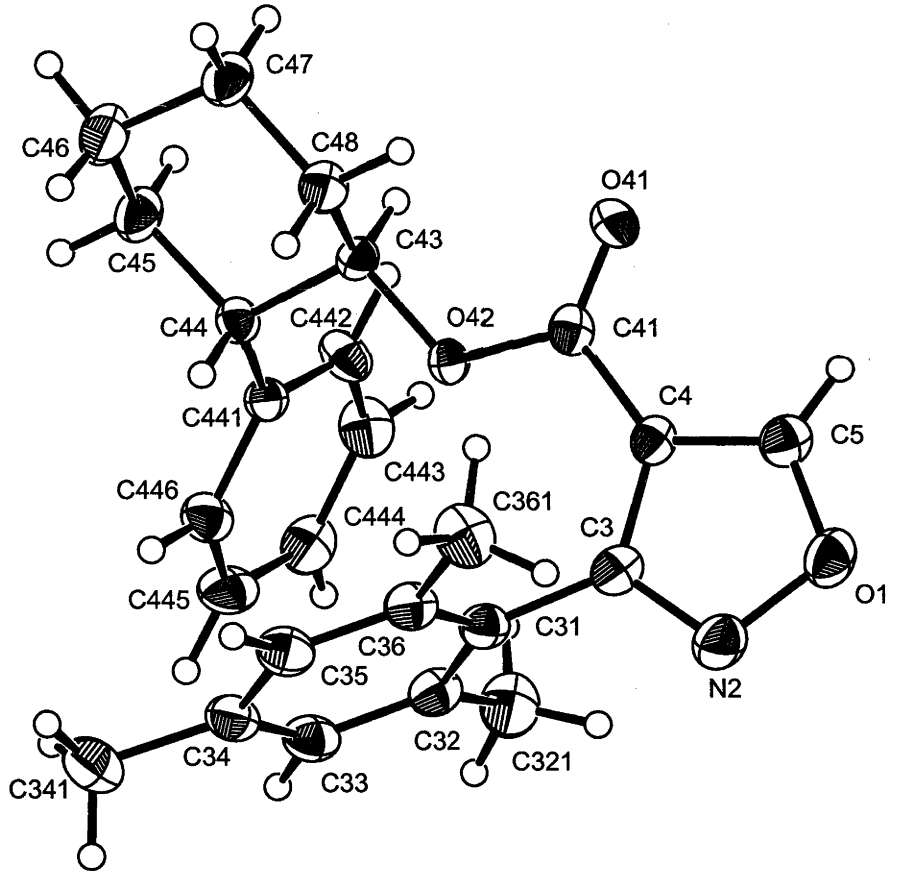
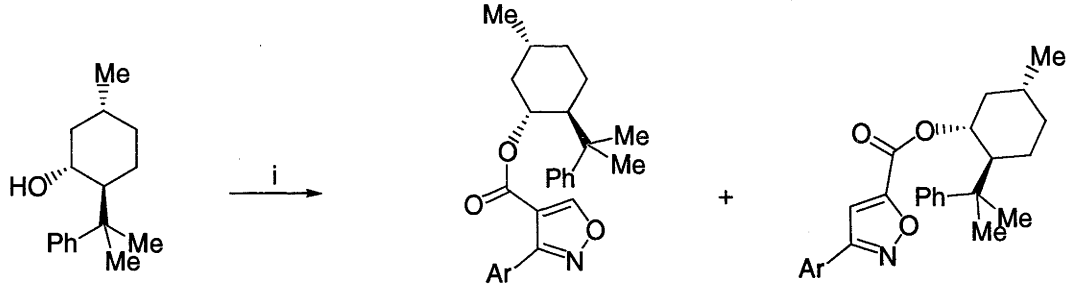


Figure 30. ORTEP derived from single crystal X-ray analysis of compound **251**.

The methodology described above was also used to effect coupling of the carboxylic acids **249** and **250** with the chiral alcohol **237**. This furnished the 4- and 5-acylisoxazoles **253** and **254** in a ratio of 1.3:1, with a combined yield of 85% (Scheme 81).



237 **253** **254**

Ar = 2,4,6-Me_3Ph

Reagents and conditions: i. **249** and **250** (1.0 equiv.), **237** (1.1 equiv.), DCC (1.1 equiv.), DMAP (0.1 equiv.), Et_2O, 18 °C, 2 days.

Scheme 81

The chiral isoxazoles **253** and **254** were separated by chromatography and characterized. Using the EI method, the parent ion of each of the isoxazoles **253** and **254** was detected at *m/z* 445 for which the molecular composition was determined to be $C_{29}H_{35}NO_3$. In the ^1H NMR spectrum of the 4-acylisoxazole **253**, the signal of the C1 proton of the chiral auxiliary was seen as a one proton triplet of doublets at δ 4.86 ppm (J = 10.9, 4.3 Hz). The signal of the C5 isoxazole proton was observed as a one proton singlet, uncharacteristically upfield at δ 7.74 ppm. This implies π-stacking interactions between the phenyl group and the isoxazole ring. Restricted motion was indicated by the non-equivalent signals of the two mesityl ring protons, which gave rise to two distinct singlets at δ 6.91 ppm and δ 6.95 ppm, integrating for one proton each. In the infrared

spectrum, the carbonyl stretching vibration was observed as an intense absorption band at 1723 cm^{-1}.

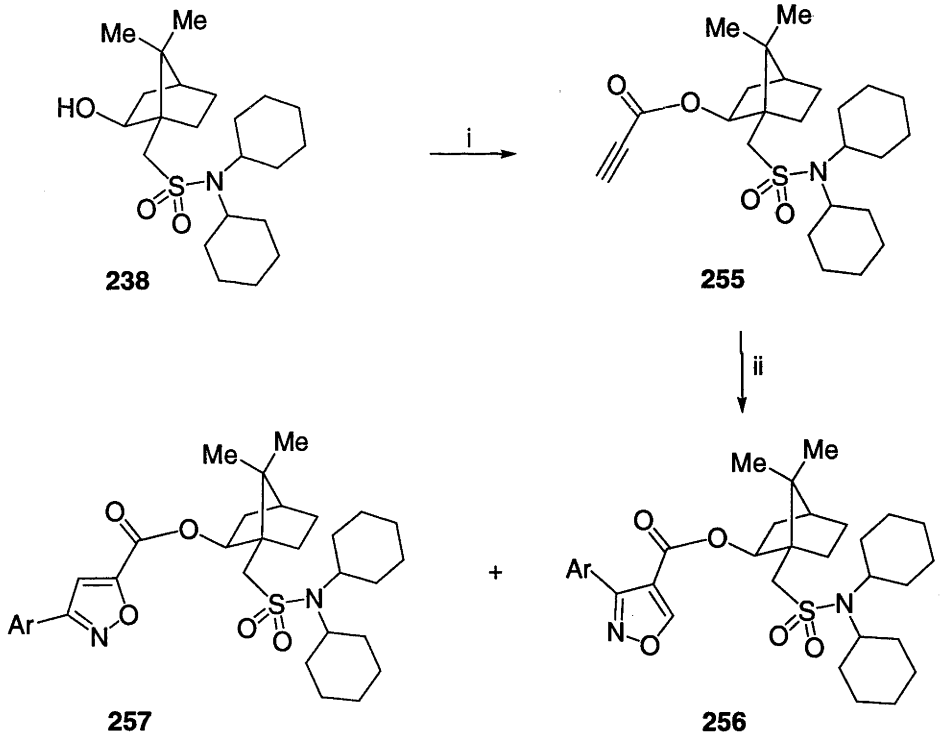
For the 5-acylisoxazole **254**, there was no evidence of π-stacking or restricted motion. The signal of the C4 isoxazole proton was observed as a one proton singlet at δ 6.29 ppm. The mesityl *o,o'*-methyl and *p*-methyl groups resonated as two singlets at δ 2.11 ppm and δ 2.33 ppm, integrating for six and three protons, respectively. A triplet of doublets at δ 5.12 ppm (J = 10.6, 4.1 Hz), integrating for one proton, was assigned to the C1 proton of the chiral auxiliary. In the infrared spectrum, the carbonyl stretching vibration was seen as an intense absorption band at 1733 cm^{-1}.

Coupling of the camphor-based auxiliary **238** with the isoxazolecarboxylic acids **249** and **250** was also attempted using DCC/DMAP. However, esterification was not effected even after prolonged reflux in THF for 2 days. This is possibly due to the steric bulk of the chiral auxiliary **238**. These putative unfavorable steric effects were overcome through synthesizing the 4-acylisoxazole **256** through the cycloaddition of dipole **5** with chiral dipolarophile **255**. The chiral dipolarophile **255** was prepared in 95% yield from trimethylaluminium-catalysed transesterification of methyl propiolate **11** with alcohol **238** (Scheme 82).

The structure of the chiral alkyne **255** was deduced from EI mass spectrometry and ^1H NMR spectroscopy. Accurate mass measurement of the parent ion at *m/z* 449 indicated the molecular composition of $C_{25}H_{39}NO_4S$. In the ^1H NMR spectrum, the signal of the C1 proton of the chiral auxiliary was observed as a doublet of doublets at δ 5.10 ppm (J = 7.6, 2.7 Hz), integrating for one proton. The alkynyl proton was seen as a one proton singlet at δ 2.80 ppm. In the infrared spectrum, the carbonyl stretching vibration was observed as an intense absorption band at 1713 cm^{-1}.

The regioisomeric isoxazoles **256** and **257** were separated by chromatography and characterized. Using the EI method, accurate mass measurement of the parent ion at *m/z* 610 for each of the isomers **256** and **257** indicated the molecular composition of $C_{35}H_{50}N_2O_5S$. In the ^1H NMR spectrum of the 4-acylisoxazole **256**, the signal of the isoxazole C5 proton was observed as a one proton singlet at δ 8.90 ppm. As seen for

4-acylisoxazoles **251** and **253**, restricted motion was also indicated for the isoxazole **256**. The signals of the mesityl methyl protons were observed as three distinct singlets, integrating for three protons each, at δ 2.06 ppm, δ 2.09 ppm and δ 2.30 ppm. Restricted motion is likely to be a consequence of the steric interactions between the camphor-based auxiliary and the mesityl ring. The C1 proton of the chiral auxiliary was observed as a doublet of doublets at δ 5.14 ppm (J = 7.8, 3.0 Hz), integrating for one proton. In the infrared spectrum, an intense absorption band at 1731 cm^{-1} was assigned to the carbonyl stretching vibration.



Reagents and conditions: i. **238** (1.0 equiv.), **11** (1.2 equiv.), $AlMe_3$ (1.1 equiv.), toluene, reflux, 72 h; ii. **5** (1.0 equiv.), **255** (1.0 equiv.), THF, reflux, 7 days.

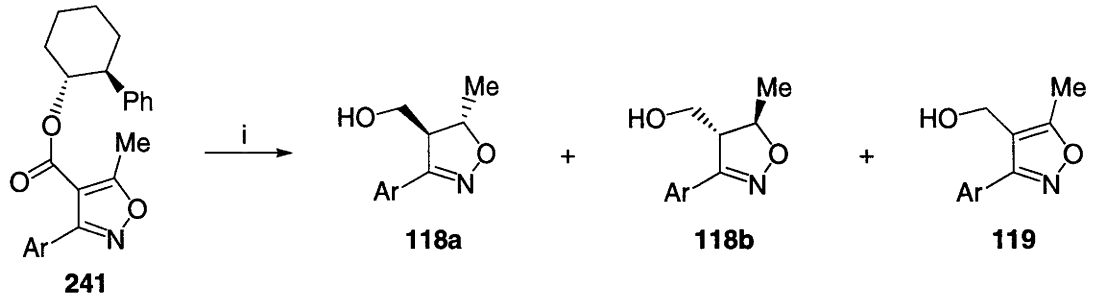
Scheme 82

For the 5-acylisoxazole **257**, the signal of the isoxazole C4 proton was seen as a one proton singlet at δ 6.97 ppm. No evidence of restricted motion was indicated for the 5-acylisoxazole **257**, as the mesityl *o*,*o*'-methyl and *p*-methyl groups were observed as two singlets at δ 2.12 ppm and δ 2.33 ppm, integrating for six and three protons, respectively. The signal of the C1 proton of the chiral auxiliary resonated as a one proton doublet of doublets at δ 5.31 ppm (J = 7.7, 3.2 Hz). In the infrared spectrum, the carbonyl stretching vibration was observed at 1731 cm^{-1}.

The regioisomeric isoxazoles **256** and **257** were produced in yields of 19% and 56%, respectively. Whilst formation of the 4-acylisoxazole **256** is favoured by polar effects, the 5-acylisoxazole **257** is the major product due to dominant steric effects as unfavorable steric interactions between the chiral auxiliary and the mesityl group are less severe in the reaction transition state leading to the 5-acylisoxazole **257**. The slow rate observed for cycloaddition of dipole **5** with the chiral dipolarophile **255** is consistent with steric effects associated with the bulk of the chiral auxiliary.

5.2.3. Reductions of Chiral 4-Acylisoxazoles

The stereoselectivity of the borohydride reduction of the chiral 4-acylisoxazoles **241**, **245** and **247** was examined. Isoxazole **241** was initially treated with sodium borohydride in refluxing ethanol (Scheme 83). The rate of the reduction was impractically slow. After 7 days, the *trans*-2-isoxazoline **118** and the isoxazole **119** were afforded in yields of 14% and 7%, respectively. None of the *cis*-2-isoxazoline **137** was detected in the product mixture by ^{1}H NMR spectroscopy. The 2-isoxazolines **118** and **137**, and isoxazole **119** were synthesized previously through reduction of isoxazole **117** with sodium borohydride and lithium borohydride (see Chapter 3, Sections 3.3 and 3.5.). The ratio of the 2-isoxazoline **118** and the isoxazole **119** seen in the reduction of the isoxazole **241** with sodium borohydride is the same as that observed for the analogous reaction with achiral isoxazole **117** (see Chapter 3, Section 3.3.).



Ar = 2,4,6-Me_3Ph

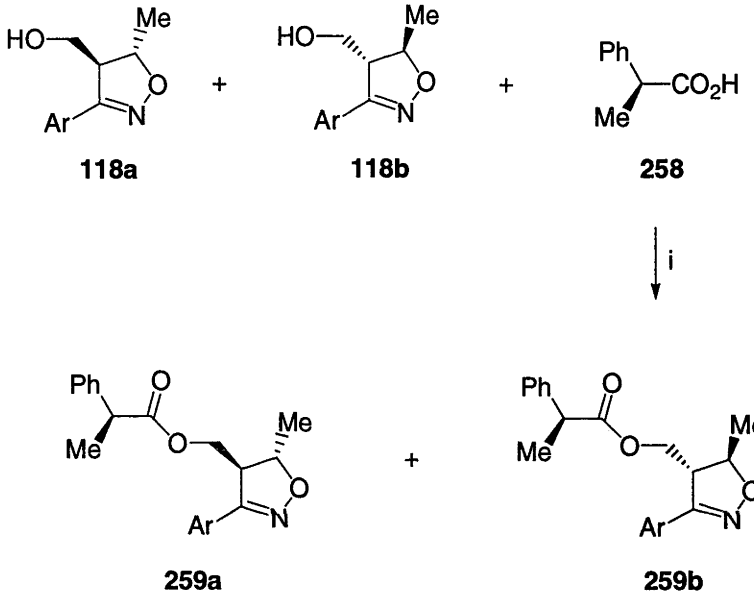
Reagents and conditions: i. **241** (1.0 equiv.), $NaBH_4$ (15.0 equiv.), EtOH, reflux, 7 days

Scheme 83

The enantiopurity of the 2-isoxazoline **118** was determined with the chiral resolving agent, (*S*)-2-phenylpropionic acid **258**[185] (Scheme 84). The chiral ester **259** was produced with the DCC/DMAP coupling reagent. Disappointingly, ^1H NMR analysis indicated the chiral ester **259** was formed with 10% *d.e.* This indicates that the borohydride reduction of chiral isoxazole **241** also proceeded with 10% *e.e.*

The major diastereomer of **259** was isolated from the mixture. Using the EI method, accurate mass measurement of the molecular ion at *m/z* 365 indicated the structural composition of $C_{23}H_{27}NO_3$. In the ^1H NMR spectrum, the signal of the C4 isoxazoline proton was seen as a one proton multiplet at δ 3.39 ppm whilst that of the C5 isoxazoline proton was observed as an apparent pentet, integrating for one proton, at δ 4.49 ppm (J = 6.8 Hz). Two multiplets at δ 4.00 ppm and δ 4.09 ppm, each integrating for one proton, were assigned to the methylene protons. The signal of the methine proton *alpha* to the carbonyl group was observed as a one proton quartet at δ 3.59 ppm (J = 7.3 Hz). In the upfield region, two doublets at δ 1.31 ppm (J = 6.2 Hz) and δ 1.42 ppm (J = 7.3 Hz), each integrating for three protons, were assigned to the methyl groups at C5 and *beta* to the carbonyl group. An intense absorption band at 1736 cm^{-1} was assigned to the carbonyl stretching vibration. The minor diastereomer of **259** was not isolated. In the ^1H NMR spectrum of the product mixture, two doublets at δ 1.33

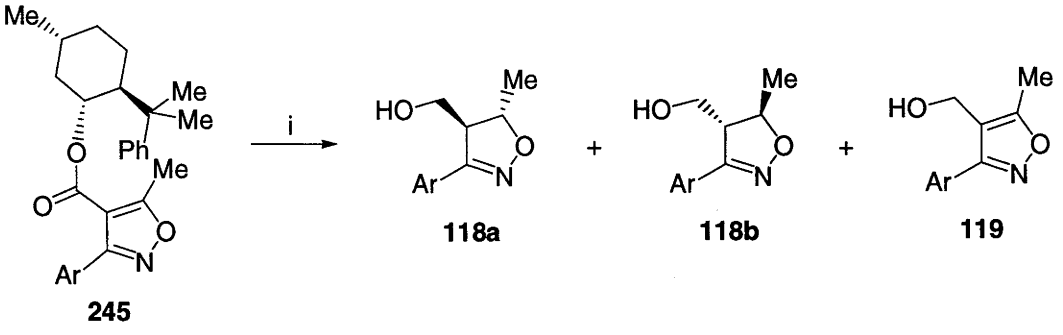
ppm (J = 6.2 Hz) and δ 1.40 ppm (J = 7.3 Hz), each integrating for three protons, were assigned to the methyl groups at C5 and *beta* to the carbonyl group of the minor diastereomer of **259**. The signals of the C4- and C5-isoxazoline protons, the methylene protons and the methine proton *alpha* to the carbonyl group were not distinct from those of the major diastereomer of **259**.



Reagents and conditions: i. **118** (1.0 equiv.), **258** (1.0 equiv.), DCC (1.1 equiv.), DMAP (0.1 equiv.), Et_2O, 18 °C, 48 h.

Scheme 84

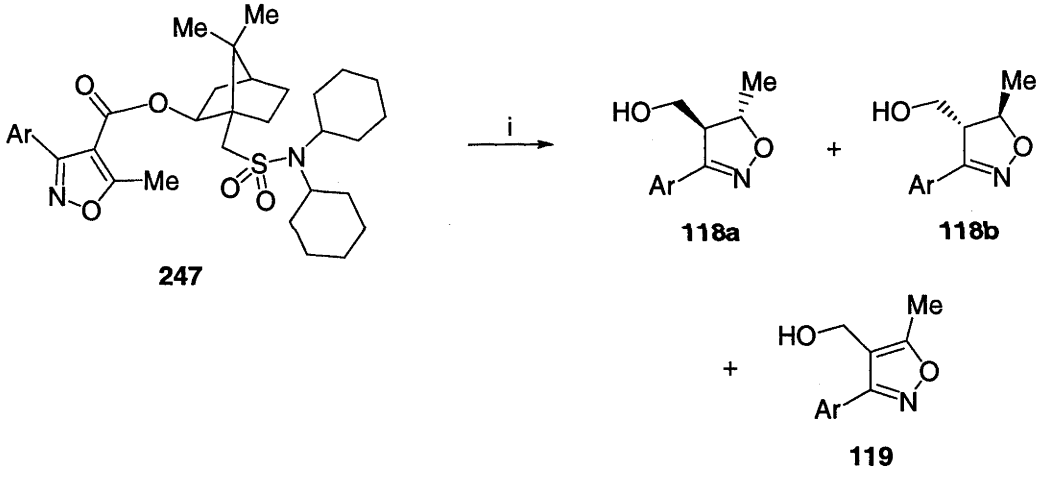
In an attempt to achieve a more enantioselective reaction, the sterically more hindered 4-acylisoxazoles **245** and **247** were treated with sodium borohydride (Schemes 85 and 86).



Ar = 2,4,6-Me_3Ph

Reagents and conditions: i. **245** (1.0 equiv.), $NaBH_4$ (15.0 equiv.), EtOH, reflux, 16 days.

Scheme 85



Ar = 2,4,6-Me_3Ph

Reagents and conditions: i. **247** (1.0 equiv.), $NaBH_4$ (15.0 equiv.), EtOH, reflux, 16 days.

Scheme 86

Presumably, due to the steric bulk of the chiral auxiliaries, the reactions of borohydride with isoxazoles **245** and **247** were even slower than that observed with **241**. Analysis of the product mixtures indicated formation of the *trans*-2-isoxazoline **118** and

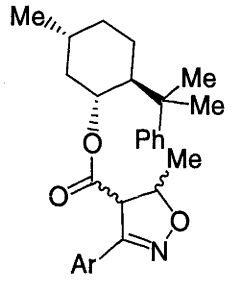
isoxazole **119** in a 2:1 ratio, with none of the *cis*-isomer **137** produced. The 2-isoxazoline **118** was obtained in yields of *ca.* 10-15%. Coupling of these samples of 2-isoxazoline **118** with the chiral carboxylic acid **258** gave rise to stereoisomers **259a,b** (as described above for Scheme 84), with a diastereomeric excess of *ca.* 8-10%. The reactions of chiral isoxazoles **241**, **245** and **247** with sodium borohydride therefore show complete selectivity for formation of *trans*-2-isoxazolines, also observed in analogous reactions with the achiral system **117**. Despite this, poor facial selectivity is seen in reductions of **241**, **245** and **247**.

The low facial selectivity observed in the reductions of chiral isoxazoles **241**, **245** and **247** led to the use of L-Selectride® as an alternative reducing agent. Reaction of isoxazole **247** with L-Selectride® was initially examined. The isoxazole **247** was treated with a stoichiometric amount of L-Selectride® at 0 °C for 10 minutes. However, ^{1}H NMR analysis of the mixture indicated no reaction had occurred. A similar mixture was then left for 18 hours but again, no reaction resulted. The inert behaviour of **247** to L-Selectride® is probably because the chiral auxiliary provides too much steric hindrance.

Reactions of isoxazole **245** with L-Selectride® were next examined (Table 31). The mixtures were analyzed by ^{1}H NMR spectroscopy. Four stereoisomers of 2-isoxazoline **260a-d** were observed and distinguished by their C4 isoxazoline protons, which resonate as doublets at δ 3.00 ppm (J = 11.6 Hz), δ 3.34 ppm (J = 10.6 Hz), δ 3.70 ppm (J = 9.2 Hz) and δ 3.90 ppm (J = 10.3 Hz). Of the four stereoisomers **260a-d**, two of them are *trans* whilst the remaining are *cis*. The relative configuration of **260a,c** and **260b,d** are assigned as *trans* and *cis*, respectively. Since the $J_{4,5}$ coupling constants of *cis*-2-isoxazolines are always larger than those of the *trans*-isomers,[72] the *trans*-2-isoxazolines **260a,c** are therefore likely to be those with $J_{4,5}$ = 9.2 Hz and $J_{4,5}$ = 10.3 Hz.

Compared to the reactions of achiral isoxazole **117** with L-Xelectride® where *trans*- and *cis*-2-isoxazolines **21c** and **140** were obtained in ratios of 1.2:1 to 1.5:1, reductions of isoxazole **245** with L-Selectride® also showed poor stereoselectivity across a range of reaction conditions. Initially, treatment of **245** with L-Selectride® at

–78 °C for 20 hours gave rise to the *trans*-isoxazoline **260a** and the *cis*-isomers **260b,d** in a ratio of 1:2.4:1. Increasing the reaction time from 30 min to 18 h and the reaction temperature from –78 °C to 0 ° C decreased the *cis* to *trans* ratio. The shift from the *cis*-isoxazolines **260b,d** to the *trans*-isoxazolines **260a,c** being the dominant products indicates that the *cis*-isomers **260b,d** are the kinetic products whilst the *trans*-isomers **260a,c** are the thermodynamic products. Due to the equilibrating product mixtures, isolation of any discrete stereoisomers of **260** was impractical.



260a-d

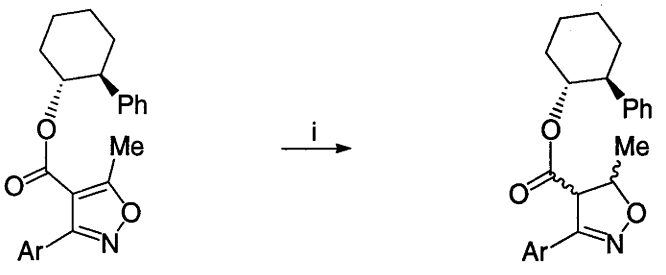
Ar = 2,4,6-Me_3Ph

Table 31. L-Selectride® reductions of isoxazole **245**

Reagents (equiv.)	Conditions	Ratio of 260a:260b:260c:260d
245 (1.0), L-Selectride® (1.1)	Et_2O, - 78 °C, 20 h	1:2.4:0:1
245 (1.0), L-Selectride® (1.1)	Et_2O, 0 °C, 30 min	1 4.8:0:2.2
245 (1.0), L-Selectride® (1.1)	Et_2O, 0 °C, 2 h	1:2.1:0.29:0.76
245 (1.0), L-Selectride® (1.1)	Et_2O, 0 °C, 18 h	1:0.21:1.44:0

Finally, reaction of isoxazole **241** with L-Selectride® (1.1 equivalent) was examined (Scheme 87). Of the four possible stereoisomers of **261**, only two were detected in the product mixture by ^1H NMR spectroscopy. The two diastereomeric

products **261a,b** were differentiated by the signals of the C4 isoxazoline protons, which resonate as doublets at δ 3.70 ppm (J = 10.4 Hz) and δ 3.80 ppm (J = 10.8 Hz). The 2-isoxazolines **261a,b** were produced in a ratio of 2:1.



241 **261a,b**

Ar = 2,4,6-Me_3Ph

Reagents and conditions: i. **241** (1.0 equiv.), L-Selectride® (1.1 equiv.), Et_2O, 0 °C, 18 h.

Scheme 87

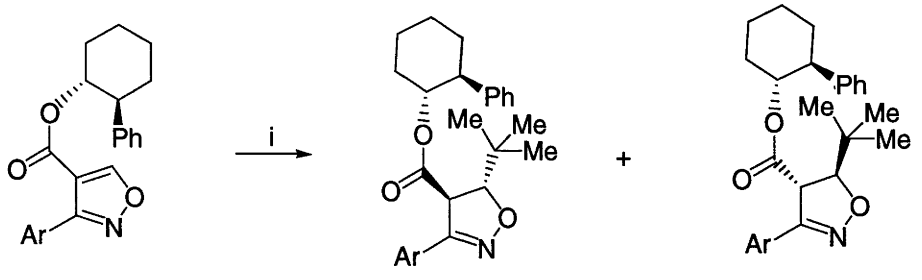
Since reactions of achiral isoxazole **117** with L-Selectride® under similar reaction conditions usually give rise to a mixture of the *trans*-2-isoxazoline **21c** and the *cis*-isomer **140** in ratios of 1.2:1 to 1.5:1, this suggests that the major diastereomer of **261** (with $J_{4,5}$ = 10.4 Hz) is likely to be of *trans*-configuration, given that it also has the smaller coupling constant of the two diastereomers **261a,b**. Assignment of the relative configuration of the minor diastereomer of **261** is more difficult. Since the $J_{4,5}$ coupling constant of the minor diastereomer is similar to that of the major diastereomer of **261**, it may be that the relative configuration of the minor diastereomer is also *trans*, thereby indicating that the reduction occurred with no facial selectivity but with complete selectivity for the *trans*-configured isoxazolines. It is also possible that the relative configuration of the minor diastereomer is *cis*, by analogy to the product mixture of *trans*- and *cis*-isoxazolines **21c** and **140** observed in the reactions of **117** with L-Selectride®. This would then imply that the reaction of **241** with L-Selectride® showed

complete facial selectivity whilst no selectivity was observed for the relative configuration of the isoxazoline products **261a,b**.

Overall, the reactions of the chiral isoxazoles **241**, **245** and **247** with sodium borohydride and L-Selectride® show selectivity for formation of isoxazolines of *trans*-configuration, similar to that observed in analogous reactions with achiral isoxazole **117**. Despite this, poor facial stereoselectivity was observed in reactions of **241**, **245** and **247** with sodium borohydride and L-Selectride®.

5.2.4. Alkylations of Chiral 4-Acylisoxazoles

Unsuccessful with developing an asymmetric borohydride reduction of chiral 4-acylisoxazoles, an alternative route to enantioenriched 2-isoxazolines was pursued, *via* the alkylation methodology established in Chapter 4. Sonication of the chiral 4-acylisoxazole **251** and *tert*-butyl iodide **207** in the presence of a zinc-copper(I) iodide couple gave rise to 2-isoxazolines **262a,b** in 88% yield (Scheme 88).



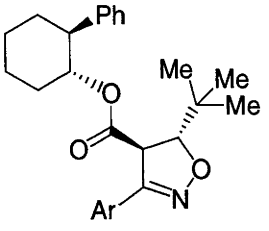
251 **262a** **262b**

Ar = 2,4,6-Me_3Ph

Reagents and conditions: i. **251** (1.0 equiv.), **207** (4 × 3.0 equiv.), Zn (24 × 2.7 equiv.), CuI (24 × 0.8 equiv.), 65% aq. MeOH, ultrasound, 5 °C, 8 days.

Scheme 88

Of the four possible diastereomers of **262** comprising two *trans*- and two *cis*-2-isoxazolines, only **262a** and **262b** were detected by ^{1}H NMR spectroscopy. The structural elements of the major diastereomer **262a** were deduced by EI mass spectrometry and ^{1}H NMR spectroscopy. The molecular ion was detected at *m/z* 447, for which accurate mass measurement indicated the structural composition of $C_{29}H_{37}NO_3$. In the ^{1}H NMR spectrum, a one proton triplet of doublets at δ 4.85 ppm (J = 10.8, 4.1 Hz) was assigned to the C1 proton of the chiral auxiliary. Upfield, the *tert*-butyl group resonated as a singlet, integrating for nine protons, at δ 0.68 ppm. The signals of the C4- and C5-isoxazoline protons were observed as doublets, each integrating for one proton, at δ 3.96 ppm (J = 11.4 Hz) and δ 4.57 ppm (J = 11.4 Hz), respectively. As discussed in Chapter 4, the magnitude of the $J_{4,5}$ coupling constant is affected by the steric bulk of the C4- and C5-substituents. The relative configuration of the major diastereomer of **262** therefore could not be unequivocally assigned based on the $J_{4,5}$ coupling constant. In order to determine the relative and absolute configuration of the major diastereomer of **262**, crystals were grown from vapour diffusion of hexanes and ether at 0 °C. The material was analyzed by X-ray crystallography and the ORTEP diagram is shown in Figure 31. From the ORTEP diagram, the structure of the major diastereomer was determined to be **262a**, with *trans* configuration across the C4-C5 bond. The absolute configuration at the C5 stereochemical centre was shown to be *S*. In the infrared spectrum, an intense absorption band at 1734 cm^{-1} was assigned to the carbonyl stretching vibration.



262a

Ar = 2,4,6-Me_3Ph

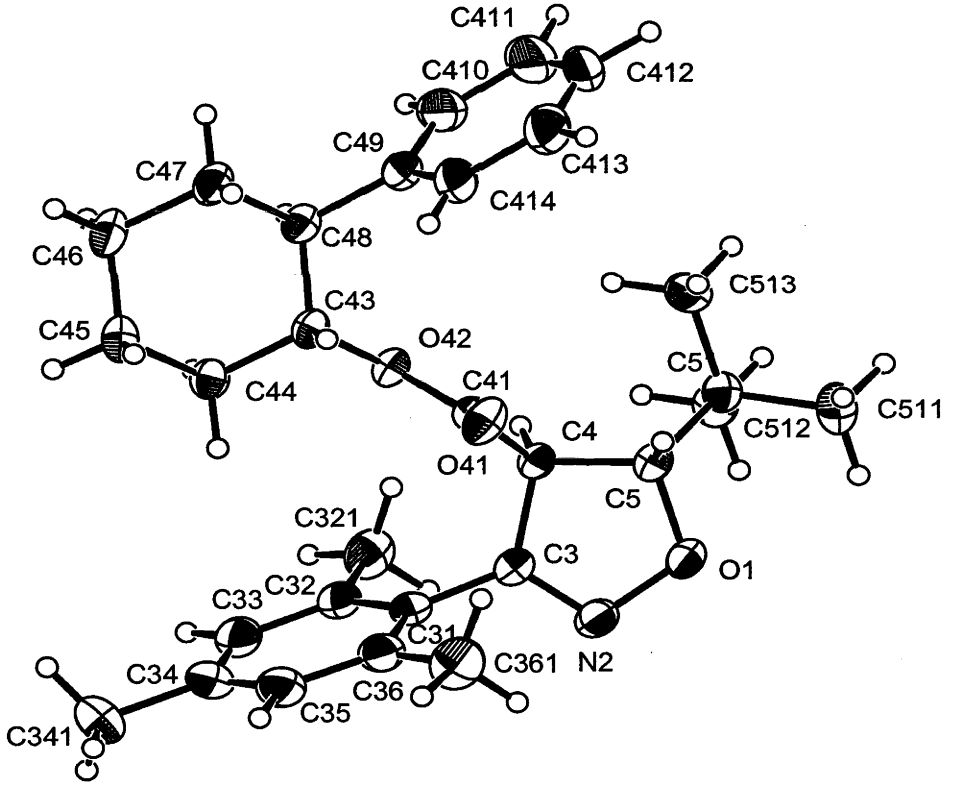


Figure 31. ORTEP derived from single crystal X-ray analysis of compound **262a**.

In the ^{1}H NMR spectrum of the product mixture, the signal of the C1 proton of the chiral auxiliary of the minor diastereomer **262b** was observed as a one proton triplet of doublets, at δ 5.05 ppm (J = 10.7, 4.2 Hz). The *tert*-butyl group resonated as a nine proton singlet, at δ 0.73 ppm. The signals of the C4- and C5-isoxazoline protons of the minor diastereomer **262b** were observed as two doublets, integrating for one proton each, at δ 3.77 ppm (J = 11.5 Hz) and δ 4.59 ppm (J = 11.5 Hz). Comparison of the $J_{4,5}$ coupling constant of **262b** with that of **262a** indicates that the relative configuration of the minor diastereomer is most likely to be *trans*. The *trans*-configuration observed in **262a,b** is also seen in the 2-isoxazoline **208**, produced from the analogous reaction of achiral isoxazole **12f** with *tert*-butyl iodide **207**.

The major diastereomer **262a** was produced in *ca.* 95% *d.e.* Exceptional relative and absolute stereoselectivity were attained in the reaction of chiral 4-acylisoxazole **251** with *tert*-butyl iodide **207**, since one of the four possible stereoisomers was observed in an overwhelming excess.

Isoxazole **251** was examined for structural properties leading to the highly enantioselective reaction. However, the ORTEP diagram of **251** (Figure 30) does not show steric hindrance at either face of the isoxazole ring. This may be attributed to intermolecular interactions in the crystal lattice. To overcome this, the gas phase structure of **251** was modelled using the MM2 method. In the minimum energy conformation, the *Re*-face of the isoxazole ring is shielded by the phenyl ring of the chiral auxiliary, thus restricting approach of *tert*-butyl iodide **207** to the *Si*-face (Figure 32).

Alkylation of the chiral isoxazole **251** with isopropyl iodide **185** was also examined. Of the four possible stereoisomers of **263**, only two were produced. The 2-isoxazolines **263a,b** were afforded in 86% yield (Scheme 89).

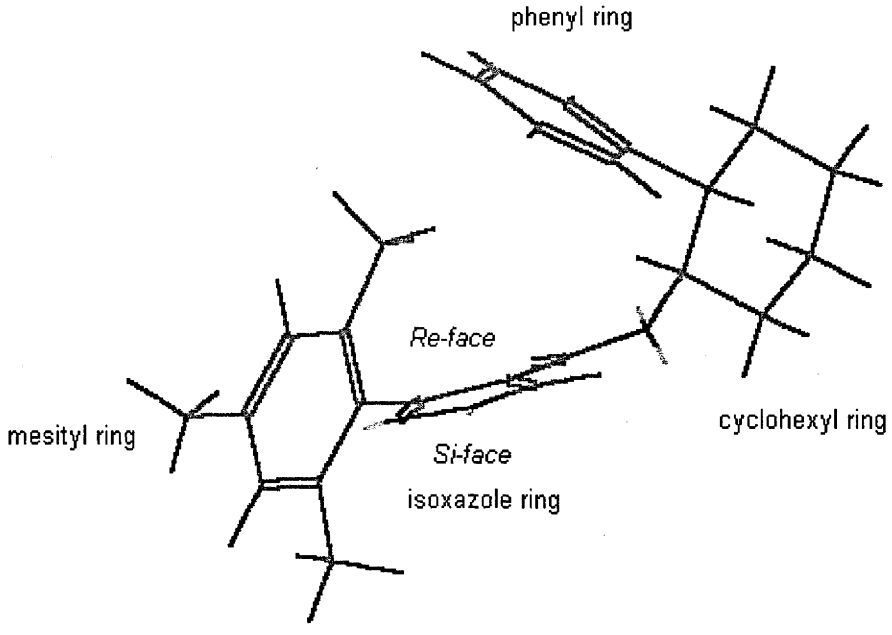
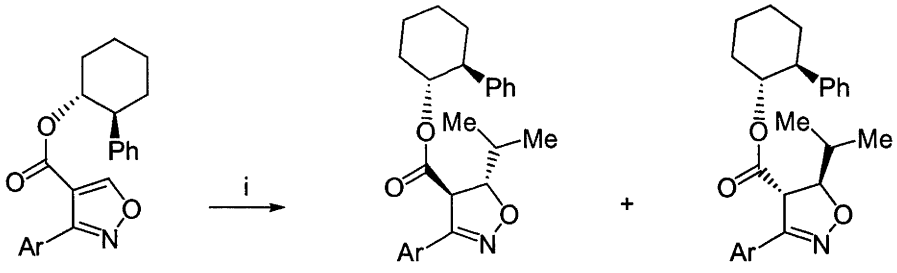


Figure 32. MM2 geometry optimized model of isoxazole **251**



251 **263a** **263b**

Ar = 2,4,6-Me_3Ph

Reagents and conditions: i. **251** (1.0 equiv.), **185** (36 × 3.0 equiv.), Zn (36 × 2.7 equiv.), CuI (36 × 0.8 equiv.), 65% aq. MeOH, ultrasound, 5 °C, 12 days.

Scheme 89

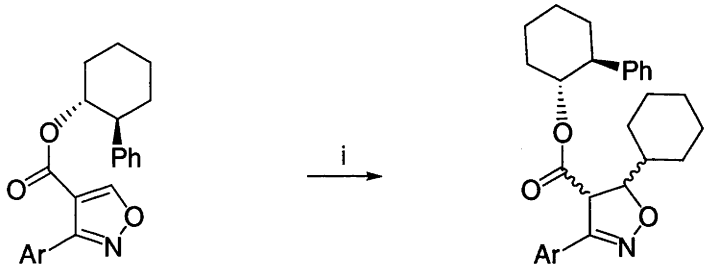
The structural elements of major diastereomer **263a** were deduced from mass spectrometry and ^{1}H NMR spectroscopy. Using the EI method, accurate mass measurement of the parent ion at *m/z* 433 indicated the molecular composition of $C_{28}H_{35}NO_3$. In the ^{1}H NMR spectrum of **263a**, a one proton doublet at δ 3.90 ppm (J = 11.1 Hz) and a one proton doublet of doublets at δ 4.49 ppm (J = 11.1, 7.5 Hz) were assigned to the C4- and C5-isoxazoline protons, respectively. The relative configuration of the major isomer **263a** is likely to be *trans*, by analogy to that of **262a**. A triplet of doublets, integrating for one proton, at δ 4.85 ppm (J = 11.0, 4.3 Hz), was ascribed to the C1 proton of the chiral auxiliary. In the ^{1}H NMR spectrum of the product mixture, the signal of the C4 isoxazoline proton of the minor diastereomer **263b** was observed as a doublet at δ 3.65 ppm (J = 11.0 Hz), whilst the signal of the C5 isoxazoline proton was not distinct from that of the major diastereomer **263a**. The relative configuration of the minor diastereomer **263b** is likely to be *trans*, given the similarity of the $J_{4,5}$ coupling constant of **263b** to that of **263a**. The C1 proton of the chiral auxiliary was seen as a one proton triple of doublets, at δ 5.06 ppm (J = 10.9, 4.2 Hz).

The 2-isoxazoline **263a** was obtained in 93% *d.e.* In order to determine the absolute configuration at the C5 isoxazoline centre, attempts to grow crystals of **263a** were made, however, they were unsuccessful. Despite this, the absolute configuration at C5 of **263a** is deduced to be *S* by analogy to that seen for **262a**.

In the previous chapter, alkylation of the isoxazole **12f** with cyclohexyl iodide **213** gave rise to the 2-isoxazoline **214**, as a mixture of *cis*- and *trans*-isomers in a ratio of 1:1.3. The effect of the chiral auxiliary on the stereoselectivity in the reaction of chiral isoxazole **251** with the alkyl iodide **213** was also examined (Scheme 90).

The resulting product mixture was analyzed by ^{1}H NMR spectroscopy. Three of the four possible stereoisomers of **264** were detected. These were distinguished by the signals of the C4- and C5-isoxazoline protons. The chemical shifts and multiplicities of the signals of the C4- and C5-isoxazoline protons of **264a-c** are shown in Table 32. The stereoisomers **264a-c** were formed in a ratio of 1:1.7:2, respectively. Based on the magnitude of the $J_{4,5}$ coupling constants, stereoisomers **264b,c** with the smaller $J_{4,5}$ coupling constants were deduced to be *trans*, whilst **264a** is *cis*. The ratio of the

isomeric 2-isoxazolines **264a-c** indicates that alkylation of **251** with cyclohexyl iodide **213** occurred with little control of relative and absolute stereochemistry at C4 and C5. This is possibly due to the conformational mobility of the cyclohexyl ring, as noted above for reaction of the achiral analogue **12f**.



251 **264a-c**

Ar = 2,4,6-Me_3Ph

Reagents and conditions: i. **251** (1.0 equiv.), **213** (3 × 3.0 equiv.), Zn (28 × 2.7 equiv.), CuI (28 × 0.8 equiv.), 65% aq. MeOH, ultrasound, 5 °C, 14 days.

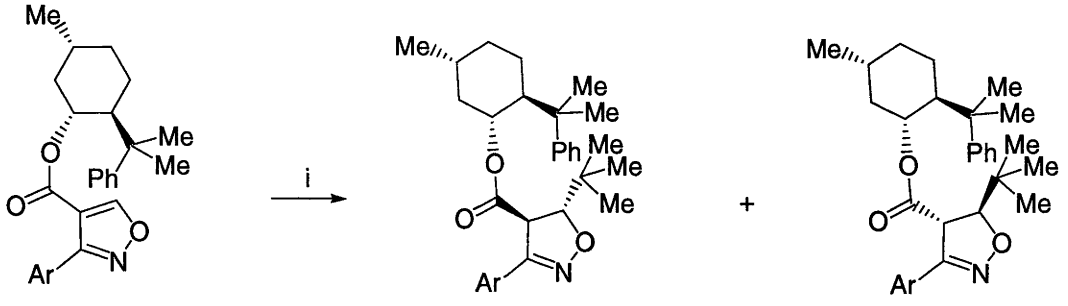
Scheme 90

Table 32. Chemical shifts (ppm) of the signals of the C4- and C5-isoxazoline protons of 2-isoxazolines **264a-c**

Compound	H4	H5
264a	δ 3.82 ppm (d, J = 11.9 Hz)	δ 4.51 ppm (dd, J = 11.9, 7.9 Hz)
264b	δ 3.92 ppm (d, J = 9.8 Hz)	δ 4.91 ppm (app. t, J = 9.8 Hz)
264c	δ 3.97 ppm (d, J = 9.8 Hz)	δ 4.28 ppm (app. t, J = 9.8 Hz)

The effect of the menthyl-based auxiliary on the reaction of the chiral isoxazole **253** with *tert*-butyl iodide **207** was also examined. Of the four possible stereomers of

265, only the *trans*-2-isoxazolines **265a,b** were detected by ^{1}H NMR spectroscopy. The 2-isoxazolines **265a,b** were produced in 87% yield (Scheme 91).



253 **265a** **265b**

Ar = 2,4,6-Me_3Ph

Reagents and conditions: i. **253** (1.0 equiv.), Zn (24 × 2.7 equiv.), CuI (24 × 0.8 equiv.), **207** (24 × 3.0 equiv.), 65% aq. MeOH, ultrasound, 5 °C, 8 days.

Scheme 91

Structural elements of 2-isoxazoline **265a** were determined from EI mass spectrometry and ^{1}H NMR spectroscopy. Accurate mass measurement of the parent ion at *m/z* 503 indicated the molecular composition of $C_{33}H_{45}NO_3$. In the ^{1}H NMR spectrum of **265a**, a one proton triplet of doublets at δ 4.59 ppm (J = 10.6, 4.3 Hz) was assigned to the C1 proton of the chiral auxiliary. The signal of the *tert*-butyl group was observed upfield, as a nine proton singlet at δ 1.00 ppm. The signals of the C4- and C5-isoxazoline protons of **265a** were seen as doublets, each integrating for one proton, at δ 3.78 ppm (J = 11.7 Hz) and δ 4.83 ppm (J = 11.7 Hz). In the ^{1}H NMR spectrum of the product mixture, the signals of the C4- and C5-isoxazoline protons of the minor diastereomer **265b** were observed as one proton doublets at δ 4.19 ppm (J = 11.7 Hz) and δ 4.69 ppm (J = 11.7 Hz). By analogy to the $J_{4,5}$ coupling constant of **262a**, the relative configuration of **265a,b** is deduced to be *trans*.

The 2-isoxazoline **265a** was produced in 94% *d.e.* The relative and absolute configuration of **265a** could not be determined by X-ray crystallography since the material did not crystallize. Instead, the precursor isoxazole **253** was modelled using the MM2 method in order to predict the absolute configuration at the C5 centre of the 2-isoxazoline **265a**. The geometry optimized model of isoxazole **253** shows that the *Re*-face of the minimum energy conformer is shielded by the phenyl ring of the chiral auxiliary (Figure 33). This therefore implies that alkylation is likely to have occurred from the *Si*-face, and hence the absolute configuration at C5 is deduced to be *S*.

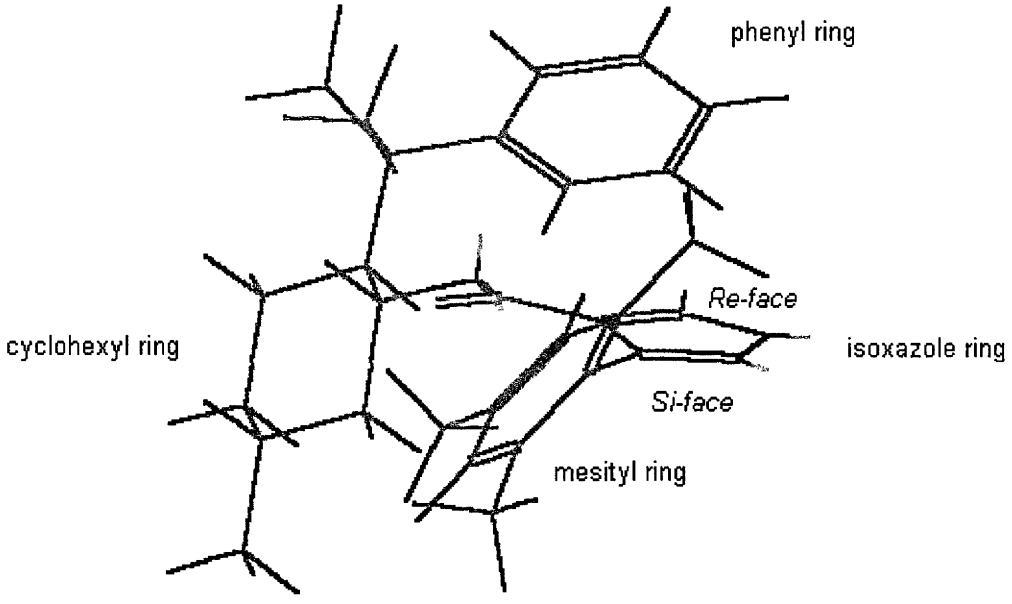
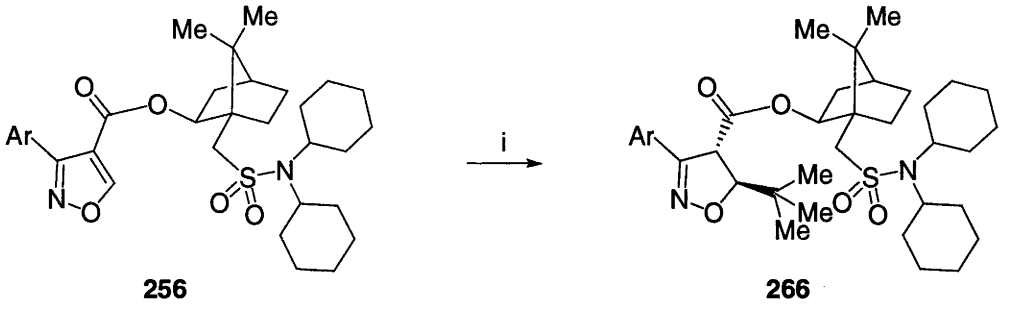


Figure 33. MM2 geometry optimized model of isoxazole **253**

The highly enantioselective alkylations of chiral 4-acylisoxazoles **251** and **253** may be attributed to π-stacking interactions between the phenyl ring of the chiral auxiliaries and the isoxazole cores. To examine if alkylation would still proceed with high facial selectivity in the absence of π-stacking effects, reaction of *tert*-butyl iodide **207** with isoxazole **256** which has attached a non-aryl chiral auxiliary was examined. Only one of the four possible diastereomeric 2-isoxazolines **266** was detected in the

product mixture by ^{1}H NMR spectroscopy. The 2-isoxazoline **266** was produced in ≥98% *d.e.*, and in 87% yield (Scheme 92).



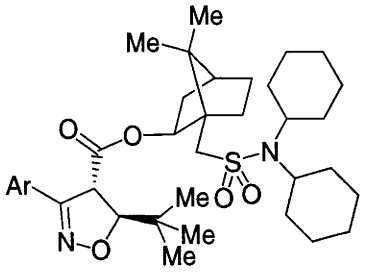
256 **266**

Ar = 2,4,6-Me_3Ph

Reagents and conditions: i. **256** (1.0 equiv.), Zn (39 × 2.7 equiv.), CuI (39 × 0.8 equiv.), **207** (39 × 3.0 equiv.), 65% MeOH, ultrasound, 5 °C, 13 days.

Scheme 92

The structure of the 2-isoxazoline **266** was deduced by EI mass spectrometry and ^{1}H NMR spectroscopy. The molecular ion was detected at *m/z* 668, for which accurate mass measurement for the molecular composition of $C_{39}H_{60}N_2O_5S$ was obtained. In the ^{1}H NMR spectrum, the C1 proton of the chiral auxiliary resonated as a one proton doublet of doublets at δ 4.75 ppm (J = 7.8, 3.5 Hz). The signal of the *tert*-butyl group was seen as a singlet at δ 1.06 ppm, integrating for nine protons. The signals of the C4- and C5-isoxazoline protons were observed as doublets, each integrating for one proton, at δ 4.19 ppm (J = 11.0 Hz) and δ 5.03 ppm (J = 11.0 Hz), respectively. By analogy to the $J_{4,5}$ coupling constant of 2-isoxazoline **262a**, the relative configuration of **266** was deduced to be *trans*. To confirm this, crystals of the 2-isoxazoline **266** were grown from hexanes and ether at 0 °C and the material was analyzed by X-ray crystallography. The ORTEP diagram of **266** (Figure 34) shows that the relative configuration of the 2-isoxazoline **266** is *trans*, and the absolute configuration at the isoxazoline C5 centre is of the *R*-configuration.



266

Ar = 2,4,6-Me_3Ph

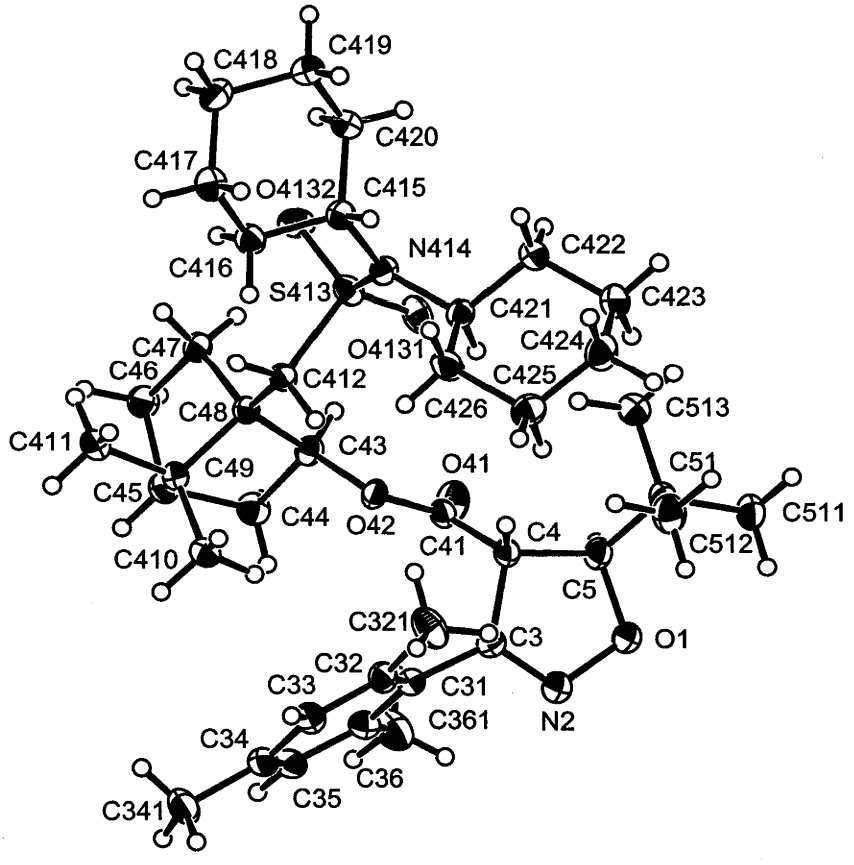


Figure 34. ORTEP derived from single crystal X-ray analysis of compound **266**.

The stereochemical outcome of the alkylation was rationalized using a MM2-derived molecular model of isoxazole **256**. The minimum energy conformer shows extensive shielding of the *Si*-face of the isoxazole ring by the cyclohexyl rings (Figure 35), indicating alkylation must have occurred at the *Re*-face. This is consistent with the observed *R*-configuration at C5, as shown in the ORTEP diagram of 2-isoxazoline **266** (Figure 34).

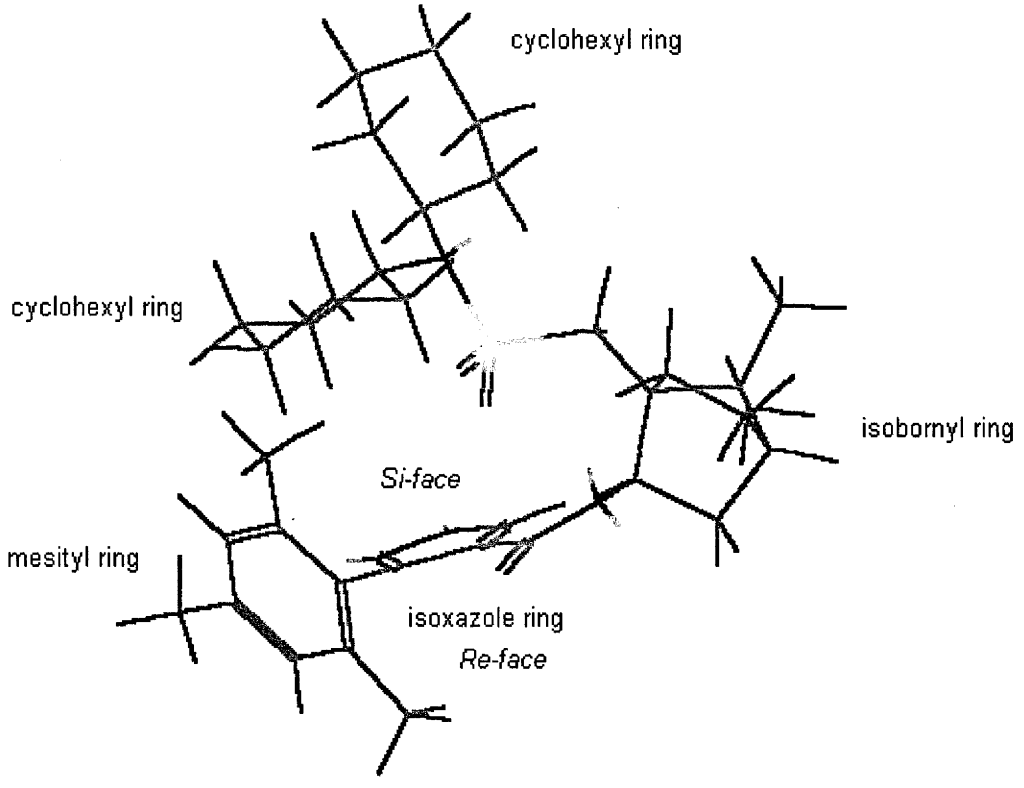


Figure 35. MM2 geometry optimized model of isoxazole **256**

The reactions above show that chiral 4-alkoxycarbonylisoxazoles can be successfully used as acrylate synthons for asymmetric synthesis of 2-isoxazolines of the *trans*-configuration, and in high enantiopurity. Access to *trans*-2-isoxazolines with

either *S*- or *R*-configuration at C5 is possible through use of (-)-(1*R*,2*S*)-2-phenyl-1-cyclohexanol or (+)-dicyclohexylsulfamoyl-L-isoborneol as chiral auxiliaries. The asymmetric alkylation methodology of 4-acylisoxazoles may be applied towards the stereoselective synthesis of polyfunctional molecules *via* ring-opening of the enantioenriched products of the reaction, the 2-isoxazolines.

CHAPTER 6

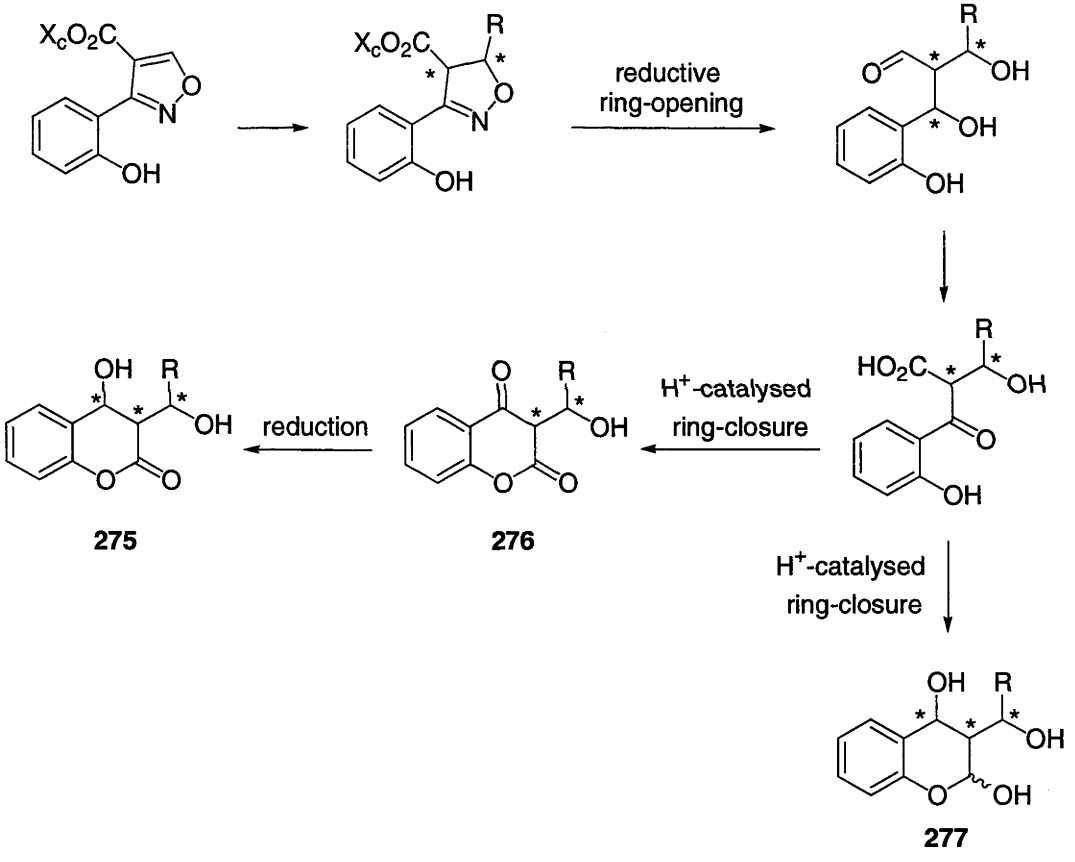
CONCLUSION AND FUTURE DIRECTIONS

6.1. Conclusion

In conclusion, the successful development of an asymmetric alkylation methodology for 4-acylisoxazoles stemmed from observations of some unusual substituent effects in ring-opening reactions of alkoxycarbonyl-substituted isoxazoles. Investigation into the basis of these peculiar effects using X-ray crystallography and theoretical methods uncovered interesting acrylate-like structural and electronic properties of 4-acylisoxazoles. The hypothesized acrylate-like behaviour of 4-alkoxycarbonyl-substituted isoxazoles was then experimentally verified, first by reactions with borohydrides, and later, with alkyl halides, to give 2-isoxazolines through 1,4-additions. The scope of these Michael reactions was extended to 4-amidoisoxazoles, and reactions were also shown to be feasible for 4-acylisoxazoles with alkyl- or aryl-substituents at C3 and C5. The generally high diastereoselectivity observed in these reduction and alkylation processes demonstrates the potential of 4-acylisoxazoles as versatile acrylate synthons. Finally, the synthetic utility of 4-acylisoxazoles was highlighted in asymmetric alkylations. Reactions of chiral 4-acylisoxazoles with alkyl halides not only allow for synthesis of 5-functionalized *trans*-2-isoxazolines in exceptionally high enantiopurity, but they also provide access to *trans*-2-isoxazolines with either absolute configuration at C5 through suitable choice of the chiral auxiliary. The work described herein shows that the versatility and stereoselectivity of the asymmetric zinc-copper(I) iodide-mediated reaction of chiral 4-acylisoxazoles with alkyl halides makes it a superior method to the conventional asymmetric nitrile oxide cycloaddition methodology in stereoselective synthesis of 2-isoxazolines.

6.2. Future Directions - Synthesis of Polyfunctional Molecules

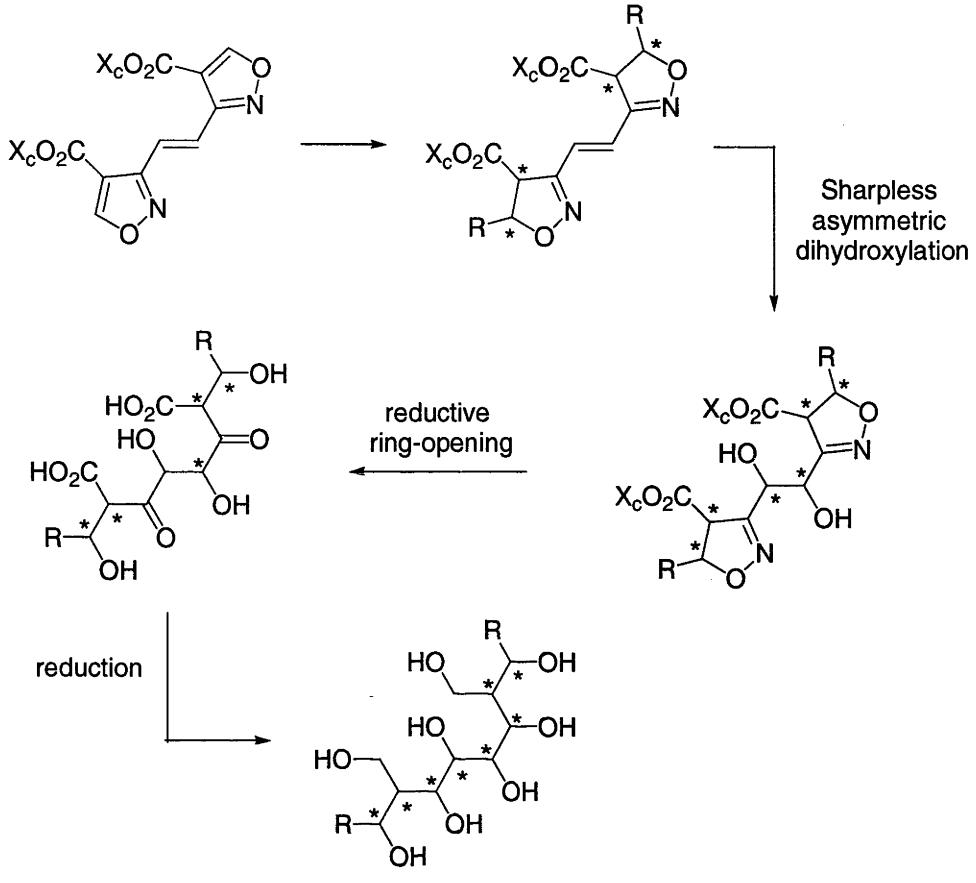
The methodology outlined above potentially provides access to polyfunctional molecules in with high enantiopurity. Possible applications include the asymmetric synthesis of coumarins **275-277**, octaols **278** and β-amino acids **279**, which may be accessible in enantiopure form *via* ring-opening of intermediate 2-isoxazolines (Schemes 89-91).



X_c = chiral auxiliary

* = chiral centre

Scheme 89

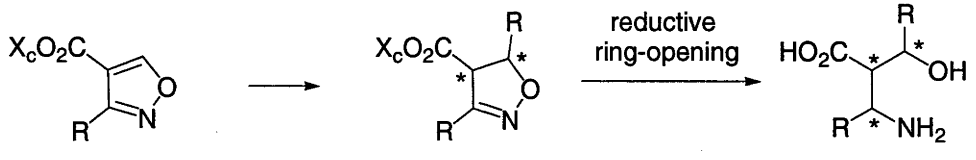


278

X_c = chiral auxiliary

* = chiral centre

Scheme 90



279

X_c = chiral auxiliary

* = chiral centre

Scheme 91

CHAPTER 7

EXPERIMENTAL SECTION

7.1. General

Analytical thin layer chromatography (TLC) was performed on aluminium backed 0.2 mm thick silica gel 60 F254 plates as supplied by Merck. Eluted plates were visualized through use of a 254 nm UV lamp and/or by treatment with suitable dip followed by heating. A potassium permanganate dip [potassium permanganate (3 g), potassium hydrogencarbonate (20 g), 5% wt/v aqueous sodium hydroxide (5 mL) and water (300 mL)] was used to visualize isoxazoles and 2-isoxazolines without UV-active chromophores. An anisaldehyde dip [anisaldehyde (15 g), concentrated sulfuric acid (2.5 mL), ethanol (250 mL)] was used to visualize compounds **246** and **255**.

Flash column chromatography refers to purification of compounds by elution through a column of Kieselgel 60 (0.040-0.0063 mm) silica with analytical grade solvents, driven by a positive pressure of nitrogen.

Reactions employing air and/or moisture sensitive reagents and intermediates were carried out under an atmosphere of dry nitrogen. In all cases, the glassware was oven dried then cooled under an atmosphere of dry nitrogen prior to the addition of solvents, starting materials and reagents. When the reactions were conducted at, or below 0 °C, the internal temperature was monitored using an alcohol thermometer. Reaction temperatures were controlled using dry ice-acetone (-78 °C, -20 °C) and ice (0 °C) baths.

Starting materials and reagents were generally available from Aldrich, Avocado, Fluka, Merck and TCI Chemical Companies. Drying agents and other inorganic salts were purchased from Aldrich, AJAX and Unilab Chemical Companies. Reaction solvents were purified according to the methods defined by Perrin and Amarego.[186] Tetrahydrofuran and diethyl ether were distilled from sodium benzophenone ketyl. Methanol and ethanol were distilled from their respective magnesium alkoxide salts. Toluene, dichloromethane and *N*,*N*-dimethylformamide were distilled from calcium hydride. Pyridine, triethylamine and tri-*n*-butylamine were all distilled from and stored over potassium hydroxide pellets.

Solutions of dichloromethane, diethyl ether, 1,2-dimethoxyethane, ethanol, ethyl acetate, hexanes, methanol, tetrahydrofuran and toluene were concentrated under reduced pressure at *ca.* 78 mm Hg on a rotary evaporator connected to a water condenser, with the water bath temperature generally not exceeding 30 °C. Solutions of acetic acid were concentrated under vacuum at *ca.* 0.1 mm Hg on a rotary evaporator connected to a dry ice-acetone condenser with the water bath temperature maintained at 25 °C.

Melting points were determined on a Kofler hot-stage apparatus under a Reichert microscope and are uncorrected.

Proton (^{1}H), carbon (^{13}C) and attached proton test (APT) NMR spectra were recorded on a Varian Gemini 300 or a Varian Mercury 300 spectrometer, operating at 300 MHz for proton and 75.4 MHz for carbon; an Inova 500 spectometer, operating at 500 MHz for proton and 125 Hz for carbon; and an Inova 600 spectrometer, operating at 600 MHz for proton and 150 MHz for carbon. ^{1}H NMR spectra were acquired in $CDCl_3$ at 20 °C unless otherwise stated (the singlet peak at δ 7.26 ppm and tetramethylsilane were used as references). Chemical shifts were recorded as δ values in parts per million (ppm). ^{1}H NMR spectral data are recorded as follows: chemical shift (δ), multiplicity, coupling constant *J* (Hz), where multiplicity is defined as s = singlet, d = doublet, t = triplet, p = pentet, q = quartet, m = multiplet, dd = doublet of doublets, dq = doublet of quartets, dt = doublet of triplets, td = triplet of doublets, ddd = doublet of doublets of doublets, br = broad. For ^{13}C NMR spectra, the central peaks of the $CDCl_3$ triplet (δ 77.0 ppm), d_6-acetone septet (δ 29.8 ppm) and d_4-MeOH septet (δ 49.0 ppm) were used as references for the APT and the proton decoupled spectra. For ^{13}C NMR spectra the data is given as chemical shift (δ), and the protonicity is defined as: C = quaternary; CH = methine; CH_2 = methylene; CH_3 = methyl.

Infrared spectra (ν_{max}) were recorded on either a Perkin-Elmer 1800 Fourier Transform Infrared Spectrometer or a Perkin-Elmer Spectrum One Instrument. Samples were analyzed as thin films on KBr plates. Absorption maxima (ν_{max}) are recorded in wavenumbers (cm^{-1}).

Low and high resolution mass spectra were recorded on a VG Fisons AutoSpec three sector (E/B/E) double-focussing mass spectrometer, using positive-ion electron impact techniques at 70 eV. The samples were inserted through a solid direct injection probe with a source temperature of 200 °C. Mass spectral data are listed as: mass-to-charge ratio (*m/z*) [(assignment where possible), percentage abundance relative to the base peak].

Elemental analyses were performed by the Microanalytical Laboratory, Research School of Chemistry, Australian National University.

Optical rotations were measured with a Perkin-Elmer 241 polarimeter at the sodium-D line (589 nm) and the concentrations (*c*) (g/100 mL) indicated using spectroscopic grade $CHCl_3$. The measurements were carried out in a cell with a path length (*l*) of 1 dm. Specific rotations $[\alpha]_D$ were calculated (at the temperature listed) using the equation $[\alpha]_D = 100.\alpha/(c.l)$ and are given in $10^{-1}.deg.cm^2.g^{-1}$.

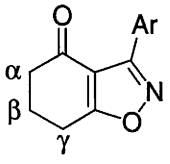
Single crystal X-ray analyses were performed on either a Nonius Kappa CCD or a Rigako AFC 6R instrument. Full data reports are provided in Appendix 1.

For reactions requiring sonication, a Transsonic Digital ultrasonic bath, model T 710 DH operating at 120% efficiency was used. The sonic bath was filled with deionised water to *ca.* 66% of its volume capacity. The reaction vessels were three-neck round bottom flasks fitted to a nitrogen inlet tap, a subaseal and a sealed adapter cone. The round bottom flasks were secured at the upper joint of the adaptor cone and were submerged in water, *ca.* 10 cm from the base of the sonic bath. The bath temperature was regulated at 5 °C by use of a Lauda water cooler.

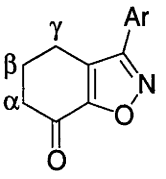
In the experimental section only optimum procedures are reported unless stated otherwise.

7.2. Experimental for Chapter 2

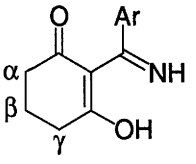
Competitive Hydrogenation of 3-(2,6-Dichlorophenyl)-6,7-dihydro-1,2-benzisoxazol-4(*5H*)-one 48a and 3-(2,6-Dichlorophenyl)-5,6-dihydro-1,2-benzisoxazol-7(*4H*)-one 52a



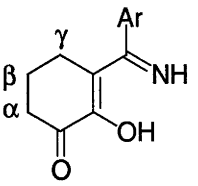
48a



52a



50a



53a

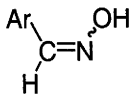
Ar = 2,6-Cl_2Ph

10% Palladium on carbon (2 mg) was added to a mixture of **48a** (10.0 mg, 35.1 μmol) and **52a** (10.0 mg, 35.1 μmol) in MeOH (2 mL) at 18 °C. After stirring under an atmosphere of hydrogen at 18 °C for 2.5 h, the suspension was filtered through a pad of Celite®. The filter cake was washed with MeOH (5 × 10 mL) and the filtrate was concentrated *in vacuo*. ^{1}H NMR analysis indicated the product mixture consisted of isoxazoles and ring-opened species **48a**, **50a**, **52a** and **53a** in a ratio of 1:6:5:2, as determined from integration of the methylene proton signals.

^{1}H NMR (300 MHz) for **48a**: δ 2.29 (p, 2H, J = 6 Hz, C_β), 2.54 (t, 2H, J = 6 Hz, C_α), 3.12 (t, 2H, J = 6 Hz, C_γ); **52a**: δ 2.24 (p, 2H, J = 6 Hz, C_β), 2.63 (t, 2H, J = 6 Hz, C_α), 2.73 (t, 2H, J = 6 Hz, C_γ); **50a**: δ 1.97 (p, 2H, J = 6.5 Hz, C_β), 2.43 (t, 2H, J = 6.5 Hz, C_α), 2.65 (t, 2H, J = 6.5 Hz, C_γ); **53a**: δ 2.24 (p, 2H, J = 6 Hz, C_β), 2.46 (t, 2H, J = 6 Hz, C_α), 2.98 (t, 2H, J = 6 Hz, C_γ).

The aromatic protons of **48a**, **52a**, **50a** and **53a** are observed as multiplets at δ 7.20-7.80 ppm. The physical and spectral data of compounds **48a**, **52a** and **50a** were reported previously.[55,65]

Mesitaldoxime 63



63

Ar = 2,4,6-Me_3Ph

Hydroxylamine hydrochloride (2.50 g, 36.0 mmol) was added to a stirred solution of 50% wt/v aq. NaOH (2.9 mL, 36 mmol) in 30% aq. EtOH (14 mL) at 0-5 °C (ice bath). Mesitaldehyde **62** (5.03 g, 33.9 mmol) was added over 30 min to the mixture at 10 °C (external cooling with ice-bath) and stirring was continued at 18 °C for 3 h. After the EtOH was removed under reduced pressure, the mixture was poured into H_2O (75 mL) and extracted with Et_2O (4 × 100 mL). The combined organic solution was washed with H_2O (2 × 75 mL) and brine (1 × 75 mL), dried (anhydrous $MgSO_4$) and concentrated *in vacuo*. The residue was recrystallized from EtOH to afford the *title compound* ***63*** (5.01 g, 91%) as colourless prisms, mp 125-127 °C [lit.[9] mp 125-127 °C].

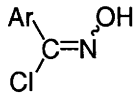
^{1}H NMR (300 MHz) δ 2.23 (br s, 1H, OH), 2.28 (s, 3H, *p*-$MesCH_3$), 2.97 (s, 6H, *o,o'*-$MesCH_3$), 6.88 (s, 2H, 2 × MesH), 8.41 (s, 1H, C<u>H</u>=NOH).

IR (KBr, thin film) ν_{max} 3248, 2966, 2916, 2855, 1610, 1486, 1457, 1420, 1375, 1310, 1298, 960, 944, 915, 838, 722 cm^{-1}.

LRMS (EI) *m/z* (%) 163 ($M^{\bullet+}$, 68), 148 ($M^{\bullet+}$-CH_3, 72), 132 ($M^{\bullet+}$-NOH, 100), 120 ($M^{\bullet+}$-CNOH, 5), 115 (17), 103 (16), 91 (23), 77 (19), 65 (11), 59 (3).

The ^{1}H NMR spectral data of compound **63** are consistent with literature values.[9]

Mesitohydroximinoyl Chloride 2e



2e

Ar = 2,4,6-Me_3Ph

NCS (1.67 g, 12.5 mmol) was added to a stirred solution of mesitaldoxime **63** (2.04 g, 12.5 mmol) in DMF at 0-5 °C (ice bath) over 30 min. The internal temperature of the reaction mixture was maintained between 20-25 °C during the addition by external cooling (ice bath). After the reaction mixture was stirred at 20-25 °C for 3.5 h, it was poured into ice-H_2O (75 mL) and taken up in Et_2O (100 ml). The aqueous layer was separated and extracted with Et_2O (6 × 100 mL). The combined organic solution was washed with H_2O (5 × 75 mL) and brine (1 × 75 mL), dried (anhydrous $MgSO_4$) and concentrated *in vacuo* to afford the *title compound* ***2e*** (2.11 g, 85%) as a pale yellow solid, mp 61-69 °C [lit.[9] mp 61-69 °C].

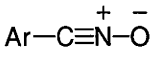
^{1}H NMR (300 MHz) δ 2.31 (s, 3H, *p*-$MesCH_3$), 2.32 (s, 6H, *o,o'*-$MesCH_3$), 6.92 (s, 2H, 2 × MesH), 8.10 (br s, 1H, OH).

IR (KBr, thin film) ν_{max} 3306, 2921, 1630, 1611, 1444, 1378, 1300, 1230, 1154, 1035, 962, 900, 851, 736, 620, 592 cm^{-1}.

LRMS (EI) *m/z* (%) 199, 197 ($M^{\bullet+}$, 18 and 42), 180 (37), 167 (3), 161 (100), 154 (3), 145 (75), 130 (58), 115 (49), 105 (30), 91 (63), 77 (40), 65 (28).

The ^{1}H NMR spectral data are consistent with reported values.[9]

Mesitonitrile Oxide 5



5

Ar = 2,4,6-Me_3Ph

Triethylamine (1.3 mL, 9.1 mmol) was added dropwise to a stirred solution of mesitohydroximinoyl chloride **2e** (1.50 g, 7.62 mmol) in Et_2O (30 mL). After stirring at 18 °C for 2 h, the mixture was poured into H_2O (57 mL). The aqueous phase was separated and extracted with Et_2O (3 × 100 mL). The combined organic solution was washed with H_2O (2 × 75 mL) and brine (1 × 75 mL), dried (anhydrous $NaSO_4$) and concentrated *in vacuo* to give the *title compound* ***5*** (1.20 g, 98%) as a colourless solid, mp 110-112 °C [lit.[9] mp 110-112 °C].

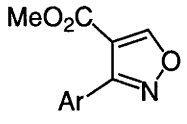
^{1}H NMR (300 MHz) δ 2.30 (s, 3H, *p*-$MeCH_3$), 2.42 (s, 6H, *o,o'*-$MesCH_3$), 6.91 (s, 2H, 2 × MesH).

IR (KBr, thin film) ν_{max} 2293, 1607, 1432, 1375, 1334, 1300, 1176, 1068, 1030, 867, 714, 563 cm^{-1}.

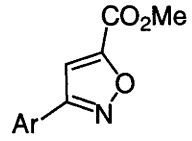
LRMS (EI) *m/z* (%) 161 ($M^{\bullet+}$, 100), 145 ($M^{\bullet+}$-O, 34), 130 (32), 115 (30), 105 (17), 91 (48), 77 (21), 63 (14).

The ^{1}H NMR spectral data of compound **5** are consistent with literature values.[9]

3-(2,4,6-Trimethylphenyl)isoxazole-4-carboxylic Acid Methyl Ester 12f and 3-(2,4,6-Trimethylphenyl)isoxazole-5-carboxylic Acid Methyl Ester 13f



12f



13f

Ar = 2,4,6-Me_3Ph

A mixture of mesitonitrile oxide **5** (400 mg, 2.48 mmol) and methyl propiolate **11** (208 mg, 2.48 mmol) in THF (65 mL) was heated at reflux for 2 days. After the solvent was removed under reduced pressure, the residue was taken up in Et_2O (100 mL) and washed with H_2O (1 × 75 mL). The aqueous phase was separated and extracted with Et_2O (3 × 75 mL). The combined organic solution was washed with brine (1 × 75 mL), dried (anhydrous $MgSO_4$) and concentrated *in vacuo*. Flash column chromatography of the residue, eluting with hexanes-Et_2O (7:3) afforded the *title compounds* ***12f***[24] (425 mg, 70%) as colourless blocks, after recrystallization from vapour diffusion of hexanes and Et_2O at 18 °C, mp 75-77 °C; and ***13f***[24] (164 mg, 27%) as a colourless oil.

Compound 12f

^{1}H NMR (300 MHz) δ 2.05 (s, 6H, *o,o'*-MesCH_3), 2.33 (s, 3H, *p*-MesCH_3), 3.73 (s, 3H, CH_3O), 6.94 (s, 2H, 2 × MesH), 9.06 (s, 1H, H5).

^{13}C NMR (75.4 MHz) δ 19.8 (2 × CH_3), 21.1 (CH_3), 51.7 (CH_3O), 113.7 (C4), 123.7 (C), 128.1 (2 × CH), 136.8 (2 × C), 138. 9 (C), 160.8 (C3 and C=O), 163.2 (C5).

IR (KBr, thin film) ν_{max} 1724, 1610, 1573, 1457, 1394, 1306, 1136, 1018, 839, 407 cm^{-1}.

LRMS (EI) *m/z* (%) 245 ($M^{\bullet+}$, 100), 228 (20), 214 ($M^{\bullet+}$-CH_3O, 21), 198 (6), 186 ($M^{\bullet+}$-CH_3O_2C, 58), 170 ($M^{\bullet+}$-$C_4H_{11}O$, 29), 158 (84), 149 (6), 142 ($M^{\bullet+}$-$C_5H_{11}O_2$, 23), 130 (26), 115 (28), 103 (16), 91 (36), 84 (15), 77 (28), 65 (13), 57 (15).

HRMS (EI) Found: $M^{\bullet+}$, 245.105328. $C_{14}H_{15}NO_3$ requires $M^{\bullet+}$, 245.105194.

Elemental Analysis Found: C, 68.22; H, 6.03; N, 5.60. $C_{14}H_{15}NO_3$ requires C, 68.56; H, 6.16; N, 5.71.

X-Ray Crystallographic Analysis Appendix 1.6.

Compound 13f

^{1}H NMR (300 MHz) δ 2.13 (s, 6H, *o*,*o*'-MesCH$_3$), 2.38 (s, 3H, *p*-MesCH$_3$), 4.01 (s, 3H, CH$_3$O), 6.90 (s, 1H, H4), 6.96 (s, 2H, 2 × MesH).

^{13}C NMR (75.4 MHz) δ 20.1 (2 × CH$_3$), 21.0 (CH$_3$), 52.7 (CH$_3$O), 110.9 (C4), 124.7 (C), 128.4 (2 × CH), 137.0 (C), 139.2 (2 × C), 157.2 (C3), 159.9 (C=O), 162.6 (C5).

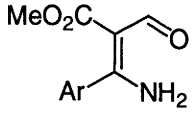
IR (KBr, thin film) ν_{max} 2955, 1749, 1653, 1613, 1585, 1505, 1457, 1384, 1305, 1286, 1235, 1221, 1171, 1123, 1002, 852, 770 cm^{-1}.

LRMS (EI) *m/z* (%) 245 ($M^{\bullet+}$, 59), 214 ($M^{\bullet+}$-CH$_3$O, 5), 186 ($M^{\bullet+}$-CH$_3$O$_2$C, 100), 171 (12), 158 (70), 143 (26), 133 (18), 119 (20), 115 (24), 103 (15), 91 (30), 77 (22), 62 (9), 57 (8).

HRMS (EI) Found: $M^{\bullet+}$, 245.105605. $C_{14}H_{15}NO_3$ requires $M^{\bullet+}$, 245.105194.

Elemental Analysis Found: C, 68.46; H, 6.25; N, 5.58. $C_{14}H_{15}NO_3$ requires C, 68.56; H, 6.16; N, 5.71.

(*E*)-3-Amino-2-formyl-3-(2,4,6-trimethylphenyl)acrylic Acid Methyl Ester 64



64

Ar = 2,4,6-Me_3Ph

A solution of 3-(2,4,6-trimethylphenyl)isoxazole-4-carboxylic acid methyl ester **12f** (100 mg, 0.408 mmol) in MeOH (1 mL) was added to a suspension of 10% palladium on carbon (10 mg) in MeOH (5 mL) under an atmosphere of hydrogen. After stirring at 18 °C for 24 h, the mixture was filtered through a pad of Celite®. The filter cake was washed with MeOH (5 × 10 mL) and the combined filtrate was concentrated under reduced pressure. Flash column chromatography of the residue, eluting with hexanes-EtOAc (4:1) afforded the *title compound **64*** (99 mg, 98%) as a colourless oil.

^{1}H NMR (300 MHz) δ 2.22 (s, 6H, *o*,*o*'-MesCH_3), 2.30 (s, 3H, *p*-MesCH_3), 3.76 (s, 3H, CH_3O), 5.81 (br s, 2H, NH_2), 6.89 (s, 2H, 2 × MesH), 10.2 (s, 1H, CHO).

^{13}C NMR (75.4 MHz) δ 19.0 (2 × CH_3), 21.1 (CH_3), 50.8 (CH_3O), 101.9 ($\underline{C}CO_2CH_3$), 128.1 (2 × CH), 133.4 (2 × C), 133.9 (C), 138.4 (C), 166.6 ($\underline{C}NH_2$), 170.8 (C=O), 191.9 (CHO).

IR (KBr, thin film) ν_{max} 3440, 3319, 2948, 2924, 1731, 1600, 1535, 1436, 1270, 1186, 1125 cm^{-1}.

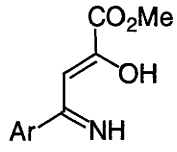
LRMS (EI) *m/z* (%) 247 ($M^{\bullet+}$, 8), 232 ($M^{\bullet+}$-CH_3, 100), 217 [$M^{\bullet+}$-(2 × CH_3), 60], 202 [$M^{\bullet+}$-(3 × CH_3), 66], 186 (25), 172 (50), 158 (40), 146 (85), 130 (21), 115 (17), 88 (11), 77 (14).

HRMS (EI) Found: $M^{\bullet+}$, 247.120694. $C_{14}H_{17}NO_3$ requires $M^{\bullet+}$, 247.120844.

Elemental Analysis Found: C, 67.96; H, 6.90; N, 5.62. $C_{14}H_{17}NO_3$ requires C, 68.00; H, 6.93; N, 5.66.

The relative configuration of compound **64** is assumed to be *E*, based on the structure of the precursor isoxazole **12f**.

(*Z*)-2-Hydroxy-4-imino-4-(2,4,6-trimethylphenyl)but-2-enoic Acid Methyl Ester 65



65

Ar = 2,4,6-Me_3Ph

A solution of 3-(2,4,6-trimethylphenyl)isoxazole-5-carboxylic acid methyl ester **13f** (100 mg, 0.408 mmol) in MeOH (1 mL) was added to a suspension of 10% palladium on carbon (10 mg) in MeOH (3 mL) under an atmosphere of hydrogen. After stirring at 18 °C for 10 days, the mixture was filtered through a pad of Celite®. The filter cake was washed with MeOH (5 × 10 mL) and the combined filtrate was concentrated under reduced pressure. Flash column chromatography of the residue, eluting with hexanes-EtOAc (4:1) afforded the *title compound* **65** (99 mg, 98%) as a colourless oil.

^{1}H NMR (300 MHz) δ 2.26 (s, 6H, *o*,*o*'-MesCH_3), 2.30 (s, 3H, *p*-MesCH_3), 3.85 (s, 3H, CH_3O), 5.76 (br s, 1H, NH or OH), 5.90 (s, 1H, CH), 6.90 (s, 2H, 2 × MesH), 10.5 (br s, 1H, NH or OH).

^{13}C NMR (75.4 MHz) δ 19.2 (2 × CH_3), 21.0 (CH_3), 52.6 (CH_3O), 94.4 (CH), 128.3 (2 × CH), 133.5 (C), 134.7 (2 × C), 139.0 (C), 164.0 (CCO_2Me), 168.0 (C=NH), 178.4 (C=O).

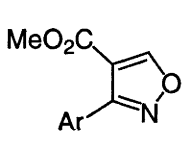
LRMS (EI) *m/z* (%) 247 ($M^{\bullet+}$, 14), 188 ($M^{\bullet+}$-CH_3O_2C, 100), 158 (7), 145 (36), 130 (23), 115 (9), 105 (6), 91 (8), 77 (6).

HRMS (EI) Found: $M^{\bullet+}$, 247.120986. $C_{14}H_{17}NO_3$ requires $M^{\bullet+}$, 247.120844.

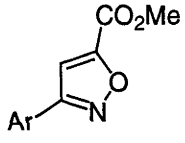
Elemental Analysis Found: C, 67.92; H, 6.91; N, 5.63. $C_{14}H_{17}NO_3$ requires C, 68.00; H, 6.93; N, 5.66.

The relative configuration of compound **65** is assumed to be *Z*, based on the structure of the precursor isoxazole **13f**.

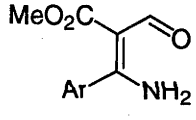
Competitive Hydrogenation of 3-(2,4,6-Trimethylphenyl)isoxazole-4-carboxylic Acid Methyl Ester 12f and 3-(2,4,6-Trimethylphenyl)isoxazole-5-carboxylic Acid Methyl Ester 13f



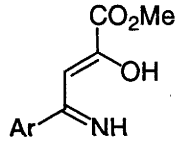
12f



13f



64



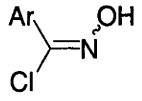
65

Ar = 2,4,6-Me_3Ph

To a mixture of 3-(2,4,6-trimethylphenyl)isoxazole-4-carboxylic acid methyl ester **12f** (50.0 mg, 0.204 mmol) and 3-(2,4,6-trimethylphenyl)isoxazole-5-carboxylic acid methyl ester **13f** (50.0 mg, 0.204 mmol) in MeOH (5 mL) was added 10% palladium on carbon (10 mg) under an atmosphere of hydrogen. After the suspension was stirred at 18 °C for 2 days, the mixture was filtered through a pad of Celite®. The filter cake was washed with MeOH (5 × 10 mL), and the combined filtrate was concentrated under reduced pressure. ^{1}H NMR analysis indicated the mixture was composed of (*E*)-3-amino-2-formyl-3-(2,4,6-trimethylphenyl)acrylic acid methyl ester **64** (described above), 3-(2,4,6-trimethylphenyl)isoxazole-5-carboxylic acid methyl ester

13f (described above) and (*Z*)-2-hydroxy-4-imino-4-(2,4,6-trimethylphenyl)but-2-enoic acid methyl ester **65** (described above) in a ratio of 11:10:1.

2,6-Dichlorobenzohydroximinoyl Chloride 69



69

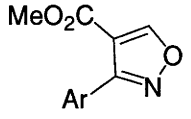
Ar = 2,6-Cl_2Ph

NCS (7.02 g, 52.6 mmol) was added over 30 min to a stirred solution of 2,6-dichlorobenzaldoxime **68** (10.0 g, 52.6 mmol) in DMF at 0-5 °C (ice bath). The internal temperature of the reaction mixture was maintained between 15-20 °C during the addition by external cooling (ice bath). After stirring at 20-25 °C for 3.5 h, the mixture was poured into ice-H_2O (75 mL) and taken up in Et_2O (150 mL). The aqueous layer was separated and extracted with Et_2O (6 × 100 mL). The combined organic solution was washed with H_2O (5 × 75 mL) and brine (1 × 75 mL), dried (anhydrous $MgSO_4$) and evaporated *in vacuo* to afford the *title compound* ***69*** (10.3 g, 87%) as colourless prisms after recrystallization from hexanes and Et_2O, mp 91-92 °C [lit.[66] mp 91-92 °C].

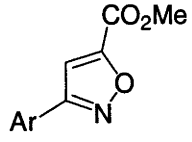
^{1}H NMR (300 MHz) δ 7.37 (m, 3H, 3 × PhH), 8.31 (s, 1H, OH).

The ^{1}H NMR spectral data of compound **69** are consistent with literature values.[66]

3-(2,6-Dichlorophenyl)isoxazole-4-carboxylic Acid Methyl Ester 71 and 3-(2,6-Dichlorophenyl)isoxazole-5-carboxylic Acid Methyl Ester 60a



71



60a

Ar = 2,6-Cl_2Ph

Triethylamine (0.70 mL, 5.0 mmol) was added dropwise over 15 min to a stirred mixture of 2,6-dichlorobenzohydroximinoyl chloride **69** (1.0 g, 4.5 mmol) and methyl propiolate **11** (0.47 g, 5.6 mmol) in THF (20 mL) at 18 °C. After heating at reflux for 2 days, the solvent was removed under reduced pressure. The residue was taken up in Et_2O (100 mL) and washed with H_2O (2 × 75 mL). The aqueous layer was separated and extracted with Et_2O (3 × 75 mL). The combined organic solution was washed with brine (1 × 50 mL), dried (anhydrous $MgSO_4$) and concentrated *in vacuo*. Flash column chromatography of the residue, eluting with hexanes-EtOAc (4:1) afforded the *title compounds 71* (233 mg, 19%) as colourless needles, after recrystallization from vapour diffusion from hexanes and Et_2O at 18 °C, mp 85-87 °C; and ***60a*** (700 mg, 57%) as a colourless solid, mp 114-116 °C [lit.[65] mp 114-116 °C].

Compound 71

^{1}H NMR (300 MHz) δ 3.76 (s, 3H, CH_3O), 7.34-7.45 (m, 3H, 3 × PhH), 9.08 (s, 1H, H5).

^{13}C NMR (75.4 MHz) δ 52.1 (CH_3O), 114.2 (C4), 126.8 (C), 127.9 (2 × CH), 132.0 (CH), 135.4 (2 × C), 154.9 (C3), 158.7 (C=O), 163.2 (C5).

IR (KBr, thin film) ν_{max} 1732, 1576, 1561, 1433, 1395, 1306, 1196, 1148, 1128, 1105, 1075, 1017, 861, 775, 730 cm^{-1}.

LRMS (EI) *m/z* (%) 238, 236 (M^{+} - Cl, 51 and 100), 212 (22), 198 (13), 184 (8), 171 (6), 157 (5), 148 (8), 136 (4), 109 (7), 100 (3), 75 (5).

HRMS (EI) Found: $M^{\bullet+}$-^{37}Cl, 238.008496. $C_{11}H_7{}^{37}ClNO_3$ requires $M^{\bullet+}$-^{37}Cl, 238.008496. Found: $M^{\bullet+}$-^{35}Cl, 236.011167. $C_{11}H_7{}^{35}ClNO_3$ requires 236.011446.

X-Ray Crystallographic Analysis Appendix 1.1.

Compound 60a

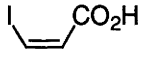
^{1}H NMR (300 MHz) δ 4.03 (s, 3H, CH_3O), 7.08 (s, 1H, H4), 7.27-7.50 (m, 3H, 3 × PhH).

IR (KBr, thin film) ν_{max} 1736, 1593, 1581, 1459, 1377, 1307, 1232, 1198, 1152, 1100, 1079, 1001, 953, 915, 851, 807, 789, 772, 730, 710 cm^{-1}.

LRMS (EI) *m/z* (%) 277, 275, 273 ($M^{\bullet+}$, 5, 23 and 46), 216 (29), 214 (75), 212 (100), 186 (38), 184 (46).

The ^{1}H NMR spectral data are consistent with reported values.[65]

(*Z*)-3-Iodopropenoic Acid 73



73

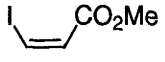
Sodium iodide (8.50 g, 57.0 mmol) was added to a solution of propiolic acid **72** (2.3 mL, 37.0 mmol) in AcOH (14 mL). The mixture was heated in a pre-heated oil bath at 115 °C for 90 min. After cooling to 18 °C, the solvent AcOH was removed under vacuum (0.1 mm Hg). The dark brown residue was treated with Et_2O (150 mL) and filtered through a pad of Celite®. The collected material was washed with Et_2O (2 × 200 mL) and the filtrate was concentrated under reduced pressure to a volume of *ca.* 100 mL. The organic solution was washed with H_2O (75 mL), the aqueous layer was separated and extracted with Et_2O (3 × 50 mL). The combined organic solution was washed with H_2O (1 × 75 mL), aq. $Na_2S_2O_4$ (1 × 75 mL) and brine (1 × 75 mL), dried (anhydrous

Na_2SO_4) and concentrated *in vacuo*. The residue was recrystallized from hexanes and Et_2O to give the *title compound 73* (5.21 g, 72%) as colourless prisms, mp 62-64 °C [lit.[70] mp 62-64 °C].

^{1}H NMR (300 MHz) δ 6.99 (d, 1H, J = 9.5 Hz, H2), 7.68 (d, 1H, J = 9.5 Hz, H3), 11.9 (br s, 1H, OH).
^{13}C NMR (75.4 MHz) δ 98.0 (C2), 129.4 (C3), 169.7 (C=O).

The ^{1}H NMR spectral data of compound **73** are consistent with literature values.[70]

(*Z*)-3-Iodopropenoic Acid Methyl Ester 74



74

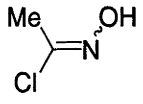
A mixture of (*Z*)-3-iodopropenoic acid **73** (1.00 g, 5.05 mmol) and conc. H_2SO_4 (0.16 mL) in MeOH (53 mL) was heated at reflux for 36 h. After the MeOH was evaporated *in vacuo*, the residue was poured into ice-H_2O (1 × 100 mL) and extracted into Et_2O (3 × 75 mL). The combined organic solution was washed with H_2O (2 × 75 mL) and brine (1 × 75 mL), dried (anhydrous $MgSO_4$) and concentrated *in vacuo* to afford the *title compound 74* (706 mg, 66%) as a pale yellow liquid.

^{1}H NMR (300 MHz) δ 3.79 (s, 3H, CH_3O), 6.92 (d, 1H, J = 8.8 Hz, H2), 7.49 (d, 1H, J = 8.8 Hz, H3).
^{13}C NMR (75.4 MHz) δ 51.3 (CH_3O), 95.0 (C2), 129.4 (C3), 164.7 (C=O).
IR (KBr, thin film) ν_{max} 2951, 2927, 1731, 1598, 1434, 1326, 1206, 1168, 998, 908, 809, 738, 641, 546 cm^{-1}.

LRMS (EI) *m/z* (%) 212 ($M^{\bullet+}$, 100), 202 (5), 192 (9), 181 ($M^{\bullet+}$-CH_3O, 80), 170 (7), 160 (15), 153 ($M^{\bullet+}$-CH_3O_2C, 24), 141 (6), 127 (27), 117 (29), 96 (9), 85 ($M^{\bullet+}$-I, 19), 77 (10), 64 (50).

The ^{1}H NMR spectral data are consistent with reported values.[70]

Acetohydroximinoyl Chloride 2c



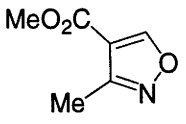
2c

NCS (4.80 g, 35.9 mmol) was added to a stirred solution of acetaldoxime **75** (2.11 g, 35.8 mmol) in DMF (30 mL) at 0-5 °C (ice bath) over 15 min. Stirring was continued for another 3.5 h with the internal temperature maintained at 20-25 °C by external cooling (ice bath). The mixture was poured into ice-H_2O (75 mL) and extracted into Et_2O (5 × 100 mL). The organic layer was separated and washed with H_2O (5 × 100 mL), brine (1 × 75 mL) and dried (anhydrous $MgSO_4$). The filtrate was concentrated under reduced pressure to afford the *title compound* ***2c*** (2.50 g, 75%) as a colourless liquid.

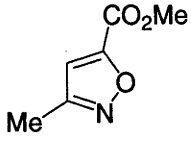
^{1}H NMR (300 MHz) δ 2.28 (s, 3H, CH_3), 8.11 (br s, 1H, O<u>H</u>).

The ^{1}H NMR spectral data are consistent with reported values.[71]

3-Methylisoxazole-4-carboxylic Acid Methyl Ester 12d
and 3-Methylisoxazole-5-carboxylic Acid Methyl Ester 13d



12d



13d

To a stirred mixture of (*Z*)-3-iodopropenoic acid methyl ester **74** (11.3 g, 53.4 mmol) and acetohydroximinoyl chloride **2c** (620 mg, 6.67 mmol) at 18 °C was added over 16 h a solution of triethylamine (1.02 mL, 7.34 mmol) in dry Et_2O (4 mL). After stirring at 18 °C for a further 24 h, the mixture was poured into H_2O (75 mL) and the layers were separated. The aqueous phase was extracted with Et_2O (3 × 75 mL) and the combined organic solution was washed with brine (1 × 75 mL) then dried (anhydrous $MgSO_4$). The ethereal solvent was distilled off at atmospheric pressure and flash column chromatography of the residue, eluting with hexanes-EtOAc (4:1) afforded the *title compounds* ***12d***[24] (197 mg, 21%) as colourless blocks, after recrystallization from hexanes and Et_2O at 0 °C, mp 24-25 °C; and ***13d***[24] (508 mg, 54%) as colourless plates, after recrystallization from hexanes and Et_2O at 0 °C, mp 94-95 °C.

Compound 12d

^{1}H NMR (300 MHz) δ 2.50 (s, 3H, CH_3), 3.86 (s, 3H, CH_3O), 8.84 (s, 1H, H5).

^{13}C NMR (75.4 MHz) δ 10.1 (CH_3), 51.2 (CH_3O), 112.7 (C4), 158.2 (C3), 161.3 (C=O), 162.5 (C5).

IR (KBr, thin film) ν_{max} 1734, 1592, 1491, 1435, 1405, 1299, 1249, 1133, 1109, 805, 772 cm^{-1}.

X-Ray Crystallographic Analysis Appendix 1.2.

Compound 13d

^{1}H NMR (300 MHz) δ 2.38 (s, 3H, CH_3), 3.96 (s, 3H, CH_3O), 6.80 (s, 1H, H4).

^{13}C NMR (75.4 MHz) δ 11.3 (CH_3), 52.7 (CH_3O), 110.0 (C4), 157.2 (C3), 159.7 (C5), 160.4 (C=O).

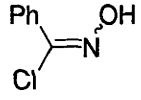
IR (KBr, thin film) ν_{max} 1731, 1444, 1382, 1299, 1233, 1093, 1004, 932, 900, 851, 771 cm^{-1}.

LRMS (EI) *m/z* (%) 141 ($M^{\bullet+}$, 76), 115 (6), 110 ($M^{\bullet+}$-CH_3O, 23), 102 (10), 91 (3), 82 ($M^{\bullet+}$-CH_3O_2C, 100), 77 (3), 73 (10), 63 (2), 59 (8), 54 (23).

HRMS (EI) Found: $M^{\bullet+}$, 141.042510. $C_6H_7NO_3$ requires $M^{\bullet+}$, 141.042593.

X-Ray Crystallographic Analysis Appendix 1.3.

Benzohydroximinoyl Chloride 6



6

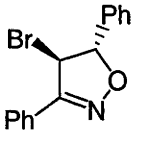
NCS (2.20 g, 16.5 mmol) was added to a stirred solution of benzaldoxime **78** (2.00 g, 16.5 mmol) in DMF at 0-5 °C (ice bath) over 30 min. The internal temperature of the reaction mixture was maintained between 20-25 °C during the addition by external cooling (ice bath). After stirring at 20-25 °C for 3.5 h, it was poured into ice-H_2O (1 × 50 mL) and taken up in Et_2O (100 mL). The aqueous layer was separated and extracted with Et_2O (6 × 75 mL). The combined organic solution was washed with H_2O (5 × 75 mL), brine (1 × 75 mL) and dried (anhydrous $MgSO_4$). The filtrate was concentrated *in vacuo* to afford the *title compound* ***6*** (2.25 g, 88%) as a cream coloured solid, mp 42-46 °C [lit.[187] mp 42-46 °C].

^{1}H NMR (300 MHz) δ 1.67 (br s, 1H, OH), 7.33-7.51 (m, 3H, 3 × PhH), 7.74-8.01 (m, 2H, 2 × PhH).

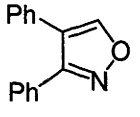
IR (KBr, thin film) ν_{max} 3289, 1629, 1605, 1578, 1493, 1315, 1287, 1182, 1162, 1079, 842, 617, 590, 481, 466, 408 cm^{-1}.

The ^{1}H NMR spectral data of compound **6** are consistent with literature values.[187]

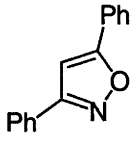
***trans*-4-Bromo-3,5-diphenyl-Δ^2-isoxazoline 81b,**
3,4-Diphenylisoxazole 9b and
3,5-Diphenylisoxazole 10b



rac.
81b



9b



10b

A solution of triethylamine (1.7 mL, 12 mmol) in Et_2O (4.1 mL) was added over 3 days to a stirred mixture of benzohydroximinoyl chloride **6** (96 mg, 6.2 mmol) and β-bromostyrene **79** (2.83 g, 15.5 mmol) in Et_2O (50 mL) at 18 °C. After stirring at 18 °C for a further 4 days, the mixture was poured into H_2O (10 mL). The aqueous layer was separated and extracted with Et_2O (3 × 20 mL). The combined organic solution was washed with H_2O (2 × 15 mL) and brine (1 × 15 mL), dried (anhydrous $MgSO_4$) and concentrated under reduced pressure. Flash column chromatography of the residue, eluting with hexanes-Et_2O (3:2), afforded the *title compounds* ***81b*** (1.23 g, 66%) as colourless needles, after recrystallization from boiling hexanes, mp 151-152 °C [lit.[73] mp 152-153 °C]; ***9b*** (150 mg, 11%) as colourless needles, after recrystallization from boiling hexanes, mp 91 °C [lit.[74] mp 88-89 °C]; and ***10b*** (15 mg, 1%) as a colourless solid, mp 141 °C [lit.[76] mp 140 °C].

Compound 81b

^{1}H NMR (300 MHz) δ 5.38 (d, J = 2.0 Hz, 1H, H4), 6.06 (d, J = 2.0 Hz, 1H, H5), 7.30-7.48 (m, 8H, 8 × PhH), 7.74-7.84 (m, 2H, 2 × PhH).

^{13}C NMR (75.4 MHz) 52.6 (C4), 91.6 (C5), 125.0 (2 × CH), 126.7 (C), 127.1 (2 × CH), 128.7 (2 × CH), 128.8 (2 × CH), 129.0 (CH), 130.6 (CH), 137.3 (C), 155.4 (C3).

IR (KBr, thin film) ν_{max} 3018, 1353, 1155, 1149, 1076, 951, 917, 903, 767, 750, 711, 689 cm^{-1}.

LRMS (EI) *m/z* (%) 303, 301 ($M^{\bullet+}$, 26 and 25), 271 (3), 222 (25), 206 (7), 191 (40), 165 (12), 144 (6), 119 (4), 105 (100), 91 (31), 77 (57).

HRMS (EI) Found $M^{\bullet+}$, 301.009889. $C_{15}H_{12}{}^{79}BrNO$ requires $M^{\bullet+}$, 301.010225.

X-Ray Crystallographic Analysis Appendix 1.4.

Compound 9b

^{1}H NMR (300 MHz) δ 7.22-7.58 (m, 10H, 10 × PhH), 8.52 (s, 1H, H5).

^{13}C NMR (75.4 MHz) δ 120.2 (C4), 127.9 (CH), 128.3 (C), 128.4 (2 × CH), 128.5 (2 × CH), 128.6 (2 × CH), 128.7 (2 × CH), 128.8 (C), 129.5 (CH), 159.1 (C5), 160.0 (C3).

IR (KBr, thin film) ν_{max} 1615, 1570, 1492, 1452, 1436, 1373, 1310, 1281, 1119, 1073, 1026, 972, 883, 837, 761, 716, 696, 670, 558 cm^{-1}.

LRMS (EI) *m/z* (%) 221 ($M^{\bullet+}$, 34), 204 (4), 193 (38), 165 (26), 152 (3), 139 (2), 126 (2), 116 (14), 104 (4), 89 (49), 77 (27), 63 (17).

HRMS (EI) Found: $M^{\bullet+}$, 221.083678. $C_{15}H_{11}NO$ requires $M^{\bullet+}$, 221.084064.

X-Ray Crystallographic Analysis Appendix 1.5.

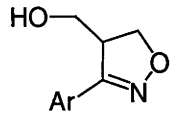
Compound 10b

^{1}H NMR (300 MHz) δ 6.82 (s, 1H, H4), 7.25-7.50 (m, 5H, 5 × PhH), 7.78-7.91 (m, 5H, 5 × PhH).

The ^{1}H NMR spectral data of **9b** and **10b** are consistent with reported values.[74-76]

7.3. Experimental for Chapter 3

4-Hydroxymethyl-3-(2,4,6-trimethylphenyl)-Δ^2-isoxazoline 101



101

Ar = 2,4,6-Me_3Ph

Sodium borohydride (185 mg, 4.89 mmol) was added over 15 min to a stirred solution of 3-(2,4,6-trimethylphenyl)isoxazole-4-carboxylic acid methyl ester **12f** (80.0 mg, 0.326 mmol) in dry EtOH (5 mL) at 0-5 °C (ice bath). After heating at reflux for 24 h, the mixture was cooled to 0-5 °C (ice bath) and quenched by dropwise addition of 1M HCl (to pH 2). The solvent was evaporated *in vacuo*, the residue was taken up in Et_2O (10 mL) and washed with H_2O (1 × 7 mL). The aqueous layer was separated and extracted with Et_2O (3 × 7 mL). The combined organic solution was washed with H_2O (1 × 7 mL), aq. $NaHCO_3$ (1 × 7 mL) and brine (1 × 7 mL), dried (anhydrous $MgSO_4$) and concentrated *in vacuo*. Flash column chromatography of the residue, eluting with hexanes-EtOAc (4:1) afforded the *title compound **101*** (65 mg, 91%) as a colourless oil.

^{1}H NMR (300 MHz) δ 1.55 (br s, 1H, OH), 2.28 (s, 6H, *o,o'*-MesCH_3), 2.30 (s, 3H, *p*-MesCH_3), 3.69 (m, 2H, CH_2O), 3.75 (m, 1H, H4), 4.50 (m, 2H, H5 and H5'), 6.91 (s, 2H, 2 × MesH).

^{13}C NMR (75.4 MHz) δ 20.0 (2 × CH_3), 21.1 (CH_3), 54.5 (C4), 61.0 (CH_2O), 71.8 (C5), 124.9 (C), 128.7 (2 × CH), 136.7 (2 × C), 138.8 (C), 158.3 (C3).

IR (KBr, thin film) ν_{max} 3369, 2962, 2922, 2208, 2088, 1612, 1453, 1378, 1313, 1261, 1140, 1102, 975, 852, 733, 573 cm^{-1}.

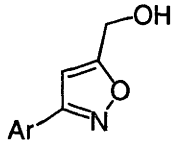
LRMS (EI) *m/z* (%) 219 ($M^{\bullet+}$, 100), 202 ($M^{\bullet+}$-OH, 51), 188 ($M^{\bullet+}$-NOH, 47), 172 (90), 164 (4), 158 ($M^{\bullet+}$-C_3H_9O, 55), 146 (76), 130 (48), 121 (20), 115 (42), 103 (26), 91 (55), 77 (4), 65 (22), 57 (4).

HRMS (EI) Found: $M^{\bullet+}$, 219.125774. $C_{13}H_{17}NO_2$ requires $M^{\bullet+}$, 219.125929.

Elemental Analysis Found: C, 71.11; H, 7.71; N, 6.12. $C_{13}H_{17}NO_2$ requires C, 71.21; H, 7.81; N, 6.39.

The ^1H NMR data are fully consistent with reported values.[102]

5-Hydroxymethyl-3-(2,4,6-trimethylphenyl)isoxazole 102



102

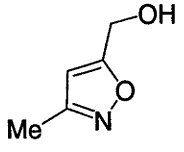
Ar = 2,4,6-Me_3Ph

Sodium borohydride (185 mg, 4.89 mmol) was added over 15 min to a stirred solution of 3-(2,4,6-trimethylphenyl)isoxazole-5-carboxylic acid methyl ester **13f** (80.0 mg, 0.326 mmol) in dry EtOH (6 mL) at 0-5 °C (ice bath). After heating at reflux for 24 h, the mixture was cooled to 0-5 °C (ice bath) and quenched by dropwise addition of 1M HCl (to pH 2). The solvent was removed under reduced pressure, the residue was taken up in Et_2O (10 mL) and washed with H_2O (1 × 7 mL). The aqueous layer was separated and extracted with Et_2O (3 × 10 mL). The combined organic solution was washed with H_2O (1 × 7 mL), aq. $NaHCO_3$ (1 × 7 mL) and brine (1 × 7 mL), dried (anhydrous $MgSO_4$) and concentrated *in vacuo*. Flash column chromatography of the residue,

eluting with hexanes-EtOAc (4:1) afforded the *title compound* ***102*** (66 mg, 93%) as a colourless oil.

^{1}H NMR (300 MHz) δ 1.20 (br s, 1H, OH), 2.15 (s, 6H, *o,o'*-$MesCH_3$), 2.33 (s, 3H, *p*-$MesCH_3$), 4.87 (s, 2H, CH_2O), 6.21 (s, 1H, H4), 6.95 (s, 2H, 2 × MesH).
^{13}C NMR (75.4 MHz) δ 20.1 (2 × CH_3), 21.0 (CH_3), 56.3 (CH_2O), 103.2 (C4), 125.7 (C), 128.3 (2 × CH), 137.0 (2 × C), 138.9 (C), 162.1 (C3), 171.7 (C5).
IR (KBr, thin film) ν_{max} 3382, 2923, 2860, 1612, 1457, 1393, 1363, 1173, 1142, 1076, 1036, 996, 888, 852, 813, 575 cm^{-1}.
LRMS (EI) *m/z* (%) 217 ($M^{\bullet+}$, 64), 205 (3), 186 (100), 171 (13), 143 (26), 131 (17), 119 (22), 115 (21), 103 (12), 91 (30), 77 (19), 65 (9), 53 (6).
HRMS (EI) Found: $M^{\bullet+}$, 217.065797. $C_{13}H_{15}NO_2$ requires $M^{\bullet+}$, 217.065340.
Elemental Analysis Found: C, 71.63; H, 6.91; N, 6.56. $C_{13}H_{15}NO_2$ requires C, 71.87; H, 6.96; N, 6.45.

5-Hydroxylmethyl-3-methylisoxazole 104



104

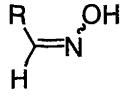
Sodium borohydride (401 mg, 10.6 mmol) was added over 15 min to a solution of 3-methylisoxazole-5-carboxylic acid methyl ester **13d** (100 mg, 0.709 mmol) in dry EtOH (5 mL) at 0-5 °C (ice bath). After heating at reflux for 24 h, the mixture was cooled to 0-5 °C (ice bath) and quenched by dropwise addition of 1M HCl (to pH 2). The solvent was removed *in vacuo*, the residue was taken up in Et_2O (10 mL) and washed with H_2O (7 mL). The aqueous layer was separated and extracted with Et_2O (3 ×

10 mL). The combined organic solution was washed with H_2O (2 × 7 mL) and brine (1 × 7 mL), dried (anhydrous $MgSO_4$) and evaporated under reduced pressure. Flash column chromatography of the residue, eluting with hexanes-EtOAc (7:3) afforded the *title compound **104*** (64 mg, 80%) as a colourless oil, bp 138-140 °C (25 mm Hg) [lit.[104] bp 138-140 °C (25 mm Hg)].

^{1}H NMR (300 MHz) δ 1.60 (br s, 1H, OH), 2.32 (s, 3H, CH_3), 4.76 (s, 2H, CH_2O), 6.11 (s, 1H, H4).

The ^{1}H NMR data and bp of compound **104** are consistent with literature values.[104]

Decylaldoxime 106



106

R = $(CH_2)_8CH_3$

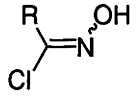
An aqueous solution (50 mL) of $NaHCO_3$ (2.7 g, 32 mmol) and hydroxylamine hydrochloride (834 mg, 12.0 mmol) was added dropwise to stirred decyl aldehyde **105** (1.56 g, 10.0 mmol) at 0 °C (ice bath). After stirring at 0 °C for 15 min, the mixture was poured into Et_2O (100 mL). The aqueous layer was separated and extracted with Et_2O (3 × 100 mL). The organic solution was washed with brine (1 × 75 mL), dried (anhydrous $MgSO_4$) and concentrated *in vacuo*. The residue was recrystallized from EtOH to afford the *title compound **106*** (1.53 g, 89%) as colourless prisms, mp 48-52 °C [lit.[105] mp 69 °C].

^{1}H NMR (300 MHz) δ 0.88 (t, J = 6.6 Hz, 3H, C$\underline{H}_3$CH$_2$), 1.11-1.38 (m, 8H, 4 × CH$_2$), 1.39-1.52 (m, 4H, 2 × CH$_2$), 2.19 (m, 2H, CH$_2$), 2.39 (m, 2H, CH$_2$), 6.70 (br s, 1H, OH), 7.30 (t, J = 6.1 Hz, 1H, CH=N).

IR (KBr, thin film) ν_{max} 3194, 2956, 2921, 2848, 1667, 1466, 1445, 1322, 932, 855, 721 cm^{-1}.

LRMS (EI) *m/z* (%) 172 ($M^{\bullet+}$, 44), 154 ($M^{\bullet+}$-OH$_2$, 74), 143 (4), 138 (14), 128 ($M^{\bullet+}$-CHNOH, 44), 114 (53), 100 (100), 86 (75), 72 (44), 59 (52).

Decylhydroximinoyl Chloride 107



107

R = (CH$_2$)$_8$CH$_3$

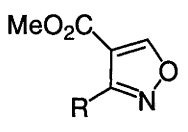
NCS (4.01 g, 30.0 mmol) was added over 30 min to a solution of decylaldoxime **106** (5.16 g, 30.0 mmol) in DMF (100 mL) at 0-5 °C (ice bath). Stirring was continued at 20-25 °C for a further 3 h with the internal temperature of the reaction mixture maintained between 20-25 °C by external cooling (ice bath). The mixture was poured into ice-H$_2$O (75 mL) and extracted with Et$_2$O (6 × 100 mL). The combined organic solution was washed with H$_2$O (5 × 75 mL) and brine (1 × 75 mL), dried (anhydrous MgSO$_4$) and concentrated *in vacuo* to afford the *title compound **107*** (5.4 g, 87%) as a pale yellow liquid.

^{1}H NMR (300 MHz) δ 0.89 (t, J = 7.1 Hz, 3H, C$\underline{H}_3$CH$_2$), 1.21-1.40 (m, 12H, 6 × CH$_2$), 1.65 (p, J = 7.3 Hz, 2H, CH$_2$), 2.51 (t, J = 7.3 Hz, 2H, CH$_2$), 7.31 (s, 1H, OH).

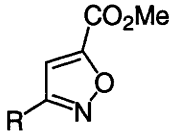
^{13}C NMR (75.4 MHz) δ 14.0 (CH_3), 22.6 (CH_2), 26.2 (CH_2), 28.4 (CH_2), 29.1 (CH_2), 29.2 (CH_2), 29.4 (CH_2), 31.8 (CH_2), 36.5 (CH_2), 141.9 (C).

IR (KBr, thin film) ν_{max} 2926, 2855, 1640, 1465, 1100 cm^{-1}.

3-Nonylisoxazole-4-carboxylic Acid Methyl Ester 111 and
3-Nonylisoxazole-5-carboxylic Acid Methyl Ester 112



111



112

R = $(CH_2)_8CH_3$

A solution of triethylamine (0.37 mL, 2.60 mmol) in Et_2O (10 mL) was added over 18 h to a stirred solution of (*Z*)-3-iodopropenoic acid methyl ester **74** (4.00 g, 18.9 mmol) and decylhydroximinoyl chloride **107** (485 mg, 2.36 mmol) in dry Et_2O (100 mL) at 18 °C. After stirring at 18 °C for a further 24 h, the mixture was poured into H_2O (50 mL). The aqueous layer was separated and extracted with Et_2O (3 × 100 mL). The combined organic solution was washed with brine (1 × 75 mL), dried (anhydrous $MgSO_4$) and concentrated *in vacuo*. Flash column chromatography of the residue, eluting with hexanes-CH_2Cl_2 (1:1) afforded the *title compounds **111*** (102 mg, 17%) as a colourless oil; and ***112*** (258 mg, 43%) as a colourless solid, mp 50-52 °C.

Compound 111

^{1}H NMR (300 MHz) δ 0.89 (t, *J* = 6.7 Hz, 3H, $C\underline{H}_3CH_2$), 1.20-1.45 (m, 12H, 6 × CH_2), 1.72 (p, *J* = 7.7 Hz, 2H, CH_2), 2.92 (t, *J* = 7.7 Hz, 2H, CH_2), 3.87 (s, 3H, CH_3O), 8.85 (s, 1H, H5).

^{13}C NMR (75.4 MHz) δ 14.1 (CH_3), 22.6 (CH_2), 25.2 (CH_2), 27.6 (CH_2), 29.24 (CH_2), 29.2 (CH_2), 29.3 (CH_2), 29.4 (CH_2), 31.8 (CH_2), 51.8 (CH_3O), 112.7 (C4), 161.7 (C3), 162.5 (C=O), 163.0 (C5).

IR (KBr, thin film) ν_{max} 2926, 2855, 1735, 1586, 1436, 1297, 1245, 1134, 1103, 806, 778 cm^{-1}.

LRMS (EI) *m/z* (%) 253 ($M^{\bullet+}$, 25), 238 ($M^{\bullet+}$-CH_3, 7), 222 ($M^{\bullet+}$-CH_3O, 18), 210 ($M^{\bullet+}$-$COCH_3$, 12), 194 ($M^{\bullet+}$- CH_3O_2C, 14), 182 (17), 168 (13), 154 (49), 141 (100), 122 (26), 110 (7), 96 (16), 83 (19), 68 (19).

HRMS (EI) Found: $M^{\bullet+}$, 253.167549. $C_{14}H_{23}NO_3$ requires $M^{\bullet+}$, 253.167794.

Elemental Analysis Found: C, 66.62; H, 9.39; N, 5.74. $C_{14}H_{23}NO_3$ requires C, 66.37; H, 9.15; N, 5.53.

Compound 112

^{1}H NMR (300 MHz) δ 0.88 (t, J = 7.0 Hz, 3H, $C\underline{H}_3CH_2$), 1.28-1.43 (m, 12H, 6 × CH_2), 1.67 (p, J = 7.5 Hz, 2H, CH_2), 2.72 (t, J = 7.5 Hz, 2H, CH_2), 3.96 (s, 3H, CH_3O), 6.81 (s, 1H, H4).

^{13}C NMR (75.4 MHz) δ 14.0 (CH_3), 22.6 (CH_2), 25.9 (CH_2), 28.1 (CH_2), 29.0 (CH_2), 29.2 (2 × CH_2), 29.4 (CH_2), 31.8 (CH_2), 52.7 (CH_3O), 109.2 (C4), 157.3 (C3), 159.3 (C=O), 164.7 (C5).

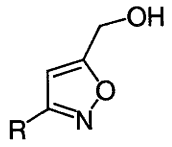
IR (KBr, thin film) ν_{max} 2953, 2914, 2848, 1731, 1470, 1291, 1274, 1088, 1007, 908, 851, 770, 717 cm^{-1}.

LRMS (EI) *m/z* (%) 253 ($M^{\bullet+}$, 11), 238 ($M^{\bullet+}$-CH_3, 6), 224 (3), 210 (5), 194 ($M^{\bullet+}$-CH_3O_2C, 58), 182 (4), 166 (21), 154 (43), 141 (100), 122 (7), 108 (6), 96 (11), 82 (16), 68 (16).

HRMS (EI) Found: $M^{\bullet+}$, 253.167601. $C_{14}H_{23}NO_3$ requires $M^{\bullet+}$, 253.167794.

Elemental Analysis Found: C, 66.28; H, 8.72; N, 5.37. $C_{14}H_{23}NO_3$ requires C, 66.37; H, 9.15; N, 5.53.

5-Hydroxymethyl-3-nonylisoxazole 114



114

R = $(CH_2)_8CH_3$

Sodium borohydride (224 mg, 5.93 mmol) was added over 15 min to a solution of 3-nonylisoxazole-4-carboxylic acid methyl ester **112** (100 mg, 0.395 mmol) in dry EtOH (5 mL) at 0-5 °C (ice bath). After heating at reflux for 24 h, the reaction mixture was cooled to 0-5 °C (ice bath) and quenched by the dropwise addition of 1M HCl (to pH 2). The solvent was evaporated *in vacuo*, the residue was taken up in Et_2O (10 mL) and washed with H_2O (7 mL). The aqueous phase was separated and extracted with Et_2O (3 × 7 mL). The combined organic solution was washed with H_2O (2 × 7 mL) and brine (1 × 7 mL), dried (anhydrous $MgSO_4$) and evaporated under reduced pressure. Flash column chromatography of the residue, eluting with hexanes-EtOAc (7:3) afforded the *title compound **114*** (82 mg, 92%) as a colourless solid, mp 34-35°C.

^{1}H NMR (300 MHz) δ 0.89 (t, J = 6.8 Hz, 3H, $C\underline{H}_3CH_2$), 1.38-1.42 (m, 12H, 6 × CH_2), 1.50-1.75 (m, 3H, CH_2 and OH), 2.67 (t, J = 7.3 Hz, 2H, CH_2), 4.76 (s, 2H, CH_2O), 6.11 (s, 1H, H4).

^{13}C NMR (75.4 MHz) δ 14.0 (CH_3), 22.6 (CH_2), 25.9 (CH_2), 28.2 (CH_2), 29.1 (CH_2), 29.2 (2 × CH_2), 29.4 (CH_2), 31.8 (CH_2), 56.1 (CH_2O), 101.4 (C4), 164.2 (C3), 171.3 (C5).

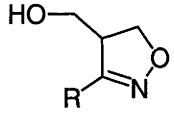
IR (KBr, thin film) ν_{max} 3368, 2928, 2856, 1669, 1134, 1071, 999, 802 cm^{-1}.

LRMS (EI) *m/z* (%) 225 ($M^{\cdot+}$, 4), 194 ($M^{\cdot+}$-NOH, 34), 182 (6), 168 (7), 154 (3), 140 (5), 126 (44), 96 (13), 82 (11), 68 (11), 55 (20).

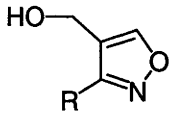
HRMS (EI) Found: $M^{\cdot+}$, 225.172695. $C_{13}H_{23}NO_2$ requires $M^{\cdot+}$, 225.172879.

Elemental Analysis Found: C, 69.35; H, 10.01; N, 6.08. $C_{13}H_{23}NO_2$ requires C, 69.29; H, 10.29; N, 6.22.

4-Hydroxymethyl-3-nonyl-Δ^2-isoxazoline 115 and
4-Hydroxymethyl-3-nonylisoxazole 116



115



116

R = $(CH_2)_8CH_3$

Sodium borohydride (186 mg, 4.92 mmol) was added over 15 min to a solution of 3-nonylisoxazole-4-carboxylic acid methyl ester **111** (83.0 mg, 0.328 mmol) in dry EtOH (17 mL) at 0-5 °C (ice bath). After heating at reflux for 24 h, the reaction mixture was cooled to 0-5 °C (ice bath) and quenched by dropwise addition of 1M HCl (to pH 2). The solvent was evaporated under reduced pressure, the residue was taken up in Et_2O (10 mL) and washed with H_2O (7 mL). The aqueous phase was separated and extracted with Et_2O (3 × 10 mL). The combined organic solution was washed with H_2O (2 × 7 mL) and brine (1 × 7 mL), dried (anhydrous $MgSO_4$) and evaporated *in vacuo*. Flash column chromatography of the residue, eluting with hexanes-EtOAc (7:3) afforded the *title compounds **115*** (54 mg, 73%) and ***116*** (13 mg, 18%) as colourless oils.

Compound 115

^{1}H NMR (300 MHz) δ 0.88 (t, J = 6.7 Hz, 3H, $C\underline{H}_3CH_2$), 1.20-1.40 (m, 10H, 5 × CH_2), 1.50-1.71 (m, 5H, 2 × CH_2 and OH), 2.26 (m, 1H, CH_2), 2.45 (m, 1H, CH_2), 3.39 (m, 1H, H4), 3.78 (m, 2H, CH_2O), 4.26 (m, 2H, H5 and H5').

^{13}C NMR (75.4 MHz) δ 14.1 (CH_3), 22.6 (CH_2), 26.1 (CH_2), 26.5 (CH_2), 29.1 (CH_2), 29.2 (CH_2), 29.3 (CH_2), 29.4 (CH_2), 31.8 (CH_2), 52.4 (C4), 61.0 (CH_2O), 71.0 (C5), 159.9 (C3).

IR (KBr, thin film) ν_{max} 3400, 2926, 2854, 1466, 1378, 1095, 1043, 929, 873, 722 cm^{-1}.

LRMS (EI) *m/z* (%) 227 ($M^{\bullet+}$, 26), 210 ($M^{\bullet+}$-OH, 5), 196 ($M^{\bullet+}$-NOH, 16), 180 ($M^{\bullet+}$-NO_2H, 13), 156 (5), 140 (6), 128 (61), 115 (100), 108 (9), 98 (15), 85 (25), 69 (20), 55 (29).

HRMS (EI) Found: $M^{\bullet+}$, 227.188299. $C_{13}H_{25}NO_2$ requires $M^{\bullet+}$, 227.188529.

Elemental Analysis Found: C, 68.67; H, 11.38; N, 5.85. $C_{13}H_{25}NO_2$ requires C, 68.68; H, 11.08; N, 6.16

Compound 116

^{1}H NMR (300 MHz) δ 0.88 (t, J = 7.0 Hz, 3H, $C\underline{H}_3CH_2$), 1.18 (m, 13H, 6 × CH_2 and OH), 1.71 (p, J = 7.7 Hz, 2H, CH_2), 2.71 (t, J = 7.7 Hz, 2H, CH_2), 4.58 (s, 2H, CH_2O), 8.30 (s, 1H, H5).

^{13}C NMR (75.4 MHz) δ 14.1 (CH_3), 22.7 (CH_2), 24.9 (CH_2), 27.7 (CH_2), 29.2 (CH_2), 29.3 (CH_2), 29.5 (CH_2), 29.7 (CH_2), 31.9 (CH_2), 53.9 (CH_2O), 118.4 (C4), 156.1 (C5), 162.0 (C3).

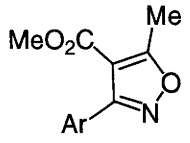
IR (KBr, thin film) ν_{max} 3400, 2926, 2854, 1609, 1465, 1417, 1117, 1020, 873 cm^{-1}.

LRMS (EI) *m/z* (%) 225 ($M^{\bullet+}$, 4), 208 ($M^{\bullet+}$-OH, 9), 196 (6), 182 (7), 154 (8), 136 (14), 126 (57), 113 (100), 98 [$M^{\bullet+}$-$(CH_2)_8CH_3$, 8], 85 (11), 69 (8), 55 (19).

HRMS (EI) Found: $M^{\bullet+}$, 225.172714. $C_{13}H_{23}NO_2$ requires $M^{\bullet+}$, 225.172879.

Elemental Analysis Found: C, 69.68; H, 10.54; N, 6.15. $C_{13}H_{23}NO_2$ requires C, 69.29; H, 10.29; N, 6.22.

5-Methyl-3-(2,4,6-trimethylphenyl)isoxazole-4-carboxylic Acid Methyl Ester 117



117

Ar = 2,4,6-Me_3Ph

A mixture of mesitonitrile oxide **5** (500 mg, 3.10 mmol) and methyl tetrolate **17a** (304 mg, 3.10 mmol) in a solution of THF (25 mL) was heated at reflux for 4 days. After the solvent was removed *in vacuo*, the residue was taken up in Et_2O (100 mL) and washed with H_2O (1 × 75 mL). The aqueous layer was separated and extracted with Et_2O (3 × 100 mL). The combined organic solution was washed with H_2O (1 × 75 mL) and brine (1 × 75 mL), dried (anhydrous $MgSO_4$) and evaporated under reduced pressure. Flash column chromatography of the residue, eluting with hexanes-Et_2O (4:1) afforded the *title compound **117*** (787 mg, 98%) as colourless blocks, after recrystallization from vapour diffusion of hexanes and Et_2O at 18 °C, mp 76-78 °C.

^{1}H NMR (300 MHz) δ 2.05 (s, 6H, *o,o'*-MesCH_3), 2.31 (s, 3H, *p*-MesCH_3), 2.77 (s, 3H, CH_3), 3.67 (s, 3H, CH_3O), 6.91 (s, 2H, 2 × MesH).

^{13}C NMR (75.4 MHz) δ 13.6 (CH_3), 19.9 (2 × CH_3), 21.2 (CH_3), 51.6 (CH_3O), 109.1 (C4), 124.2 (C), 128.0 (2 × CH), 136.8 (2 × C), 138.6 (C), 161.9 (C3), 162.2 (C=O), 175.4 (C5).

IR (KBr, thin film) ν_{max} 2952, 2923, 2858, 1730, 1719, 1603, 1441, 1409, 1311, 1297, 1250, 1191, 1096, 1035, 994, 980, 851, 806, 770 cm^{-1}.

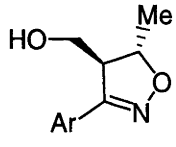
LRMS (EI) *m/z* (%) 259 ($M^{\bullet+}$, 100), 244 ($M^{\bullet+}$-CH_3, 28), 228 ($M^{\bullet+}$-CH_3O, 42), 212 ($M^{\bullet+}$-CH_3O_2, 65), 200 ($M^{\bullet+}$-CH_3O_2C, 24), 185 (92), 171 (57), 157 (59), 144 (17), 130 (22), 115 (30), 103 (20), 91 (28), 77 (31).

HRMS (EI) Found: $M^{\bullet+}$, 259.121324. $C_{15}H_{17}NO_3$ requires $M^{\bullet+}$, 259.120844.

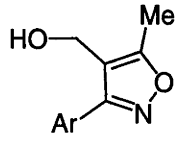
Elemental Analysis Found: C, 69.40; H, 6.41; N, 5.68. $C_{15}H_{17}NO_3$ requires C, 69.48; H, 6.61; N, 5.40.

X-Ray Crystallographic Analysis Appendix 1.7.

***trans*-4-Hydroxymethyl-5-methyl-3-(2,4,6-trimethylphenyl)-Δ^2-isoxazoline 118 and 4-Hydroxymethyl-5-methyl-3-(2,4,6-trimethylphenyl)isoxazole 119**



rac.
118



119

Ar = 2,4,6-Me_3Ph

Sodium borohydride (219 mg, 5.79 mmol) was added over 15 min to a solution of 5-methyl-3-(2,4,6-trimethylphenyl)isoxazole-4-carboxylic acid methyl ester **117** (100 mg, 0.386 mmol) in dry EtOH (5 mL) at 0-5 °C (ice bath). After heating at reflux for 24 h, the mixture was cooled to 0-5 °C (ice bath) and quenched by dropwise addition of 1M HCl (to pH 2). The solvent was evaporated under reduced pressure, the residue was taken up in Et_2O (5 mL) and washed with H_2O (3 mL). The aqueous layer was separated and extracted with Et_2O (3 × 3 mL). The combined organic solution was washed with H_2O (2 × 3 mL) and brine (1 × 3 mL), dried (anhydrous $MgSO_4$) and evaporated *in vacuo*. Flash column chromatography of the residue, eluting with CH_2Cl_2-Et_2O (9:1) afforded the *title compounds **118*** (55 mg, 61%) and ***119*** (27 mg, 30%) as colourless oils.

Compound 118

^{1}H NMR (300 MHz) δ 1.51 (d, J = 6.3 Hz, 3H, C$\underline{H}_3$CH), 1.60 (br s, 1H, OH), 2.27 (s, 6H, *o*,*o*'-MesCH$_3$), 2.29 (s, 3H, *p*-MesCH$_3$), 3.34 (ddd, J = 7.2, 6.5, 5.6 Hz, 1H, H4), 3.67 (m, 2H, CH$_2$O), 4.72 (dq, J = 7.2, 6.3 Hz, 1H, H5), 6.90 (s, 2H, 2 × MesH).

^{13}C NMR (75.4 MHz) δ 20.1 (CH$_3$), 20.8 (2 × CH$_3$), 21.0 (CH$_3$), 60.7 (C4), 61.3 (CH$_2$O), 80.2 (C5), 125.4 (C), 128.8 (2 × CH), 136.8 (2 × C), 138.8 (C), 157.9 (C3).

IR (KBr, thin film) ν_{max} 3400, 2971, 2924, 2872, 1612, 1454, 1377, 1323, 1207, 1044, 880, 853, 800, 737, 591, 573 cm^{-1}.

LRMS (EI) *m/z* (%) 233 ($M^{\bullet+}$, 58), 218 (100), 200 (8), 188 (26), 172 (62), 158 (29), 130 (27), 119 (21), 103 (11), 91 (28), 77 (18), 65 (8).

HRMS (EI) Found: $M^{\bullet+}$, 233.141293. $C_{14}H_{19}NO_2$ requires $M^{\bullet+}$, 233.141579.

Elemental Analysis Found: C, 72.29; H, 8.55; N, 5.78. $C_{14}H_{19}NO_2$ requires C, 72.07; H, 8.21; N, 6.00.

Compound 119

^{1}H NMR (300 MHz) δ 1.54 (br s, 1H, OH), 2.09 (s, 6H, *o*,*o*'-MesCH$_3$), 2.33 (s, 3H, *p*-MesCH$_3$), 2.53 (s, 3H, CH$_3$), 4.28 (s, 2H, CH$_2$O), 6.94 (s, 2H, 2 × MesH).

^{13}C NMR (75.4 MHz) δ 11.4 (CH$_3$), 19.9 (2 × CH$_3$), 21.2 (CH$_3$), 53.9 (CH$_2$O), 114.0 (C4), 125.1 (C), 128.8 (2 × CH), 137.2 (2 × C), 138.9 (C), 160.0 (C3), 167.6 (C5).

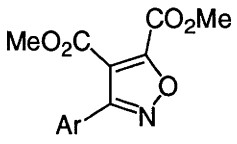
IR (KBr, thin film) ν_{max} 3392, 2924, 1627, 1432, 1378, 1274, 1209, 1018, 851 cm^{-1}.

LRMS (EI) *m/z* (%) 231 ($M^{\bullet+}$, 64), 216 (38), 198 (18), 188 (68), 170 ($M^{\bullet+}$-NOCH$_2$OH, 100), 158 (46), 130 (26), 119 (33), 103 (22), 91 (60), 77 (42), 65 (18).

HRMS (EI) Found: $M^{\bullet+}$, 231.125902. $C_{14}H_{17}NO_2$ requires $M^{\bullet+}$, 231.125929.

Elemental Analysis Found: C, 72.48; H, 7.40; N, 6.03. $C_{14}H_{17}NO_2$ requires C, 72.70; H, 7.41; N, 6.06.

3-(2,4,6-Trimethylphenyl)isoxazole-4,5-dicarboxylic Acid Dimethyl Diester 120



120

Ar = 2,4,6-Me_3Ph

A solution of dimethyl acetylenedicarboxylate **32** (442 mg, 3.11 mmol) and mesitonitrile oxide **5** (501 mg, 3.11 mmol) in THF (40 mL) was heated at reflux for 2 days. After the solvent was evaporated under reduced pressure, the residue was taken up in Et_2O (50 mL) and washed with H_2O (30 mL). The aqueous layer was separated and extracted with Et_2O (3 × 30 mL). The organic solution was combined and washed with brine (1 × 30 mL), dried (anhydrous $MgSO_4$) and evaporated *in vacuo*. Flash column chromatography of the residue, eluting with hexanes-Et_2O (7:3) afforded the *title compound **120*** (914 mg, 97%) as a colourless solid, mp 56-57 °C.

^{1}H NMR (300 MHz) δ 2.08 (s, 6H, *o,o'*-MesCH_3), 2.33 (s, 3H, *p*-MesCH_3), 3.74 (s, 3H, CH_3O), 4.05 (s, 3H, CH_3O), 6.93 (s, 2H, 2 × MesH).

^{13}C NMR (75.4 MHz) δ 19.9 (2 × CH_3), 21.1 (CH_3), 52.6 (CH_3O), 53.4 (CH_3O), 116.3 (C4), 123.2 (C), 128.2 (2 × CH), 137.2 (2 × C), 139.5 (C), 156.8 (C3), 160.1 (C=O), 160.6 (C=O), 162.0 (C5).

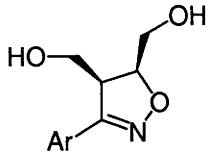
IR (KBr, thin film) ν_{max} 3332, 2955, 2926, 1739, 1612, 1441, 1384, 1310, 1297, 1275, 1216, 1169, 1125, 1066, 991, 801 cm^{-1}.

LRMS (EI) *m/z* (%) 303 ($M^{\bullet+}$, 48), 272 ($M^{\bullet+}$-CH_3O, 4), 244 ($M^{\bullet+}$-CH_3O_2C, 100), 228 (2), 212 (50), 200 (2), 185 [$M^{\bullet+}$-$(CH_3CO_2)_2$, 93], 170 ($M^{\bullet+}$-$C_5H_9O_4$, 10), 157 (44), 144 (26), 128 (14), 119 ($M^{\bullet+}$-$C_7H_6NO_5$, 23), 103 (16), 77 (24), 59 (27).

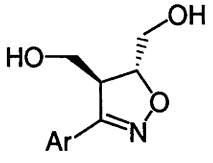
HRMS (EI) Found: $M^{\bullet+}$, 303.110694. $C_{16}H_{17}NO_5$ requires $M^{\bullet+}$, 303.11073.

The ^{1}H NMR spectral data of compound **120** are consistent with reported values.[106]

cis-4,5-Di(hydroxymethyl)-3-(2,4,6-trimethylphenyl)-Δ^2-isoxazoline 121a and _trans_-4,5-Di(hydroxymethyl)-3-(2,4,6-trimethylphenyl)-Δ^2-isoxazoline 121b



rac.
121a



rac.
121b

Ar = 2,4,6-Me_3Ph

Sodium borohydride (187 mg, 4.95 mmol) was added over 15 min to a stirred solution of 3-(2,4,6-trimethylphenyl)isoxazole-4,5-dicarboxylic acid dimethyl diester **120** (100 mg, 0.330 mmol) in dry EtOH (5 mL) at 0-5 °C (ice bath). After heating at reflux for 24 h, the reaction was quenched at 0-5 °C (ice bath) by dropwise addition of 1M HCl (to pH 2). The solvent was removed under reduced pressure and the residue was taken up in Et_2O (10 mL). The solution was washed with H_2O (7 mL), and the aqueous phase was separated and extracted with Et_2O (3 × 10 mL). The combined organic solution was washed with H_2O (2 × 7 mL) and brine (1 × 7 mL), dried (anhydrous $MgSO_4$) and evaporated *in vacuo*. Flash column chromatography of the residue, eluting with hexanes-EtOAc (7:3) afforded the *title compounds **121a*** (57 mg, 70%) as a colourless solid, mp 102-103 °C; and ***121b*** (16 mg, 20%) as a colourless solid, mp 85-86 °C.

Compound 121a

^{1}H NMR (500 MHz) δ 1.60 (br s, 2H, OH), 2.27 (s, 6H, *o,o'*-MesCH_3), 2.29 (s, 3H, *p*-MesCH_3), 3.65 (m, 1H, H4), 3.90 (m, 2H, CH_2O), 4.05 (m, 1H, CH_2O), 4.13 (m, 1H, CH_2O), 4.89 (ddd, J = 10.0, 6.0, 3.5 Hz, 1H, H5), 6.90 (s, 2H, 2 × MesH).

^{13}C NMR (75.4 MHz) δ 20.0 (2 × CH_3), 21.0 (CH_3), 55.4 (C4), 57.8 (CH_2O), 59.8 (CH_2O), 81.7 (C5), 124.8 (C), 128.2 (2 × CH), 136.8 (2 × C), 139.1 (C), 159.0 (C3).

IR (KBr, thin film) ν_{max} 3332, 2953, 2925, 1612, 1438, 1118, 1031 cm^{-1}.

LRMS (EI) *m/z* (%) 249 ($M^{\bullet+}$, 48), 229 (14), 218 ($M^{\bullet+}$-CH_2OH, 77), 188 (100), 172 ($M^{\bullet+}$-$C_2H_5O_3$, 61), 158 (52), 146 (42), 130 (38), 119 ($M^{\bullet+}$-$C_5H_8NO_3$, 53), 103 (20), 91 (58), 77 (31), 65 (13).

HRMS (EI) Found: $M^{\bullet+}$, 249.136012. $C_{14}H_{19}NO_3$ requires $M^{\bullet+}$, 249.136494.

Elemental Analysis Found: C, 67.42; H, 7.62; N, 5.60. $C_{14}H_{19}NO_3$ requires C, 67.45; H, 7.68; N, 5.62.

Compound 121b

^{1}H NMR (500 MHz) δ 1.61 (br s, 2H, OH), 2.26 (s, 6H, *o*,*o*'-$MesCH_3$), 2.28 (s, 3H, *p*-$MesCH_3$), 3.62-3.77 (m, 3H, CH_2O and H4), 3.81 (m, 1H, CH_2O), 3.97 (m, 1H, CH_2O), 4.72 (dt, J = 7.5, 3.5 Hz, 1H, H5), 6.91 (s, 2H, 2 × MesH).

^{13}C NMR (75.4 MHz) δ 20.2 (2 × CH_3), 21.2 (CH_3), 56.1 (C4), 61.4 (CH_2O), 63.5 (CH_2O), 84.4 (C5), 124.7 (C), 128.7 (2 × CH), 136.8 (2 × C), 138.9 (C), 158.4 (C3).

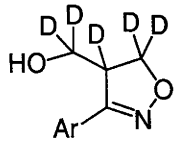
IR (KBr, thin film) ν_{max} 3369, 2921, 2874, 1611, 1453, 1081, 1042, 851 cm^{-1}.

LRMS (EI) *m/z* (%) 249 ($M^{\bullet+}$, 45), 218 ($M^{\bullet+}$-CH_2OH, 100), 205 (21), 188 (80), 172 (54), 158 (47), 145 (42), 130 (44), 119 ($M^{\bullet+}$-$C_5H_8NO_3$, 34), 103 (17), 91 (41), 77 (29), 57 (48).

HRMS (EI) Found: $M^{\bullet+}$, 249.136551. $C_{14}H_{19}NO_3$ requires $M^{\bullet+}$, 249.136494.

Elemental Analysis Found: C, 67.40; H, 7.65; N, 5.61. $C_{14}H_{19}NO_3$ requires C, 67.45; H, 7.68; N, 5.62.

4-(Hydroxy-d_2-methyl)-3-(2,4,6-trimethylphenyl)-4,5,5-d_3-Δ^2-isoxazoline 123



123

Ar = 2,4,6-Me_3Ph

Sodium borodeuteride (128 mg, 3.06 mmol) was added to a stirred solution of 3-(2,4,6-trimethylphenyl)isoxazole-4-carboxylic acid methyl ester **12f** (50.0 mg, 0.204 mmol) in dry EtOD (5 mL) at 0-5 °C (ice bath) over 15 min. After heating at reflux for 24 h, the mixture was cooled to 0-5 °C (ice bath) and quenched by dropwise addition of 1M HCl (to pH 2). The solvent was evaporated under reduced pressure and the residue was taken up in Et_2O (10 mL). The solution was washed with H_2O (1 × 7 mL), the aqueous layer was separated and extracted with Et_2O (3 × 10 mL). The combined organic solution was washed with H_2O (1 × 7 mL), aq. $NaHCO_3$ (1 × 7 mL) and brine (1 × 7 mL), dried (anhydrous $MgSO_4$) and concentrated *in vacuo*. Flash column chromatography of the residue, eluting with hexanes-EtOAc (4:1) afforded the *title compound **123*** (40 mg, 87%) as a colourless oil.

^{1}H NMR (300 MHz) δ 1.58 (br s, 1H, OH), 2.27 (s, 6H, *o,o'*-MesCH_3), 2.29 (s, 3H, *p*-MesCH_3), 6.91 (s, 2H, 2 × MesH).

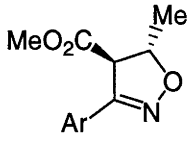
IR (KBr, thin film) ν_{max} 3402, 2922, 2203, 2093, 1612, 1454, 1378, 1312, 1203, 1173, 1151, 1038, 974, 884, 852, 733, 572.

LRMS (EI) *m/z* (%) 224 ($M^{\bullet+}$, 45), 207 ($M^{\bullet+}$-OH, 9), 191 ($M^{\bullet+}$-CD_2OH ,12), 175 ($M^{\bullet+}$-CD_2HO_2, 73), 160 (32), 147 (33), 145 (58), 130 (79), 115 (17), 103 (16), 91 (26), 77 (20), 62 (100), 57 (13).

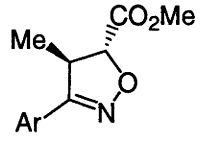
HRMS (EI) Found: $M^{\bullet+}$, 224.157224. $C_{13}H_{12}D_5NO_2$ requires $M^{\bullet+}$, 224.157313.

trans-5-Methyl-3-(2,4,6-trimethylphenyl)-Δ^2-isoxazoline-4-carboxylic Acid Methyl Ester 21c and

trans-4-Methyl-3-(2,4,6-trimethylphenyl)-Δ^2-isoxazoline-5-carboxylic Acid Methyl Ester 22c



rac.
21c



rac.
22c

Ar = 2,4,6-Me_3Ph

A mixture of *trans*-methyl crotonate **20** (124 mg, 1.24 mmol) and mesitonitrile oxide **5** (200 mg, 1.24 mmol) in THF (15 mL) was heated at reflux for 24 h. The solvent was evaporated under reduced pressure, the residue was taken up in Et_2O (10 mL) and the solution was washed with H_2O (1 × 7 mL). The aqueous phase was separated and extracted with Et_2O (3 × 10 mL). The combined organic solution was washed with brine (1 × 7 mL), dried (anhydrous $MgSO_4$) and evaporated *in vacuo*. Flash column chromatography of the residue, eluting with hexanes-Et_2O (17:3) afforded the *title compounds* ***21c***[24] (230 mg, 71%) as a pale yellow solid, mp 27-28 °C; and ***22c***[24] (84 mg, 26%) as a pale yellow solid, mp 55-56 °C.

Compound 21c

^{1}H NMR (300 MHz) δ 1.54 (d, J = 6.2 Hz, 3H, $C\underline{H}_3CH$), 2.24 (s, 6H, *o,o'*-$MesCH_3$), 2.28 (s, 3H, *p*-$MesCH_3$), 3.58 (s, 3H, CH_3O), 4.02 (d, J = 8.7 Hz, 1H, H4), 5.19 (dq, J = 8.7, 6.2 Hz, 1H, H5), 6.89 (s, 2H, 2 × MesH).

^{13}C NMR (75.4 MHz) δ 19.6 (CH_3), 19.8 (2 × CH_3), 20.9 (CH_3), 52.3 (CH_3O), 62.5 (C4), 80.4 (C5), 124.6 (C), 128.4 (2 × CH), 136.7 (2 × C), 138.7 (C), 153.8 (C3), 168.4 (C=O).

IR (KBr, thin film) ν_{max} 2954, 2925, 1742, 1612, 1436, 1378, 1309, 1279, 1249, 1203, 1177, 1027, 879, 853 cm^{-1}.

LRMS (EI) *m/z* (%) 261 ($M^{\bullet+}$, 85), 246 ($M^{\bullet+}$-CH_3, 100), 214 (27), 202 ($M^{\bullet+}$- CH_3O_2C, 15), 186 ($M^{\bullet+}$-$C_2H_3O_3$, 92), 158 (71), 144 (24), 130 (24), 115 (27), 103 (14), 91 (37), 77 (23), 69 (27).

HRMS (EI) Found: $M^{\bullet+}$, 261.136311. $C_{15}H_{19}NO_3$ requires $M^{\bullet+}$, 261.136494.

Elemental Analysis Found: C, 68.65; H, 7.27; N, 5.15. $C_{15}H_{19}NO_3$ requires C, 68.94; H, 7.33; N, 5.36.

Compound 22c

^{1}H NMR (300 MHz) δ 1.25 (d, J = 7.4 Hz, 3H, C$\underline{H}_3$CH), 2.23 (s, 6H, *o*,*o*'-MesCH_3), 2.29 (s, 3H, *p*-MesCH_3), 3.80 (m, 1H, H4), 3.84 (s, 3H, CH_3O), 4.76 (d, J = 6.1 Hz, 1H, H5), 6.89 (s, 2H, 2 × MesH).

^{13}C NMR (75.4 MHz) δ 16.0 (CH_3), 19.6 (2 × CH_3), 20.7 (CH_3), 50.8 (C4), 52.3 (C5), 83.7 (CH_3O), 123.8 (C), 128.4 (2 × CH), 136.7 (2 × C), 138.6 (C), 160.5 (C3), 170.6 (C=O).

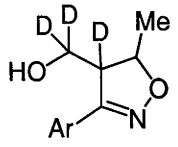
IR (KBr, thin film) ν_{max} 3319, 2934, 2923, 1741, 1612, 1456, 1437, 1382, 1292, 1274, 1204, 1181, 1018 cm^{-1}.

LRMS (EI) *m/z* (%) 261 ($M^{\bullet+}$, 47), 236 (5), 202 ($M^{\bullet+}$-CH_3O_2C, 100), 187 ($M^{\bullet+}$-$C_3H_6O_2$, 7), 172 ($M^{\bullet+}$-$C_2H_3NO_3$, 43), 158 (41), 145 (34), 130 (25), 119 ($M^{\bullet+}$-$C_6H_8NO_3$, 34), 103 (13), 91 (33), 77 (19), 65 (8).

HRMS (EI) Found: $M^{\bullet+}$, 261.136583. $C_{15}H_{19}NO_3$ requires $M^{\bullet+}$, 261.136494.

Elemental Analysis Found: C, 69.12; H, 7.26; N, 5.44. $C_{15}H_{19}NO_3$ requires C, 68.94; H, 7.33; N, 5.36.

4-(Hydroxy-d_2-methyl)-5-methyl-3-(2,4,6-trimethylphenyl)-4-d_1-Δ^2-isoxazoline 126



126

Ar = 2,4,6-Me_3Ph

Sodium borodeuteride (121 mg, 2.88 mmol) was added to a solution of *trans*-5-methyl-3-(2,4,6-trimethylphenyl)-Δ^2-isoxazoline-4-carboxylic acid methyl ester **21c** (50.0 mg, 0.192 mmol) at 0-5 °C (ice bath) over 15 min. After heating at reflux for 24 h, the reaction was quenched by dropwise addition of 1M HCl (to pH 2) to the mixture at 0-5 °C (ice bath). The solvent was evaporated under reduced pressure, the residue was taken up in Et_2O (10 mL) and the solution was washed with H_2O (7 mL). The aqueous phase was separated and extracted with Et_2O (2 × 10 mL). The combined organic solution was washed with aq. $NaHCO_3$ (7 mL), H_2O (7 mL) and brine (7 mL), dried (anhydrous $MgSO_4$) and concentrated *in vacuo*. Flash column chromatography of the residue, eluting with hexanes-EtOAc (5:1) afforded the *title compound* ***126*** as a colourless oil (40 mg, 87%).

^{1}H NMR (300 MHz) δ 1.50 (d, J = 6.3 Hz, 3H, $C\underline{H}_3CH$), 1.62 (br s, 1H, OH), 2.26 (s, 6H, *o,o'*-$MesCH_3$), 2.29 (s, 3H, *p*-$MesCH_3$), 4.72 (q, J = 6.3 Hz, 1H, H5), 6.88 (s, 2H, 2 × MesH).

IR (KBr, thin film) ν_{max} 3400, 2972, 2923, 2739, 2201, 2083, 1612, 1453, 1377, 1324, 1175, 1134, 1108, 1048, 977, 851, 735 cm^{-1}.

LRMS (EI) *m/z* (%) 236 ($M^{\bullet+}$, 50), 221 (64), 203 (5), 189 ($M^{\bullet+}$-NO_2H, 12), 175 (52), 163 (64), 146 (75), 131 (100), 115 (23), 103 (19), 91 (36), 77 (26), 65 (13).

HRMS (EI) Found: $M^{\bullet+}$, 236.160246. $C_{14}H_{16}D_3NO_2$ requires $M^{\bullet+}$, 236.160409.

The relative configuration of 2-isoxazoline **126** could not be assigned since the proton at C5 is not coupled to the deuterium at C4.

Reaction of 3-(2,4,6-Trimethylphenyl)isoxazole-4-carboxylic Acid Methyl Ester 12f with d_3-Sodium Methoxide -
2,4,6-Trimethylbenzonitrile 128
and 3-Amino-2-d_3-methoxycarbonyl-3-(2,4,6-trimethylphenyl)acrylic Acid d_3-Methyl Ester 129

Ar = 2,4,6-Me_3Ph

Sodium (24.0 mg, 1.02 mmol) was added to dry d_4-methanol (5 mL) at 18 °C. To the mixture was added a solution of 3-(2,4,6-trimethylphenyl)isoxazole-4-carboxylic acid methyl ester **12f** (167 mg, 0.68 mmol) in dry d_4-methanol (0.5 mL) and stirring was continued at 18 °C for 16 h. The mixture was quenched with aq. NH_4Cl (5 mL) and the solvent was evaporated under reduced pressure. The residue was taken up in EtOAc (10 mL), and the solution was washed with H_2O (7 mL). The aqueous layer was separated and extracted with EtOAc (3 × 10 mL). The combined organic solution was washed with brine (7 mL), dried (anhydrous $MgSO_4$) and evaporated *in vacuo*. Flash column chromatography of the residue, eluting with hexanes-EtOAc (4:1) afforded the *title compounds **128*** as a colourless solid (62 mg, 63%), mp 50-51 °C [lit.[107] mp 50-52 °C]; and ***129*** as colourless blocks (60 mg, 31%), after recrystallization from hexanes and Et_2O, mp 187-188 °C.

Compound 128

^{1}H NMR (300 MHz) δ 2.24 (s, 3H, *p*-MesCH$_3$), 2.50 (s, 6H, *o*,*o*'-MesCH$_3$), 6.95 (s, 2H, 2 × MesH).

IR (KBr, thin film) ν_{max} 2925, 2856, 1723, 1612, 1283, 1086 cm^{-1}.

LRMS (EI) *m/z* (%) 145 ($M^{\bullet+}$, 77), 137 (5), 130 (100), 119 ($M^{\bullet+}$-CN, 5), 115 (9), 111 (18), 104 (10), 97 (30), 91 (14), 83 (36), 77 (19), 69 (48), 60 (8), 55 (83).

HRMS (EI) Found: $M^{\bullet+}$, 145.088795. $C_{10}H_{11}N$ requires $M^{\bullet+}$, 145.089149.

The ^{1}H NMR data of compound **128** are in full agreement to literature values.[107]

Compound 129

^{1}H NMR (300 MHz) δ 2.25 (s, 6H, *o*,*o*'-MesCH$_3$), 2.26 (s, 3H, *p*-MesCH$_3$), 4.95 (br s, 1H, NH), 6.84 (s, 2H, 2 × MesH), 8.98 (br s, 1H, NH).

IR (KBr, thin film) ν_{max} 3392, 3287, 1694, 1661, 1602, 1525, 1314, 1279, 1183, 1147, 1124, 1086, 973, 854, 803, 748, 600.

LRMS (EI) *m/z* (%) 283 ($M^{\bullet+}$, 64), 268 (78), 231 (5), 221 ($M^{\bullet+}$ - CD_3CO_2, 7), 213 (82), 186 (100), 158 [$M^{\bullet+}$ -(2 × CD_3CO_2), 91], 146 (63), 130 (30), 115 (22), 103 (12), 91 (18), 78 (6), 62 (12).

HRMS (EI) Found: $M^{\bullet+}$, 283.168802. $C_{15}H_{13}D_6NO_4$ requires $M^{\bullet+}$, 283.169069.

X-Ray Crystallographic Analysis Appendix 1.8.

Reaction of 3-(2,4,6-Trimethylphenyl)isoxazole-4-carboxylic Acid Methyl Ester 12f with Sodium Methoxide -
2,4,6-Trimethylbenzonitrile 128
and 3-Amino-2-methoxycarbonyl-3-(2,4,6-trimethylphenyl)acrylic Acid Methyl Ester 133

Ar = 2,4,6-Me_3Ph

Using the procedure described for the reaction of 3-(2,4,6-trimethylphenyl)isoxazole-4-carboxylic acid methyl ester **12f** with d_3-sodium methoxide, reaction of **12f** (167 mg, 0.68 mmol) with sodium methoxide, formed from reaction of sodium (24.0 mg, 1.02 mmol) with dry methanol (5 mL), afforded *title compounds **128*** (62 mg, 63%) (described above) as a colourless solid; and ***133*** (58 mg, 31%) as a colourless solid, mp 187-188 °C, after flash column chromatography, eluting with hexanes-EtOAc (4:1).

Compound 133

^{1}H NMR (300 MHz) δ 2.26 (s, 6H, *o,o'*-MesCH_3), 2.27 (s, 3H, *p*-MesCH_3), 3.33 (s, 3H, CH_3O), 3.78 (s, 3H, CH_3O), 4.95 (br s, 1H, NH), 6.84 (s, 2H, 2 × MesH), 8.98 (br s, 1H, NH).

^{13}C NMR (75.4 MHz) δ 19.0 (2 × CH_3), 21.1 (CH_3), 51.2 (CH_3O), 51.4 (CH_3O), 94.6 [$\underline{C}(CO_2CH_3)_2$], 128.0 (2 × CH), 133.4 (C), 134.9 (2 × C), 138.4 (C), 163.9 (CNH_2), 167.3 (C=O), 168.7 (C=O).

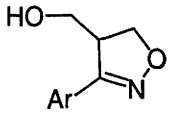
IR (KBr, thin film) ν_{max} 3392, 3286, 1696, 1661, 1602, 1526, 1314, 1280, 1148, 1088, 855 cm^{-1}.

LRMS (EI) *m/z* (%) 277 ($M^{\bullet+}$, 69), 262 (3), 246 (90), 230 (6), 213 (67), 186 (100), 158 (80), 146 (56), 131 (19), 115 (20), 103 (7), 91 (17), 77 (11), 59 (8).

HRMS (EI) Found: $M^{\bullet+}$, 277.131222. $C_{15}H_{19}NO_4$ requires $M^{\bullet+}$, 277.131408.

Elemental Analysis Found: C, 64.91; H, 6.90; N, 5.06. $C_{15}H_{19}NO_4$ requires C, 64.97; H, 6.91; N, 5.05.

Reaction of 3-(2,4,6-Trimethyphenyl)isoxazole-4-carboxylic Acid Methyl Ester 12f with Lithium Borohydride

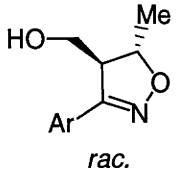


101

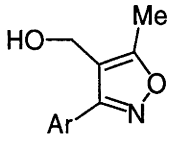
Ar = 2,4,6-Me_3Ph

Lithium borohydride (3.1 mL of a 2M solution in THF, 6.2 mmol) was added to a solution of 3-(2,4,6-trimethyphenyl)isoxazole-4-carboxylic acid methyl ester **12f** (100 mg, 0.407 mmol) in THF (5 mL) at 0-5 °C (ice bath). After heating at reflux for 24 h, the reaction was quenched by dropwise addition of 1M HCl (to pH 2) to the mixture at 0-5 °C (ice bath). The solvent was evaporated under reduced pressure, the residue was taken up in Et_2O (10 mL) and the solution was washed with H_2O (7 mL). The aqueous phase was separated and extracted with Et_2O (2 × 10 mL). The combined organic solution was washed with aq. $NaHCO_3$ (7 mL), H_2O (7 mL) and brine (7 mL), dried (anhydrous $MgSO_4$) and concentrated *in vacuo*. Flash column chromatography of the residue, eluting with hexanes-EtOAc (5:1) afforded 4-hydroxymethyl-3-(2,4,6-trimethylphenyl)-Δ^2-isoxazoline ***101*** (described above) as a colourless oil (80 mg, 90%).

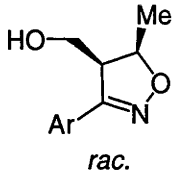
Reaction of 5-Methyl-3-(2,4,6-trimethylphenyl)isoxazole-4-carboxylic Acid Methyl Ester 117 with Lithium Borohydride



rac.
118



119



rac.
137

Ar = 2,4,6-Me_3Ph

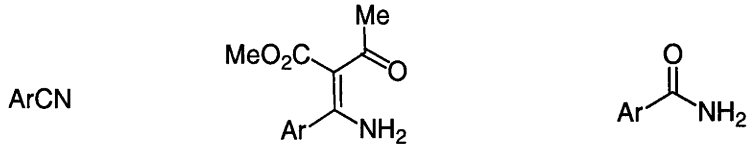
Lithium borohydride (3.1 mL of a 2M solution in THF, 6.2 mmol) was added to a solution of 5-methyl-3-(2,4,6-trimethylphenyl)isoxazole-4-carboxylic acid methyl ester **117** (105 mg, 0.407 mmol) in THF (5 mL) at 0-5 °C (ice bath). After heating at reflux for 24 h, the reaction was quenched by dropwise addition of 1M HCl (to pH 2) at 0-5 °C (ice bath). The solvent was evaporated under reduced pressure, the residue taken up in Et_2O (10 mL) and the solution was washed with H_2O (7 mL). The aqueous phase was separated and extracted with Et_2O (2 × 10 mL). The combined organic solution was washed with aq. $NaHCO_3$ (7 mL), H_2O (7 mL) and brine (7 mL), dried (anhydrous $MgSO_4$) and concentrated *in vacuo*. ^1H NMR analysis of the product mixture indicated *trans*-4-hydroxymethyl-5-methyl-3-(2,4,6-trimethylphenyl)-Δ^2-isoxazoline **118** (described above) and *cis*-4-hydroxymethyl-5-methyl-3-(2,4,6-trimethylphenyl)-Δ^2-isoxazoline **137**, and 4-hydroxymethyl-5-methyl-3-(2,4,6-trimethylphenyl)isoxazole **119** (described above) were formed in a ratio of 4:2:1.

Compound 137

^1H NMR (300 MHz) δ 1.50 (d, J = 6.3 Hz, 3H, $C\underline{H}_3CH$), 1.80 (br s, 1H, OH), 2.28 (s, 6H, *o,o'*-$MesCH_3$), 2.30 (s, 3H, *p*-$MesCH_3$), 3.33 (m, 1H, H4), 3.70 (m, 2H, CH_2O), 4.90 (dq, J = 8.6, 6.2 Hz, 1H, H5), 6.89 (s, 2H, 2 × MesH).

Reaction of 5-Methyl-3-(2,4,6-trimethylphenyl)isoxazole-4-carboxylic Acid Methyl Ester 117 with Catecholborane-

(*E*)-2-Acetyl-3-amino-3-(2,4,6-trimethylphenyl)acrylic Acid Methyl Ester 138, 2,4,6-Trimethylbenzamide 139 and 2,4,6-Trimethylbenzonitrile 128



128 **138** **139**

Ar = 2,4,6-Me_3Ph

Catecholborane (53 μL, 0.50 mmol) and Wilkinson's catalyst (4.2 mg, 5 μmol) were added to a solution of 5-methyl-3-(2,4,6-trimethylphenyl)isoxazole-4-carboxylic acid methyl ester **117** (65 mg, 0.25 mmol) in dry THF (3 mL) at –20 °C (dry ice-acetone bath). After stirring at –20 °C for 24 h, the mixture was evaporated under reduced pressure and the residue was dissolved in 95% aq. EtOH (3 mL). The solution was cooled to 0 °C (ice bath), 1M NaOH (3 mL) and 30% hydrogen peroxide (1 mL) were added, and stirring was continued at 18 °C for 20 h. The solvent was removed under reduced pressure, the residue was diluted with 1M NaOH (15 mL) and the solution was extracted with Et_2O (3 × 10 mL). The layers were separated and the combined organic solution was washed with H_2O (2 × 7 mL) and brine (1 × 7 mL), dried (anhydrous $MgSO_4$) and concentrated *in vacuo*. Flash column chromatography of the residue, eluting with CH_2Cl_2-Et_2O (9:1) afforded the *title compounds* ***128***[107] (described above) (5 mg, 13%) as a colourless solid; ***138*** (30 mg, 46%) as a colourless oil and ***139*** (9 mg, 23%) as a colourless solid, mp 187-188 °C [lit.[112] mp 187-188 °C].

Compound 138

^{1}H NMR (300 MHz) δ 2.22 (s, 6H, *o,o'*-MesCH_3), 2.35 (s, 3H, CH_3), 2.76 (s, 3H, *p*-MesCH_3), 3.31 (s, 3H, CH_3O), 5.40 (br s, 1H, NH), 6.82 (s, 2H, 2 × MesH), 11.1 (br s, 1H, NH).

^{13}C NMR (75.4 MHz) δ 18.9 (CH_3), 21.0 (2 × CH_3), 29.7 (CH_3), 50.8 (CH_3O), 104.6 ($\underline{C}CO_2CH_3$), 127.8 (2 × CH), 128.0 (2 × C), 134.1 (C), 138.0 (C), 166.6 (CNH_2), 169.3 (C=O), 197.3 (C=O).

IR (KBr, thin film) ν_{max} 3334, 2923, 1704, 1594, 1462, 1433, 1291, 1128, 1053, 977, 851, 800, 706, 624, 532 cm^{-1}.

LRMS (EI) *m/z* (%) 261 ($M^{\bullet+}$, 6), 246 ($M^{\bullet+}$ -CH_3, 31), 230 ($M^{\bullet+}$ -CH_3O, 5), 214 (11), 202 ($M^{\bullet+}$ -CH_3O_2C, 17), 184 (36), 170 (7), 158 ($M^{\bullet+}$ -$C_3H_5NO_3$, 42), 145 (58), 130 (100), 115 (47), 103 (25), 91 (50), 77 (42), 65 (21).

HRMS (EI) Found: $M^{\bullet+}$, 261.136269. $C_{15}H_{19}NO_3$ requires $M^{\bullet+}$, 261.136494.

Elemental Analysis Found: C, 68.84; H, 7.29; N, 5.38. $C_{15}H_{19}NO_3$ requires C, 68.94; H, 7.33; N, 5.36.

The relative configuration of compound **138** is assumed to be *E* based on the structure of the precursor isoxazole **117**.

Compound 139

^{1}H NMR (300 MHz) δ 2.28 (s, 3H, *p*-$MesCH_3$), 2.34 (s, 6H, *o,o'*-$MesCH_3$), 5.63 (br s, 1H, NH), 5.87 (br s, 1H, NH), 6.87 (s, 2H, 2 × MesH).

IR (KBr, thin film) ν_{max} 3398, 3209, 2921, 1637, 1611, 1386, 1116, 849, 648 cm^{-1}.

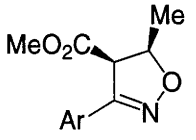
LRMS (EI) *m/z* (%) 163 ($M^{\bullet+}$, 65), 147 ($M^{\bullet+}$-NH_2, 83), 130 (25), 119 ($M^{\bullet+}$-$CONH_2$, 96), 103 (45), 91 (100), 77 (75), 65 (37).

HRMS (EI) Found: $M^{\bullet+}$, 163.099716. $C_{10}H_{13}NO$ requires $M^{\bullet+}$, 163.099714.

The ^{1}H NMR data of amide **139** are in full accord to those reported.[112]

The melting point, ^{1}H NMR spectroscopic and EI mass spectrometric data of nitrile **128** are described above.

Reaction of 5-Methyl-3-(2,4,6-trimethylphenyl)isoxazole-4-carboxylic Acid Methyl Ester 117 with L-Selectride®



rac.
140

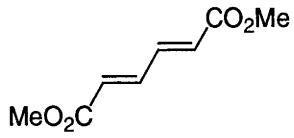
L-Selectride® (1M solution in THF) was added to 5-methyl-3-(2,4,6-trimethylphenyl)isoxazole-4-carboxylic acid methyl ester **117** (50.0 mg, 0.193 mmol) in THF (3 mL) and the reactions were carried out according to the conditions specified in Table 25 (Chapter 3, Section 3.5.2). The mixtures were then cooled to 0 °C (ice bath), quenched by dropwise addition of 1M HCl (to pH 2) and stirred for a further 15 min. The solvent was removed under reduced pressure, the residue was taken up in Et_2O (10 mL) and washed with aq. NH_4Cl (3 × 5 mL). The aqueous layer was separated and extracted with Et_2O (3 × 10 mL). The combined organic solution was washed with brine (10 mL), dried (anhydrous $MgSO_4$) and evaporated *in vacuo*. The reaction mixture was analyzed by ^1H NMR spectroscopy and the results are shown in Table 25.

The ^1H NMR data of the *trans*-2-isoxazoline **21c** (described above) are identical to those seen for the sample obtained from the reaction of *trans*-methyl crotonate **20** with mesitonitrile oxide **5**.

Compound 140

^1H NMR (300 MHz) δ 1.46 (d, J = 6.4 Hz, 3H, $C\underline{H}_3CH$), 2.28 (s, 6H, *o,o'*-$MesCH_3$), 2.33 (s, 3H, *p*-$MesCH_3$), 3.63 (s, 3H, CH_3O), 4.41 (d, J = 10.4 Hz, 1H, H4), 5.05 (dq, J = 10.4, 6.4 Hz, 1H, H5), 6.88 (s, 2H, 2 × MesH).

***trans,trans*-Hexa-2,4-dienedioic Acid Dimethyl Diester 146**



146

To a solution of *trans,trans*-muconic acid **145** (500 mg, 3.52 mmol) in dry MeOH (35 mL) was dropwise added conc. H_2SO_4 (0.5 mL). After heating at reflux for 24 h, the solvent was evaporated under reduced pressure. The residue was taken up in EtOAc (60 mL) and the solution was washed with H_2O (1 × 40 mL). The aqueous layer was separated and extracted with EtOAc (3 × 60 mL). The combined organic solution was washed with aq. $NaHCO_3$ (2 × 40 mL) and brine (1 × 40 mL), dried (anhydrous $MgSO_4$) and concentrated *in vacuo*. Flash column chromatography of the residue, using hexanes-Et_2O (3:7) as eluent afforded the *title compound* ***146*** (449 mg, 75%) as a colourless solid, mp 155-157 °C [lit.[116] mp 155-156 °C].

^{1}H NMR (300 MHz) δ 3.79 (s, 6H, 2 × CH_3O), 6.20 (d, J = 11.6 Hz, 2H, C3 and C4), 7.32 (d, J = 11.6 Hz, 2H, C2 and C5).

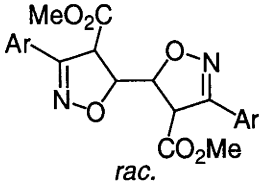
^{13}C NMR (75.4 MHz) δ 51.9 (2 × CH_3O), 128.0 (C3 and C4), 140.9 (C2 and C5), 166.2 (2 × C=O).

IR (KBr, thin film) ν_{max} 3327, 2955, 1701, 1615, 1437, 1315, 1262, 1167, 1032, 411, 406 cm^{-1}.

LRMS (EI) *m/z* (%) 170 ($M^{\bullet+}$, 39), 155 ($M^{\bullet+}$-CH_3, 11), 139 ($M^{\bullet+}$-CH_3O, 51), 123 (24), 111 ($M^{\bullet+}$-CH_3O_2C, 100), 95 (6), 79 (32), 68 (13), 59 (26).

The ^{1}H NMR data of compound **146** are fully consistent with literature values.[116]

***trans,trans*-3,3'-Di(2,4,6-trimethylphenyl)-[5,5']-di-Δ^2-isoxazoline-4,4'-dicarboxylic Acid Dimethyl Diester 147**



rac.

147

Ar = 2,4,6-Me_3Ph

A mixture of mesitonitrile oxide **5** (853 mg, 5.30 mmol) and *trans,trans*-hexa-2,4-dienedioic acid dimethyl diester **146** (451 mg, 2.65 mmol) in THF (100 mL) was heated at reflux for 4 days. The solvent was removed under reduced pressure, the residue was taken up in EtOAc (100 mL) and the solution was washed with H_2O (1 × 75 mL). The aqueous layer was separated and extracted with EtOAc (3 × 100 mL). The combined organic solution was washed with brine (75 mL), dried (anhydrous $MgSO_4$) and concentrated *in vacuo*. Flash column chromatography of the residue, eluting with hexanes-Et_2O (22:3) afforded the *title compound **147*** (1.10 g, 84%) as a colourless solid, mp 170-172 °C.

^{1}H NMR (300 MHz) δ 2.24 (s, 12H, 2 × *o,o'*-MesCH_3), 2.30 (s, 6H, 2 × *p*-MesCH_3), 3.61 (s, 6H, 2 × CH_3O), 4.45 (d, J = 4.7 Hz, 2H, 2 × H4), 5.27 (d, J = 4.7 Hz, 2H, 2 × H5), 6.90 (s, 4H, 4 × MesH).

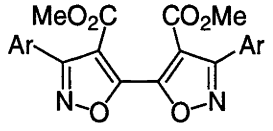
^{13}C NMR (75.4 MHz) δ 19.8 (4 × CH_3), 21.1 (2 × CH_3), 53.0 (2 × CH_3O), 59.2 (2 × C4), 83.0 (2 × C5), 123.7 (4 × C), 128.7 (4 × CH), 137.0 (2 × C), 139.0 (2 × C), 154.1 (2 × C3), 167.9 (2 × C=O).

IR (KBr, thin film) ν_{max} 3855, 3564, 2955, 1743, 1613, 1436, 1265, 1199, 1031, 853, 646 cm^{-1}.

LRMS (EI) *m/z* (%) 492 ($M^{\bullet+}$, 35), 433 ($M^{\bullet+}$-CH_3O_2C, 4), 347 (4), 331 (9), 296 (6), 281 (11), 246 (100), 232 (9), 218 (91), 186 (81), 158 (95), 130 (93), 91 (4), 77 (19).

HRMS (EI) Found: $M^{\bullet+}$, 492.226466. $C_{28}H_{32}N_2O_6$ requires $M^{\bullet+}$, 492.226037.
Elemental Analysis Found: C, 68.07; H, 6.54; N, 5.62. $C_{28}H_{32}N_2O_6$ requires C, 68.28; H, 6.55; N, 5.69.

3,3'-Di(2,4,6-trimethylphenyl)-[5,5']-diisoxazole-4,4'-dicarboxylic Acid Dimethyl diester 148



148

Ar = 2,4,6-Me_3Ph

A solution of *trans,trans*-3,3'-di(2,4,6-trimethylphenyl)-[5,5']-di-Δ^2-isoxazoline-4,4'-dicarboxylic acid dimethyl diester **147** (194 mg, 0.395 mmol) was added to a suspension of γ-activated manganese dioxide (1.72 g, 1.98 mmol) in dry toluene (30 mL). After heating at reflux for 36 h, the suspension was filtered through a pad of Celite®. The filter cake was washed with EtOAc (4 × 100 mL) and the filtrate was concentrated under reduced pressure. Flash column chromatography of the residue, eluting with hexanes-EtOAc (22:3) afforded the *title compound **148*** (160 mg, 83%) as colourless blocks, mp 185-187 °C, after recrystallization from hexanes and Et_2O at 18 °C.

^{1}H NMR (300 MHz) δ 2.14 (s, 12H, 2 × *o,o'*-MesCH_3), 2.35 (s, 6H, 2 × *p*-MesCH_3), 3.61 (s, 6H, 2 × CH_3O), 6.98 (s, 4H, 4 × MesH).
^{13}C NMR (75.4 MHz) δ 20.0 (4 × CH_3), 21.3 (2 × CH_3), 52.2 (2 × CH_3O), 114.6 (2 × C4), 123.3 (2 × C), 128.3 (4 × CH), 137.0 (4 × C), 139.5 (2 × C), 159.2 (2 × C3), 160.0 (2 × C5), 162.4 (2 × C=O).

IR (KBr, thin film) ν_{max} 2980, 2951, 2923, 1736, 1723, 1647, 1578, 1444, 1404, 1375, 1241, 1191, 1130, 1087, 920, 863, 794, 740 cm^{-1}.

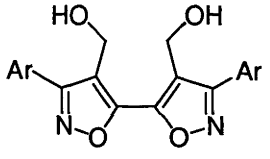
LRMS (EI) *m/z* (%) 488 ($M^{\bullet+}$, 54), 429 ($M^{\bullet+}$-CH_3O_2C, 8), 396 (10), 369 (8), 244 ($M^{\bullet+}$-$C_{14}H_{14}NO_3$, 100), 212 (16), 184 (64), 172 (10), 156 (20), 144 (10), 128 (12), 119 ($M^{\bullet+}$-$C_{19}H_{17}N_2O_6$, 14), 91 (18), 77 (8), 59 (12).

HRMS (EI) Found: $M^{\bullet+}$, 488.193504. $C_{28}H_{28}N_2O_6$ requires $M^{\bullet+}$, 488.194737.

Elemental Analysis Found: C, 68.65; H, 5.76; N, 5.72. $C_{28}H_{28}N_2O_6$ requires C, 68.84; H, 5.78; N, 5.73.

X-Ray Crystallographic Analysis Appendix 1.9.

4,4'-Di(hydroxymethyl)-3,3'-di-(2,4,6-trimethylphenyl)-[5,5']diisoxazole 152



152

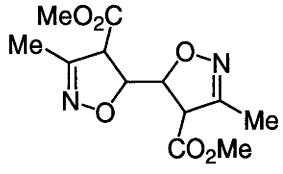
Ar = 2,4,6-Me_3Ph

Sodium borohydride (234 mg, 6.18 mmol) was added over 15 min to a stirred solution of 3,3'-di(2,4,6-trimethylphenyl)-[5,5']-diisoxazole-4,4'-dicarboxylic acid dimethyl diester **148** (101 mg, 0.206 mmol) in dry EtOH (12 mL) at 0-5 °C (ice bath). After heating at reflux for 24 h, the mixture was cooled to 0-5 °C (ice bath) and quenched by dropwise addition of 1M HCl (to pH 2). The solvent was removed under reduced pressure, the residue was taken up in EtOAc (50 mL) and washed with H_2O (35 mL). The aqueous phase was separated and extracted with EtOAc (3 × 50 mL). The combined organic solution was washed with aq. $NaHCO_3$ (2 × 35 mL) and brine (1 × 35 mL), dried (anhydrous $MgSO_4$) and evaporated *in vacuo*. Flash column chromatography

of the residue, eluting with hexanes-EtOAc (3:2) afforded the *title compound* ***152*** (80 mg, 90%) as a colourless solid, mp 222-225 °C.

^{1}H NMR (300 MHz) δ 1.59 (br s, 2H, 2 × OH), 2.15 (s, 12H, 2 × *o,o'*-MesCH$_3$), 2.36 (s, 6H, 2 × *p*-MesCH$_3$), 4.65 (s, 4H, 2 × CH$_2$O), 7.00 (s, 4H, 4 × MesH).
^{13}C NMR (75.4 MHz) δ 20.1 (4 × CH$_3$), 21.2 (2 × CH$_3$), 53.3 (2 × CH$_2$O), 119.3 (2 × C4), 123.3 (2 × C), 128.5 (4 × CH), 137.5 (4 × C), 139.7 (2 × C), 156.1 (2 × C3), 162.9 (2 × C5).
IR (KBr, thin film) ν_{max} 3400, 2923, 1612, 1457, 1431, 1378, 1281, 1030, 909, 851, 735 cm^{-1}.
LRMS (EI) *m/z* (%) 432 (M$^{\bullet+}$, 54), 420 (8), 414 (26), 396 (100), 385 (26), 371 (42), 357 (14), 341 (14), 325 (8), 270 (12), 241 (11), 224 (11), 216 (M$^{\bullet+}$-C$_{13}$H$_{14}$NO$_2$, 66), 198 (30), 186 (46), 172 (30), 158 (40), 145 (18).
HRMS (EI) Found: M$^{\bullet+}$, 432.204638. C$_{26}$H$_{28}$N$_2$O$_4$ requires M$^{\bullet+}$, 432.204908.
Elemental Analysis Found: C, 72.43; H, 6.57; N, 6.41. C$_{26}$H$_{28}$N$_2$O$_4$ requires C, 72.20; H, 6.53; N, 6.48.

trans,trans-3,3'-Dimethyl-[5,5']-di-Δ^2-isoxazoline-4,4'-dicarboxylic Acid Dimethyl Ester 153



rac.
153

Triethylamine (0.90 mL, 5.9 mmol) was added over 24 h to a stirred solution of acetohydroximinoyl chloride **2c** (500 mg, 5.36 mmol) and *trans,trans*-hexa-2,4-

dienedoic acid dimethyl diester **146** (9.11 g, 53.6 mmol) in dry THF (100 mL) at 18 °C. After stirring for a further 24 h at 18 °C, the solvent was removed under reduced pressure. The residue was taken up in EtOAc (50 mL) and the solution was washed with H_2O (1 × 35 mL). The aqueous layer was separated and extracted with EtOAc (3 × 50 mL). The combined organic solution was washed with brine (1 × 35 mL), dried (anhydrous $MgSO_4$) and concentrated *in vacuo*. Flash column chromatography of the residue, eluting with hexanes-EtOAc (9:1) afforded the *title compound* ***153*** (1.10 g, 72%) as a colourless solid, mp 158-159 °C.

^{1}H NMR (300 MHz) δ 2.12 (s, 6H, 2 × CH_3), 3.83 (s, 6H, 2 × CH_3O), 3.98 (d, J = 4.0 Hz, 2H, 2 × H4), 4.86 (d, J = 4.0 Hz, 2H, 2 × H5).

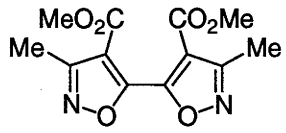
^{13}C NMR (75.4 MHz) δ 12.4 (2 × CH_3), 53.0 (2 × C4), 58.7 (2 × CH_3O), 82.1 (2 × C5), 167.9 (2 × C=O and 2 × C3).

IR (KBr, thin film) ν_{max} 2946, 1726, 1434, 1386, 1340, 1300, 1242, 971, 917, 851 cm^{-1}.

LRMS (EI) *m/z* (%) 253 ($M^{\bullet+}$-CH_3O, 6), 221 [$M^{\bullet+}$-$(CH_3O)_2$, 3], 167 (4), 142 ($M^{\bullet+}$-$C_6H_8NO_3$, 100), 110 (14), 98 (29), 82 (76), 72 (10), 56 (74).

HRMS (EI) Found: $M^{\bullet+}$-CH_3O, 253.082152. $C_{11}H_{13}N_2O_5$ requires $M^{\bullet+}$-CH_3O, 253.082447.

3,3'-Dimethyl-[5,5']-diisoxazole-4,4'-dicarboxylic Acid Dimethyl Diester 154



154

A solution of *trans,trans*-3,3'-dimethyl-[5,5']-di-Δ^2-isoxazoline-4,4'-dicarboxylic acid dimethyl ester **153** (100 mg, 0.352 mmol) and γ-activated manganese

dioxide (153 mg, 1.76 mmol) in dry toluene (15 mL) was heated at reflux for 48 h. After the suspension was filtered through a pad of Celite®, the filter cake was washed with EtOAc (100 mL) and the filtrate was concentrated under reduced pressure. Flash column chromatography of the residue, eluting with hexanes-EtOAc (7:3) afforded the *title compound **154*** (82 mg, 83%) as colourless blocks, after recrystallization from a mixture of hot hexanes and Et_2O, mp 87-89 °C.

^{1}H NMR (300 MHz) δ 2.57 (s, 6H, 2 × CH_3), 3.78 (s, 6H, 2 × CH_3O).

^{13}C NMR (75.4 MHz) δ 11.4 (2 × CH_3), 52.2 (2 × CH_3O), 113.9 (2 × C4), 159.3 (2 × C3), 160.2 (2 × C=O), 160.8 (2 × C5).

IR (KBr, thin film) ν_{max} 3446, 2954, 1736, 1565, 1484, 1456, 1402, 1316, 1290, 1189, 1110, 939, 810, 783 cm^{-1}.

LRMS (EI) *m/z* (%) 280 ($M^{\bullet+}$, 13), 250 (8), 239 (100), 181 (67), 168 (11), 153 (8), 140 ($M^{\bullet+}$-$C_6H_6NO_3$, 44), 96 (7).

HRMS (EI) Found: $M^{\bullet+}$, 280.070129. $C_{12}H_{12}N_2O_6$ requires $M^{\bullet+}$, 280.069536.

Elemental Analysis Found: C, 51.29; H, 4.36; N, 9.97. $C_{12}H_{12}N_2O_6$ requires C, 51.43; H, 4.32; N, 10.00.

X-Ray Crystallographic Analysis Appendix 1.10.

4,4'-Di(hydroxymethyl)-3,3'-dimethyl-[5,5']diisoxazole 156

156

Sodium borohydride (405 mg, 10.7 mmol) was added to a stirred solution of 3,3'-dimethyl-[5,5']diisoxazole-4,4'-dicarboxylic acid dimethyl diester **154** (100 mg, 0.357 mmol) in dry EtOH (30 mL) at 0-5 °C (ice bath) over 15 min. After heating at reflux for 1 day, the mixture was cooled to 0-5 °C (ice bath) and quenched by dropwise addition of 1M HCl (to pH 2). The solvent was removed under reduced pressure, the residue was taken up in EtOAc (10 mL) and the solution was washed with H_2O (10 mL). The aqueous phase was separated and extracted with EtOAc (3 × 10 mL). The combined organic solution was washed with aq. $NaHCO_3$ (2 × 10 mL) and brine (1 × 10 mL), dried (anhydrous $MgSO_4$) and evaporated *in vacuo*. Flash column chromatography of the residue, eluting with hexanes-EtOAc (1:4) afforded the *title compound* ***156*** (70 mg, 88%) as a colourless solid, mp 182-183 °C.

^{1}H NMR (300 MHz) δ 2.05 (br s, 2H, 2 × OH), 2.43 (s, 6H, 2 × CH_3), 4.81 (s, 4H, 2 × CH_2O).

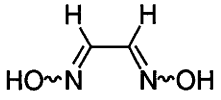
^{13}C NMR (75.4 MHz) δ 9.37 (2 × CH_3), 53.1 (2 × CH_2O), 120.0 (2 × C4), 156.3 (2 × C3), 162.4 (2 × C5).

IR (KBr, thin film) ν_{max} 3406, 2923, 2524, 1581, 1480, 1433, 1406, 1303, 1249, 1159, 1045, 1026, 1015, 917, 736 cm^{-1}.

LRMS (EI) *m/z* (%) 224 ($M^{\bullet+}$, 29), 207 ($M^{\bullet+}$-OH, 3), 190 ($M^{\bullet+}$-2 × OH, 2), 177 (5), 163 (8), 149 (17), 136 (7), 124 (32), 109 (32), 96 (35), 81 (100), 68 (39).

HRMS (EI) Found: $M^{\bullet+}$, 224.079653. $C_{10}H_{12}N_2O_4$ requires $M^{\bullet+}$, 224.079707.

Glyoxime 158



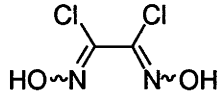
158

Glyoxal **157** (4.35 g of a 40% wt aqueous solution, 30 mmol) was added to an aqueous solution (6 mL) of hydroxylamine hydrochloride (4.59 g, 66.0 mmol) and 50% wt/v aq. NaOH (5.3 mL, 66 mmol) at 18 °C. After stirring for a further 4 h, the mixture was extracted with EtOAc (3 × 100 mL). The organic solution was separated and washed with H_2O (50 mL) and brine (50 mL), dried (anhydrous $MgSO_4$) and evaporated *in vacuo*. The residue was recrystallized from a mixture of hot hexanes and EtOAc to afford the *title compound **158*** (2.4 g, 91%) as a colourless solid, mp 185-187 °C [lit.[119] mp 172-173 °C].

^{1}H NMR (300 MHz) δ 7.13 (s, 1H, C<u>H</u>=NOH), 8.32 (s, 1H, C<u>H</u>=NOH), 10.8 (s, 1H, OH), 11.0 (s, 1H, OH) (*syn* and *anti*-isomers).
^{13}C NMR (75.4 MHz) δ 136.4 (CH), 146.8 (CH) (*syn* and *anti*-isomers).
LRMS (EI) *m/z* (%) 88 ($M^{\bullet+}$, 100), 70 (78), 59 (80), 53 (27).

The ^{1}H NMR data of compound **158** are in full accord to literature values.[119]

Dichloroglyoxime 159



159

NCS (908 mg, 6.80 mmol) was added to a solution of glyoxime **158** (300 mg, 3.40 mmol) in dry DMF at 0-5 °C (ice bath) over 30 min. After stirring at 20-25 °C for 3

h, the mixture was poured into ice-H_2O (10 mL), extracted into Et_2O (5 × 50 mL) and washed with H_2O (1 × 30 mL). The aqueous layer was separated and extracted with Et_2O (6 × 50 mL). The combined organic solution was washed with H_2O (5 × 30 mL) and brine (1 × 30 mL), dried (anhydrous $MgSO_4$) and evaporated *in vacuo* to afford the *title compound* ***159***[120] (506 mg, 93%) as a colourless solid, mp 180-185 °C.

^{1}H NMR (300 MHz) δ 4.92 (s, 2H, 2 × OH).

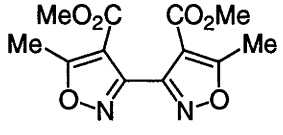
IR (KBr, thin film) ν_{max} 3254, 1714, 1411, 1329, 1250, 1163, 1002, 963, 860, 817, 700, 652 cm^{-1}.

LRMS (EI) *m/z* (%) 160, 158, 156 ($M^{\bullet+}$, 4, 22 and 35), 149 (5), 144 (2), 138 (4), 125 (31), 121 (100), 113 (2), 108 (12), 99 (6), 90 (17), 84 (29), 62 (15), 54 (13).

HRMS (EI) Found: $M^{\bullet+}$, 159.943433. $C_2H_2{}^{37}Cl_2N_2O_2$ requires $M^{\bullet+}$, 159.943825.

The spectral data of compound **159** are consistent with literature values.[120]

5,5'-Dimethyl-[3,3']-diisoxazole-4,4'-dicarboxylic Acid Dimethyl Diester 161



161

Triethylamine (0.18 mL, 1.3 mmol) was added over 48 h to a stirred mixture of dichloroglyoxime **159** (102 mg, 0.64 mmol) and methyl tetrolate **17a** (627 mg, 6.40 mmol) in Et_2O (4 mL) at 18 °C. The mixture was stirred for a further 32 h at 18 ° C. After the solvent was removed under reduced pressure, the residue was taken up in EtOAc (50 mL) and the solution was washed with H_2O (1 × 30 mL). The aqueous layer was separated and extracted with EtOAc (3 × 50 mL). The combined organic solution

was washed with brine (1 × 35 mL), dried (anhydrous $MgSO_4$) and concentrated *in vacuo*. Flash column chromatography of the residue, eluting with hexanes-EtOAc (7:3) afforded the *title compound* ***161*** (118 mg, 66%) as colourless blocks, after recrystallization from hexanes and Et_2O at 18 °C, mp 162-164 °C.

^{1}H NMR (300 MHz) δ 2.78 (s, 6H, 2 × CH_3), 3.74 (s, 6H, 2 × CH_3O).

^{13}C NMR (75.4 MHz) δ 13.3 (2 × CH_3), 50.8 (2 × CH_3O), 110.0 (2 × C4), 152.9 (2 × C3), 161.3 (2 × C5), 175.0 (2 × C=O).

IR (KBr, thin film) ν_{max} 1728, 1447, 1404, 1329, 1125 cm^{-1}.

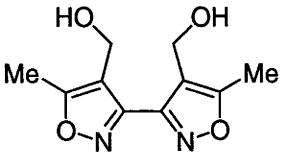
LRMS (EI) *m/z* (%) 280 ($M^{\bullet+}$, 83), 265 (13), 248 (100), 235 (5), 221 ($M^{\bullet+}$-CH_3O_2C, 20), 195 (5), 175 (13), 149 (6), 137 (21), 109 (17), 82 (14), 59 (21).

HRMS (EI) Found: $M^{\bullet+}$, 280.069340. $C_{12}H_{12}N_2O_6$ requires $M^{\bullet+}$, 280.069536.

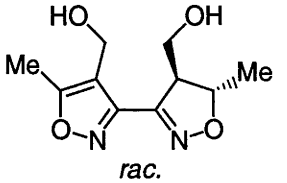
Elemental Analysis Found: C, 51.25; H, 4.31; N, 10.20. $C_{12}H_{12}N_2O_6$ requires C, 51.43; H, 4.32; N, 10.00.

X-Ray Crystallographic Analysis Appendix 1.11.

Sodium Borohydride Reduction of
5,5'-Dimethyl-[3,3']diisoxazole-4,4'-dicarboxylic Acid Dimethyl Diester 161 -
4,4'-Di(hydroxymethyl)-5,5'-dimethyl-[3,3']diisoxazole 162 and
4,4'-Di(hydroxymethyl)-5,5'-dimethyl-3,3'-isoxazole-Δ^2-isoxazoline 163



162



rac.
163

Sodium borohydride (412 mg, 10.9 mmol) was added over 15 min to a stirred solution of 5,5'-dimethyl-[3,3']-diisoxazole-4,4'-dicarboxylic acid dimethyl diester **161** (100 mg, 0.362 mmol) in dry EtOH (5 mL) at 0-5 °C (ice bath). After heating at reflux for 24 h, the mixture was cooled to 0-5 °C (ice bath) and quenched by dropwise addition of 1M HCl (to pH 2). The solvent was removed under reduced pressure, the residue was taken up in EtOAc (50 mL) and the solution was washed with H_2O (35 mL). The aqueous phase was separated and extracted with EtOAc (3 × 50 mL). The combined organic solution was washed with aq. $NaHCO_3$ (2 × 35 mL) and brine (1 × 35 mL), dried (anhydrous $MgSO_4$) and evaporated *in vacuo*. ^{1}H NMR analysis of the reaction mixture indicated the *title compounds **162*** and ***163*** were formed in a ratio of 3:1 (combined yield: 75 mg)

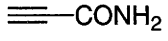
Compound 162

^{1}H NMR (300 MHz) δ 1.51 (s, 6H, 2 × CH_3), 4.61 (s, 4H, 2 × CH_2O).

Compound 163

^{1}H NMR (300 MHz) δ 1.49 (d, J = 6.3 Hz, 3H, $C\underline{H}_3CH$), 2.46 (s, 3H, CH_3), 3.48 (ddd, J = 8.5, 6.5, 4.5 Hz, 1H, H4), 3.91 (m, 2H, CH_2O), 4.61 (s, 2H, CH_2O), 4.65 (m, 1H, H5).

Propiolamide 166



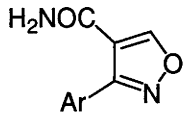
166

Methyl propiolate **11** (1.00 g, 11.9 mmol) was added dropwise to liquid ammonia (100 mL) and the mixture was stirred at –78 °C (dry ice/acetone bath) for 24 h. After ammonia was evaporated to dryness, the residue was taken up in EtOAc (150 mL) and the solution was washed with H_2O (3 × 100 mL). The aqueous layer was separated and extracted with EtOAc (3 × 150 mL). The combined organic solution was washed with brine (1 × 100 mL), dried (anhydrous $MgSO_4$) and concentrated *in vacuo*. Flash column chromatography of the residue, eluting with hexanes-EtOAc (3:2) afforded the *title compound **166*** (698 mg, 85%) as a colourless solid, mp 60-62 °C [lit.[122] mp 61-62 °C].

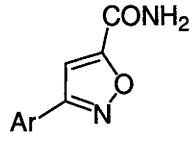
^{1}H NMR (300 MHz) δ 2.87 (s, 1H, C≡CH), 5.84 (br s, 1H, NH), 6.95 (br s, 1H, NH).
IR (KBr, thin film) ν_{max} 3290, 2111, 1662, 1373, 1124, 821 cm^{-1}.
LRMS (EI) *m/z* (%) 69 ($M^{\bullet+}$, 82), 57 (10), 53 ($M^{\bullet+}$-NH_2, 100), 44 (23), 41 (55), 32 (12), 28 (62), 25 ($M^{\bullet+}$-$CONH_2$, 10).

The ^{1}H NMR data of compound **166** are fully consistent with literature values.[122]

3-(2,4,6-Trimethylphenyl)isoxazole-4-carboxylic Acid Amide 167 and 3-(2,4,6-Trimethylphenyl)isoxazole-5-carboxylic Acid Amide 168



167



168

Ar = 2,4,6-Me_3Ph

A mixture of propiolamide **166** (214 mg, 3.10 mmol) and mesitonitrile oxide **5** (500 mg, 3.10 mmol) in THF (25 mL) was heated at reflux for 3 days. After the solvent was evaporated under reduced pressure, the residue was taken up in EtOAc (100 mL) and the solution was washed with H_2O (75 mL). The aqueous layer was separated and extracted with EtOAc (3 × 75 mL). The combined organic solution was washed with brine (1 × 75 mL), dried (anhydrous $MgSO_4$) and concentrated *in vacuo*. Flash column chromatography of the residue, eluting with hexanes-EtOAc (7:3) afforded the *title compounds **167*** (227 mg, 32%) as colourless rods, after recrystallization from a mixture of hexanes and acetone at 18 °C, mp 195-200 °C; and ***168*** (454 mg, 64%) as colourless plates after recrystallization from a mixture of hexanes and acetone at 18 °C, mp 135-137 °C.

Compound 167

^{1}H NMR (300 MHz) δ 2.10 (s, 6H, *o,o'*-$MesCH_3$), 2.35 (s, 3H, *p*-$MesCH_3$), 5.28 (br s, 1H, NH), 5.44 (br s, 1H, NH), 7.02 (s, 2H, 2 × MesH), 9.16 (s, 1H, H5).

^{13}C NMR (75.4 MHz) δ 19.9 (CH_3), 21.3 (2 × CH_3), 116.5 (C4), 122.7 (C), 129.1 (2 × CH), 137.5 (2 × C), 140.5 (C),158.2 (C3), 158.3 (C=O), 163.8 (C5).

IR (KBr, thin film) ν_{max} 3422, 3324, 2922, 2392, 1662, 1583, 1401, 1378, 1136, 1034, 855, 775, 739 cm^{-1}.

LRMS (EI) *m/z* (%) 230 ($M^{\bullet+}$, 37), 213 (49), 186 ($M^{\bullet+}$-$CONH_2$, 27), 170 (13), 157 (100), 142 (16), 130 (14), 115 (18), 103 (10), 91 (24), 77 (21), 65 (11).

HRMS (EI) Found: $M^{\bullet+}$, 230.105694. $C_{13}H_{14}N_2O_2$ requires $M^{\bullet+}$, 230.105528.

Elemental Analysis Found: C, 67.65; H, 6.15; N, 12.09. $C_{13}H_{14}N_2O_2$ requires C, 67.81; H, 6.13; N, 12.17.

X-Ray Crystallographic Analysis Appendix 1.12.

Compound 168

^{1}H NMR (300 MHz) δ 2.14 (s, 6H, *o*,*o*'-$MesCH_3$), 2.33 (s, 3H, *p*-$MesCH_3$), 5.27 (br s, 1H, NH), 6.55 (br s, 1H, NH), 6.91 (s, 1H, H4), 6.96 (s, 2H, 2 × MesH).

^{13}C NMR (75.4 MHz) δ 20.3 (2 × CH_3), 21.2 (CH_3), 109.3 (C4), 124.6 (C), 128.4 (2 × CH), 136.9 (2 × C), 139.3 (C), 157.8 (C3), 162.5 (C=O), 163.1 (C5).

IR (KBr, thin film) ν_{max} 3391, 3185, 2923, 1672, 1613, 1460, 1364, 1244, 1118, 1033, 851 cm^{-1}.

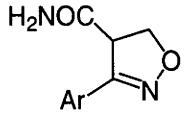
LRMS (EI) *m/z* (%) 230 ($M^{\bullet+}$, 70), 186 ($M^{\bullet+}$-$CONH_2$, 100), 171 (6), 158 (60), 143 (16), 130 (9), 115 (16), 103 (9), 91 (24), 77 (18), 65 (8).

HRMS (EI) Found: $M^{\bullet+}$, 230.105387. $C_{13}H_{14}N_2O_2$ requires $M^{\bullet+}$, 230.105528.

Elemental Analysis Found: C, 67.72; H, 6.09; N, 12.21. $C_{13}H_{14}N_2O_2$ requires C, 67.81; H, 6.13; N, 12.17.

X-Ray Crystallographic Analysis Appendix 1.13.

3-(2,4,6-Trimethylphenyl)-Δ^2-isoxazoline-4-carboxylic Amide 169



169

Ar = 2,4,6-Me_3Ph

Trifluoroacetic acid (0.17 mL, 2.16 mmol) was added dropwise to a stirred solution of sodium borohydride (82.0 mg, 2.16 mmol) in dry THF (2.5 mL) at 18 °C. After stirring for 30 min, a solution of 3-(2,4,6-trimethylphenyl)isoxazole-4-carboxylic acid amide **167** (33.0 mg, 0.144 mmol) in dry THF (0.5 mL) was added and the mixture was stirred for a further 30 h at 18 °C. After cooling to 0-5 °C (ice bath), the reaction was quenched by dropwise addition of 1M HCl (to pH 2) and the solvent was evaporated *in vacuo*. The residue was taken up in EtOAc (50 mL) and the solution was washed with H_2O (2 × 30 mL). The aqueous layer was separated and extracted with EtOAc (3 × 50 mL). The combined organic solution was washed with brine (30 mL), dried (anhydrous $MgSO_4$) and concentrated *in vacuo*. Flash column chromatography of the residue, eluting with hexanes-EtOAc (3:22) afforded *the title compound **169*** (31 mg, 92%) as a colourless solid, mp 175-176 °C.

^{1}H NMR (300 MHz) δ 2.27 (s, 6H, *o,o'*-MesCH_3), 2.30 (s, 3H, *p*-MesCH_3), 4.25 (dd, *J* = 10.8, 8.2 Hz, 1H, H4), 4.64 (m, 1H, H5), 5.01 (m, 1H, H5'), 5.10 (br s, 1H, NH), 5.29 (br s, 1H, NH), 6.92 (s, 2H, 2 × MesH).

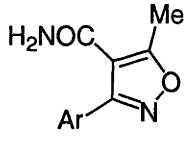
^{13}C NMR (125 MHz, CD_3OD) δ 19.9 (2 × CH_3), 21.2 (CH_3), 58.6 (C4), 73.2 (C5), 125.8 (C), 129.5 (2 × CH), 138.6 (2 × C), 140.3 (C), 157.1 (C3), 172.1 (C=O).

IR (KBr, thin film) ν_{max} 3334, 3194, 2923, 1677, 1611, 1455, 1394, 1337, 1306, 1289, 1195, 1118, 1035, 943, 908, 852, 730 cm^{-1}.

LRMS (EI) *m/z* (%) 232 ($M^{\bullet+}$, 67), 214 (26), 201 (33), 185 (90), 171 (31), 158 (83), 144 (100), 130 (55), 121 (5), 115 (48), 103 (27), 91 (63), 77 (45), 71 (32), 65 (20), 59 (5).

HRMS (EI) Found: $M^{\bullet+}$, 232.120979. $C_{13}H_{16}N_2O_2$ requires $M^{\bullet+}$, 232.121178.
Elemental Analysis Found: C, 67.28; H, 6.97; N, 12.07. $C_{13}H_{16}N_2O_2$ requires C, 67.22; H, 6.94; N, 12.06.

5-Methyl-3-(2,4,6-trimethylphenyl)isoxazole-4-carboxylic Acid Amide 171



171

Ar = 2,4,6-Me_3Ph

A mixture of mesitonitrile oxide **5** (500 mg, 3.11 mmol) and tetrolamide **170** (258 mg, 3.11 mmol) in THF (25 mL) was heated at reflux for 6 days. After the solvent was evaporated under reduced pressure, the residue was taken up in EtOAc (50 mL) and the solution was washed with H_2O (25 mL). The aqueous layer was separated and extracted with EtOAc (3 × 50 mL). The combined organic solution was washed with brine (50 mL), dried (anhydrous $MgSO_4$) and concentrated under reduced pressure. Flash column chromatography of the residue, eluting with hexanes-EtOAc (7:3) afforded the *title compound 171* (721 mg, 95%) as colourless needles, after recrystallization from a mixture of hexanes and acetone at 18 °C, mp 214-215 °C.

^{1}H NMR (300 MHz) δ 2.11 (s, 6H, *o*,*o*'-MesCH_3), 2.34 (s, 3H, *p*-MesCH_3), 2.83 (s, 3H, CH_3), 5.02 (br s, 1H, NH), 5.21 (br s, 1H, NH), 7.00 (s, 2H, 2 × MesH).
^{13}C NMR (75.4 MHz) δ 13.6 (CH_3), 19.8 (2 × CH_3), 21.2 (CH_3), 109.9 (C4), 124.1 (C), 129.1 (2 × CH), 137.5 (2 × C), 140.3 (C), 159.3 (C3), 163.5 (C=O), 176.0 (C5).

IR (KBr, thin film) ν_{max} 3439, 1683, 1601, 1449, 1353, 1183, 1155, 902, 873, 767, 750, 711, 689, 502 cm^{-1}.

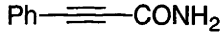
LRMS (EI) *m/z* (%) 244 ($M^{\bullet+}$, 89), 227 (49), 212 (42), 202 (5), 185 ($M^{\bullet+}$-C_2H_5NO, 100), 171 (50), 157 (100), 142 (15), 130 (19), 115 (31), 103 (18), 91 (45), 77 (35), 63 (7).

HRMS (EI) Found: $M^{\bullet+}$, 244.121622. $C_{14}H_{16}N_2O_2$ requires $M^{\bullet+}$, 244.121178.

Elemental Analysis Found: C, 68.78; H, 6.55; N, 11.41. $C_{14}H_{16}N_2O_2$ requires C, 68.83; H, 6.60; N, 11.47.

X-Ray Crystallographic Analysis Appendix 1.14.

3-Phenylpropynoic Acid Amide 173



173

3-Phenylpropynoic acid ethyl ester **172** (1.00 g, 5.74 mmol) was stirred in liquid ammonia (60 mL) at –78 °C (dry ice-acetone bath) for 24 h. The cold bath was removed and the liquid ammonia was allowed to evaporate off at 18 °C. The resultant residue was taken up in EtOAc (150 mL) and the solution was washed with H_2O (2 × 100 mL). The aqueous layer was separated and extracted with EtOAc (4 × 150 mL). The combined organic solution was washed with brine (1 × 100 mL), dried (anhydrous $MgSO_4$) and evaporated *in vacuo*. The residue was recrystallized from a mixture of hexanes and acetone at 18 °C to afford the *title compound* ***173*** (666 mg, 80%) as colourless prisms, mp 105-107 °C [lit.[125] mp 105-107 °C].

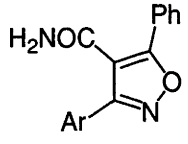
^{1}H NMR (300 MHz) δ 5.63 (br s, 1H, NH), 5.82 (br s, 1H, NH), 7.30-7.40 (m, 3H, 3 × PhH), 7.54 (m, 2H, 2 × PhH).

IR (KBr, thin film) ν_{max} 3881, 3175, 2222, 1650, 1609 cm^{-1}.

LRMS (EI) *m/z* (%) 145 ($M^{\bullet+}$, 66), 129 ($M^{\bullet+}$-NH_2, 100), 117 (16), 101 ($M^{\bullet+}$-$CONH_2$, 20), 89 ($M^{\bullet+}$-C_2H_2NO, 11), 75 (39), 63 (11), 59 (9).

The ^1H NMR data of compound **172** are in full agreement with literature values.[125]

5-Phenyl-3-(2,4,6-trimethylphenyl)isoxazole-4-carboxylic Acid Amide 174



174

Ar = 2,4,6-Me_3Ph

A mixture of 3-phenylpropynoic acid amide **173** (90.0 mg, 0.621 mmol) and mesitonitrile oxide **5** (100 mg, 0.621 mmol) in dry THF (6 mL) was heated at reflux for 6 days. After the solvent was removed under reduced pressure, the residue was taken up in EtOAc (50 mL) and the solution was washed with H_2O (1 × 35 mL). The aqueous layer was separated and extracted with EtOAc (3 × 50 mL). The combined organic solution was washed with brine (1 × 35 mL), dried (anhydrous $MgSO_4$) and evaporated *in vacuo*. Flash column chromatography of residue, eluting with hexanes-EtOAc (3:2) afforded the *title compound* ***174*** (177 mg, 93%) as colourless blocks, after recrystallization from a mixture of hexanes and acetone at 18 °C, mp 192-193 °C.

^1H NMR (300 MHz) δ 2.18 (s, 6H, *o,o'*-MesCH_3), 2.36 (s, 3H, *p*-MesCH_3), 5.15 (br s, 1H, NH), 5.35 (br s, 1H, NH), 7.02 (s, 2H, 2 × MesH), 7.51-7.56 (m, 3H, 3 × PhH), 8.10-8.14 (m, 2H, 2 × PhH).

^{13}C NMR (75.4 MHz) δ 19.8 (CH_3), 21.1 (2 × CH_3), 110.3 (C4), 124.1 (C), 126.8 (C), 128.2 (2 × CH), 128.3 (2 × CH), 128.9 (2 × CH), 131.1 (CH), 137.4 (2 × C), 140.0 (C), 160.6 (C3), 163.1 (C5), 172.2 (C=O).

IR (KBr, thin film) ν_{max} 3304, 2921, 2853, 1677, 1611, 1422, 1363, 1131, 1035, 853, 691 cm^{-1}.

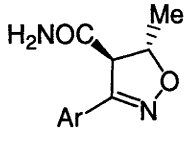
LRMS (EI) *m/z* (%) 306 ($M^{\bullet+}$, 50), 289 (30), 277 (2), 262 ($M^{\bullet+}$-$CONH_2$, 5), 233 (100), 218 (4), 184 (2), 158 (4), 130 (3), 105 (100), 91 (7), 77 ($M^{\bullet+}$-$C_{13}H_{13}N_2O_2$, 41), 65 (2).

HRMS (EI) Found: $M^{\bullet+}$, 306.136828. $C_{19}H_{18}N_2O_2$ requires $M^{\bullet+}$, 306.136880.

Elemental Analysis Found: C, 74.38; H, 5.86; N, 9.16. $C_{19}H_{18}N_2O_2$ requires C, 74.49; H, 5.92; N, 9.14.

X-Ray Crystallographic Analysis Appendix 1.15.

***trans*-5-Methyl-3-(2,4,6-trimethylphenyl)-Δ^2-isoxazoline-4-carboxylic Acid Amide 175**



rac.

175

Ar = 2,4,6-Me_3Ph

Trifluoroacetic acid (0.46 mL, 6.1 mmol) was added dropwise to a stirred suspension of sodium borohydride (231 mg, 6.1 mmol) in dry THF (5 mL) at 0-5 °C (ice bath) over 15 min. After stirring at 18 °C for 30 min, a solution of 5-methyl-3-(2,4,6-trimethylphenyl)isoxazole-4-carboxylic acid amide **171** (100 mg, 0.408 mmol) in dry THF (1 mL) was added dropwise and stirring was continued for a further 5 days at 18 °C. The reaction mixture was cooled to 0-5 °C (ice bath) and quenched by addition of

1M HCl (to pH 2). After the solvent was removed under reduced pressure, the residue was taken up in EtOAc (15 mL) and the solution was washed with H_2O (2 × 10 mL). The aqueous layer was separated and extracted with EtOAc (4 × 15 mL). The combined organic solution was washed with brine (10 mL), dried (anhydrous $MgSO_4$) and evaporated *in vacuo*. Flash column chromatography of the residue, eluting with hexanes-EtOAC (3:2) afforded the *title compound* ***175*** (90 mg, 90%) as a colourless solid, mp 191-193 °C [lit.[126] mp 196-197 °C].

^{1}H NMR (300 MHz) δ 1.53 (d, J = 6.3 Hz, 3H, C$\underline{H_3}$CH), 2.27 (s, 6H, *o,o'*-MesCH_3), 2.29 (s, 3H, *p*-MesCH_3), 3.82 (d, J = 8.0 Hz, 1H, H4), 5.06 (br s, 2H, NH), 5.29 (dq, J = 8.0, 6.3 Hz, 1H, H5), 6.91 (s, 2H, 2 × MesH).

^{13}C NMR (75.4 MHz) δ 19.9 (CH_3), 20.3 (2 × CH_3), 21.1 (CH_3), 63.6 (C4), 80.1 (C5), 124.7 (C), 129.0 (2 × CH), 137.2 (2 × C), 139.5 (C), 153.8 (C3), 168.3 (C=O).

IR (KBr, thin film) ν_{max} 3326, 2923, 1678, 1612, 1446, 1440, 1379, 1307, 1138, 871, 850 cm^{-1}.

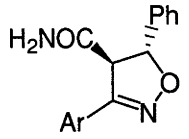
LRMS (EI) *m/z* (%) 246 ($M^{\bullet+}$, 39), 231 ($M^{\bullet+}$-CH_3, 16), 214 (10), 202 ($M^{\bullet+}$-$CONH_2$, 6), 185 (86), 157 (52), 144 (27), 130 (100), 115 (29), 101 (23), 91 (37), 77 (34), 69 (22), 57 (23).

HRMS (EI) Found: $M^{\bullet+}$, 246.136564. $C_{14}H_{18}N_2O_2$ requires $M^{\bullet+}$, 246.136828.

Elemental Analysis Found: C, 68.13; H, 7.41; N, 11.42. $C_{14}H_{18}N_2O_2$ requires C, 68.27; H, 7.37; N, 11.37.

The ^{1}H NMR data are in full accord with reported values.[126]

***trans*-5-Phenyl-3-(2,4,6-trimethylphenyl)-Δ^2-isoxazoline-4-carboxylic Acid Amide 176**



rac.

176

Ar = 2,4,6-Me_3Ph

Trifluoroacetic acid (0.38 mL, 4.9 mmol) was added to a stirred suspension of sodium borohydride (185 mg, 4.90 mmol) in dry THF (6 mL) at 0-5 °C (ice bath) over 15 min. After stirring at 18 °C for 30 min, a solution of 5-phenyl-3-(2,4,6-trimethylphenyl)isoxazole-4-carboxylic acid amide **174** (100 mg, 0.327 mmol) in dry THF (1 mL) was added dropwise to the mixture and stirring was continued for a further 8 days. The mixture was cooled to 0-5 °C (ice bath) and quenched by dropwise addition of 1M HCl (to pH 2). The solvent was concentrated under reduced pressure, the residue was taken up in EtOAc (50 mL) and the solution was washed with H_2O (2 × 35 mL). The aqueous layer was separated and extracted with EtOAc (4 × 50 mL). The combined organic solution was washed with brine (35 mL), dried (anhydrous $MgSO_4$) and evaporated *in vacuo*. Flash column chromatography of the residue, eluting with hexanes-EtOAc (3:2) afforded the *title compound **176*** (93 mg, 92%) as a colourless solid, mp 196-198 °C [lit.[126] mp 214-215 °C].

^{1}H NMR (300 MHz) δ 2.23 (s, 6H, *o*,*o*'-MesCH_3), 2.29 (s, 3H, *p*-MesCH_3), 4.14 (d, J = 8.2 Hz, 1H, H4), 4.98 (br s, 1H, NH), 5.21 (br s, 1H, NH), 6.27 (d, J = 8.2 Hz, 1H, H5), 6.91 (s, 2H, 2 × MesCH), 7.30-7.50 (m, 5H, 5 × PhH).

^{13}C NMR (75.4 MHz) δ 19.9 (2 × CH_3), 21.1 (CH_3), 65.7 (C4), 84.9 (C5), 124.2 (C), 125.7 (2 × CH), 128.4 (CH), 128.9 (2 × CH), 129.0 (2 × CH), 137.3 (2 × C), 139.6 (C), 140.0 (C), 153.2 (C3), 168.0 (C=O).

IR (KBr, thin film) ν_{max} 3434, 3180, 2922, 1650, 1398, 1030, 891, 849, 738, 697 cm^{-1}.

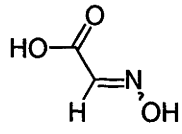
LRMS (EI) *m/z* (%) 308 ($M^{\bullet+}$, 27), 290 (2), 264 ($M^{\bullet+}$-$CONH_2$, 100), 207 (2), 187 ($M^{\bullet+}$-C_7H_7NO, 11), 163 (33), 103 (32), 77 ($M^{\bullet+}$-$C_{13}H_{15}N_2O_2$, 34).

HRMS (EI) Found: $M^{\bullet+}$, 308.152852. $C_{19}H_{20}N_2O_2$ requires $M^{\bullet+}$, 308.152478.

Elemental Analysis Found: C, 73.88; H, 6.58; N, 8.98. $C_{19}H_{20}N_2O_2$ requires C, 74.00; H, 6.54; N, 9.08.

The ^1H NMR data are in full accord with reported values.[126]

Glyoxylic Acid Aldoxime 178



178

Glyoxylic acid monohydrate **177** (9.20 g, 0.100 mol) was added to a stirred aqueous solution (100 mL) of hydroxylamine hydrochloride (6.95 g, 0.100 mol) and $NaHCO_3$ (8.40 g, 0.100 mol). After stirring at 18 °C for 24 h, the mixture was extracted into EtOAc (100 mL). The aqueous phase was separated and extracted with EtOAc (3 × 75 mL). The combined organic solution was washed with H_2O (2 × 50 mL) and brine (1 × 50 mL), dried (anhydrous Na_2SO_4) and evaporated *in vacuo* to afford the *title compound **178*** (8.7 g, 98%) as a colourless solid, mp 134-138 °C [lit.[131] mp 134-136 °C].

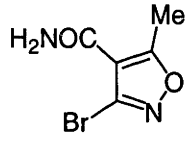
^1H NMR (300 MHz) δ 4.90 (s, 2H, OH), 7.49 (s, 1H, C<u>H</u>NOH).

IR (KBr, thin film) ν_{max} 3552, 3270, 1995, 1670, 1618, 1496, 1301, 1270, 1005, 937, 747, 714 cm^{-1}.

LRMS (EI) *m/z* (%) 89 ($M^{\bullet+}$, 3), 72 ($M^{\bullet+}$-OH, 100), 59 (5), 55 (10).

The ^{1}H NMR data and the melting point of compound **178** are consistent with literature values.[131]

3-Bromo-5-methylisoxazole-4-carboxylic Acid Amide 181



181

NBS (1.57 g, 8.80 mmol) was added to a stirred solution of glyoxylic acid aldoxime **178** (392 mg, 4.40 mmol) in H_2O-DME (6 mL:10 mL) at 0-5 °C (ice bath) and stirring was continued at 18 °C for 40 min. The mixture was added to a stirred solution of tetrolamide **170** (3.65 g, 44.0 mmol) and $KHCO_3$ (881 mg, 8.80 mmol) in H_2O-DME (30 mL:50 mL) over 11 days, reaction was continued for a further 24 h at 18 °C. The solvent was removed under reduced pressure, the residue taken up in EtOAc (200 mL) and the solution was washed with H_2O (2 × 150 mL). The aqueous layer was separated and extracted with EtOAc (200 mL). The combined organic solution was washed with brine (1 × 150 mL), dried (anhydrous $MgSO_4$) and concentrated *in vacuo*. Flash column chromatography of the residue, using hexanes-EtOAc (13:7) afforded the *title compound **181*** (601 mg, 67%) as colourless blocks, after recrystallization from vapour diffusion from a mixture of hexanes and acetone at 18 °C, mp 129-131 °C.

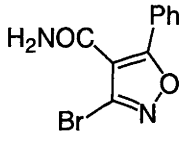
^{1}H NMR (300 MHz) δ 2.76 (s, 3H, CH_3), 6.39 (br s, 1H, NH), 6.48 (br s, 1H, NH).
^{13}C NMR (75.4 MHz) δ 13.7 (CH_3), 111.5 (C4), 137.7 (C3), 161.3 (C5), 177.3 (C=O).
IR (KBr, thin film) ν_{max} 3421, 3208, 1690, 1667, 1608, 1584, 1447, 1336, 1237, 1130, 987, 787 cm^{-1}.

LRMS (EI) *m/z* (%) 206, 204 ($M^{\bullet+}$, 96 and 100), 188 (22), 164 (5), 149 (14), 115 (6), 89 (14), 73 (27).

HRMS (EI) Found: $M^{\bullet+}$, 205.951852. $C_5H_5{}^{81}BrN_2O_2$ requires $M^{\bullet+}$, 205.951392. Found: $M^{\bullet+}$, 203.953839. $C_5H_5{}^{79}BrN_2O_2$ requires $M^{\bullet+}$, 203.953439.

X-Ray Crystallographic Analysis Appendix 1.16.

3-Bromo-5-phenylisoxazole-4-carboxylic Acid Amide 182



182

NBS (1.57 mg, 8.80 mmol) was added to a stirred solution of glyoxylic acid oxime **178** (392 mg, 4.40 mmol) in H_2O-DME (1.2 mL:2 mL) at 0-5 °C (ice bath) and stirring was continued at 18 °C for 40 min. After the mixture was added to a stirred solution of 3-phenylpropynoic acid amide **173** (6.38 g, 44.0 mmol) and $KHCO_3$ (881 mg, 8.80 mmol) in H_2O-DME (30 mL:50 mL) over 11 days, reaction was continued for a further 24 h at 18 °C. The solvent was removed under reduced pressure, the residue taken up in EtOAc (200 mL) and the solution was washed with H_2O (2 × 150 mL). The aqueous layer was separated and extracted with EtOAc (200 mL). The combined organic solution was washed with brine (1 × 150 mL), dried (anhydrous $MgSO_4$) and concentrated *in vacuo*. Flash column chromatography of the residue, using CH_2Cl_2-Et_2O (9:1) afforded the *title compound* ***182*** (784 mg, 67%) as colourless blocks, after recrystallization from vapour diffusion from a mixture of hexanes and acetone at 18 °C, mp 193-195 °C.

^{1}H NMR (300 MHz) δ 5.80 (br s, 1H, NH), 6.00 (br s, 1H, NH), 7.48-7.60 (m, 3H, 3 × PhH), 7.87-7.90 (m, 2H, 2 × PhH).

^{13}C NMR (125 MHz, d_6-acetone) δ 115.6 (C4), 126.9 (C), 128.0 (2 × CH), 130.0 (2 × CH), 132.3 (CH), 140.7 (C3), 162.3 (C5), 169.0 (C=O).

IR (KBr, thin film) ν_{max} 3367, 3175, 1649, 1430, 1338, 1104, 1054, 712, 685 cm^{-1}.

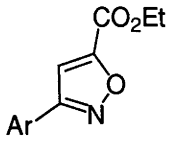
LRMS (EI) *m/z* (%) 268, 266 ($M^{\bullet+}$, 65 and 64), 250 (10), 186 (17), 170 (2), 144 (4), 131 (2), 116 (6), 105 (100), 97 (3), 89 (8), 77 (77), 63 (7).

HRMS (EI) Found: $M^{\bullet+}$, 265.968864. $C_{10}H_7{}^{79}BrN_2O_2$ requires $M^{\bullet+}$, 265.969089.

X-Ray Crystallographic Analysis Appendix 1.17.

7.4. Experimental for Chapter 4

3-(2,4,6-Trimethylphenyl)isoxazole-5-carboxylic Acid Methyl Ester 205



205

Ar = 2,4,6-Me_3Ph

A suspension of zinc powder (155 mg, 2.38 mmol) and copper(I) iodide (134 mg, 0.704 mmol) in a 65% aq. EtOH (5 mL) was sonicated at 5 °C for 5-10 min, until the suspension turned black. 3-(2,4,6-Trimethylphenyl)isoxazole-5-carboxylic acid methyl ester **13f** (216 mg, 0.88 mmol) was added and the mixture was sonicated at 10-15 °C for 2 days. The reaction was quenched by addition of aq. NH_4Cl (1 mL) and the mixture was filtered through a pad of Celite®. The filter cake was washed with EtOAc (3 × 100 mL) and the filtrate was concentrated under reduced pressure. The residue was taken up in Et_2O (30 mL) and the solution was washed with H_2O (1 × 20 mL). The aqueous phase was separated and extracted with Et_2O (3 × 20 mL). The combined organic solution was washed with aq. $Na_2S_2O_4$ (1 × 50 mL), H_2O (1 × 50 mL) and brine (1 × 50 mL), dried (anhydrous $MgSO_4$) and evaporated *in vacuo*. Flash column chromatography of the residue, eluting with hexanes-Et_2O (17:3) afforded the *title compound **205*** (55 mg, 24%) as a colourless oil.

^{1}H NMR (300 MHz) δ 1.45 (t, J = 7.1 Hz, 3H, $C\underline{H}_3CH_2O$), 2.14 (s, 6H, *o,o'*-$MesCH_3$), 2.33 (s, 3H, *p*-$MesCH_3$), 4.48 (q, J = 7.1 Hz, 2H, $CH_3C\underline{H}_2O$), 6.91 (s, 1H, H4), 6.96 (s, 2H, 2 × MesH).

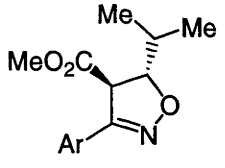
^{13}C NMR (75.4 MHz) δ 14.1 ($\underline{C}H_3CH_2$), 20.2 (2 × CH_3), 21.1 (CH_3), 62.3 (CH_2O), 110.9 (C4), 124.8 (C), 128.5 (2 × CH), 137.1 (2 × C), 139.3 (C), 156.9 (C3), 160.3 (C=O), 162.7 (C5).

IR (KBr, thin film) ν_{max} 2980, 2924, 1741, 1612, 1584, 1458, 1302, 1282, 1234, 1216, 1174, 1122, 1017, 853, 770 cm^{-1}.

LRMS (EI) *m/z* (%) 259 ($M^{\bullet+}$, 62), 244 ($M^{\bullet+}$-CH_3, 4), 231 (2), 214 ($M^{\bullet+}$-CH_3CH_2O, 6), 186 ($M^{\bullet+}$-$CH_3CH_2O_2C$, 100), 171 (8), 158 (73), 143 (21), 130 (13), 119 ($M^{\bullet+}$-$C_6H_6NO_3$, 20), 103 (13), 91 (35), 77 (21), 63 (5).

HRMS (EI) Found: $M^{\bullet+}$, 259.120867. $C_{15}H_{17}NO_3$ requires $M^{\bullet+}$, 259.120844.

***trans*-5-Isopropyl-3-(2,4,6-trimethylphenyl)-Δ^2-isoxazoline-4-carboxylic Acid Methyl Ester 206**



rac.

206

Ar = 2,4,6-Me_3Ph

A suspension of zinc powder (35 mg, 0.54 mmol) and copper(I) iodide (31 mg, 0.16 mmol) in a 65% aq. MeOH (3 mL) was sonicated at 5 °C for 5-10 min, until the suspension turned black. After 3-(2,4,6-trimethylphenyl)isoxazole-4-carboxylic acid methyl ester **12f** (50.0 g, 0.204 mmol) was added, isopropyl iodide **185** (60 μL, 0.60 mmol) was added to the sonicating mixture at 5 °C over 2 h. Ultrasound irradiation was continued at 5 °C for a further 2.5 days, with addition of zinc powder (35 mg, 0.54 mmol), copper(I) iodide (31 mg, 0.16 mmol), isopropyl iodide **185** (60 μL, 0.60 mmol)

and 65% aq. MeOH (4 mL) at 8 h intervals. The reaction was quenched by addition of aq. NH_4Cl (1 mL), and the suspension was filtered through a pad of Celite®. The filter cake was washed with EtOAc (3 × 100 mL) and the filtrate was concentrated under reduced pressure. The residue was taken up in Et_2O (30 mL) and the solution was washed with H_2O (1 × 20 mL). The aqueous phase was separated and extracted with Et_2O (3 × 10 mL). The combined organic solution was washed with aq. $Na_2S_2O_4$ (1 × 30 mL), H_2O (1 × 30 mL) and brine (1 × 30 mL), dried (anhydrous $MgSO_4$) evaporated *in vacuo*. Flash column chromatography of the residue, eluting with hexanes-Et_2O (17:3) afforded the *title compound* ***206*** (48 mg, 82%) as a colourless oil.

^{1}H NMR (300 MHz) δ 1.00 [d, J = 6.7 Hz, 3H, $(C\underline{H}_3)_2CH$], 1.09 [d, J = 6.7 Hz, 3H, $(C\underline{H}_3)_2CH$], 2.05 [m, 1H, $(CH_3)_2C\underline{H}$], 2.24 (s, 6H, *o,o'*-$MesCH_3$), 2.28 (s, 3H, *p*-$MesCH_3$), 3.56 (s, 3H, CH_3O), 4.16 (d, J = 10.0 Hz, 1H, H4), 4.86 (dd, J = 10.0, 7.1 Hz, 1H, H5), 6.87 (s, 2H, 2 × MesH).

^{13}C NMR (75.4 MHz) δ 17.6 [$(\underline{C}H_3)_2CH$], 18.1 [$(\underline{C}H_3)_2CH$], 19.7 (2 × CH_3), 20.9 (CH_3), 31.6 [$(CH_3)_2\underline{C}H$], 52.4 (C4), 58.8 (CH_3O), 89.6 (C5), 124.6 (C), 128.4 (2 × CH), 136.8 (2 × C), 138.6 (C), 153.6 (C3), 169.0 (C=O).

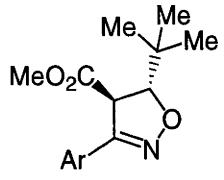
IR (KBr, thin film) ν_{max} 2960, 2926, 2875, 1742, 1611, 1595, 1435, 1266, 1198, 1168, 1031, 897, 851 cm^{-1}.

LRMS (EI) *m/z* (%) 289 ($M^{\bullet+}$, 34), 246 [$M^{\bullet+}$-$(CH_3)_2CH$, 100], 218 (17), 186 (95), 158 (52), 146 (24), 119 ($M^{\bullet+}$-$C_8H_{12}NO_3$, 12), 101 (7), 91 (12).

HRMS (EI) Found: $M^{\bullet+}$, 289.167849. $C_{17}H_{23}NO_3$ requires $M^{\bullet+}$, 289.167794.

Elemental Analysis Found: C, 70.36; H, 8.06; N, 4.80. $C_{17}H_{23}NO_3$ requires C, 70.56; H, 8.01; N, 4.84.

trans-5-_tert_-Butyl-3-(2,4,6-trimethylphenyl)-Δ^2-isoxazoline-4-carboxylic Acid Methyl Ester 208



rac.
208

Ar = 2,4,6-Me_3Ph

A suspension of zinc powder (35 mg, 0.54 mmol) and copper(I) iodide (31 mg, 0.16 mmol) in a 65% aq. MeOH (3 mL) was sonicated at 5 °C for 5-10 min, until the suspension turned black. After 3-(2,4,6-trimethylphenyl)isoxazole-4-carboxylic acid methyl ester **12f** (50.0 mg, 0.204 mmol) was added, *tert*-butyl iodide **207** (70 μL, 0.60 mmol) was added over 2 h to the sonicating mixture at 5 °C. Sonication was continued at 5 °C for 9 h. The reaction was quenched by addition of aq. NH_4Cl (1 mL) and the mixture was filtered through a pad of Celite®. The filter cake was washed with EtOAc (3 × 100 mL) and the filtrate was concentrated under reduced pressure. The residue was taken up in Et_2O (30 mL) and the solution was washed with H_2O (1 × 20 mL). The aqueous phase was separated and extracted with Et_2O (3 × 10 mL). The combined organic solution was washed with aq. $Na_2S_2O_4$ (1 × 30 mL), H_2O (1 × 30 mL) and brine (1 × 30 mL), dried (anhydrous $MgSO_4$) and evaporated *in vacuo*. Flash column chromatography of the residue, eluting with hexanes-Et_2O (17:3) afforded the *title compound **208*** (59 mg, 96%) as a colourless solid, mp 59-62 °C.

^{1}H NMR (300 MHz) δ 1.02 [s, 9H, $(CH_3)_3C$], 2.23 (s, 6H, *o*,*o*'-$MesCH_3$), 2.27 (s, 3H, *p*-$MesCH_3$), 3.54 (s, 3H, CH_3O), 4.20 (d, J = 10.7 Hz, 1H, H4), 4.85 (d, J = 10.7 Hz, 1H, H5), 6.86 (s, 2H, 2 × MesH).

^{13}C NMR (75.4 MHz) δ 20.0 (2 × CH_3), 21.2 (CH_3), 25.3 [($\underline{C}H_3)_3C$], 33.7 [$(CH_3)_3\underline{C}$], 52.7 (CH_3O), 57.4 (C4), 92.7 (C5), 124.7 (C), 128.4 (2 × CH), 136.9 (2 × C), 138.7 (C), 153.4 (C3), 169.3 (C=O).

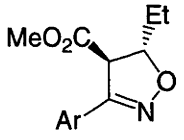
IR (KBr, thin film) ν_{max} 2956, 2871, 1743, 1610, 1434, 1398, 1367, 1306, 1292, 1199, 1026, 1000, 906, 851, 781 cm^{-1}.

LRMS (EI) *m/z* (%) 303 ($M^{\bullet+}$, 31), 246 [$M^{\bullet+}$-$(CH_3)_3C$, 100], 218 (59), 186 (68), 158 (54), 146 (24), 119 (10), 91 (10), 77 (6).

HRMS (EI) Found: $M^{\bullet+}$, 303.183535. $C_{18}H_{25}NO_3$ requires $M^{\bullet+}$, 303.183444.

Elemental Analysis Found: C, 71.14; H, 8.28; N, 4.66. $C_{18}H_{25}NO_3$ requires C, 71.26; H, 8.31; N, 4.62.

trans-5-Ethyl-3-(2,4,6-trimethylphenyl)-Δ^2-isoxazoline-4-carboxylic Acid Methyl Ester 210



rac.

210

Ar = 2,4,6-Me_3Ph

A suspension of zinc powder (35 mg, 0.54 mmol) and copper(I) iodide (31 mg, 0.16 mmol) in a 65% aq. MeOH (3 mL) was sonicated at 5 °C for 5-10 min, until the suspension turned black. After 3-(2,4,6-trimethylphenyl)isoxazole-4-carboxylic acid methyl ester **12f** (50.0 g, 0.204 mmol) was added, iodoethane **209** (48 μL, 0.60 mmol) was added at 5 °C over 2 h. Ultrasound irradiation was continued at 5 °C for 8 days, with addition of zinc (35 mg, 0.54 mmol) copper(I) iodide (31 mg, 0.16 mmol), iodoethane **209** (48 μL, 0.60 mmol) and 65% aq. MeOH (3 mL) at 8 h intervals. The

reaction was quenched by addition of aq. NH_4Cl (1 mL) and the mixture was filtered through a pad of Celite®. The filter cake was washed with EtOAc (3 × 100 mL) and the filtrate was concentrated under reduced pressure. The residue was taken up in Et_2O (30 mL) and the solution was washed with H_2O (1 × 20 mL). The aqueous layer was separated and extracted with Et_2O (3 × 10 mL). The combined organic solution was washed with aq. $Na_2S_2O_4$ (1 × 30 mL), H_2O (1 × 30 mL) and brine (1 × 30 mL), dried (anhydrous $MgSO_4$) and evaporated *in vacuo*. Flash column chromatography of the residue, eluting with hexanes-CH_2Cl_2 (2:3) afforded the *title compound* ***210*** (18 mg, 32%) as a colourless oil.

^{1}H NMR (300 MHz) δ 1.08 (t, J = 7.4 Hz, 3H, $C\underline{H}_3CH_2$), 1.79 (m, 1H, $CH_3C\underline{H}_2$), 1.92 (m, 1H, $CH_3C\underline{H}_2$), 2.24 (s, 6H, *o,o'*-MesCH_3), 2.29 (s, 3H, *p*-MesCH_3), 3.58 (s, 3H, CH_3O), 4.08 (d, J = 8.9 Hz, 1H, H4), 5.02 (dt, J = 8.9, 6.5 Hz, 1H, H5), 6.88 (s, 2H, 2 × MesH).

^{13}C NMR (75.4 MHz) δ 9.3 (CH_3), 20.0 (2 × CH_3), 21.2 (CH_3), 27.4 (CH_2), 52.6 (CH_3O), 60.9 (C4), 85.7 (C5), 124.6 (C), 128.5 (2 × CH), 136.9 (2 × C), 138.8 (C), 153.7 (C3), 168.8 (C=O).

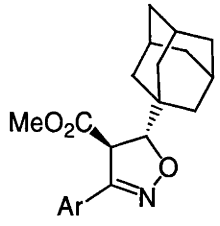
IR (KBr, thin film) ν_{max} 1741, 1611, 1434, 1378, 1309, 1151, 1033, 893, 852 cm^{-1}.

LRMS (EI) *m/z* (%) 275 ($M^{\bullet+}$, 49), 256 (27), 246 ($M^{\bullet+}$-CH_3CH_2, 95), 230 (7), 214 (19), 202 (7), 186 (100), 170 (12), 158 (65), 144 (20), 130 (27), 115 (24), 103 (14), 91 (38), 77 (23), 65 (10), 57 (14).

HRMS (EI) Found: $M^{\bullet+}$, 275.151828. $C_{16}H_{21}NO_3$ requires $M^{\bullet+}$, 275.152144.

Elemental Analysis Found: C, 69.71; H, 7.63; N, 5.04. $C_{16}H_{21}NO_3$ requires C, 69.79; H, 7.69; N, 5.09.

***trans*-5-(Adamantan-1-yl)-3-(2,4,6-trimethylphenyl)-Δ^2-isoxazoline-4-carboxylic Acid Methyl Ester 212**



rac.

212

Ar = 2,4,6-Me_3Ph

A suspension of zinc powder (35 mg, 0.54 mmol) and copper(I) iodide (31 mg, 0.16 mmol) in a 65% aq. MeOH (3 mL) was sonicated at 5 °C for 5-10 min, until the suspension turned black. After 3-(2,4,6-trimethylphenyl)isoxazole-4-carboxylic acid methyl ester **12f** (50.0 g, 0.204 mmol) was added, 1-iodoadamantane **211** (157 mg, 0.60 mmol) was added over 2 h to the sonicating mixture at 5 °C. Ultrasound irradiation was continued at 5 °C for a further 8 h, followed by addition of zinc powder (35 mg, 0.540 mmol), copper(I) iodide (31 mg, 0.16 mmol) and 65% aq. MeOH (4 mL). The mixture was sonicated for a further 6 h, then quenched by addition of aq. NH_4Cl (1 mL). The mixture was filtered through a pad of Celite® and the filter cake was washed with EtOAc (3 × 100 mL). The filtrate was concentrated under reduced pressure and the residue was taken up in Et_2O (30 mL). The solution was washed with H_2O (1 × 20 mL) and the aqueous phase was separated and extracted with Et_2O (3 × 10 mL). The combined organic solution was washed with aq. $Na_2S_2O_4$ (1 × 30 mL), H_2O (1 × 30 mL) and brine (1 × 30 mL), dried (anhydrous $MgSO_4$) and evaporated *in vacuo*. Flash column chromatography of the residue, eluting with hexanes-Et_2O (17:3) afforded the *title compound 212* (74 mg, 95%) as colourless plates, after recrystallization from a mixture of hexanes and Et_2O at 18 °C, mp 82-84 °C.

^{1}H NMR (300 MHz) δ 1.18-1.37 (m, 6H, 3 × CH_2), 1.51-1.62 (m, 6H, 3 × CH_2), 2.00-2.09 (m, 3H, CH), 2.22 (s, 6H, *o*,*o*'-MesCH_3), 2.27 (s, 3H, *p*-MesCH_3), 3.53 (s, 3H, CH_3O), 4.27 (d, *J* = 11.1 Hz, 1H, H4), 4.69 (d, *J* = 11.1 Hz, 1H, H5), 6.85 (s, 2H, 2 × MesH).

^{13}C NMR (75.4 MHz) δ 20.4 (2 × CH_3), 21.5 (CH_3), 28.3 (2 × CH), 30.8 (CH), 35.3 (CH_2), 36.5 (CH_2), 36.7 (CH_2), 36.9 (CH_2), 37.8 (CH_2), 38.4 (CH_2), 41.0 (C), 53.0 (CH_3O), 56.0 (C4), 93.1 (C5), 125.1 (C), 128.8 (2 × CH), 137.2 (2 × C), 139.0 (C), 153.3 (C3), 170.0 (C=O).

IR (KBr, thin film) ν_{max} 2904, 2849, 1743, 1612, 1434, 1306, 1289, 1198, 1168, 1003, 897, 867, 850 cm^{-1}.

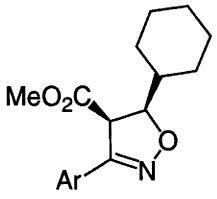
LRMS (EI) *m/z* (%) 381 ($M^{\bullet+}$, 18), 246 ($M^{\bullet+}$-$C_{10}H_{15}$, 100), 218 (9), 186 (34), 158 (12), 135 (69), 108 (7), 93 (13), 79 (19), 66 (10).

HRMS (EI) Found: $M^{\bullet+}$, 381.230289. $C_{24}H_{31}NO_3$ requires $M^{\bullet+}$, 381.230394.

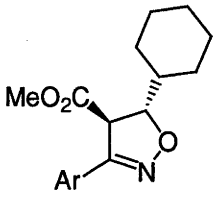
Elemental Analysis Found: C, 75.49; H, 8.14; N, 3.63. $C_{24}H_{31}NO_3$ requires C, 75.56; H, 8.19; N, 3.67.

X-Ray Crystallographic Analysis Appendix 1.18

cis-5-Cyclohexyl-3-(2,4,6-trimethylphenyl)-Δ^2-isoxazoline-4-carboxylic Acid Methyl Ester 214a and
trans-5-Cyclohexyl-3-(2,4,6-trimethylphenyl)-Δ^2-isoxazoline-4-carboxylic Acid Methyl Ester 214b



rac.
214a



rac.
214b

Ar = 2,4,6-Me_3Ph

A suspension of zinc powder (35 mg, 0.54 mmol) and copper(I) iodide (31 mg, 0.16 mmol) in a 65% aq. MeOH (4 mL) was sonicated at 5 °C for 5-10 min, until the suspension turned black. After 3-(2,4,6-trimethylphenyl)isoxazole-4-carboxylic acid methyl ester **12f** (50.0 mg, 0.204 mmol) was added, cyclohexyl iodide **213** (78 μL, 0.60 mmol) was added to the sonicating mixture at 5 °C over 2 h. Ultrasound irradiation was continued at 5 °C for 6 days, with addition of zinc powder (35 mg, 0.54 mmol), copper(I) iodide (31 mg, 0.16 mmol) and 65% aq. MeOH (4 mL) at 8 h intervals. The reaction was quenched by dropwise addition of aq. NH_4Cl and the mixture was filtered through a pad of Celite®. The filter cake was washed with EtOAc (3 × 100 mL) and the filtrate was concentrated under reduced pressure. The residue was taken up in Et_2O (30 mL) and the solution was washed with H_2O (1 × 20 mL). The aqueous phase was separated and extracted with Et_2O (3 × 10 mL). The combined organic solution was washed with aq. $Na_2S_2O_4$ (1 × 30 mL), H_2O (1 × 30 mL) and brine (1 × 30 mL), dried (anhydrous $MgSO_4$) and evaporated *in vacuo*. Flash column chromatography of the residue, eluting with hexanes-Et_2O (17:3) afforded the *title compounds* ***214a*** (13 mg, 20%) and ***214b*** (16 mg, 25%) as colourless oils.

Compound 214a

^{1}H NMR (300 MHz) δ 1.00-1.50 (m, 6H, 3 × CH_2), 1.60-1.94 (m, 4H, 2 × CH_2), 1.97-2.09 (m, 1H), 2.22 (s, 6H, *o,o'*-MesCH_3), 2.27 (s, 3H, *p*-MesCH_3), 3.53 (s, 3H, CH_3O), 4.18 (d, *J* = 10.5 Hz, 1H, H4), 4.83 (dd, *J* = 10.5, 7.3 Hz, 1H, H5), 6.86 (s, 2H, 2 × MesH).

^{13}C NMR (75.4 MHz) δ 20.0 (2 × CH_3), 21.1 (CH_3), 25.6 (CH_2), 25.8 (CH_2), 26.3 (CH_2), 28.4 (CH_2), 29.0 (CH_2), 41.6 (CH), 52.6 (CH_3O), 59.1 (C4), 89.1 (C5), 124.6 (C), 128.5 (2 × CH), 136.9 (2 × C), 138.7 (C), 153.8 (C3), 169.1 (C=O).

IR (KBr, thin film) ν_{max} 2925, 2853, 1742, 1611, 1449, 1378, 1309, 1275, 1208, 1171, 1032, 999, 906, 886, 851, 782, 576 cm^{-1}.

LRMS (EI) *m/z* (%) 329 ($M^{\bullet+}$, 45), 270 ($M^{\bullet+}$-CH_3O_2C, 2), 246 ($M^{\bullet+}$-C_6H_{11}, 100), 218 (31), 202 (4), 186 (67), 158 (34), 145 (20), 130 (25), 119 (24), 101 (12), 91 (25), 67 (8).

HRMS (EI) Found: $M^{\bullet+}$, 329.199350. $C_{20}H_{27}NO_3$ requires $M^{\bullet+}$, 329.199094.

Elemental Analysis Found: C, 72.73; H, 8.24; N, 4.23. $C_{20}H_{27}NO_3$ requires C, 72.92; H, 8.26; N, 4.25.

Compound 214b

^{1}H NMR (300 MHz) δ 1.00-1.40 (m, 6H, 3 × CH_2), 1.58-1.87 (m, 4H, 2 × CH_2), 1.88-2.09 (m, 1H), 2.27 (s, 6H, *o,o'*-MesCH_3), 2.31 (s, 3H, *p*-MesCH_3), 3.64 (s, 3H, CH_3O), 4.15 (d, *J* = 9.5 Hz, 1H, H4), 4.43 (app. t, *J* = 9.5 Hz, 1H, H5), 6.88 (s, 2H, 2 × MesH).

^{13}C NMR (75.4 MHz) δ 20.1 (2 × CH_3), 21.1 (CH_3), 25.4 (CH_2), 25.7 (CH_2), 26.2 (CH_2), 30.1 (CH_2), 30.3 (CH_2), 37.9 (CH), 52.1 (CH_3O), 58.2 (C4), 88.5 (C5), 124.9 (C), 128.7 (2 × CH), 137.0 (2 × C), 138.9 (C), 155.7 (C3), 167.7 (C=O).

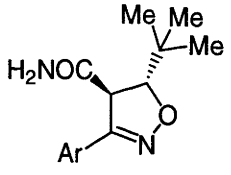
IR (KBr, thin film) ν_{max} 2925, 2853, 1740, 1611, 1450, 1434, 1311, 1245, 1202, 1173, 1152, 1034, 888, 850 cm^{-1}.

LRMS (EI) *m/z* (%) 329 ($M^{\bullet+}$, 51), 312 (2), 270 ($M^{\bullet+}$-CH_3O_2C, 6), 246 ($M^{\bullet+}$-C_6H_{11}, 100), 201 (5), 186 (79), 168 (10), 158 (66), 145 (25), 130 (30), 119 (22), 103 (11), 91 (30), 67 (10).

HRMS (EI) Found: $M^{\bullet+}$, 329.199025. $C_{20}H_{27}NO_3$ requires $M^{\bullet+}$, 329.199094.

Elemental Analysis Found: C, 72.75; H, 8.30; N, 4.21. $C_{20}H_{27}NO_3$ requires C, 72.92; H, 8.26; N, 4.25.

***trans*-5-*tert*-Butyl-3-(2,4,6-trimethylphenyl)-Δ^2-isoxazoline-4-carboxylic Acid Amide 215**



rac.
215

Ar = 2,4,6-Me_3Ph

A suspension of zinc powder (38 mg, 0.59 mmol) and copper(I) iodide (33 mg, 0.17 mmol) in a 65% aq. MeOH (3 mL) was sonicated for 5-10 min, until the suspension turned black. After 3-(2,4,6-trimethylphenyl)isoxazole-4-carboxylic acid amide **167** (50.0 mg, 0.217 mmol) was added, *tert*-butyl iodide **207** (75 μL, 0.65 mmol) was added to the sonicating mixture at 5 °C over 2 h. Ultrasonic irradiation was continued at 5 °C for 48 h, with addition of zinc powder (38 mg, 0.59 mmol), copper(I) iodide (33 mg, 0.17 mmol), *tert*-butyl iodide **207** (75 μL, 0.65 mmol) and 65% aq. MeOH (3 mL) at 8 h intervals. The reaction mixture was quenched by addition of aq. NH_4Cl (1 mL) and filtered through a pad of Celite®. The filter cake was washed with EtOAc (3 × 100 mL) and the filtrate was concentrated under reduced pressure. The residue was taken up in EtOAc (30 mL) and the solution was washed with H_2O (1 × 20 mL). The aqueous phase was separated and extracted with EtOAc (3 × 10 mL). The combined organic solution was washed with aq. $Na_2S_2O_4$ (1 × 30 mL), H_2O (1 × 30 mL) and brine (1 × 30 mL), dried (anhydrous $MgSO_4$) and evaporated *in vacuo*. Flash column chromatography of

the residue, eluting with hexanes-EtOAc (7:3) afforded the *title compound* ***215*** (61 mg, 97%) as a colourless solid, mp 143-146 °C.

^{1}H NMR (300 MHz) δ 1.02 [s, 9H, $(CH_3)_3C$], 2.24 (s, 6H, *o*,*o*'-MesCH_3), 2.28 (s, 3H, *p*-MesCH_3), 3.96 (d, J = 10.1 Hz, 1H, H4), 4.20 (br s, 1H NH), 5.02 (d, J = 10.1 Hz, 1H, H5), 6.00 (br s, 1H, NH), 6.89 (s, 2H, 2 × MesH).

^{13}C NMR (75.4 MHz) δ 20.1 (2 × CH_3), 21.2 (CH_3), 25.4 [($\underline{C}H_3)_3C$], 33.7 [$(CH_3)_3\underline{C}$], 58.0 (C4), 91.6 (C5), 124.9 (C), 128.8 (2 × CH), 137.2 (2 × C), 139.1 (C), 152.9 (C3), 168.7 (C=O).

IR (KBr, thin film) ν_{max} 3369, 3175, 1693, 1601, 1400, 1365, 1349, 1307, 1247, 1039, 895, 845, 728 cm^{-1}.

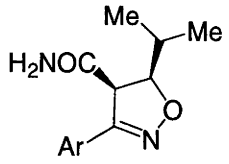
LRMS (EI) *m/z* (%) 288 ($M^{\bullet+}$, 14), 255 (2), 231 [$M^{\bullet+}$-$(CH_3)_3C$, 24], 214 (14), 203 (17), 185 (39), 146 (30), 130 (20), 119 ($M^{\bullet+}$-$C_8H_{13}N_2O_2$, 16), 103 (8), 86 (100), 77 (12), 65 (5), 57 ($M^{\bullet+}$-$C_{13}H_{15}N_2O_2$, 37).

HRMS (EI) Found: $M^{\bullet+}$, 288.184254. $C_{17}H_{24}N_2O_2$ requires $M^{\bullet+}$, 288.183778.

Elemental Analysis Found: C, 70.76; H, 8.32; N, 9.70. $C_{17}H_{24}N_2O_2$ requires C, 70.80; H, 8.39; N, 9.71.

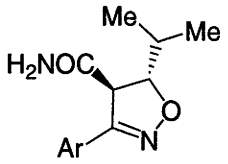
cis-5-Isopropyl-3-(2,4,6-trimethylphenyl)-Δ^2-isoxazoline-4-carboxylic Acid Amide 216a and

trans-5-Isopropyl-3-(2,4,6-trimethylphenyl)-Δ^2-isoxazoline-4-carboxylic Acid Amide 216b



rac.

216a



rac.

216b

Ar = 2,4,6-Me_3Ph

A suspension of zinc powder (38 mg, 0.59 mmol) and copper(I) iodide (33 mg, 0.17 mmol) in a 65% aq. MeOH (3 mL) was sonicated for 5-10 min, until the suspension turned black. After 3-(2,4,6-trimethylphenyl)isoxazole-4-carboxylic acid amide **167** (50.0 mg, 0.217 mmol) was added, isopropyl iodide **185** (65 μL, 0.65 mmol) was added to the sonicating mixture at 5 °C over 2 h. Ultrasonic irradiation was continued at 5 °C for 12 days with addition of zinc powder (38 mg, 0.59 mmol), copper(I) iodide (33 mg, 0.17 mmol), isopropyl iodide **185** (65 μL, 0.65 mmol) and 65% aq. MeOH (3 mL) at 12 h intervals. The reaction mixture was quenched by addition of aq. NH_4Cl (1 mL) and filtered through a pad of Celite®. The filter cake was washed with EtOAc (3 × 100 mL) and the filtrate was concentrated under reduced pressure. The residue was taken up in EtOAc (30 mL) and the solution was washed with H_2O (1 × 20 mL). The aqueous phase was separated and extracted with EtOAc (3 × 10 mL). The combined organic solution was washed with aq. $Na_2S_2O_4$ (1 × 30 mL), H_2O (1 × 30 mL) and brine (1 × 30 mL), dried (anhydrous $MgSO_4$) and evaporated *in vacuo*. Flash column chromatography of the residue, eluting with CH_2Cl_2-Et_2O (9:1) afforded the *title compound **216*** as an inseparable mixture (45 mg, 75%) of *cis-trans* isomers in a ratio of 1:2 respectively.

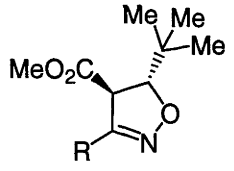
***cis*-Isomer 216a**

^{1}H NMR (300 MHz) δ 1.04 [d, J = 6.6 Hz, 3H, $(C\underline{H}_3)_2CH$], 1.20 [d, J = 6.6 Hz, 3H, $(C\underline{H}_3)_2CH$], 2.28 [m, 1H, $(CH_3)_2C\underline{H}$], 2.33 (s, 6H, *o,o'*-MesCH_3), 2.46 (s, 3H, *p*-MesCH_3), 3.88 (d, J = 10.4 Hz, 1H, H4), 4.35 (dd, J = 10.4, 8.1 Hz, 1H, H5), 5.57 (br s, 1H, NH), 5.77 (br s, 1H, NH), 6.89 (s, 2H, 2 × MesH).

***trans*-Isomer 216b**

^{1}H NMR (300 MHz) δ 1.00 [d, J = 6.7 Hz, 3H, $(C\underline{H}_3)_2CH$], 1.08 [d, J = 6.7 Hz, 3H, $(C\underline{H}_3)_2CH$], 2.03 [m, 1H, $(CH_3)_2C\underline{H}$], 2.26 (s, 6H, *o,o'*-MesCH_3), 2.29 (s, 3H, *p*-MesCH_3), 3.92 (d, J = 9.0 Hz, 1H, H4), 5.01 (dd, J = 9.0, 6.9 Hz, 1H, H5), 5.02 (br s, 1H, NH), 5.27 (br s, 1H, NH), 6.90 (s, 2H, 2 × MesH).

***trans*-5-*tert*-Butyl-3-nonyl-Δ^2-isoxazoline-4-carboxylic Acid Methyl Ester 217**



rac.

217

R = $(CH_2)_8CH_3$

A suspension of zinc powder (35 mg, 0.54 mmol) and copper(I) iodide (31 mg, 0.16 mmol) in a 65% aq. MeOH (3 mL) was sonicated at 5 °C for 5-10 min, until the suspension turned black. After 3-nonylisoxazole-4-carboxylic acid methyl ester **111** (52.0 mg, 0.204 mmol) was added, *tert*-butyl iodide **207** (72 μL, 0.60 mmol) was added to the sonicating mixture at 5 °C over 2 h. Ultrasound irradiation was continued at 5 °C for a further 9 h. The reaction was quenched by the addition of aq. NH_4Cl (1 mL) and

the mixture was filtered through a pad of Celite®. The filter cake was washed with EtOAc (3 × 100 mL) and the filtrate was concentrated under reduced pressure. The residue was taken up in Et_2O (30 mL) and the solution was washed with H_2O (1 × 20 mL). The aqueous phase was separated and extracted with Et_2O (3 × 10 mL). The combined organic solution was washed with aq. $Na_2S_2O_4$ (1 × 30 mL), H_2O (1 × 30 mL) and brine (1 × 30 mL), dried (anhydrous $MgSO_4$) and evaporated *in vacuo*. Flash column chromatography of the residue, eluting with hexanes-Et_2O (17:3) afforded the *title compound **217*** (60 mg, 95%) as a colourless oil.

^{1}H NMR (300 MHz) δ 0.88 (t, J = 6.8 Hz, 3H, $C\underline{H}_3CH_2$), 0.91 [m, 9H, $(CH_3)_3C$], 1.20-1.38 (m, 12H, 6 × CH_2), 1.42-1.68 (m, 2H, CH_2), 2.18-2.32 (m, 1H, CH_2), 2.33-2.48 (m, 1H, CH_2), 3.76 (s, 3H, CH_3O), 3.77 (d, J = 8.4 Hz, 1H, H4), 4.54 (d, J = 8.4 Hz, 1H, H5).

^{13}C NMR (75.4 MHz) δ 14.2 (CH_3), 22.7 (CH_2), 25.0 [$(\underline{C}H_3)_3C$], 26.1 (CH_2), 26.9 (CH_2), 29.1 (CH_2), 29.2 (CH_2), 29.3 (CH_2), 29.5 (CH_2), 31.9 (CH_2), 34.1 [$(CH_3)_3\underline{C}$], 52.8 (CH_3O), 56.0 (C4), 91.8 (C5), 154.8 (C3), 169.8 (C=O).

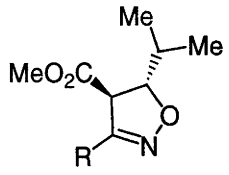
IR (KBr, thin film) ν_{max} 2955, 2926, 2855, 1743, 1466, 1435, 1366, 1292, 1164, 1026, 907 cm^{-1}.

LRMS (EI) *m/z* (%) 311 ($M^{\bullet+}$, 34), 282 (3), 268 (7), 254 [$M^{\bullet+}$-$(CH_3)_3C$, 40], 236 (3), 226 (23), 212 (34), 199 (66), 182 (7), 167 (5), 154 (25), 141 (22), 128 (13), 110 (8), 100 (24), 85 (31), 72 (42), 57 ($M^{\bullet+}$-$C_{14}H_{24}NO_3$, 100).

HRMS (EI) Found: $M^{\bullet+}$, 311.246163. $C_{18}H_{33}NO_3$ requires $M^{\bullet+}$, 311.246044.

Elemental Analysis Found: C, 69.26; H, 10.61; N, 4.56. $C_{18}H_{33}NO_3$ requires C, 69.41; H, 10.68; N, 4.50.

***trans*-5-Isopropyl-3-nonyl-Δ^2-isoxazoline-4-carboxylic Acid Methyl Ester 218**



rac.
218

R = $(CH_2)_8CH_3$

A suspension of zinc powder (35 mg, 0.54 mmol) and copper(I) iodide (31 mg, 0.16 mmol) in a 65% aq. MeOH (3 mL) was sonicated for 5-10 min, until the suspension turned black. After 3-nonylisoxazole-4-carboxylic acid methyl ester **111** (52.0 mg, 0.204 mmol) was added, isopropyl iodide **185** (60 μL, 0.60 mmol) was added to the sonicating mixture at 5 °C over 2 h. Ultrasound irradiation was continued at 5 °C for 2.5 days, with addition of zinc powder (35 mg, 0.54 mmol), copper(I) iodide (31 mg, 0.16 mmol), isopropyl iodide **185** (60 μL, 0.60 mmol) and 65% aq. MeOH (3 mL) at 8 h intervals. The reaction was quenched by addition of aq. NH_4Cl (1 mL) and filtered through a pad of Celite®. The filter cake was washed with EtOAc (3 × 100 mL) and the filtrate was concentrated under reduced pressure. The residue was taken up in Et_2O (30 mL) and the solution was washed with H_2O (1 × 20 mL). The aqueous phase was separated and extracted with Et_2O (3 × 10 mL). The combined organic solution was washed with aq. $Na_2S_2O_4$ (1 × 30 mL), H_2O (1 × 30 mL) and brine (1 × 30 mL), dried (anhydrous $MgSO_4$) and evaporated *in vacuo*. Flash column chromatography of the residue, eluting with hexanes-Et_2O (17:3) afforded the *title compound **218*** (44 mg, 74%) as a colourless oil.

^{1}H NMR (300 MHz) δ 0.88 (t, J = 6.9 Hz, 3H, $C\underline{H}_3CH_2$), 0.91 [d, J = 6.8 Hz, 3H, $(C\underline{H}_3)_2CH$], 0.97 [d, J = 6.8 Hz, 3H, $(C\underline{H}_3)_2CH$], 1.18-1.38 (m, 12H, 6 × CH_2), 1.42-1.64

(m, 2H, CH_2), 1.87 [m, 1H, $(CH_3)_2C\underline{H}$], 2.26 (m, 1H, CH_2), 2.42 (m, 1H, CH_2), 3.74 (d, J = 8.2 Hz, 1H, H4), 3.77 (s, 3H, CH_3O), 4.59 (dd, J = 8.2, 6.6 Hz, 1H, H5).

^{13}C NMR (75.4 MHz) δ 14.2 [$(CH_3)_3C$], 17.7 [$(CH_3)_2CH$], 17.9 [$(CH_3)_2CH$], 22.7 (CH_2), 26.2 (CH_2), 27.0 (CH_2), 29.1 (CH_2), 29.2 (CH_2), 29.3 (CH_2), 29.5 (CH_2), 31.9 (CH_2), 32.9 (CH), 52.8 (CH_3O), 57.6 (C4), 88.9 (C5), 155.1 (C3), 169.6 (C=O).

IR (KBr, thin film) ν_{max} 2956, 2926, 2855, 1743, 1466, 1435, 1369, 1267, 1201, 1167, 1027, 905 cm^{-1}.

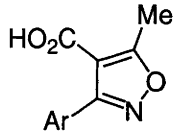
LRMS (EI) *m/z* (%) 297 ($M^{\bullet+}$, 19), 268 (3), 254 [$M^{\bullet+}$-$(CH_3)_2CH$, 65], 240 (5), 226 (10), 210 (3), 198 (53), 185 (100), 168 (11), 154 (13), 141 (11), 126 (19), 110 (9), 101 (30), 85 (21), 71 (37), 57 (42).

HRMS (EI) Found: $M^{\bullet+}$, 297.231111. $C_{17}H_{31}NO_3$ requires $M^{\bullet+}$, 297.230394.

Elemental Analysis Found: C, 68.43; H, 10.48; N, 4.73. $C_{17}H_{31}NO_3$ requires C, 68.65; H, 10.51; N, 4.68.

7.5. Experimental for Chapter 5

5-Methyl-3-(2,4,6-trimethylphenyl)isoxazole-4-carboxylic Acid 240



240

Ar = 2,4,6-Me_3Ph

A mixture of 2-butynoic acid **239** (417 mg, 4.96 mmol) and mesitonitrile oxide **5** (800 mg, 4.96 mmol) in dry THF (55 mL) was heated at reflux for 2 days. After the solvent was removed under reduced pressure, the residue was taken up in Et_2O (60 mL) and the solution was washed with H_2O (1 × 40 mL). The aqueous phase was separated and extracted with Et_2O (3 × 50 mL). The combined organic solution was washed with brine (1 × 40 mL), dried (anhydrous Na_2SO_4) and evaporated *in vacuo*. The residue was recrystallized from a mixture of hexanes and Et_2O to give the *title compound **240*** (1.18 g, 97%) as a colourless solid, mp 205-207 °C.

^{1}H NMR (300 MHz) δ 2.02 (br s, 1H, OH), 2.08 (s, 6H, *o,o'*-MesCH_3), 2.34 (s, 3H, *p*-MesCH_3), 2.80 (s, 3H, CH_3), 6.91 (s, 2H, 2 × MesH).

^{13}C NMR (75.4 MHz) δ 13.8 (CH_3), 19.9 (2 × CH_3), 21.2 (CH_3), 108.5 (C4), 124.8 (C), 128.1 (2 × CH), 136.9 (2 × C), 138.8 (C), 161.8 (C3), 166.8 (C5), 177.5 (C=O).

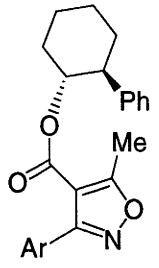
IR (KBr, thin film) ν_{max} 2922, 1688, 1595, 1453, 1313, 1145, 1093, 1035, 979, 944, 849, 796, 772, 735 cm^{-1}.

LRMS (EI) *m/z* (%) 245 ($M^{\bullet+}$, 100), 228 ($M^{\bullet+}$-OH, 9), 212 ($M^{\bullet+}$-O_2H, 32), 201 (17), 186 (52), 170 (15), 158 (77), 142 (10), 128 (10), 115 (19), 103 (11), 91 (27), 77 (21), 65 (9).

HRMS (EI) Found: $M^{\bullet+}$, 245.105077. $C_{14}H_{15}NO_3$ requires $M^{\bullet+}$, 245.105194.

Elemental Analysis Found: C, 68.31; H, 6.21; N, 5.69. $C_{14}H_{15}NO_3$ requires C, 68.56; H, 6.16; N, 5.71.

5-Methyl-3-(2,4,6-trimethylphenyl)isoxazole-4-carboxylic Acid (1*R*,2*S*)-2-Phenyl-1-cyclohexyl Ester 241



241

Ar = 2,4,6-Me_3Ph

A solution of (-)-(1*R*,2*S*)-2-phenyl-1-cyclohexanol **236** (187 mg, 1.06 mmol) and 5-methyl-3-(2,4,6-trimethylphenyl)isoxazole-4-carboxylic acid **240** (236 mg, 0.963 mmol) in dry Et_2O (10 mL) was cooled to 0-5 °C (ice bath). DMAP (12 mg, 0.096 mmol) was added and stirring was continued at 0-5 °C (ice bath) for 10 min, followed by the addition of DCC (219 mg, 1.06 mmol). After stirring for a further 48 h at 18 °C, the mixture was diluted with Et_2O (50 mL) and filtered through a pad of Celite®. The filter cake was washed with Et_2O (6 × 100 mL) and the combined filtrate was evaporated under reduced pressure to *ca.* 100 mL. The solution was washed with 1M HCl (3 × 75 mL), aq. $NaHCO_3$ (2 × 50 mL), H_2O (1 × 50 mL) and brine (1 × 50 mL), dried (anhydrous $MgSO_4$) and evaporated *in vacuo*. Flash column chromatography of the residue, eluting with hexanes-Et_2O (3.7:0.3) afforded the *title compound **241*** (338 mg, 87%) as a colourless oil.

^{1}H NMR (300 MHz) δ 1.10-2.60 (complex m, 9H, 4 × CH_2 and C<u>H</u>Ph), 1.73 (s, 3H, *o*-MesCH_3), 1.95 (s, 3H, *o*'-MesCH_3), 2.37 (s, 3H, *p*-MesCH_3), 2.59 (s, 3H, CH_3), 5.05 (td, *J* = 10.6, 4.6 Hz, 1H, CO_2CH), 6.86-6.97 (m, 4H, 2 × MesH and 2 × PhH), 7.10-7.23 (m, 3H, 3 × PhH).

^{13}C NMR (75.4 MHz) δ 13.3 (CH_3), 19.8 (CH_3), 19.9 (CH_3), 21.3 (CH_3), 24.6 (CH_2), 25.7 (CH_2), 32.1 (CH_2), 34.5 (CH_2), 49.3 (CHPh), 75.5 (CO_2CH), 109.1 (C4), 125.6 (C), 126.3 (CH), 127.2 (CH), 127.4 (CH), 127.6 (CH), 128.1 (CH), 128.2 (CH), 128.3 (CH), 136.7 (C), 136.8 (C), 138.3 (C), 142.5 (C), 153.0 (C3), 161.1 (C5), 161.6 (C=O).

IR (KBr, thin film) ν_{max} 2929, 1716, 1611, 1434, 1308, 1296, 1285, 1181, 1134, 1096, 1070, 1033, 1016, 980, 851, 790 cm^{-1}.

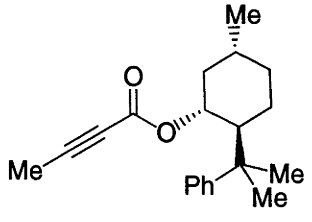
LRMS (EI) *m/z* (%) 403 ($M^{\bullet+}$, 13), 273 (1), 246 (37), 228 ($M^{\bullet+}$-$C_{12}H_{15}O$, 21), 212 (17), 201 (13), 186 (59), 171 (6), 158 (100), 129 (13), 117 (20), 104 (8), 91 (85), 67 (9).

HRMS (EI) Found: $M^{\bullet+}$, 403.215060. $C_{26}H_{29}NO_3$ requires $M^{\bullet+}$, 403.214744.

Elemental Analysis Found: C, 77.16; H, 7.28; N, 3.46. $C_{26}H_{29}NO_3$ requires C, 77.39; H, 7.24; N, 3.47.

Specific Rotation $[\alpha]_D$ -53.3 (*c* 0.9, $CHCl_3$).

But-2-ynoic Acid (1*R*,2*S*,5*R*)-5-Methyl-2-(1'-methyl-1'-phenylethyl)-1-cyclohexyl Ester 244



244

DMAP (21 mg, 0.18 mmol) was added to a stirred mixture of (-)-8-phenylmenthol **237** (455 mg, 1.96 mmol) and 2-butynoic acid **239** (150 mg, 1.78 mmol) in Et_2O (15 mL) at 0-5 °C (ice bath). After 10 min, DCC (404 mg, 1.96 mmol) was added and stirring was continued at 18 °C for a further 48 h. The mixture was diluted with Et_2O (50 mL) and filtered through a pad of Celite®. The filter cake was washed with Et_2O (6 × 100 mL) and the combined filtrate was evaporated under reduced

pressure to *ca.* 50 mL. The solution was washed with 1M HCl (3 × 30 mL), aq. $NaHCO_3$ (2 × 30 mL), H_2O (1 × 30 mL) and brine (1 × 30 mL), dried (anhydrous $MgSO_4$) and evaporated *in vacuo*. Flash column chromatography, eluting with hexanes-Et_2O (3.7:0.3) afforded the *title compound* ***244*** (456 mg, 86%) as a colourless solid, mp 53-55 °C [lit.[183] mp 53-55 °C].

^{1}H NMR (300 MHz) δ 0.85 (d, J = 6.8 Hz, 3H, $C\underline{H}_3CH$), 0.90-1.10 (m, 4H, 2 × CH_2), 1.26 (m, 3H, CH_2 and $CH_3C\underline{H}$), 1.35 (s, 3H, CH_3), 1.55 (s, 3H, CH_3), 1.89 (s, 3H, $C{\equiv}CCH_3$), 1.90-2.10 (m, 1H, $C\underline{H}C(CH_3)_2Ph$), 4.85 (td, J = 11.4, 4.5 Hz, 1H, CO_2CH), 7.10-7.30 (m, 5H, 5 × PhH).

^{13}C NMR (75.4 MHz) δ 4.6 ($\underline{C}H_3CH$), 22.6 [$CHC(\underline{C}H_3)_2Ph$], 27.2 [$CHC(\underline{C}H_3)_2Ph$], 27.7 ($CH_2$), 27.8 ($\underline{C}H_3C{\equiv}C$), 32.2 ($CH_3\underline{C}H$), 35.2 ($CH_2$), 40.8 [$CH\underline{C}(CH_3)_2Ph$], 42.4 ($CH_2$), 51.4 [$\underline{C}HC(CH_3)_2Ph$], 73.9 ($C{\equiv}\underline{C}CH_3$), 77.0 ($CO_2\underline{C}H$), 86.0 ($\underline{C}{\equiv}CCH_3$), 126.0 (CH), 126.4 (2 × CH), 128.9 (2 × CH), 151.6 (C), 154.0 (C=O).

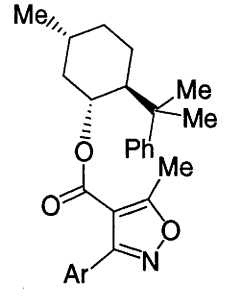
IR (KBr, thin film) ν_{max} 3390, 2954, 2922, 2871, 2243, 1702, 1600, 1495, 1455, 1443, 1288, 1258, 1065, 1031, 976, 763, 750, 700 cm^{-1}.

LRMS (EI) *m/z* (%) 298 ($M^{\bullet+}$, 2), 246 (1), 214 (13), 199 (3), 179 [$M^{\bullet+}$-$(CH_3)_2CPh$, 6], 132 (4), 119 (100), 105 (12), 91 (41), 67 (43).

Specific Rotation $[\alpha]_D$ = +10.5 (*c* 3.3, $CHCl_3$).

The ^{1}H and ^{13}C NMR data, and optical rotation of compound **244** are consistent with literature values.[183]

5-Methyl-3-(2,4,6-trimethylphenyl)isoxazole-4-carboxylic Acid (1*R*,2*S*,5*R*)-5-Methyl-2-(1'-methyl-1'-phenylethyl)-1-cyclohexyl Ester 245



245

Ar = 2,4,6-Me_3Ph

A mixture of but-2-ynoic acid (1*R*,2*S*,5*R*)-5-methyl-2-(1'-methyl-1'-phenylethyl)-1-cyclohexyl ester **244** (456 mg, 1.53 mmol) and mesitonitrile oxide **5** (246 mg, 1.53 mmol) in dry THF (25 mL) was heated at reflux for 5 days. After the solvent was removed by reduced pressure, the residue was taken up in Et_2O (50 mL) and the solution was washed with H_2O (35 mL). The aqueous layer was separated and extracted with Et_2O (30 mL). The combined organic solution was washed with brine (1 × 25 mL), dried (anhydrous $MgSO_4$) and evaporated *in vacuo*. Flash column chromatography of the residue, eluting with hexanes-CH_2Cl_2 (3:2) afforded the *title compound **245*** (654 mg, 93%) as a colourless oil.

^{1}H NMR (300 MHz) δ 0.85 (d, J = 6.6 Hz, 3H, C$\underline{H}_3$CH), 1.06 (m, 1H), 1.08 [s, 3H, C(C$\underline{H}_3$)$_2$Ph], 1.17 [s, 3H, C(C$\underline{H}_3$)$_2$Ph], 1.24-1.60 (m, 4H, 2 × CH_2), 1.72 (td, J = 11.4, 4.1 Hz, 1H, C$\underline{H}$C(CH$_3$)$_2$Ph), 1.77-1.88 (m, 2H, CH_2), 2.04 (s, 3H, *o*-MesCH$_3$), 2.11 (s, 3H, *o*'-MesCH$_3$), 2.36 (s, 3H, *p*-MesCH$_3$), 2.43 (s, 3H, CH$_3$), 4.98 (td, J = 10.7, 4.1 Hz, 1H, CHO), 6.94 (s, 1H, MesH), 6.96 (s, 1H, MesH), 7.07-7.17 (m, 3H, 3 × PhH), 7.19-7.24 (m, 2H, 2 × Ph).

^{13}C NMR (75.4 MHz) δ 13.2 (CH$_3$), 19.9 (CH$_3$), 20.0 (CH$_3$), 21.1 (CH$_3$), 21.6 (CH$_3$), 25.6 (CH), 26.6 (CH_2), 26.8 (CH$_3$), 31.1 (CH$_3$), 34.1 (CH_2), 39.7 (CH_2), 41.9

[C(CH$_3$)$_2$Ph], 50.2 [CHC(CH$_3$)$_2$Ph], 74.3 (CO$_2$CH), 109.3 (C4), 125.1 (CH), 125.3 (2 × CH), 127.8 (3 × CH), 128.0 (CH), 136.6 (C), 136.7 (C), 138.7 (2 × C), 151.1 (C), 160.8 (C3), 161.7 (C5), 175.3 (C=O).

IR (KBr, thin film) ν_{max} 2953, 2922, 2869, 1712, 1599, 1436, 1307, 1136, 1089, 986, 849, 700 cm^{-1}.

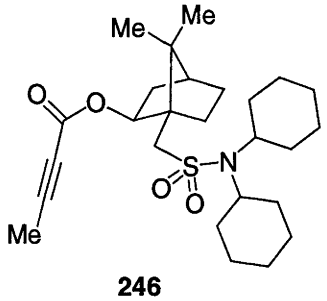
LRMS (EI) *m/z* (%) 459 (M$^{\bullet+}$, 7), 341 (9), 246 (74), 228 (M$^{\bullet+}$-C$_{16}$H$_{23}$O, 8), 214 (2), 201 (6), 186 (31), 158 (22), 119 (M$^{\bullet+}$-C$_{21}$H$_{26}$NO$_3$, 100), 105 (38), 91 (48).

HRMS (EI) Found: M$^{\bullet+}$, 459.277894. C$_{30}$H$_{37}$NO$_3$ requires M$^{\bullet+}$, 459.277344.

Elemental Analysis Found: C, 78.58; H, 8.05; N, 3.01. C$_{30}$H$_{37}$NO$_3$ requires C, 78.40; H, 8.11; N, 3.05.

Specific Rotation $[\alpha]_D$ –40.4 (*c* 0.6, CHCl$_3$).

But-2-ynoic Acid (1*R*,2*S*)-[1-(Dicyclohexylsulfamoyl)methyl]-7,7'-dimethyl-bicyclo[2.2.1]-hept-2-yl Ester 246



246

Trimethylaluminium (0.35 mL of a 2M solution in hexanes, 0.69 mmol) was added dropwise to a solution of methyl tetrolate **17a** (56 mg, 0.57 mmol) in dry toluene (3 mL) at 18 °C. After stirring for 20 min at 18 °C, a solution of (+)-dicyclohexylsulfamoyl-L-isoborneol **238** (250 mg, 0.630 mmol) in dry toluene (0.5 mL) was added and the mixture was heated at reflux for 3 days. After cooling to 0-5 °C (ice bath), the reaction was quenched by addition of aq. NH$_4$Cl (1 mL). The solvent was

evaporated under reduced pressure, the residue was taken up in EtOAc (50 mL) and the solution was washed with H_2O (30 mL). The aqueous layer was separated and extracted with EtOAc (3 × 30 mL). The combined organic solution was washed with brine (30 mL), dried (anhydrous Na_2SO_4) and concentrated *in vacuo*. Flash column chromatography of the residue, eluting with hexanes-Et_2O (17:3) afforded the *title compound* ***246*** (252 mg, 95%) as a colourless solid, mp 132-134 °C.

^{1}H NMR (300 MHz) δ 0.87 (s, 3H, CH_3), 0.99 (s, 3H, CH_3), 1.01-1.40 (complex m, 7H, 3 × CH_2 and CH), 1.50-1.62 (complex m, 2H, CH_2), 1.65-1.84 (complex m, 16H, 8 × CH_2), 1.85-2.04 (complex m, 2H, CH_2), 1.92 (s, 3H, C≡CCH_3), 2.64 (d, J = 13.3 Hz, 1H, CH_2S), 3.15-3.35 (complex m, 2H, 2 × NCH), 3.27 (d, J = 13.3 Hz, 1H, CH_2S), 5.04 (dd, J = 7.9, 3.0 Hz, 1H, CO_2CH).

^{13}C NMR (75.4 MHz) δ 15.0 (CH_3), 20.0 (CH_3), 20.4 (CH_3), 25.0 (3 × CH_2), 25.2 (2 × CH_2), 25.8 (CH_2), 26.4 (CH_2), 26.5 (CH_2), 29.8 (CH_2), 32.5 (CH_2), 32.7 (CH_2), 32.9 (CH_2), 39.2 (CH_2), 44.4 (CH, bridgehead), 49.0 (C, bridgehead), 49.3 (C, bridgehead), 53.3 (CH_2S), 57.6 (2 × NCH), 73.1 (C≡$\underline{C}CH_3$), 79.8 ($CO_2\underline{C}H$), 84.1 ($\underline{C}$≡CCH_3), 151.3 (C=O).

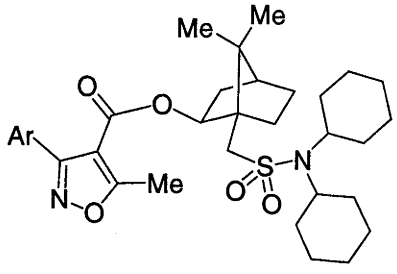
IR (KBr, thin film) ν_{max} 2929, 2854, 1708, 1452, 1325, 1258, 1165, 1143, 1110, 1048, 982, 854, 824 cm^{-1}.

LRMS (EI) *m/z* (%) 463 ($M^{\bullet+}$, 11), 420 (3), 315 (3), 298 (32), 272 (7), 244 ($M^{\bullet+}$-$C_{14}H_{19}O_2$, 27), 216 (5), 180 (36), 153 (8), 135 (44), 110 (6), 93 (24).

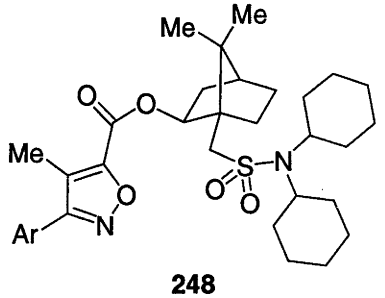
HRMS (EI) Found: $M^{\bullet+}$, 463.274606. $C_{26}H_{41}NO_4S$ requires $M^{\bullet+}$, 463.275631.

Specific Rotation $[\alpha]_D$ +16.2 (*c* 0.12, $CHCl_3$).

5-Methyl-3-(2,4,6-trimethylphenyl)isoxazole-4-carboxylic Acid (1*R*,2*S*)-[1-(Dicyclohexylsulfamoyl)methyl]-7,7'-dimethyl-bicyclo[2.2.1]hept-2-yl Ester 247 and 4-Methyl-3-(2,4,6-trimethylphenyl)isoxazole-5-carboxylic Acid (1*R*,2*S*)-[1-(Dicyclohexylsulfamoyl)methyl]-7,7'-dimethyl-bicyclo[2.2.1]hept-2-yl Ester 248



247



248

Ar = 2,4,6-Me_3Ph

A mixture of but-2-ynoic acid (1*R*,2*S*)-[1-(dicyclohexylsulfamoyl)methyl]-7,7'-dimethyl-bicyclo[2.2.1]-hept-2-yl ester **246** (222 mg, 0.479 mmol) and mesitonitrile oxide **5** (116 mg, 0.719 mmol) in dry THF (10 mL) was heated at reflux for 10 days. After the solvent was removed under reduced pressure, the residue was taken up in Et_2O (50 mL) and the solution was washed with H_2O (30 mL). The aqueous layer was separated and extracted with Et_2O (3 × 30 mL). The combined organic solution was washed with brine (30 mL), dried (anhydrous Na_2SO_4) and concentrated *in vacuo*. Flash column chromatography of the residue, eluting with hexanes-Et_2O (4:1) afforded the *title compounds **247*** (40 mg, 13%) as a colourless solid, mp 200-202 °C and ***248*** (242 mg, 81%) as a colourless solid, mp 205-208 °C.

Compound 247

^{1}H NMR (300 MHz) δ 0.95 (s, 3H, CH_3), 1.13 (s, 3H, CH_3), 1.00-1.40 (complex m, 7H, 3 × CH_2 and CH), 1.48-2.01 (complex m, 20H, 10 × CH_2), 2.01 (s, 3H, *o*-MesCH_3), 2.03 (s, 3H, *o*'-MesCH_3), 2.08 (s, 3H, *p*-MesCH_3), 2.33 (s, 3H, CH_3), 2.72 (d, J = 13.3 Hz, 1H, CH_2S), 3.22 (complex m, 2H, 2 × NCH), 3.53 (d, J = 13.3 Hz, 1H, CH_2S), 5.27 (dd, J = 7.8, 3.0 Hz, 1H, CO_2CH), 6.95 (s, 2H, 2 × MesH).

^{13}C NMR (75.4 MHz) δ 7.9 (CH_3), 19.8 (CH_3), 19.9 (CH_3), 20.2 (CH_3), 20.4 (CH_3), 21.1 (CH_3), 25.2 (2 × CH_2), 26.2 (CH_2), 26.3 (CH_2), 27.0 (CH_2), 29.6 (CH_2), 30.1 (CH_2), 32.5 (CH_2), 33.0 (3 × CH_2), 39.4 (2 × CH_2), 44.5 (CH, bridgehead), 49.2 (C, bridgehead), 49.5 (C, bridgehead), 53.3 (CH_2S), 57.4 (2 × NCH), 79.8 ($CO_2\underline{C}H$), 122.2 (C4), 124.2 (C), 128.3 (CH), 128.4 (CH), 137.1 (C), 137.3 (C), 139.3 (C), 155.6 (C3), 156.4 (C5), 164.3 (C=O).

IR (KBr, thin film) ν_{max} 2929, 2855, 1723, 1614, 1454, 1326, 1291, 1165, 1144, 1048, 982, 854, 776 cm^{-1}.

LRMS (EI) *m/z* (%) 624 ($M^{\bullet+}$, 15), 337 (25), 298 (12), 272 (7), 246 (42), 200 (34), 180 (100), 136 (37), 107 (15), 83 (22).

HRMS (EI) Found: $M^{\bullet+}$, 624.359467. $C_{36}H_{52}N_2O_5S$ requires $M^{\bullet+}$, 624.359695.

Specific Rotation $[\alpha]_D$ +27.7 (*c* 0.60, $CHCl_3$).

Compound 248

^{1}H NMR (300 MHz) δ 0.83 (s, 3H, CH_3), 0.88 (s, 3H, CH_3), 1.05-1.40 (complex m, 7H, 3 × CH_2 and CH) 1.50-1.84 (complex m, 18H, 9 × CH_2), 1.85-2.00 (complex m, 2H, CH_2), 2.04 (s, 3H, *o*'-MesCH_3), 2.12 (s, 3H, *o*-MesCH_3), 2.29 (s, 3H, *p*-MesCH_3), 2.63 (d, *J* = 13.3 Hz, 1H, CH_2S), 2.74 (s, 3H, CH_3), 3.05 (d, *J* = 13.3 Hz, 1H, CH_2S), 3.09-3.21 (m, 2H, 2 × NCH), 5.22 (dd, *J* = 8.0, 3.6 Hz, 1H, CO_2CH), 6.87 (s, 2H, 2 × MesH).

^{13}C NMR (75.4 MHz) δ 13.2 (CH_3), 19.6 (CH_3), 19.7 (CH_3), 19.9 (CH_3), 20.0 (CH_3), 20.9 (CH_3), 24.7 (CH_2), 24.9 (CH_2), 26.1 (3 × CH_2), 26.3 (CH_2), 26.7 (CH_2), 29.6 (CH_2), 30.5 (CH_2), 32.5 (2 × CH_2), 38.7 (CH_2), 39.0 (CH_2), 44.1 (CH, bridgehead), 48.6 (C, bridgehead), 49.3 (C, bridgehead), 53.6 (CH_2S), 57.2 (NCH), 57.3 (NCH), 78.2 ($CO_2\underline{C}H$), 110.1 (C4), 124.8 (C), 127.9 (CH), 128.0 (CH), 136.4 (C), 136.5 (C), 138.4 (C), 160.4 (C3), 161.7 (C=O), 173.1 (C5).

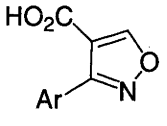
IR (KBr, thin film) ν_{max} 2931, 2856, 1725, 1613, 1452, 1326, 1255, 1165, 1143, 1144, 1048, 982, 853, 774, 643 cm^{-1}.

LRMS (EI) *m/z* (%) 624 ($M^{\bullet+}$, 2), 380 (100), 316 (16), 298 (22), 246 (36), 228 (96), 186 (72), 158 (24), 146 (12), 135 (100), 119 ($M^{\bullet+}$-$C_{27}H_{41}N_2O_5S$, 6), 107 (22), 93 (28), 83 (32), 67 (10).

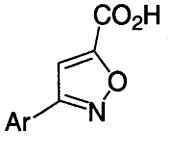
HRMS (EI) Found $M^{\bullet+}$, 624.359486. $C_{36}H_{52}N_2O_5S$ requires $M^{\bullet+}$, 624.359695.

Specific Rotation $[\alpha]_D$ +33.3 (*c* 0.60, $CHCl_3$).

3-(2,4,6-Trimethylphenyl)-4-isoxazole Carboxylic Acid 249 and 3-(2,4,6-Trimethylphenyl)-5-isoxazole Carboxylic Acid 250



249



250

Ar = 2,4,6-Me_3Ph

A mixture of mesitonitrile oxide **5** (1.00 g, 6.21 mmol) and propiolic acid **72** (435 mg, 6.21 mmol) in dry THF (60 mL) was heated at reflux for 48 h. After the solvent was removed by reduced pressure, the residue was taken up in Et_2O (100 mL) and the solution was washed with H_2O (70 mL). The aqueous layer was separated and extracted with Et_2O (2 × 50 mL). The combined organic solution was washed with brine (1 × 50 mL), dried (anhydrous Na_2SO_4) and filtered. The filtrate was evaporated *in vacuo* to afford the *title compounds **249*** and ***250*** as an inseparable mixture (total yield: 1.39 g, 97%) in a ratio of 1.3:1, respectively.

Compound 249

^{1}H NMR (300 MHz) δ 2.06 (s, 6H, *o,o*'-MesCH_3), 2.33 (s, 3H, *p*-MesCH_3), 6.94 (s, 2H, 2 × MesH), 8.40-9.10 (br s, 1H, OH), 9.16 (s, 1H, H5).

Compound 250

^{1}H NMR (300 MHz) δ 2.13 (s, 6H, *o*,*o*'- MesCH$_3$), 2.33 (s, 3H, *p*-MesCH$_3$), 6.96 (s, 2H, MesH), 6.98 (s, 1H, H4), 8.40-9.10 (br s, 1H, OH).

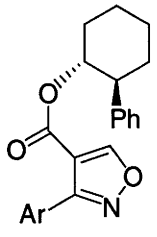
Compounds 249 and **250**

IR (KBr, thin film) ν_{max} 2924, 2361, 2338, 1700, 1652, 1576, 1506, 1457, 1295, 1140, 910, 851, 732, 667 cm^{-1}.

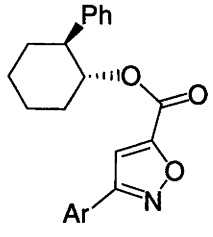
LRMS (EI) *m/z* (%) 231 ($M^{\bullet+}$, 100), 213 (5), 203 (10), 186 ($M^{\bullet+}$-CO_2H, 84), 170 (31), 158 (100), 144 (34), 130 (27), 115 (40), 103 (23), 91 (53), 77 (44), 65 (22).

HRMS (EI) Found: $M^{\bullet+}$, 231.089796. $C_{13}H_{13}NO_3$ requires $M^{\bullet+}$, 231.0289543.

3-(2,4,6-Trimethylphenyl)isoxazole-4-carboxylic Acid (1*R*,2*S*)-2-Phenyl-1-cyclohexyl Ester 251 and
3-(2,4,6-Trimethylphenyl)isoxazole-5-carboxylic Acid (1*R*,2*S*)-2-Phenyl-1-cyclohexyl Ester 252



251



252

Ar = 2,4,6-Me$_3$Ph

A solution of (-)-(1*R*,2*S*)-2-phenyl-1-cyclohexanol **236** (252 mg, 1.43 mmol) and a 1.3:1 mixture of 3-(2,4,6-trimethylphenyl)-4-isoxazole carboxylic acid **249** and 3-(2,4,6-trimethylphenyl)-5-isoxazole carboxylic acid **250** (300 mg, 1.30 mmol) in dry Et_2O (10 mL) was cooled to 0-5 °C (ice bath). DMAP (16 mg, 0.13 mmol) was added

and stirring was continued at 0-5 °C (ice bath) for 10 min, followed by addition of DCC (295 mg, 1.43 mmol). After the mixture was stirred at 18 °C for a further 2 days, it was diluted with Et_2O (50 mL) and filtered through a pad of Celite®. The filter cake was washed with Et_2O (6 × 100 mL) and the combined filtrate was evaporated under reduced pressure to *ca.* 100 mL. The solution was washed with 1M HCl (3 × 75 mL), aq. $NaHCO_3$ (2 × 75 mL), H_2O (1 × 75 mL) and brine (1 × 75 mL), dried (anhydrous $MgSO_4$) and evaporated *in vacuo*. Flash column chromatography of the residue, eluting with hexanes-Et_2O (37:3) afforded the *title compounds* ***251*** (252 mg, 50%) as colourless plates, after recrystallization from a mixture of hexanes and Et_2O at 18 °C, mp 119-121 °C; and ***252*** (193 mg, 38%) as a colourless oil.

Compound 251

^{1}H NMR (300 MHz) δ 1.10-1.66 (complex m, 4H, 2 × CH_2), 1.80 (s, 3H, *o*-MesCH_3), 1.68-2.00 (complex m, 2H, CH_2), 1.91 (s, 3H, *o*'-MesCH_3), 2.04-2.16 (m, 2H, CH_2), 2.26-2.38 (m, 1H, C<u>H</u>Ph), 2.37 (s, 3H, *p*-MesCH_3), 5.06 (td, *J* = 10.6, 4.4 Hz, 1H, CO_2CH), 6.89 (s, 1H, MesH), 6.92 (s, 1H, MesH), 6.98 (s, 1H, PhH), 7.01 (s, 1H, PhH), 7.10-7.25 (m, 3H, 3 × PhH), 8.87 (s, 1H, H5).

^{13}C NMR (75.4 MHz) δ 19.6 (CH_3), 19.7 (CH_3), 21.2 (CH_3), 24.2 (CH_2), 25.5 (CH_2), 32.0 (CH_2), 33.9 (CH_2), 49.4 (<u>C</u>HPh), 76.6 (CO_2<u>C</u>H), 114.3 (C4), 124.2 (C), 126.3 (CH), 127.2 (2 × CH), 127.7 (CH), 128.1 (CH), 128.6 (2 × CH), 136.9 (2 × C), 138.6 (C), 142.5 (C), 159.9 (C3), 160.4 (C=O), 163.3 (C5).

IR (KBr, thin film) ν_{max} 2930, 2858, 1717, 1583, 1449, 1390, 1288, 1172, 1134, 1120, 1015, 851, 776, 699, 531 cm^{-1}.

LRMS (EI) *m/z* (%) 389 ($M^{\bullet+}$, 5), 279 (1), 231 (12), 186 ($M^{\bullet+}$-$C_{13}H_{15}O_2$, 9), 130 (17), 91 (93).

HRMS (EI) Found $M^{\bullet+}$, 389.200280. $C_{25}H_{27}NO_3$ requires $M^{\bullet+}$, 389.199094.

Elemental Analysis Found C, 76.90; H, 6.89; N, 3.51. $C_{25}H_{27}NO_3$ requires C, 77.09; H, 6.99; N, 3.60.

Specific Rotation $[\alpha]_D$ -22.6 (*c* 0.5, $CHCl_3$).

X-Ray Crystallographic Analysis Appendix 1.19.

Compound 252

^{1}H NMR (300 MHz) δ 1.11-1.78 (complex m, 4H, 2 × CH_2), 1.78-2.13 (complex m, 2H, CH_2), 2.07 (s, 6H, *o*,*o*'-MesCH_3), 2.25-2.38 (m, 2H, CH_2), 2.31 (s, 3H, *p*-MesCH_3), 2.85 (td, *J* = 11.4, 4.0 Hz, 1H, C<u>H</u>Ph), 5.20 (td, *J* = 10.6, 4.0 Hz, 1H, CO_2CH), 6.63 (s, 1H, H4), 6.92 (s, 2H, 2 × MesH), 7.12-7.28 (m, 5H, 5 × PhH).

^{13}C NMR (75.4 MHz) δ 20.2 (2 × CH_3), 21.1 (CH_3), 24.7 (CH_2), 25.6 (CH_2), 32.1 (CH_2), 33.3 (CH_2), 49.5 (<u>C</u>HPh), 78.7 (CO_2<u>C</u>H), 110.5 (C4), 124.8 (C), 126.6 (CH), 127.5 (2 × CH), 128.3 (2 × CH), 128.4 (2 × CH), 137.1 (2 × C), 139.2 (C), 142.3 (C), 156.1 (C3), 160.2 (C=O), 162.4 (C5).

IR (KBr, thin film) ν_{max} 2930, 2856, 2118, 1739, 1450, 1294, 1280, 1216, 1119, 1007, 851, 768, 755, 699, 532 cm^{-1}.

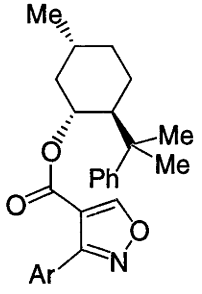
LRMS (EI) *m/z* (%) 389 ($M^{\bullet+}$, 6), 224 (4), 206 (2), 186 ($M^{\bullet+}$-$C_{13}H_{15}O_2$, 20), 158 (100), 130 (14), 91 (44).

HRMS (EI) Found: $M^{\bullet+}$, 389.199935. $C_{25}H_{27}NO_3$ requires $M^{\bullet+}$, 389.199094.

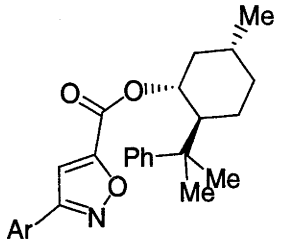
Elemental Analysis Found C, 76.93; H, 6.92; N, 3.52. $C_{25}H_{27}NO_3$ requires C, 77.09; H, 6.99; N, 3.60.

Specific Rotation $[\alpha]_D$ −116.1 (*c* 0.3, $CHCl_3$).

3-(2,4,6-Trimethylphenyl)isoxazole-4-carboxylic Acid (1*R*,2*S*,5*R*)-(5-Methyl-2-(1'-methyl-1'-phenylethyl)-1-cyclohexyl Ester 253 and 3-(2,4,6-Trimethylphenyl)isoxazole-5-carboxylic Acid (1*R*,2*S*,5*R*)-5-Methyl-2-(1'-methyl-1'-phenylethyl)-1-cyclohexyl Ester 254



253



254

Ar = 2,4,6-Me_3Ph

DMAP (14 mg, 0.12 mmol) was added to a stirred mixture of (-)-8-phenylmenthol **237** (300 mg, 1.29 mmol), and a 1.3:1 mixture of 3-(2,4,6-trimethylphenyl)-4-isoxazole carboxylic acid **249** and 3-(2,4,6-trimethylphenyl)-5-isoxazole carboxylic acid **250** (270 mg, 1.17 mmol) in dry Et_2O (25 mL) at 0-5 °C (ice bath). After stirring for 15 min, DCC (266 mg, 1.29 mmol) was added and the mixture was stirred for further 2 days at 18 °C. The mixture was diluted with Et_2O (50 mL) and filtered through a pad of Celite®. The filter cake was washed with Et_2O (6 × 100 mL) and the combined filtrate was evaporated under reduced pressure to *ca.* 100 mL. The solution was washed with 1M HCl (3 × 50 mL), aq. $NaHCO_3$ (2 × 50 mL), H_2O (1 × 50 mL) and brine (1 × 50 mL), dried (anhydrous $MgSO_4$) and evaporated *in vacuo*. Flash column chromatography of the residue, eluting with hexanes-Et_2O (3.7:0.3) afforded the *title compounds **253*** (250 mg, 48%) and ***254*** (193 mg, 37%) as a colourless oils.

Compound 253

^{1}H NMR (300 MHz) δ 0.86 (d, J = 6.6 Hz, 3H, $C\underline{H}_3CH$), 0.90-1.10 (m, 1H), 1.14 [s, 3H, $C(C\underline{H}_3)_2Ph$], 1.20 [s, 3H, $C(C\underline{H}_3)_2Ph$], 1.24-1.54 (m, 3H), 1.61-1.74 (m, 1H), 1.78-1.92

(m, 2H), 1.97 (s, 3H, *o*-MesCH$_3$), 2.10 (s, 3H, *o*'-MesCH$_3$), 2.28 [m, 1H, C<u>H</u>C(CH$_3$)$_2$Ph], 2.32 (s, 3H, *p*-MesCH$_3$), 4.86 (td, J = 10.9, 4.3 Hz, 1H, CO$_2$CH), 6.91 (s, 1H, MesH), 6.95 (s, 1H, MesH), 7.08-7.18 (m, 1H, PhH), 7.19-7.25 (m, 4H, 4 × PhH), 7.74 (s, 1H, H5).

^{13}C NMR (75.4 MHz) δ 19.8 (CH$_3$), 21.1 (2 × CH$_3$), 21.5 (CH), 22.7 (CH$_3$), 26.3 (CH$_2$), 29.5 (CH$_3$), 31.1 (CH$_3$), 34.3 (CH$_2$), 39.2 (CH$_2$), 41.1 (C), 49.7 [<u>C</u>HC(CH$_3$)$_2$Ph], 74.5 (CO$_2$<u>C</u>H), 113.1 (C4), 123.9 (C), 124.8 (CH), 125.0 (2 × CH), 127.8 (2 × CH), 127.9 (CH), 128.0 (CH), 136.6 (C), 136.7 (C), 138.7 (C), 152.2 (C), 159.4 (C3), 160.4 (C=O), 162.8 (C5).

IR (KBr, thin film) ν_{max} 2954, 2922, 1723, 1573, 1457, 1392, 1304, 1295, 1172, 1129, 1012, 849, 778, 700 cm^{-1}.

LRMS (EI) *m/z* (%) 445 ($M^{\bullet+}$, 9), 327 (17), 232 (60), 214 ($M^{\bullet+}$-$C_{13}H_{13}NO_3$, 31), 199 (6), 186 (9), 158 (18), 143 (8), 119 (100), 105 (38), 91 (42), 77 ($M^{\bullet+}$-$C_{23}H_{30}NO_3$, 11).

HRMS (EI) Found: $M^{\bullet+}$, 445.261894. $C_{29}H_{35}NO_3$ requires $M^{\bullet+}$, 445.261694.

Elemental Analysis Found C, 78.01; H, 7.88; N, 3.10. $C_{29}H_{35}NO_3$ requires C, 78.17; H, 7.92; N, 3.14.

Specific Rotation $[\alpha]_D$ –77.3 (*c* 0.8, $CHCl_3$).

Compound 254

^{1}H NMR (300 MHz) δ 0.91 (d, J = 6.6 Hz, 3H, C<u>H</u>$_3$CH), 0.91-1.02 (m, 1H), 1.10-1.38 (m, 2H), 1.25 [s, 3H, C(C<u>H</u>$_3$)$_2$Ph], 1.38 [s, 3H, C(C<u>H</u>$_3$)$_2$Ph], 1.48-1.60 (m, 1H), 1.66-1.78 (m, 1H), 1.79-1.92 (m, 1H), 1.93-2.05 (m, 1H), 2.11 (s, 6H, *o*,*o*'-MesCH$_3$), 2.21 [td, J = 10.6, 4.1 Hz, 1H, C<u>H</u>C(CH$_3$)$_2$Ph], 2.33 (s, 3H, *p*-MesCH$_3$), 5.12 (td, J = 10.6, 4.1 Hz, 1H, CO$_2$CH), 6.29 (s, 1H, H4), 6.94-6.91 (m, 3H, 2 × MesH and PhH), 7.15-7.18 (m, 2H, 2 × PhH), 7.26-7.32 (m, 2H, 2 × PhH).

^{13}C NMR (75.4 MHz) δ 20.2 (2 × CH$_3$), 21.1 (CH$_3$), 21.7 (CH), 24.0 (CH$_3$), 26.4 (CH$_2$), 28.8 (CH$_3$), 31.3 (CH$_3$), 34.3 (CH$_2$), 39.5 (CH$_2$), 41.4 (C), 50.2 [<u>C</u>HC(CH$_3$)$_2$Ph], 65.8 (CO$_2$<u>C</u>H), 110.2 (C4), 124.9 (C), 125.1 (2 × CH), 125.2 (2 × CH), 127.9 (2 × CH), 128.4 (CH), 137.0 (2 × C), 139.1 (C), 151.1 (C), 156.0 (C3), 160.1 (C=O), 162.3 (C5).

IR (KBr, thin film) ν_{max} 2956, 2923, 2869, 1733, 1613, 1583, 1495, 1456, 1388, 1378, 1296, 1218, 1173, 1121, 1050, 994, 850, 763, 700 cm^{-1}.

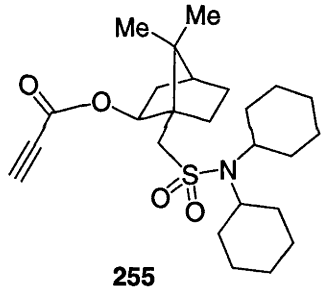
LRMS (EI) *m/z* (%) 445 ($M^{\bullet+}$, 10), 326 (10), 283 (33), 232 (92), 214 (8), 186 (20), 158 (18), 143 (8), 119 (100), 105 (17), 91 (38).

HRMS (EI) Found: $M^{\bullet+}$, 445.261745. $C_{29}H_{35}NO_3$ requires $M^{\bullet+}$, 445.261694.

Elemental Analysis Found C, 78.28; H, 7.87; N, 3.11. $C_{29}H_{35}NO_3$ requires C, 78.17; H, 7.92; N, 3.14.

Specific Rotation $[\alpha]_D$ +0.20 (*c* 0.6, $CHCl_3$).

Propynoic Acid (1*R*,2*S*)-[1-(Dicyclohexylsulfamoyl)methyl]-7,7'-dimethyl-bicyclo[2.2.1]hept-2-yl Ester 255



255

Trimethylaluminium (0.35 mL of a 2M solution in hexanes, 0.70 mmol) was added dropwise to a solution of methyl propiolate **11** (65 μL, 0.73 mmol) in dry toluene (3 mL). After stirring for 20 min, a solution of (+)-dicyclohexylsulfamoyl-L-isoborneol **238** (250 mg, 0.630 mmol) in dry toluene (0.5 mL) was added and the mixture was heated at reflux for 72 h. The reaction was quenched by the addition of aq. NH_4Cl (1 mL) at 0-5 °C (ice bath). After the solvent was evaporated under reduced pressure, the residue was taken up in EtOAc (50 mL) and the solution was washed with H_2O (30 mL). The aqueous layer was separated and extracted with EtOAc (3 × 30 mL). The combined organic solution was washed with brine (30 mL), dried (anhydrous Na_2SO_4) and

concentrated *in vacuo*. Flash column chromatography of the residue, eluting with hexanes-Et_2O (17:3) afforded the *title compound* ***255*** (269 mg, 95%) as a colourless solid, mp 225-230 °C.

^{1}H NMR (300 MHz) δ 0.89 (s, 3H, CH_3), 1.00 (s, 3H, CH_3), 1.01-1.40 (complex m, 7H, 3 × CH_2 and CH), 1.50-1.66 (complex m, 2H, CH_2), 1.67-1.88 (complex m, 16H, 8 × CH_2), 1.90-2.08 (complex m, 2H, CH_2), 2.67 (d, J = 13.3 Hz, 1H, CH_2S), 2.80 (s, 1H, C≡CH), 3.20-3.34 (m, 2H, 2 × NCH), 3.27 (d, J = 13.3 Hz, 1H, CH_2S), 5.10 (dd, J = 7.6, 2.7 Hz, 1H, CO_2CH).

^{13}C NMR (75.4 MHz) δ 19.9 (CH_3), 20.3 (CH_3), 25.1 (2 × CH_2), 26.4 (3 × CH_2), 29.8 (2 × CH_2), 32.6 (2 × CH_2), 32.7 (2 × CH_2), 39.0 (2 × CH_2), 44.4 (CH, bridgehead), 49.0 (C, bridgehead), 49.4 (C, bridgehead), 53.3 (CH_2S), 57.4 (2 × NCH), 73.7 (C≡CH), 80.4 (CO_2CH and C≡CH), 151.3 (C=O).

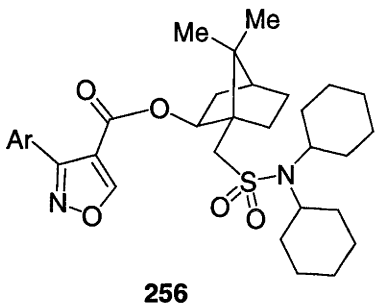
IR (KBr, thin film) ν_{max} 3233, 2935, 2856, 2115, 1713, 1452, 1321, 1165, 1141, 1123, 1109, 1049, 982, 894, 858, 733, 641 cm^{-1}.

LRMS (EI) *m/z* (%) 449 ($M^{\bullet+}$, 30), 406 (19), 298 (87), 272 (9), 259 (6), 244 (80), 205 ($M^{\bullet+}$-$C_{12}H_{22}NO_2S$, 17), 180 (64), 162 (13), 135 (100), 121 (16), 107 (42), 83 (49).

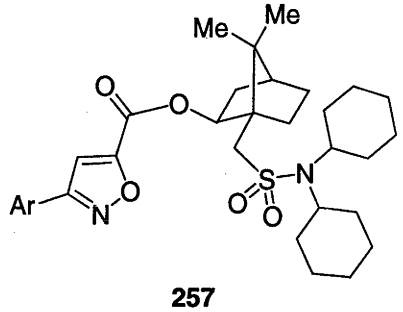
HRMS (EI) Found: $M^{\bullet+}$, 449.260062. $C_{25}H_{39}NO_4S$ requires $M^{\bullet+}$, 449.259981.

Specific Rotation $[\alpha]_D$ +3.88 (*c* 0.5, $CHCl_3$).

3-(2,4,6-Trimethylphenyl)isoxazole-4-carboxylic Acid (1*R*,2*S*)-[1-(Dicyclohexylsulfamoyl)methyl]-7,7'-dimethyl-bicyclo[2.2.1]hept-2-yl Ester 256 and 3-(2,4,6-Trimethylphenyl)isoxazole-5-carboxylic Acid (1*R*,2*S*)-[1-(Dicyclohexylsulfamoyl)methyl]-7,7'-dimethyl-bicyclo[2.2.1]hept-2-yl Ester 257



256



257

Ar = 2,4,6-Me_3Ph

A mixture of propynoic acid (1*R*,2*S*)-[1-(dicyclohexylsulfamoyl)methyl]-7,7'-dimethyl-bicyclo[2.2.1]hept-2-yl ester **255** (270 mg, 0.601 mmol) and mesitonitrile oxide **5** (97.0 mg, 0.601 mmol) in dry THF (15 mL) was heated at reflux for 7 days. The solvent was removed under reduced pressure, the residue was taken up in Et_2O (60 mL) and the solution was washed with H_2O (1 × 40 mL). The aqueous layer was separated and extracted with Et_2O (3 × 40 mL). The combined organic solution was washed with brine (40 mL), dried (anhydrous Na_2SO_4) and concentrated *in vacuo*. Flash column chromatography, eluting with hexanes-Et_2O (17:3) afforded the *title compounds **256*** (70 mg, 19%) as a colourless oil; and ***257*** (205 mg, 56%) as a colourless solid, mp 200-202 °C.

Compound 256

^{1}H NMR (300 MHz) δ 0.95 (s, 3H, CH_3), 1.13 (s, 3H, CH_3), 1.14-1.39 (complex m, 7H, 3 × CH_2 and CH), 1.50-1.84 (complex m, 18H, 9 × CH_2), 1.86-2.00 (complex m, 2H, CH_2), 2.06 (s, 3H, *o*-MesCH_3), 2.09 (s, 3H, *o*'-MesCH_3), 2.30 (s, 3H, *p*-MesCH_3), 2.68 (d, J = 13.3 Hz, 1H, CH_2S), 3.08-3.30 (complex m, 2H, 2 × CHN), 3.17 (d, J = 13.3 Hz,

1H, CH_2S), 5.14 (dd, J = 7.8, 3.0 Hz, 1H, CO_2CH), 6.92 (s, 2H, 2 × MesH), 8.90 (s, 1H, H5).

^{13}C NMR (75.4 MHz) δ 19.7 (CH_3), 19.9 (CH_3), 20.0 (CH_3), 20.3 (CH_3), 21.1 (CH_3), 25.0 (CH_2), 26.2 (2 × CH_2), 26.3 (CH_2), 26.9 (CH_2), 30.3 (2 × CH_2), 32.6 (2 × CH_2), 32.7 (2 × CH_2), 39.2 (2 × CH_2), 44.3 (CH, bridgehead), 48.9 (C, bridgehead), 49.4 (C, bridgehead), 53.8 (CH_2S), 57.4 (2 × NCH), 78.7 ($CO_2\underline{C}H$), 114.6 (C4), 123.5 (C), 128.2 (2 × CH), 136.6 (C), 137.0 (C), 139.0 (C), 158.8 (C3), 161.0 (C=O), 161.7 (C5).

IR (KBr, thin film) ν_{max} 2931, 2855, 1731, 1612, 1454, 1324, 1282, 1236, 1166, 1143, 1111, 1048, 982, 910, 894, 853, 770, 732, 654, 515 cm^{-1}.

LRMS (EI) *m/z* (%) 610 ($M^{\bullet+}$, 23), 439 (7), 421 (2), 380 (100), 316 (7), 298 (12), 246 (14), 214 (43), 180 (21), 158 (18), 135 (76), 107 (20), 83 ($M^{\bullet+}$-$C_{29}H_{39}N_2O_5S$, 35).

HRMS (EI) Found: $M^{\bullet+}$, 610.343491. $C_{35}H_{50}N_2O_5S$ requires $M^{\bullet+}$, 610.344045.

Specific Rotation $[\alpha]_D$ +22.4 (*c* 0.45, $CHCl_3$).

Compound 257

^{1}H NMR (300 MHz) δ 0.94 (s, 3H, CH_3), 1.13 (s, 3H, CH_3), 1.20-1.39 (complex m, 7H, 3 × CH_2 and CH), 1.46-1.58 (m, 2H, CH_2), 1.62-2.20 (complex m, 18H, 9 × CH_2), 2.12 (s, 6H, *o*,*o*'-MesCH_3), 2.33 (s, 3H, *p*-MesCH_3), 2.73 (d, J = 13.5 Hz, 1H, CH_2S), 3.22 (complex m, 2H, 2 × NCH), 3.49 (d, J = 13.5 Hz, 1H, CH_2S), 5.31 (dd, J = 7.7, 3.2 Hz, 1H, CO_2CH), 6.95 (s, 2H, 2 × MesH), 6.97 (s, 1H, H4).

^{13}C NMR (75.4 MHz) δ 19.9 (CH_3), 20.1 (2 × CH_3), 20.2 (CH_3), 20.9 (CH_3), 24.9 (2 × CH_2), 26.0 (2 × CH_2), 26.1 (2 × CH_2), 26.8 (CH_2), 29.9 (CH_2), 32.4 (2 × CH_2), 32.7 (2 × CH_2), 39.1 (CH_2), 44.3 (CH, bridgehead), 49.0 (C, bridgehead), 49.4 (C, bridgehead), 53.2 (CH_2S), 57.3 (2 × NCH), 80.1 ($CO_2\underline{C}H$), 111.3 (C4), 124.7 (C), 128.3 (2 × CH), 136.8 (2 × C), 139.1 (C), 155.2 (C3), 160.8 (C=O), 162.4 (C5).

IR (KBr, thin film) ν_{max} 3769, 2929, 2855, 1731, 1612, 1453, 1325, 1282, 1165, 1143, 1111, 1048, 1029, 982, 894, 853, 769, 732 cm^{-1}.

LRMS (EI) *m/z* (%) 610 ($M^{\bullet+}$, 9), 380 (22), 323 (11), 298 (14), 259 (11), 232 (23), 214 (14), 180 (100), 158 (23), 135 (89), 107 (42), 83 ($M^{\bullet+}$-$C_{29}H_{39}N_2O_5S$, 70).

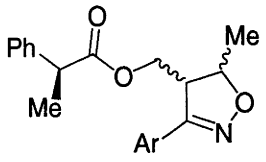
HRMS (EI) Found: $M^{\bullet+}$, 610.343295. $C_{35}H_{50}N_2O_5S$ requires $M^{\bullet+}$, 610.344045.
Specific Rotation $[\alpha]_D$ +32.3 (*c* 0.50, $CHCl_3$).

Reductions of 5-Methyl-3-(2,4,6-trimethylphenyl)isoxazole-4-carboxylic Acid Esters 241, 245 and 247 with Sodium Borohydride

General Procedure

To a cooled solution of 5-methyl-3-(2,4,6-trimethylphenyl)isoxazole-4-carboxylic acid esters **241**, **245** or **247** (0.160 mmol) in dry EtOH (3 mL) at 0 °C (ice bath) was added sodium borohydride (91 mg, 2.4 mmol). After heating at reflux (7 days for compound **241**, 16 days for compounds **245** and **247**), the mixture was quenched with 1M HCl (to pH 2) at 0 °C (ice bath) and concentrated under reduced pressure. The residue was extracted in Et_2O (10 mL) and the solution was washed with 1M HCl (5 mL). The aqueous layer was separated and extracted with Et_2O (3 × 10 mL). The combined organic solution was washed with 1M HCl (1 × 5 mL), aq. $NaHCO_3$ (1 × 5 mL), H_2O (1 × 5 mL) and brine (1 × 5 mL), dried (anhydrous $MgSO_4$) and concentrated *in vacuo*. Flash column chromatography of the residue, eluting with CH_2Cl_2-Et_2O (9:1), afforded *trans*-4-hydroxymethyl-5-methyl-3-(2,4,6-trimethylphenyl)-Δ^2-isoxazoline **118** (described above) and 4-hydroxymethyl-5-methyl-3-(2,4,6-trimethylphenyl)isoxazole **119** (described above) in a ratio of *ca.* 2:1.

Chiral Resolution with (*S*)-2-Phenylpropionic Acid 258 - (*S*)-2-Phenylpropionic Acid 5-Methyl-3-(2,4,6-trimethylphenyl)-Δ^2-isoxazoline-4-Methyl Ester 259



259

trans

Ar = 2,4,6-Me_3Ph

(*S*)-2-Phenylpropionic acid **258** (32 mg, 0.22 mmol), DMAP (3 mg, 0.02 mmol) and DCC (65 mg, 0.32 mmol) were added to a solution of *trans*-4-hydroxymethyl-5-methyl-3-(2,4,6-trimethylphenyl)-Δ^2-isoxazoline **118** (50 mg, 0.22 mmol) in dry Et_2O (50 mL) at 0 °C (ice bath). After stirring at 18 °C for 2 days, the mixture was filtered through a pad of Celite®. The filter cake was washed with Et_2O (50 mL) and concentrated to a volume of *ca.* 50 mL. The filtrate was washed with 1M HCl (3 × 10 mL) and the separated aqueous solution was extracted with Et_2O (3 × 50 mL). The combined organic solution was washed with 1M HCl (3 × 50 mL), H_2O (2 × 50 mL), brine (1 × 50 mL), dried (anhydrous $MgSO_4$) and evaporated *in vacuo*. Flash column chromatography of the residue, eluting with hexanes-CH_2Cl_2 (3:7) afforded the *title compound **259*** as a mixture of diastereomers. The major diastereomer of **259** was isolated as a colourless solid, mp 70-71 °C.

Using the above procedure, reaction of sodium borohydride with isoxazole **241** for 7 days and subsequent chiral resolution with (*S*)-2-phenylpropionic acid **258** afforded material **259** as a mixture of the *trans*-diastereomers in a ratio of 1.21:1.

Using the above procedure, reaction of sodium borohydride with isoxazole **245** for 16 days and subsequent chiral resolution with (*S*)-2-phenylpropionic acid **258** afforded material **259** as a mixture of the *trans*-diastereomers in a ratio of 1.17:1.

Using the above procedure, reaction of sodium borohydride with isoxazole **247** for 16 days and subsequent chiral resolution with (*S*)-2-phenylpropionic acid **258** afforded material **259** as a mixture of the *trans*-diastereomers in a ratio of 1.18:1.

Major Diastereomer of Compound 259

^{1}H NMR (300 MHz) δ 1.31 (d, J = 6.2 Hz, 3H, CH_3), 1.42 (d, J = 7.3 Hz, 3H, CH_3), 2.22 (s, 6H, *o*,*o*'-MesCH_3), 2.29 (s, 3H, *p*-MesCH_3), 3.39 (m, 1H, H4), 3.59 (q, J = 7.3 Hz, 1H, C<u>H</u>Ph), 4.00 (m, 1H, CH_2O), 4.09 (m, 1H, CH_2O), 4.49 (app. p, J = 6.8 Hz, 1H, H5), 6.88 (s, 2H, 2 × MesH), 7.15-7.25 (m, 2H, 2 × PhH), 7.26-7.35 (m, 3H, 3 × PhH).

^{13}C NMR (75.4 MHz) δ 18.0 (CH_3), 20.0 (2 × CH_3), 20.4 (CH_3), 21.0 (CH_3), 45.3 (<u>C</u>HCH_3Ph), 57.1 (C4), 62.8 (CH_2O), 80.3 (C5), 127.3 (CH), 127.4 (2 × CH), 128.7 (2 × CH), 128.8 (2 × CH), 136.8 (2 × C), 138.9 (2 × C), 139.8 (C), 157.0 (C3), 174.1 (C=O).

IR (KBr, thin film) ν_{max} 2973, 2923, 2852, 1736, 1611, 1453, 1376, 1324, 1199, 1162, 1068, 1031, 878, 852, 769, 736, 698 cm^{-1}.

LRMS (EI) *m/z* (%) 365 ($M^{\bullet+}$, 29), 350 ($M^{\bullet+}$-CH_3, 34), 232 (14), 216 ($M^{\bullet+}$-$C_9H_8O_2$, 59), 200 (100), 172 (59), 145 (31), 130 (25), 105 (85), 91 (34), 77 ($M^{\bullet+}$-$C_{17}H_{22}NO_3$, 49).

HRMS (EI) Found: $M^{\bullet+}$, 365.198914. $C_{23}H_{27}NO_3$ requires $M^{\bullet+}$, 365.199094.

Elemental Analysis Found C, 75.48; H, 7.41; N, 3.87. $C_{23}H_{27}NO_3$ requires C, 75.59; H, 7.45; N, 3.83.

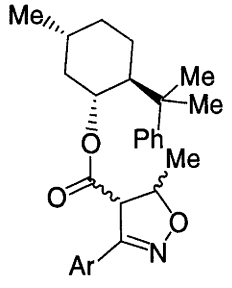
Specific Rotation $[\alpha]_D$ +23.3 (*c* 0.3, $CHCl_3$).

Minor Diastereomer of Compound 259

^{1}H NMR (300MHz) δ 1.33 (d, J = 6.2 Hz, 3H, CH_3), 1.40 (d, J = 7.3 Hz, 3H, CH_3).

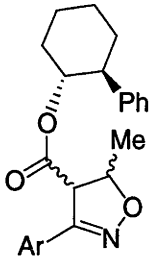
Other proton signals are not distinct from those of the major diastereomer.

Reductions of 5-Methyl-3-(2,4,6-trimethylphenyl)isoxazole-4-carboxylic Acid Esters 241, 245 and 247 with L-Selectride®



260a-d

cis and *trans*



261a,b

Ar = 2,4,6-Me_3Ph

General Procedure

L-Selectride® (180 μL of 1M solution in THF, 0.180 mmol) was added over 5 min to a solution of 5-methyl-3-(2,4,6-trimethylphenyl)isoxazole-4-carboxylic acid methyl ester **241**, **245** and **247** (0.160 mmol) in dry Et_2O (1 mL). The reaction was quenched by the addition of aq. NH_4Cl (1 mL) and stirred for a further 20 min at 18 °C. The aqueous layer was separated and extracted with Et_2O (3 × 10 mL). The combined organic solution was washed with 1M HCl (1 × 5 mL), H_2O (1 × 5 mL) and brine (1 × 5 mL), dried (anhydrous $MgSO_4$) and evaporated *in vacuo*.

Using the procedure described above, no reaction was observed when 5-methyl-3-(2,4,6-trimethylphenyl)isoxazole-4-carboxylic acid (1*R*,2*S*)-[1-(dicyclohexylsulfamoyl)methyl]-7,7'-dimethyl-bicyclo[2.2.1]hept-2-yl ester **247** was treated with L-Selectride® at 0 °C (ice bath) for 18 h.

Compounds 260a-d

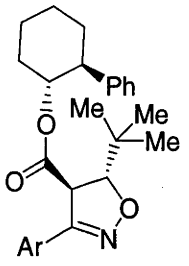
Using the procedure described above, reactions of 5-methyl-3-(2,4,6-trimethylphenyl)isoxazole-4-carboxylic acid (1*R*,2*S*,5*R*)-5-methyl-2-(1'-methyl-1'-phenylethyl)-1-cyclohexyl ester **245** with L-Selectride® afforded 5-methyl-3-(2,4,6-trimethylphenyl)-Δ^2-isoxazoline-4-carboxylic acid (1*R*,2*S*,5*R*)-5-methyl-2-(1'-methyl-1'-phenylethyl)-1-cyclohexyl ester **260a-d** as mixtures of stereoisomers. In the ^{1}H NMR spectra, the stereoisomers of **260** are differentiated by the signals of the C4 protons, which are seen as doublets at δ 3.00 ppm (J = 11.6 Hz), δ 3.34 ppm (J = 10.6 Hz), δ 3.70 ppm (J = 9.2 Hz) and δ 3.90 ppm (J = 10.3 Hz), respectively. At –78 °C for a reaction time of 20 h, **260a**, **260b** and **260d** were observed in a ratio of 1:2.4:1, respectively; at 0 °C for a reaction time of 30 min, **260a**, **260b** and **260d** were detected in a ratio of 1:4.8:2.2, respectively; at 0 °C for a reaction time of 2 h, **260a**, **260b**, **260c** and **260d** were seen in a ratio of 1:2.1:0.29:0.76, respectively; and at 0 °C for a reaction time of 18 h, **260a**, **260b** and **260c** were discerned in a ratio of 1:0.21:1.44, respectively (see Chapter 5, Section 5.2.3., Table 31).

LRMS (EI) *m/z* (%) 461 ($M^{\bullet+}$, 18), 446 ($M^{\bullet+}$-CH_3, 3), 343 (3), 248 (39), 232 ($M^{\bullet+}$-$C_{14}H_{15}NO_2$, 16), 203 (48), 188 (31), 158 (9), 119 (100), 105 (53), 91 (43), 69 (19).
HRMS (EI) Found: $M^{\bullet+}$, 461.292956. $C_{30}H_{39}NO_3$ requires $M^{\bullet+}$, 461.292994.

Compounds 261a,b

Using the procedure described above, reaction of 5-methyl-3-(2,4,6-trimethylphenyl)isoxazole-4-carboxylic acid (1*R*,2*S*)-2-phenyl-1-cyclohexyl ester **241** with L-Selectride® at 0 °C for 18 h afforded 5-methyl-3-(2,4,6-trimethylphenyl)-Δ^2-isoxazoline-4-carboxylic acid (1*R*,2*S*)-2-phenyl-1-cyclohexyl ester **261a,b** as a 2:1 mixture of stereoisomers. In the ^{1}H NMR spectrum, the stereoisomeric 2-isoxazolines **261a,b** are distinguished by the signals of the C4 protons, which are observed as doublets at δ 3.70 ppm (J = 10.4 Hz) and δ 3.80 ppm (J = 10.8 Hz), respectively.

(4*R*,5*S*)-5-*tert*-Butyl-3-(2,4,6-trimethylphenyl)-Δ^2-isoxazoline-4-carboxylic Acid (1*R*,2*S*)-2-Phenyl-1-cyclohexyl Ester 262a



262a

Ar = 2,4,6-Me_3Ph

A suspension of zinc powder (16 mg, 0.24 mmol) and copper(I) iodide (14 mg, 0.072 mmol) in 65% aq. MeOH solution (4 mL) was sonicated for 5-10 min, until the suspension turned black. After 3-(2,4,6-trimethylphenyl)isoxazole-4-carboxylic acid (1*R*,2*S*)-2-phenyl-1-cyclohexyl ester **251** (35 mg, 0.090 mmol) was added, *tert*-butyl iodide **207** (32 μL, 0.27 mmol) was added to the sonicating mixture at 5 °C over 2 h. The suspension was sonicated for 8 days with addition of zinc powder (16 mg, 0.24 mmol), copper(I) iodide (14 mg, 0.072 mmol), *tert*-butyl iodide **207** (32 μL, 0.27 mmol) and 65% aq. MeOH (4 mL) at 8 h intervals. The reaction was quenched by addition of aq. NH_4Cl (1 mL) and the mixture was filtered through a pad of Celite®. The filter cake was washed with EtOAc (6 × 100 mL) and the filtrate was concentrated under reduced pressure. The residue was taken up in Et_2O (50 mL) and the solution was washed with H_2O (1 × 30 mL). The aqueous phase was separated and extracted with Et_2O (3 × 30 mL). The combined organic solution was washed with aq. $Na_2S_2O_4$ (1 × 30 mL), H_2O (1 × 30 mL) and brine (1 × 30 mL), dried (anhydrous $MgSO_4$) and evaporated *in vacuo*. Flash column chromatography of the residue, eluting with hexanes-Et_2O (17:3) afforded the *title compound* ***262a*** (35 mg, 88%) as colourless blocks, after recrystallization from a mixture of hexanes and Et_2O at 0 °C, mp 92-93 °C.

^{1}H NMR (300 MHz) δ 0.68 [s, 9H, $(CH_3)_3C$], 1.10-1.91 (m, 8H, 4 × CH_2), 2.20 (s, 6H, *o*,*o*'-MesCH_3), 2.29 (s, 3H, *p*-MesCH_3), 2.42 (m, 1H, C<u>H</u>Ph), 3.96 (d, *J* = 11.4, 1H, H4), 4.57 (d, *J* = 11.4 Hz, 1H, H5), 4.85 (td, *J* = 10.8, 4.1 Hz, 1H, CO_2CH), 6.86 (s, 2H, 2 × MesH), 6.90-7.27 (m, 5H, 5 × PhH).

^{13}C NMR (75.4 MHz) δ 20.1 (2 × CH_3), 20.7 (CH_3), 24.6 (CH_2), 25.1 [(<u>C</u>$H_3)_3$C], 25.6 (CH_2), 31.0 (CH_2), 33.1 (CH_2), 33.1 [$(CH_3)_3$<u>C</u>], 49.6 (<u>C</u>HPh), 56.9 (CO_2<u>C</u>H), 76.9 (C4), 92.1 (C5), 124.9 (C), 126.4 (CH), 127.2 (2 × CH), 128.2 (CH), 128.3 (CH), 128.4 (CH), 128.7 (CH), 137.0 (2 × C), 138.6 (C), 142.5 (C), 153.7 (C3), 168.0 (C=O).

IR (KBr, thin film) ν_{max} 2934, 2860, 1734, 1611, 1448, 1398, 1367, 1293, 1191, 1170, 1124, 1026, 960, 899, 851 cm^{-1}.

LRMS (EI) *m/z* (%) 447 ($M^{\bullet+}$, 46), 424 (3), 390 [$M^{\bullet+}$-$(CH_3)_3C$, 72], 346 (3), 290 (16), 270 (2), 232 (43), 204 (28), 188 (55), 159 (66), 130 (19), 117 ($M^{\bullet+}$-$C_{20}H_{28}NO_3$, 25), 91 (100).

HRMS (EI) Found: $M^{\bullet+}$, 447.277049. $C_{29}H_{37}NO_3$ requires $M^{\bullet+}$, 447.277344.

Elemental Analysis Found: C, 77.76; H, 8.30; N, 3.18. $C_{29}H_{37}NO_3$ requires C, 77.82; H, 8.33; N, 3.13.

Specific Rotation $[\alpha]_D$ −116.5 (*c* 0.2, $CHCl_3$).

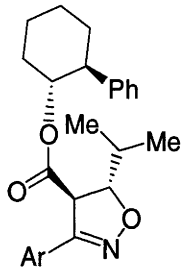
X-Ray Crystallographic Analysis Appendix 1.20.

Analysis of the crude product mixture by ^{1}H NMR spectroscopy showed that **262a** was produced in 95% *d.e.* Proton signals of the minor diastereomer were observed as follows:

^{1}H NMR (300 MHz) δ 0.73 [s, 9H, $(CH_3)_3C$], 3.77 (d, *J* = 11.5 Hz, 1H, H4), 4.59 (d, *J* = 11.5 Hz, 1H, H5), 5.05 (td, *J* = 10.7, 4.2 Hz, 1H, CO_2CH).

Other proton signals are not distinct from those of the major diastereomer.

(4*R*,5*S*)-5-Isopropyl-3-(2,4,6-trimethylphenyl)-Δ^2-isoxazoline-4-carboxylic Acid (1*R*,2*S*)-2-Phenyl-1-cyclohexyl Ester 263a



263a

Ar = 2,4,6-Me_3Ph

A suspension of zinc powder (16 mg, 0.24 mmol) and copper(I) iodide (14 mg, 0.072 mmol) in 65% aq. MeOH solution (4 mL) was sonicated for 5-10 min, until the suspension turned black. After 3-(2,4,6-trimethylphenyl)isoxazole-4-carboxylic acid (1*R*,2*S*)-2-phenyl-1-cyclohexyl ester **251** (35 mg, 0.090 mmol) was added, isopropyl iodide **185** (0.26 μL, 0.27 mmol) was added to the sonicating mixture at 5 °C over 2 h. The mixture was sonicated for 12 days at 5 °C with addition of zinc powder (16 mg, 0.24 mmol), copper(I) iodide (14 mg, 0.072 mmol), isopropyl iodide **185** (0.26 μL, 0.27 mmol) and 65% aq. MeOH (4 mL) at 8 h intervals. The reaction was quenched by addition of aq. NH_4Cl (1 mL) and the suspension was filtered through a pad of Celite®. The filter cake was washed with EtOAc (6 × 100 mL) and the filtrate was concentrated under reduced pressure. The residue was taken up in Et_2O (30 mL) and the solution was washed with H_2O (1 × 30 mL). The aqueous phase was separated and extracted with Et_2O (3 × 30 mL). The combined organic solution was washed with aq. $Na_2S_2O_4$ (1 × 30 mL), H_2O (1 × 30 mL) and brine (1 × 30 mL), dried (anhydrous $MgSO_4$) and evaporated *in vacuo*. Flash column chromatography of the residue, eluting with hexanes-Et_2O (17:3) afforded the *title compound* ***263a*** (34 mg, 86%) as a colourless oil.

^{1}H NMR (300 MHz) δ 0.80 [d, J = 6.6 Hz, 3H, $(C\underline{H}_3)_2CH$], 0.82 [d, J = 6.6 Hz, 3H, $(C\underline{H}_3)_2CH$], 1.05-2.10 [m, 9H, 4 × CH_2 and $(CH_3)_2C\underline{H}$] 2.19 (s, 6H, *o,o'*-MesCH_3), 2.29 (s, 3H, *p*-MesCH_3), 2.42 (m, 1H, C$\underline{H}$Ph), 3.90 (d, J = 11.1 Hz, 1H, H4), 4.49 (dd, J = 11.1, 7.5 Hz, 1H, H5), 4.85 (td, J = 11.0, 4.3 Hz, 1H, CO_2CH), 6.85 (s, 2H, 2 × MesCH), 7.02-7.30 (m, 5H, ArH).

^{13}C NMR (125 MHz) δ 17.3 [$(\underline{C}H_3)_2CH$], 18.4 [$(\underline{C}H_3)_2CH$], 20.1 (2 × CH_3), 21.1 (CH_3), 24.5 (CH_2), 25.5 (CH_2), 31.0 (CH_2), 31.5 [$(CH_3)_2\underline{C}H$], 33.8 (CH_2), 49.6 ($\underline{C}$HPh), 58.5 ($CO_2\underline{C}H$), 77.9 (C4), 89.6 (C5), 125.0 (C), 126.6 (2 × CH), 128.4 (2 × CH), 128.5 (2 × CH), 128.8 (CH), 137.1 (2 × C), 138.7 (C), 142.6 (C), 154.4 (C3), 167.9 (C=O).

IR (KBr, thin film) ν_{max} 2930, 2858, 1734, 1611, 1492, 1448, 1378, 1271, 1123, 1032, 894, 851, 756, 699 cm^{-1}.

LRMS (EI) *m/z* (%) 433 ($M^{\bullet+}$, 31), 390 [$M^{\bullet+}$-$(CH_3)_2CH$, 60], 274 ($M^{\bullet+}$-$C_{12}H_{15}$, 10), 232 (33), 203 (11), 188 ($M^{\bullet+}$-$C_{12}H_{14}NO$, 27), 158 ($M^{\bullet+}$-$C_{16}H_{21}NO_3$, 53), 171 (16), 91 (100).

HRMS (EI) Found: $M^{\bullet+}$, 433.262110. $C_{28}H_{35}NO_3$ requires $M^{\bullet+}$, 433.261694.

Elemental Analysis Found: C, 77.48; H, 8.17; N, 3.25. $C_{28}H_{35}NO_3$ requires C, 77.56; H, 8.14; N, 3.23.

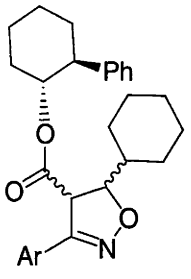
Specific Rotation $[\alpha]_D$ –110.2 (*c* 0.1, $CHCl_3$).

Analysis of the crude product mixture by ^{1}H NMR spectroscopy showed that **263a** was produced in 93% *d.e.* Proton signals of the minor diastereomer were observed as follows:

^{1}H NMR (300 MHz) δ 3.65 (d, J = 11.0 Hz, 1H, H4), 5.06 (td, J = 10.9 Hz, 1H, CO_2CH).

Other proton signals are not distinct from those of the major diastereomer.

5-Cyclohexyl-3-(2,4,6-trimethylphenyl)-Δ^2-isoxazoline-4-carboxylic Acid (1*R*,2*S*)-2-Phenyl-1-cyclohexyl Ester 264a-c



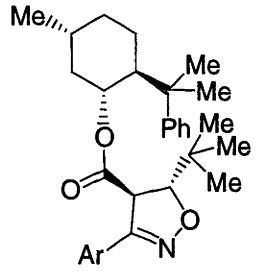
264a-c

Ar = 2,4,6-Me_3Ph

A suspension of zinc powder (16 mg, 0.24 mmol) and copper(I) iodide (14 mg, 0.072 mmol) in 65% aq. MeOH solution (4 mL) was sonicated for 5-10 min, until the suspension turned black. After 3-(2,4,6-trimethylphenyl)isoxazole-4-carboxylic acid (1*R*,2*S*)-2-phenyl-1-cyclohexyl ester **251** (35 mg, 0.090 mmol) was added, cyclohexyl iodide **213** (35 μL, 0.27 mmol) was added to the sonicating mixture at 5 °C over 2 h. The suspension was sonicated for 14 days at 5 °C with addition of zinc powder (16 mg, 0.24 mmol), copper(I) iodide (14 mg, 0.072 mmol) and 65% aq. MeOH (4 mL) to the sonicating mixture at 12 h intervals, and addition of cyclohexyl iodide **213** (35 μL, 0.27 mmol) at 4 day intervals. The reaction was quenched with aq. NH_4Cl (1 mL) and the mixture was filtered through a pad of Celite®. The filter cake was washed with EtOAc (6 × 100 mL) and the filtrate was concentrated under reduced pressure. The residue was taken up in Et_2O (30 mL) and the organic solution was washed with H_2O (1 × 20 mL). The aqueous phase was separated and extracted with Et_2O (3 × 30 mL). The combined organic solution was washed with aq. $Na_2S_2O_4$ (1 × 30 mL), H_2O (1 × 30 mL) and brine (1 × 30 mL), dried (anhydrous $MgSO_4$) and evaporated *in vacuo*. Analysis of the mixture by ^1H NMR spectroscopy indicated **264** consisted of three stereoisomers in a ratio of *ca.* 1:1:7.2. These were differentiated by the signals of their C4- and C5-isoxazoline protons.

^{1}H NMR (300 MHz) for **264a**: δ 3.82 (d, J = 11.9 Hz, 1H, H4), δ 4.51 (dd, J = 11.9, 7.9 Hz, 1H, H5); for **264b**: δ 3.92 (d, J = 9.8 Hz, 1H, H4), δ 4.91 (app. t, J = 9.8 Hz, 1H, H5); for **264c**: δ 3.97 (d, J = 9.8 Hz, 1H, H4), δ 4.28 (app. t, J = 9.8 Hz, 1H, H5).

(4*R*,5*S*)-5-*tert*-Butyl-3-(2,4,6-trimethylphenyl)-Δ^2-isoxazoline-4-carboxylic Acid (1*R*,2*S*,5*R*)-5-Methyl-2-(1'-methyl-1'-phenylethyl)cyclohexyl Ester 265a



265a

Ar = 2,4,6-Me_3Ph

A suspension of zinc powder (16 mg, 0.24 mmol) and copper(I) iodide (14 mg, 0.072 mmol) in 65% aq. MeOH solution (4 mL) was sonicated for 5-10 min, until the suspension turned black. After 3-(2,4,6-trimethylphenyl)isoxazole-4-carboxylic acid (1*R*,2*S*,5*R*)-5-methyl-2-(1'-methyl-1'-phenylethyl)-1-cyclohexyl ester **253** (40 mg, 0.090 mmol) was added, *tert*-butyl iodide **207** (31 μL, 0.27 mmol) was added to the sonicating mixture at 5 °C over 2 h. The suspension was sonicated for 8 days at 5 °C with addition of zinc powder (16 mg, 0.24 mmol), copper(I) iodide (14 mg, 0.072 mmol), *tert*-butyl iodide **207** (31 μL, 0.27 mmol) and 65% aq. MeOH (4 mL) to the sonicating mixture at 8 h intervals. The reaction was quenched with aq. NH_4Cl (1 mL) and the mixture was filtered through a pad of Celite®. The filter cake was washed with EtOAc (3 × 100 mL) and the filtrate was concentrated under reduced pressure. The residue was taken up in

Et_2O (30 mL) and the organic solution was washed with H_2O (1 × 30 mL). The aqueous phase was separated and extracted with Et_2O (3 × 30 mL). The combined organic solution was washed with aq. $Na_2S_2O_4$ (1 × 30 mL), H_2O (1 × 30 mL) and brine (1 × 30 mL), dried (anhydrous $MgSO_4$) and evaporated *in vacuo*. Flash column chromatography of the residue, eluting with hexanes-Et_2O (17:3) afforded the *title compound* ***265a*** (39 mg, 87%) as a colourless oil.

^{1}H NMR (300 MHz) δ 0.65 (d, J = 6.4 Hz, 3H, $C\underline{H}_3CH$), 0.70-1.85 (m, 6H, 3 × CH_2), 1.00 [s, 9H, $(CH_3)_3C$], 1.14 [s, 3H, $C(C\underline{H}_3)_2Ph$], 1.22 [s, 3H, $C(C\underline{H}_3)_2Ph$], 1.44 (m, 1H), 1.73 (m, 1H, CH), 2.13 (s, 6H, *o*,*o*'-$MesCH_3$), 2.27 (s, 3H, *p*-$MesCH_3$), 3.78 (d, J = 11.7 Hz, 1H, H4), 4.59 (td, J = 10.6, 4.3 Hz, 1H, CO_2CH), 4.83 (d, J = 11.7 Hz, 1H, H5), 6.82 (s, 2H, 2 × MesH), 7.08-7.32 (m, 5H, 5 × PhH).

^{13}C NMR (75.4 MHz) δ 15.4 (CH_3), 18.0 (2 × CH_3), 20.3 (CH), 21.1 (CH_3), 21.6 (CH_3), 25.6 (2 × CH_3), 26.6 (CH_2), 26.8 (CH_3), 29.8 [$(CH_3)_3\underline{C}$], 30.8 (CH_3), 33.2 (CH_2), 34.2 (CH_2) 39.8 [$\underline{C}(CH_3)_2Ph$], 49.7 [$\underline{C}HC(CH_3)_2Ph$], 56.6 ($CO_2\underline{C}H$), 76.4 (C4), 91.8 (C5), 124.9 (2 × C), 125.1 (CH), 125.3 (CH), 125.5 (CH), 127.9 (CH), 128.0 (CH), 128.4 (CH), 128.7 (CH), 137.3 (C), 138.7 (C), 151.0 (C), 153.7 (C3), 167.9 (C=O).

IR (KBr, thin film) ν_{max} 2954, 2919, 1730, 1611, 1455, 1367, 1294, 1191, 1170, 1031, 850, 764, 700 cm^{-1}.

LRMS (EI) *m/z* (%) 503 ($M^{\bullet+}$, 34), 446 [$M^{\bullet+}$-$(CH_3)_3C$, 27], 385 (4), 328 (4), 290 (47), 232 (46), 214 (12), 188 (89), 158 (19), 119 ($M^{\bullet+}$-$C_{24}H_{34}NO_3$, 100).

HRMS (EI) Found: $M^{\bullet+}$, 503.340406. $C_{33}H_{45}NO_3$ requires $M^{\bullet+}$, 503.339945.

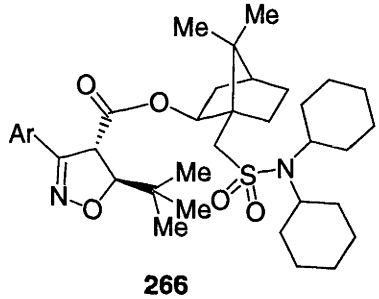
Elemental Analysis Found: C, 78.59; H, 8.97; N, 2.81. $C_{33}H_{45}NO_3$ requires C, 78.69; H, 9.00; N, 2.78.

Specific Rotation $[\alpha]_D$ -53.8 (*c* 1.7, $CHCl_3$).

Analysis of the crude product mixture by ^{1}H NMR spectroscopy showed that **265a** was produced in 94% *d.e.* Proton signals of the minor diastereomer were observed as follows:

^{1}H NMR (300 MHz) δ 4.19 (d, J = 11.7 Hz, 1H, H4), 4.69 (d, J = 11.7 Hz, 1H , H5). Other proton signals are not distinct from those of the major diastereomer.

(4*S*,5*R*)-5-*tert*-Butyl-3-(2,4,6-trimethylphenyl-Δ^2-isoxazoline-4-carboxylic Acid (1*R*,2*S*)-[1-(Dicyclohexylsulfamoyl)methyl]-7,7'-dimethyl-bicyclo[2.2.1]hept-2-yl Ester 266



266

Ar = 2,4,6-Me_3Ph

A suspension of zinc powder (15.8 mg, 0.24 mmol) and copper(I) iodide (13.7 mg, 0.072 mmol) in 65% aq. MeOH solution (4 mL) was sonicated for 5-10 min, until the suspension turned black. After 3-(2,4,6-trimethylphenyl)isoxazole-4-carboxylic acid (1*R*,2*S*)-[1-(dicyclohexylsulfamoyl)methyl]-7,7'-dimethyl-bicyclo[2.2.1]hept-2-yl ester **256** (55 mg, 0.090 mmol) was added, *tert*-butyl iodide **207** (32 μL, 0.27 mmol) was added to the sonicating mixture at 5 °C over 2 h. The suspension was sonicated for 13 days at 5 °C with addition of zinc powder (15.8 mg, 0.24 mmol), copper(I) iodide (13.7 mg, 0.072 mmol), *tert*-butyl iodide **207** (32 μL, 0.27 mmol) and 65% aq. MeOH (4 mL) to the sonicating mixture at 8 h intervals. The reaction was quenched with aq. NH_4Cl (1 mL) and the mixture was filtered through a pad of Celite®. The filter cake was washed with EtOAc (3 × 100 mL) and the filtrate was concentrated under reduced pressure. The residue was taken up in Et_2O (30 mL) and the solution was washed with H_2O (1 × 30

mL). The aqueous phase was separated and extracted with Et_2O (3 × 30 mL). The combined organic solution was washed with aq. $Na_2S_2O_4$ (1 × 30 mL), H_2O (1 × 30 mL) and brine (1 × 30 mL), dried (anhydrous $MgSO_4$) and evaporated *in vacuo*. Flash column chromatography of the residue, eluting with hexanes-Et_2O (17:3) afforded the *title compound* ***266*** (52 mg, 87%), as colourless plates, after recrystallization from a mixture of hexanes and Et_2O at 0 °C, mp 245-246 °C.

^{1}H NMR (300 MHz) δ 0.80-1.90 (m, 27H, 13 × CH_2 and CH), 1.06 [s, 9H, $(CH_3)_3C$], 1.25 (s, 3H, CH_3), 1.44 (s, 3H, CH_3), 2.20 (s, 6H, *o,o'*-MesCH_3), 2.25 (s, 3H, *p*-MesCH_3), 2.51 (d, J = 13.3 Hz, 1H, CH_2S), 3.00 (d, J = 13.3 Hz, 1H, CH_2S), 3.21 (p, J = 7.5 Hz, 2H, 2 × NCH), 4.19 (d, J = 11.0 Hz, 1H, H4), 4.75 (dd, J = 7.8, 3.5 Hz, 1H, CO_2CH), 5.03 (d, J = 11.0 Hz, 1H, H5), 6.81 (s, 2H, 2 × MesH).

^{13}C NMR (150 MHz) δ 18.6 (CH_3), 19.8 (2 × CH_3), 20.2 (CH_3), 21.0 (CH_3), 25.0 (2 × CH_2), 25.5 [($\underline{C}H_3)_3C$], 26.4 (2 × CH_2), 26.5 (2 × CH_2), 26.8 (CH_2), 29.7 (CH_2), 31.2 (CH_2), 32.5 (CH_2), 32.9 (2 × CH_2), 33.4 (CH_2), 38.9 [$(CH_3)_3\underline{C}$], 44.2 (CH, bridgehead), 48.7 (C, bridgehead), 49.1 (C, bridgehead), 53.9 (CH_2S), 56.6 (NCH), 57.6 (NCH), 80.3 ($CO_2\underline{C}H$ and C4), 92.4 (C5), 125.4 (C), 128.7 (2 × CH), 136.9 (2 × C), 139.0 (C), 153.2 (C3), 167.7 (C=O).

IR (KBr, thin film) ν_{max} 2929, 2856, 1737, 1613, 1372, 1327, 1280, 1190, 1166, 1144, 1109, 1049, 1028, 981, 908, 853, 775, 741, 643 cm^{-1}.

LRMS (EI) *m/z* (%) 668 ($M^{\bullet+}$, 0.2), 611 [$M^{\bullet+}$-$(CH_3)_3C$, 4], 425 (2), 414 (0.4), 397 (2), 380 (56), 316 (8), 298 (20), 259 (6), 246 (18), 228 (34), 203 (10), 180 (32), 158.1 (12), 146 (18), 135 (100), 107 (30), 93 (36), 83 (46), 67 (16).

HRMS (EI) Found: $M^{\bullet+}$, 668.421894. $C_{39}H_{60}N_2O_5S$ requires $M^{\bullet+}$, 668.422295.

Specific Rotation $[\alpha]_D$ +129.3 (*c* 0.15, $CHCl_3$).

X-Ray Crystallographic Analysis Appendix 2.12.

No other stereoisomer was observed in the crude product mixture, as indicated by ^{1}H NMR spectroscopic analysis. On that basis, compound **266** is assumed to have been produced with ≥ 98% *d.e.*

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