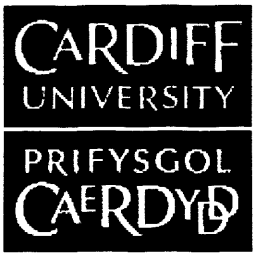

One–Pot Methodology for the Synthesis of Polysubstituted Pyridines and Terpyridines

Thesis submitted for the Degree of Doctor of Philosophy at Cardiff University

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September 2008

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In Loving Memory of my Father

DECLARATION

This work has not previously been accepted in substance for any degree and is not being concurrently submitted in candidature of any degree.

Signed.....K. Ogam.....

Date.....03/05/09.....

STATEMENT ONE

This thesis is the result of my own investigations, except where otherwise stated. Other sources are acknowledged by footnotes giving explicit references.

Signed.....K. Ogam.....

Date...03/05/09.....

STATEMENT TWO

I herby give my consent for my thesis, if accepted, to be available for photocopying and for inter-library loan, and for the title and summary to be made available to outside organisations.

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Date.....03/05/09.....

ABSTRACT

Polysubstituted pyridines are prepared by a one–pot three–component cyclocondensation process, developed by modification and improvement of the traditional Bohlmann–Rahtz reaction. The synthesis combines a 1,3–dicarbonyl compound, ammonia, and an alkynone without the use of an additional acid catalyst. This three–component heteroannulation reaction proceeds by tandem Michael addition–heterocyclization with total control of regiochemistry and the resulting library of pyridines is isolated in good yield.

Modified Bohlmann-Rahtz procedures were applied to the synthesis of a range of terpyridines, by a two– and three–component condensation of 2,6-propynoylpyridine derivatives and a range of enamines, or 1,3–dicarbonyl compounds and ammonia, proceeding in moderate to good yield using a range of conditions.

The synthesis of fluorescent cyanopyridines with desirable photophysical properties from β–aminocrotononitrile and a variety of heterocyclic alkynones was established by one–pot Bohlmann–Rahtz reaction in excellent yields. These cyanopyridines can be generated in good yield, rapidly, using microwave irradiation.

Primary thioamides are prepared in excellent yield from the corresponding nitriles by treatment with ammonium sulfide in methanol, at room temperature for electron deficient aromatic nitriles or under microwave irradiation at 80 °C or 130 °C in 15–30 minutes for other aromatic and aliphatic nitriles without the need for chromatographic purification.

ACKNOWLEDGEMENTS

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A final thank you goes to everyone working in the administrative and workshop sections of the Chemistry department at Cardiff, Dr. Jenkins, Rob and Dave.

ABBREVIATIONS

Ac	Acetyl
APcI	Atmospheric pressure chemical ionization
aq	Aqueous
Ar	Unspecified aryl substituent
Bu	Butyl
BuLi	Butyllithium
c	Concentration
cat.	Catalytic/catalyst
CF	Continuous Flow
CI	Chemical Ionization
DCM	Dicloromethane
DDQ	2,3–Dicloro–5,6–dicyanobenzoquinone
DMF	*N,N*–Dimethylformamide
DMSO	Dimethyl sufoxide
DMT	Dimethyltrityl
DNA	Deoxyribonucleic acid
ε	Molar absorbtivity
EI	Electron Impact
equiv. or eq.	Equivalent
Et	Ethyl
FTIR	Fourrier Transform Infra Red
g	Grams
h	hour/s
HMRS	High Resolution Mass Spectroscometry
Hz	Hertz
IBX	*o*–Iodoxybenzoic acid
IR	Infra Red
J	Joules
lit.	Literature
LRMS	Low Resolution Mass Spectroscometry
M	Molar

MAOS	Microwave–Assisted Organic Synthesis
MCR	Multiple Component Reaction
Me	Methyl
MHz	Megahertz
min	Minutes
μM	Micromolar
mol	Moles
Mp	Melting point
MS	Mass Spectroscometry
NBS	*N*–Bromosuccinimide
NIS	*N*– Iodosuccinimide
NMR	Nuclear Magnetic Resonance
P	*Para*
$Pd(OAc)_2$	Palladium(II) acetate
$Pd_2(dba)_3$	Tris(dibenzylideneacetone)dipalladium(0)
Ph	Phenyl
Ppm	parts per million
quant.	Quantitative
R	Specific Substituent
R_f	Retention factor
RNA	Ribose Nucleic Acid
RT	Room Temperature
Silica/SiO_2	Merck Kieselgel 60 H silica or Matrex silica 60
Tert	Tertiary
TLC	Thin Layer Chromatography
TMS	Trimethylsilyl
UV	Ultraviolet
vs	Versus

CONTENTS

CHAPTER TWO – RESULTS AND DISCUSSION

CHAPTER THREE – RESULTS AND DISCUSSION

CHAPTER FOUR – EXPERIMENTAL

CHAPTER ONE – INTRODUCTION

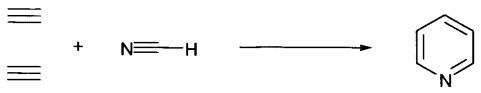
1.0 THE DISCOVERY OF PYRIDINE

The synthesis of pyridines and our understanding of their physical and chemical properties has come a long way since the isolation of the first pyridine base, picoline, from bone oil was in 1846 by Thomas Anderson,[1] but it was not until Wilhelm Körner (1869) and James Dewar (1871) independently formulated a mono–aza–analogue of benzene, that pyridine chemistry was born.[2] Understanding the pyridine structure **6** enabled different synthetic routes to be founded in the latter half of that century. Baeyer[3,4] passed acrolein **1** through aqueous ammonia **3** and, after purification, obtained a small amount of basic material which was identified as the 2–picoline derivative **3** (Scheme 1).

1 **2** **3**

Scheme 1. Synthesis of 2–picoline **3**.

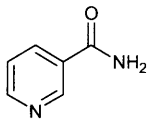
The original laboratory preparation of pyridine **1** in 1876 was discovered by Ramsey by passing acetylene **4** and hydrogen cyanide **5** through a red–hot tube (Scheme 2).[5]



4 **5** **6**

Scheme 2. Synthesis of pyridine **6**.

For decades, pyridines were little regarded. The required quantities were obtained by coal tar distillation, and yet pyridines came to distinction in the 1930's when Elvehjem and his colleague Koehn later were able to isolate and identify nicotinamide **7** and niacin **8** from vitamin B_2 (Scheme 3).[6] His discovery led directly to the cure of human pellagra, a vitamin deficiency causing dermatitis and dementia.



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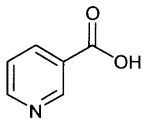

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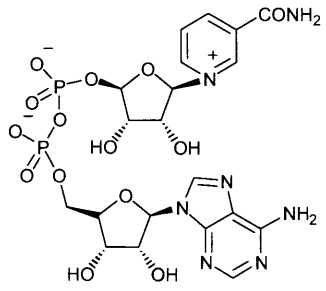
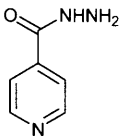
Scheme 3. Structures of nicotinamide **7** and niacin **8**.

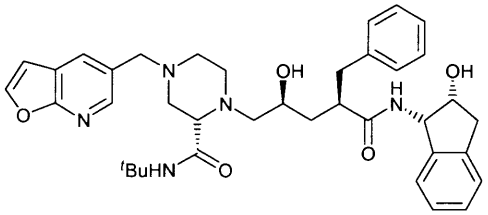
Since the middle of the last century, pyridines have held an important role in our understanding of the chemistry and properties of biological systems. They play a key role in both biological and chemical coordination.



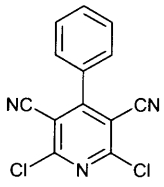
NADP



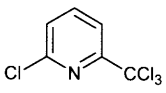
Isoniazide
(antituberculosis)



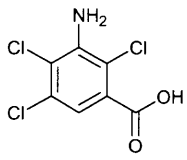
L–754,394 (Potent HIV protease inhibitor)



Pyridinenitrile
(Fungicide)



Nitrapyrin
(Bactericide)



Picloram
(Herbicide)

Figure 1. Structures of drugs and agrochemicals.

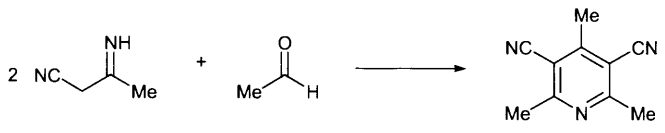
The pyridine motif is the most common heterocyclic compound, and is found in many enzymes of living organisms: the prosthetic pyridine nucleotide (NADP) is involved in various oxidation–reduction processes,[7] and this heterocyclic motif is found in over 7000 pharmaceutical drugs, including isoniazide, an antituberculosis drug, and the HIV inhibitor L–754, 394, agrochemicals[8] and a large number of natural products (Figure 1).[9]

1.1 CYANOPYRIDINES

1.1.1 Initial Studies

The directed construction of carbon–carbon bonds have always been a central theme in synthetic organic chemistry, structural diversity and the biological importance of nitrogen–containing heterocycles have made them attractive targets for synthesis over many years. Of these, cyanopyridines have drawn continuing efforts in the development of novel synthetic strategies, such as involving vinamidium salts,[10] one–pot reactions,[11] and microwave[12] and ultrasound irradiation.[13] The pyridine motif is among the most common heterocyclic compounds found in various therapeutic agents.[14] It is a building block for the synthesis of nicotinic acid, its amide (nicotinamide), are used in pharmaceutical formulations, such as additives in food, animal feed, and possessing fluorescent properties, making them ideal for tools in the synthesis of dyes. Thus extensive efforts have been exerted over the years on the methodology for the synthesis of pyridine derivatives.

Initial experiments for the synthesis of cyanopyridines date as far back as 1908, when Meyer prepared 2,4,6–trimethyl–3,5–dicyanopyridine **11** by reaction of acetaldehyde **10**. The intermediate dihydropyridine was oxidised to achieve the cyanopyridine compound (Scheme 4).[15]

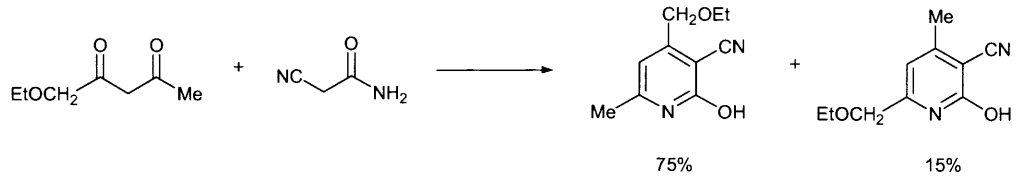


9 **10** **11**

Scheme 4. Synthesis of 2,4,6–trimethyl–3,5–dicyanopyridine **11.**

Many studies for the synthesis of cyanopyridines followed this initial discovery, including the production of a valuable intermediate for the synthesis of vitamin B_6

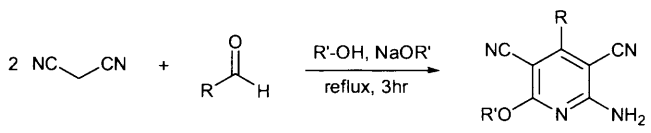
(pyridoxine) by Harris, Stiller and Folkers[16] from which extensive studies by Wenner and Platti found that two isomers were formed from the reaction, compromising 75% of the expected isomer and 15% of the isomeric 3–cyano–6–ethoxymethyl–4–methyl–2–hydroxypyridine (Scheme 5).[17]



12 **13** **14** **15**

Scheme 5. Synthesis of cyanopyridine isomers **14** and **15**.

The synthesis of pyridine derivatives from malononitrile as a starting material can be carried out by several methods, such as by reacting dinitrile **16** with tetracyanopropene salts, obtained from orthoesters;[18] however the corresponding pyridine products required two steps to form, and the necessary orthoesters are not easily obtainable. In 1970, Alvares–Insúla, Lora–Tamayo, and Soto developed a method whereby the reaction of aldehydes and malononitrile in the presence of an alcohol/alkoxide provided a single step route for the synthesis of 4–substituted 2–amino–3,5–dicyano–6–alkoxypyridines **18** (Scheme 6).[19]



16 **17** **18**

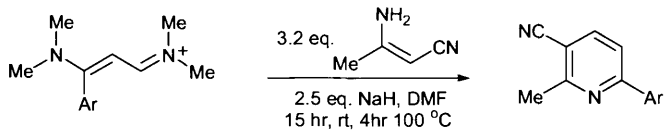
Scheme 6. Synthetic route to 3,5–dicyanopyridienes **18**.

Table 1. One–pot synthesis of pyridines from aldehydes.

Entry	Starting Aldehyde	R	Yield (%)
1	Acetaldehyde	Methy	3
2	Propionaldehyde	Ethyl	7
3	Isobutyraldehyde	Isopropyl	32
4	Pivaldehyde	*tert*–Butyl	5
5	Valeraldehyde	*n*–Butyl	25
6	Benzaldehyde	Phenyl	50
7	*p*–Tolualdehyde	*p*–Tolyl	31
8	*m*–Tolualdehyde	*m*–Tolyl	49
9	*p*–Chlorobenzaldehyde	*p*–Chlorophenyl	40
10	3–Pyridinealdehyde	3–Pyridyl	39

Various pyridines were prepared from aldehydes from this route and the pyridines were generated in moderate yields when aromatic aldehydes were employed (Table 1) with aliphatic and alicyclic aldehydes generating lower yields. Reactions involving aromatic aldehydes and α,β–unsaturated aldehydes failed to produce the corresponding pyridines. Although the one this one–step reaction proceeds to the polysubstituted pyridines, the yields were moderate, and hence further research into the synthesis of pyridine derivatives continued.

Application of vinylogous iminium salts led to the synthesis of trisubstituted cyanopyridines in 1995 by Sikorski and co–workers. Previous work within the group used vinylogous iminium salts for the formation of five–membered rings such as pyrroles.[20] With the methodology established, combined with previous work reported by Jutz and co–workers[21] 2,3,5–trisubstituted pyridines were synthesized using the reaction of β–aminocrotononitrile **20** with 2–substituted symmetrical vinamidinium salts **19** under basic conditions (Scheme 7).



19 **20** **21**

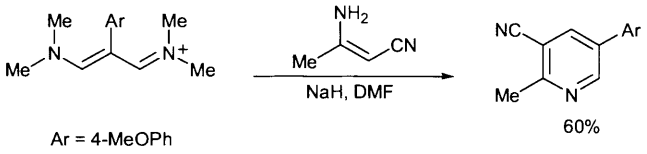
Scheme 7. Synthesis of 3–cyanopyridines from β–aminocrotononitrile.

Two regioisomeric pyridines could be formed by the reaction of β–aminocrotononitrile **20** and vinamidinium salts **19**. Nucleophilic attack on unsymmetrical vinamidinium salts have been shown to be under steric control; attack by the nitrogen of the enamine at the least sterically hindered carbon of the vinamidinium salt will result in 2,3,4–trisubstituted pyridine, whereas attack by the carbon of the enamine is favoured resulting in 2,3,6–trisubstituted pyridine **21** as the major product.

Table 2. Synthesis of 2,3,6–trisubstituted pyridine **21**.

Entry	Ar	Product Yield (%)
1	4'–C_6H_4OMe	80
2	4'–C_6H_4Me	74
3	4'–C_6H_4Cl	58
4	4'–C_6H_4Br	49
5	Ph	67
6	4'–$C_6H_4NO_2$	52
7	4'–C_6H_4F	67
8	3',4'–$C_6H_4(OMe)_2$	65
9	3'–$C_6H_4NO_2$	55

The scope of this reaction was extended using a range of substrates and generated the trisubstituted pyridines in moderate to good yields. The use of symmetrical vinamidinium salts gave the corresponding 2,3,5–trisubstituted pyridine in 60% yield (Scheme 8).

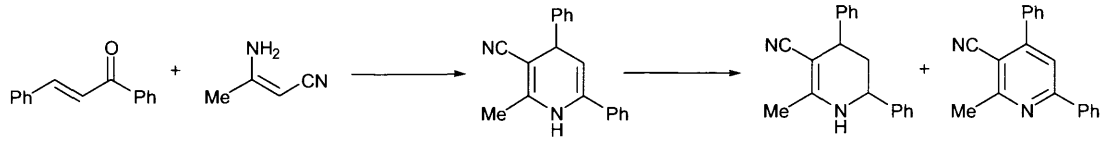


22 **20** **23**

Scheme 8. Synthesis of of 2,3,5–trisubstituted pyridine.

Although this methodology formed 2,3,5–trisubstituted **23** and 2,3,6–trisubstituted pyridine **21** in acceptable yields, it required the initial preparation of vinylogous salts in addition to inert, dry conditions, somewhat limiting its applicability.

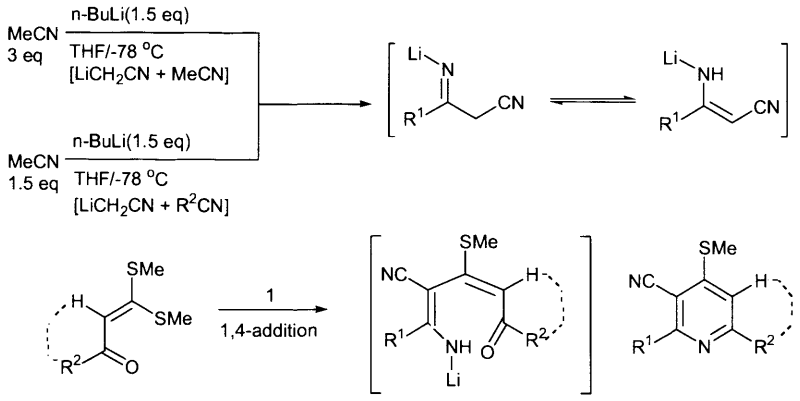
Other reactions incorporating enamine precursors for the formation of pyridine derivatives was reported by J. N. Chatterjea in 1952.[22] He reported two products were formed from the reaction of β–aminocronotonitrile with chalcone, namely compounds **26** and **27** although no yields were reported (Scheme 9).



24 **20** **25** **26** **27**

Scheme 9. Synthetic path to pyridines via Michael addition.

An alternative method emerged for the synthesis of 3–cyanopyridines by Gupta and co–workers in 1990, although this complicated procedure required dry conditions and the use of *n*–butyllithium (Scheme 10).



28 **29**

Scheme 10. Reaction scheme for the synthesis of tetrasubstituted pyridines.

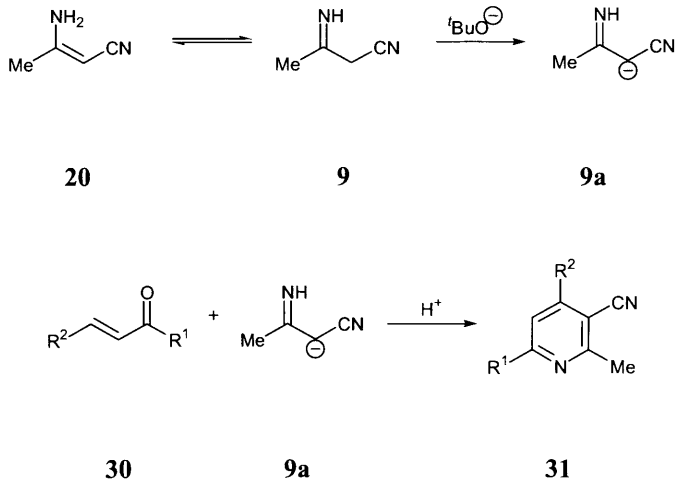
Table 3. Synthesis of 2,6–substituted–4–(methylthio)–3–cyanopyridines **29**.

Entry	R^2	R^1	Product Yield (%)
1	Me	4'–C_6H_4OMe	92
2	Me	Ph	86
3	Me	4'–C_6H_4Cl	90
4	Me	2'–Naphthyl	92
5	Me	2'–Furyl	85
6	Me	2'–Thienyl	82
7	Me	3'–Pyridyl	62
8	Me	Me	30
9	Ph	2'–Furyl	87
10	Ph	Me	57
11	2'–Thienyl	Ph	65
12	2'–Furyl	Ph	76

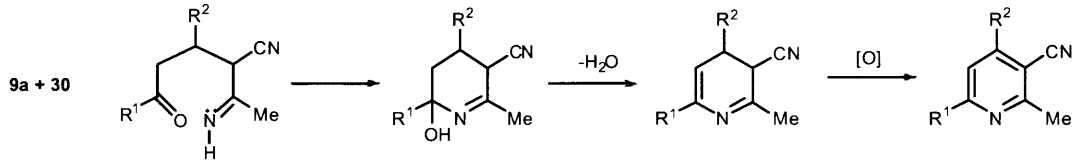
The lithiated β–amino–β–substituted acrylonitriles were first generated *in situ* by treating excess acetonitrile (3 eq) with *n*–butyllithium (1.5 eq), and this was reacted with a range of enones **28** generating cyanopyridines (Table 3). The overall yields produced from this method ranged from moderate to excellent, however the experimental procedure makes this method to some extent laborious.

The fluorescent properties of cyanopyridines have sparked much interest in its synthesis to explore their photophysical potential in application. In 1992, a similar reaction to Chatterjea was reported by Matsui and co–workers.[23]

The synthesis of 4,6–disubstituted–3–cyano–2–methylpyridines **31** were prepared by the treatment of α,β–unsaturated carbonyl compounds with β–aminocrotononitrile **20** in the presence of *tert*–butoxide and these were found to show intense fluorescence in the region of 400–552 nm.



Scheme 11. Synthesis of 3–cyanopyridines.

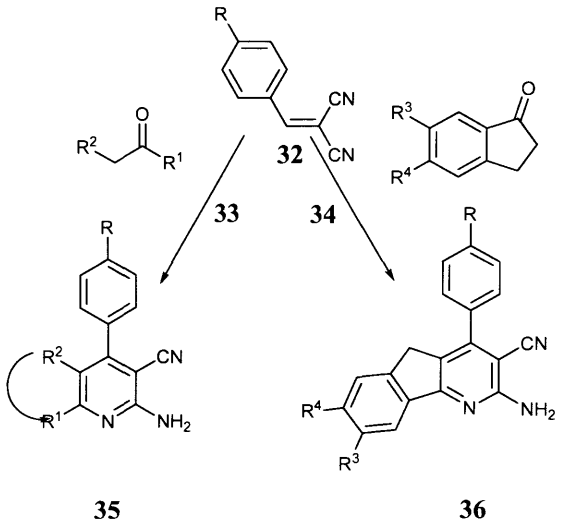


Scheme 12. Proposed mechanism of the synthesis of 3–cyanopyridines.

The mechanism proposed by Matsui and co–workers is very similar to the Bohlmann–Rahtz pyridine synthesis which will be discussed in further detail later on in this chapter. β–Aminocrotononitrile can exist as an amino **20** or an imino **9** isomer in solution. Michael addition of the carbanion of the imino isomer **9a** to **30**, followed by cyclization, with subsequent dehydration gave the 3–cyanopyridines. A variety of 3–cyanopyridines were generated and fluorescence excitation maxima and emission maxima were observed.

With a view to their pharmacological properties, use as important intermediates in preparing heterocyclic compounds and with various synthetic routes available for the synthesis of 2–amino–3–cyanopyridines, these derivative continues to attract much interest. More recently methodology has turned towards optimizing efficiency and facility in the synthesis of cyanopyridines, involving the use of microwave dielectric

heating as a valuable alternative to conventional conductive heating methods for a range of synthetic chemistry.[24]



Scheme 13.

An efficient and simple method was developed by Paul, Gupta and Loupy[25] in 1998 for the rapid synthesis of 2–amino–3–cyanopyridines from arylidenemalanonitriles **32** and ketones **33** or **34** in the presence of ammonium acetate without solvent/containing traces of solvent under microwave irradiation, reducing the reaction times with improvement to yields in comparison to conductive heating.

Table 4. Comparison of yields for 3-cyanopyridines using microwave and classical heating methods.

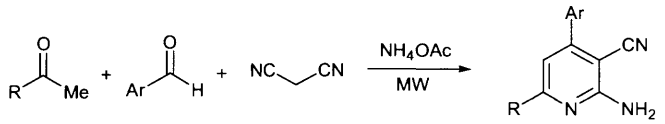
Compound	A (%)	B (%)	C (%)
55a	52	72	49
55b	43	75	46
55c	58	78	69
55d	52	69	46

A=Without solvent in MW. B=Trace solvent in MW. C=Classical reflux with benzene.

The classical approach to the synthesis of cyanopyridines is at reflux in benzene. The same reaction performed under microwave conditions required 3–5 minutes; the yields

observed increased under microwave assisted conditions and were enhanced further by the addition of small amounts of solvent.

Following on from this method, a few years later, Tu and co–workers prepared a series of 2–amino–3–cyanopyridines derivatives by one–pot condensation from malononitrile, methyl ketone **37**, aromatic aldehyde **38** and ammonium acetate under microwave irradiation in the absence of solvents (Scheme 14).



37 **38** **16** **39**

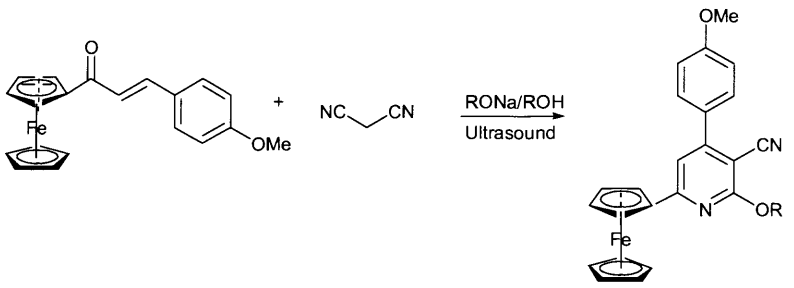
Scheme 14. One–pot synthesis of 2–amino–3–cyanopyridines.

Table 5. Synthesis of 2–amino–3–cyanopyridine **39** microwave irradiation.

Entry	Ar	R	Time (min)	Product Yield (%)
1	4'–C_6H_4Cl	4'–C_6H_4OMe	8	83
2	4'–C_6H_4OMe	4'–C_6H_4OMe	7	80
3	4'–C_6H_4OMe	2',4'–C_6H_4 $(Cl)_2$	7	75
4	4'–C_6H_4OMe	Ph	9	85
5	4'–C_6H_4Cl	2',4'–C_6H_4 $(Cl)_2$	9	72
6	4'–C_6H_4Cl	4'–C_6H_4F	8	78
7	3'–Indolyl	4'–C_6H_4OMe	7	86
8	4'–C_6H_4Cl	Me	8	84

When a mixture of **37, 38** and **16** with ammonium acetate was irradiated in a domestic microwave oven, reactions were almost complete in 7–9 min. The reaction mixtures were washed with a small amount of ethanol and crude products were recrystallized to afford cyanopyridine derivatives in good yields (Table 5). This reaction proceeds via imine formation from aldehyde/ketone and ammonium acetate, followed by reaction of the corresponding enamine with the alkylidenemalononitrile formed by the condensation of aromatic aldehyde and malononitrile, followed by cyclization to form the 2–amino–3–cyanopyridines **39**.

Metallocenes are known to exhibit a wide range of biological properties, one being that ferrocene has attracted special attention since it is a neutral, chemically stable, non–toxic entity that is able to cross cell membranes.[26] The synthesis of 3–cyanopyridine compounds via the condensation of chalcone with malononitriles had been studied previously, but reaction with ferrocenyl (Fc) substituents was not investigated until Ji[27] and co–worker developed an efficient synthesis of ferrocenyl substituted 3–cyanopyridine derivatives via the condensation of ferrocenyl substituted chalcones **40** with malononitrile in a sodium alkoxide solution under ultrasonic irradiation (Scheme 15).

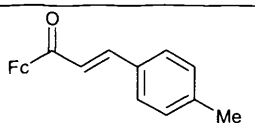
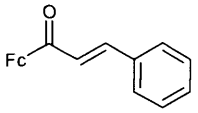
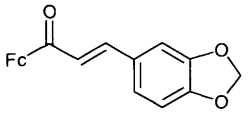
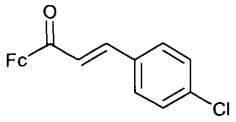
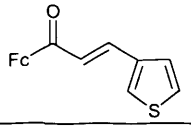


40 **16** **41**

Scheme 15. Synthesis of ferrocenyl substituted 3–cyanopyridine derivatives.

The acceleration of reactions by ultrasound to achieve higher yields, shorter reaction times and improved efficiency was applied to the reaction of chalcone and malononitrile by immersing the mixture into the water bath of a KQ–250E ultrasonic cleaner at 50-60 °C.

Table 6. Reactions with various ferrocenyl substituted chalcones with malononitrile in ethanol.[a]

Entry	Chalcone	Time (h)	Product Yield (%)[b]
1		5	66
2		3	64
3		4	71
4		2	73
5		6	68

Ji and co–workers investigated the effects of ultrasonic irradiation on a range of substrates conducted in EtOH (Table 6). Both phenyl substituted chalcones and the heterocyclic ring containing chalcones reacted efficiently with malononitriles to afford the target products (entries 1–5) in moderate to good yields. It was concluded that a mild, efficient and ultrasound–assisted method for the synthesis of ferrocenyl substituted derivatives had been developed, which could be used as intermediates, ligands for transition–metal ions or new drugs.

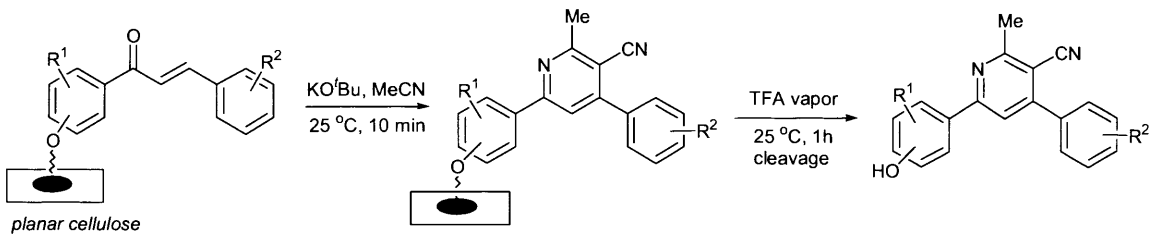
1.1.2 Synthetic Applications

Fluorescent probes have become an essential tool for the investigation of biological systems. Suitable dyes be utilized in their own right, but they can also be incorporated into metal–based architectures where their chromophoric properties can be exploited. This is particularly true of lanthanide–derived assemblies, where the chromophore acts as a sensitizing component facilitating lanthanide–based phosphorescence, which has been exploited in bioassay, responsive chemosensors and intracellular fluorescence imaging.[28]

Therefore, the investigation of new chromophoric dyes that are biologically compatible, from a photophysical perspective, is key to the ongoing development of many of these applications. The photophysical potential of 3–cyanopyridines has been demonstrated recently by Bowman, Jacobsen and Blackwell.[29]

Furthermore, the non–linear optical properties of a series of 2–(pyrrolidin–1–yl)nicotinonitrile derivatives have also been reported.[30] In view of these precedents, it was apparent that a facile, rapid and efficient route to 3–cyanopyridines, that could incorporate a number of points of diversity for modulating electronic and photophysical properties, would be a worthwhile endeavour and might enable the preparation of new and improved fluorescent materials.

In the elegant study by Bowman, Jacobsen and Blackwell, the SPOT synthesis of heterocyclic macroarrays identified fluorescent 3–cyanopyridines that exhibited large Stokes shifts, promising solvatofluorochromic properties and exceptionally high quantum yields. Small molecules of cyanopyridines and deazumazines were generated in high purity via a spatially addressed synthesis on planar cellular supports.



42 **43** **44**

Scheme 16. Synthesis of heterocyclic macroarrays and cyanopyridines.

Table 7. Structures, purity data and spectral properties of selected cyanopyridines **44**.

Entry	R^1	R^2	λ_{ex} (nm)	λ_{em} (nm)	Φf^b	Product Yield (%)[a]
1	4'–OH	H	341	433	0.07	81
2	4'–OH	4'–F	342	430	0.06	81
3	4'–OH	4'–Br	342	440	0.12	82
4	4'–OH	4'–OMe	339	423	0.12	70
5	4'–OH	4'–NMe_2	366	524	0.09	74
6	3'–OMe, 4'–OH	H	351	469	0.03	74
7	3'–OMe, 4'–OH	3'–OMe	351	473	0.02	89
8	3'–OMe, 4'–OH	4'–F	351	466	0.04	71
9	3'–OMe, 4'–OH	4'–Br	352	475	0.02	70

[a] Determined by integration of HPLC traces with UV detection at 254 nm. [b] Relative quantum yields measured in ethanol.

Chalcone macroarray **42** was converted into cyanopyridine macroarray **43** with the treatment of 3–aminocrotononitrile generated in situ from acetonitrile and potassium *tert*–butoxide (Scheme 16). Spotting a presonicated mixture of these reagents onto individual chalcone array at room temperature gave cyanopyridines in good yields (Table 7).

In addition to their fluorescent properties, Bowman and co–workers used these small–molecule macroarrays to identify bacterial agents effective against *Staphylococcus aureus*.[31] These infections represent one of the largest health threats in hospitals and communities. The effectiveness of current antibacterial agents against *S. aureus* has become limited due to the ever increasing resistance of the strain, Bowman and co–workers applied the small –molecule macroarray approach to the synthesis and screening of new antibacterial agents effective against *S. aureus*. Macroarrays of chalcones and heterocycles were constructed and subjected to a suite of antibacterial assays conducted either on or off the macroarray support. Their studies revealed that the chalcones and cyanopyridine derivatives with in vitro MIC (minimum inhibitory concentration) values against *S. aureus* prepared on support were comparable to established antibacterial agents. Furthermore, these compounds displayed similar activity against a methicillin resistant *S. aureus* with selectively for certain Gram–positive bacteria.

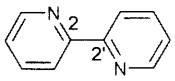
1.1.3 Conclusion

There are a range of efficient methods for the synthesis of cyanopyridine derivatives. For each desired pyridine, the number, nature and pattern of substituents is dictated by the suitability of each strategy. There is a continuing need to improve and expand on the different methodologies available for pyridine synthesis. With synthetic applications, drug discovery, antibacterial agents and in view of their fluorescent properties, it has become ever more demanding now to discover new synthetic strategies and uses for cyanopyridines.

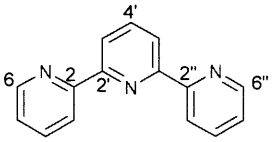
1.2 BIPYRIDINES AND TERPYRIDINES SYNTHESIS

1.2.1 Introduction

Within synthetic organic chemistry, pyridines are extensively utilised in coordination chemistry: bipyridines **45**, terpyridines **46**, and oligopyridines, have an excellent ability to complex various metal ions, including ruthenium, zinc and copper. These functional ligands have found a multitude of applications in building blocks of ribozyme mimics,[32] photochemistry,[33,34] highly sensitive analytical reagents sensor systems, photocatalysis, luminescent chemosensors, electroluminescent materials,[35,36] luminescent agents for labelled peptide synthesis and building blocks for supramolecular chemistry [37] since the first discovery of terpyridines in 1932 by Burstall and Morgan almost 70 years ago.[38]



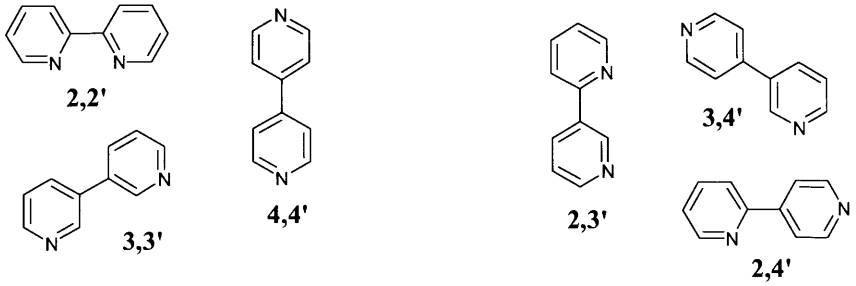
45



46

Scheme 17. Structures of 2,2'–bipyridine and 2,2':6',2''–terpyridine.

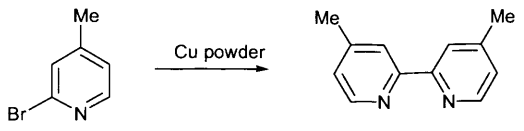
Since the discovery of bipyridines at the end of the nineteenth century,[39] the pyridine ligand has been used extensively in the complexation of metals. The isomers of bipyridines can be (2,2', 3,3' and 4,4') or asymmetrical (2,3', 2,4' and 3,4') (Scheme 18).



Scheme 18. Symmetrical and asymmetrical isomers of bipyridine **45**.

1.2.2 Initial Studies

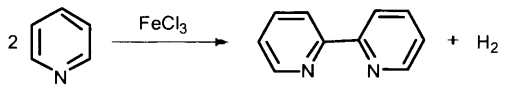
Many methods have been developed for the synthesis of bipyridines and terpyridines. Some reactions incorporate the use of metals, or alkylpyrdinium salts and α,β–unsaturated ketones with ammonium acetate as a source of nitrogen. Some of the initial studies performed for the synthesis of bipyridines usually gave poor yields. In 1938, Burstall[38] treated 2–bromo–4–methylpyridine **47** with copper powder and synthesized 4,4'–dimethyl–2,2'–bipyridine **48** in a 33% yield. It was found that the bromide was preferable to iodide or chloride and in addition, the presence of a *p*–nitro group did not improve the efficiency, for example, achieving a 2.2% yield for 5,5'–dinitro–2,2'–bipyridine from 2–iodo–5–nitropyridine.



47 **48**

Scheme 19. Synthesis of 4,4'–dimethyl–2,2'–bipyridine.

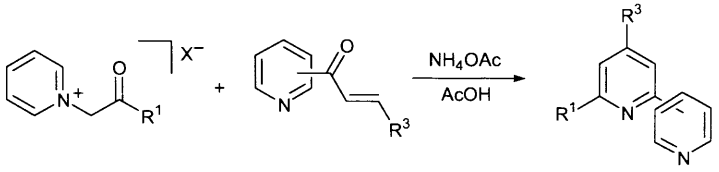
By increasing the reaction temperature greatly to 300–350 °C, 2,2'–bipyridine **45** was formed as the predominant product resulting from the reaction of ferric chloride and pyridine (Scheme 20).[38, 40]



6 **45**

Scheme 20. Synthesis of 2,2'–bipyridine.

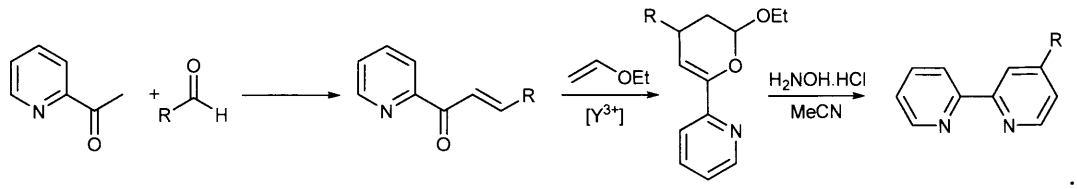
A well known procedure developed by Krönke, and occasionally used today, is the reaction of pyridinium salt **49**, (obtained from an aldehyde and an acetylpyridine) with ammonium acetate giving rise to a bipyridine, one pyridine nucleus of which originates from the unsaturated pyridyl ketone **50**. Bipyridines were generally formed in low yields (usually around 30%) by this method (Scheme 21).[41]



49 **50** **51**

Scheme 21. Synthesis of 2,2'–bipyridine.

More recently Bergmann, McCusker and Cordaro[42] developed a new synthetic route to the substituted 2,2'–bipyridines **51** (Scheme 21). Previous studies on the synthesis of terpyridines have lead to these compounds being formed *via* an aldol condensation and Michael addition utilizing acetylpyridine and substituted benzaldehydes.[43] Based on this methodology, Bergmann and his group synthesized bipyridines using the product of the aldol condensation reaction. Employing freshly distilled 2–acetylpyridine **52** and substituted benzaldehyde, heterodiene products **53** were isolated in 40–85% yield.



52 **17** **53** **54** **55**

Scheme 22. Synthetic route to bipyridines.

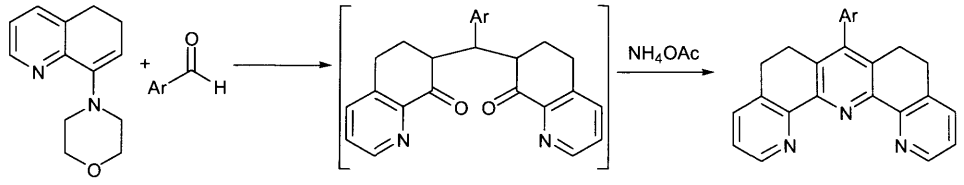
Although this reaction was successful in synthesizing bipyridine derivatives, the procedure does require multi–step preparation. The conversion of enone **53**, to dihydropyran **54** was catalyzed by commercially available yttrium (III) hexafluoroacetylacetonate, (abb [Y^{3+}]) with ethyl vinyl ether in THF or DCM at room temperature. As a source of nitrogen $H_2NOH{\cdot}HCl$ was used for the final synthesis to the product. A range of substituents were applied to this three step synthetic reaction sequence and the yields for the final product isolation ranged between 10–40%.

Table 8. Yields for the synthesis of bipyridines products.

Entry	R	Product Yield (%)[a]
1	4'–C_6H_4F	35
2	4'–C_6H_4Br	41
3	2',4',6'–$C_6H_4(OMe)_3$	41
4	4'–C_6H_4OMe	36
5	Ph	25
6	4'–$C_6H_4NO_2$	18

[a] Bipyridine yield with isolation of intermediate

The use of ammonium acetate is widely prevalent in the synthesis of terpyridines as a valuable nitrogen source. Thummel, Hedge and Yang[44] treated enamines, with paraformaldehyde followed by hydrolysis. Diketone intermediate **57** was formed and reacted directly without isolation with ammonium acetate to give the polycyclic terpyridines **58** albeit in poor yield.



56 **38** **57** **58**

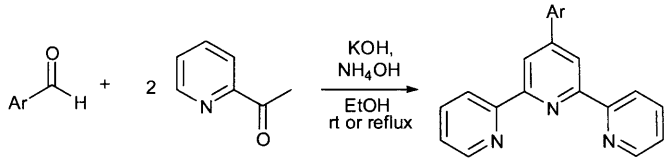
Scheme 23. Synthesis of terpyridines.

Table 9. Preparation of 4'–substituted bis–annelated terpyridines from aromatic aldehydes.

Entry	Aldehyde	Terpyridine Yield (%)
1	Benzaldehyde	20
2	*p*–Tolualdehyde	39
3	*p*–Chlorobenzaldehyde	35
4	*p*–Nitrobenzaldehyde	19
5	4–Benzyloxyaldehyde	31
6	3–Pyridinecarboxaldehyde	53
7	4–Pyridinecarboxaldehyde	36
8	Ferrocenecarboxadlehyde	26

A range of aldehydes were used to explore the scope of this method and generated the corresponding terpyridines in relatively low to moderate yields with aromatic aldehydes reacting favourably (Table 9). Reactions performed with aliphatic aldehydes did not produce the desired terpyridines.

Transition metal complexes of polypyridyl ligands have been a target in coordination chemistry due to their potential utility in a range of applications, As part of their studies into the Ru(II) complexes of terpyridines, Hanan and Wang[45] developed a facile route to a variety of 4'–aryl–terpyridine ligands.



38 **52** **59**

Scheme 24. One–pot synthesis of 4'–aryl–2,2':6',2"–terpyridine.

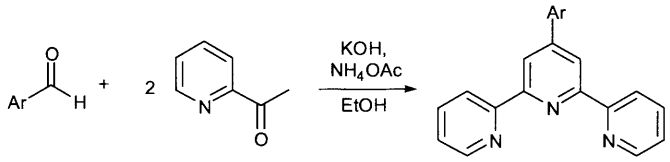
This study led to the development of a one–step reaction of aryl aldehydes and 2–acetylpyridine (Scheme 24). The enolate of 2–acetylpyridine can be generated by KOH, followed by aldol condensation and Michael addition, which all proceeded at room temperature. The soluble diketone intermediate then formed the pyridine ring with an aqueous ammonium nitrogen source, and the ligands precipitated from the reaction mixture.

Table 10. One–pot synthesis of 4'–aryl–2,2':6',2"–terpyridine.

Enrty	R	Time (hr)	Product Yield (%)
1	Ph	2	53
2	4'–C_6H_4Me	2	49
3	4'–C_6H_4CN	4	42
4	4'–C_6H_4OH	12	43
5	4'–C_6H_4NBr	2	56
5	4'–$C_6H_4N(Me)_2$	12	25
6	4'–$C_6H_4NO_2$	4	51
7	4'–C_6H_4OMe	12	20
8	2',3'–$C_6H_4(OMe)_2$	24	27
9	2'–Pyridyl	4	42
10	4'–Biphenyl	4	48
11	4'–Napthyl	4	42

The synthesis of a range of phenyl–based pyridine ligands was realized, generating terpyridines in low to moderate yield. These findings led the group to apply these conditions and introduce organic chromophores into the tpy moiety, a step which prolonged the room temperature luminescence lifetime of $Ru(tpy)_2^{2+}$ complexes by the bichromophore approach.[46]

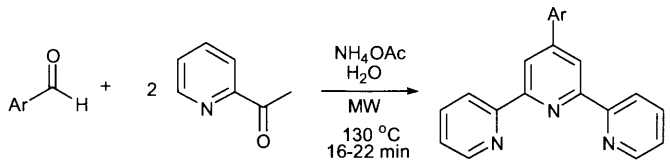
Following on from the procedure developed by Hanan and Wang, a very similar synthesis of terpyridines was also performed using microwave irradiation, a choice of system that is growing in popularity due to improvements in efficiency and speed that can be realized for a range of organic reactions when compared to conventional heating methods. Tu[47] and co–workers in 2006 accomplished a one–pot Krönke reaction process for the synthesis of terpyridines **59** from 2–acetylpyridine **52** with aromatic aldehyde **38** and ammonium acetate in glycol under microwave irradiation.



38 **52** **59**

Scheme 25. General Krönke reaction for the synthesis of terpyridines.

The general method for the Krönke reaction for the synthesis of terpyridines is highlighted in scheme 26. Tu and co–workers exploited this method for the synthesis of 2,2':6',2" terpyridines **59** with the use of microwave irradiation (Scheme 26).



38 **52** **59**

Scheme 26. Synthesis of terpyridine under microwave irradiation.

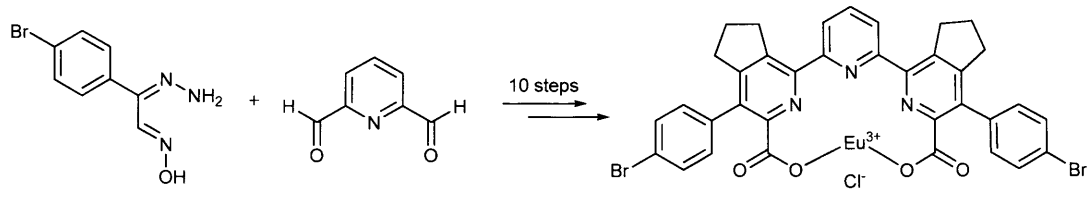
Table 11. Synthesis of 2,2':6',2" terpyridine under MW and conventional heating at 130 °C.

Entry	Ar	Microwave Time (min)	Irradiation Yield (%)	Conventional Time (min)	Heating Yield (%)
1	4'–C_6H_4Cl	16	92	240	78
2	4'–C_6H_4Br	16	91	180	81
3	2'–C_6H_4Cl	16	90	180	70
4	4'–C_6H_4F	18	90	240	72
5	Ph	24	82	300	71
6	4'–$C_6H_4NO_2$	22	92	300	80
7	3'–$C_6H_4NO_2$	22	87	300	75

A series of products were synthesized using both heating methods and a comparison was made. Results indicated that all reactions performed under microwave irradiation generated the resulting products in good yield (Table 11) indicating that microwave irradiation exhibited several advantages over conventional heating by significantly reducing the reaction time and improving the reaction yields.

1.2.3 Synthetic Applications

The potential properties of terpyridines have enabled chemists to take advantage of these compounds and use then in a range of applications. One such example are europium chelates, that are widely used in due to their unique luminescence properties for various bioanalytical applications such as non–radioactive in time–resolved fluorescence immunoassays or DNA hybridization assays.[48] In 2003, Kozhenikov, König[49] and co–workers synthesized the substituted terpyridines via triazine intermediates. These intermediates allowed the introduction of cyano groups, which were converted into amino diacetic acid moieties. Together with the terpyridine nitrogen atoms they shielded coordinated europium (III) ions completely from the solvent.

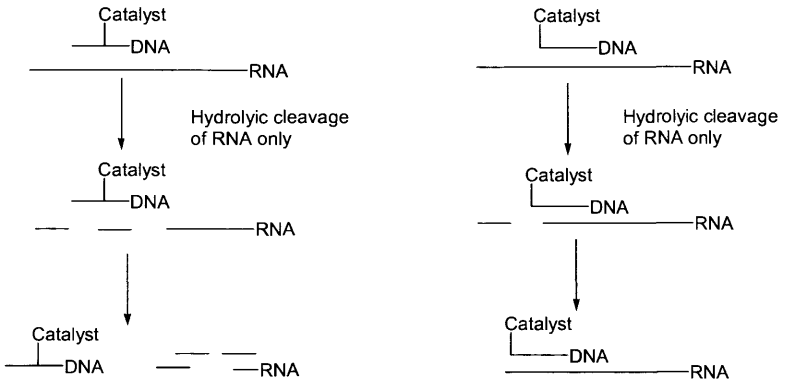


60 **61** **62**

Scheme 27. Synthesis of europium complex.

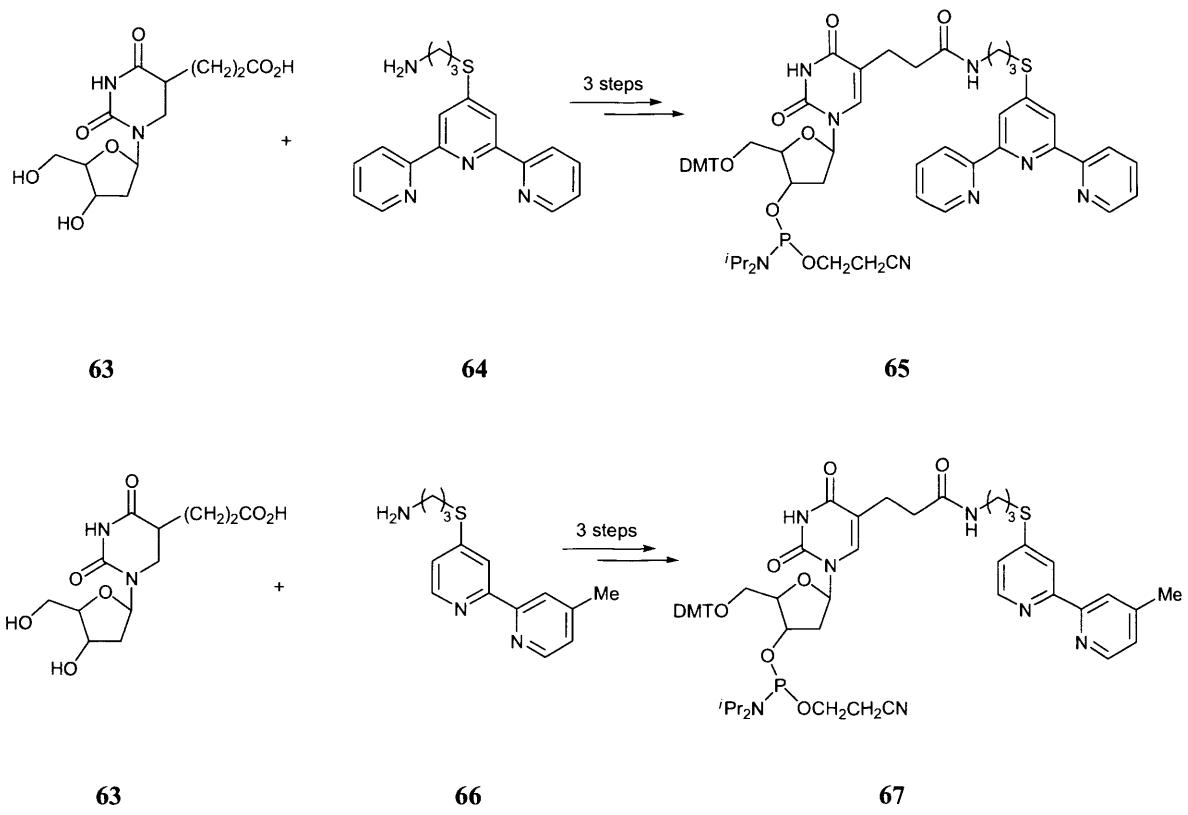
The terpyridines were further functionalised for specific applications as ligands, using bromo substituents in standard transition metal mediated coupling methods, making these terpyridines valuable intermediates for the preparation of luminescence probes in biochemistry, medicinal diagnostics and material sciences. The main advantages for Eu^{3+} luminescence probes are their long emission wavelength excitation lifetimes, allowing easy separation of the output signal from short–lived background noise in the sample. However, solvated lanthanide metals ions have a weak absorption and fluorescence, and a harvesting ligand is required to enhance photophysical properties. Light energy absorbed by the ligand is intramolecularly transferred to the Eu^{3+} ion and emitted as the characteristic spectrum of Eu^{3+}. The terpyridine moiety coordinates directly to the europium ion, harvesting light energy and efficiently transfering the energy to Eu^{3+} (Scheme 27).

Since 1986, Baskin and co–workers[50] had been working on the preparation of catalytically active ribozyme mimics, sequence–specific reagents for the hydrolytic cleavage of RNA. These ribozyme mimics contain a deoxyoligonucleotide, designed to form a sequence–specific RNA/DNA duplex by Watson–Crick base–pairing, and a pendent metal complex designed to cleave the target RNA.



Scheme 28. Diagramatic representation of RNA cleavage.

The catalytic cycle involved the binding of the ribozyme mimic to the RNA target, cleaving the RNA and releasing the cleaved RNA fragment to regenerate the catalyst. Failure to release the RNA fragments would result in product inhibition. The use of the DNA building blocks avoided product inhibition and achieving a turnover. Cleavage of the *internal* residue in the RNA/DNA duplex decreases the stability of the duplex and allowed the product fragments to be displayed by the new substrate molecule, due the RNA–DNA binding constants depending on the length and sequence of the duplex. Cleavage *outside* the duplex has no effect on the RNA–DNA binding, therefore product cannot be released efficiently from the "catalyst" (Scheme 28).



63 **64** **65**

63 **66** **67**

Scheme 29. Synthesis of the ribozyme mimics; conjugates of terpyridine and bipyridine with nucleosides.

The incorporation of 2,2',:6',2''–terpyridyl complex of Cu(II) **64** into a deoxyoligonucleotide **63** resulted in the formation of the ribozyme mimics containing 2,2'–bipyridines **66** or terpyridyl ligands **64**. The ligands were attached to either a nucleobase or sugar to allow attack across either the major groove or minor groove of an RNA/DNA duplex, thus forming modified nucleoside building blocks for rybozyme mimics (Scheme 29).

1.2.4 Conclusion

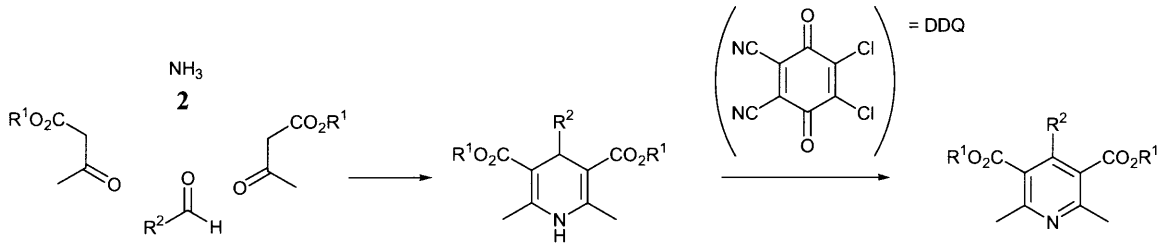
The chemistry of pyridines, bipyridines and terpyridines has been a subject of wide and increasing interest. With importance to analytical and coordination chemistry, studies on their chemical, biological and photophysical properties have been an enhanced by organic chemists in the pursuit of improved synthetic routes, optimizing the yields, scope and efficiency of reactions.

1.3 PYRIDINE SYNTHESIS

With an ever increasing interest in the synthesis of pyridines, numerous diverse routes have been developed, of the many ways to conduct these heterocycles, most syntheses of pyridines rely upon one of two approaches: the condensation of carbonyl compounds or cycloaddition reactions, which will be discussed in turn.

1.3.1 Hantzsch Pyridine Synthesis

The classical Hantzsch pyridine synthesis was first published by Hantzsch in 1882.[51] Symmetrical pyridines are normally generated via this four–component route by the condensation of two equivalents of a 1,3–diacarbonyl compound **63**, aldehyde **17** and ammonia **2** to generate the 1,4–dihydropyridine **133** which in turn is readily oxidized with DDQ **65**, nitrous acid or a plethora of alternative oxidants to give a pentasubstituted pyridine **66** (Scheme 30).

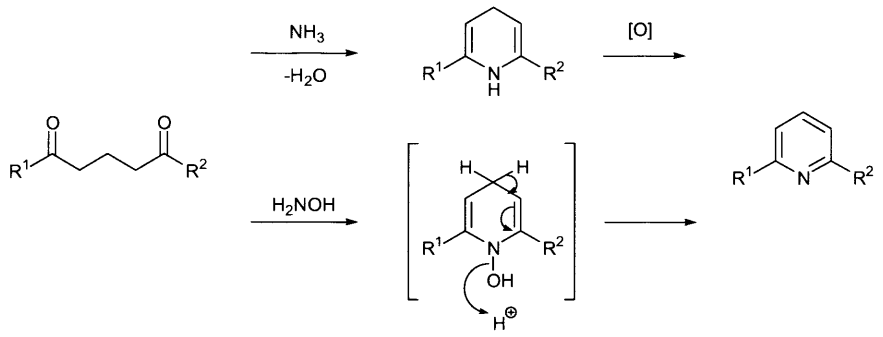


Scheme 30. Hantzsch pyridine synthesis.

Although yields for this reaction are usually good, the initial product requires an additional oxidation step before the desired pyridine is formed, although the intermediate dihydropyridines **64** have interesting biological properties as Ca channel antagonists in their own right.

1.3.2 Condensation Of 1,5–Dicarbonyl Compounds

A simple approach to pyridines involves a 1,5–diketone **67** reacting with ammonia, losing two equivalents of water to produce a 1,4–dihydropyridine **68** precursor which in turn is oxidised (usually by nitric acid) to the disubstituted pyridine **69**.[52] The 1,5–dicarbonyl systems can also be accessed by Michael addition of enolate to enone, or by ozonolysis of cyclopentenes.[53]



67 **68** **69**

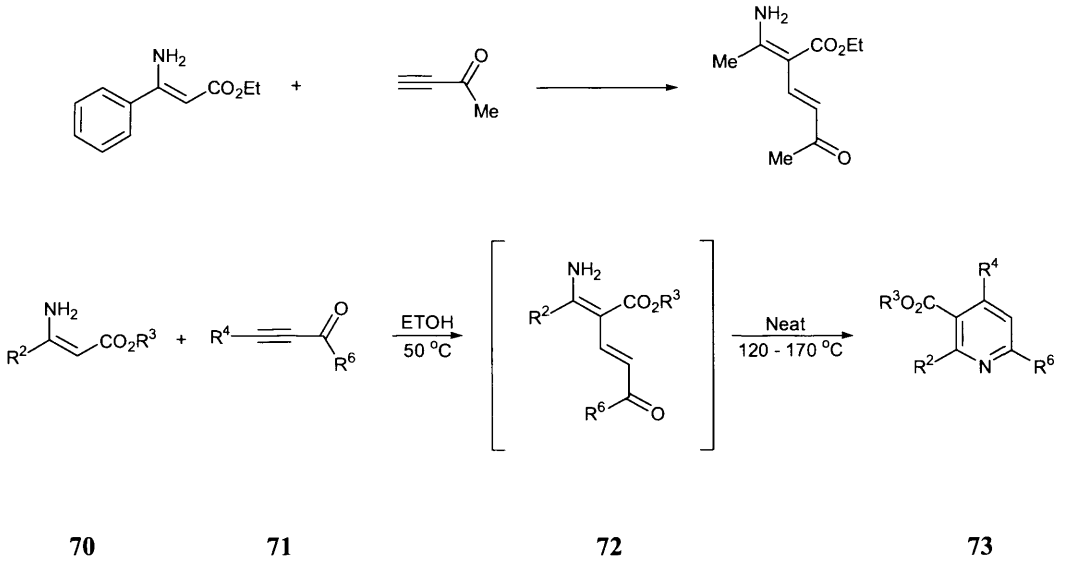
Scheme 31. 1,5–Dicarbonyl condensation pyridine synthesis.

To avoid an additional oxidation step 1,5–diketone **67** can react with hydroxylamine to form the pyridines directly on elimination of water (Scheme 31).[54]

1.3.3 Bohlmann–Rahtz Pyridine Synthesis

Bohlmann and Rahtz first reported the synthesis of trisubstituted pyridines from ethyl aminocrotonate and ethynyl ketones back in 1957.[55] This process had seen little use since its discovery for the synthesis of trisubstituted pyridines and had not been used at all for the synthesis of tetrasubstituted products until Bagley and co-workers began to exploit this method.

The traditional synthesis of trisubstituted pyridine product **73** is a two step process involving initial reaction by Michael addition of an enamine **70** and an ethynyl carbonyl compound **71**, firstly heated in ethanol at 50 °C for 5 hours to provide the corresponding aminodienone **72** in almost quantitative yields. The aminodienone intermediate in turn is isolated and heated at high temperatures to facilitate cyclodehydration to form the corresponding pyridine **73** in good yields after purification (Scheme 32).



70 **71** **72** **73**

Scheme 32. The traditional Bohlmann–Rahtz heteroannulation reaction.

1.3.4 Improvements In The Bohlmann–Rahtz Reaction

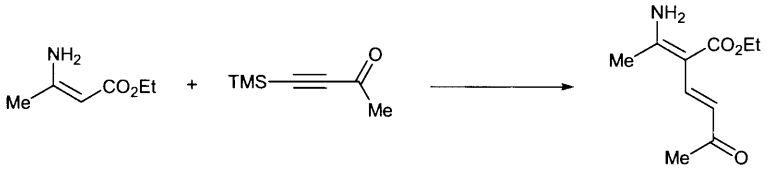
Over the past ten years Bagley and co–workers have been focusing on the potential of the Bohlmann–Rahtz reaction for application in heterocyclic chemistry, and have published numerous improved alternative methodologies that employ various solvents, catalysts, tandem processes and microwave dielectric heating, under milder improved reaction conditions, to give a range of polysubstituted pyridines in good yields. In this chapter the development and modifications of the Bohlmann–Rahtz reaction will be reviewed.

1.3.5 Acid–Catalysed One–Step Bohlmann–Rahtz

Increasing the scope of the Bohlmann–Rahtz reaction, research was carried out to overcome some of the problems found in the original experiment, for example the high temperatures used in the cyclodehydration of the aminodienone, and to develop a one–step procedure. A series of reactions were conducted in order to investigate the improvements, using Brønsted and Lewis acid catalyst for the cyclodehydration of the aminodienone.

Using the standard Bohlmann–Rahtz reaction,[16,56] the aminoheptadienone was prepared from ethyl β–aminocrotonate **74** and 4–(trimethylsilyl)but–3–yn–2–one **75** in ethanol (EtOH) at 50 °C to give the pure cyclodehydration precursor in 98% yield following purification. However due to the shortages in the availability of but–3–yn–2–one, concerns about its volatility and in order to expand the scope of range of alkynone substrates an alternative route to the intermediate was required.

Table 12. Michael addition of **74** and **75** in various solvents at 50 °C



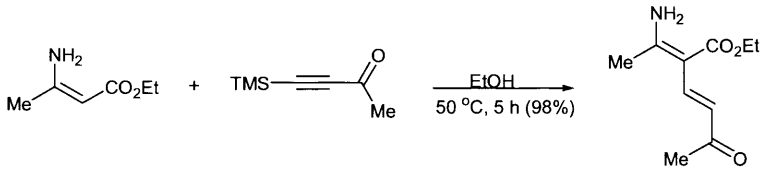
74 **75** **76**

Solvent	Results	Solvent	Results
Acetone	No reaction	Diethyl ether	No reaction
Toluene	No reaction	Neat	No reaction
DCM	No reaction	DMSO	Product 3a (59%)
Chloroform	No reaction	Ethanol	Product 3a (98%)

Therefore a mixture of ethyl β–aminocrotonate **74** and 4–(trimethylsilyl)but–3–yn–2–one **75**, which was cheaper than but–3–yn–2–one, more readily available and less volatile, was heated to 50 °C in a range of different solvents (Table 12).

In most cases, only unreacted starting material was isolated from the mixture. However when a solution of β–aminocrotonate **74** and 4–(trimethylsilyl)but–3–yn–2–one **75** was

stirred in ethanol or DMSO at 50 °C for 5 hours, the aminodienone **76** was produced in 98% or 59% yield respectively, after purification, with the protic solvent ethanol giving better yields than the aprotic solvent DMSO. In both solvents protodesilylation occurred spontaneously under the reaction conditions and, in view of the improvement that this transformation offered over the original procedure, this became the method of choice for the preparation of aminodienone **76** (Scheme 33).

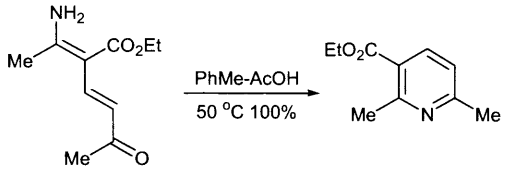


74 **75** **76**

Scheme 33. Synthesis of aminodienone using alkynone **75**.

In order to avoid harsh conditions for the cyclodehydration, it was proposed that the use of Brønsted[57] or Lewis[17] catalysts would promote double bond isomerisation for the aminodienone intermediate **76**, and result in spontaneous cyclodehydration at a lower temperature and thus obviating the need to isolate the conjugate addition product.

This hypothesis was confirmed by stirring aminodienone **76** in toluene (PhMe) and acetic acid (5:1) to generate pyridine **78** in quantitative yield and without the need for further purification (Scheme 34).

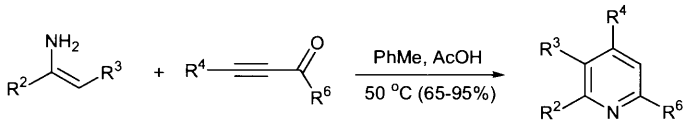


76 **78**

Scheme 34. Synthesis of aminodienone **76** using alkynone **75.**

Further reactions were conducted with a range of enamine esters,[58] which were prepared, and alkynones at 50 °C in toluene–acetic acid (5:1) to produce highly functionalised pyridines in good to excellent yields in a single step (Table 2).[18] Only reactions involving β–aminocrotonitrile were unsuccessful and failed to generate the desired pyridine, attributed to the acid catalysed decomposition of the material. All other experiments were realized in good to excellent yields. Failure to form pyridine (entries 7) was possibly due to the need for ethyl ester/electron withdrawing group in the R^6 position of the alkynone, which clearly enhances for the formation of pyridine in entry 3 (95% yield).

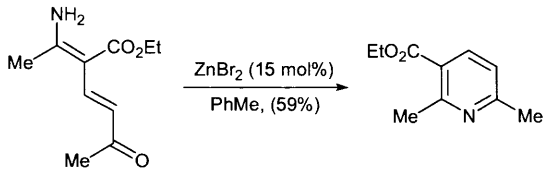
Table 13. Synthesis of functionalised pyridines.



79 **71** **80**

Entry	R^2	R^3	R^4	R^6	Pyridine Yield%
1	Me	EtO_2C	TMS	Me	79
2	Me	EtO_2C	Et	Me	85
3	Me	EtO_2C	Ph	EtO_2C	95
4	Ph	EtO_2C	Et	Me	65
5	Ph	EtO_2C	H	Me	73
6	2'–Furyl	EtO_2C	TMS	Me	80
7	Me	NC	Et	Me	0
8	Me	EtO_2C	Ph	Me	0
9	Me	$^tBuO_2C$	TMS	Me	0

These findings provided a breakthrough in the search for a one–step Bohlmann–Rahtz reaction protocol and a basis for further investigation into alternative methods to promote the cyclodehydration that were compatible with a range of functional groups. To that end, aminodienone **76** was reacted with a number of Lewis acids under a range of conditions.

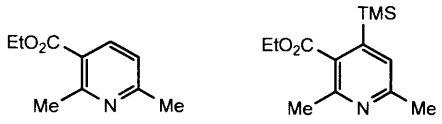


76 **78**

Scheme 35. Pyridine formation from aminodienone by Lewis acid catalyst.

Although the Lewis acids chosen appeared to be less effective than the acetic acid, zinc(II) bromide (15 mol%) in toluene at reflux produced the corresponding pyridine **78** in 59% yield (Scheme 35) when compared to other Lewis acids. and therefore provided possible course for further investigation for an alternative one–step procedure (Table 14).

Table 14. The Lewis acid catalysed cyclodehydration of aminodienone **76** to form pyridine **78** and **79**.



78 **81**

Lewis acid	Conditions	Compound
$BF.OEt_2$	DCM, reflux, 4 h	**78** (no reaction)
$FeCl_3$ (10 mol%)	DCM, reflux, 3.5 h	**78, 81** (3:2)
$Sc(OTf)_3$ (100%)	DCM, reflux, 24 h	**78, 81** (1:3)
$ZnBr_2$ (100 mol%)	DCM, reflux, 24 h	**79** (46%)
$ZnBr_2$ (15 mol%)	PhMe, reflux, 5 h	**79** (59%)

A solution of ethyl β–aminocrotonate **74** and 4–(trimethylsilyl)but–3–yn–2–one **75** in either dichloromethane or toluene was heated at reflux overnight in the presence of 10–100 mol% of a range of Lewis acid catalysts. No reaction occurred in the absence of a Lewis acid catalyst, but in all other experiments pyridine **78** was formed, showing that Lewis acid catalysis promotes both the Michael addition and subsequent spontaneous cyclodehydration. The efficiency of the reactions varied depending on the type and quantity of the Lewis acid and the reaction time and found that the best conditions involved ytterbium(III) triflate (20 mol%), at reflux for 18 hours (90% yield) or zinc(III)

bromide which gave optimum yields when used (15 mol%) at reflux for 5 hours (90%) yield.

With conditions established and to increase the scope of the methodology, a range of enamines and alkynones were reacted by heating in toluene–acetic acid solution in the presence of 15 mol% of zinc(III) bromide for 5 h or by heating in the presence of ytterbium(III) triflate (15 mol%) overnight (Table 15).

Table 15. Comparison of heteroannulation catalysed by $ZnBr_2$ and $Yb(OTf)_3$.

R^2	R^3	R^4	R^6	$ZnBr_2$ Yield (%)	$Yb(OTf)_3$ Yield (%)
Me	CO_2Et	TMS	Me	90[a]	90
Me	CO_2Et	Et	Me	83	67
Me	CO_2Et	Ph	EtO_2C	55	85[b]
Me	CO_2Et	TMS	EtO_2C	33	44[c]
Ph	CO_2Et	Et	Me	32	72
Ph	CO_2Et	Ph	Me	68	62
Ph	CO_2Et	Ph	EtO_2C	44	65
Ph	CO_2Et	H	Me	58	70
2'–Pyridyl	CO_2Et	Et	Me	68	62
Me	$CO_2{}^tBu$	Et	Me	70	14

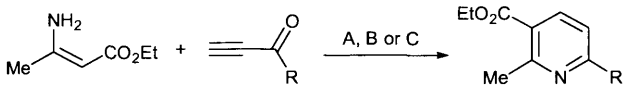
[a]20 mol% catalyst was used. [b]10 mol% catalyst was used.
[c]Desilyliated pyridine (R^4 = H) produced

In almost all cases investigated the desired pyridines were produced in moderate to excellent yield with a few exceptions. Reactions catalysed by zinc(II) bromide provided the better yields, increasing the efficiency of the reaction significantly in shorter time when compared to ytterbium(III) triflate, where prolonged reaction times were required to facilitate complete conversion. Reaction catalysed by zinc(II) bromide gave rise to protodesilylated trisubstituted pyridines in one–step by reaction of the enamine and the alkynone, compared to the two–step traditional Bolmann–Ratz reaction and proved to be an excellent modification of this process for the synthesis of tri- and tetrasubstituted pyridines.

With the success of establishing an acid–catalysed one–pot heteroannulation method, a comparison was made between the acid catalysed routes and the traditional two–step Bohlmann–Rahtz. But–3–yn–2–one **82** or less volatile 1–phenylprop–2–yn–1–one **83**

was reacted with ethyl β–aminocrotonate by the traditional two–step Bohlmann–Rahtz procedure[16] (Method A) and the one–step acid–catalyzed methods (Methods B and C) (Table 16).

Table 16. Comparing the Bohlmann–Rahtz heteroannulation methods.



74 **71** **80**

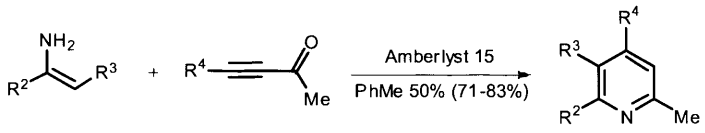
Entry	R	Method	Catalyst	Pyridine Yield (%)
1	Me	A	None	85
2	Me	B	AcOH	77
3	Me	C	$ZnBr_2$	65
4	Ph	A	None	80
5	Ph	B	AcOH	85
6	Ph	C	$ZnBr_2$	86

Reagents: A= EtOH, 50 °C, 5 h; then 140-160 °C; B= PhMe-AcOH (5:1), 50 °C; C= $ZnBr_2$, (15 mol%), PhMe, reflux, 5.5 h.

All three reactions gave the desired pyridine products in excellent yield (Table 16). The least efficient route to the pyridine being the traditional two–step procedure (entry 4). In contrast the direct study shows that the one–step reactions using but–3–yn–2–one **82**, although more convenient, were still not as efficient as the traditional Bohlmann–Rahtz method for this transformation.

Further milder conditions where explored by Bagley, Dale and Bower for conjugate addition–cyclodehydration that were compatible with acid sensitive substrates. A solution of alkynone and enamine in toluene was stirred overnight in the presence of Amberlyst 15 ion exchange resin and the corresponding pyridines were produced in good yields (Table 17).[18]

Table 17. Synthesis of functionalised pyridines catalysed by Amberlyst 15 ion exchange resin.



74 **84** **85**

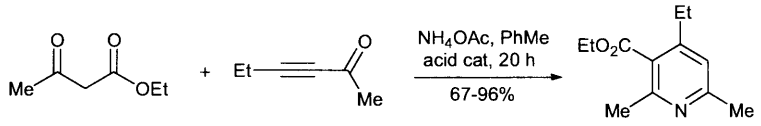
Entry	R^2	R^3	R^4	R^6	Pyridine Yield (%)
1	2'–Furyl	CO_2Et	TMS	Me	73
2	Me	CO_2Et	Ph	Me	71
3	Me	$CO_2{}^tBu$	TMS	Me	83[a]
4	Me	$CO_2{}^tBu$	Et	Me	80
5	Me	$CO_2{}^tBu$	Ph	Me	76

[a]Protodesilyliated pyridine (R^4 = H) produced.

Although reactions involving β–aminocrotononitrile under conditions using a Brønsted acid or acidic resin were unsuccessful (these experiments failed to provide either the aminodienone or pyridine and only recovered starting materials were isolated), all other experiments formed the pyridine were formed in good yield. Also worthy of note was that the protodesilylated pyridine was not produced in the synthesis of pyridine (entry 1). Overall the new methods compared favourably due to their simplicity over other procedures for the synthesis of tri– and tetrasubstituted pyridines avoiding the harsh conditions.

Having explored a range of successful reactions and conditions for the two–component reaction, further improvements were needed to overcome another weakness of the Bohlmann–Rahtz method: the poor availability of enamine substrates which restrict the applicability of the reaction. Bagley, Dale and Bower proposed that the enamine could be generated *in situ* from the reaction of β–ketoester and ammonia. Once formed, the enamine would then react with the alkynone, generating the pyridine product, improving the whole process considerably in a new multiple–component condensation reaction.[59]

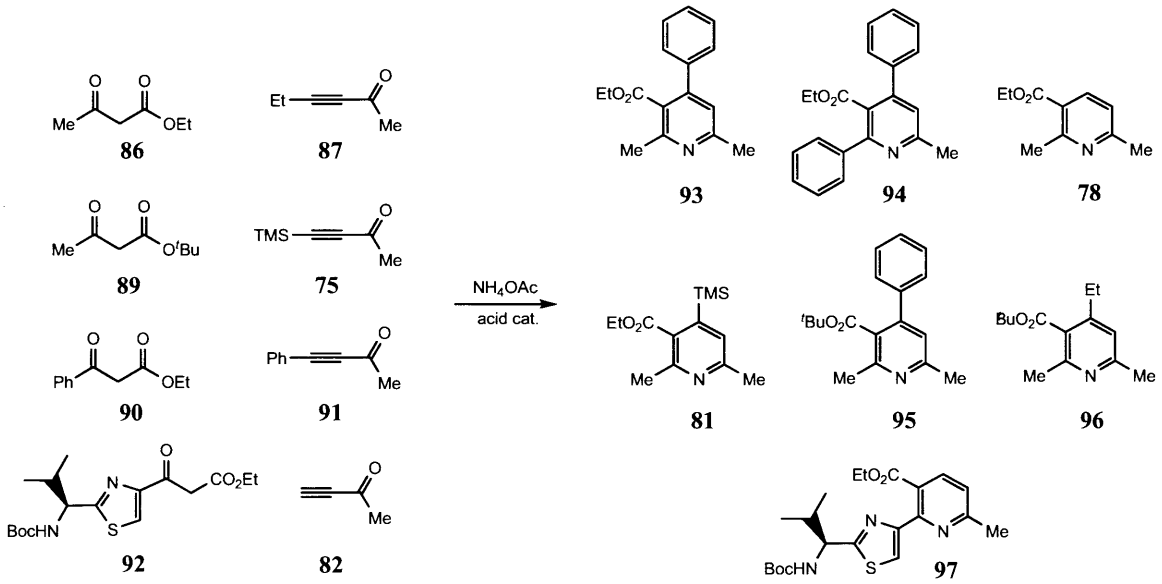
In order to test the validity of the proposal for the one–step synthesis of polysubstituted pyridines via a three–component condensation, ethyl acetoacetate **86** was reacted with either one or two equivalents of hex–3–yn–2–one **87** and ammonium acetate in toluene, heated at reflux in the presence of either acetic acid or zinc(II) bromide (Scheme 36).



86 **87** **88**

Scheme 36. Three component condensation under acidic conditions.

In all cases, pyridine **88** was formed directly as the only reaction product isolated in good to excellent yield in a single preparative step, formed as a single regioisomer. Optimum results were found when two equivalents of alkynone, the zinc(II) bromide catalyzed reaction gave the best result (96%), compared to acetic acid (78%).



Scheme 37. Three–component heteroannulation of β–ketoester, alkynone and ammonia under acidic conditions.

Having found a general set of conditions that performed well, a range of β-ketoesters **86, 89, 90,** and **92** and alkynones **75, 82, 87** and **91** were reacted under acidic conditions in the presence of ammonium acetate (Scheme 37). In all cases that were investigated, the pyridine was isolated in good to excellent yield, ranging from a reasonable 49% to an excellent 96% as the only regioisomeric reaction product (Table 18).

Table 18. Examining the scope of the heteroannulation reaction refluxed in toluene.

Entry	β–Ketoester **132**	Alkynone **141**	Equivalents of **141**	Acid catalyst	Product	Yield (%)[a]
1	**86**	**87**	2	$ZnBr_2$	**88**	96
2	**86**	**91**	2	AcOH	**93**	80
3	**90**	**91**	2	AcOH	**94**	70
4	**90**	**91**	2	$ZnBr_2$	**94**	88
5	**90**	**75**	2	$ZnBr_2$	**81, 96**	55
6	**86**	**75**	2	AcOH	**78**	75
7	**89**	**87**	3	$ZnBr_2$	**96**	49
8	**89**	**91**	2	Amberlyst 15	**95**	53
9	**89**	**91**	3	Amberlyst 15	**95**	60
10	**89**	**87**	3	Amberlyst 15	**96**	55
11	**92**	**82**	3	AcOH	**97**	68[b]
12	**92**	**82**	3	AcOH	**97**	71[bc]

[a] Yield of pure isolated product. [b]Formed in 78% *ee* (entry 1) or 98% *ee* (entry 12) by HPLC analysis [Chiralpak AD column, hexane-IPA]. [c]Refluxed in benzene.

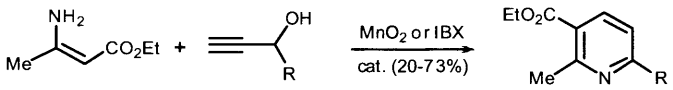
When 4–(trimethylsilyl)but–3–yn–2–one **75** was reacted with ethyl acetoacetate **166** in the presence of zinc(II) bromide, partial protodesilylation occurred to give a mixture of pyridine **81** and **96** (entry 5). However, by employing acetic acid as the catalyst, only a single pyridine **78** was produced in 75% yield (entry 6). The use of *tert*–butyl acetoacetate **89** caused a reduction in the efficiency of the process but pyridine **165** was still isolated in moderate yield under zinc(II) bromide or Amberlyst 15 ion exchange resin catalyzed conditions (entries 7 and 9). The synthesis of the *N*–*tert*–butoxycarbonyl–protected valine derived thiazolyl pyridine **97**, resulted in a high degree of racemisation in toluene (entry 11), which is likely due to protonation of the nitrogen, although these problems were overcome by switching to benzene as a solvent.[20] There was now further scope for the development of novel methods for three component heteroannulation in the synthesis of pyridines.

1.3.6 Tandem Oxidation–Heteroannulation Bohlmann–Rahtz Pyridine Synthesis

Extending the findings for a new method for the synthesis of pyridine heterocycles led to the development of a facile one–pot transformation involving the *in situ* oxidation–heteroannulation of propargylic alcohols **174** with ethyl β–aminocrotonate **144** using *o*–iodobenzoic acid (IBX) or manganese dioxide as oxidant, to form pyridines in good

yields.[60] A range of conditions were investigated and optimum conditions involved heating the enamine **86** and a one–fold excess of both the propargylic alcohol **98** and IBX in dimethylsulphoxide–acetic acid (5:1) at 65 °C overnight to give pyridine **99**, in 70% isolated yield after purification on silica.

With successful conditions established for the tandem process, a range of propargylic alcohols **98** was submitted to *in situ* oxidation–heteroannulation with ethyl β–aminocrotonate **99** mediated by IBX in DMSO–acetic acid (5:1) at 65 °C (Scheme 38).



86 **98** **99**

Scheme 38. Tandem oxidation–heteroannulation of propargylic alcohols **98** in the synthesis of pyridines **99**.

It was found that the efficiency of the reaction was highly dependent on the nature of the propargylic alcohol and the corresponding pyridines **99** were generated in between 20% and 73% yield (Table 19).

Table 19. One–pot synthesis of pyridines mediated by IBX.

Entry	Alcohol R	Pyridine Yield (%)[a]
1	Ph	70
2	Me	45
3	Et	20
4	4'–C_6H_4Cl	73
5	4'–C_6H_4OMe	53

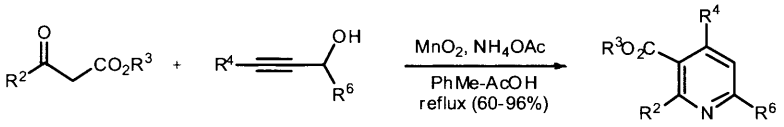
[a] Isolated yield after purification on silica

It was postulated that the moderate yields of the one–pot process was a consequence of the oxidative degradation of ethyl β–aminocrotonate **86** under the reaction conditions. Thus, generating the enamine **70** *in situ* by the condensation of the β–ketoester precursor

and ammonia should help reduce enamine degradation and establish a new three–component condensation route in a single preparative step.

When a range of propargylic alcohols **98**, β–ketoesters **101** and ammonium acetate were heated at reflux in toluene–acetic acid (5:1) in the presence of manganese dioxide, pyridines **73** were formed in high yield and with total regiocontrol.[21]

Table 20. Synthesis of pyridines via propargylic alcohol and β–Ketoester mediated by MnO_2.



100 **101** **73**

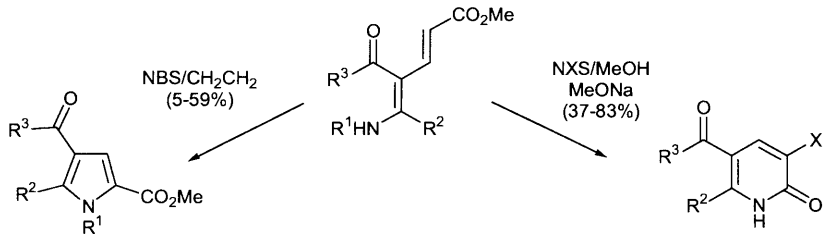
Entry	R^2	R^3	R^4	R^6	Pyridine Yield (%)
1	Me	CO_2Et	H	Me	66
2	Me	CO_2Et	H	4'–C_6H_4Cl	96
3	Me	CO_2Et	H	4'–C_6H_4OMe	85
4	Me	$CO_2{}^tBu$	Et	Me	60
5	Me	$CO_2{}^tBu$	H	Ph	73
6	Ph	CO_2Et	H	4'–C_6H_4Cl	63

A one–pot synthesis of pyridines involving the *in situ* oxidation–heteroannulation of propargylic alcohols and the simultaneous formation of enamines using either IBX or manganese dioxide provides an alternative tandem route to tri– and tetrasubstituted pyridines, effecting up to four separate synthetic transformations in a single preparative step.[21]

1.3.7 *N*–Halosuccinimide–Mediated Reactions For Pyridine Synthesis.

In continuing the development of new routes able to incorporate increased diversity in the synthesis of polysubstituted heterocycles, the bromocyclization of aminodienone intermediates generated by the traditional Bohlmann–Rahtz reaction was explored.

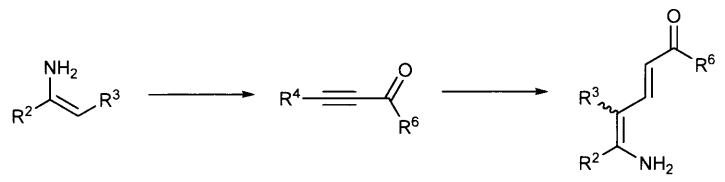
Dechoux reported that when δ–dienaminoesters **103** where were treated with *N*–bromosuccinimide (NBS) under neutral conditions, 1,2,3,4–tetrasubstituted pyrroles were formed,[61,62] whereas under basic conditions treatment with *N*–halosuccinimides generated the corresponding 3–halo–2–1*H*–pyridones **104** in reasonable yield.[63]



102 **103** **104**

Scheme 39. Dechoux's synthesis of pyrroles **102**[22] and pyridones **104**.[23]

Based upon this precedent, the NBS–mediated bromocyclization of Bohlmann–Rahtz intermediates, generated by a Michael addition, under neutral conditions was expected to provide a two–step route to pyrrole heterocycles (Scheme 39).

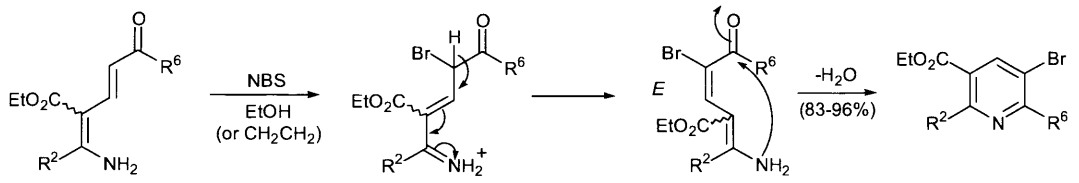


70 **71** **72**

Scheme 40. Synthesis of Bolmann–Rahtz intermediates.

In order to examine the scope of the heteroannulation procedure, a subset of aminodienones was first prepared.[16] Bromocyclization of aminodienone (R^2=Me, R^3=CO_2Et) with NBS was investigated in DCM at 0 °C according to the reported conditions.[22] Surprisingly, no pyrrole **102** could be isolated from the reaction mixture and instead a facile bromination–cyclodehydration occurred to give the bromopyridine

108 (Scheme 42) in 63% yield along with a trace of trisubstituted pyridine, which could be easily separated from the main product by washing with dilute acid as a consequence of the reduced basicity of the 5–bromopyridine.[64]



105 **106** **107** **108**

Scheme 41. Proposed mechanistic course for bromocyclisation.

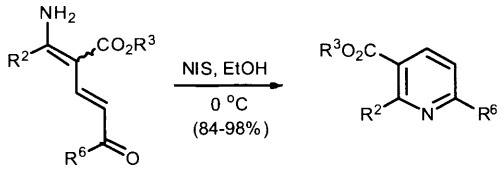
The course of the reaction was rationalized by considering initial regioselective addition to give *s–cis* bromide **106**, in equilibrium with the *s–trans* conformer (Scheme 41). Deprotonation rather than intramolecular nucleophilic substitution, prevents the formation of pyrrole **102**, and gives (4*E*)–hexa–dienone intermediate **196**, thus avoiding the need for double bond isomerisation and undergoing spontaneous cyclodehydration under mild conditions to give the pyridine **108**. It was expected that the cyclization of bromodienone **107** to pyridines **73** would be much more facile than the corresponding cyclization of δ–dienaminoesters, to give pyridinones, and so this proceeded under milder conditions in the absence of sodium methoxide base. In order to explore the bromination–heteroannulation procedure, a range of different aminodienones was treated with NBS at 0 °C for between 30 and 60 minutes. It was found that reactions conducted in EtOH, as opposed to CH_2Cl_2, were much more efficient, reducing the formation of the trisubstituted pyridines as a byproduct to give the corresponding 5–bromopyridines in excellent yields (Scheme 41, Table 21).

Table 21. Bromocyclization of Aminodienones.

Entry	R^2	R^4	R^6	Yield (%)
1	Me	Et	Ph	92
2	Me	Et	4'–C_6H_4OMe	88
3	Me	Et	4'–C_6H_4Cl	89
4	Me	Et	Me	96
5	Ph	Et	Ph	83[a]
6	Ph	Et	Me	>98
7	Me	^{t}Bu	Me	97

[a] Reaction run at –10 °C to prevent formation of pyridine

It was further decided to investigate other *N*–halosuccinimides in the halogenation/ heteroannulation process. The use of *N*–chlorosuccinimide in EtOH at 0 °C led to a complex mixture of products. However when aminodienones (entries 1–9) were treated with *N*–iodosuccinimide (NIS) under the same conditions, none of the 5–iodopyridines were produced. Instead an extremely facile cyclodehydration of the normally stable dienes **72** occurred to give the 2,3,4–trisubstituted pyridines (Scheme 42, Table 22).[17] Furthermore, the use of catalytic quantities of NIS (20 mol%) did not adversely affect the course or efficiency of the reaction, generating pyridine **73**, in quantitative yields.



72 **73**

Scheme 42. NIS–Mediated cyclodehydration of aminodienones.

Table 22. Cyclodehydration of aminodienones **73** with NIS.

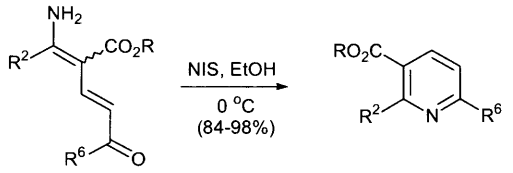
Entry	Product	R^2	R^6	Yield (%)
1	Me	Et	Ph	>98
2[a]	Me	Et	Ph	>98
3	Me	Et	4'–C_6H_4OMe	>98
4	Me	Et	4'–C_6H_4Cl	97
5	Me	Et	Me	66
6[b]	Me	Et	Me	71
7[c]	Me	Et	Me	84
8	Ph	Et	Me	>98
9[b]	Me	^{t}Bu	Me	>98

[a] A catalytic (20 mol%) quantity of NIS was used.
[b] Reactions were run in the presence of $NaHCO_3$.
[c] Reaction was run over the course of 4 h rather than 1 h.

It was proposed that the Lewis acidity of NIS was responsible for this facile cyclodehydration, that traditionally requires temperature in excess of 120 °C, and this was supported with further experimentation. Repeating the process in the absence of NIS returned only unreacted starting material, aminodienone, **72**. When the NIS was purified by recrystallization prior to use, or employed in the presence of $NaHCO_3$ (to remove HI present or generated in the course of the reaction), this did not affect the yield of pyridine **73**, and in some instances improved the reaction efficiency, thus representing a mild method for the low. This procedure therefore represented a very mild method for cyclodehydration to give trisubstituted pyridines.

1.3.8 Iodine Mediated Cyclodehydration

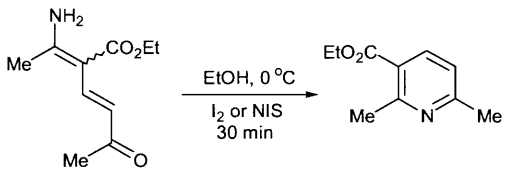
Although it was evident that traces of HI had not catalyzed the NIS process, it could not be ruled out that traces of iodine (generated by photochemical decomposition) were mediating the reaction. To test this hypothesis aminodienone **72**, the least efficient substrate in the *N*–iodosuccinimide cyclodehydration reactions, was reacted with a stoichiometric amount of either iodine or *N*–iodosuccinimide in ethanol at 0 °C for 30 minutes (Scheme 43).



72 **73**

Scheme 43. NIS mediated cyclodehydration.

Under these conditions both reactions gave efficient conversion to pyridine **78** (Scheme 44), but the iodine cyclodehydration was superior, generating the product in quantitative yield after a simple work up.



76 **78**

Scheme 44. Cyclodehydration of B–R intermediate.

These transformations were then repeated in the presence of two equivalents of sodium thiosulphate, added prior to the cyclodehydrating agent, to establish if iodine generated from *N*–iodosuccinimide was responsible for the reaction's facility (Table 23). As expected, the iodine mediated reaction now failed, giving only a 9% yield of product and predominantly returning unreacted starting material **76** (91% recovery). In contrast, the cyclodehydration mediated by *N*–iodosuccinimide was chiefly unaffected by the presence of sodium thiosulphate and gave pyridine **78** in 80% yield, supporting the hypothesis that it was the Lewis acidity of *N*–iodosuccinimide and not the generation of iodine *in situ*, that was responsible for the reactivity.

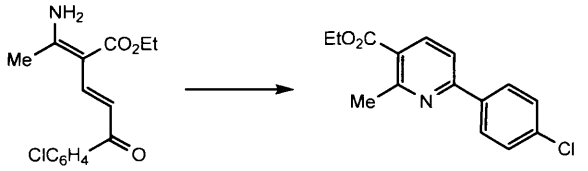
Table 23. Comparing stoichiometric I_2 and NIS.

Entry	Reagent	Yield (%)	Yield (%)[a]
1	I_2	>98	9[b]
2	NIS	88[c]	80[c]

[a] Reaction was run in the presence of $Na_2S_2O_3$. [b] Starting material **76** was recovered (91%). [c] Purification on silica was required.

Following the success of this study, an alternative aminodienone **105** was reacted with iodine (0.1–100 mol%) in ethanol at room temperature for 30 minutes in an effort to establish if a process could be developed that was catalytic in reagent. Essentially quantitative conversions to pyridine were observed under catalytic conditions even at very low iodine concentrations (0.5 mol%, Table 24).

Table 24. Room temperature cyclodehydration of **105** varying quantity of I_2.



105 **106**

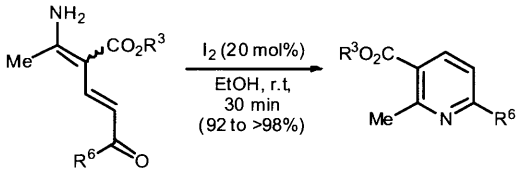
Entry	I_2 (mol%)	Yield (%)
1	100	>98
2	20	>98
3	20	>98
4	10	>98
5	1.0	>98
6	0.5	>98
7	0.1	18[a,b]

[a] From ^{1}H NMR analysis of the crude reaction mixture. [b] A mixture of 146:148 (5:1) was obtained.

With conditions established for catalytic cyclodehydration, a range of aminodienones were reacted with catalytic iodine (20 mol%) in ethanol at room temperature for 30 minutes. After a simple aqueous work up with sodium thiosulphate solution, the 2,3,6–trisubstituted pyridines were obtained in excellent yield (Table 25). Only in the case of

the iodine catalyzed cyclodehydration of dienone **105** (entry 4) was any further purification required and this was attributed to the poor solubility of the substrate in ethanol.[65]

Table 25. Cyclodehydration of aminodienone **3** using catalytic quantities of iodine (20 mol%).



72 **73**

Entry	R^3	R^6	Pyridine Yield (%)[a]
1	EtO_2C	Me	>98
2	EtO_2C	Ph	>98
3	EtO_2C	4'–C_6H_4Cl	>98
4	EtO_2C	4'–C_6H_4OMe	92[b]
5	$CO_2{}^tBu$	Me	>98
6	$CO_2{}^tBu$	Ph	97
7	$CO_2{}^tBu$	4'–C_6H_4Cl	92[b]
8	$CO_2{}^tBu$	4'–C_6H_4OMe	>98

[a] Isolated yield of pure **73** after an aqueous work up. [b] Yield of pyridine from analysis of ^1H NMR spectrum which showed corresponding dienone (8%) was also present.

In conclusion, the iodine–mediated catalytic cyclodehydration of B–R aminodienone intermediates are rapid at ambient temperatures and this procedure has a number of advantages over equivalent methods using NIS[25] or other Lewis acids[17].

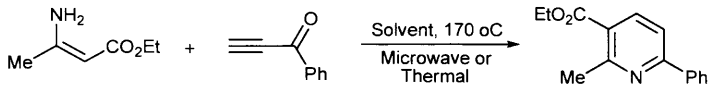
1.3.9 Microwave–Assisted Pyridine Synthesis

Microwave–assisted organic synthesis (MAOS) as an alternative heating method has received increasing interest in recent years, and has become a valuable and alternative route to conventional conductive heating methods for accelerating chemical reactions in synthetic chemistry,[66] with increasing application in the biosciences[67] with no direct

contact between the chemical reactants and the energy source, microwave–assisted chemistry can provide faster heating rates, improved efficiency and rapid optimization of procedures.

In order to explore a microwave–assisted method for the synthesis of the modified Bohlmann–Rahtz pyridines, Bagley, Lunn and Xiong performed a pyridine synthesis under a range of conditions in a self tuning single mode CEM Discover™ Focused Synthesiser.[68] A solution of ethyl β–aminocrotonate **74**, and an excess of phenylpropynone **162** (Ph), was stirred in toluene or DMSO, as from previous studies these solvents had been shown to promote Michael addition in the traditional Bohlmann–Rahtz reactions,[17] at 170 °C by irradiating initially at 150 or 160W (Table 26). The reaction conducted in toluene was found to be sluggish, providing pyridine **178** in 76% yield after 90 min following purification by column chromatography on silica (entry 1). The reaction in DMSO, a more polar solvent that can couple more efficiently in a microwave irradiation, resulted in a more rapid heating profile and facilitated reaction. Michael addition and spontaneous cyclodehydration was complete after 20 min, giving the pyridine **178** in 87% yield (entry 2).

Table 26. Reactions under microwave–assisted conditions and in a sealed tube using conventional heating techniques.



74 **83** **107**

Entry	Solvent	Time	Microwave Yield (%)	Thermal Yield (%)
1	PhMe	90	76	54
2	DMSO	20	87	80
3	PhMe–$ZnBr_2$	10	80	33
4	PhMe–AcOH (5:1)	10	98	95
5	Neat	20	84	93

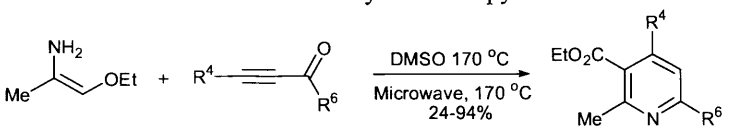
Reactions conducted in toluene were accelerated dramatically as expected, by the presence of a Lewis acid catalyst, zinc(II) bromide (15 mol%), providing the product in 80% yield after 10 min at 170 °C (entry 3). However, optimum conditions for this

transformation employed acetic acid as a Brønsted acid catalyst. After stirring for 10 min in a solution of toluene–acetic acid (5:1) at 170 °C (160W), pyridine **107** was isolated in a 98% yield following purification on silica. In a bid to explore solventless reaction conditions, a mixture of enamine **74**, and alkynone **83** was irradiated at 170 °C (150W) for 29 min to give the product in 84% yield (entry 5). Although this final experiment was not as efficient, the use of solventless reaction conditions does have intrinsic ecological and chemical values.[23c]

All of the microwave–assisted experiments facilitated both Michael addition and cyclodehydration in a single synthetic step and generated the pyridine **107** as a single regioisomer. Although the use of microwave irradiation had been successful, an investigation of traditional conductive heating methods was carried out in order to establish the potential of this method as a one–pot transformation. In order to make a comparison, the same reactions were repeated in a sealed tube using an oil bath as an external heat (Table 26). In almost all of the experiments, the microwave–assisted reactions gave higher yields, particularly the reaction conducted in toluene, with 15 mol% zinc(II) bromide (entry 3), although in many instances comparable yields were obtained (entries 2, 4 and 5). Only the solventless reaction (entry 5) gave superior results in a Carius tube, possibly due to poorer energy transfer when neat reagents were irradiated under the microwave conditions.

With an established procedure in place, ethyl β–aminocrotonate **74** was reacted with a range of alkynones by irradiating a solution in DMSO at 170 °C for 20 min. In all experiments, a single regioisomeric product was formed (Table 27).

Table 27. Microwave–assisted synthesis of pyridines.



74 **71**

Entry	R^4	R^6	Pyridine Yield (%)
1	Ph	Me	24
2	H	Ph	87
3	H	Me	62
4	Et	Me	94
5	H	4'–C_6H_4Cl	75
6	H	4'–C_6H_4OMe	66

Although the efficiency of the reaction between enamine **74** and 4–phenybut–3–yn–2–one **91** was low (entry 1),[24] this alkynone has been known to be problematic in similar heteroannulation reactions. [18] The remaining reactions gave pyridine products (entry 1–6) in good yields after purification by column chromatography (entries 2-6), illustrating that the one–pot microwave–assisted Bohlmann–Rahtz reactions represents a simple and highly expedient route to tri– and tetrasubstituted pyridines.

1.3.10 Continuous Flow Reactors

From early experiments in domestic ovens to multimodal and monomodal instruments designed for organic synthesis, microwave technology has been implemented worldwide for small scale synthetic operations and continues to be developed, enabling further improvements in existing methodologies and the discovery of new synthetic reactions.[69,24d] However, although modern monomodal instruments dedicated for MAOS are very successful in small scale operations, efforts to process this technology in continuous flow (CF) reactors are frustrated by physical limitations of microwave heating, with a penetration depth of only a few centimetres and the limited dimensions of the standing wave cavity. Current technology has attempted to overcome these obstacles with conventional instruments by the use of CF reactors that pump the reagents through a small heated coil that winds in and out of the cavity,[70] with external temperature

monitoring using a fibre optic sensor, although alternative methods, such as using a multimode batch or CF reactor, have also been described. Recently Bagley, Jenkins, Lubinu, Mason and Wood reported a method for carrying out MAOS under CF processing under a commercially–available monomodal microwave synthesizer.[71]

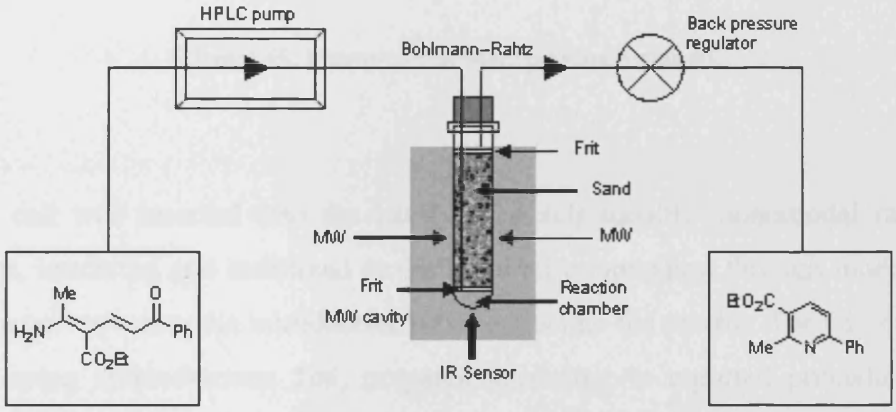
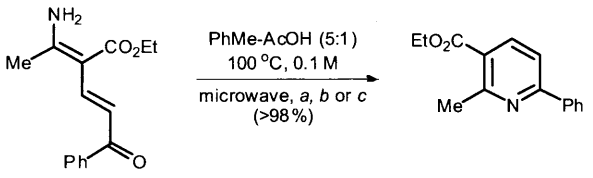


Figure 2. Schematic diagram of cell flow microwave reactor.

The principal design of this flow cell featured the need to make optimum use of the cavity and to be able to monitor the temperature of reaction simply using the instrument's in–built IR sensor as shown in detail in Figure 2 shows in detail the tube flow cell set up. A standard 10 mL Pyrex tube was fitted with a custom built steel head, filled with sand (~10 g) held between two drilled frits and sealed using PTFE washers. The inlet tube of the flow cell was connected to a HPLC pump and a back pressure regulator was connected to the outlet tube, allowing experiments to be run under pressure. The flow cell was inserted into the cavity of the CEM Discover® microwave synthesizer and the temperature monitored using the instrument's in–built IR sensor, situated at the bottom of the microwave chamber. Feed–back microprocessor control was connected to the CEM Discover® microwave synthesizer, thereby allowing the operator to preset temperature, power, cooling and to monitor the temperature–pressure and power profile of reactions (Figure 2).



108 **107**

Scheme 45. Microwave–assisted pyridine synthesis.

The flow cell was inserted into the cavity of a self–tunable monomodal microwave synthesizer, irradiated and stabilized at the required temperature through moderation of microwave power before the introduction of reagents into the reactor. The CF reactor was tested by using aminodienone **108**, prepared according to reported procedures,[17] and cyclodehydrated with CF processing under homogeneous conditions in toluene–acetic acid (5:1) over sand, comparing the results to batch experiments carried out in a sealed tube and to the corresponding homogeneous CF process with a Teflon heating coil (Scheme 45). The process was successfully transferred to continuous flow process using the tube flow cell without the need for further modifications.

Table 28. Comparing MAOS of pyridine **107** using Sealed Tube or CF Processing.

	Sealed Tube[a]	CF Coil[b]	CF Coil[b]	CF Glass Tube[c]	CF Glass Tube[c]
Isolated yield, %	>98	>98	85[d]	>98	>98
Residency time,[e] min	2	5[f]	3.3[f]	3	2
Flow rate, mL min^{-1}		1	1.5	1	1.5
Processing rate, mmol min^{-1}		0.1	0.15	0.1	0.15
Total energy,[g] Kj		1411	762	850	735

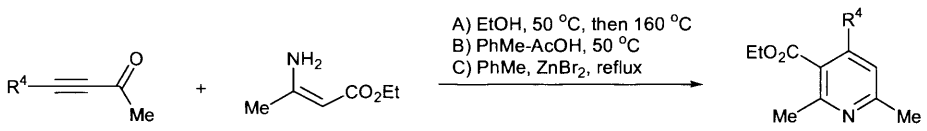
[a]Batch experiment in a sealed glass tube. [a]CF processing in a Teflon heating coil. [c]CF tubing in a glass tube reactor charge with sand. [d]Based upon ^1H NMR analysis of crude reaction mixture. [e]Residency in microwave cavity. [f]Residency in heating oil. [g]Energy delivered by the magnetron in flow reaction.

Under conditions that gave efficient conversion (>98%) to pyridine **178**, the processing rates using the glass tube reactor charged with sand were higher (Table 28). Additionally, CF reactions run at the same flow rate used less magnetron energy in a

glass tube than in the heating coil, demonstrating that the glass tube CF reactor offers (i) improved heating efficiency, (ii) potential for operation on a large scale, (iii) successful transfer from batch to CF processing and (iv) improved performance over commercial Teflon heating coils (method b).

1.3.11 Combinatorial Chemistry

The development of new methods for the synthesis of heterocyclic compound libraries, both in solution and on solid phase, is an ever-expanding area in combinatorial chemistry. To examine the behaviour of the different Bohlmann-Rahtz heteroannulation methods, both the traditional method and the procedures developed in our laboratories,[56] a number of methods for library synthesis were investigated, and the pyridine products were isolated and analysed by ^{1}H NMR spectroscopy. Data were compared to spectra of pure pyridines isolated from previous studies to determine the product ratios, by integration of pyridine 4–H and 5–H resonances, and library purity, by reference to a known quantity of tetramethylsilane as an internal standard according to established methodology. A small library of pyridines was generated using each of the three methods, the traditional Bohlmann-Rahtz (method A), stirring in acetic acid–toluene (method B) and the Lewis acid-catalyzed heteroannulation process (method C), and the products were isolated and analyzed by ^{1}H NMR spectroscopic methods (Scheme 46).



75 R^4 = TMS
77 R^4 = Et
91 R^4 = Ph

78 R^4 = H
81 R^4 = TMS
88 R^4 = Et
93 R^4 = Ph

Scheme 46. Combinatorial synthesis of pyridines.

Using the traditional two step procedure (method A), heating at 50 °C in ethanol, isolating the intermediate, then heating to 160 °C for three hours to effect cyclodehydration resulted in the isolation of four pyridines **78, 81, 88** and **93** with protodesilylation occurring throughout the course of the reaction. With this in mind, product ratios Lewis were large and varied between $1 < R < 25$, although the overall yield and product purity were good. Some protodesilylation also accompanied the reaction conducted in toluene–acetic acid (method B) and although the product ratio improved, varying between $1 < R < 8.3$, the overall yield was low (30%). However the Lewis acid catalyzed reaction (method C) resulted in no protodesilylation and thus gave rise to only three pyridines **81, 88** and **93** in high purity, good overall yield and in a product ratio that only varied between $1 < R < 2$.

Table 29. Comparision of Bohlmann–Rahtz heteroannulation procedures for the combinatorial synthesis of pyridines **78, 81, 88** and **93**.

Method	Products	Yield (%)	Ratio	Library Purity (%)
A	**78, 81, 88, 93**	62	100:65:4:54	75
B	**78, 81, 88, 93**	30	52:100:67:12	80
C	**81, 88, 93**	64	100:73:50	86

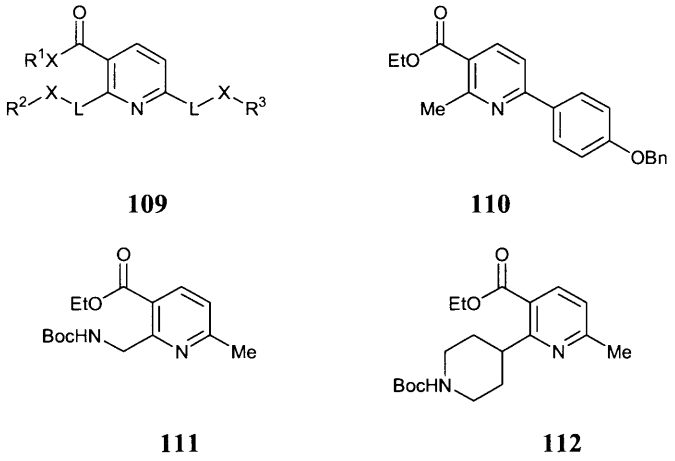
It was curious to note that the product ratio varied between the heteroannulation procedures, as did the identity of the major product, indicating that the alkynones display different reactivity profiles according to the method used (Table 29). The Bohlmann–Rahtz heteroannulation reaction was successful for the combinatorial synthesis of pyridine libraries in solution, with low levels of impurities and even with the use of problematic alkynones, the Lewis acid–catalyzed method seemed to be the most successful.[72]

1.3.12 Applications In Natural Product Synthesis And Drug Discovery

The growing knowledge of the structural diversity and biological importance of nitrogen containing heterocycles have made them attractive targets for synthesis and justify continuing efforts in the development of new synthetic strategies. The Bohlmann–Rahtz

heteroannulation reaction has been little used since its discovery in 1957, although in the last 10 years, synthesis methodology has improved significantly and extensively, it has been employed in the synthesis of the core domains of many naturally occurring compounds with interesting biological properties.

In addition, simple low molecular weight heterocycles molecules make ideal scaffolds in which to base high throughput synthesis of libraries of drug–like compounds. Examples include the use of 1,2,3–thiadiazolidin–3–one–1,1–dioxide and pyrimidine scaffolds in the synthesis of serine proteinase and kinase inhibitors respectively,[73] and the use of simple pyridine scaffolds to generate libraries of inhibitors of HIV–1 protease and Factor Xa.[74] A programme was designed in 2003 by Moody and co–workers to develop heterocyclic scaffolds for library synthesis based on trisubstituted pyridines produced by modified Bohlmann–Rahtz methodology (Figure 3).

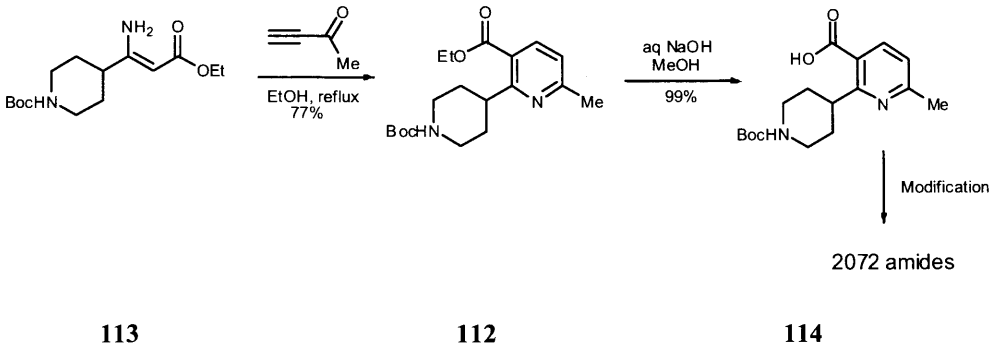


109 **110**

111 **112**

Figure 3. Trisubstituted pyridine scaffold.

Pyridine **112** was obtained when enamine **113** was reacted with butynone in boiling ethanol in a 77% yield, which upon hydrolysis of the ester, gave the acid **214** for use in library synthesis.



113 **112** **114**

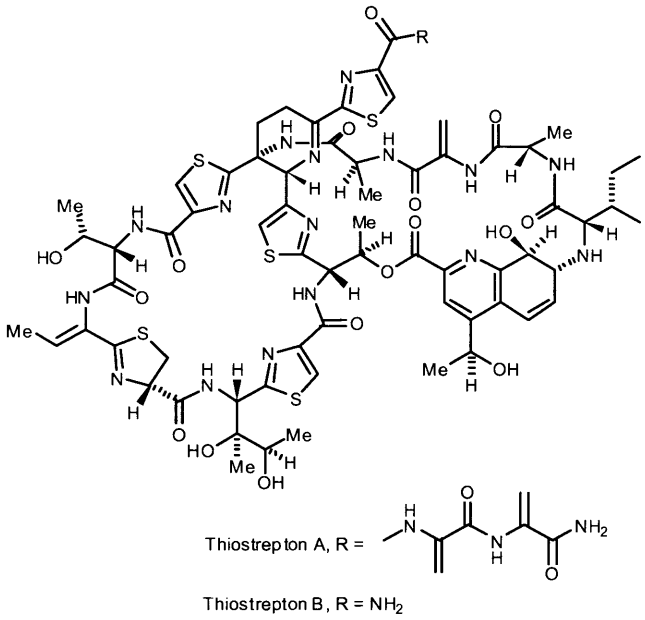
Scheme 47. B–R application to drug design library synthesis.

Following the design process, acid **114**, was coupled to a range of amines to provide 14 protected intermediates in 61–87% yield on a 100 mmol scale. Further modification generated a larger library by reacting the piperidine nitrogen with **78** various carboxylic acids to produce 2072 amides for drug screening (Scheme 47).

The modified Bohlmann–Rahtz reaction has also been incorporated into the synthesis of the central domain of a range of antibiotics. Thiopeptides are naturally occurring sulphur containing, highly modified, macrocyclic peptides, nearly all of which inhibit protein synthesis in bacteria. These complex natural products share a number of common structural features: a tri– or tetrasubstituted nitrogen heterocycle clustered in a pyridine domain part of a macrocyclic framework consisting of thiazoles, oxazoles, indoles and dehydroamino acids.

These biologically active substances are secondary metabolites produced by actinomycetes, Gram–positive mycelial sporulating bacteria, largely of *Streptomyces* that can be subdivided into 29 different antibiotic families and containing over 76 structurally distinct entities. The first member of the family, micrococcin was isolated in 1948,[75] and the parent of the thiopeptide family, thiostrepton (diagram 1) was later discovered in 1954 (Diagram 1).[76,77] Many of these antibiotics share a similar biological profile, displaying activity against Gram–positive bacteria, they are highly active inhibitors of the protein synthesis and in many cases active against methicillin–resistant *Staphylococcus aureus* (MRSA), a bacterial strain that is resistant to most conventional treatments.

Figure 4. The structure of Thiostrepton.



Thiopeptide antibiotics can be categorised into four distinct classes according to the oxidation state of their core heterocyclic domain, and there are five distinct series (Table 30).

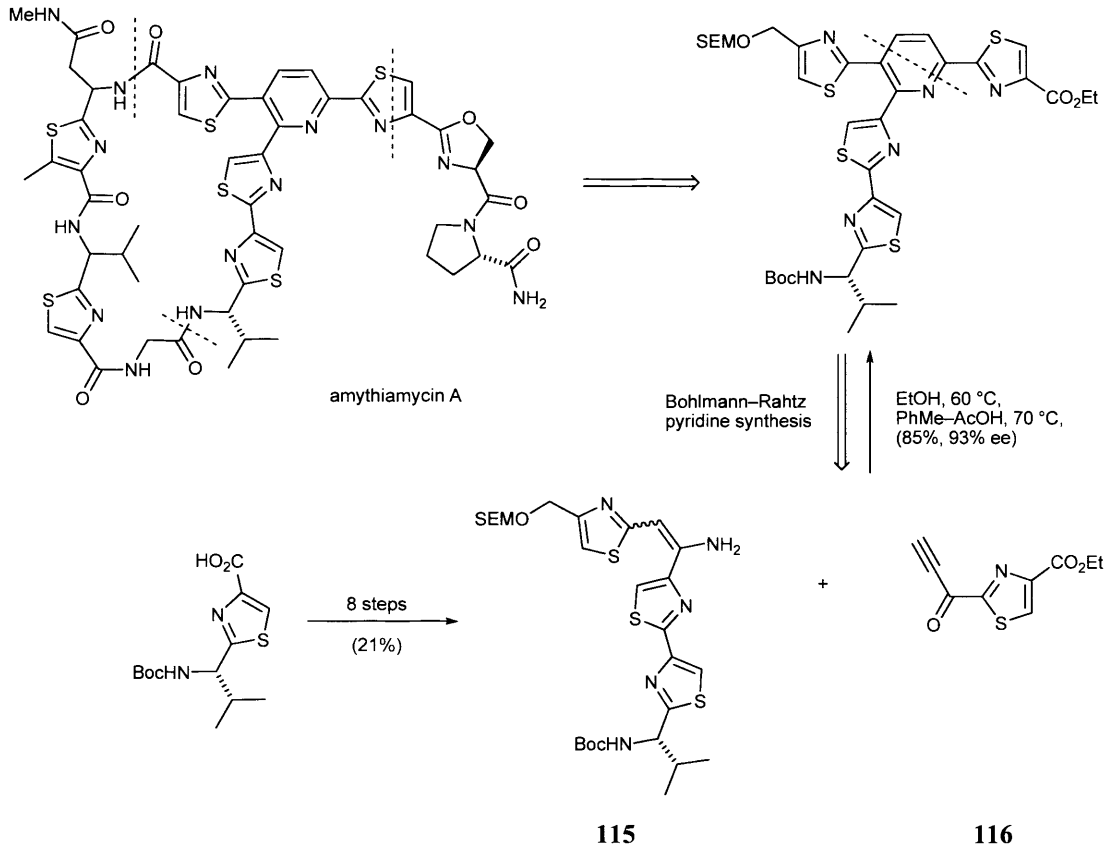
Table 30. Thiopeptide antibiotic families classified according to their central heterocyclic domain.

series *a* and *b*	series *c*	series *d*		series *e*
bryamycin (A–8506)[a]	Sch 40832	A10255	promothiocin	glycothiohexide α
Sch 18640 (68–1147)		amythiamicin	AN3323	MJ347–81F4
siomycin		berninamycin	radamycin	multhiomycin[b]
thiactin[a]		cyclothiazomycin	sulfomycin	nocathiacin
thiopeptin		GE2270	thioactin	nosiheptide
thiostrepton		GE37468	thiocillin	S–54832
		geninthiocin	thiotipin	
		methylsulfomycin	thioxamycin	
		micrococcin	YM-266183–4	
		promoinducin		

[a] Shown to be identical to thiostrepton. [b] Shown to be identical to nosiheptide.

Series *a* and *b* thiopeptides can be identified by their dehydropiperidine or piperidine domain, series *c* represent only one thiopeptide (Sch 40832), series d possesses the 2,3,6–tetrasubstituted pyridine domain and is shared by 19 different families including the micrococcins. Finally series *e* thiopeptides, such as nosiheptide, exhibit a structurally

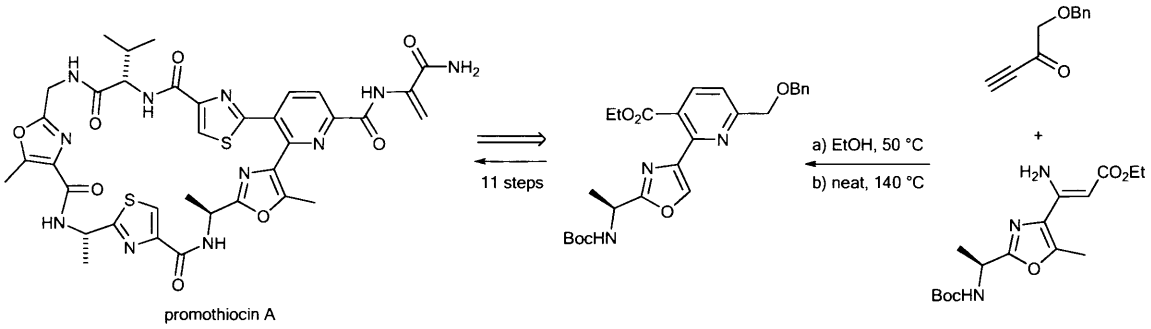
related central motif, oxidized in comparison to series *d*, containing a tetrasubstituted hydroxypyridine. Bagley, Dale, Jenkins and Bower set out to establish a rapid route to the heterocyclic core of the amythiamicins by Michael addition–cyclodehydration of enamine **115** and alkynone **116** that would proceed with total regiocontrol and generate the pyridine with the correct oxidation state.



Scheme 48. Synthetic approach to the central amythiamicin domain.

Utilizing conditions successful for the synthesis of other pyridines, the Michael addition of enamine **115** and propynone **116** in ethanol followed by acetic acid–catalysed cyclodehydration at 70 °C, gave the amythiamicins heterocyclic domain in 85% yield and 93% *ee* (Scheme 48).[78]

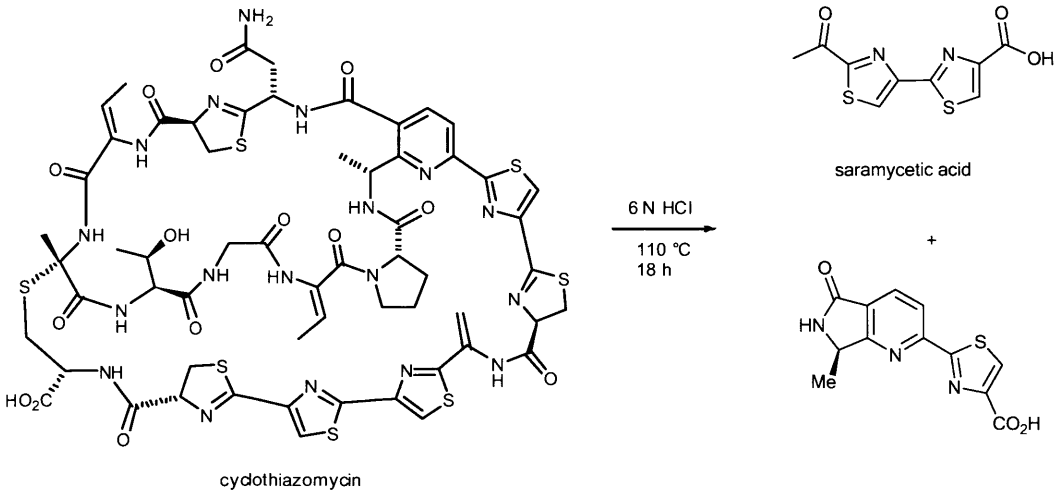
The structure of promothiocin A, a series *d* antibiotic, isolated from *Streptomyces* sp. SF2741, first proposed in 1994 by Yun, Hidaka, Furihata and Seto ^{1}H NMR spectroscopic studies.[79] The stereochemical assignment of promothiocin A by Moody and Bagley[80,81] established the (*S*)–configuration of the three stereogenic centres in the natural product. This was later supported by degradation studies and molecular modelling.[82]



Scheme 49. total synthesis incorporating the B–R reaction.

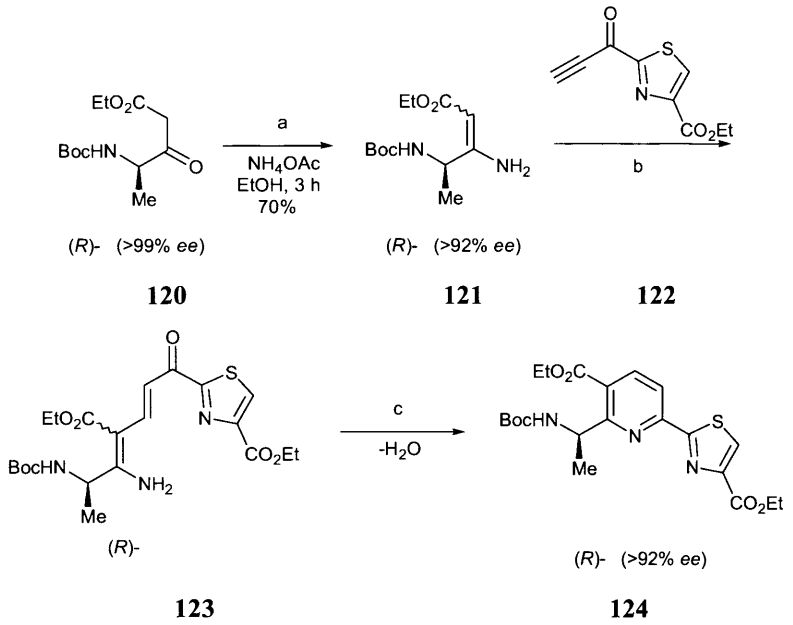
Promothiocin A also first synthesized by Moody, Bagley, Bashford and Hesketh.[82] The synthesis featured the Bohlmann–Rahtz heteroannulation reaction to establish the central oxazole–thiazole–pyridine domain. Pyridine **117** was generated from alkynone **118** and enamine **119** proceeding via a two step Michael addition at 50 °C and subsequent double bond isomerization–cyclization at 140 °C in the absence of solvent yielding pyridine **117** (83%). The 400 MHz ^{1}H and 100 MHz ^{13}C spectra were identical to those reported for the natural product.[80]

Cyclothiazomycin, a series *d* thiopeptide isolated by the fermentation broth of *Streptomyces* sp. NR0516 from soil sample collected at Kanagawa, Japan, is a selective inhibitor of human plasma renin at an IC_{50} of 1.7 μM.[83] Its unique structure consists of a (1–amino–1–ethyl)pyridine heterocyclic domain embedded in two macrocyclic peptide loops,[84] the absolute stereochemistry of which was proposed using a combination of spectroscopic and analytical methods. From chemical degradation studies of the thiopeptide, heterocyclic amino acid γ–lactam and saramycetic acid were isolated (Scheme 50).



Scheme 50. Cyclothiazomycin and its hydrolysates.

The preparation of some of the unusual structural motifs present in cyclothiazomycin has attracted interest,[85] but the stereoselective synthesis of its γ–amino acid central domain had not been addressed until 2004 by Bagley and Xiong,[86] where a Bohlmann–Rahtz reaction was utilized to assemble the pyridine domain. However the effectiveness of this strategy relied upon the availability of the chiral enamine **121** which needed to proceed through the heterannulation without racemization.



Scheme 51. Synthetic of the cyclothiazomycin domain.

Reacting the known (*R*)–ketoester **120**[87] with ammonium acetate gave enamine **121**, however during the formation or purification, the chiral intermediate racemized on exposure to heat (ethanol at reflux), Brønsted acids (5:1 toluene–acetic acid), or silica gels. It could only be isolated in 70% yield and 92% *ee* by carrying out the reaction at room temperature in ethanol and using the crude material without purification (Scheme 51).

Table 31. Reagent and conditions for modified B–R reaction.

Entry	Reagents and Conditions (Yield)	*ee*%
1	(b) EtOH, 50 °C, 10 min; (c) neat, 135 °C, 4 h (73%)	14
2	(b) & (c) microwave, 170 °C, 20 min (20%)	33
3	(b) & (c) PhMe, AcOH, 60 °C, 90 min (73%)	47
4	(b) EtOH, 50 °C, 10 min; (c) PhMe–AcOH, 60 °C, 90 min (66%)	81
5	(b) EtOH, 50 °C, 10 min; (c) NIS, 0 °C, 15 min (71%)	92
6	(a)–(c) NH4OAc, EtOH, 4 h; 50, 1 h; NIS, 0 °C, 15 min (55%)	96

A range of modified methods were investigated for Bohlmann–Rahtz reaction of enamine **121**. Michael addition at 50 °C for 10 min followed by cyclodehydration at 135 °C (Table 31, entry 1), gave pyridine **124** as a single regioisomer in 73% yield, although only in 14% *ee*. The microwave–assisted reaction resulted in a significant loss of material but did improve the optical purity somewhat (entry 2). As predicted the one–pot acid–catalyzed heteroannulation process was much more efficient but did little to prevent racemization throughout the process (entry 3). However, in combination with a Michael addition under traditional Bohlmann–Rahtz conditions, the acid–catalyzed cyclodehydration of the diaminodienone intermediate **123** at 60 °C caused a significant increase in the optical activity of pyridine **124**. Changing the cyclodehydrating agent from Brønsted acid to *N*–iodosuccinimide (NIS), further improved the stereoselectivity of the process (entry 5), giving pyridine **124** in 92% *ee*. Although the results were excellent, the optical purity of the product was limited by the stereochemical instability of enamine **123** following isolation of this precursor. This was overcome by adding ammonium acetate to the β–ketoester **120** (>99% *ee*) in ethanol. After 4 hours at room temperature, thiazolylpropynone **122** was added to the mixture to complete the Michael addition, then cooled to 0 °C. *N*–Iodosuccinimide was then added (Scheme 23, entry 6). After column chromatography, pyridine **124** was isolated directly in 55% yield and 96% *ee* from the one–pot reaction, thus demonstrating a facile stereoselective route to cyclothiazomycin precursor **124**.

1.3.13 Conclusion

Within the last decade we have seen the Bohlmann–Rahtz reaction being exploited to its full potential and justifies the continuing need to discover new and improved methods for pyridine synthesis. Detailed studies have provided a number of modified procedures of this original two step method to produce tri– and tetrasubstituted pyridines, with different methods suitable for various pyridine targets. This highlights the usefulness of the modified Bohlmann–Rahtz reaction not only in the synthesis of individual pyridine compounds but also the incorporation of the pyridine domain into natural product synthesis.

1.3.14 References

[1] Anderson, T. *Trans. R. Soc. Edinb. I* **1849**, 16, 123.

[2] Dobbin, L, *J. Chem. Educ.*, **1934**, *11*, 596.

[3] Baeyer, *Ber.*, **1869**, *2*, 398.

[4] Baeyer, *Ann.*, **1870**, *155*, 281.

[5] Ramsey W, *Philos. Mag.*, **1876**, *2*, 269.

[6] Koehn C. J.; Elvehjem C.A. **1937**, *J. Bio. Chem.*, **118**, *3*: 693.

[7] Fahanullah; Agatwal, N.; Goel, A.; Ram, V. J. *J. Org. Chem.*, **2003**, *68*, 2983.

[8] Matocsy, G. *Pesticide Chemistry*; Elsevier Scientific; Amsterdam Oxford, **1998**, 427.

[9] Henkel, T.; Brunne, R. M.; Müller, H.; Reichel, F. *Angew. Chem., Int. Ed. Engl.*, **1999**, *38*, 643.

[10] Petrich, S. A.; Hicks. F. A.; Wilkinson, D. R.; Tarrant J. G.; Bruno, S. M. ; Vargas, M. ; Hosein, K. N.; Gupton, J. T.; Sikorski, J. *Tetrahedron.* **1995**, *51*, 1575.

[11] Alvares-Insúla, A. S.; Lora-Tamayo, M.; Soto, J. L. *Synthesis of Organic Compounds II*, **1970**, 1308.

[12] Shi, F.; Tu, S.; Fang, F.; Li, T. *ARKIVOC*, **2005**, 137.

[13] Zhou, W. J.; Ji, S. J.; Shen, Z. L. *J. Organomet. Chem.*, **2006**, 1356.

[14] Roth, H. J.; Kleemann, A. In *Pharmaceutical Chemistry. Volume 1: Drug Synthesis*; John Wiley & Sons: New York, **1988**.

[15] (a) Meyer. *J. prakt. Chem.,* **1908**, *78*, 497. (b) Meyer. *J. prakt. Chem.,* **1915**, *90*, 1. (c) Meyer. *J. prakt. Chem.,* **1915**, *92*, 174.

[16] Harris; Stiller; Folkers. *J. Am. Chem. Soc.,* **1939**, *61*, 1242.

[17] Wenner; Platti. *J. Org. Chem.*, **1946**, *11*, 751.

[18] (a) Little. E. L.; Middleton, W. J.; Coffman, D. D.; Englehardt, V. A.; Sausen, G. N. *J. Am. Chem Soc.* **1958**, *80*, 3832. (b) Cottis, S. G.; Tieckelmann, H. *J. Org. Chem.*, **1961**, *26*, 79.

[19] Alvares–Insúla; Lora–Tamayo; Soto. *Synthesis of Heterocyclics II.* **1970**, *7*, 1305.

[20] (a) Gupton, J.; Krolikowski. D.; Yu, R.; Riesinger, S.; Sikorski, J. *J. Org. Chem.*, **1990**, 55, 4735. (b) Gupton, J.; Krolikowski. D.; Yu, R.; Sikorski, J.; Dahl. M.; Jones, C. *J. Org. Chem.* **1992**, 57, 5480.

[21] Jutz, C.; Lobering, H.–G.; Trinkl, K.–H. *Synthesis*, **1977**, 326.

[22] Chatterjea, J. N. *J. Indian. Chem. Soc.*, **1952**, 29, 323.

[23] Matsui, M.; Oji, A.; Hiramatsu, K.; Shibata, K.; Maramatsu, H. *J. Chem. Soc., Perkin Trans. 2.* **1992**, *2*, 201.

[24] Reviews on microwave chemistry include: (a) Gabriel, C.; Gabriel, S.; Grant, E. H.; Halstead, B. S. J.; Mingos, D. M. P. *Chem. Soc. Rev.,* **1998**, *27*, 213; (b) Kuhnert, N. *Angew. Chem. Int. Ed.*, **2002**, *41*, 1863; (c) Lidström, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron.* **2001**, *57*, 9225; (d) Loupy, A.; Petit, A.; Hamelin, J.; Texier-Boullet, F.; Jacquault, P.; Mathé, D. *Synthesis.* **1998**, 1213; (e) Galema, S. A. *Chem. Soc. Rev.*, **1997**, *26*, 233; (f) Caddick, S. *Tetrahedron.* **1995**, *51*, 10403; (g) Strauss, C. R.; Trainor, R. W. *Aust. J. Chem.*, **1995**, *48*, 1665.

[25] Paul, S.; Gupta, R.; Loupy, A. *J. Chem. Research.* **1998**, S, 330.

[26] Dombrowski. K. E.; Baldwin, W.; Sheats, J. *J. Organomet. Chem.*, **1986**, 302, 281.

[27] Zhou, W. J.; Ji, S. J.; Shen, Z. L. *J. Organomet. Chem.*, **2006**, 691, 1356.

[28] (a) Pandya, S.; Yu, J.; Parker, D. *Dalton Trans.*, **2006**, 2757. (b) Gunnlaugsson, T.; Stomeo, F. *Org. Biomol. Chem.*, **2007**, *5*, 1999. (c) Bunzli, J-C.G.; Piguet, C. *Chem. Soc. Rev.*, **2005**, *34*, 1048. (d) Gunnlaugsson, T.; Leonard, J.P. *Chem. Commun.*, **2005**, 3114. (e) Chauvin, A-S.; Vandevyer, C.; Comby S.; Bunzli, J-C. G. *Chem. Commun.*, **2007**, 1716. (f) Parker, D.; Pal, R. *Chem. Commun.* **2007**, 474. (g) Faulkner S.; Pope, S.J.A.; Burton-Pye, B.P. *Appl. Spectrosc. Rev.*, **2005**, *40*, 1.

[29] Bowman, M. D.; Jacobsen, M. M.; Blackwell, H. E. *Org. Lett.*, **2006**, 8, 1645.

[30] Raghukumar, V.; Thirumalai, D.; Ramakrishnan, V. T.; Karunakara, V.; Ramamurthy, P. *Tetrahedron.* **2003**, *59*, 3761.

[31] Bowman, M. D.; Neill, J. O.; Sringer, J. S.; Blackwell, H. E.*Chem. & Biol.*, **2007**, 14, 351.

[32] Bashkin, J. K.; Xie, J.; Daniher, A. T. ; Sampath, U. ; Kao, J. L.-F. *J. Org. Chem.*, **1996**, *61*, 2314.

[33] Sun, L. C.; Hammarstrom, L.; Åkermark, B.; Styring, S. *Chem. Soc. Rev.*, **2001**, *30*, 36; (b) Kleverlaan. C. J.; Indelli, M. T.; Bignozzi, C. A.; Pavanin, L.; Scandola, F.; Hasselman, G. M.; Meyer, G. J. *J. Am. Chem. Soc.*, **2001**, *122*, 2840.

[34] Kleverlaan. C. J.; Indelli, M. T.; Bignozzi, C. A.; Pavanin, L.; Scandola, F.; Hasselman, G. M.; Meyer, G. J. *J. Am. Chem. Soc.,* **2001**, *122*, 2840.

[35] Demas, J. M.; DeGra, B. A. *Coord. Chem. Rev.,* **2001**, *211*, 317.

[36] Sauvage, J. P.; Collin, J. P.; Chambron, J.C.; Guillerez, S.; Coudret, C.; Balzani, V.; Barigelletti, F.; De Cola, L.; Flamigni, L. *Chem. Rev.,* **1994**, *94*, 993.

[37] Kozhevnikov, V. N.; Kozhevnikov , D. N.; Nikitina, T. V.; Rusinov, V. L.; Chupakhin, O. L.; Zabel, M.; Konig, B. *J. Org. Chem.,* **2003**, *68*, 2882.

[38] (a) Morgan, G. T.; Burstall, F. H. *J. Chem. Soc.*, **1932**, 20. (b) Burstall, F. H. *J. Chem. Soc.*, **1938**, 1662.

[39] Blau, F. *Monatsh. Chem.,* **1888**, *10*, 375.

[40] Hein; Schwelder. *Ber.*, **1935**, *68*, 681.

[41] Krönke, F.; *Synthesis*. **1976**, 1.

[42] Cordaro, J. G.; McCusker J. K.; Bergmann, R. G. *Chem. Comm.*, **2002**, 1496.

[43] Cave, G. W. V.; Raston, C. L. *J. Chem. Soc., Perkin Trans. 1* **2001**, 3258.

[44] Hedge, V.; Jahng, Y.; Thummel, R. P. *Tetrahedron Lett.* **1987**, 4023.

[45] Wang, J; Hanan, G. S. *Synlett.* **2005**, 8, 1251.

[46] Wang, J; Hanan, G. S. *Chem. Comm.*, **2002**, 3931.

[47] Tu, S.; Jia, R.; Jiang, B.; Zhang, J.; Zhang, Y.; Yao, C.; Ji, S. *Tetrahedron.* **2007**, 63, 381.

[48] Christopoulus, T. K. *Anal. Chem.* **1990**, 62, 1149A.

[49] Kozhevnikov, V. N.; Kozhevnikov, D. N.; Rusinov, V. L.; Chupakhin, O. N.; König, B. *Synthesis*. **2003**, 15, 2400.

[50] (a) Bashkin, J. K.; Xie, J.; Daniher, A. T.; Sampath, U.; Kao, J. L. –F. *J. Chem. Soc.*, **1996**, *61*, 2314. (b) Putman, W. C.; Daniher, A. T.; Tranwick, B. N.; Bashkin, J. K. *Nucleic Acids Res.,* **2001**, *29*, 2199. (c) Tranwick, B. N.; Osiek, T. A.; Bashkin, J. K. *Bioconjugate Chem*, **2001**, *12*, 900

[51] Hantzsch, A, *Liebigs Ann. Chem.*, **1882**, *215*, 1.

[52] Katritzky, A. R.; Rees, C. W. *Comp. Heterocycl. Chem.*, **1984**, 398.

[53] Joule, J.; Smith, G.; Mills, K. *Heterocyclic Chemistry.*3rd Ed. Chapman and Hall **1995**, 72.

[54] Nozaki, H.; Fujita, S.; Mori, T. *Bull. Chem. Soc. Jpn.*, **1969,** *42*, 1163.

[55] Bohlmann, F.; Rahtz, D, *Chem. Ber.* **1957**, 90, 2265.

[56] Bagley, M. C.; Brace, C.; Dale, J. W.; Ohnesorge, M.; Phillips, N. G.; Xiong, X.; Bower, J. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1663.

[57] Bagley, M. C.; Dale, J. W.; Bower, J. *Synlett.* **2001**, 1149.

[58] Baraldi, P. G.; Simoni, D.; Manfredini, S. *Synthesis.* **1983**, 902.

[59] Bagley, M. C.; Dale, J. W.; Bower, J. *J. Chem. Comm.*, **2002**, 1682.

[60] Bagley, M. C.; Hughes, D. D.; Sabo, H. M.; Taylor, P. H.; Xiong, X. *Synlett.* **2003**, 1443.

[61] Agami, C.; Dechoux, L.; Hebbe, S. *Synlett.* **2001**, 1440.

[62] Agami, C.; Dechoux, L.; Hamon, L.; Hebbe, S. *Synthesis.* **2003**, 859.

[63] Agami, C.; Dechoux, L.; Hebbe, S.; Moulinas, J. *Synlett.* **2002**, 79.

[64] Bagley, M. C.; Glover, C.; Merrit, E.; Xiong, X. *Synlett.* **2004**, 811.

[65] Bagley, C. M.; Glover, C.; Chevis, D. *Synlett.* **2005**, 649.

[66] Gabriel, C.; Gabriel, S.; Grant, E. H.; Halstead, B. S. J.; Mingos, D. M. P. *Chem. Soc. Rev.*, **1998**, *27*, 213.

[67] Collins, J. M.; Leadbeater, N. E. *Org. Biomol. Chem.*, **2007,** *5*, 1141.

[68] Bagley, M. C.; Lunn, R.; Xiong, X.; *Tetrahedron Lett.*, **2002**, *43*, 8331.

[69] Raner, K. D.; Strauss, C. R.; Trainor, R. W.; Thorn. J. S. *J. Org. Chem.*, **1995**, *60*, 2456.

[70] http://www.cemsynthesis.com.

[71] Bagley, M. C.; Jenkins, R. L.; Lubinu, M. C.; Mason, C.; Wood, R. *J. Org. Chem.*, **2005**, *70*, 7003.

[72] Bagley, M. C.; Dale, J. W.; Ohnesroge, M.; Xiong, X.; Bower, J. *J. Chem. Comm.*, **2002**, *5*, 41.

[73] (a) Gilchrist, T. L. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2849; (b) Gilchrist, T. L. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2491.

[74] (a) Bouras, A.; Boggetto, N.; Benatalah, Z.; de Rosny, E.; Sicsic, S.; Reboud–Ravaux, M. *J. Med. Chem.,* **1999**, *42*, 957; (b) Phillips, G.; Davey, D. D.; Eagen, K. A.; Koovakkat, S. E.; Liang, A.; Ng, H. P.; Pinkerton, M.; Trinh, L.; Whitlow, M,; Beatty, A. M.; Morrissey, M. M.; *J. Med. Chem.,* **1999**, *42*, 1749.

[75] SU, T. L.: Micrococcin. An antibacterial substance formed by a strain of Micrococcus. Brit. J Exptl. Path. 1948, *29*, 473.

[76] Vandeputte, J.; Dutcher, J. D. *Antibiot. Ann.*, **1956**, 560.

[77] Steinberg, B. A.; Jambor, W. P.; Snydam, L. O. *Antibiot. Ann.*, **1956**, 562.

[78] Bagley, M. C.; Dale, J. W.; Jenkins. R. L.; Bower, J. *Chem. Commun.*, **2004**, 192.

[79] Yun, B. S.; Hidaka, T.; Furihata, K.; Seto, H. *J. Antibiot.*, **1994**, *47*, 510.

[80] Moody, C. J.; Bagley, M. C. *Chem. Comm.*, **1998**, 2049.

[81] Bagley, M. C.; Bashford, K. E.; Hesketh, C. L.; Moody, C. J. *J. Am. Chem. Soc.*, **2000**, *122*, 3301.

[82] Yun, B. S.; Hidaka, T.; Furihata, K.; Seto, H. *Tetrahedron Lett.*, **2001**, 57, 9683.

[83] Aoki, M.; Ohtshka, T.; Yamada, K. *J. Antibiot.*, **1991**, *44*, 582–588.

[84] Aoki, M.; Ohtshka, T.; Itezono, Y.; Yokose, K.; Furihata, K.; Seto, H. . *Tetrahedron Lett.*, **1991**, *32*, 221.

[85] (a) Shin, C.; Okabe, A.; Ito, A.; Ito, A.; Yonezawa, Y. *Bull. Chem. Soc. Jpn.*, **2002**, *75*, 1583; (b) Endoh, N.; Yonezawa, Y.; Shin, C. *Bull. Chem. Soc. Jpn.*, **2003**, *76*, 643.

[86] Bagley. M. C.; Xiong, X. *Org. Lett.*, **2004**, *6*, 3401.

[87] Honore, T.; Hjeds, H.; Krogsgaard–Larsen, P.; Christiansen, T. R. *Eur. J. Med. Chem.*, **1978**, 13, 429.

CHAPTER TWO – RESULTS AND DISCUSSION

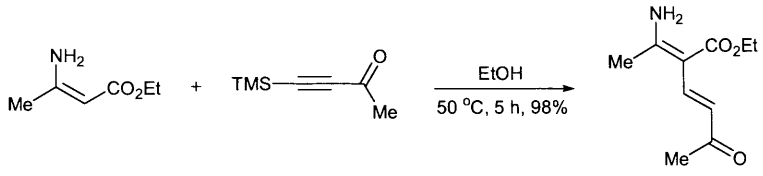
2.1 DEVELOPMENT OF NEW METHODOLOGY FOR PYRIDINE SYNTHESIS

2.1.0 Aims

A series of modifications of the Bohlmann–Rahtz reaction by Bagley and co–workers led to a range of efficient routes to tri– and tetrasubstituted pyridines using an assortment of conditions and catalysts including zinc(II) bromide, acetic acid or Amberlyst 15 ion exchange resin. These methods can proceed in a single step without the need for isolation of the aminodienone intermediate and can avoid the use of high temperatures, to effect cyclodehydration. As part of this ongoing investigation in the search for alternative methods, our aims were to explore a new one step three–component condensation process for the synthesis of pyridine heterocycles that avoided the use of high temperatures, acid catalysts and the need to initially generate the enamine precursor, forming it instead *in situ*, to improve the facility and capability of the Bohlmann–Rahtz reaction.

2.1.1 The Traditional Bohlmann–Rahtz Reaction

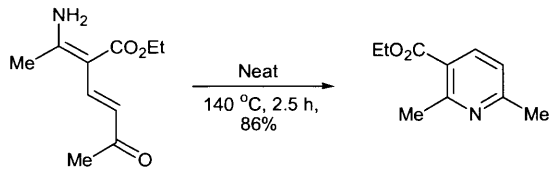
The Bohlmann-Rahtz pyridine synthesis[55] was first used to prepare polysubstituted pyridines, in order to establish the efficiency of the traditional procedure. Ethyl 3–aminocrotonate **74** was reacted according to the original report by Bohlmann and Rahtz, firstly heating in ethanol at 50 °C with an excess of 4–(trimethylsilyl)but–3–yn–2–one (2.5 equiv.) **75** for 5 hours, to affect the conjugate Michael addition, providing the corresponding aminodienone **76** in near quantitative yield (98%) (Scheme 52). Reducing the quantity of alkynone in this case lowered the yield obtained of the product due to the volatile nature of the alkynone precursor.



74 **75** **76**

Scheme 52. Formation of dienone **76**.

Aminodienone **76** was isolated as a pale yellow solid and identified by use of ^{1}H NMR spectroscopy. The aminodienone **76**, in a flask fitted with a drying tube, was heated at 140 °C for 2.5 hours, after which the compound was purified on silica to facilitate cyclodehydration to the corresponding trisubstituted pyridine **78** as a pale yellow oil in 86% yield (Scheme 53).



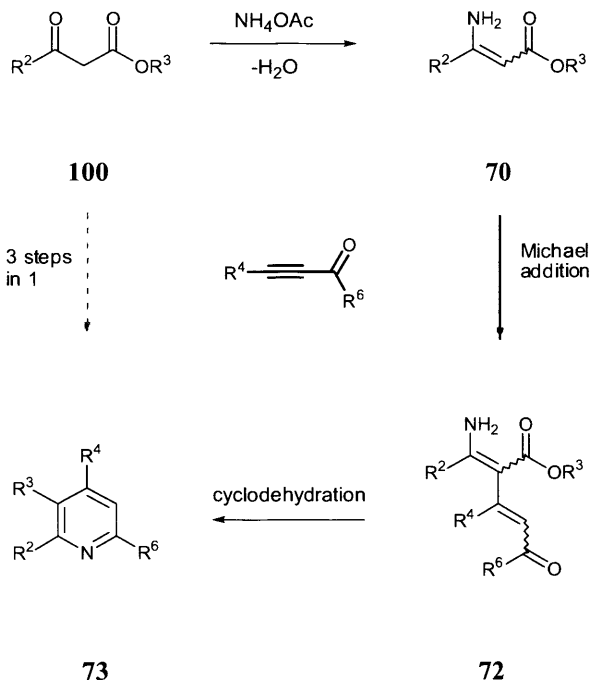
76 **78**

Scheme 53. Cyclodehydration of aminodienone **76**.

With the traditional route to a substituted pyridine established, a modification of this method could now be investigated in order to improve the efficiency and facility of the process in terms of substrate tolerance, the yield and milder reaction conditions.

2.1.2 One–Pot Three–Component Method Development

In order to overcome poor substrate availability, and the relatively harsh reaction conditions, a more facile one–pot three–component method was investigated. The goal was to establish an alternative experimental procedure for the preparation of polysubstituted pyridines in a single step and generate a range of pyridines in good yield with total regiocontrol by reaction of an alkynone, 1,3–dicarbonyl compound **100** and an excess of ammonium acetate in alcoholic solvents. It was hoped that by carrying out this multistep process in a protic solvent, the need for an additional Brønsted or Lewis acid would be avoided and that cyclodehydration would proceed spontaneously under reaction conditions (Scheme 54).



Scheme 54. Bohlmann-Rahtz and three-component pyridine synthesis.

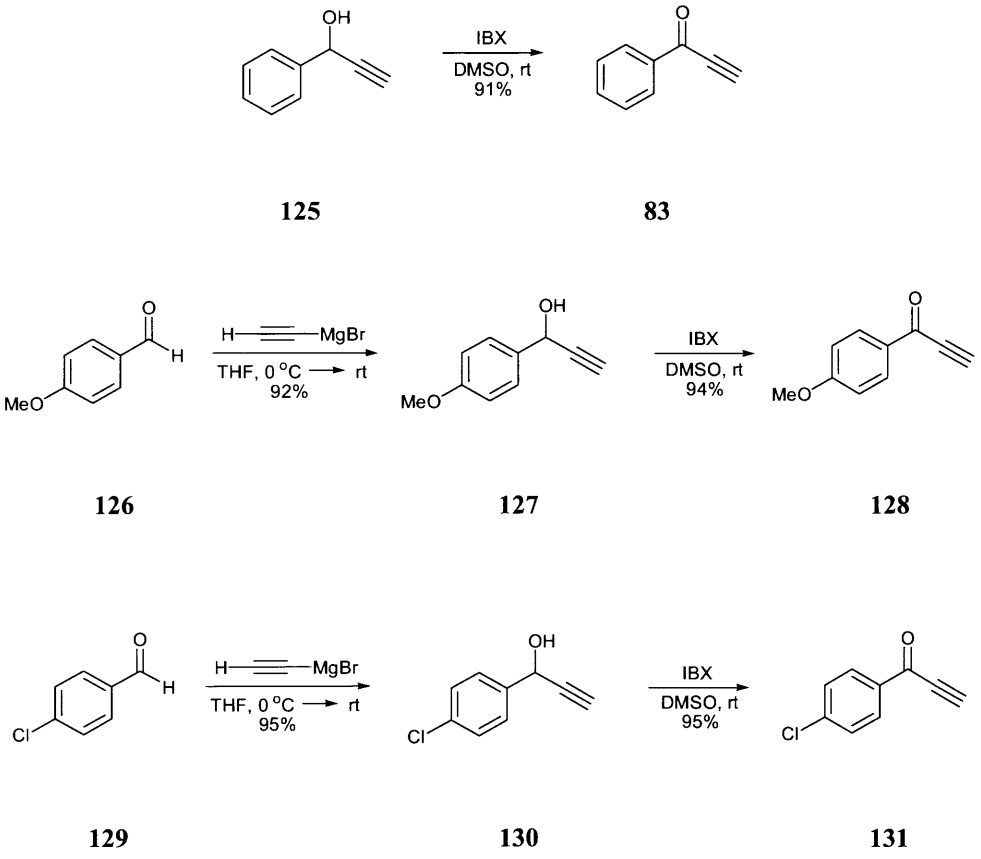
2.1.3 Synthesis Of Bohlmann-Rahtz Precursors

Before carrying out an investigation into this new Bohlmann–Rahtz process, a small library of pyridine analogues was synthesized. Various aromatic and non-aromatic

substituents were to be incorporated into the pyridine motif, some of the substrates originating from commercially available precursors. However, due to the limited availability of functionalised enamines and alkynones, a number of precursors were prepared to provide an interesting variety of substitution patterns in the pyridine library.

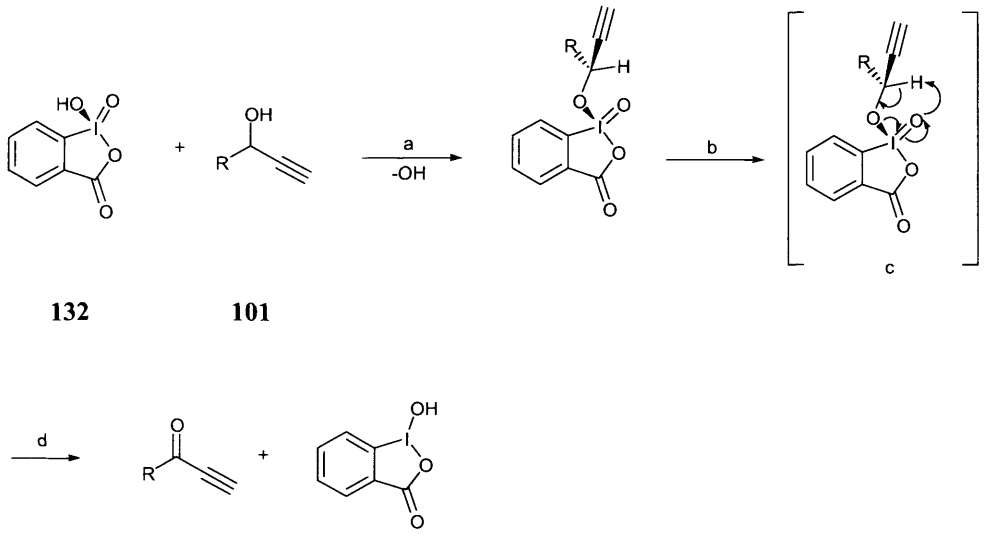
2.1.3.1 Alkynone Synthesis

Alkynones were prepared from arylaldehydes by Grignard addition at 0 °C in dry tetrahydrofuran under a nitrogen atmosphere to form the initial propargylic alcohols. After purification by column chromatography, oxidation of the propargylic alcholols using 1.3 equivalents of *o*–iodoxybenzoic acid (IBX)[83] stirring in dimethylsulphoxide afforded the desired alkynones in good yields (Scheme 56).



Scheme 55. Preparation of alkynones **83, 128** and **131**.

The choice of IBX **132** was used as a mild oxidising agent for the conversion of propargylic alcohols to their corresponding alcohols. The hypervalent iodine located in IBX is the site for molecular interaction and firstly ligand exchange must occur, replacing the OH group with the hydroxyl of the propargylic alcohol (Scheme 55).

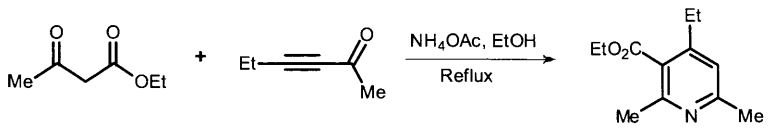


Scheme 56. Conversion of propargylic alcohols to alkynones using IBX.

To bring all the ligands bonded to the iodine into the same plane, a hypervalent twist action occurs allowing the complex to undergo a concerted rearrangement that results in the formation of the corresponding alkynone **71** (Scheme 56).

2.1.4 Initial Optimization Studies

In order to investigate if the one–pot three–component heteroannulation procedure was possible under mild conditions without an acid catalyst, optimization studies were first performed using ethyl acetoacetate **166** and hex–3–yn–2–one **167** with a number of equivalents of ammonium acetate.



133 **78** **88**

Scheme 57. Synthesis of pyridine **88**.

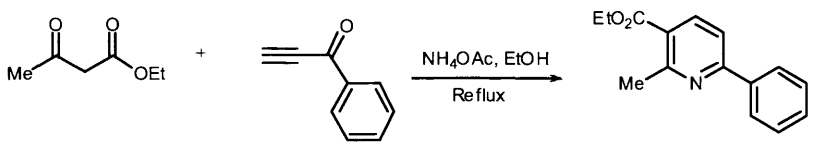
Table 32. Optimising the one–pot synthesis of ethyl 2,6–dimethyl–4–ethylpyridine–3–carboxylate.

Entry	Ratio of **166/167**	NH_4OAc equiv.	Temperature	Time (h)	Yield (%)[a]
1	1	1	Reflux	24	**88** (15)
2	1	2	Reflux	24	**133, 78**
3	1	4	Reflux	24	**133, 78**
4	1	10	Reflux	24	**88** (38)

[a] Isolated yield after column chromatography is given in parentheses.

The reaction did not go completion, and with 10 equivalents of NH_4OAc, the reaction provided tetrasubstituted pyridine **88** in 38% yield. This was attributed to the choice of alkynone, as hex–3–yn–2–one is a less reactive terminally substituted substrate.

Further optimization was carried out by using a mixture of ethyl acetoacetate **133**, 1–phenylpropyn–2–yn–1–one **83** in various ratios, and a number of equivalents of ammonium acetate by stirring in ethanol for up to three days.



133 **83** **107**

Scheme 58. Synthesis of pyridine **107.**

Table 33. Optimising the one–pot synthesis of ethyl–2–methyl–6–phenylpyridine–3–carboxylate.

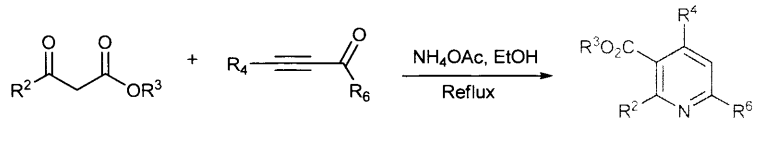
Entry	Ratio of **133/83.**	NH_4OAc equiv.[a]	Temperature (°C)	Time (h)	Product (Yield[b] %)
1	1	5	Room temp.	72	**108** (70) and **107** (23)[c]
2	1	1	Reflux	24	**74** and **107** (trace)
3	1	2	Reflux	24	**74** and **107** (1:1)[c]
4	1	4	Reflux	24	**74** and **107** (1.4:1)[c]
5	1	10	Reflux	24	**108** (89)

[a] Equivalents of NH_4OAc with respect to β–ketoester **133**. [b] Isolated yield after purification on silica. [c] Reations carried out by Xin Xiong.

Reactions conducted at room temperature or at reflux with up to 4 equivalents of ammonium acetate did not go to completion, giving a mixture of pyridine **107**, aminodienone **108**, and/or enamine **74** (Table 33). However when the reaction was carried out at reflux with a large excess of ammonium acetate, pyridine **107** was isolated as the only product in excellent yield, cyclodehydration occurring spontaneously under the reaction conditions without the use of an acid catalyst. The optimal system used a large excess of ammonium acetate and was heated at reflux for 24 hours (Table 33).

2.1.5 Library Synthesis

With an effective means established for the one–pot three–component reaction, the scope of this process was investigated. A range of different 1,3–dicarbonyl compounds **51** and alkynones **141** were heated at reflux in ethanol with either 1 or 10 equivalents of ammonium acetate (Table 34).



100 **71** **73**

Scheme 59. One–pot three–component condensation reaction for the synthesis of tetra–substituted pyridines **73**.

Table 34. Examining the scope of a one–pot three–component reaction for the synthesis of tetra–substituted pyridines.

Entry	1,3–Dicarbonyl compound	Alkynone	R^2	R^3	R^4	R^6	NH_4OAc equiv.[a]	Product	Yield (%)[b]
1	**133**	**83**	Me	OEt	H	Ph	10	**107**	89
2	**133**	**75**	Me	OEt	TMS	Me	1	**78**	90[d]
3	**133**	**75**	Me	OEt	TMS	Me	10	**78**	90[d]
4	**133**	**131**	Me	OEt	H	4'– C_6H_4Cl	10	**106**	90
5	**133**	**129**	Me	OEt	H	4'–C_6H_4OMe	10	**136**	88
6	**89**	**78**	Me	O'Bu	Et	Me	1	**96**	71
7	**89**	**78**	Me	O'Bu	Et	Me	10	**96**	63
8	**89**	**83**	Me	O'Bu	H	Ph	10	**137**	89
9	**89**	**75**	Me	O'Bu	TMS	Me	1	**138**	98[d]
10	**89**	**75**	Me	O'Bu	TMS	Me	10	**138**	97[d]
11	**89**	**129**	Me	O'Bu	H	4'–C_6H_4OMe	10	**139**	73
12	**134**	**83**	Me	OMe	H	Ph	1	**140**	90
13	**134**	**75**	Me	OMe	TMS	Me	1	**141**	90[d]
14	**134**	**75**	Me	OMe	TMS	Me	10	**141**	91[d]
15	**134**	**131**	Me	OMe	H	4'– C_6H_4Cl	10	**142**	96
16	**134**	**129**	Me	OMe	H	4'–C_6H_4OMe	10	**143**	87
17	**134**	**147**	Me	OMe	H	2–Furyl	10	**144**	77
18	**135**	**83**	Me	NH_2	H	Ph	1	**145**	98
19	**135**	**83**	Me	NH_2	H	Ph	10	**145**	98
20	**135**	**75**	Me	NH_2	TMS	Me	10	**146**	71[d]

[a] Equivalents of NH_4OAc with respect to 1,3–dicarbonyl compound **89, 133, 134,** and **135**. [b] Isolated yield of pyridine after purification on silica. [d] Only protodesilylated pyridine (R^4 = H) was formed.

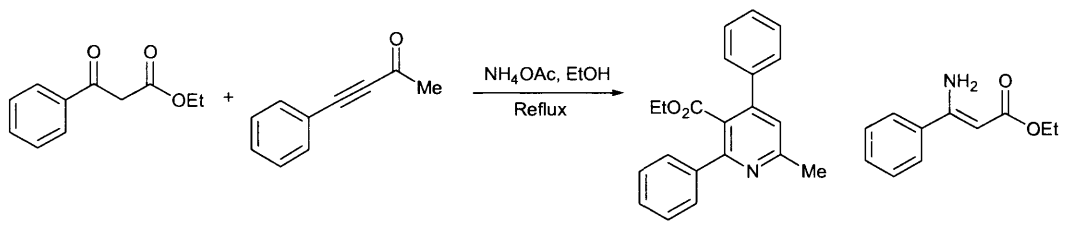
For the most part, pyridines (Table 34) were generated in good to excellent yields, with cyclodehydration occurring spontaneously under the reaction conditions, without the use of an additional catalyst. It was noteworthy that some reactions required only 1 equivalent of ammonium acetate. Reactions with 4–(trimethylsilyl)but–3–yn–2–one **75** in ethanol gave only the protodesilylated pyridines **78, 138, 141** and **146**.

Table 35. Examining the scope of a one–pot three–component reaction with terminally substituted alkynones.

Entry	1,3–Dicarbonyl compound	Alkynone	R^2	R^3	R^4	R^6	NH_4OAc eqiv.[a]	Product	Yield
1	**133**	**78**	Me	OEt	Et	Me	1	**88**	15
2	**133**	**78**	Me	OEt	Et	Me	10	**88**	38
3	**133**	**91**	Me	OEt	Ph	Me	1	**93**	51
4	**133**	**91**	Me	OEt	Ph	Me	10	**93**	53
5	**89**	**78**	Me	O^{t}Bu	Et	Me	1	**96**	71
6	**89**	**78**	Me	O^{t}Bu	Et	Me	10	**96**	63
7	**89**	**91**	Me	O^{t}Bu	Ph	Me	10	**95**	33
8	**90**	**91**	Ph	OEt	Ph	Me	10	**94**	<8[b]

[a] Equivalents of NH_4OAc with respect to 1,3–dicarbonyl compounds **89, 133,** and **91**. [b] ^1H NMR analysis of the crude product.

The use of terminally substituted alkynones such as hex–3–yn–2–one **78** or 4–phenylbut–3–yn–2–one **91** did cause a reduction in the efficiency of the process but pyridines **88, 93, 94** and **95** were still isolated in low to moderate yield as a single regioisomeric product (Table 35).



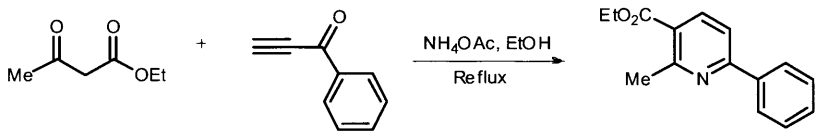
90 **91** **94** **148**

Scheme 61. Synthesis of pyridine **172** (entry 8).

Unfortunately reactions carried out with a mixture of ethyl benzoylacetate **90** (entry 8), ammonium acetate and 1–arylprop–2–yones did not give the desired pyridines and instead produced the corresponding enamine, ethyl 3–amino–3–phenylpropenoate **148**, and a number of side products with degradation of the alkynone. Similarly reactions of

ethyl benzoylacetate **90** and 4–phenylbut–3–yn–2–one **91** gave only a trace of the desired product **94** in the absence of an acid catalyst.

With the initial reaction a success, and a one–pot heteroannulation reaction established, an effort was made to investigate alternative reaction conditions and determine the relationship between the amount of alkynone and the yield of isolated product to explain the poor efficiency observed in some transformations. Firstly, a series of reactions were performed with ethyl acetoacetate **133**, 1–phenylprop–2–yn–1–one **83** and 10 equivalents of ammonium acetate at reflux in ethanol for 24 hours.



166 **83** **107**

Scheme 61. One–pot three–component condensation reaction of ethyl–2–methyl–6–phenylpyridine–3–carboxylate.

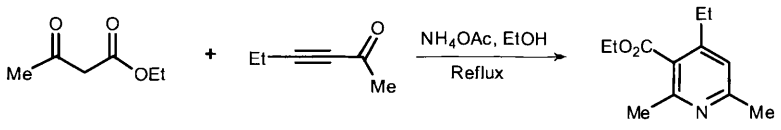
Table 36. Optimizing alkynone equivalents.

Entry	Equivalents of **83**	Product	Yield (%)
1	1	**107**	89
2	2	**107**	93
3	3	**107**	96

The results show there was a small but marked increase in yield obtained with increased stoichiometry of alkynones, 3 equivalents providing the best conditions for the synthesis of pyridine **107** (Table 36).

This study was repeated with the terminally substituted alkynone hex–3–yn–2–one (**78**), to see if an improvement in the yield for the synthesis of pyridine **88** could be achieved (Table 37). As expected, increasing the number of equivalents of this alkynone also noticeably increased the yield of pyridine **88**.

Table 37. Optimizing alkynone equivalents.



133 **78** **88**

Entry	Equivalents of **78**	Pyridine **88** Yield (%)
1	1	38
2	2	42
3	3	51

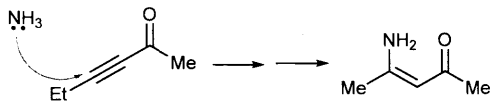
Reactions previously performed in the Bagley group involved using a series of acid catalysts, with a range of enamines and alkynones, including a number of reactions between 1,3–dicarbonyl compound and alkynones. In order to draw a comparison between this one–pot three–component reaction and similar reaction conditions previously performed by the Bagley group, differences in the yield of a number of methods were contrasted (Table 38).

Table 38. Comparing the four one step heteroannulation methods for the synthesis of pyridines.

Entry	1,3–Dicarbonyl compound	Alkynone	Product	Method A (Yield %)	Method B (Yield %)	Method C (Yield %)	Method D (Yield %)
1	**133**	**87**	**88**	38	49	60	38
2	**133**	**91**	**93**	89	84	90	
3	**133**	**75**	**78**	90	80	69	53
4	**133**	**90**	**93**	53	42		53
5	**135**	**83**	**145**	98	84		99

Method A= NH_4OAc 10 equiv., EtOH, reflux. Method B = NH_4OAc 10 equiv., $ZnBr_2$, PhMe, reflux. Method C = NH_4OAc 10 equiv., PhMe–AcOH (5:1), reflux. Method D = NH_4OAc 10 equiv., EtOH–AcOH (5:1), reflux.

The use of AcOH as a Brønsted acid in ethanol at reflux (method D), gave in general a lower yield of pyridine **88** in comparison with the use of ethanol alone (method A). Analysis by ^1H NMR spectroscopy indicated the presence of a few side products including possible structure **149**, from the attack of NH_3 on the terminally substituted hex–3–yn–2–one **87**.



87 **149**

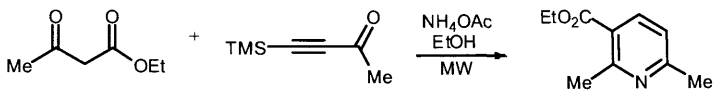
Scheme 62. Possible mechanism for side product formation as elucidated by ^{1}H NMR spectroscopy.

When comparing the efficiency of various processes, it was apparent that in some cases the use of acid catalysts increased the yield of pyridine formation, (Table 38, entry 1, method A, B and C). However despite these limitations, the reaction was successful in a number of cases for a wide variety of substrates and thus constitutes a mild method for the regiospecific synthesis of polysubstituted pyridines without the need to isolate the intermediate, a range enamines or aminodienones intermediates, avoiding the use of high temperatures and harsh acidic conditions to promote cyclodehydration.

2.1.6 Microwave Synthesis

Previous studies were conducted by Bagley, Lunn, Xiong and Lubinu to explore a microwave–assisted method for the synthesis of the modified Bohlmann–Rahtz pyridines. In a sealed microwave tube using toluene as a solvent and acetic acid as the catalyst, a range of conditions were investigated using the self tuning single mode CEM Discover^{TM} Focused Synthesizer.[88]

In order to determine if a more direct process could be established, the condensation of β–ketoester, alkynone and ammonium acetate, with the enamine and aminodienone formed in situ were investigated. The use of ethyl acetoacetate **133**, 4–(trimethylsilyl)but–3–yn–2–one **75**, and ammonium acetate (10 equivalents) in ethanol was chosen as a test reaction for this purpose in a sealed reaction tube.



133 **75** **78**

Scheme 63. Synthesis of aminodienone using alkynone

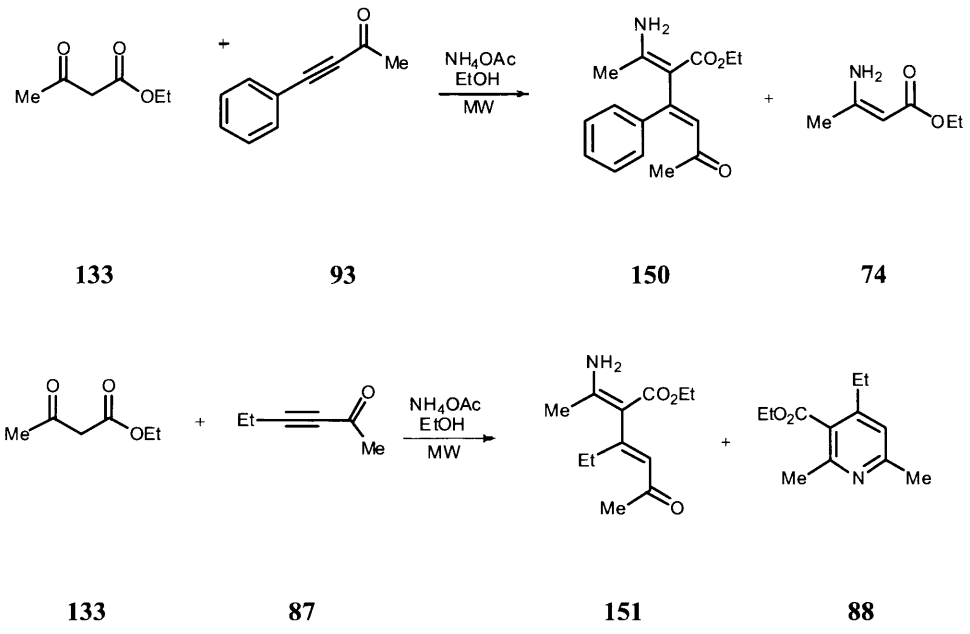
A range of reaction conditions were conducted in the microwave synthesizer, with temperatures ranging from room temperature to 140 °C.

Table 39. Reactions under microwave–assisted conditions for pyridine **78**.

Entry	Conditions[a]	Results[b]
1	60 min, 25 °C	Enamine 42%
2	60 min, 85 °C	**76** and **78** mixture
3	60 min, 100 °C	**76** and **78** mixture
4	60 min, 120 °C	**76** and **78** mixture
5	60 min, 140 °C	**76** and **78** mixture

[a] Reactions were performed at the required temperature through moderation of microwave power (initial power 120 W). [b] Results determined by ^{1}H NMR spectroscopic analysis of crude reaction mixture.

In conclusion it was found that microwave irradiation of the reactions for the synthesis of pyridine **78** did produce the desired products. When the first reaction was conducted at room temperature, ^{1}H NMR analysis showed the enamine present, but no trace of the intermediate **76** or product **78** was formed. Upon increasing the temperature, the ^{1}H NMR spectroscopic analysis showed the corresponding pyridine was formed, but also that the reaction had not gone to completion, as aminodienone **76** was still present. Even when the temperature was increased to 140 °C, the reaction still had unfortunately not gone to completion (Table 39).

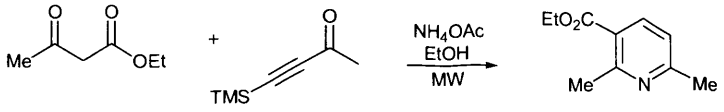


Scheme 64. Reactions performed under microwave–assisted conditions.

Reactions were also performed with two alternative alkynones, hex–3–yn–2–one (**87**) and 4–phenylbut–3–yn–2–one (**93**), with ethyl acetoacetate and predictably these reactions did not go to completion, only forming the corresponding mixtures of the enamine, aminodienone and pyridine product (Scheme 64).

It was decided that further reactions would need to be conducted using microwave heating, and an open vessel microwave reactions was investigated. A round bottomed flask and condenser were fitted into the microwave cavity enabling the microwaves to be passed through the reaction flask.

Table 40. Effect of temperature on the three–component Bohlmann–Rahtz pyridine synthesis.



133 **75** **78**

Entry	NH_4OAc equiv.[a]	Conditions[b]	Results
1	1	60 min, 25 °C	Enamine[c]
2	1	60 min, 25 °C	Enamine[c]
3	1	10 min, 85 °C	**78** and Intermediate 1:4
4	1	60 min, 85 °C	**78** and Intermediate 1:3
5	1	60 min, 85 °C	**78** and Intermediate 1:3
6	1	60 min, 100 °C	**78** (20%)
7	10	60 min, 85 °C	**78** (55%)

[a] Equivalents of NH_4OAc with respect to β–ketoester **133**. [b] Under open vessel microwave conditions. [c] formation of enamine **74**.

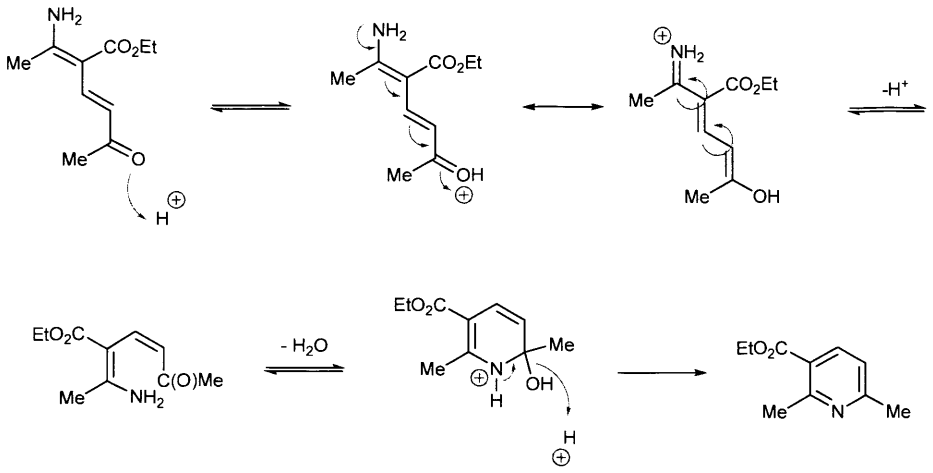
After conducting these experiments, the ^1H NMR spectroscopic analysis showed the reactions at room temperature, had only formed the enamine (Table 40, entries 1–2). On heating, reactions proceeded to give the corresponding intermediate and pyridine, although did not go to completion (entries 3–5). Finally when the number of equivalents of ammonium acetate increased, the pyridine **78** was isolated in 55% yield (Table 40, entry 7).

In many circumstances, microwave irradiation of organic reactions provide a facile and rapid route to the desired products, and this has been well documented for the synthesis of tri– and tetrasubstituted pyridines both by cyclodehydration of the corresponding aminodienone and in a two–step heteroannulation reaction of a β–ketoester and alkynone.

Conducting reactions for the three component heteroannulation in the microwave have not produced the desired pyridine as efficiently as the thermal conditions, possibly as they require longer reaction times.

The proposed mechanism for this reaction is given; the free acid will coordinate to both the nitrogen and C=O heteroatoms rapidly and reversibly. When coordination occurs to

the carbonyl group, the free movement of electrons allows the single and double bonds along the backbone of the molecule to switch and rotation to occur. Once rotation has taken place, in this configuration, cyclodehydration occurs spontaneously under the reaction conditions (Scheme 65)

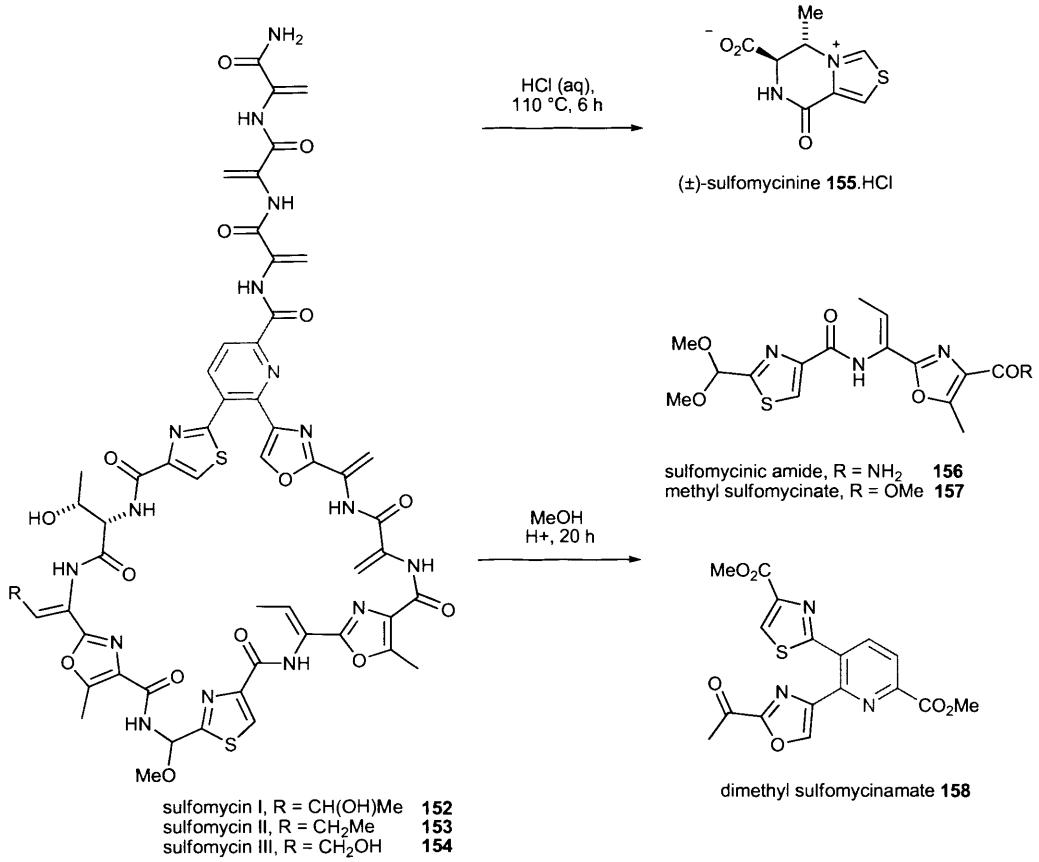


Scheme 65. Proposed mechanism for Bohlmann–Rahtz pyridine synthesis.

2.1.7 Natural Product Chemistry

The incorporation of this methodology into natural product chemistry has led to the synthesis of dimethyl sulfomycinamate, the acid methanolysis product of the sulfomycin family of thiopeptide antibiotics. The sulfomycins are members of the series *d* thiopeptide family of antibiotics, isolated from *Streptomyces viridochromogenes*. These cyclic peptides are characterized by a common oxazole–thiazole–pyridine central heterocyclic core, embedded in a macrocyclic backbone containing a number of heterocyclic and dehydroamino acid residues. An investigation as long ago as 1978 by Abe, Takaishi and Okuda of the sulfomycin hydrolysates, combined with FAB mass spectrometric data and ^{1}H and ^{13}C NMR spectroscopic analyses, elucidated the structure of these natural products. As part of these studies, the sulfomycins **152–154** were heated to 110 °C in 6 N HCl for 6 hours to give the degradation product (±)–sulfomycinine **155** hydrochloride. Furthermore when sulfomycin I **152** was heated at reflux in methanol in

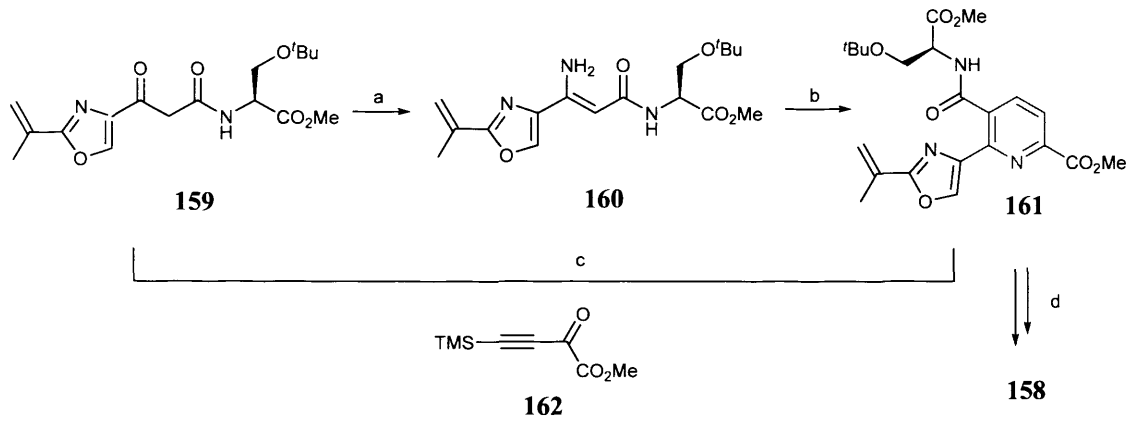
the presence of Amberlyst 15 ion–exchange resin for 20 hours, a number of degradation products were isolated, including sulfomycinic amide **156**, methyl sulfomycinate **157** and dimethyl sulfomycinamate **158**, the structure of the latter of which was determined by X–ray crystallography (Scheme 66).[89]



Scheme 66. Structure and chemical degradation of sulfomycins.

The synthesis of dimethyl sulfomycinamate **158** (Scheme 24) was achieved by Bagley, Dale, Bower and Xiong in 2003 starting from 2–methacrylamide and generated β–keto amide **160** as a mixture of tautomers in 5 steps and 44% overall yield. Ketone **159** was heated at reflux overnight in methanol in the presence of ammonium acetate to give the Bohlmann–Rahtz precursor, enamine **160**, in a single tautomeric form (80% yield) (a). The key heteroannelation reaction was achieved by stirring a solution of enamine **160** and methyl oxobutynoate **162** in methanol at room temperature to facilitate Michael addition, surprisingly under these conditions spontaneous cyclodehydration occurred at ambient

temperature to give pyridine **161** in excellent yield (93%), as a single regioisomer (b).[90] However, the pyridine synthesis was later improved. Heating β–keto amide **159**, used as a tautomeric mixture, methyl oxobutynoate **162**, and ammonium acetate (10 equiv) at reflux in methanol for 5 hours gave pyridine **161** directly in 81% yield, presumably via the corresponding enamine in a one–pot Bohlmann–Rahtz heteroannelation reaction (c) in accordance with our established conditions.



Reagents and conditions: (a) MeOH, NH_4OAc, reflux, 18 h (80%); (b) MeOH, RT, 24 h (93%); (c) MeOH, NH_4OAc, reflux, 5 h (81%); (d) 6 step (24%).

Scheme 67. Synthesis of dimethyl sulfomycinate by two different Bohlmann–Rahtz aynthesis

Elaboration of oxazole–pyridine **161** was achieved in a further 6 steps resulting in the synthesis of dimethyl sulfomycinamate **158** with total regiocontrol in 13 steps and 8% overall yield, by the Bohlmann–Rahtz heteroannelation of enamine **160**, or in 12 steps and 9% overall yield by a three–component cyclocondensation with β–keto amide **159** and ammonia in methanol.[90,91,92]

2.1.8 Conclusion

The Bohlmann-Rahtz reaction, first reported in 1957, is the reaction between an enamine, often generated from the corresponding β-ketoester, and an alkynone, which undergoes an initial conjugate Michael addition reaction to generate an aminodienone intermediate. Cyclodehydration facilitated by the use of high temperatures is used to generate tri- or tetrasubstituted pyridines. Our aim was to investigate useful modifications that would facilitate the generation of substituted pyridines in a facile manner, reducing the reaction times and carrying out the reaction under less harsh.

Our method for the regioselective synthesis of 2,3,6–trisubstituted and 2,3,4,6–tetrasubstituted pyridines from *β*–ketoesters and amides using a one–pot three–component Bohlmann–Rahtz heteroannulation reaction gave the resulting polysubstituted pyridines in moderate to excellent yield and as a single regioisomer. This facile route to pyridines is effective in alcoholic solvents at reflux in the absence of any added acid catalysts. The advantage of this mild heteroannulation methodology would be in its use for acid sensitive targets, and are highlighted by its application in the total synthesis of dimethyl sulfomycinamate, the acid methanolysis degradation product of the sulfomycin thiopeptide antibiotics, and now could be extended to prepare components of other thiopeptide antibiotics.

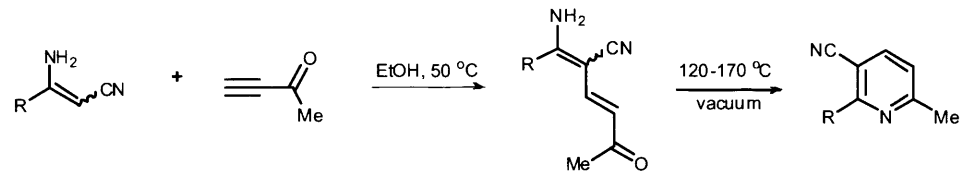
2.2 DEVELOPMENT OF NEW METHODOLOGY FOR 3–CYANOPYRIDINE SYNTHESIS

2.2.0 Aims

Microwave activation as a non conventional energy source has become an important method that can be used to carry out a wide range of reactions within a short time and with high yields. Our aim was to synthesize a range of 3–cyanopyridines **21** using microwave dielectric heating and to see if the reaction time could be shortened and yields improved when compared to the traditional thermal conductive heating for the reaction between 3–aminocrotonitrile and a range of alkynones.

2.2.1 Two–Component Method Development

Bohlmann and Rahtz first reported the synthesis of 3–cyanopyridines by the cyclocondensation of 3–aminocrotononitrile **20** or 3–aminocinnamonitrile **152** and prop–3–yn–2–one **147** in 1957.[4] This two–step sequence proceeds by initial Michael addition to give an aminodienone intermediate **153** that is isolated and purified and then cyclodehydrated at high temperature to give the corresponding nicotinonitrile **20** and **152** in good yield and with total regiocontrol (Scheme 68).



20 R = Me
152 R = Ph

82

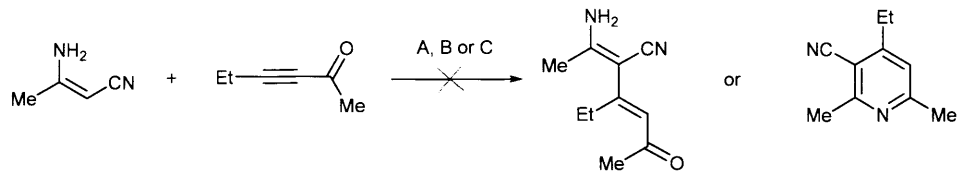
153

154 = Me (72%)
155 = Ph (77%)

Scheme 68. Bohlmann–Rahtz 3–cyanopyridine synthesis in 1957.

Previously within the group, James Dale examined the use of this type of precursor, aminocrotononitrile **20** or **152** and an alkynone, in the presence of either a Brønsted acid or acidic resin and compared these to the traditional stepwise procedure (Scheme 69). Unexpectedly all three experiments failed to provide either the aminodienone or pyridine and only recovered starting materials were isolated.

Although there has been a lot of interest in the Bohlmann–Rahtz synthesis of the related nicotinoate esters,[5] which has been applied in the synthesis of pyridine combinatorial libraries, pyridine–containing natural products and a whole range of heterocyclic building blocks in target synthesis,[6–25] there have been no further developments in the use of this heterocyclocondensation reaction for the synthesis of 3–cyanopyridines since the original Bohlmann–Rahtz report. In fact it would appear that efforts to accelerate the synthesis of 3–cyanopyridines from aminocrotononitrile and an alkynone using a Brønsted acid catalyst under traditional conductive heating, employed effectively for the synthesis of nicotinoate esters, were unsuccessful (Scheme 69).[7]



20 **87** **156** **157**

Scheme 69. Synthesis of 3–cyanopyridines via method A = $PhCH_3$–AcOH (5:1), 50 °C, 5 h; method B = $PhCH_3$, Amberlyst 15, 50 °C, 12 h or method C = EtOH, 50 °C, 5 h.

However, following the success of our previous studies into the acceleration of heterocyclocondensation reactions under microwave dielectric heating,[24–29] in particular in the synthesis of nicotinoate esters in the presence of an acid catalyst,[14–18] and based on previous results obtained for the synthesis of tri–and tetrasubstituted pyridines, a reinvestigation of the reaction conditions was deemed necessary to develop a facile one–step microwave–assisted method for the preparation of 3–cyanopyridine dyes from the reaction of an enamine and alkynone.

2.2.2 Initial Optimization Studies

With this aim in mind, to realize the synthesis of 3–cyanopyridines under microwave conditions, a series of experiments were performed in ethanol, and in a mixture of toluene–acetic acid (5:1) with 3–aminocrotononitrile **20** and 1–phenylprop–2–yn–1–one **83**, varying the time of the reaction at 120 °C using dielectric heating.

It was found that the reaction was complete in 30 minutes using dielectric heating and this time frame was applied to reactions performed in the microwave synthesizer (Table 41).

Table 41. Optimising the synthesis of 3–Cyano–6–phenyl–2–methylpyridine.

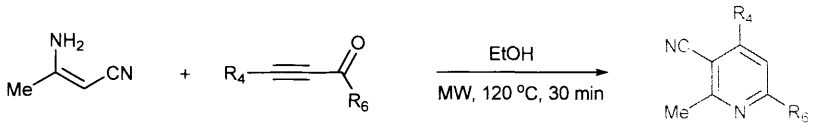
Entry	Solvent	Yields [a]		
		5 min	15 min	30 min
1	EtOH	20	56	73
2	PhMe:AcOH (5:1)	34	70	99

Yields refer to isolated yields after for these stated times at 120 °C and purified by column chromatography on SiO_2, microwave irradiation

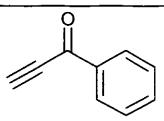
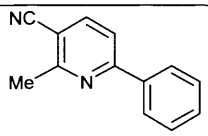
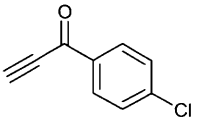
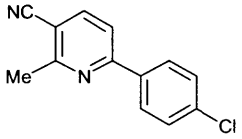
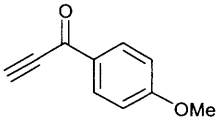
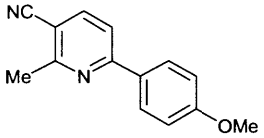
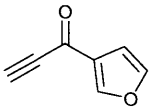
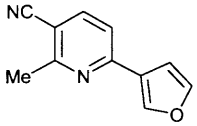
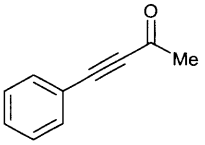
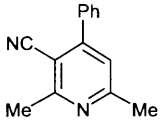
2.2.3 Library Synthesis

In order to compare reaction conditions for the synthesis of 3–cyanopyridines, a range of procedures were performed under various reaction conditions, both in the microwave and using conventional conductive heating. 3–Aminocrotononitrile and a range of alkynones were heated at reflux in ethanol for 24 hours and the results were compared to reactions performed under microwave dielectric heating at 120 °C, using an initial power of 150 W for 30 minutes (Table 41). The results suggested that the there is a general trend for the two–component heteroannulation reaction for the synthesis of 3–cyanopyridines to occur in comparable yield or even slightly more efficiently when conducted under microwave irradiation. However there were a few anomalies, most notable of which was that cyanopyridine **158** was obtained in higher yield of 90% when the reaction was carried out at reflux in ethanol compared to 73% yield when conducted in the microwave (Table 42).

Table 42. MAOS of 3–cyanopyridines in EtOH at 120 °C, (150 W) for 30 min.



20 **71** **31**

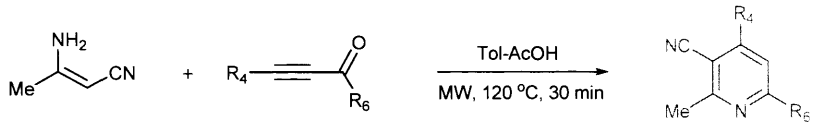
Entry	Alkynone	Product		EtOH reflux Yield	EtOH MW Yield
1			**158**	90	73
2			**159**	58	59
3			**160**	58	68
4			**161**	80	75
5			**162**	15	29

In an effort to improve the yield of the process, a modification of these conditions was explored using a Brønsted acid catalyst. Previous work within the group on the synthesis of tri– and tetra–substituted pyridines had showed that higher yields were generally achieved when reactions were conducted in toluene and acetic acid (5:1). Using this solvent system, the same set of reaction were investigated using both microwave dielectric heating at 120 °C, using an initial power set at 150 W, for 30 minutes and at reflux for 24 hours.

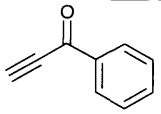
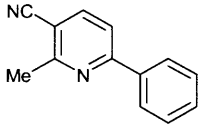
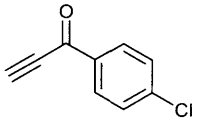
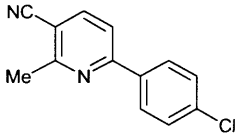
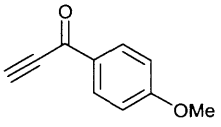
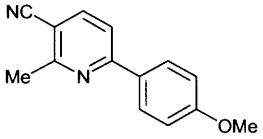
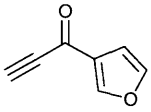
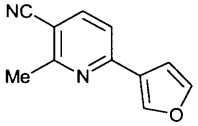
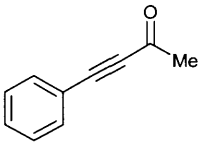
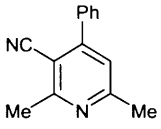
The results suggested that acid–mediated conditions gave higher yields in comparison to the efficiency of reactions performed in ethanol (Table 42). These reactions generally provided moderate to excellent yields for the synthesis of 3–cyanopyridines, and for all

the reactions subjected to the microwave conditions, were more efficient when compared to reaction yields conducted at reflux (Table 43, entries 1–5).

Table 43. MAOS of 3–cyanopyridines in Tol–AcOH, 120 °C, (150 W) for 30 min.



20 **71** **31**

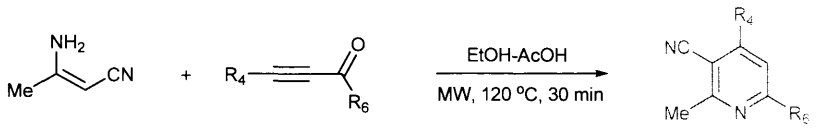
Entry	Alkynone	Product		Tol:AcOH reflux Yield	Tol:AcOH MW Yield
1			**158**	92	99
2			**159**	92	94
3			**160**	77	82
4			**161**	83	93
5			**162**	45	57

Further reactions were conducted in ethanol and acetic acid (5:1) to see if the combination of a Brønsted acid and protic solvent was a more powerful driving force for the synthesis of 3–cyanopyridines (Table 44). However when compared to reactions performed in toluene and acetic acid (5:1), in those cases 3–cyanopyridines were produced in higher yields (Table 43).

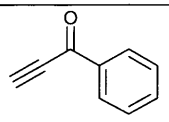
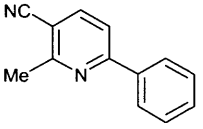
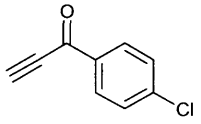
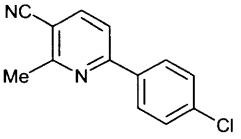
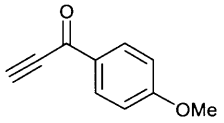
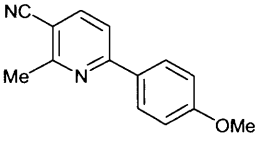
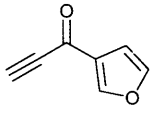
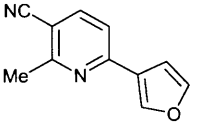
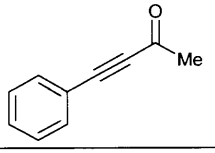
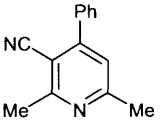
Reaction between 3–aminocrotononitrile and terminally substituted 4–phenylbut–3–yn–2–one **91** did predictably cause a reduction in the efficiency of the reaction, however

reactions performed using microwave heating proceeded in higher yield when compared to yields generated under reflux conditions (Table 42, entry 5, table 43 entry 5).

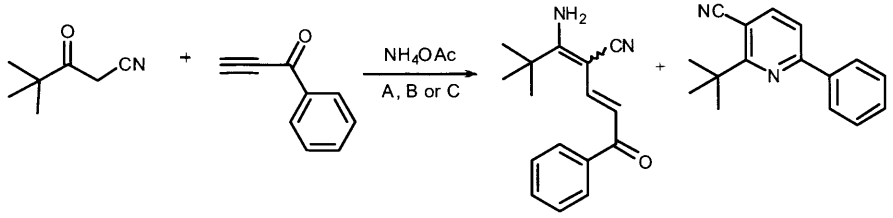
Table 44. MAOS of 3–cyanopyridines in EtOH–AcOH, 120 °C at (150 W) for 30 min.



20 **71** **31**

Entry	Alkynone	Product		EtOH:AcOH MW Yield
1			**158**	91
2			**159**	75
3			**160**	29
4			**161**	80
5			**162**	15

An effort was made to apply this technology in a one–pot process using a β–ketonitrile precursor. The one–pot three–component reaction was performed under a series of conditions using 4,4–dimethyl–2–oxopentanenitrile (**163**), ammonium acetate, and 1–phenyl–2–propyn–1–one (**83**) but did not produce the corresponding pyridine. Unfortunately, the reaction formed a mixture aminodienone **164** and of pyridine **165** and it was not possible to separate both products via flash chromatography (Scheme 70).



(1:1)

163 **83** **164** **165**

Scheme 70.

Although a one–pot process using β–ketonitrile had not been entirely successful, using the corresponding enamines had, for all five methods, A–E. The products were formed with total regiocontrol, and in moderate to excellent yields. The use of ethanol provided alternative milder conditions both thermally and under microwave heating conditions, which should be compatible with acid sensitive alkynones.

2.2.4 Conclusion

In conclusion, a new and efficient method for the modified Bohlmann–Rahtz synthesis of a range of 3–cyanopyridines has been achieved. This modified Bohlmann-Rahtz reaction is performed by microwave irradiation to give the 3–cyanopyridines in higher yield then reactions performed using conventional conductive heating. This extremely rapid and facile process provides the target pyridines with or without the need for purification in good to excellent yields, hence providing an alternative method for the synthesis of 3–cyanopyridines.

2.3 DEVELOPMENT OF NEW METHODOLOGY FOR TERPYRIDINE SYNTHESIS

2.3.0 Aims

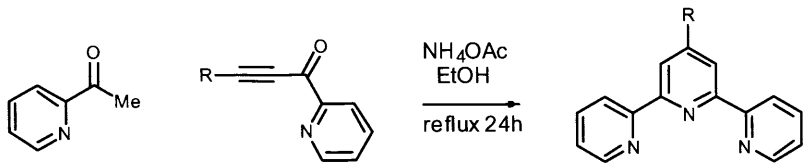
Having established a one–pot three–component heteroannulation reaction for the synthesis of tri and tetrasubstituted pyridines and a number of new methods for the synthesis of 3–cyanopyridines, efforts were now made to apply this methodology to synthesize a series of terpyridines.

2.3.1 Two–Component Method Development

A range conditions have been shown to promote the one–pot two–component Bohlmann–Rahtz synthesis of pyridine, in particular using Lewis and Brønsted acid catalysts. However, it was envisaged that relatively mild conditions may be required when applied to terpyridine synthesis. Thus, establishing suitable reaction conditions became the first point of study.

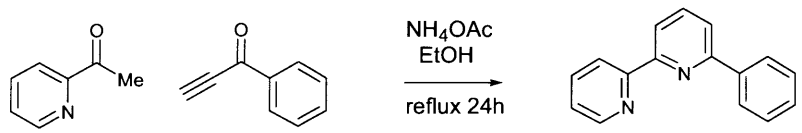
2.3.2 Initial Optimization Studies

The initial plan was to synthesize the terpyridine **89** from 2–acetylpyridine **52**, a pyridine–containing alkynone **166** and ammonia at reflux in ethanol as outlined in scheme 72. However due to the limited availability of the corresponding alkynone 1–phenyl–2–propyn–1–one **83** was used instead in this bipyridine synthesis as a test reaction to validate a potential route to terpyridines (Scheme 71).[41]



52 **166** **167**

Scheme 71: Proposed synthesis of terpyridine **167.**

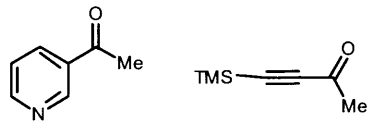


52 **83** **168**

Scheme 72: Proposed synthesis of bipyridine **168**.

A range of test reactions were performed using ammonium acetate or ammonium hydroxide[41] as a source of ammonia by stirring at room temperature or heating at reflux with 2–acetylpyridine (**52**), and one of two alkynones, 1–phenyl–2–propyn–1–one (**83**) or with 4–(trimethylsilyl)but–3–yn–2one (**75**) (Table 45).

Table 45: Investigating the three–component synthesis of bipyridines under different conditions.

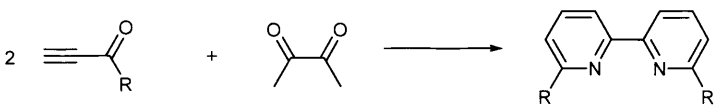


169 **75**

Entry	Acetyl Pyridine	Alkynone	Ammonia source	Base	Temperature (°C)	Time (h)	Yield (%)
1	**169**	**83**	NH_4OH	KOH	Reflux	24	0
2	**169**	**83**	NH_4OH	KOH	stir rt	4	0
4	**169**	**83**	NH_4OAc	KOH	Reflux	24	0
6	**169**	**83**	NH_4OAc	-	Reflux	24	0
5	**52**	**83**	NH_4OH	KOH	Reflux	24	0
6	**52**	**83**	NH_4OH	KOH	stir rt	4	0
7	**52**	**83**	NH_4OAc	KOH	Reflux	24	0
8	**52**	**83**	NH_4OAc	-	Reflux	24	0
9	**52**	**75**	NH_4OAc	-	Reflux	24	0
10	**52**	**75**	NH_4OH	KOH	stir rt	4	0

Unfortunately the reaction did not give the corresponding bipyridine and in all cases unreacted 2–acetylpyridine (**52**) was isolated from the reaction mixture. The degradation of alkynones **75** and 83 as confirmed from ^1H NMR spectroscopic analysis, gave rise to concerns that this route was unfeasible.

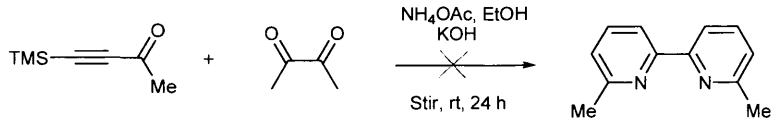
The continued search for available synthesis of bipyridines continued. Understanding that the previous system had not worked, 2–acetylpyridine **52** was replaced by 2,3–butanedione **170**, and was subjected to the same reaction conditions (Scheme 73).



71 **170** **171**

Scheme 73: Proposed synthesis of bipyridine **171**.

In order to investigate an alternative approach, 2,3–butanedione **170** was added to a solution of 2.5 equivalents of 4–(trimethylsilyl)but–3–yn–2one **75** in ethanol in the presence of 2 equivalents of potassium hydroxide and 1.5 equivalents of ammonium acetate, and this mixture was stirred for 24 h (Scheme 74). However, ^{1}H NMR spectroscopic analysis of the crude reaction mixture showed the reaction had not worked, with no pyridine resonances to indicate that the corresponding bipyridines had formed (Table 46).



75 **170** **48**

Scheme 74: Synthesis of bipyridine **263**.

Table 46. Investigating the synthesis of a three-component reaction of bipyridines in ethanol under different conditions.

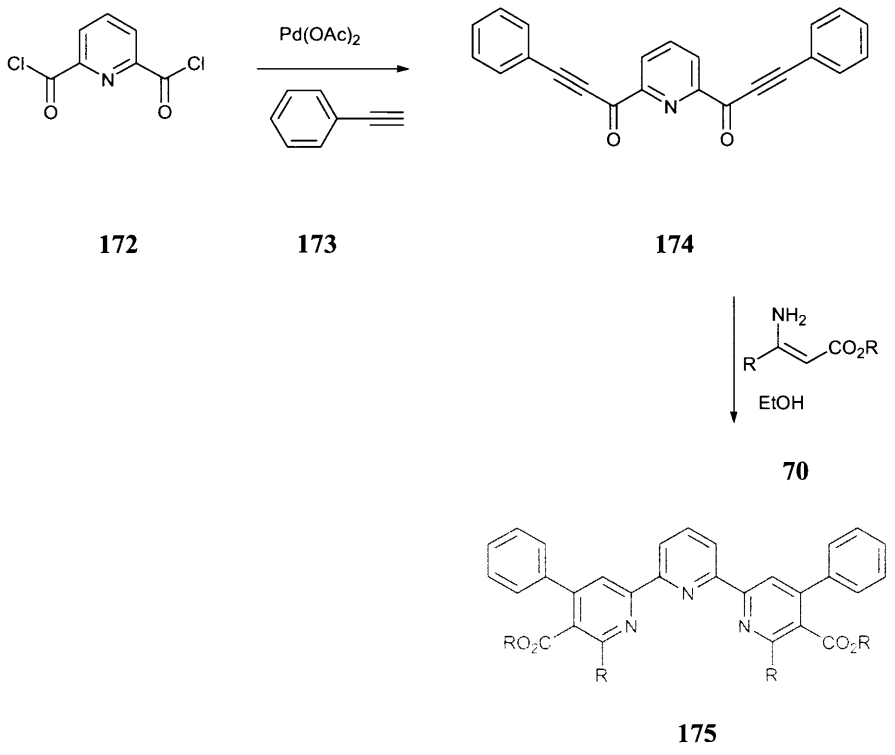
Entry	Ammonia source	Base	Temp (°C)	Time (h)	Yield (%)
1	NH_4OH	KOH	stir rt	24	0
2	NH_4OH	KOH	reflux	24	0
3	NH_4OH		stir rt	24	0
4	NH_4OH		reflux	24	0
5	NH_4OAc	KOH	stir rt	24	0
6	NH_4OAc	KOH	reflux	24	0
7	NH_4OAc		stir rt	24	0
8	NH_4OAc		reflux	24	0

Although the reaction had not been successful for the model system (Scheme 74), reactions were repeated under a range of alternative conditions (Table 45) to investigate if there was another possible method for the synthesis of bipyridines **45**. ^{1}H NMR spectroscopic analysis once more provided no evidence that the bipyridine had formed. It was unclear as to why the reaction had not worked, although it was possible that the ethanol may have reacted with the 2,3–butanedione **170**. An effort was made to change the solvent to a mixture of toluene and acetic acid (Table 47). Unsurprisingly these reactions also did not give the corresponding bipyridine.

Table 47. Investigating the synthesis of a three-component reaction of bipyridines in toluene–acetic acid (5:1) under different conditions.

Entry	Ammonia source	Base	Temp (°C)	Time (h)	Yield (%)
1	NH_4OH	KOH	stir rt	24	0
3	NH_4OH		stir rt	24	0
4	NH_4OH		reflux	24	0
4	NH_4OAc	KOH	stir rt	24	0
4	NH_4OAc		stir rt	24	0

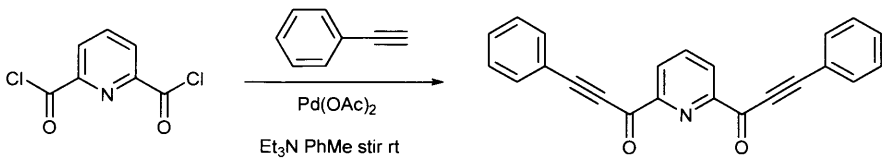
After exhausting various possibilities for the synthesis bipyridines, and hence terpyridines, an alternative synthetic route was proposed (Scheme 75).



Scheme 75: Proposed synthetic route to terpyridine **175**.

2.3.3 Bisalkynone Synthesis

A series of palladium–catalyzed coupling reactions were performed using catalysts $Pd(OAc)_2$ or $Pd_2(dba)_3$ with 2,6–pyridinedicarbonyldichloride **172**, phenylacetylene **173** and triethylamine in toluene either heated at reflux or stirred at room temperature for 24 hours to optimize the yield of 2,6-bis(3–phenylprop–2–yn–1–oyl)pyridine, **174** (Scheme 76, Table 46).[93]



172 **173** **174**

Scheme 76. Synthesis of 2,6–pyridinedicarbonyldichloride **174**.

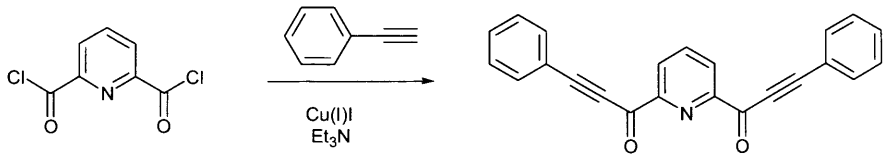
It was apparent the efficiency of the coupling reaction catalyzed by $Pd(OAc)_2$ was dependent upon the quantity of catalyst, base and equivalents of acetylene used (Table 48).

Table 48: Conditions investigated for the synthesis of bisalkynone **174**.

Entry	Acetylene Equiv **173**	Et_3N Equiv.	Pd (%)	Yield (%)
1	2.2	3	5% $Pd(OAc)_2$	8
2	2.2	3	5% $Pd_2(dba)_3$	-
3	10	3	5% $Pd(OAc)_2$	18
4	20	4	5% $Pd(OAc)_2$	22
5	20	4	10% $Pd(OAc)_2$	30
7	10	10	10% $Pd(OAc)_2$	39

The synthesis of bisalkynone was successful with an optimum yield of 39% but the limitations involved using costly palladium catalyst and difficulties in the removal of the metal after alumina column chromatography. To eliminate the problem of palladium contamination, the use of an alternative catalyst, copper (I) iodide,[94] was investigated (Scheme 77, Table 49).

This proceeded in lower yield, but did provide an alternative method for the preparation of bisalkynone **174**.



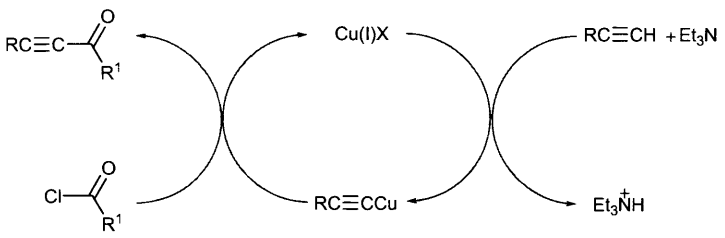
172 **173** **174**

Scheme 77: Synthesis of bisalkynone **174** via copper catalyzed coupling reaction.

Table 49: Optimizing the copper catalyzed coupling reaction.

Entry	Acetylene Equiv	Cu(I)I (%)	Yield (%)
1	10	15	13
2	20	30	19
3	20	40	33

It was proposed that the mechanism for the synthesis of 2,6-bis(3–phenylprop2–yn–1–oyl)pyridine **174** involved the following steps (Scheme 78). The copper salt of the alkynes are formed from the terminal alkynes in the presence of cuprous iodide, and triethylamine. The reaction of the copper acetylides with the acid chlorides leads to the formation of the acetylenic ketones and copper (I) chloride which could participate in the catalytic cycle again.[96]

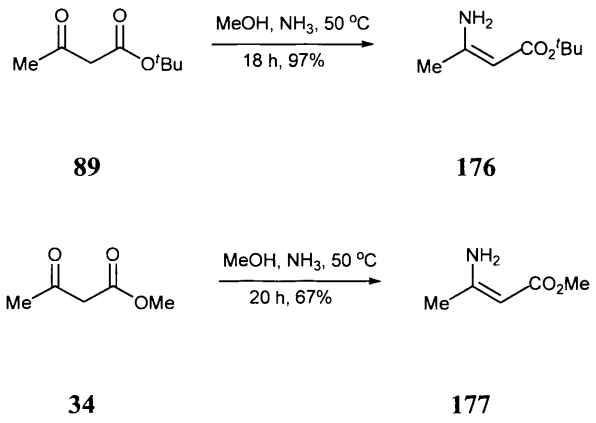


Scheme 78. Mechanism of copper (I) catalysed cross–coupling reaction.

Having established a method for the synthesis of pyridine bisalkynone we were now able to test the synthesis of terpyridines via the modified Bohlmann–Rahtz mechanism.

2.3.4 Enamine Synthesis

Before any methodologies could be investigated, the corresponding enamines needed to be generated to react with the bisalkynone in a one–pot two–component heteroannulation reaction. To that end, 1,3–dicarbonyl compounds were reacted according to literature procedures to generate primary enamines, methyl β–aminocrotonate, and *tert*–butyl β–aminocrotonate[95] in good yields (Scheme 79).



89 **176**

34 **177**

Scheme 79. Synthesis of enamines.

2.3.5 Library Synthesis

For the synthesis of terpyridines, ethyl β–aminocrotonate was reacted with the bisalkynone **174**, heated at reflux in ethanol for 24 h (Scheme 80) to give terpyridine **178** in 70% isolated yield.

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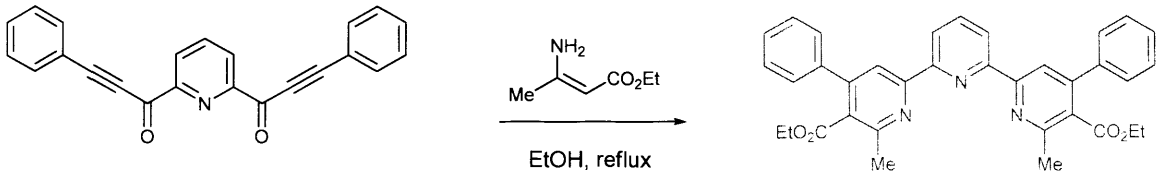


70%

74

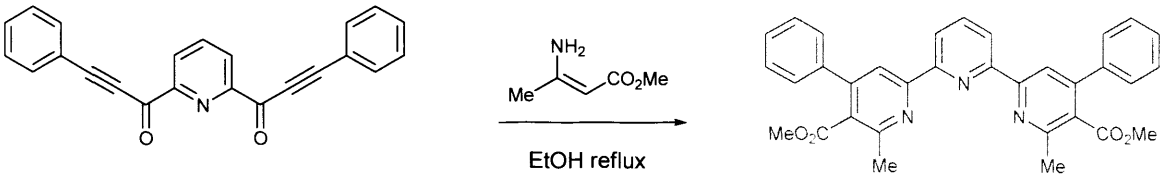
174 **178**

Scheme 80. One–pot two–component synthesis of terpyridine **178**.

Terpyridine **178** was identified by ^{1}H NMR and ^{13}C NMR spectroscopic analysis and high resolution mass spectrometric data.

The reaction had proceeded to form the corresponding pyridine **178** in good yield. Although the product required purification, this method offered considerable potential for the synthesis of terpyridines by avoiding high cyclodehydration temperatures and proceeding in a single one–step procedure, hence increasing the scope and utility of the Bohlmann–Rahtz reaction.

In order to investigate the scope of this reaction the alternative enamines, methyl β–aminocrotonate **177** (Scheme 81) and *tert*–butyl β–aminocrotonate **176** (Scheme 83) were reacted with bisalkynone **174** in ethanol to yield the corresponding terpyridines in moderate to good yield.



54%

177

174 **179**

Scheme 81. One–pot two–component synthesis of terpyridine **179**.

Terpyridine **179** was identified by ^{1}H NMR and ^{13}C NMR spectroscopic analysis, high resolution mass spectrometric data and X–ray crystallography (Figure 4).

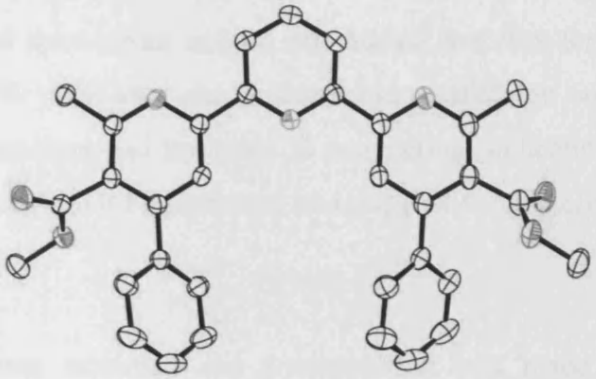
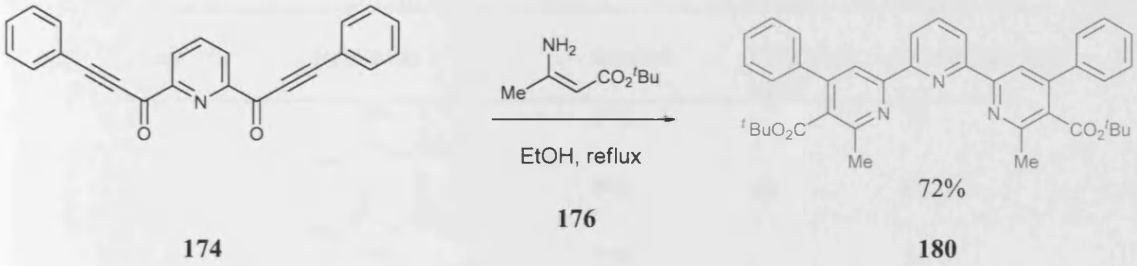


Figure 5. X–ray crystal structure of terpyridine **179**.
[See APPENDIX A for X–ray crystallography data]



174 **176** **180**

Scheme 82. One–pot two–component synthesis of terpyridine **180**.

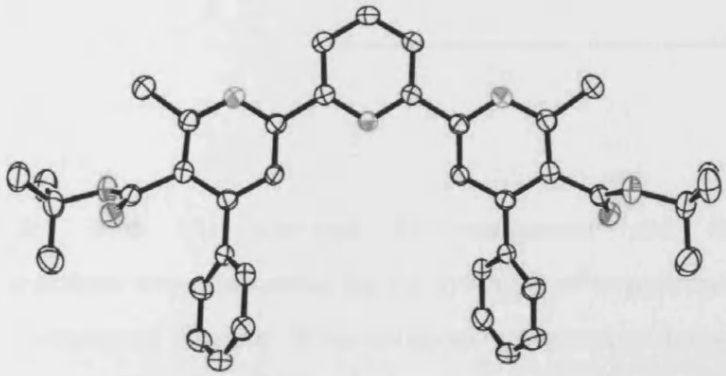
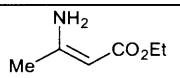
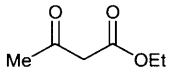
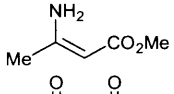
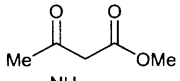
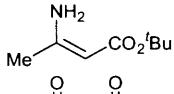
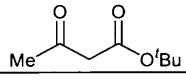


Figure 6. X–ray crystal structure of terpyridine**180**.
[See APPENDIX B for X–ray crystallography data]

With success in the preparation of terpyridine **178–180**, formed under mild modified Bohlmann–Rahtz conditions, our attention turned to the original method established for the synthesis of pyridines that combines a 1,3–dicarbonyl compound, ammonia, and alkynone, in a one–pot three–component heteroannulation reaction. Applying this methodology to the synthesis of terpyridines, a mixture of bisalkynone **174**, methyl acetoacetate (**134**) and ammonium acetate was heated at reflux for 24 h, and this gave terpyridine **179** in 41% yield after chromatographic purification on silica. From the ^{1}H NMR spectrum, the reaction had not gone to completion, indicating that aminodienone was present, but this could not be separated and purified completely and so could not be quantified.

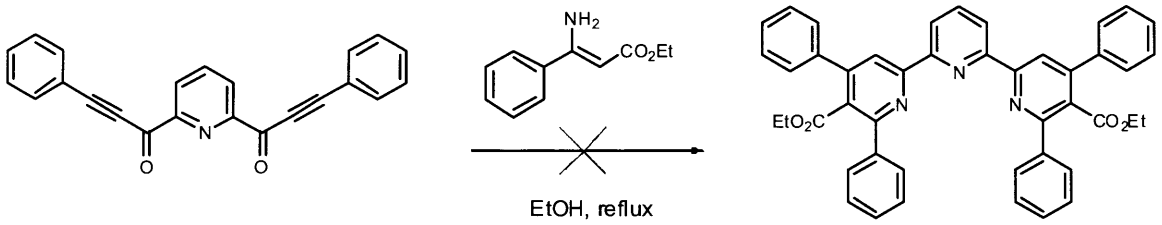
The reaction scope was extended and a comparison was made between the yields achieved for the three component and two component reactions (Table 50).

Table 50. Comparison of the synthesis of terpyridines **178–180** under the one–pot two –component and three–component heteroannulation reactions.

Entry	Substrate	Product	NH_4OAc equiv	Yield (%)
1		**178**	-	70
2		**178**	10	63
3		**179**	-	54
4		**179**	10	41
5		**180**	-	72
6		**180**	10	70

The reactions for both the one–pot two–component and three–component heteroannulation reactions were successful for the synthesis of terpyridines **178–179**. The reaction yields as expected for the three–component heteroannulation were slightly lower, however, the reactions succeeded in generating the corresponding terpyridine directly and so constitute a more direct route to these motifs.

In order to further expand the scope of the reaction, bisalkynone **174** and an alternative enamine, ethyl 3–amino–3–phenylpropenoate **(148)**, was heated at reflux in ethanol. However, use of this alternative precursor produced a mixture of a number of products that could not be distinguished by ^{1}H NMR spectroscopic analysis and so this study was abandoned (Scheme 83).

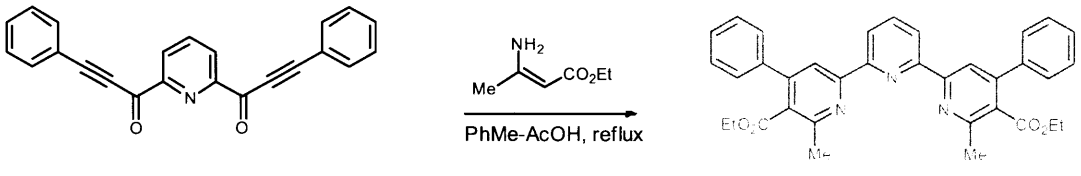


174 **148** **181**

Scheme 83. One–pot two–component synthesis of terpyridine **181**.

To complement and expand the scope of this reaction, the heteroannulation–cyclodehydration off bisalkynone **174** and enamine **74** was investigated in alternative solvent.

A solution of the substrates in toluene–glacial acetic acid (5:1) was heated at reflux for 24 hours to furnish terpyridine **178** in 76% yield after column chromatography. Spectroscopic analysis showed it to be identical to the previously isolated material (Scheme 84).



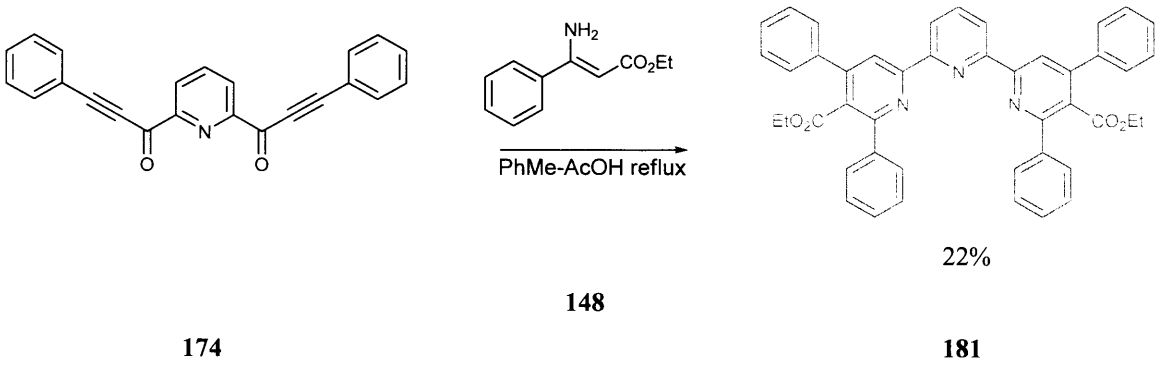
76%

74

266 **178**

Scheme 84. One–pot two–component synthesis of terpyridine **178**.

Applying the same reaction conditions, namely toluene–glacial acetic acid (5:1) at reflux, to the reaction of bisalkynone **174** and ethyl 3–amino–3–phenylpropenoate (**148**) gave pyridine **181**, which was characterized by ^{1}H NMR spectroscopic analysis. However the reaction has not gone to completion, forming the terpyridine in only 22% yield along with a number of side products (Scheme 85).



174 **148** **181**

Scheme 85. One–pot two–component synthesis of terpyridine **181**.

2.3.6 Conclusion

The synthesis of 2,2':6',2"–terpyridines had been achieved via a modified two–component and three–component Bohlmann–Rahtz pyridine synthesis in general in good yield. This methodology opens the possibility of forming a range of terpyridines by a Bohlmann–Rahtz approach. From the table of results, a number of conclusions can be drawn. Although only one reaction was performed for the synthesis of terpyridine **269** and **271**, not surprisingly, using toluene–acetic acid provided a more improved yield to the synthesis of terpyridine. The synthesis of this small library has provided us with enough evidence regarding the usefulness of this modification and the possibility for further studies to investigate whether other catalysts could be used effectively to extend the versatility of the modified procedure.

2.3.7 References

[88] Bagley, M. C.; Lunn, R.; Xiong, X.; *Tetrahedron Lett.*, **2002**, *43*, 8331.

[89] Abe, H.; Takaishi, T.; Okuda, T. *Tetrahedron Lett.*, **1978**, 2791.

[90] Bagley, M. C.; Dale, J. W.; Xiong, X.; Bower, J. *Org. Lett.*, **2003,** *5*, 4421.

[91] Xiong, X.; Bagley, M. C.; Chapaneri, K. *Tetrahedron Lett.*, **2004**, *45,* 6124.

[92] Bagley, M. C.; Chapaneri, K.; Dale, J. W.; Xiong, X.; Bower, J. *J. Org. Chem.*, **2005**, *70*, 1389.

[93] Alonso, D. D.; Nájera, C.; Pacheco, M. C. *J. Org. Chem.,* **2004**, *5,* 1615.

[94] Chowdhury, C.; Kundu, N. G. *Tetrahedron.* **1999**, *55*, 7011.

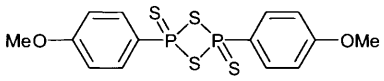
[95] Baraldi, P. G.; Simoni, D.; Manfredini, S. *Synthesis.* **1983**, 902.

CHAPTER THREE – RESULTS AND DISCUSSION

3 DEVELOPMENT OF NEW METHODOLGY FOR THIOAMIDE SYNTHESIS

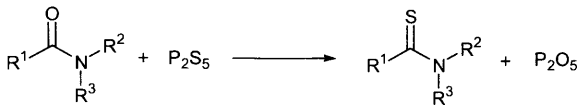
3.1.0 Introduction

The use of thioamides as building blocks in the Hantzsch thiazole synthesis has found broad applicability in many areas of chemistry. [96] In the past and over the last few years there have been many synthetic strategies aimed at their preparation from simple and readily available precursors. In general there are two strategies adopted for the synthesis of thioamides: the first is the thionation of the corresponding amide with an electrophilic reagent,[97] such as Lawesson's reagent[98] **182** (Figure 7) or phosphorus pentasulfide P_2S_5,[99] a method first reported in 1878 by A. W. Hofmann, to access a variety of thioamides. Hofmann used inert diluents in many of his preparations with stoichiometric amounts of powdered phosphorus pentasulfide, heating the amides at reflux for 1 hour to generate thioamides in moderate to good yields (Scheme 86, Table 49).



182

Figure 7. Lawesson's reagent.



183 **184**

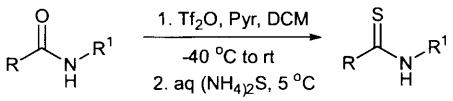
Scheme 86. Thionation of amide **184** using P_2S_5.

Table 51. Synthesis of thioamides from P_2S_5 and amides.

Entry	Thioamide Product	Yield (%)
1	$HCSNH_2$	30-50
2	CH_3CSNH_2	35-40
3	$(CH_3)_2CHCSNH_2$	30-50
4	4'– $NO_2C_6H_4CSNH_2$	70-90

This procedure was later improved by the use of dry, inert solvents and although side products were formed, they were generally insoluble in the solvent.

The second strategy for the synthesis of thioamides is by reaction with a nucleophilic thionating reagent, following electrophilic activation of an amide. Recent work by Charette and co-workers in 2003, showed whereby the slow addition of a mixture of pyridine and trifluoromethanesulfonic anhydride dropwise into aqueous $(NH_2)_4S$ generated secondary thioamides **186**.[100]

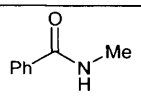
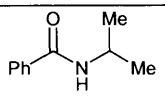
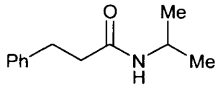
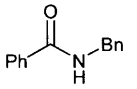
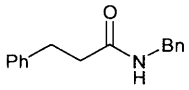
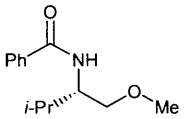
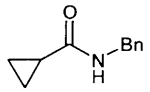
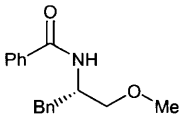
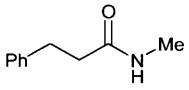


185 **186**

Scheme 87. Synthesis of secondary thioamides using nucleophilic thionating agents.

Modest to good yields of the corresponding thioamide were obtained for a range of substrates, however the reaction required strict maintenance of temperature, which ranged from –40 °C to room temperature, and the products required further purification (Scheme 87, Table 52).

Table 52. Synthesis of thioamides using aqueous ammonium sulfide by Charette.[102]

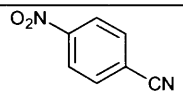
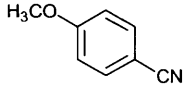
Entry	Substrate	Yield (%)	Entry	Substrate	Yield (%)
1		37 (A)	11		89 (A)[a]
2		91 (B)			
3		33 (A)	12		90 (A)
4		62 (B)	13		88 (A)
5		42 (A)	14		82 (A)
6		83 (B)			
7		35 (A)	15		86 (A)
8		75 (B)			
9		41 (A)			
10		80 (B)			

Method A: addition of ammonium sulfide to the reaction mixture. Method B: slow addition of reaction mixture to ammonium sulfide. [a]Addition done at -15 °C.

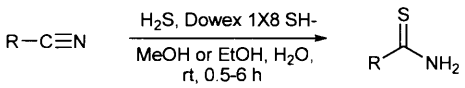
A more simple process has been described that uses the corresponding nitrile as a precursor.[101] This method used hydrogen sulfide with triethylamine or pyridine as a base at atmospheric pressure and proceeds well for aromatic nitriles but is highly problematic for the synthesis of aliphatic thioamides. Inevitably, with a toxic gaseous reagent, the experimental procedure was somewhat involved, whereby dry hydrogen sulphide was passed in a steady stream through a solution of the cyanide, pyridine and triethylamine for 2–4 hours.[102] The use of alkali–metal hydrogen sulfides or ammonium sulfide did simplify the procedure considerably,[103] but usually required high pressures[104] and was restricted to electron-deficient aromatic nitriles.[105]

More convenient sources of hydrogen sulfide have been used for this transformation, such as thioacids[106] and the synthesis of thioamides from nitriles utilizing thioacetamide as a source of ammonium sulfide under acidic conditions, and these gave the thionated products in appreciable yields (Table 53). A method applicable to aliphatic nitriles and aromatic nitriles containing either electron–withdrawing or electron–donating substituents, where one equivalent of nitrile is heated on a steam–bath for 15–30 min, with two equivalents of thioacetamide in dimethylformamide saturated with dry hydrogen chloride has been reported by Taylor and Zoltewicz in 1960[107] although these conditions are somewhat harsh and the procedure somewhat involved.

Table 53. Synthesis of thioamides from nitriles using thioacetamide.

Entry	Nitrile	Product Yield (%)
1		83
2		87
3	$Me(CN)_2$	63
4	$NC(CH_2)_4CN$	78

Alternative reagents, such as $(P_4S_{11})Na_2$,[108] or sodium trimethylsilanethiolate,[109] all of which require initial preparation, have been explored together with the use of Dowex SH^- by Bobek, Zyka and Liboska[110] who developed a method for the conversion of nitriles to primary thioamides **188** (Scheme 88).



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Scheme 88. Synthesis of primary thioamides using Dowex SH^-.

Initially, the Dowex 1X8 Cl^- is washed in aqueous NaOH, and distilled water and stored (OH^-) form at 4 °C in MeOH–H_2O (20%). The resulted Dowex 1X8 SH^- is filtered immediately washing with water, distilled twice before use, and then added to the nitrile in MeOH–H_2O mixture, followed by a slow stream of hydrogen sulfide. Following this procedure, primary thioamides are produced in moderate to excellent yields (Table 54).

Table 54. Preparation of primary thioamides from nitriles.

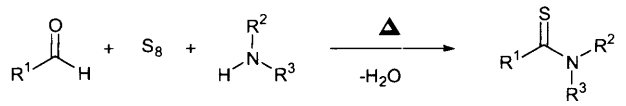
Entry	Substrate	Yield (%)[a]
1	$CH_3(CH_2)_6$	25
2	$NCCH_2$	38
3	$PhCH_2$	69
4	$BnO(CO)NHCH_2$	94
5	Ph	61
6	4'– C_6H_4Cl	75
7	4'–C_6H_4Me	67
8	4'–C_6H_4OMe	80
9	2–Pyridyl	91
10	3–Pyridyl	93

[a] Yield of isolated product.

Clearly, the challenge of establishing a simple method that is successful for a wide range of different substrates and that proceeds under straightforward experimental conditions using commercially available non-gaseous reagents remains.

Microwave dielectric heating has emerged as a valuable alternative to conventional conductive heating methods in recent years to increase the rate of synthetic transformations[111] and has been used in the three-component combinatorial Kindler synthesis of thioamides from aldehydes, amines and elemental sulfur (Scheme 89).[112]

The Kindler reaction first reported in 1923 allows for the easy introduction of diversity into the thioamide backbone by simple variation of aldehyde and amine components in the condensation step.



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Scheme 89. Three component coupling of aldehyde and amine.

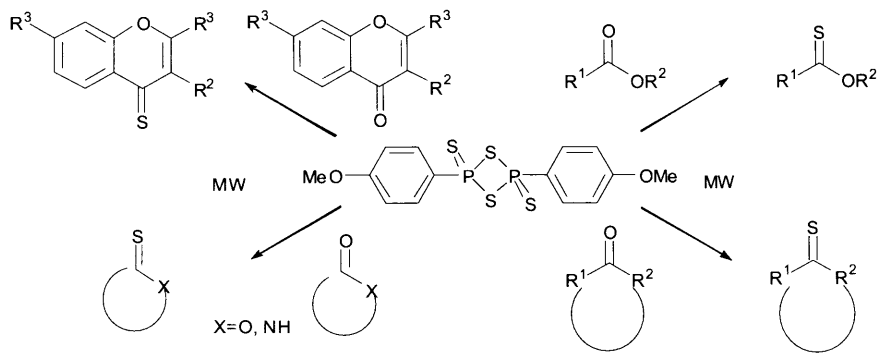
The microwave enhanced variation of the Kindler thioamide reaction takes advantage of this methodology (Table 55).

Table 55. Synthesis of a range of thioamides.

Entry	R^1	R^2, R^3	Temp °C	Time (min)	Yield (%)
1	Ph	$-(CH_2)_5-$	100	3	95
2	4-(NO_2)Ph	$-(CH_2)_5-$	130	2	94
3	$PhCH_2$	$-(CH_2)_5-$	100	3	73
4	3-indolyl	$-(CH_2)_5-$	100	8	72
5	3-(NO_2)Ph	$-(CH_2)_5O-(CH_2)_2-$	110	3	92
6	3-(MeO)-4-(OH)Ph	$-(CH_2)_5O-(CH_2)_2-$	120	10	92
7	2-thiophenyl	$-(CH_2)_5N(Ph)(CH_2)_2-$	120	3	99
8	4-(Me)Ph	$-(CH_2)_4-$	110	3	91
9	Ph	H, $PhCH_2$	170	3	>99
10	3-(Me)Ph	H, 3-(Cl)$PhCH_2$	140	12	85
11	2-(Me)Ph	H, $PhCH_2CH_2$	160	20	43
12	Ph	H, $PhCH_2CH_2$	180	4	>99
13	1-Pentyl	H, $PhCH_2CH_2$	140	10	39
14	Ph	H, H	180	20	44
15	4-(Me)Ph	H, H	170	20	36
16	4-(Cl)Ph	H, H	170	20	46
17	3-(Cl)Ph	H, propyl	140	12	90
18	3-(NO_2)Ph	H, propyl	150	12	95
19	1-Pentyl	H, propyl	140	10	54

In a majority of cases the reactions proceed in low to quantitative yield and required further purification by flash chromatography. Reactions involving aliphatic aldehydes generated lower yields (entry 3, 13, and 19). Other limitations of the Kindler modified three-component reaction involve *ortho*-substituted aromatic aldehydes (entry 11)which similarly give lower yields.[114]

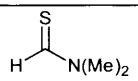
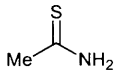
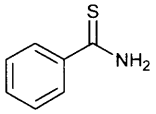
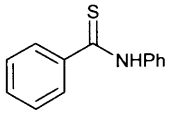
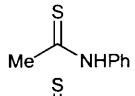
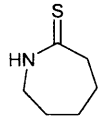
In 1999, Varma and Kumar developed a microwave-assisted reaction, accelerating the synthesis of thioamides by utilizing Lawesson's reagent.[113] Lawesson's reagent has been commonly used for the efficient conversion of oxygen functionalities into their thionated analogues (Scheme 90).



Scheme 90. General system for synthesis of thio analogues with Lawesson's reagent.

The simple process involves microwave irradiation of substrates and Lawesson's reagent under solventless conditions to give the corresponding thioamides in good to excellent yields (Table 56).

Table 56. Synthesis of thioamides under solvent–free conditions.

Entry	Product	Time (min)	Yield (%)
1		2	97
2		2	87
3		2	93
4		2	97
5		2	96
6		2	88

3.1.1 Aims

Having used microwave-assisted methods in the synthesis of the sulfur-containing heterocyclic domain of the cyclic thiazolylpeptide amythiamicin[114] and the acidic methanolysis product of the sulfomycins, dimethyl sulfomycinamate,[115] we set out to establish a predictable method for the conversion of both aliphatic and aromatic nitriles to primary thioamides using microwave irradiation.

3.1.2 Initial Optimization Studies

The synthesis of an aromatic electron–deficient substrate, 2–cyanopyridine (**190**) was chosen as the reaction of study for the synthesis of pyridine–2–thiocarboxamide (**191**). 2–Cyanopyridine was initially reacted with sodium hydrosulfide under a range of conditions, both thermally and under microwave irradiation but the experiments failed to give appreciable yields (Table 57).

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Scheme 91. Synthesis of pyridine–2–thiocarboxamide.

Table 57. Synthesis of pyridine–2–thiocarboxamide.

Entry	Sulfide	Conditions	Yield (%)
1	NaSH	Et_3N, MeOH-H_2O (3:2), RT, 18 h	26
2	NaSH	MeOH, RT, 18 h	24
3	NaSH	MeOH, MW (80°C, 100W), 30 min	30

These studies with 2–cyanopyridine (**190**) were repeated using ammonium sulfide under a variety of different conditions, to provide thioamide **191** in essentially quantitative yield after an aqueous work up without any need for further purification (Table 58).

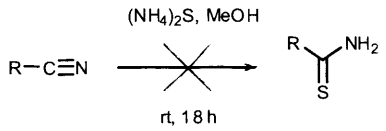
Table 58. Synthesis of pyridine–2–thiocarboxamide.

Entry	Sulfide	Conditions	Yield (%)
1	$(NH_4)_2S$	Et_3N, MeOH-H_2O (3:2), RT, 18 h	>98
2	$(NH_4)_2S$	MeOH, RT, 18 h	>98
3	$(NH_4)_2S$	MeOH, MW (80°C, 100W), 15 min	>98
4	$(NH_4)_2S$	MeOH, MW (130°C, 130W), 30 min	>98

The facile nature of this transformation, which proceeded at room temperature without the use of high pressures, was at first very surprising, even though the precursor was an electron-deficient aromatic substrate, and represents an experimentally simple procedure for the synthesis of primary thioamides that avoids the use of hydrogen sulfide gas, making this the reagent of choice to use for further investigation and expansion of this simple methodology.

3.1.3 Thermal Studies

From the data obtained from the initial optimization studies, a series of reactions were first performed at room temperature using a range of aliphatic and aromatic nitriles on reaction with ammonium sulfide in methanolic solvent at room temperature. Unfortunately as expected under these conditions these nitriles did not produce their corresponding thiamides (Scheme 92).



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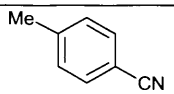
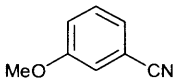
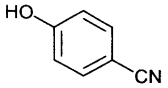
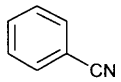
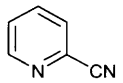
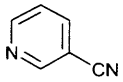
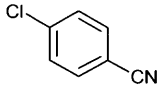
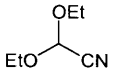
Scheme 92. Facile methods for synthesis of primary thioamides.

Table 59. Reactions of nitriles with ammonium sulfide.

Entry	Substrate		Product	Yield (%)
1		**192**	**193**	0
2		**194**	**195**	0
3		**196**	**197**	0
4		**198**	**199**	0
5	MeCN	**200**	**201**	0

However, a range of alternative aromatic, electron deficient nitriles were reacted with ammonium sulfide in methanolic solvent at room temperature, giving the corresponding thioamide in essentially quantitative yields. For nitrile **206**, the corresponding thioamide was formed in 37% yield (Table 60).

Table 60. Reactions of nitriles with ammonium sulphide

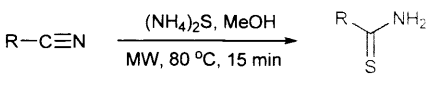
Entry	Substrate		Product	Mp (°C)[a]	Yield (%)[b]
1		**190**	**191**	137–138 (138–139)	>98
2		**202**	**203**	186–189 (190–192)	>98
3		**204**	**205**	116–117 (129–130)	>98
4		**206**	**207**	94–95 (81–92)[116]	37

[a] The range in parentheses refers to literature melting points (ref.[110], unless otherwise stated). [b] Isolated yield of pure product.

3.1.4 Microwave Studies

In order to establish the scope of these new methods and improve the yields of the process, a range of aliphatic and aromatic nitriles was reacted with ammonium sulfide in methanolic solvent under microwave-assisted conditions at either 80 °C or 130 °C for the synthesis of thioamides (Scheme 93, Table 61).[117]

With electron-deficient aromatic nitriles, the thionation reaction proceeded in essentially quantitative yield without the use of microwave irradiation or the requirement of any further purification, although irradiation did dramatically accelerate the transformation. Most aliphatic and electron-rich aromatic nitriles failed to give good yields of the product at room temperature, but when irradiated generated the corresponding thioamide in improved yield.



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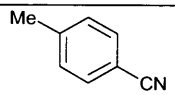
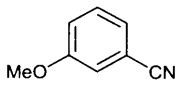
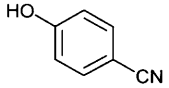
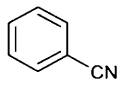
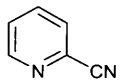
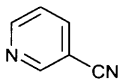
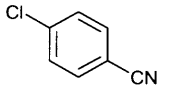
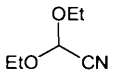
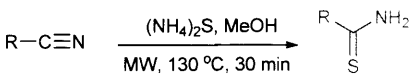
Scheme 93. Facile methods for synthesis of primary thioamides under MW irradiation at 80 °C.

Table 61. Reactions of nitriles with ammonium sulfide under MW irradiation at 80 °C for 15 min.

Entry	Substrate		Product	Mp (°C)[a]	Yield (%)[b]
1		**192**	**193**	171–172 (169–170)	>98
2		**194**	**195**	111–112 (145–147)[133]	21
3		**196**	**197**		8
4		**198**	**199**	112–114 (117–118)	90
5	MeCN	**200**	**201**	121–122 (108–109)	53
6		**190**	**191**	137–138 (138–139)	>98
7		**202**	**203**	186–189 (190–192)	>98
8		**204**	**205**	116–117 (129–130)	>98
9		**206**	**207**	94–95 (81–92)[21]	>98

[a] The range in parentheses refers to literature melting points (ref.[110], unless otherwise stated). [b] Isolated yield of pure product.

Nitriles **194**, **196** and **200** failed to give appreciable yields at 80 °C and so the thionation of these substrates was repeated under harsher conditions, at 130 °C (130 W initial power) and this seemed to improve the efficiency of the process somewhat. Although the thionation of 4–cyanophenol **196** did not go to completion under any of the conditions investigated, prolonged irradiation at 130 °C for 30 min gave thioamide **196** improving the yield to 40%.



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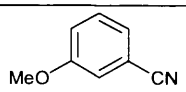
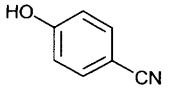
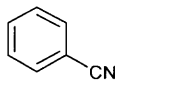
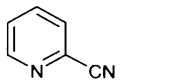
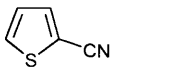
Scheme 94. Facile methods for synthesis of primary thioamides under MW irradiation at 130 °C.

Table 62. Reactions of nitriles with ammonium sulfide under MW irradiation at 130 °C for 30 min.

Entry	Substrate		Product	Mp (°C)[a]	Yield (%)[b]
2		**194**	**195**	111–112 (145–147)[133]	93
3		**196**	**197**	69–74 (108–109)	40
4		**198**	**199**	112–114 (117–118)	82
5	MeCN	**200**	**201**	121–122 (108–109)[101]	39
6		**190**	**191**	137–138 (138–139)	>98
7		**208**	**209**	108–109 (108–109)	90

[a] The range in parentheses refers to literature melting points (ref.[110], unless otherwise stated). [b] Isolated yield of pure product.

A series of products were synthesized using these methods and a comparison was made. Results indicated that all reactions performed under microwave irradiation generated the resulting products in good yields (Table 62) indicating that microwave irradiation exhibited several advantages over conventional heating by significantly reducing the reaction time and improving the reaction yields, whilst offering a convenient and reliable means to carry out the transformation.

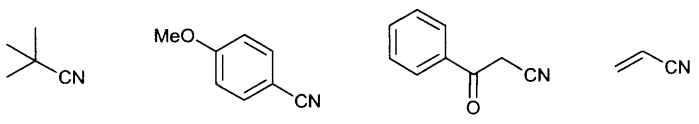


Figure 8. Nitriles that failed to give the corresponding thioamides when reacted with ammonium sulfide both at ambient temperature and under microwave irradiation.

The thionation of a number of nitriles failed to give any of the required thioamide products under all of the conditions investigated (Figure 8). Despite these restrictions, this method does prove a facile access to primary thioamides without the use of base or gaseous reagents.

3.1.5 Conclusion

In conclusion we have shown that ammonium sulphide in methanol at room temperature or under microwave irradiation is an extremely simple method and suitable replacement for hydrogen sulphide for the conversion of nitriles to primary thioamides and is effective for both electron-deficient and many electron-rich aliphatic and aromatic substrates, to give the product without need for purification and, usually, in quantitative yield. The application of this methodology has been incorporated into the synthesis of thiopeptide antibiotics, producing an alternative simple and more efficient route for the synthesis of thioamides.

3.1.6 References

[96] (a) Takahata, H.; Yamazaki, T. *Heterocycles* **1988**, *27*, 1953. (b) Hurd, R. N.; Delamater, G. T, ; *Chem Rev.*

[97] Brillon, D. *Sulpfur Rep.* **1992**, *12*, 297.

[98] Cava, M. P.; Levinson, M. I. *Tetrahedron* **1985**, *41*, 5061.

[99] Hartke, K.; Gerber, H.-D. *J. Prakt. Chem.* **1996**, *338*, 763.

[100] Charette, A. B.; Grenon, M. *J. Org. Chem.* **2003**, *68*, 5792

[101] Walter, W.; Bode, K. D. *Angew. Chem., Int. Ed. Engl.* **1996**, *5*, 447.

[102] Fairfull, A. E. S.; Lowe, J. L.; Peak, D. A. *J. Chem. Soc.* **1952**, 742.

[103] (a) Kindler, K. *Liebigs Ann. Chem.* **1923**, *431*, 187. (b) Wang, C. –H.; Hwang, F. –Y.; Chen, C. –T. *Herterocycles*.**1979**, *12*, 1191.

[104] Gabriel, S.; Heymann, P. *Ber. Dtsch. Chem. Ges.* **1890**, *23*, 157.

[105] Erlenmeyer, H.; Degen, K. *Helv. Chim. Acta* **1946**, *29*, 1080.

[106] Albert, A. *Ber. Dtsch. Chem. Ges.* **1915**, *48*, 470.

[107] Taylor, E. C.; Zoltewicz, J. A. *J. Am. Chem. Soc.* **1960**, *82*, 2656.

[108] Brillon, D. *Synth. Commun.* **1992**, *22*, 1397.

[109] Shiao, M. J.; Lai, L. L.; Ku, W. S.; Lin, P. Y.; Hwu, J. R. *J. Org. Chem.* **1993**, *58*, 4742.

[110] Liboska, R.; Zyka, D.; Bobek, M. *Synthesis* **2002**, 1649.

[111] Reviews on microwave chemistry include: (a) Gabriel, C.; Gabriel, S.; Grant, E. H.; Halstead, B. S. J.; Mingos, D. M. P. *Chem. Soc. Rev.* **1998**, *27*, 213; (b) Kuhnert, N. *Angew. Chem. Int. Ed.* **2002**, *41*, 1863; (c) Lidström, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225; (d) Loupy, A.; Petit, A.; Hamelin, J.; Texier-Boullet, F.; Jacquault, P.; Mathé, D. *Synthesis* **1998**, 1213; (e) Galema, S. A. *Chem. Soc. Rev.* **1997**, *26*, 233; (f) Caddick, S. *Tetrahedron* **1995**, *51*, 10403; (g) Strauss, C. R.; Trainor, R. W. *Aust. J. Chem.* **1995**, *48*, 1665.

[112] Zbruyev, O. I.; Stiasni, N.; Kappe, C. O. *J. Comb. Chem.* **2003**, *5*, 102.

[113] Varma, R. S.; Kumar, D. *Org. Lett.* **1999**, *1*, 697.

[114] Bagley, M. C.; Dale, J. W.; Jenkins, R. L.; Bower, J. *Chem. Commun.* **2004**, 102.

[115] Bagley, M. C.; Dale, J. W.; Xiong, X.; Bower, J. *Org. Lett.* **2003**, *5*, 4421.

[116] Inami, K.; Shiba, T. Bull. *Chem. Soc. Jpn.* **1985**, *58*, 352–360.

[117] Bagley, M. C.; Chapaneri, K.; Glover, C.; Merritt, E. *Synlett.* **2004**, *14*. 2615.

CHAPTER FOUR – EXPERIMENTAL

4.0 EXPERIMENTAL

4.1.0 Experimental Techniques

Commercially available reagents were used without further purification; solvents were dried by standard procedures. Light petroleum refers to the fraction with bp 40–60 °C, ether (Et_2O) refers to diethyl ether and EtOAc refers to ethyl acetate. Column chromatography was carried out using Merck Kieselgel 60 H silica or Matrex silica 60. Analytical thin layer chromatography was carried out using aluminium–backed plates coated with Merck Kieselgel 60 GF_{254} that were visualised under UV light (at 254 and/or 360 nm). Melting points (mp) were determined on a Kofler hot stage apparatus and are uncorrected. Infra–red (IR) spectra were recorded in the range 4000–600 cm^{-1} on a Perkin–Elmer 1600 series FTIR spectrometer using KBr disks for solid samples and thin films between NaCl plates for liquid samples or as a nujol mull and are reported in cm^{-1}. Nuclear magnetic resonance (NMR) spectra were recorded in $CDCl_3$ at 25 °C unless stated otherwise using a Bruker DPX 400 instrument operating at 400 MHz for ^1H spectra and 100 MHz for ^{13}C spectra and were reported in ppm; *J* values were recorded in Hz and multiplicities were expressed by the usual conventions (s=singlet, d=doublet, t=triplet, app=apparent, m=multiplet). Low–resolution mass spectra (MS) were determined using a Fisons VG Platform II Quadrupole instrument using atmospheric pressure chemical ionization (APcI) unless otherwise stated. ES refers to electrospray ionization, CI refers to chemical ionization (ammonia) and EI refers to electron impact. High-resolution mass spectra were obtained courtesy of the EPSRC Mass Spectrometry Service at Swansea, UK using the ionisation methods specified. Microanalyses were recorded using a Perkin–Elmer 240C Elemental Analyzer. *In vacuo* refers to evaporation at reduced pressure using a rotary evaporator and diaphragm pump, followed by the removal of trace volatiles using a vacuum (oil) pump. Microwave experiments were carried out in a CEM Discover microwave synthesizer at the temperature and initial power stated. All single crystal X–ray data was collected at 150K on a Bruker/Nonius Kappa CCD diffractometer using graphite monochromated Mo–Kα radiation (λ = 0.71073 Å), equipped with an Oxford Cryostream cooling apparatus. The data was corrected for Lorentz and polorization effects and for absorption using SORTAV.[118]

Structure solution was achieved by Patterson methods (Dirdiff–99 program system [119] and refined by full–matrix least–squares on F^2 (SHELXL–97). Molecular structures were drawn with Ortep 3.0 for Window (version 1.08).[120]

4.2.0 General Experimental Procedures

4.2.1 General Procedure For One–Pot Three–Component Pyridine Synthesis In Ethanol With 1 equiv. Of Ammonium Acetate

A solution of 1,3–dicarbonyl compound **101** (~1 mmol, 1 equiv.), alkynone **71** (1 equiv.) and ammonium acetate (1 equiv.) in ethanol was heated at reflux for 24 hours, allowed to cool and evaporated *in vacuo*. The mixture was partitioned between ethyl acetate (10 ml) and sodium hydrogen carbonate (10 ml), the aqueous layer was further extracted with ethyl acetate (2 x 10 ml) and the combined organic extracts were washed sequentially with sodium hydrogen carbonate (10 ml) and brine (10 ml), dried (Na_2SO_4), and evaporated *in vacuo* to give the crude pyridine **73**.

4.2.2 General Procedure For One–Pot Three–Component Pyridine Synthesis In Ethanol With 10 equiv. Of Ammonium Acetate

A solution of 1,3–dicarbonyl compound **101** (~1 mmol, 1 equiv.), alkynone **71** (1 equiv.) and ammonium acetate (10 equiv.) in ethanol was heated at reflux for 24 hours, allowed to cool and evaporated *in vacuo*. The mixture was partitioned between ethyl acetate (10 ml) and sodium hydrogen carbonate (10 ml), the aqueous layer was further extracted with ethyl acetate (2 x 10 ml) and the combined organic extracts were washed sequentially with sodium hydrogen carbonate (10 ml) and brine (10 ml), dried (Na_2SO_4), and evaporated *in vacuo* to give the crude pyridine **73**.

4.2.3 General Procedure For One–Pot Three–Component Pyridine Synthesis In Ethanol With 2 equiv. Of Alkynone

A solution of 1,3–dicarbonyl compound **133** (~1 mmol, 1 equiv.), alkynone **83** and **87** (2 equiv.) and ammonium acetate (10 equiv.) in ethanol was heated at reflux for 24 hours, allowed to cool and evaporated *in vacuo*. The mixture was partitioned between ethyl acetate (10 ml) and sodium hydrogen carbonate (10 ml), the aqueous layer was further extracted with ethyl acetate (2 x 10 ml) and the combined organic extracts were washed sequentially with sodium hydrogen carbonate (10 ml) and brine (10 ml), dried (Na_2SO_4), and evaporated *in vacuo* to give the crude pyridine **88** or **107**.

4.2.4 General Procedure For One–Pot Three–Component Pyridine Synthesis In Ethanol With 3 equiv. Alkynone

A solution of 1,3–dicarbonyl compound **133** (~1 mmol, 1 equiv.), alkynone **83** and **87** (3 equiv.) and ammonium acetate (10 equiv.) in ethanol was heated at reflux for 24 hours, allowed to cool and evaporated *in vacuo*. The mixture was partitioned between ethyl acetate (10 ml) and sodium hydrogen carbonate (10 ml), the aqueous layer was further extracted with ethyl acetate (2 x 10 ml) and the combined organic extracts were washed sequentially with sodium hydrogen carbonate (10 ml) and brine (10 ml), dried (Na_2SO_4), and evaporated *in vacuo* to give the crude pyridine **88** or **107**.

4.2.5 General Procedure For One–Pot Three–Component Pyridine Synthesis Using $ZnBr_2$

A solution of 1,3–dicarbonyl compound **101** (~1 mmol, 1 equiv.), alkynone **71** (1 equiv.), ammonium acetate (10 equiv.) and zinc(II) bromide in toluene (10 ml) was heated at reflux for 20 hours, allowed to cool and evaporated *in vacuo*. The mixture was partitioned between ethyl acetate (10 ml) and sodium hydrogen carbonate (10 ml), the aqueous layer was further extracted with ethyl acetate (2 x 10 ml) and the combined organic extracts

were washed sequentially with sodium hydrogen carbonate (10 ml) and brine (10 ml), dried (Na_2SO_4), and evaporated *in vacuo* to give the crude pyridine **73**.

4.2.6 General Procedure For One–Pot Three–Component Pyridine Synthesis In toluene–Acetic Acid

A solution of 1,3–dicarbonyl compound **101** (~1 mmol, 1 equiv.), alkynone **71** (1 equiv.) and ammonium acetate (10 equiv.) in toluene–glacial acetic acid (5.1) was heated at reflux for 20 hours, allowed to cool and evaporated *in vacuo*. The mixture was partitioned between ethyl acetate (5 ml) and sodium hydrogen carbonate (5 ml), the aqueous layer was further extracted with ethyl acetate (2 x 5 ml) and the combined organic extracts were washed sequentially with sodium hydrogen carbonate (10 ml) and brine (10 ml), dried (Na_2SO_4), and evaporated *in vacuo* to give the crude pyridine **73**.

4.2.7 General Procedure For One–Pot Three–Component Pyridine Synthesis In Ethanol–Acetic Acid

A solution of 1,3–dicarbonyl compound **101** (~1 mmol, 1 equiv.), alkynone **71** (1 equiv.) and ammonium acetate (10 equiv.) in ethanol–acetic acid (5.1) was heated at reflux for 20 hours, allowed to cool and evaporated *in vacuo*. The mixture was partitioned between ethyl acetate (5 ml) and sodium hydrogen carbonate (5 ml), the aqueous layer was further extracted with ethyl acetate (2 x 5 ml) and the combined organic extracts were washed sequentially with sodium hydrogen carbonate (10 ml) and brine (10 ml), dried (Na_2SO_4), and evaporated *in vacuo* to give the crude pyridine **73**.

4.2.8 General Procedure For Microwave–Assisted One–Pot Three–Component Pyridine Synthesis In Ethanol

A solution of ethyl acetoacetate **133** (1 mmol, 1 equiv.), 4–(trimethylsilyl)but–3–yn–2–one **75** (1 equiv.) and ammonium acetate (10 equiv.) in ethanol (2 ml) in a sealed pressure–rated reaction tube (10 ml) was irradiated at 25 °C, 85 °C, 100 °C, 120 °C or 140 °C (initial power 120 W) for 60 minutes in a self tuning single mode CEM Discover™ Synthesizer and then cooled by passing a flow of cool compressed air through the microwave cavity for 5 minutes. The mixture was partitioned between ethyl acetate (5 ml) and sodium hydrogen carbonate (5 ml). The aqueous layer was further extracted with ethyl acetate (2 x 5 ml) and the combined organic extracts were washed sequentially with sodium hydrogen carbonate (10 ml) and brine (10 ml), dried (Na_2SO_4), and evaporated *in vacuo* to give the crude pyridine **78**.

4.2.9 General Procedure For Microwave–Assisted Cyanopyridine Synthesis In Ethanolic Solvent

A solution of 3–aminocrotonitrile **20** (1 mmol, 1 equiv.) and alkynone **71** (1 equiv.) in ethanol (2 ml) in a sealed pressure-rated reaction tube (10 ml) was irradiated at 150 °C (initial power 150 W) for 30 minutes in a self tuning single mode CEM Discover™ Synthesizer and then cooled by passing a flow of compressed air through the microwave cavity for 5 minutes. The mixture was partitioned between ethyl acetate (5 ml) and sodium hydrogen carbonate (5 ml), the aqueous layer was further extracted with ethyl acetate (2 x 5 ml) and the combined organic extracts were washed sequentially with sodium hydrogen carbonate (10 ml) and brine (10 ml), dried (Na_2SO_4), and evaporated *in vacuo* to give the crude pyridine **159–162**.

4.2.10 General Procedure For Cyanopyridine Synthesis In Ethanolic Solvent

A solution of 3–aminocrotonitrile **20** (1 mmol, 1 equiv.) and alkynone **71** (1 equiv.) in ethanol (5 ml) was heated at reflux for 24 hours, allowed to cool and evaporated *in vacuo*. The mixture was partitioned between ethyl acetate (5 ml) and sodium hydrogen carbonate (5 ml), the aqueous layer was further extracted with ethyl acetate (2 x 5 ml) and the combined organic extracts were washed sequentially with sodium hydrogen carbonate (10 ml) and brine (10 ml), dried (Na_2SO_4), and evaporated *in vacuo* to give the crude pyridine **159–162**.

4.2.11 General Procedure For Microwave–Assisted Cyanopyridine Synthesis In The Presence Of Acetic Acid

A solution of 3–aminocrotonitrile **20** (1 mmol, 1 equiv.) and alkynone **71** (1 equiv.) in ethanol–glacial acetic acid (5.1) (2 ml) or toluene–acetic acid (2 ml) in a sealed pressure-rated reaction tube (10 ml) was irradiated at 150 °C (initial power 150 W) for 30 minutes in a self tuning single mode CEM Discover™ Synthesizer and then cooled by passing a flow of compressed air through the microwave cavity for 5 minutes. The mixture was partitioned between ethyl acetate (5 ml) and sodium hydrogen carbonate (5 ml), the aqueous layer was further extracted with ethyl acetate (2 x 5 ml) and the combined organic extracts were washed sequentially with sodium hydrogen carbonate (10 ml) and brine (10 ml), dried (Na_2SO_4), and evaporated *in vacuo* to give the crude pyridine **158, 24, 159–162**.

4.2.12 General Procedure For Cyanopyridine Synthesis In The Presence Of Acetic Acid

A solution of 3–aminocrotonitrile **20** (1 mmol, 1 equiv.) and alkynone **71** (1 equiv.) in toluene–glacial acetic acid (5:1) was heated at reflux for 24 hours, allowed to cool and evaporated *in vacuo*. The mixture was partitioned between ethyl acetate (5 ml) and

sodium hydrogen carbonate (5 ml), the aqueous layer was further extracted with ethyl acetate (2 x 5 ml) and the combined organic extracts were washed sequentially with sodium hydrogen carbonate (10 ml) and brine (10 ml), dried (Na_2SO_4), and evaporated *in vacuo* to give the crude pyridine **159–162**.

4.2.13 General Procedure For Terpyridine Synthesis In Ethanolic Solvent

A solution of the enamine **70, 176** or **177** (1 mmol, 6 equiv.) and 2,6–bis(3–phenylprop2–yn–1–oyl)pyridine **174** (1 equiv.) in ethanol (5 ml) was heated at reflux for 24 hours, allowed to cool and evaporated *in vacuo*. The mixture was partitioned between ethyl acetate (5 ml) and sodium hydrogen carbonate (5 ml). The aqueous layer was further extracted with ethyl acetate (2 x 5 ml) and the combined organic extracts were washed sequentially with sodium hydrogen carbonate (10 ml) and brine (10 ml), dried (Na_2SO_4), and evaporated *in vacuo* to give the crude terpyridine **178–180**.

4.2.14 General Procedure For One–pot Two–Component Terpyridine Synthesis In Ethanolic Solvent

A solution of the 1,3–dicarbonyl compound **89, 133** or **134** (1 mmol, 6 equiv.), ammonium acetate (10 equiv.) and 2,6–bis(3–phenylprop2–yn–1–oyl)pyridine **174** (1 equiv.) in ethanol (5 ml) was heated at reflux for 24 hours, allowed to cool and evaporated *in vacuo*. The mixture was partitioned between ethyl acetate (5 ml) and sodium hydrogen carbonate (5 ml). The aqueous layer was further extracted with ethyl acetate (2 x 5 ml) and the combined organic extracts were washed sequentially with sodium hydrogen carbonate (10 ml) and brine (10 ml), dried (Na_2SO_4), and evaporated *in vacuo* to give the crude terpyridine **178–180**.

4.2.15 General Procedure For Terpyridine Synthesis In The Presence Of Acetic Acid

A solution of the enamine **74** and **148** (1 mmol, 6 equiv.) and 2,6–bis(3–phenylprop2–yn–1–oyl)pyridine **174** (1 equiv.) in toluene–glacial acetic acid (5.1) (5 ml) was heated at reflux for 24 hours, allowed to cool and evaporated *in vacuo.* The mixture was partitioned between ethyl acetate (5 ml) and sodium hydrogen carbonate (5 ml), the aqueous layer was further extracted with ethyl acetate (2 x 5 ml) and the combined organic extracts were washed sequentially with sodium hydrogen carbonate (10 ml) and brine (10 ml), dried (Na_2SO_4), and evaporated *in vacuo* to give the crude terpyridine **178** or **181**.

4.2.16 General Procedure For Thioamide Synthesis In Ethanolic Solvent

A solution of nitrile **284, 286, 288, 290, 292, 294, 296, 298** and **300** (1 mmol, 1 equiv.) and ammonium sulphide (1 mmol, 1 equiv; 50 wt.% in H_2O) in methanol (5 ml) was stirred at room temperature for 18 hours and evaporated *in vacuo.* The mixture was partitioned between ethyl acetate (5 ml) and water (5 ml). The aqueous layer was further extracted with ethyl acetate (2 x 5 ml) and the combined organic extracts were washed brine (10 ml), dried (Na_2SO_4), and evaporated *in vacuo* to give the thioamide **285, 287, 289, 289, 293 295, 297, 299** and **301**.

4.2.17 General Procedure For Microwave–Assisted For Thioamide Synthesis At 80 °C

A solution of nitrile **190, 192, 194, 196, 198, 200, 202, 204** and **206** (1 mmol, 1 equiv.) and ammonium sulphide (1 mmol, 1 equiv; 50 wt.% in H_2O) in methanol (5 ml)) was irradiated in a sealed pressure–rated reaction tube (10 ml) at 80 °C (initial power 150 W) for 15 minutes in a self tuning single mode CEM Discover™ Synthesizer then cooled by passing a flow of compressed air through the microwave cavity for 5 minutes, the mixture was partitioned between ethyl acetate (5 ml) and water (5 ml), the aqueous layer was further extracted with ethyl acetate (2 x 5 ml) and the combined organic extracts were

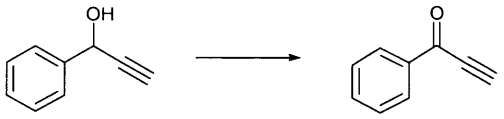
washed with brine (10 ml), dried (Na_2SO_4), and evaporated *in vacuo* to give the thioamide **191, 193, 195, 197, 199 201, 203, 205** and **207**.

4.2.18 General Procedure For Microwave–Assisted For Thioamide Synthesis At 130 °C

A solution of nitrile **191, 194, 196, 198, 200** and **208** (1 mmol, 1 equiv.) and ammonium sulphide (1 mmol, 1 equiv; 50 wt.% in H_2O) in methanol (5 ml)) was irradiated in a sealed pressure–rated reaction tube (10 ml) at 130 °C (initial power 150 W) for 30 minutes in a self tuning single mode CEM Discover™ Synthesizer then cooled by passing a flow of compressed air through the microwave cavity for 5 minutes. The mixture was partitioned between ethyl acetate (5 ml) and water (5 ml). The aqueous layer was further extracted with ethyl acetate (2 x 5 ml) and the combined organic extracts were washed with brine (10 ml), dried (Na_2SO_4), and evaporated *in vacuo* to give the thioamide **285, 191, 195, 197, 199, 201** and **209**.

4.3.0 Experimental Procedures

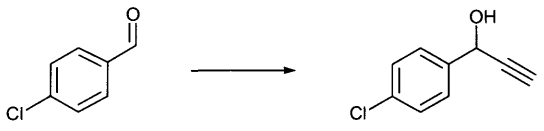
1–Phenylprop–2–yn–1–one (83)



125 **83**

A solution of *o*–iodoxybenzoic acid (IBX) (5.32 g, 19.0 mmol) in DMSO (144 ml) was stirred for 15 min at room temperature until homogeneous. A solution of 1–phenyl–2–propyn–1–ol **125** (0.94 ml, 7.57 mmol) in DMSO (5 ml) was added and the mixture was stirred for 5 h. Water (15 ml) was added and the mixture was stirred at room temperature for 10 min, cooled in ice and partitioned between water (120 ml) and ether (90 ml). The mixture was filtered through Celite® and the aqueous layer was further extracted with ether (75 ml). The organic extracts were combined, washed sequentially with water (3 x 120 ml), saturated aqueous sodium hydrogen carbonate solution (95 ml) and brine (95 ml), dried (Na_2SO_4) and evaporated *in vacuo* to give the *title compound*[56] as a pale yellow solid (896 mg, 91%), mp 49–50 °C (MeOH) (lit.[122] mp 47–48 °C) (Found: M^+, 130.0415. C_9H_6O (M^+) requires 130.0413); ν_{max}(KBr)/cm^{-1} 3250, 2090, 1641, 1600, 1545, 1461, 1310, 1287, 1180, 1044, 712; δ_H(400 MHz; $CDCl_3$) 8.10 (2 H, m, *o*–Ph*H*), 7.58 (1 H, m, *p*–Ph*H*), 7.44 (2 H, m, *m*–Ph*H*), 3.37 (1 H, s, CH); δ_C(100 MHz; $CDCl_3$) 179 (C), 137 (C), 135 (CH), 130 (CH), 129 (CH), 82 (C), 81 (CH); *m/z* (EI) 130 ($M^{\cdot+}$, 79%), 77 (34).

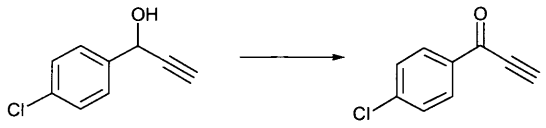
1–(4–Chlorophenyl)prop–2–yn–1–ol (130)



129 **130**

A solution of 4–chlorobenzaldehyde **129** (1.03g, 7.34 mmol) in dry THF (10 ml) was added to a stirred solution of ethynylmagnesium bromide in THF (0.5 M; 22 ml, 7.34 mmol) at 0 °C. The mixture was stirred at 0 °C for 2 h, warmed to room temperature and stirred overnight. Saturated aqueous ammonium chloride solution (5 ml) was added, the mixture was evaporated *in vacuo* and partitioned between diethyl ether (30 ml) and saturated aqueous ammonium chloride solution (30 ml). The ethereal layer was washed with brine (30 ml), dried (Na_2SO_4) and evaporated *in vacuo,* gave the *title compound*[64] as a pale yellow oil (1.12 g, 95%) (Found: M^+, 166.0181. $C_9H_7Cl^{37}O$ (M^+) requires 166.0180); ν_{max}(film)/cm^{-1} 3390, 3297, 2880, 2209, 1902, 1650, 1597, 1490, 1406, 1257, 1192, 1092, 1011, 950, 907; δ_H(400 MHz; $CDCl_3$) 7.38 (2 H, d, *J* 8.5, 2',6'–PhH), 7.26 (2 H, d, *J* 8.5, 3',5'–PhH), 5.33 (1 H, s, 1–H), 2.70 (1 H, s, OH), 2.59 (1 H, s, 3–H); δ_C(100 MHz; $CDCl_3$) 138 (C), 134 (C), 128 (CH), 128 (CH), 82 (CH), 76 (C), 63 (CH); *m/z* (EI) 166 ($C_9H_7{}^{37}ClO^{\cdot+}$, 11%), 164 ($C_9H_7{}^{35}ClO^{\cdot+}$, 26), 113 (15), 53 (100).

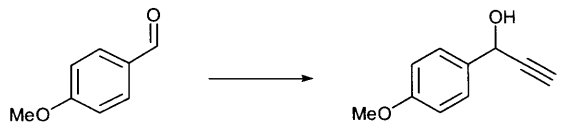
1–(4–Chlorophenyl)prop–2–yn–1–one (131)



130 **131**

A solution of *o*–iodoxybenzoic acid (IBX) (2.96 g, 10.56 mmol) in DMSO (160 ml) was stirred for 15 min at room temperature until homogeneous. A solution of 1–(4–chlorophenyl)prop–2–yn–1–ol **130** (1.10 g, 6.60 mmol) in DMSO (20 ml) was added and the mixture was stirred for 5 h. Water (40 ml) was added and the mixture was stirred at room temperature for 10 min, cooled in ice and partitioned between water (120 ml) and Et_2O (90 ml). The mixture was filtered through Celite® and the aqueous layer was further extracted with ether (50 ml). The organic extracts were combined, washed sequentially with water (3 × 50 ml), aqueous sodium hydrogen carbonate solution (70 ml) and brine (70 ml), dried (Na_2SO_4) and evaporated *in vacuo* (R_f 0.45), gave the *title compound*[72] as a pale yellow solid (1,03 g, 95%), mp 68–69 °C (MeOH) (lit.[72] mp 68–69 °C) (Found: M^+, 165.9991. $C_9H_5{}^{37}ClO$ [M^+] requires 165.9994); ν_{max}(KBr)/cm^{-1} 2931, 2853, 2360, 1666, 1463, 1379, 1250, 1081, 1005, 734; δ_H(400 MHz; $CDCl_3$) 7.98 (2 H, d, *J* 8.6, 3',4'–PhH), 7.41 (2 H, d, *J* 8.6, 2',5'–PhH), 3.38 (1 H, s, CH); δ_C(100 MHz; $CDCl_3$) 176.1 (C), 141.3 (C), 134.5 (C), 131.0 (CH), 129.1 (CH), 81.4 (C), 79.9 (CH); *m/z* (EI) 166 ($C_9H_5Cl^{37}O^{\cdot+}$, 7%), 164 ($C_9H_5Cl^{35}O^{\cdot+}$, 21), 138 (11), 136 (33), 113 (3), 111 (12), 53 (100).

1–(4–Methoxyphenyl)prop–2–yn–1–ol (126)



126 **127**

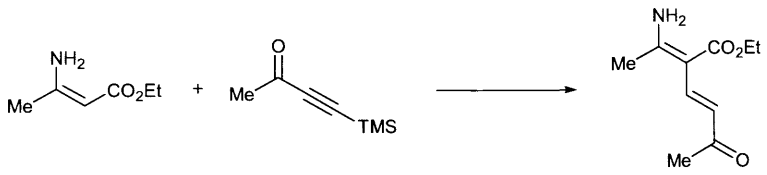
A solution of *p*–anisaldehyde **126** (1.0 g, 7.34 mmol) in dry THF (15 ml) was added to a stirred solution of ethynylmagnesium bromide in THF (0.5 M; 22 ml, 110 mmol) at 0 °C. The mixture was stirred at 0 °C for 2 h, warmed to room temperature and stirred overnight. Saturated aqueous ammonium chloride solution (5 ml) was added, the mixture was evaporated *in vacuo* and partitioned between diethyl ether (30 ml) and saturated aqueous ammonium chloride solution (30 ml). The ethereal layer was washed with brine (30 ml), dried (Na_2SO_4) and evaporated *in vacuo,* gave the *title compound*[123] as a pale yellow oil (1.10 g, 92%) (Found: MH^+, 161.0596. $C_{10}H_{10}O_2$, [MH^+] requires 161.0597); ν_{max}(film)/cm^{-1} 3438, 3284, 3003, 2935, 2837 1892 1611, 1512, 1464, 1442, 1304, 1249, 1174, 1112, 1032, 948, 833, 768; ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.50 (2 H, d, *J* 8.6, 2',6'–PhH), 6.90 (2 H, d, *J* 8.6, 3',5'–PhH), 5.42 (1 H, s, 1–H), 3.85 (3 H, s, OMe), 2.65 (1 H, s, 3–H); ^{13}C NMR (100 MHz; $CDCl_3$) δ 159.8 (C), 132.4 (C), 128.1 (CH), 114.0 (CH), 83.7 (CH), 74.7 (C), 64.0 (CH), 55.4 (Me); *m/z* (EI) 162 ($M^{\cdot+}$, 100%), 161 (54), 145 (35), 131 (38), 89 (57), 53 (43).

1–(4–Methoxyphenyl)prop–2–yn–1–one (127)

127 **128**

A solution of *o*–iodoxybenzoic acid (IBX) (3.05g, 10.85 mmol) in DMSO (160 ml) was stirred for 15 min at room temperature until homogeneous. A solution of 1–(4–methoxyphenyl)prop–2–yn–1–ol **127** (1.10 g, 6.78 mmol) in DMSO (15 ml) was added and the mixture was stirred for 5 h. Water (40 ml) was added and the mixture was stirred at room temperature for 10 min, cooled in ice and partitioned between H_2O (120 ml) and ether (90 ml). The mixture was filtered through Celite® and the aqueous layer was further extracted with ether (50 ml). The organic extracts were combined, washed sequentially with water (3 × 50 ml), aqueous sodium hydrogen carbonate solution (70 ml) and brine (70 ml), dried (Na_2SO_4) and evaporated *in vacuo* (R_f 0.45) gave the *title compound*[124] as a pale yellow solid (1.02 g, 94%), mp 86–87 °C (MeOH) (lit.[72] mp 85–87 °C) (Found: MH^+, 161.0597. $C_{10}H_9O_2$ [MH^+] requires 161.0597); ν_{max}(KBr)/cm^{-1} 3297, 2092, 1641, 1597, 1572, 1511, 1423, 1252, 1170, 1116, 1023, 841, 758, 710, 685; δ_H(400 MHz; $CDCl_3$) 8.05 (2 H, d, *J* 8.7, 2',6'–PhH), 6.88 (2 H, d, *J* 8.7, 3',5'–PhH), 3.88 (3 H, s, OMe), 3.29 (1 H, s, CH); δ_C(100 MHz; $CDCl_3$) 176 (C), 166 (C), 131 (CH), 129 (CH), 114 (CH), 81 (C), 80 (C), 55 (Me); *m/z* (APcI) 161 (MH^+, 100%).

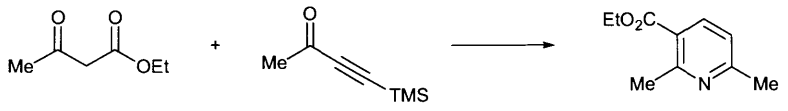
(4*E*)–2–Amino–3–ethoxycarbonylhexa–2,4–diene–6–one (76)



74 **75** **76**

A solution of enamine **75** (0.36 mmol, 1 equiv.) and 4–(trimethylsilyl)but–3–yn–2–one **75** (0.56 mmol, 1.5 equiv.) in EtOH (5 ml) was stirred at 50 °C for 4 h, cooled and evaporated *in vacuo* to give the crude aminodienone **146**. Purification by column chromatography on silica, eluting with light petroleum–ethyl acetate (1:1) (R_f 0.24), gave the *title compound*[56] as a yellow solid (58 mg, 82 %), mp 123–126 °C (light petroleum–ethyl acetate) (lit.[5] mp 125.5–126.4 °C) (Found: MH^+, 198.1125. $C_{10}H_{16}NO_3$ [MH^+] requires 198.1125); ν_{max}(film)/cm^{-1} 3340, 3193, 2979,1650, 1545, 1490, 1460, 1365, 1320, 1289, 1209, 1181, 1112, 1024, 972, 950, 851; δ_H(400 MHz; $CDCl_3$) 9.65 (1 H, bs, NH), 7.55 (1 H, d, *J* 15.6, 4–H), 6.50 (1 H, d, *J* 15.6, 5–H), 5.50 (1 H, bs, NH), 4.22 (2 H, q, *J* 7.1, OC*H*$_2$Me), 2.22 (3 H, s, Me), 2.15 (3 H, s, Me), 1.28 (3 H, t, *J* 7.1, CH$_2$*Me*); δ_C(100 MHz; $CDCl_3$) 199.0 (C), 169.7 (C), 165.7 (C), 139.5 (CH), 121.1 (CH), 94.4 (C), 60.0 (CH_2), 28.4 (Me), 22.6 (Me), 14.4 (Me); *m/z* (APcI) 198 (MH^+, 100%) and 181 (48).

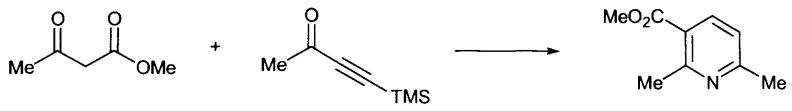
Ethyl 2,6–dimethylpyridine–3–carboxylate (78)



133 **75** **78**

Ethyl acetoacetate **133** (60 μl, 0.50 mmol), 4–(trimethylsilyl)but–3–yn–2–one **75** (80 μl, 0.50 mmol) and ammonium acetate (385 mg, 5.01 mmol) were reacted according to general procedure **4.2.1** or **4.2.2**. Purification by flash chromatography on silica, eluting with light petroleum–ethyl acetate (3:1) (R_f 0.54) gave the *title compound*[55] as a pale yellow oil (80 mg, 90%; 80 mg 90%, for methods **4.2.1** and **4.2.2** respectively) (Found: M^+, 179.0950. $C_{10}H_{13}NO_2$ [*M*] requires 179.0946); ν_{max}(film)/cm^{-1} 2981, 2929, 1723, 1592, 1568, 1462, 1387, 1372, 1274, 1236, 1200, 1149, 1080; δ_H(400 MHz; $CDCl_3$) 8.02 (1 H, d, *J* 8.0, 4–Py*H*), 6.99 (1 H, d, *J* 8.0, 5–Py*H*), 4.29 (2 H, q, *J* 7.1, OC*H*$_2$Me), 2.74 (3 H, s, 2–Me), 2.50 (3 H, s, 6–Me), 1.32 (3 H, t, *J* 7.1 OCH$_2$*Me*); δ_C(100 MHz; $CDCl_3$) 167.1 (C), 161.6 (C), 159.7 (C), 139.2 (CH), 123.1 (C), 120.8 (CH), 61.4 (CH_2), 25.2 (Me), 25.1 (Me), 14.7 (Me); *m/z* (EI) 179 ($M^{\cdot+}$, 96%), 134 (100), 106 (56).

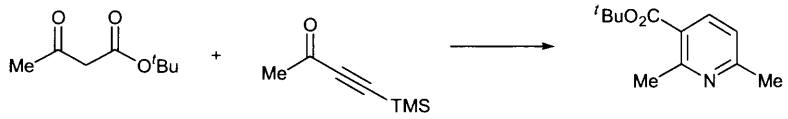
Methyl 2,6–dimethylpyridine–3–carboxylate (141)



134 **75** **141**

Methyl acetoacetate **134** (50 mg, 0.43 mmol), 4–(trimethylsilyl)but–3–yn–2–one **75** (70 μl, 0.43 mmol) and ammonium acetate (33 mg, 0.43 mmol) were reacted according to general procedure **4.2.1**. Purification by flash chromatography on silica, eluting with light petroleum–ethyl acetate (3:1) (R_f 0.48), gave the *title compound* as a pale yellow oil (65 mg, 91%) (Found: M^+, 165.0783. $C_9H_{11}NO_2$ [*M*] requires 165.0790) ν_{max}(film)/cm^{-1} 2978, 2927, 2872, 1721, 1591, 1567, 1461, 1387, 1371, 1235, 1199, 1025, 710, 665; δ_H(400 MHz; $CDCl_3$) 7.95 (1 H, d, *J* 8.0, 4–Py*H*), 6.92 (1 H, d, *J* 8.0, 5–Py*H*), 3.76 (3 H, s, OMe), 2.67 (3 H, s, 2–Me), 2.43 (3 H, s, 6–Me); δ_C(100 MHz; $CDCl_3$) 167.9 (C), 162.3 (C), 160.4 (C), 136.7 (CH), 123.2 (C), 121.3 (CH), 52.9 (Me), 25.6 (Me), 25.5 (Me); *m/z* (EI) 165 ($M^{\cdot+}$, 75%), 134 (100), 106 (77).

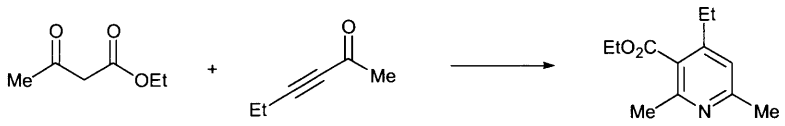
***tert*–Butyl 2,6–dimethylpyridine–3–carboxylate (138)**



89 **75** **138**

tert–Butyl acetoacetate **89** (0.16 ml, 1.0 mmol), 4–(trimethylsilyl)but–3–yn–2–one **75** (0.16 ml, 1.0 mmol) and ammonium acetate (77 mg, 1.0 mmol) were reacted according to general procedure **4.2.1** or **4.2.2**. Purification by flash chromatography on silica, eluting with light petroleum–ethyl acetate (3:1) (R_f 0.54), gave the *title compound*[56] as a pale yellow oil (200 mg, 98%; 198 mg, 97%, for methods **4.2.1** and **4.2.2** respectively) (Found: M^+, 207.1254. $C_{12}H_{17}NO_2$ [*M*] requires 207.1259); ν_{max}(film)/cm^{-1} 2923, 2842, 1734, 1591, 1466, 1378, 1274, 1165, 1124, 1080, 770, 721; δ_H(400 MHz; $CDCl_3$) 7.94 (1 H, d, *J* 7.9, 4–H), 6.97 (1 H, d, *J* 7.9, 5–H), 2.71 (3 H, s, 2–Me), 2.48 (1 H, s, 6–Me), 1.52 (9 H, s, CMe_3); δ_C(100 MHz; $CDCl_3$) 166.2 (C), 160.6 (C), 158.7 (C), 138.7 (CH), 124.4 (C), 120.4 (CH), 81.6 (C), 28.2 (Me), 24.9 (Me), 24.6 (Me); *m/z* (EI) 207 ($M^{\cdot+}$, 3%), 151 (100), 134 (46), 107 (38).

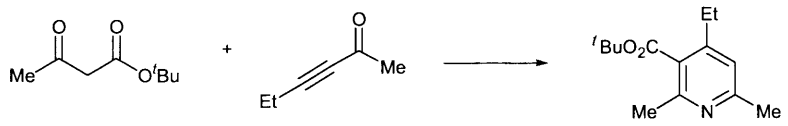
Ethyl 2,6–dimethyl–4–ethylpyridine–3–carboxylate (88)



166 **87** **88**

Ethyl acetoacetate **133** (63 μl, 0.50 mmol), hex–3–yn–2–one **87** (46 μl, 0.50 mmol) and ammonium acetate (0.384 mg, 5.00 mmol) were reacted according to general procedure **4.2.1, 4.2.2, 4.2.3, 4.2.4, 4.2.5, 4.2.6** or **4.2.7**. Purification by flash chromatography on silica, eluting with light petroleum–ethyl acetate (3:1) (R_f 0.55) gave the *title compound*[56] as a pale yellow oil (15 mg, 15%; 39 mg, 38%; 43 mg, 42%, 52 mg, 51%; 50 mg, 49%; 61 mg, 61%, for methods **4.2.1, 4.2.2, 4.2.3, 4.2.4, 4.2.5, 4.2.6** and **4.2.7**. respectively) (Found: M^+, 207.1258. $C_{12}H_{17}NO_2$ [*M*] requires 207.1259); ν_{max}(film)/cm^{-1} 2977, 2933, 1726, 1563, 1446, 1272, 1080, 750; δ_H(400 MHz; $CDCl_3$) 6.81 (1 H, s, 5–H), 4.33 (2 H, q, *J* 7.1, O*CH*$_2$Me), 2.53 (2 H, q, *J* 7.6, *CH*$_2$Me), 2.45 (3 H, s, Me), 2.44 (3 H, s, Me), 1.32 (3 H, t, *J* 7.1, OCH$_2$*Me*), 1.14 (3 H, t, *J* 7.6, CH$_2$*Me*); δ_C(100 MHz; $CDCl_3$) 169.5 (C), 158.9 (C), 154.7 (C), 151.1 (C), 126.7 (C), 120.7 (CH), 61.3 (CH_2), 26.6 (CH_2), 24.7 (Me), 23.2 (Me), 15.0 (Me), 14.5 (Me); *m/z* (EI) 207 ($M^{\cdot+}$, 100%), 178 (69), 162 (66), 134 (30).

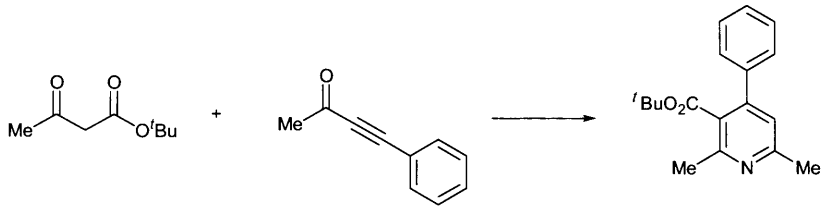
***tert*-Butyl 2,6–dimethyl–4–ethylpyridine–3–carboxylate (96)**



89 **87** **96**

tert–Butyl acetoacetate **89** (0.16 ml, 1.0 mmol), hex–3–yn–2–one **87** (0.11 ml, 1.0 mmol) and ammonium acetate (80 mg, 1.0 mmol) were reacted according to general procedure **4.2.1** or **4.2.2**. Purification by flash chromatography on silica, eluting with light petroleum–ethyl acetate (3:1) (R_f 4.8) gave the *title compound*[56] as a pale yellow oil (168 mg, 71%; 149 mg, 63% for methods **4.2.1** and **4.2.2** respectively) (Found: M^+, 235.1574. $C_{14}H_{21}NO_2$ [*M*] requires 235.1572) ν_{max}(film)/cm^{-1} 2975, 2934, 1721, 1590, 1458, 1368, 1288, 1168, 1123, 1080; δ_H(400 MHz; $CDCl_3$) 6.79 (1 H, s, 5–H), 2.55 (2 H, q, *J* 7.6, C*H*$_2$Me), 2.46 (3 H, s, Me), 2.43 (3 H, s, Me), 1.53 (9 H, s, CMe_3), 1.16, (3 H, t, *J* 7.6, CH_2*Me*); δ_C(100 MHz; $CDCl_3$) 168.4 (C), 157.9 (C), 153.7 (C), 150.3 (C), 127.8 (C), 120.4 (CH), 82.4 (C), 28.1 (Me), 26.1 (CH_2), 24.3 (Me), 22.6 (Me) 14.6 (Me); *m/z* (EI) 235 ($M^{\cdot+}$, 4%), 179 (100), 162 (84), 134 (48).

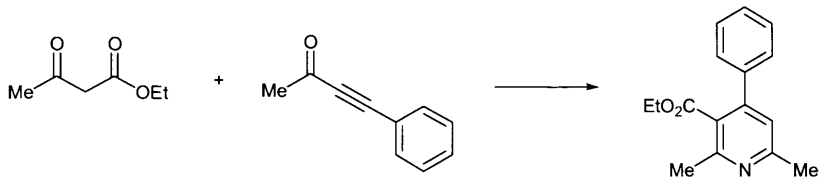
***tert*–Butyl 2,6–dimethyl–4–phenylpyridine–3–carboxylate (95)**



89 **91** **95**

tert–Butyl acetoacetate **89** (0.11 ml, 0.65 mmol), 4–phenylbut–3–yn–2–one **91** (0.10 ml, 0.65 mmol) and ammonium acetate (470 mg, 6.57 mmol) were reacted according to general procedure **4.2.2**. Purification by flash chromatography on silica, eluting with light petroleum–ethyl acetate (3:1) (R_f 0.38), gave the *title compound*[56] as a pale yellow oil (61 mg, 33%) (Found: MH^+, 236.1650 $C_{18}H_{22}NO_2$ [*M*H] requires 236.1651); ν_{max}(film)/cm^{-1} 2981, 2971, 1723, 1590, 1541, 1207, 1143, 1050, 790; δ_H(400 MHz; $CDCl_3$) 7.32 (5 H, m, Ph*H*), 6.92 (1 H, s, 4–Py*H*), 2.55 (3 H, s, Me), 2.50 (3 H, s, Me), 1.22 (9 H, s, CMe_3); δ_C(100 MHz; $CDCl_3$) 168.0 (C), 158.06 (C), 154.6 (C), 148.0 (C), 138.7 (C), 128.3 (CH), 128.3 (CH), 128.1 (CH), 127.1 (C), 121.1 (CH), 82.2 (C), 27.6 (Me), 24.4 (Me), 22.7 (Me); *m/z* (APcI) 236 (MH^+, 100%).

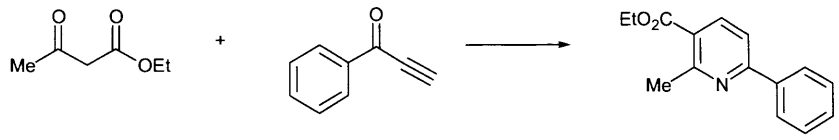
Ethyl 2,6–dimethyl–4–phenylpyridine–3–carboxylate (93)



133 **91** **93**

Ethyl acetoacetate **133** (0.13 ml, 1 mmol), 4–phenylbut–3–yn–2–one **91** (0.15 ml, 1 mmol) and ammonium acetate (77 mg, 1 mmol) were reacted according to general procedure **4.2.1, 4.2.2** or **4.2.5** Purification by flash chromatography on silica, eluting with light petroleum–ethyl acetate (3:1) (R_f 0.38), gave the *title compound*[56] as a pale yellow oil (130 mg, 51%; 135 mg, 53%; 107 mg, 42%, for methods **4.2.1, 4.2.2** and **4.2.5**, respectively) (Found: MH^+, 256.1337. $C_{16}H_{18}NO_2$ [*M*H] requires, 256.1335); ν_{max}(film)/cm^{-1} 2976, 2943, 1730, 1590, 1557, 1278, 1207, 1119, 1100, 861, 764, 699; δ_H(400 MHz; $CDCl_3$) 7.33 (5 H, Ph*H*), 6.95 (1 H, s, Py*H*), 4.02 (2 H, q, *J* 7.2, O*CH*$_2$Me), 2.55 (3 H, s, 2–Me), 2.52 (3 H, s, 6–Me), 0.91 (3 H, t, *J* 7.2, OCH$_2$*Me*) δ_C(100 MHz; $CDCl_3$) 169.5 (C), 159.9 (C), 155.8 (C), 149.1 (C), 139.3 (C), 128.9 (CH), 128.0 (CH), 126.0 (C), 121.7 (CH), 61.6 (CH_2), 25.1 (Me), 22.7 (Me), 14.3 (Me); *m/z* (APcI) 256 (MH^+, 100%).

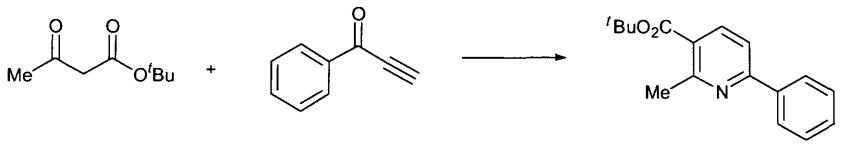
Ethyl 2–methyl–6–phenylpyridine–3–carboxylate (107)



133 **83** **107**

Ethyl acetoacetate **133** (35 μl, 0.25 mmol), 1–phenylprop–2–yn–1–one **83** (35 mg, 0.25 mmol) and ammonium acetate (190 mg, 2.50 mmol) were reacted according to general procedure **4.2.2, 4.2.3, 4.2.4, 4.2.5** or **4.2.6**. Purification by flash chromatography on silica, eluting with light petroleum–ethyl acetate (3:1) (R_f 0.78), gave the *title compound*[55] as a colourless solid (53 mg, 89%; 55 mg, 93%; 57 mg, 96%; 50 mg, 84%; 54 mg, 90% for methods **4.2.2**, **4.2.3, 4.2.4, 4.2.5** and **4.2.6** respectively), mp 44–45 °C (methanol) (lit.[55] mp 44 °C) (Found: M^+, 241.1104. $C_{15}H_{15}NO_2$ [*M*] requires 241.1103); ν_{max}(KBr)/cm^{-1} 2989, 2734, 1649, 1584, 1490, 1450, 1302, 1133 and 1026; δ_H(400 MHz; $CDCl_3$) 8.21 (1 H, d, *J* 8.2, 4–H), 7.99 (2 H, m, *o*–Ph*H*), 7.58 (1 H, d, *J* 8.2, 5–H), 7.40 (3 H, *m,p*–Ph*H*), 4.33 (2 H, q, *J* 7.1, O*CH*$_2$Me), 2.85 (3 H, s, 2–Me), 1.35 (3 H, t, *J* 7.1, OCH$_2$*Me*); δ_C(62.5 MHz; $CDCl_3$) 166.7 (C), 159.9 (C), 159.1 (C), 139.3 (CH), 138.5 (C), 129.7 (CH), 128.8 (CH), 127.3 (CH), 123.7 (C), 117.3 (CH), 61.2 (CH_2), 25.3 (Me), 14.3 (Me); *m/z* (EI) 241 (M^+, 100%), 196 (94), 168 (13).

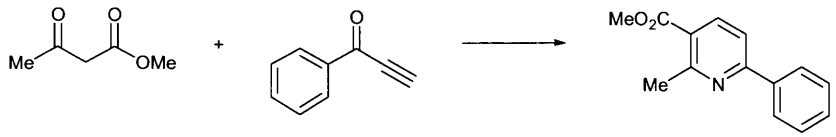
***tert*–Butyl 2–methyl–6–phenylpyridine–3–carboxylate (137)**



89 **83** **137**

tert–Butyl acetoacetate **89** (41 μl, 0.25 mmol), 1–phenylprop–2–yn–1–one **83** (32 mg, 0.25 mmol) and ammonium acetate (190 mg, 2.51 mmol) were reacted according to general procedure **4.2.2**. Purification by flash chromatography on silica, eluting with light petroleum–ethyl acetate (3:1) (R_f 0.56), gave the *title compound*[125] as a pale yellow oil (60 g, 89%) (Found: M^+, 269.1405 $C_{17}H_{19}NO_2$ [*M*] requires 269.1416); ν_{max}(film)/cm^{-1} 2976, 2931, 1714, 1581, 1455, 1382, 1367, 1282, 1147; δ_H(400 MHz; $CDCl_3$) 8.12 (1 H, d, *J* 8.2, 4–H), 7.97 (2 H, m, *o*–Ph*H*), 7.54 (1 H, d, *J* 8.2, 5–H), 7.40 (3 H, *m,p*–Ph*H*), 2.82 (3 H, s, 2–Me), 1.55 (9 H, s, CMe_3); δ_C(100 MHz; $CDCl_3$) 166.1 (C), 159.4 (C), 158.7 (C), 139.2 (C), 128.8 (CH), 127.3 (CH), 125.4 (C), 117.4 (CH), 81.8 (C), 28.3 (Me), 14.3 (Me); *m/z* (EI) 269 ($M^{\cdot+}$, 1%), 213 (100), 196 (3).

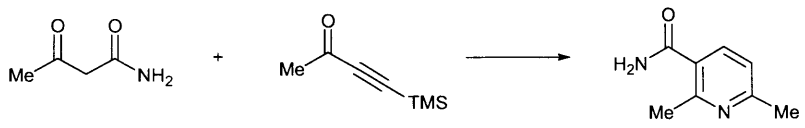
Methyl 2–methyl–6–phenylpyridine–3–carboxylate (140)



143 **83** **140**

Methyl acetoacetate **143** (46 μl, 0.43 mmol), 1–phenylprop–2–yn–1–one **83** (56 mg, 0.43 mmol) and ammonium acetate (33 mg, 0.43 mmol) were reacted according to general procedure **4.2.1**. Purification by flash chromatography on silica, eluting with light petroleum–ethyl acetate (3:1) (R_f 0.71), gave the *title compound* as a colourless solid (88 mg, 90%), mp 54–55 °C (ethanol) (Found: $M^{\cdot+}$, 227.0947. $C_{14}H_{13}NO_2$ [M^+] requires 227.0946); ν_{max}(KBr)/cm^{-1} 2992, 2946, 1719, 1580, 1433, 1270, 1089, 761, 693; δ_H(400 MHz; $CDCl_3$) 8.16 (1 H, d, *J* 8.2, 4–H), 7.97 (2 H, m, *o*–Ph*H*), 7.52 (1 H, d, *J* 8.2, 5–H), 7.38 (3 H, *m,p*–Ph*H*), 3.83 (3 H, s, Me), 2.83 (3 H, s, 2–Me); δ_C(100 MHz; $CDCl_3$) 167.0 (C), 160.1 (C), 159.1 (C), 139.4 (CH), 138.4 (C), 129.7 (CH), 128.8 (CH), 127.3 (CH), 123.2 (C), 117.4 (CH), 52.2 (Me), 25.3 (Me); *m/z* (EI) 227 ($M^{\cdot+}$, 100%), 213 (100), 196 (86), 168 (27).

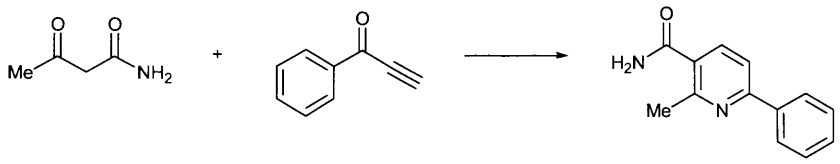
2,6–Dimethylpyridine–3–carboxylamide (146)



135 **75** **146**

Acetoacetamide **135** (300 mg, 2.97 mmol), 4–(trimethylsilyl)but–3–yn–2–one **75** (0.50 ml, 2.97 mmol) and ammonium acetate (2.33 g, 29.67 mmol) was reacted according to general procedure **4.2.2**. Purification by flash chromatography on alumina, eluting with light petroleum–ethyl acetate (3:1) (R_f 0.54), gave the *title compound*[126] as a pale yellow solid (316 mg, 71%) mp 189–191 °C (ethanol) (lit.[126] mp 44 °C) (Found: M^+, 150.0793. $C_8H_{10}N_2O$ [M^+] requires 150.0793); ν_{max}(KBr)/cm^{-1} 3337, 3100, 2360, 2341, 1675, 1612, 1591, 1470, 1391, 1364, 1261, 1099, 1030, 835, 741, 684, 601; δ_H(400 MHz; d_6–DMSO) 7.50 (1 H, d, *J* 7.8, 4–H), 7.00 (1 H, br s, NH); 6.87 (2 H, d, *J* 7.8, 5–H), 6.55 (1 H, br s, NH), 2.37 (3 H, s, Me), 2.25 (3 H, s, Me); δ_C(100 MHz; $CDCl_3$) 170.2 (C), 159.6 (C), 158.7 (C), 138.7 (CH), 124.6 (C), 121.4 (CH), 24.6 (Me), 24.2 (Me); *m/z* (EI) 150 ($M^{\cdot+}$, 100%), 134 (85), 106 (88).

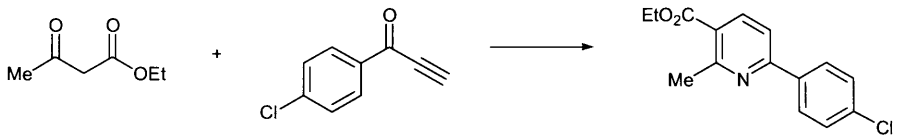
2–Methyl–6–phenylpyridine–3–carboxlyamide (145)



135 **83** **145**

Acetoacetamide **135** (50 μl, 0.5 mmol), 1–phenylprop–2–yn–1–one **83** (60 mg, 0.5 mmol) and ammonium acetate (38 mg, 0.5 mmol) were reacted according to general procedure **4.2.1, 4.2.2, 4.2.5** or **4.2.7**. Purification by flash chromatography on silica, eluting with light petroleum–ethyl acetate (3:1) (R_f 0.46), gave the *title compound* as a colourless solid (104 mg, 98%; 104 mg, 98%; 89 mg, 84%; 105 mg, 99%, for methods **4.2.1, 4.2.2, 4.2.5** and **4.2.7** respectively), mp 179–180 °C (methanol) (Found: MH^+, 213.1022. $C_{13}H_{13}N_2O$ [*M*H] requires 213.1024); ν_{max}(KBr)/cm^{-1} 3368, 3172, 1650, 1584, 1458, 1391, 842, 746, 688; δ_H(400 MHz; $CDCl_3$) 7.96 (2 H, m, *o*–Ph*H*), 7.79 (1 H, d, *J* 8.1, 4–H), 7.54 (1 H, d, *J* 8.1, 5–H), 7.41 (3 H, *m,p*–Ph*H*), 5.70 (2 H, br s, NH_2), 2.75 (3 H, s, 2–Me); δ_C(100 MHz; $CDCl_3$) 170.9 (C), 158.2 (C), 156.4 (C), 138.6 (C), 135.9 (CH), 128.8 (CH), 128.5 (C), 127.2 (CH), 117.4 (CH), 23.7 (Me); *m/z* (APcI) 213 (MH^+, 100%).

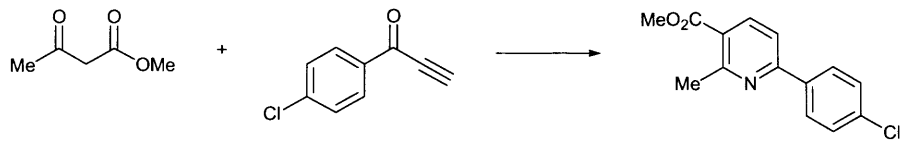
Ethyl 2–methyl–6–(4–chlorophenyl)pyridine–3–carboxylate (106)



133 **131** **106**

Ethyl acetoacetate **133** (50 μl, 0.38 mmol), 1–(4–chlorophenyl)prop–2–yn–1–one **131** (62 mg, 0.38 mmol) and ammonium acetate (290 mg, 3.76 mmol) were reacted according to general procedure **4.2.2**. Purification by flash chromatography on silica, eluting with light petroleum–ethyl acetate (3:1) (R_f 0.56), gave the *title compound*[72] as a pale yellow solid (94 mg, 90%), mp 46–47 °C (ethanol) (lit.[6] mp 47–48 °C) (Found: M^+, 275.0707. $C_{15}H_{14}NO_2{}^{35}Cl$ [M^+] requires 275.0713); ν_{max}(KBr)/cm^{-1} 2977, 2922, 1723, 1585, 1270, 1096, 779; δ_C(100 MHz; $CDCl_3$) 8.19 (1 H, d, *J* 8.2, 4–H), 7.94 (2 H, d, *J* 8.6, 3',5'–Ph*H*), 7.52 (1 H, d, *J* 8.2, 5–H), 7.34 (2 H, d, *J* 8.6, 2',6'–Ph*H*), 4.32 (2 H, q, *J* 7.1, O*C*H_2Me), 2.83 (3 H, s, 2–Me), 1.35 (3 H, t, *J* 7.1, OCH$_2$*Me*); δ_C(100 MHz; $CDCl_3$) 166.6 (C), 160.1 (C), 157.7 (C), 139.5 (CH), 136.9 (C), 135.9 (C), 129.0 (CH), 128.6 (CH), 123.9 (C), 117.1 (CH), 61.3 (CH_2), 25.3 (Me), 14.3 (Me); *m/z* (EI) 275 ($M^{\cdot+}$, 100%), 230 (88), 202 (18), 167 (27).

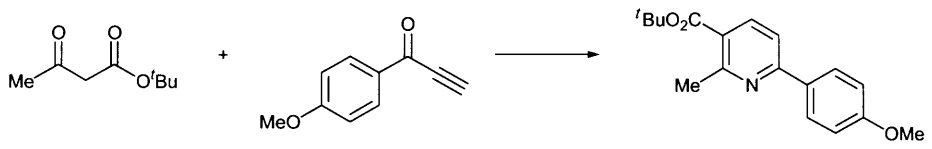
Methyl 2–methyl–6–(4–chlorophenyl)pyridine–3–carboxylate (142)



134 **131** **142**

Methyl acetoacetate **134** (70 mg, 0.60 mmol), 1–(4–chlorophenyl)prop–2–yn–1–one **131** (99 mg, 0.60 mmol) and ammonium acetate (465 mg, 6.08 mmol) were reacted according to general procedure **4.2.2**. Purification by flash chromatography on silica, eluting with light petroleum–ethyl acetate (3:1) (R_f 0.58), gave the *title compound* as a pale yellow solid (101 mg, 96%), mp 71–73 °C (Found: $M^{\cdot+}$, 261.0564. $C_{14}H_{12}NO_2{}^{35}Cl$ [*M*] requires 261.0557); ν_{max}(KBr)/cm^{-1} 2987, 2943, 1724, 1579, 1264, 1091, 779; δ_H(400 MHz; $CDCl_3$) 8.20 (1 H, d, *J* 8.2, 4–H), 7.95 (2 H, d, *J* 8.7, 3',5'–Ph*H*), 7.54 (1 H, d, *J* 8.2, 5–H), 7.38 (1 H, d, *J* 8.7, 2',6'–Ph*H*), 3.87 (3 H, s, Me), 2.84 (3 H, s, 2–Me); δ_C(100 MHz; $CDCl_3$) 166.9 (C), 160.2 (C), 157.9 (C), 139.5 (CH), 136.8 (C), 135.9 (C), 129.0 (CH), 128.6 (CH), 123.5 (C), 117.2 (CH), 52.3 (Me), 25.3 (Me); *m/z* (EI) 261 ($M^{\cdot+}$, 100%), 230 (82), 202 (21), 167 (33).

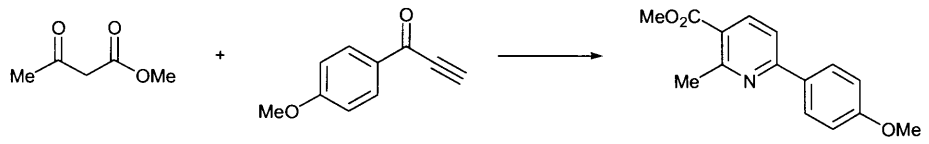
***tert*–Butyl 2–methyl–6–(4–methoxyphenyl)pyridine–3–carboxylate (205)**



169 **128** **205**

tert–Butyl acetoacetate **169** (70 μl, 0.44 mmol), 1–(4–methoxyphenyl)prop–2–yn–1–one **128** (71 mg, 0.44 mmol) and ammonium acetate (341 mg, 4.43 mmol) were reacted according to general procedure **4.2.2**. Purification by flash chromatography on silica, eluting with light petroleum–ethyl acetate (3:1) (R_f 0.71), gave the *title compound*[127] as a pale yellow solid (97 mg, 73%), mp 66–67 °C (Found: $M^{\cdot+}$, 299.1519. $C_{18}H_{21}NO_3$ [*M*] requires 299.1521); ν_{max}(KBr)/cm^{-1} 2988, 2932, 1707, 1580, 1286, 1250, 1169, 1153, 828, 787; δ_H(400 MHz; $CDCl_3$) 8.07 (1 H, d, *J* 8.3, 4–H), 7.97 (2 H, d, *J* 8.8, 3',5'–PhH), 7.47 (2 H, d, *J* 8.8, 2',6'–PhH), 6.92 (1 H, d, *J* 8.3, 5–H), 3.80 (3 H, s, OMe), 2.80 (3 H, s, Me), 1.54 (9 H, s, CMe_3);); δ_C(100 MHz; $CDCl_3$) 166.2 (C), 160.9 (C), 159.3 (C), 158.3 (C), 139.2 (CH), 131.2 (C), 128.7 (CH), 124.6 (C), 116.5 (CH), 114.2 (CH), 81.6 (C), 55.4 (Me), 29.3 (Me), 25.5 (Me); *m/z* (EI) 299 ($M^{\cdot+}$, 24%), 243 (100).

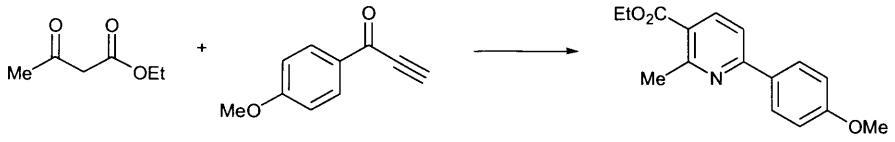
Methyl 2–methyl–6–(4–methoxyphenyl)pyridine–3–carboxylate (143)



134 **128** **143**

Methyl acetoacetate **134** (70 μl, 0.60 mmol), 1–(4–methoxyphenyl)prop–2–yn–1–one **128** (96 mg, 0.60 mmol) and ammonium acetate (465 mg, 6.03 mmol) were reacted according to general procedure **4.2.2**. Purification by flash chromatography on silica, eluting with light petroleum–ethyl acetate (3:1) (R_f 0.68), gave the *title compound* as colourless crystals (139 mg, 87%), mp 93–94 °C (Found: M^+, 257.1042. $C_{15}H_{15}NO_3$ [M^+] requires 257.1052); ν_{max}(KBr)/cm^{-1} 2950, 2842, 1718, 1581, 1511, 1427, 1268, 1177, 1089, 829, 786; δ_H(400 MHz; $CDCl_3$) 8.16 (1 H, d, *J* 8.2, 4–H), 7.97 (2 H, d, *J* 8.9, 2',6'–Ph*H*), 7.50 (1 H, d, *J* 8.2, 5–H), 6.94 (2 H, d, *J* 8.9, 3',5'–Ph*H*), 3.86 (3 H, s, Me), 3.80 (3, s, OMe), 2.83 (3 H, s, 2–Me); δ_C(100 MHz; $CDCl_3$) 167.1 (C), 161.1 (C), 160.1 (C), 158.8 (C), 139.3 (CH), 131.0 (C), 128.7 (CH), 122.4 (C), 116.5 (CH), 114.2 (CH), 55.2 (Me), 52.1 (Me), 25.4 (Me); *m/z* (EI) 257 ($M^{\cdot+}$, 100%), 226 (20).

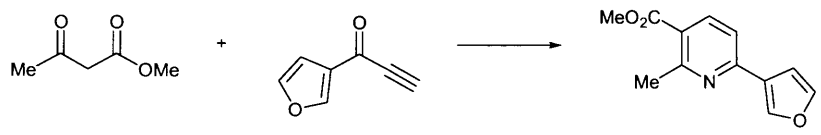
Methyl 2–methyl–6–(4–methoxyphenyl)pyridine–3–carboxylate (136)



133 **128** **136**

Ethyl acetoacetate **133** (50 μl, 0.38 mmol), 1–(4–methoxyphenyl)prop–2–yn–1–one **128** (60 mg, 0.38 mmol) and ammonium acetate (290 mg, 3.763 mmol) were reacted according to general procedure **4.2.2.** Purification by flash chromatography on silica, eluting with light petroleum–ethyl acetate (3:1) (R_f 0.68), gave the *title compound*[72] as colourless crystals (90 mg, 88%; 100 mg, 89%), mp 69–70 °C (lit.[72] mp 68–69 °C) (Found: $M^{\cdot+}$, 271.1210. $C_{16}H_{17}NO_3$ [*M*] requires 271.1208); ν_{max}(KBr)/cm^{-1} 2990, 2818, 1717, 1579, 1509, 1453, 1266, 1173, 831, 785; δ_H(400 MHz; $CDCl_3$) 8.71 (1 H, d, *J* 8.3, 4–H), 7.97 (2 H, d, *J* 8.9, 2',6'–Ph*H*), 7.50 (1 H, d, *J* 8.3, 5–H), 6.99 (2 H, d, *J* 8.9, 3',5'–Ph*H*), 4.32 (2 H, q, *J* 7.1, OC*H*$_2$Me), 3.81 (1 H, s, OMe), 2.84 (1 H, s, 2–Me), 1.35 (3 H, t, *J* 7.1, OCH$_2$*Me*); δ_C(100 MHz; $CDCl_3$) 166.9 (C), 161.1 (C), 159.9 (C), 158.7 (C), 139.3 (CH), 131.8 (C), 128.7 (CH), 122.9 (C), 116.5 (CH), 114.2 (CH), 61.1 (CH_2), 55.4 (Me), 25.3 (Me), 14.3 (Me); *m/z* (EI) 271 ($M^{\cdot+}$, 100%), 226 (50), 198 (12).

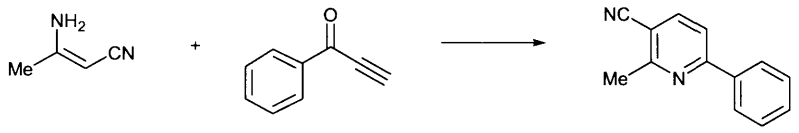
Ethyl 2–methyl–6–furylpyridine–3–carboxylate (144)



134 **147** **144**

Methyl acetoacetate **134** (70 μl, 0.603 mmol), 1–furylprop–2–yn–1–one **147** (72 mg, 0.603 mmol) and ammonium acetate (465 mg, 6.028 mmol) were reacted according to general procedure **4.2.2**. Purification by flash chromatography on silica, eluting with light petroleum–ethyl acetate (3:1) (R_f 0.72), gave the *title compound* as colourless crystals (100 mg, 77%) mp 36–37 °C (Found: $M^{\cdot+}$, 217.0743 $C_{12}H_{11}NO_3$ [*M*] requires 217.0739); ν_{max}(KBr)/cm^{-1} 3113, 2945, 1719, 1585, 1489, 1432, 1271, 1080, 787, 750; δ_H(400 MHz; $CDCl_3$) 8.17 (1 H, d, *J* 8.2, 4–H), 7.5 (1 H, m, 5–H, FuH), 7.1 (1 H, m, FuH), 6.5 (1 H, m, FuH), 3.85 (3 H, s, Me), 2.80 (3 H, s, Me); δ_C(100 MHz; $CDCl_3$) 167.5 (C), 162.3 (C), 160.1 (C), 158.8 (C), 144.5 (CH), 133.5 (CH), 131.2 (C) 125.1 (CH), 110.5 (CH), 109 (CH), 52.3 (Me), 25.3 (Me); *m/z* (EI) 217 ($M^{\cdot+}$, 100%), 186 (90), 158 (13).

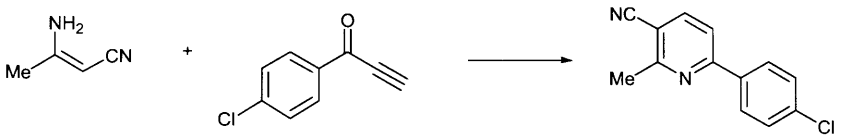
3–Cyano–6–phenyl–2–methylpyridine (158)



20 **83** **158**

3–Aminocrotononitrile **20** (19 mg, 0.230 mmol) and 1–phenylprop–2–yn–1–one **83** (30 mg, 0.230 mmol) reacted according to general procedure **4.2.9, 4.2.10, 4.2.11** or **4.2.12**. Purification by flash chromatography on silica, eluting with light petroleum–ethyl acetate (3:1) (R_f 0.68), gave the *title compound*[128] as colourless crystals (33 mg, 73%; 40 mg, 90%; 41 mg, 91%; 45 mg, 99%; 41.4 mg, 92%, for methods **4.2.9, 4.2.10, 4.2.11** and **4.2.12** respectively), mp 140–141 °C (lit.[55] mp 139–140 °C) (Found: MH^+, 195.0916. $C_9H_{12}NO_3$ [MH^+] requires 195.0917); ν_{max}(KBr)/cm^{-1} 2365, 2222, 1640, 1579, 1444, 1384, 1285, 783, 741, 694; δ_H(400 MHz; $CDCl_3$) 8.96 (2 H, m, *o*–Ph*H*), 7.86 (1 H, d, *J* 8.2, 4–H), 7.58 (1 H, d, *J* 8.2, 5–H), 7.43 (3 H, *m,p*–Ph*H*), 2.76 (3 H, s, Me); δ_C(100 MHz; $CDCl_3$) 161.6 (C), 159.8 (C), 140.7 (CH), 137.7 (C), 133.1 (C), 130.4 (CH), 129.0 (CH), 127.4 (CH), 117.4 (CH), 106.7 (C), 23.9 (Me); *m/z* (APcI) 195 (MH^+, 100%).

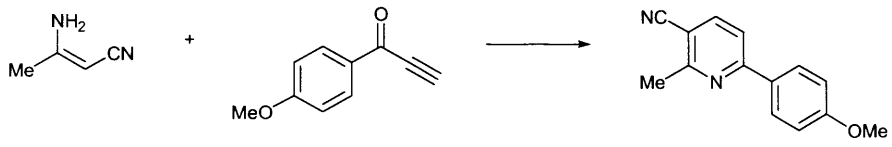
3–Cyano–6–(4–chlorophenyl)–2–methylpyridine (159)



20 **131** **159**

3–Aminocrotononitrile **20** (25 mg, 0.30 mmol) and 1–(4–chlorophenyl)prop–2–yn–1–one **131** (50 mg, 0.30 mmol) were reacted according to general procedure **4.2.9, 4.2.10, 4.2.11** or **4.2.12**. Purification by flash chromatography on silica, eluting with light petroleum–ethyl acetate (3:1) (R_f 0.57), gave the *title compound*[55] as pale yellow crystals (41 mg, 59%; 40 mg, 58%; 64 mg, 92%; 65 mg, 94%; 52 mg, 75% for methods **4.2.9, 4.2.10, 4.2.11** and **4.2.12** respectively), mp 127–128 °C (lit[8] 140–141 °C) (Found: MH^+, 229.0530. $C_{13}H_{10}{}^{37}ClN_2$ [*MH*] requires 229.0533); ν_{max}(KBr)/cm^{-1} 3250, 2364, 2451, 2221, 1640, 1601, 1442, 1383, 861, 762, 741, 699, δ_H(400 MHz; $CDCl_3$) 8.04 (2 H, d, *J* 8.7, 2',6'–Ph*H*), 7.90 (1 H, d, *J* 8.3, 4–H), 7.61 (1 H, d, *J* 8.3, 5–H), 7.02 (2 H, d, *J* 8.7, 3',5'–Ph*H*), 2.78 (3 H, s, Me); δ_C(100 MHz; $CDCl_3$ 163.7 (C), 161.5 (C), 159.3 (C), 140.9 (CH), 130.2 (C), 127.4 (CH), 128.9 (CH), 126.4 (CH), 119.1 (C), 106.2 (C), 23.8 (Me); *m/z* (ES) 229 ($C_{13}H_{10}{}^{37}ClO^+$, 11%), 227 ($C_{13}H_{10}{}^{35}ClO^+$, 26).

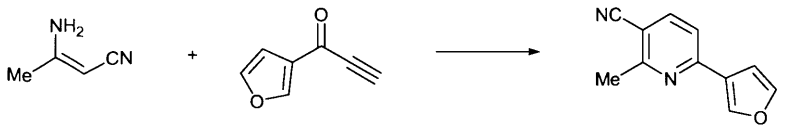
3–Cyano–6–(4–methoxyphenyl)–2–methylpyridine (160)



20 **128** **160**

3–Aminocrotononitrile **20** (24 mg, 0.281 mmol) and 1–(4–methoxyphenyl)prop–2–yn–1–one **128** (45 mg, 0.281 mmol)) were reacted according to general procedure **4.2.9, 4.2.10, 4.2.11** or **4.2.12**. Purification by flash chromatography on silica, eluting with light petroleum–ethyl acetate (3:1) (R_f 0.69), gave the *title compound* as pale yellow crystals (43 mg, 68%, 37 mg, 58%; 18 mg, 29%; 52 mg, 82%, 48 mg, 68% for methods **4.2.9, 4.2.10, 4.2.11** and **4.2.12** respectively), mp 129–139 °C (lit.[55] mp 133–135 °C) (Found: $M^{\cdot+}$, 224.0948. $C_{14}H_{12}N_2O$ [*M*] requires 224.0950); ν_{max}(KBr)/cm^{-1} 2361, 2220, 1606, 1578, 1509, 1454, 1294, 1257, 1193, 1025, 824, 760; δ_H(400 MHz; 7.94 (2 H, d, *J* 8.9, 3',5'–PhH), 7.80 (1 H, d, *J* 8.3, 4–H), 7.51 (1 H, d, *J* 8.3, 5–H), 6.93 (2 H, d, *J* 8.9, 2',6'–PhH), 3.81 (3 H, s, Me), 2.74 (3 H, s, Me); δ_C(100 MHz; $CDCl_3$) 161.6 (C), 161.5 (C), 159.3 (C), 140.5 (CH), 130.2 (C), 128.9 (CH), 117.6 (C), 116.4 (CH), 114.4 (CH), 105.9 (C), 55.5 (Me), 23.9 (Me); *m/z* (EI) 224 ($M^{\cdot+}$, 100 %).

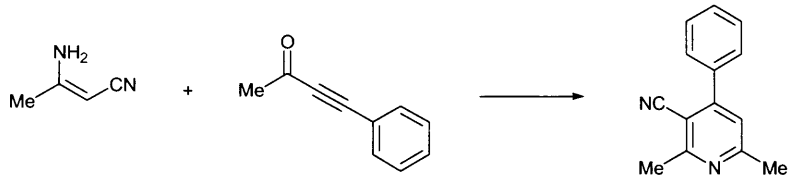
3–Cyano–6–furylpyridine–3–carboxylate (161)



20 **147** **161**

3–Aminocrotononitrile **20** (25 mg, 0.304 mmol) and 1–furylprop–2–yn–1–one **147** (37 mg, 0.304 mmol) were reacted according to general procedure **4.2.9, 4.2.10, 4.2.11** or **4.2.12.** Purification by flash chromatography on silica, eluting with light petroleum–ethyl acetate (3:1) (R_f 0.62), gave the *title compound* as pale yellow crystals (42 mg, 75%; 45 mg, 80%; 45 mg, 80%; 52 mg, 93%; 46 mg, 83% for methods **4.2.9, 4.2.10, 4.2.11** and **4.2.12** respectively), mp 88–89 °C (Found: $M^{\cdot+}$, 184.0637. $C_{11}H_8N_2O$ [*M*] requires 184.0637); ν_{max}(KBr)/cm^{-1} 2223, 1588, 1486, 105, 843, 741; δ_H(400 MHz; $CDCl_3$) 7.86 (1 H, d, *J* 8.4, 4–H), 7.52 (2 H, m, FuH), 7.15 (1 H, d, 8.4, 5–H), 6.51 (1 H, m, FuH), 2.81 (3 H, s, Me); δ_C(100 MHz; $CDCl_3$) 162.3 (C), 160.3 (C), 160.0 (C), 148.2 (CH), 142.5 (CH), 122.0 (CH), 116.4 (C)110.7 (CH), 109.5 (CH), 102.8 (C), 23.7 (Me); *m/z* (EI) 184 ($M^{\cdot+}$, 100 %), 155 (50), 128 (8).

3–Cyano–6–phenyl–2–methylpyridine (162)



20 **91** **162**

3–Aminocrotononitrile **20** (20 mg, 0.243 mmol) and 4–phenylbut–3–yn–2–one **91** (35 mg, 0.243 mmol) were reacted according to general procedure 4.2.9, 4.2.10, 4.2.11 or 4.**2.12.** Purification by flash chromatography on silica, eluting with light petroleum–ethyl acetate (3:1) (R_f 0.59), gave the *title compound*[129] as pale yellow crystals (15 mg, 29%; 8 mg, 15%; 8 mg, 15%; 29 mg, 57%; 23 mg, 45% for **4.2.9, 4.2.10, 4.2.11** and **4.2.12** respectively), mp 106–107 °C (lit.[129] mp 109–110 °C) (Found: MH^+, 207.1040. $C_{15}H_{13}N$ [*M*H] requires 207.1048); ν_{max}(KBr)/cm^{-1} 2581, 1725, 1587, 1548, 1266, 1206, 1083, 870, 767 and 701; δ_H(400 MHz; $CDCl_3$) 7.48 (2 H, m, PhH), 7.48 (1 H, m, PhH), 7.31 (2 H, m, PhH), 5.98 (1 H, s, 5–H), 2.50 (3 H, s, Me, 2.17 (3 H, s, Me); δ_C(100 MHz; $CDCl_3$); 159.5 (C), 159.1 (C), 150.5 (C), 148.9 (C), 139.2 (C), 128.9 (CH), 128.8 (CH), 128.2 (CH), 126.1 (C), 121.6 (CH), 117.8(C), 23.2 (Me) and 14.0 (Me); *m/z* (EI) 207 (MH, 100%).

Methyl β–aminocrotonate (177)

134 **177**

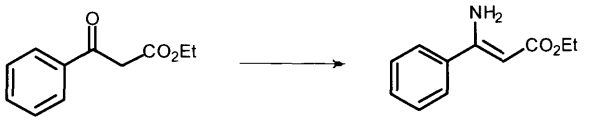
Aqueous ammonium hydroxide (35%, 20 ml) was added to solution of methyl acetoacetate **134** (2 ml, 17.22 mmol) in methanol (20 ml). The mixture was stirred overnight, concentrated *in vacuo* and partitioned between water (20 ml) and ethyl acetate (20 ml). The aqueous layer was further extracted with ethyl acetate (3 x 30 ml) and the combined organic extracts were washed with brine (15 ml), dried (Na_2SO_4) and evaporated *in vacuo* to give the *title compound*[130] as colourless crystals (1.33 g, 67%) mp 86–88 °C (lit.[130] mp 84–85 °C) (Found: $M^{\cdot+}$, 115.0632. $C_5H_9NO_2$ [*M*] requires 115.0633) ν_{max}(KBr)/cm^{-1} 3540, 3329, 2978, 2927, 1676, 1632, 1577, 1433, 1399, 1359, 1299, 1160, 989, 796; δ_H(400 MHz; $CDCl_3$) 4.35 (1 H, s, CH), 3.58 (3 H, s, OMe), 1.84 (3 H, s, Me); δ_C(100 MHz; $CDCl_3$) 169.6 (C), 160.3 (C), 89.2 (CH), 29.0 (Me) and 25.7 (Me); *m/z* (EI) 157 ($M^{\cdot+}$, 42%), 84 (100).

***tert*–Butyl β–aminocrotonate (176)**

89 **176**

Aqueous ammonium hydroxide solution (35%; 20 ml) was added to a stirred solution of *tert*-butyl acetoacetate **89** (2 ml, 1.21 mmol) in methanol (20 ml). The mixture was stirred overnight, concentrated *in vacuo* and partitioned between water (20 ml) and ethyl acetate (20 ml). The aqueous layer was further extracted with ethyl acetate (3 x 30 ml) and the combined organic extracts were washed with brine (15 ml), dried (Na_2SO_4) and evaporated *in vacuo* to give the *title compound*[131] as a pale yellow oil (1.82 g, 97%) (Found: $M^{\cdot+}$, 157.1104. $C_8H_{15}NO_2$ [*M*] requires 157.1103); IR ν_{max}(KBr)/cm^{-1}3554, 3341, 2980, 2919, 1666, 1622, 1567, 1454, 1390, 1366, 1296, 1150, 983, 790; δ_H(400 MHz; $CDCl_3$) 8.20 (1H, bs, NH), 4.20 (1H, bs, NH), 4.35 (1H, s, CH), 1.80 (3H, s, Me), 1.38 (9H, s, CMe_3); δ_C(100 MHz; $CDCl_3$); 170.3 (C), 158.8 (C), 85.9 (CH), 78.2 (C), 28.6 (Me), 22.4 (Me); *m/z* (APcI) 158 (MH^+, 77%).

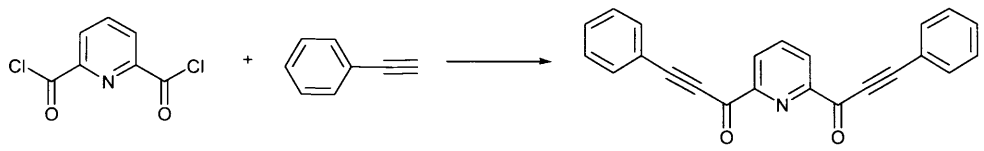
Ethyl 3–amino–3–phenylpropenoate (148)



90 **148**

Ammonium acetate (13.4 g, 0.17 mol) was added to a solution of ethyl benzoylacetate **90** (5 ml, 29.0 mmol). The mixture was heated at reflux in toluene–glacial acetic acid (5:1) (40 ml) for 20 hours and partitioned between saturated aqueous sodium hydrogen carbonate solution (20 ml) and ethyl acetate (20 ml). The aqueous layer was further extracted with ethyl acetate (2 x 20 ml) and the combined organic extracts were washed sequentially with saturated aqueous sodium hydrogen carbonate solution (10 ml) and brine (10 ml), dried (Na_2SO_4) and evaporated *in vacuo* to give the crude product. Purification by flash chromatography on silica, eluting with light petroleum–ethyl acetate (3:1) (R_f 0.41), to give *title compound*[132] as pale yellow oil (3.30 g, 59%) (Found: MNH_4^+, 209.1289. $C_{11}H_{17}N_2O_2$ [*MNH*$_4$] requires 209.1285); ν_{max}(film)/cm^{-1} 3441, 3326, 2979, 2936, 1663, 1617, 1555, 1492, 1364, 1176, 1095, 1025, 796, 772, 699; δ_H(400 MHz; $CDCl_3$) 8.35 (1H, bs, NH), 7.33–7.12 (5H, PhH), 7.00 (1H, bs, NH), 4.75 (1H, s, CH), 3.95 (2H, q, *J* 7.1, OC*H*$_2$Me), 1.05 (3H, t, *J* 7.1, CH$_2$*Me*); δ_C(100 MHz; $CDCl_3$) 170.5 (C), 160.5 (C), 137.7 (C), 130.3 (CH), 128.9 (CH), 126.2 (CH), 84.7 (CH), 59.0 (CH_2), 14.6 (Me); *m/z* (APcI) 192 (MH^+, 100%), 146 (13).

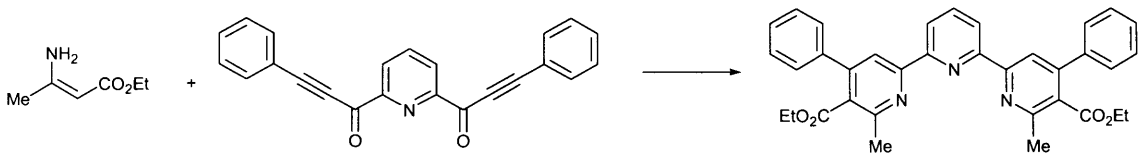
2,6–Bis(3–phenylprop2–yn–1–oyl)pyridine (174)



172 **173** **174**

Phenylacetylene **173** was added to a solution of 2,6–pyridinedicarbonyldichloride **172** (210 mg, 1 mmol) and copper(I) iodide (73 mg, 40 mol%) in dry triethylamine (20 ml) and the mixture was stirred for 24 hours under a nitrogen atmosphere. The reaction mixture was filtered through Celite® and evaporated *in vacuo*. Purification by flash chromatography on alumina, eluting with light petroleum–ethyl acetate (3:1) (R_f 0.51), gave the *title compound* as colourless solid (138 mg, 40%), mp 92–93 °C (Found: M^+, 336.1028. $C_{23}H_{14}NO_2$ [MH^+] requires 334.1025); ν_{max}(KBr)/cm^{-1} 2240, 2209, 1724, 1652, 1599, 1457, 1190, 780, 679; δ_H(400 MHz; $CDCl_3$) 8.32 (2 H, d, *J* 7.8, 3',5'–PyH), 8.01 (1 H, t, *J* 7.8, 6–PyH), 7.32 (2 H, m, *p*–Ph), 7.11 (4 H, m, *o,m*–Ph); δ_C(100 MHz; $CDCl_3$) 177.7 (C), 153.2 (C), 138.2 (CH), 133.4 (CH), 130.8 (CH), 128.5 (CH), 126.2 (CH), 120.0 (C), 96.4 (C), 87.8 (C), ; *m/z* (EI) 336 (MH^+, 90%) 206 (100).

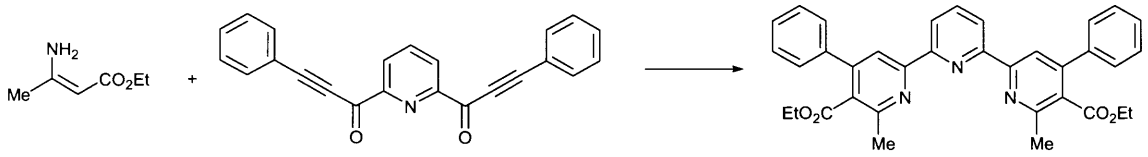
6,6''–Dimethyl–4,4''–diphenyl–2,2''–bis(phenyl)–2,2':6',2''–terpyridine–5,5''–diethyl carboxylate (178)



74 **174** **178**

2,6–Bis(3–phenylprop2–yn–1–oyl)pyridine **174** (30 mg, 0.09 mmol) and β–aminocrotonate **74** (0.03 ml, 0.21 mmol) were reacted according to general procedure **4.2.13**. Purification by flash chromatography on alumina, eluting with diethyl ether–light petroleum (2:1) (R_f 0.69), to give the *title compound* as pale yellow crystals (39 mg, 70%), mp 157–160 °C (Found: MH^+, 558.2385. $C_{35}H_{32}N_3O_4$ [*MH*] requires 558.2385); ν_{max}(KBr)/cm^{-1} 3436, 2975, 2365, 1730, 1572, 1546, 1493, 1444, 1385, 1263, 1227, 1132, 1075, 903, 830, 768, 699, 636, 571; δ_H(400 MHz; $CDCl_3$) 8.47 (2 H, d, *J* 7.9, 3',5'–PyH), 8.30 (2 H, s, 3,3''–PyH), 7.92 (1 H, t, *J* 7.9, 4'–PyH), 7.36 (10 H, m, 4,4''–Ph), 4.06 (4 H, q, *J* 7.1, CH_2), 2.66 (6 H, s, Me), 0.94 (6 H, t, *J* 7.1, Me); δ_C(100 MHz; $CDCl_3$) 169.0 (C), 155.9 (C), 155.3 (C), 154.9 (C), 149.8 (C), 138.9 (CH), 137.0 (CH), 128.5 (CH), 128.5 (C), 128.0 (CH), 122.1 (CH), 119.1 (CH), 61.4 (CH_2), 23.1 (Me), 13.7 (Me); *m/z* (EI) 558 (MH^+, 75%). 228 (100), 196 (80), 178 (20), 149 (12).

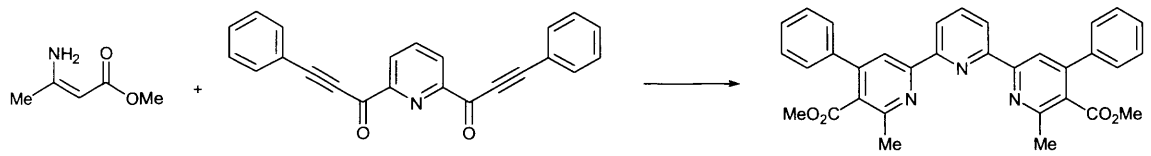
6,6''–Dimethyl–4,4''–diphenyl–2,2''–bis(phenyl)–2,2':6',2''–terpyridine–5,5''–diethyl carboxylate (269)



74 **174** **178**

2,6–Bis(3–phenylprop2–yn–1–oyl)pyridine **174** (35 mg, 0.10 mmol), ethyl acetoacetate **74** (0.01 ml, 0.10 mmol) and ammonium acetate (0.08g, 1.04 mmol) were reacted according to general procedure **4.2.14** in ethanol (1 ml) was refluxed for 24 hours. Purification by flash chromatography on alumina, eluting with diethyl ether–light petroleum (2:1) (R_f 0.69), to give the *title compound* as pale yellow crystals (40 mg, 70%), mp 157–160 °C with identical spectroscopic properties.

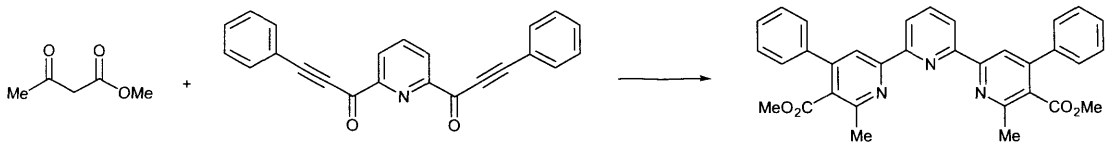
6,6''–Dimethyl–4,4''–diphenyl–2,2''–bis(phenyl)–2,2':6',2''–terpyridine–5,5''–dimethyl carboxylate (179)



177 **174** **179**

2,6–Bis(3–phenylprop2–yn–1–oyl)pyridine **174** (57 mg, 0.17 mmol), methyl β–aminocrotonate **177** (117 mg, 1.02mmol) was reacted according to procedure **4.2.13** Purification by flash chromatography on alumina, eluting with diethyl ether–light petroleum (2:1) (R_f 0.50), gave the *title compound* as colourless crystals (48 mg, 54%), mp 180–182 °C (Found: MH^+, 530.2097. $C_{33}H_{28}N_3O_4$ [*MH*] requires 530.2093); ν_{max}(KBr)/cm^{-1} 3436, 2975, 2365, 1730, 1572, 1546, 1493, 1444, 1385, 1263, 1227, 1132, 1075, 903, 830, 768, 699, 636, 571; δ_H(400 MHz; $CDCl_3$) 8.48 (2 H, d, *J* 7.8, 3',5'–PyH), 8.33 (2 H, s, 3,3''–PyH), 7.92 (1 H, t, *J* 7.8, 4'–PyH), 7.29 (10 H, m, 4,4''–Ph), 3.59 (6 H, s, Me), 2.66 (6 H, s, Me); δ_C(100 MHz; $CDCl_3$) 169.6 (C), 155.9 (C), 155.3 (C), 154.9 (C), 148.9 (C), 138.8 (CH), 137.9 (C), 128.6 (CH), 128.6 (CH), 128.1 (C), 127.9 (CH), 122.1 (CH), 119.0 (CH), 52.3 (Me), 23.1 (Me); *m/z* (EI) 530 (MH^+, 100%).

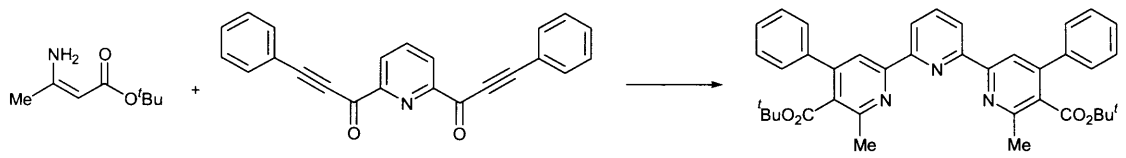
6,6''–Dimethyl–4,4''–diphenyl–2,2''–bis(phenyl)–2,2':6',2''–terpyridine–5,5''–dimethyl carboxylate (179)



134 **174** **179**

2,6–Bis(3–phenylprop2–yn–1–oyl)pyridine **174** (20 mg, 0.059 mmol), methyl acetoacetate **134** (0.04 ml, 0.36 mmol) ammonium acetate (50 mg, 0.59 mmol) were reacted according to general procedure **4.2.14**. Purification by flash chromatography on alumina, eluting with diethyl ether–light petroleum (2:1) (R_f 0.50), gave the *title compound* as colourless crystals (13 mg, 41%), mp 180–182 °C, with identical spectroscopic properties.

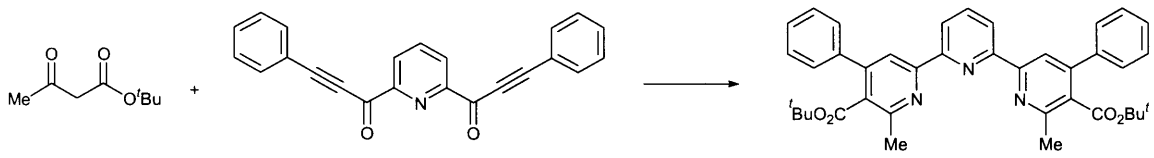
6,6''–Dimethyl–4,4''–diphenyl–2,2''–bis(phenyl)–2,2':6',2''–terpyridine–5,5''–dibutyl carboxylate (180)



176 **174** **180**

2,6–Bis(3–phenylprop2–yn–1–oyl)pyridine **174** (57 mg, 0.17 mmol), *tert*–butyl β–aminocrotonate **176** (160 mg, 1.02 mmol) was reacted according to general procedure **4.2.13.** Purification by flash chromatography on alumina, eluting with diethyl ether–light petroleum (2:1) (R_f 0.61), gave the *title compound* as colourless crystals (72 mg, 72%) mp 178–180 °C (Found: M^+, 613.2947. $C_{39}H_{39}N_3O_4$ [*M*] requires 613.2941); ν_{max}(KBr)/cm^{-1} 2975, 2936, 2876, 1729, 1584, 1474, 1384, 1278, 1055, 1086, 906, 847, 777, 745, 700, 687; δ_H(400 MHz; $CDCl_3$) 8.47 (2 H, d, *J* 7.8, 3',5'–PyH), 8.29 (2 H, s, 3,3'–PyH), 7.91 (1 H, t, *J* 7.8, 4'–PyH), 7.37 (10 H, m, 4,4''–Ph), 2.67 (6 H, s, Me), 1.24 (18 H, s, CMe_3); δ_C(100 MHz; $CDCl_3$) 168.9 (C), 156.7 (C), 154.9 (C), 153.7 (C), 149.1 (C), 138.4 (CH), 136.2 (C), 130.6 (CH), 129.6 (CH), 128.3 (C), 127.9 (CH), 123.0 (CH), 119.0 (CH), 81.2 (C) 28.3 (Me), 25.8 (Me); 25.5 (Me); *m/z* (EI) 613 ($M^{\cdot+}$, 30%), 335 (10), 146 (100), 73 (35).

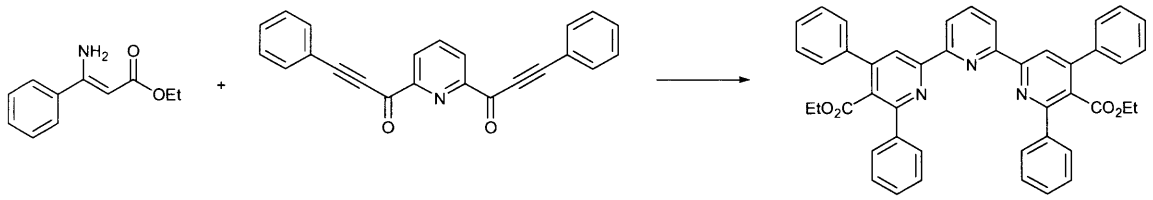
6,6''–Dimethyl–4,4''–diphenyl–2,2''–bis(phenyl)–2,2':6',2''–terpyridine–5,5''–dibutyl carboxylate (180)



89 **174** **180**

2,6–Bis(3–phenylprop2–yn–1–oyl)pyridine **174** (20 mg, 0.06 mmol), *tert*–butyl acetoacetate **89** (0.05 ml, 0.36 mmol) and ammonium acetate (50 mg, 0.59 mmol were reacted according to general procedure **4.2.14**. Purification by flash chromatography on alumina, eluting with diethyl ether–light petroleum (2:1) (R_f 0.50), gave the *title compound* as colourless crystals (26 mg, 70%), mp 181–183 °C, with identical spectroscopic properties.

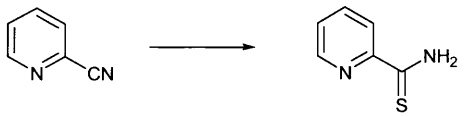
6,6''–Diphenyl–4,4''–diphenyl–2,2''–bis(phenyl)–2,2':6',2''–terpyridine–5,5''–diethyl carboxylate (181)



148 **174** **181**

A solution of 2,6–bis(3–phenylprop2–yn–1–oyl)pyridine **174** (57 mg, 1.019 mmol) and ethyl 3–amino–3–phenylpropenoate **148** (195 mg, 1.109 mmol) was reacted according to general procedure **4.2.15**. Purification by flash chromatography on alumina, eluting with diethyl ether–light petroleum (2:1) (R_f 0.61), gave the *title compound* as a brown solid (25 mg, 22%), mp 180–183 °C (Found: $M^{\cdot+}$, 681.2623. $C_{45}H_{35}N_3O_4$ [*M*] requires 681.2628); ν_{max}(KBr)/cm^{-1} ; δ_H(400 MHz; $CDCl_3$) 8.58 (2 H, d, *J* 7.7, 3',5'–PyH), 8.48 (2 H, s, 3,3''–PyH), 7.90 (1 H, t, *J* 7.7, 4'–PyH), 7.59 (2 H, m, 6,6''–PhH), 7.39 (18 H, m, 4,4''–Ph), 3.91 (4 H, q, *J* 7.2, CH_2), 0.82 (6 H, t, *J* 7.2, Me); δ_C(100 MHz; $CDCl_3$); 168.8 (C), 157.9 (C), 156.3 (C), 155.9 (C), 154.8 (C), 149.7 (C), 139.9 (C), 138.6 (C), 137.9 (C), 128.8 (CH), 128.7 (CH), 128.6 (CH), 128.6 (CH), 128.4 (CH), 128.2 (CH), 122.5 (CH), 120.0 (CH), 119.3 (C), 61.5 (CH_2), 13.5 (Me); *m/z* (EI) 681 ($M^{\cdot+}$, 20 %), 652 (100), 580 (30), 536 (10), 150 (18).

Pyridine–2–thiocarboxamide (191)



190 **191**

2–Cyanopyridine **190** (50 μl, 0.48 mmol), ammonium sulphide (50 wt. % in H_2O; 65 μl, 0.48 mmol) in methanol (5 ml) was reacted according to general procedure **4.2.16, 4.2.17** and **4.2.17.** The mixture was evaporated *in vacuo* to give the *title compound*[110] as pale yellow crystals (60 mg, 100%; 60 mg, 100% and 60 mg, 100% for methods **4.2.16, 4.2.17** and **4.2.18** respectively), mp 137–138 °C (lit.[110] mp 138–139 °C) (Found: $M^{\cdot+}$, 138.0247. $C_{13}H_9SN_2$ [*M*] requires 138.0252); ν_{max}(KBr)/cm^{-1} 3355, 3144, 2367, 1600, 1307, 993, 904, 796, 671; δ_H(400 MHz; $CDCl_3$) 9.46 (1 H, br s, NH) 8.64 (1 H, m, PyH), 8.46 (1 H, m, PyH), 7.79 (1 H, m, PyH), 7.60 (1 H, br s, NH), 7.40 (1 H, m, PyH); δ_C(100 MHz; $CDCl_3$) 195.3 (C), 150.1 (C), 147.3 (CH), 137.2 (CH), 126.6 (CH), 125.4 (CH); *m/z* (EI) 138 ($M^{\cdot+}$, 100 %), 106 (67), 79 (85).

Pyridine–3–thiocarboxamide (203)

202 **203**

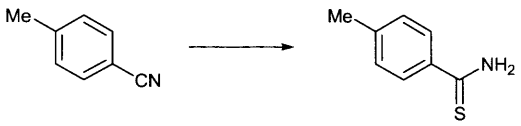
3–Cyanopyridine **202** (50 mg, 0.48 mmol) and ammonium sulphide (50 wt. % in H_2O; 65 μl, 0.48 mmol) in methanol (5 ml) was reacted according to general procedure **4.2.16** and **4.2.17.** The mixture was evaporated *in vacuo* to give the *title compound*[110] as colourless crystals (65 mg, 100%; 65 mg, 100% for methods **4.2.16** and **4.2.17** respectively), mp 186–189 °C (lit.[110] mp 190–192 °C) (Found: $M^{\cdot+}$, 138.0246. C_6H_6NS [*M*] requires 138.0252); ν_{max}(KBr)/cm^{-1} 3238, 3027, 2952, 1678, 1593, 1456, 1308, 1034, 907, 738, 696; δ_H(400 MHz; $CDCl_3$) 8.91 (1 H, m, 2–PyH), 8.52 (1 H, m, 6–PyH), 8.18 (1 H, m, 3–H), 7.46 (1 H, br s, NH), 7.37 (1 H, m, 5–PyH) 7.20 (1 H, br s, NH); δ_C(100 MHz; $CDCl_3$) 190.7 (C), 150.6 (C), 148.8 (CH), 135.8 (CH), 132.1 (C), 123.2 (CH); *m/z* (EI) 138 ($M^{\cdot+}$, 86 %), 104 (100), 77 (56).

Thiobenzamide (199)

198 **199**

A solution of benzonitrile **198** (50 μl, 0.388 mmol) and ammonium sulphide (50 wt. % in H_2O; 53 μml, 0.388 mmol) in methanol (5 ml) was reacted according to general procedure **4.2.17** and **4.2.18.** The mixture was evaporated *in vacuo* to give the *title compound*[110] as colourless crystals (47 mg, 90%; 43 mg, 82% for methods **4.2.17** and **4.2.18** respectively), mp 113–114 °C (lit.[110] mp 108–109 °C) (Found: $M^{\cdot+}$, 137.0296. C_7H_7NS [*M*] requires 137.0299); ν_{max}(KBr)/cm^{-1} 3355, 3269, 3158, 1622, 1453, 1399, 886, 690; δ_H(400 MHz; $CDCl_3$) 7.81 (2 H, m, 2',6'–PhH), 7.55 (1 H, br s, NH), 7.45 (1 H, m, 4–PhH) 6.23 (2 H, m, 3',5'–PhH), 7.12 (1 H, br s, NH); δ_C(100 MHz; $CDCl_3$) 195.9 (C), 139.8 (C), 129.8 (CH), 128.6 (CH), 127.1 (CH); *m/z* (EI) 137 ($M^{\cdot+}$, 32%), 103 (100), 76 (36).

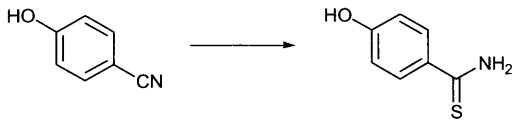
4–Methylbenzothioamide (193)



192 **193**

A solution of 4–tolunitrile **192** (30 mg, 0.26 mmol) and ammonium sulphide (50 wt. % in H_2O; 35 μl, 0.26 mmol) in methanol (5 ml) was reacted according to general procedure **4.2.17.** The mixture was evaporated *in vacuo* to give the *title compound*[110] as colourless crystals (40 mg, 100%), mp 171–172 °C (lit.[110] mp 169–170 °C) (Found: $M^{\cdot+}$, 151.045. C_8H_9NS [*M*] requires 151.0456); ν_{max}(KBr)/cm^{-1} 3361, 3257, 3154, 1622, 1461, 1387, 886, 723, 690; δ_H(400 MHz; $CDCl_3$) 7.72 (2 H, d, *J* 8.2, 2',6'–Ph*H*), 7.61 (1 H, bs, NH), 7.19 (2 H, d, *J* 8.2, 3',5'–Ph*H*), 7.14 (1 H, bs, NH), 2.32 (3 H, s, Me); δ_C(100 MHz; $CDCl_3$) 203.9 (C), 143.2 (C), 136.5 (C), 130.4 (CH), 127.3 (CH), 22.7 (Me); *m/z* (EI) 151 ($M^{\cdot+}$, 47%), 117 (100), 63 (78).

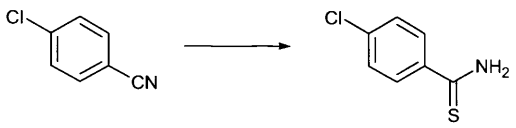
4–Hydroxythiobenzamide (197)



196 **197**

A solution of 4–cyanophenol **196** (30 mg, 0.25 mmol) and ammonium sulphide (50 wt. % in H_2O; 68 μl, 0.25 mmol) in methanol (5 ml) was reacted according to general procedure **4.2.16, 4.2.17** and **4.2.18.** The mixture was evaporated *in vacuo* to give the *title compound* as colourless crystals (8%; 40% for methods **4.2.17** and **4.2.18** respectively based on ^1H NMR analysis of crude reaction mixture), mp 69–74 °C (lit.[113] mp 108–109 °C); δ_H(400 MHz; $CDCl_3$) 9.29 (1 H, bs, OH), 8.61 (1 H, bs, NH), 8.54 (1 H, bs, NH), 7.86 (2 H, m, 2',6'–Ph*H*), 6.71 (1 H, m, 3',5'–Ph*H*).

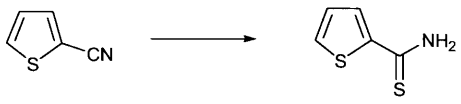
4–Chlorothiobenzamide (205)



204 **205**

4–Chlorobenzonitrile **204** (50 mg, 0.36 mmol) ammonium sulphide (50 wt. % in H_2O; 50 μl, 0.36 mmol) in methanol (5 ml) was reacted according to general procedure **4.2.16** and **4.2.17.** The mixture was evaporated *in vacuo* to give the *title compound*[110] as a yellow crystals (60 mg, 100%; 60 mg, 100% for methods **4.2.16** and **4.2.17** respectively), mp 129–130 °C (lit.[110] mp 129–130 °C) (Found: $M^{\cdot+}$, 170.9906. $C_7H_6NS^{35}Cl$ [*M*] requires 170.9909); ν_{max}(KBr)/cm^{-1} 3288, 3155, 1612, 1412, 1092, 885, 832; δ_H(400 MHz; $CDCl_3$) 7.75 (2 H, appd, *J* 8.7, 2'6'–Ph*H*), 7.69 (1 H, bs, NH), 7.31 (2 H, appd, *J* 8.7, 3'5'–Ph*H*), 7.12 (1 H, bs, NH); δ_C(100 MHz; $CDCl_3$) 202.7 (C), 141.0 (C), 133.5 (C), 129.8 (CH), 127.8 (CH); *m/z* (EI) 170 ($M^{\cdot+}$, 41%), 155 (43), 137 (100).

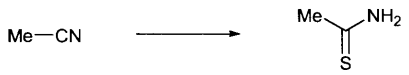
Thiophenamide (209)



208 **209**

A solution of 2–thiophenecarbonitrile **208** (70 μl, 0.64 mmol) and ammonium sulphide (50 wt. % in H_2O; 87 μl, 0.64 mmol) in methanol (5 ml) was reacted according to general procedure **4.2.18**. The mixture was evaporated *in vacuo* to give the *title compound* as colourlss crystals (83 mg, 90%), mp 108–109 °C (lit.[128] mp 108–109 °C) (Found: $M^{\cdot+}$, 142.9859 $C_5H_5NS_2$ [*M*] requires 142.9863); ν_{max}(KBr)/cm^{-1} 3325, 3248, 3154, 1623, 1518, 1429, 1364, 1122, 1056, 649; δ_H(400 MHz; $CDCl_3$) 7.51 (1 H, dd, *J* 5.0, 1.0 C–2), 7.43 (1 H, dd, *J* 1.0, 3.9 C–3), 7.15 (1 H, bs, NH), 7.03 (1 H, dd, *J* 5.0, 3.9 C– 4) 6.98 (1 H, bs, NH); δ_C(100 MHz; $CDCl_3$) 192.6 (C), 145.3 (C), 134.4 (CH), 129.5 (CH), 127.8 (CH); *m/z* (EI) 143 ($M^{\cdot+}$, 100%), 110 (55), 109 (32).

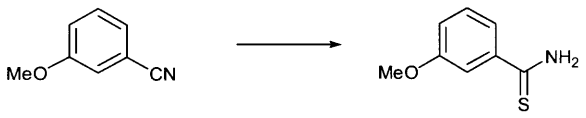
Thioacetamide (202)



201 **202**

Acetonitrile **201** (24 µl, 0.58) ammonium sulphide (50 wt. % in H_2O; 80 µl, 0.58 mmol) in methanol (5 ml) was reacted according to general procedure **4.2.16, 4.2.17** and **4.2.18.** The mixture was evaporated *in vacuo* to give the *title compound*[101] as colourless crystals (23 mg, 53%; 17 mg, 39% for methods **4.2.17** and **4.2.18** respectively), mp 113–114 °C (lit.[101] mp 108–109 °C) (Found: $M^{\cdot}$, 75.0147. C_2H_5NS [*M*] requires 75.0143); ν_{max}(KBr)/cm^{-1} 3300, 3176, 2360, 1454, 1376, 1155, 966; δ_H(400 MHz; $CDCl_3$) 7.35 (1 H, bs, NH), 6.74 (1 H, bs, NH), 2.51 (3 H, s, Me); δ_C(100 MHz; $CDCl_3$) 203.1C), 32.3 (Me); *m/z* (EI) 75 ($M^{\cdot+}$, 100%).

3–Methoxybenzamide (195)



194 **195**

3–Methoxybenzonitrile **194** (50 mg, 0.376 mmol) ammonium sulphide (50 wt. % in H_2O; 51 μml, 0.376 mmol) in methanol (5 ml) was reacted according to general procedure **4.2.16, 4.2.17** and **4.2.18.** The mixture was evaporated *in vacuo* to give the *title compound*[133] as colourless crystals (21%; 93% for methods **4.2.17** and **4.2.18** respectively based on ^{1}H NMR analysis of crude reaction mixture), mp 98–99 °C (lit.[133] mp 108–109 °C); δ_H(400 MHz; $CDCl_3$) 7.52 (1 H, bs, NH), 7.41 (1 H, m, 5–PhH), 7.29 (2 H, m, 4',6'–Ph*H*), 7.19 (1 H, bs, NH), 6.70 (1 H, m, 2–Ph*H*), 3.80 (3 H, s, Me).

Diethoxythioacetamide (207)

206 **207**

2,2–Diethoxyacetonitrile **206** (50 μl, 0.387 mmol), ammonium sulphide (50 wt. % in H_2O; 52 μl, 0.387 mmol) in methanol (5 ml) was reacted according to general procedure **4.2.16, 4.2.17** and **4.2.18.** The mixture was evaporated *in vacuo* to give the *title compound* [116] as colourless crystals (8.5 mg, 37%; 23 mg, 100%; 23 mg, 100% for methods **4.2.16, 4.2.17** and **4.2.18** respectively), mp 94–95 °C (lit.[116] mp 81–82 °C) (Found: MH^+, 164.0743. $C_6H_{14}NO_2S$ [*MH*] requires 164.0740); ν_{max}(KBr)/cm^{-1} 3363, 3260, 2972, 1602, 1428, 1119, 1056, 727; δ_H(400 MHz; $CDCl_3$) 7.95 (1 H, bs, NH), 7.79 (1 H, bs, NH), 4,98 (CH), 3.66 (2 H, dq, *J* 9.3, 7.1, 2.3 OC*H*HMe), 3.58 (2 H, dq, *J* 9.3, 7.1, 2.3 OCH*H*Me), 1.19 (6 H, t, 7.1, OCH_2*Me*); δ_C(100 MHz; $CDCl_3$) 201.3 (C), 102.5 (CH), 60.4 (CH_2), 15.3 (Me); *m/z* (EI) 163 ($M^{\cdot+}$, 2%), 118 (15), 103 (87).

4.4.0 References

[118] Blessing, R. H. *Acta. Crysrallography.* Sect. A. **1995**, *51*, 33.

[119] Beurskens, P. T.; Beurskens, G.; de Gelder, R.; Gracia–Granda, S.; Gould, R. O.; Israel, R.; Smith, J. M. M. Crystallography Laboratory, University of Nijmegen, The Netherlands. **1999**.

[120] Sheldrick, G. M. Shelex–97, Program for the refinement of Crystal Structures, University of Göttinggen, Germany. **1992**.

[122] Bagley, M. C.; Dale, J. W.; Glover, C.; Ohnesorge, M.; Phillips, N. G.; Xiong X.; Bower, J. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1663.

[123] Ameer, F.; Drewes, S. E.; Drewes M.W.; Watson, M.C. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1425.

[124] Pigge, F.; Ghasedi, F.; Zheng, Z.; Rath, N. P.; Nichols, G.; Chickos, J. S. *J. Chem. Soc., Perkin Trans. 2* **2000**, 2458.

[125] Bagley, M. C.; Glover, C.; Merrit, E. A.; Xiong, X. *Synlett* **2005**, 649–651

[126] Julia, M. *Bulletin de la Societe Chimique de France.* **1966**, *7*, 2381.

[127] Bagley, M. C.; Glover, C.; Merrit, E. A.; Xiong, X. *Synlett.* **2005**, 649.

[128] Petrich, S. A.; Hicks. F. A.; Wilkinson, D. R.; Tarrant J. G.; Bruno, S. M. ; Vargas, M. ; Hosein, K. N.; Gupton, J. T.; Sikorski, J. *Tetrahedron.* **1995**, *51*, 1575.

[129] Shibata, K. *Bull. Chem. Soc. Jpn.,* **1988**, *61* , 199.

[130] Jacobs, J. *Tetrahedron.* **2008**, *64* (32), 7545.

[131] Hiyama, T.; Kobayashi, K.; Nishide, K. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 2127.

[132] Buckler, R. T.; Hartzler, H. E. *J. Med. Chem.*, **1975**, *18*, 509.

[133] Feiring, A. E. *J. Org. Chem.*, **1976,** *41*, 146.

CHAPTER FIVE – APPENDICES

APPENDIX – A

APPENDIX A

5.1.1 X-ray crystal data for 6,6''–Bis(methyl)–5,5''–bis(methyl carboxylate)–4,4''–bis(phenyl)–2,2':6',2''–terpyridine (179).

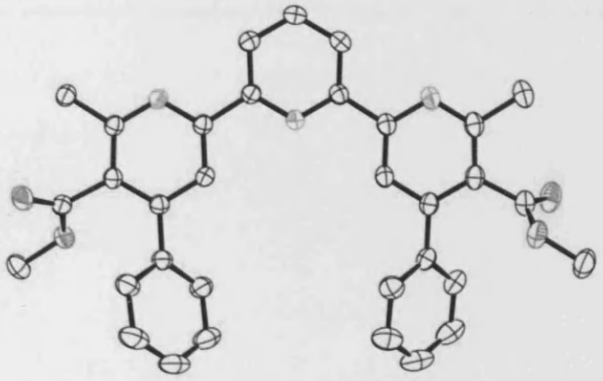


Figure 9. X–ray crystal structure of terpyridine **179**.

Table 63. Crystal data and structure refinement compound **179**.

Identification code	**179**	
Empirical formula	C33 H27 N3 O4	
Formula weight	529.58	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic, P–1	
Unit cell dimensions	a = 7.5848(15) Å	α = 98.54(3)°
	b = 10.669(2) Å	β = 98.97(3)°
	c = 17.791(4) Å	γ = 97.36(3)°
Volume	1389.3(5) $Å^3$	
Z	2	
Density (calculated)	1.266 Mg/m^3	
Absorption coefficient	0.084 mm^{-1}	
F(000)	556	
Crystal size	0.50 x 0.50 x 0.20 mm^3	
Theta range for data collection	3.18 to 27.00°.	
Limiting indices	−9<=h<=9, −13<=k<=13, −21<=l<=22	
Reflections collected / unique	11125 / 5968 [R(int) = 0.0308]	
Completeness to theta = 27.00°	98.2 %	

Max. and min. transmission	0.985 and 0.613
Refinement method	Full-matrix αβγ-squares on F^2
Data / restraints / parameters	5968 / 0 / 365
Goodness-of-fit on F^2	1.036
Final R indices [I>2sigma(I)]	R1 = 0.0437, wR2 = 0.1089
R indices (all data)	R1 = 0.0560, wR2 = 0.1157
Largest diff. peak and hole	0.193 and −0.179 e.$Å^{-3}$

Table 64. Atomic coordinates ($x10^4$) and equivalent isotropic displacement parameters ($Å^2x10^3$) for compound **179**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	−7730(1)	293(1)	88(1)	48(1)
N(1)	−4496(1)	−1153(1)	1919(1)	33(1)
C(1)	−5827(2)	−711(1)	1502(1)	33(1)
O(2)	−7638(1)	1889(1)	1076(1)	41(1)
N(2)	189(1)	−184(1)	2803(1)	28(1)
C(2)	−5552(2)	460(1)	1235(1)	32(1)
O(3)	9016(1)	2956(1)	4916(1)	44(1)
N(3)	4652(1)	−175(1)	3853(1)	28(1)
C(3)	−3847(2)	1225(1)	1429(1)	30(1)
O(4)	8936(1)	3171(1)	3679(1)	33(1)
C(4)	−2486(2)	755(1)	1872(1)	30(1)
C(5)	−2846(2)	−432(1)	2095(1)	30(1)
C(6)	−7667(2)	−1528(1)	1347(1)	42(1)
C(7)	−7083(2)	848(1)	730(1)	35(1)
C(8)	−9042(2)	2368(2)	600(1)	53(1)
C(9)	−3431(2)	2481(1)	1179(1)	32(1)
C(10)	−3985(2)	2647(1)	420(1)	40(1)
C(11)	−3523(2)	3823(2)	202(1)	55(1)
C(12)	−2507(3)	4836(2)	732(1)	62(1)
C(13)	−1946(2)	4681(2)	1482(1)	54(1)
C(14)	−2408(2)	3512(1)	1708(1)	40(1)
C(15)	−1396(2)	−960(1)	2556(1)	28(1)
C(16)	−1700(2)	−2192(1)	2729(1)	35(1)
C(17)	−354(2)	−2602(1)	3204(1)	36(1)
C(18)	1281(2)	−1809(1)	3470(1)	32(1)
C(19)	1509(2)	−613(1)	3240(1)	27(1)
C(20)	6234(2)	608(1)	4090(1)	28(1)
C(21)	6462(2)	1889(1)	3967(1)	27(1)
C(22)	5001(2)	2369(1)	3584(1)	27(1)
C(23)	3383(2)	1528(1)	3332(1)	29(1)
C(24)	3259(2)	282(1)	3481(1)	27(1)
C(25)	7755(2)	31(1)	4484(1)	34(1)
C(26)	8258(2)	2719(1)	4254(1)	30(1)
C(27)	10607(2)	4063(1)	3917(1)	43(1)
C(28)	5043(2)	3732(1)	3483(1)	30(1)

C(29)	5740(2)	4728(1)	4098(1)	37(1)
C(30)	5613(2)	5992(1)	4022(1)	47(1)
C(31)	4811(2)	6276(1)	3330(1)	49(1)
C(32)	4149(2)	5298(1)	2711(1)	46(1)
C(33)	4249(2)	4028(1)	2783(1)	36(1)

Table 65. Bond lengths [Å] and angles [°] for compound **179**.

O(1)–C(7)	1.2029(16)
N(1)–C(1)	1.3352(17)
N(1)–C(5)	1.3475(16)
C(1)–C(2)	1.4038(19)
C(1)–C(6)	1.5101(18)
O(2)–C(7)	1.3372(17)
O(2)–C(8)	1.4493(17)
N(2)–C(19)	1.3398(15)
N(2)–C(15)	1.3402(16)
C(2)–C(3)	1.4021(17)
C(2)–C(7)	1.4945(18)
O(3)–C(26)	1.2017(15)
N(3)–C(20)	1.3407(16)
N(3)–C(24)	1.3421(15)
C(3)–C(4)	1.3904(17)
C(3)–C(9)	1.4849(18)
O(4)–C(26)	1.3386(15)
O(4)–C(27)	1.4477(16)
C(4)–C(5)	1.3891(17)
C(5)–C(15)	1.4883(17)
C(9)–C(14)	1.394(2)
C(9)–C(10)	1.3953(19)
C(10)–C(11)	1.386(2)
C(11)–C(12)	1.380(3)
C(12)–C(13)	1.377(2)
C(13)–C(14)	1.386(2)
C(15)–C(16)	1.3925(17)
C(16)-C(17)	1.3798(19)
C(17)–C(18)	1.3809(18)
C(18)–C(19)	1.3948(16)
C(19)–C(24)	1.4943(17)
C(20)–C(21)	1.4088(16)
C(20)–C(25)	1.5034(17)
C(21)–C(22)	1.4032(17)
C(21)–C(26)	1.4962(17)
C(22)–C(23)	1.3926(17)
C(22)–C(28)	1.4882(16)
C(23)–C(24)	1.3879(16)

C(28)–C(29)	1.3915(19)
C(28)–C(33)	1.3952(18)
C(29)–C(30)	1.3886(19)
C(30)–C(31)	1.380(2)
C(31)–C(32)	1.380(2)
C(32)–C(33)	1.3892(19)
C(1)–N(1)–C(5)	118.30(11)
N(1)–C(1)–C(2)	122.22(11)
N(1)–C(1)–C(6)	116.32(12)
C(2)–C(1)–C(6)	121.45(12)
C(7–O(2)–C(8)	114.84(11)
C(19)–N(2)–C(15)	118.27(10)
C(3)–C(2)–C(1)	119.69(11)
C(3)–C(2)–C(7)	121.33(12)
C(1)–C(2)–C(7)	118.96(11)
C(20)–N(3)–C(24)	118.41(10)
C(4)–C(3)–C(2)	117.11(11)
C(4)–C(3)–C(9)	119.29(11)
C(2)–C(3)–C(9)	123.60(11)
C(26)–O(4)–C(27)	114.99(10)
C(5)–C(4)–C(3)	119.92(11)
N(1)–C(5)–C(4)	122.71(11)
N(1)–C(5)–C(15)	116.68(11)
C(4)–C(5)–C(15)	120.61(11)
O(1)–C(7)–O(2)	124.07(12)
O(1)–C(7)–C(2)	123.99(12)
O(2)–C(7)–C(2)	111.94(11)
C(14)–C(9)-C(10)	118.89(13)
C(14)–C(9)–C(3)	119.41(12)
C(10)–C(9)–C(3)	121.66(12)
C(11)–C(10)–C(9)	120.02(15)
C(12)–C(11)–C(10)	120.49(15)
C(13)–C(12)–C(11)	119.99(15)
C(12)–C(13)-C(14)	120.10(16)
C(13)-C(14)–C(9)	120.51(14)
N(2)–C(15)–C(16)	122.33(11)
N(2)–C(15)–C(5)	116.58(10)
C(16)–C(15)–C(5)	121.08(11)
C(17)–C(16)–C(15)	118.73(12)
C(16)–C(17)–C(18)	119.58(11)

C(17)–C(18)–C(19)	118.11(12)
N(2)–C(19)–C(18)	122.86(11)
N(2)–C(19)–C(24)	115.82(10)
C(18)–C(19)–C(24)	121.32(11)
N(3)–C(20)–C(21)	122.01(11)
N(3)–C(20)–C(25)	115.91(10)
C(21)–C(20)–C(25)	122.07(11)
C(22)–C(21)–C(20)	119.53(11)
C(22)–C(21)–C(26)	121.07(10)
C(20)–C(21)–C(26)	119.40(11)
C(23)–C(22)–C(21)	117.24(10)
C(23)–C(22)–C(28)	118.56(11)
C(21)–C(22)–C(28)	124.05(11)
C(24)–C(23)–C(22)	119.84(11)
N(3)–C(24)–C(23)	122.96(11)
N(3)–C(24)–C(19)	116.80(10)
C(23)–C(24)–C(19)	120.23(11)
O(3)–C(26)–O(4)	123.48(11)
O(3)–C(26)–C(21)	124.92(12)
O(4)–C(26)–C(21)	111.61(10)
C(29)–C(28)–C(33)	118.76(12)
C(29)–C(28)–C(22)	120.90(11)
C(33)–C(28)–C(22)	120.15(12)
C(30)–C(29)–C(28)	120.68(14)
C(31)–C(30)–C(29)	120.17(15)
C(32)–C(31)–C(30)	119.61(13)
C(31)–C(32)–C(33)	120.74(14)
C(32)–C(33)–C(28)	120.01(14)

Symmetry transformations used to generate equivalent atoms:

#1 -x+1,y,-z+5/2

Table 66. Anisotropic displacement parameters ($Å^2$ x 10^3) for compound **179**. The anisotropic displacement factor exponent takes the form: $-2\pi^2$ [$h^2 a^{*2} U^{11}$ + ... + 2 h k a* b* U^{12}].

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	42(1)	61(1)	34(1)	−5(1)	−8(1)	13(1)
N(1)	27(1)	38(1)	30(1)	3(1)	3(1)	−1(1)
C(1)	27(1)	42(1)	27(1)	0(1)	3(1)	2(1)
O(2)	31(1)	48(1)	42(1)	−2(1)	−2(1)	13(1)
N(2)	26(1)	28(1)	28(1)	5(1)	2(1)	3(1)
C(2)	27(1)	41(1)	25(1)	0(1)	2(1)	7(1)
O(3)	47(1)	46(1)	33(1)	8(1)	−8(1)	−8(1)
N(3)	29(1)	27(1)	28(1)	4(1)	1(1)	6(1)
C(3)	28(1)	36(1)	25(1)	2(1)	3(1)	7(1)
O(4)	27(1)	38(1)	33(1)	4(1)	5(1)	0(1)
C(4)	25(1)	34(1)	30(1)	4(1)	1(1)	2(1)
C(5)	26(1)	35(1)	27(1)	4(1)	4(1)	2(1)
C(6)	29(1)	53(1)	38(1)	3(1)	3(1)	−2(1)
C(7)	28(1)	42(1)	33(1)	0(1)	3(1)	6(1)
C(8)	38(1)	57(1)	62(1)	8(1)	−2(1)	19(1)
C(9)	29(1)	38(1)	32(1)	6(1)	6(1)	12(1)
C(10)	38(1)	49(1)	37(1)	11(1)	5(1)	17(1)
C(11)	66(1)	60(1)	50(1)	27(1)	14(1)	29(1)
C(12)	83(1)	41(1)	73(1)	27(1)	23(1)	22(1)
C(13)	67(1)	34(1)	63(1)	5(1)	16(1)	9(1)
C(14)	44(1)	38(1)	39(1)	5(1)	8(1)	9(1)
C(15)	27(1)	30(1)	27(1)	3(1)	4(1)	1(1)
C(16)	31(1)	31(1)	40(1)	7(1)	5(1)	−2(1)
C(17)	39(1)	27(1)	43(1)	10(1)	5(1)	1(1)
C(18)	32(1)	29(1)	33(1)	7(1)	4(1)	7(1)
C(19)	28(1)	26(1)	26(1)	3(1)	3(1)	6(1)
C(20)	28(1)	29(1)	26(1)	3(1)	3(1)	6(1)
C(21)	26(1)	30(1)	25(1)	2(1)	2(1)	4(1)
C(22)	27(1)	28(1)	27(1)	4(1)	4(1)	4(1)
C(23)	26(1)	29(1)	32(1)	7(1)	1(1)	6(1)
C(24)	26(1)	28(1)	26(1)	3(1)	3(1)	5(1)
C(25)	32(1)	33(1)	35(1)	5(1)	−2(1)	8(1)
C(26)	28(1)	29(1)	30(1)	5(1)	1(1)	5(1)
C(27)	30(1)	44(1)	52(1)	5(1)	9(1)	−3(1)
C(28)	24(1)	28(1)	38(1)	8(1)	8(1)	5(1)
C(29)	35(1)	31(1)	45(1)	4(1)	9(1)	4(1)

C(30)	47(1)	28(1)	68(1)	3(1)	20(1)	3(1)
C(31)	44(1)	31(1)	85(1)	22(1)	31(1)	12(1)
C(32)	41(1)	47(1)	63(1)	31(1)	19(1)	15(1)
C(33)	32(1)	37(1)	43(1)	14(1)	9(1)	7(1)

Table 67. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å x10^3) for compound **179**.

	x	y	z	U(eq)
H(4)	−1312	1245	2022	36
H(6A)	−7878	−2045	829	62
H(6B)	−8596	−973	1380	62
H(6C)	−7721	−2095	1731	62
H(8A)	−8654	2506	114	80
H(8B)	−9270	3182	875	80
H(8C)	−10153	1742	489	80
H(10)	−4680	1954	52	48
H(11)	−3907	3933	−315	66
H(12)	−2197	5639	578	74
H(13)	−1240	5376	1845	65
H(14)	−2025	3412	2227	48
H(16)	−2814	−2740	2523	42
H(17)	−551	−3424	3348	43
H(18)	2224	−2070	3799	38
H(23)	2367	1806	3059	35
H(25A)	7962	347	5041	51
H(25B)	8856	275	4282	51
H(25C)	7439	−906	4386	51
H(27A)	10404	4822	4257	64
H(27B)	11024	4322	3461	64
H(27C)	11525	3649	4195	64
H(29)	6309	4542	4574	44
H(30)	6079	6662	4448	57
H(31)	4714	7139	3279	59
H(32)	3620	5494	2231	56
H(33)	3778	3362	2354	44

APPENDIX – B

APPENDIX B

5.1.2 X-ray crystal data for 6,6''–Bis(methyl)–5,5''–bis(*tert*-butyl carboxylate)–4,4''–bis(phenyl)–2,2':6',2''–terpyridine (180).

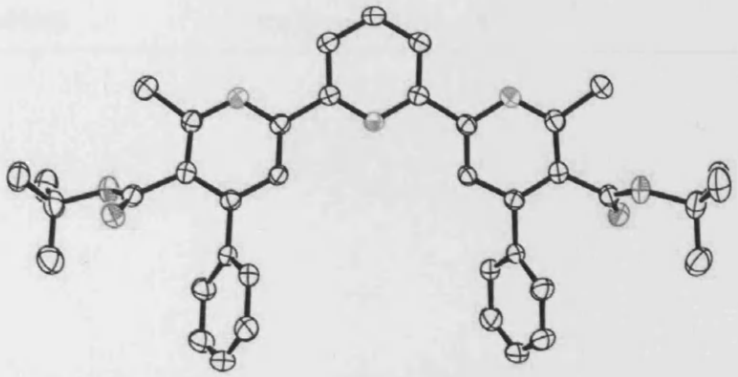


Figure 10. X–ray crystal structure of terpyridine**180**.

Table 68. Crystal data and structure refinement for compound **180.**

Identification code	**180**	
Empirical formula	C39 H39 N3 O4	
Formula weight	613.73	
Temperature	150(2) K	
Wavelength	0.71073 A	
Crystal system	Monoclinic	
Unit cell dimensions	a = 17.142(3) Å	α = 90°
	b = 16.807(3) Å	β = 90.84(3)°
	c = 11.311(2) Å	γ = 90°
Volume	3258.4(11) $Å^3$	
Z	4	
Calculated density	1.251 Mg/m^3	
Absorption coefficient	0.081 mm^{-1}	
F(000)	1304	
Crystal size	0.50 x 0.35 x 0.35 mm	
Theta range for data collection	3.40 to 27.00°	
Limiting indices	−21<=h<=21, −21<=k<=19, −14<=l<=14	
Reflections collected / unique	6146 / 3525 [R(int) = 0.0305]	

Completeness to theta = 27.00°	99.1 %
Absorption correction	Multi-scan
Max. and min. transmission	0.981 and 0.540
Refinement method	Full-matrix least-βγαsquares on F^2
Data / restraints / parameters	3525 / 0 / 213
Goodness-of-fit on F^2	1.041
Final R indices [I>2sigma(I)]	R1 = 0.0506, wR2 = 0.1240
R indices (all data)	R1 = 0.0728, wR2 = 0.1367
Largest diff. peak and hole	0.428 and −0.214 e.$Å^{-3}$

Table 69. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2x10^3$) for compound **180**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	3412(1)	2148(1)	7053(1)	38(1)
N(1)	5000	677(1)	12500	28(1)
C(1)	4607(1)	260(1)	11669(1)	28(1)
O(2)	2280(1)	1755(1)	7885(1)	40(1)
N(2)	3687(1)	302(1)	10058(1)	33(1)
C(2)	4585(1)	−569(1)	11651(1)	31(1)
C(3)	5000	−985(1)	12500	32(1)
C(4)	4195(1)	720(1)	10724(1)	29(1)
C(5)	4346(1)	1521(1)	10525(1)	28(1)
C(6)	3960(1)	1915(1)	9610(1)	29(1)
C(7)	3430(1)	1477(1)	8913(1)	30(1)
C(8)	3315(1)	666(1)	9163(1)	33(1)
C(9)	4109(1)	2773(1)	9389(1)	32(1)
C(10)	3488(1)	3312(1)	9334(2)	42(1)
C(11)	3629(1)	4112(1)	9150(2)	53(1)
C(12)	4382(2)	4380(1)	9012(2)	60(1)
C(13)	4997(1)	3853(1)	9051(2)	54(1)
C(14)	4864(1)	3049(1)	9240(2)	39(1)
C(15)	3056(1)	1843(1)	7842(1)	33(1)
C(16)	1767(1)	1983(1)	6876(2)	43(1)
C(17)	1780(1)	2870(1)	6770(2)	57(1)
C(18)	2018(1)	1551(1)	5770(2)	53(1)
C(19)	982(1)	1686(2)	7273(2)	58(1)
C(20)	2793(1)	139(1)	8419(2)	45(1)

Table 70. Bond lengths [Å] and angles [°] for compound **180**.

O(1)–C(15)	1.203(2)
N(1)–C(1)	1.3453(18)
N(1)–C(1)#1	1.3453(18)
C(1)–C(2)	1.394(2)
C(1)–C(4)	1.488(2)
O(2)–C(15)	1.340(2)
O(2)–C(16)	1.481(2)
N(2)–C(8)	1.336(2)
N(2)–C(4)	1.342(2)
C(2)–C(3)	1.377(2)
C(3)–C(2)#1	1.377(2)
C(4)–C(5)	1.389(2)
C(5)–C(6)	1.389(2)
C(6)–C(7)	1.402(2)
C(6)–C(9)	1.486(2)
C(7)–C(8)	1.407(2)
C(7)–C(15)	1.496(2)
C(8)–C(20)	1.507(2)
C(9)–C(14)	1.388(2)
C(9)–C(10)	1.399(2)
C(10)–C(11)	1.383(3)
C(11)–C(12)	1.378(3)
C(12)–C(13)	1.379(3)
C(13)–C(14)	1.388(3)
C(16)–C(17)	1.496(3)
C(16)–C(19)	1.509(3)
C(16)–C(18)	1.515(3)
C(1)–N(1)–C(1)#1	117.30(19)
N(1)–C(1)–C(2)	122.88(15)
N(1)–C(1)–C(4)	117.35(14)
C(2)–C(1)–C(4)	119.75(14)
C(15)–O(2)–C(16)	121.44(13)
C(8)–N(2)–C(4)	118.96(14)
C(3)–C(2)–C(1)	118.99(15)
C(2)#1–C(3)–C(2)	118.9(2)
N(2)–C(4)–C(5)	122.48(14)
N(2)–C(4)–C(1)	115.38(14)

C(5)–C(4)–C(1)	122.12(14)
C(6)–C(5)–C(4)	119.69(14)
C(5)–C(6)–C(7)	117.72(15)
C(5)–C(6)–C(9)	120.46(14)
C(7)–C(6)–C(9)	121.82(14)
C(6)–C(7)–C(8)	119.22(14)
C(6)–C(7)–C(15)	120.37(15)
C(8)–C(7)–C(15)	120.11(14)
N(2)–C(8)–C(7)	121.93(15)
N(2)-C(8)-C(20)	115.28(15)
C(7)–C(8)–C(20)	122.75(15)
C(14)–C(9)–C(10)	119.28(16)
C(14)–C(9)–C(6)	120.51(15)
C(10)-C(9)-C(6)	120.21(16)
C(11)–C(10)–C(9)	120.17(19)
C(12)–C(11)–C(10)	120.04(19)
C(11)–C(12)–C(13)	120.28(19)
C(12)–C(13)–C(14)	120.2(2)
C(13)–C(14)–C(9)	119.98(18)
O(1)–C(15)–O(2)	126.08(15)
O(1)–C(15)–C(7)	124.03(15)
O(2)–C(15)–C(7)	109.85(14)
O(2)–C(16)–C(17)	108.10(16)
O(2)–C(16)–C(19)	101.94(15)
C(17)–C(16)–C(19)	111.64(18)
O(2)–C(16)–C(18)	109.86(15)
C(17)–C(16)–C(18)	113.96(17)
C(19)–C(16)–C(18)	110.62(17)

Symmetry transformations used to generate equivalent atoms:

#1 -x+1,y,-z+5/2

Table 71. Anisotropic displacement parameters (A^2 x 10^3) for compound **180**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2} U^{11} + ... + 2 h k a^* b^* U^{12}]$.

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	37(1)	40(1)	36(1)	5(1)	−2(1)	1(1)
N(1)	29(1)	26(1)	28(1)	0	0(1)	0
C(1)	28(1)	28(1)	28(1)	0(1)	3(1)	−1(1)
O(2)	31(1)	53(1)	34(1)	0(1)	−7(1)	1(1)
N(2)	33(1)	31(1)	35(1)	−1(1)	−3(1)	−4(1)
C(2)	34(1)	29(1)	31(1)	−3(1)	2(1)	−3(1)
C(3)	38(1)	24(1)	34(1)	0	5(1)	0
C(4)	30(1)	29(1)	28(1)	−2(1)	1(1)	−1(1)
C(5)	30(1)	29(1)	26(1)	−4(1)	−2(1)	0(1)
C(6)	30(1)	29(1)	28(1)	−2(1)	1(1)	1(1)
C(7)	27(1)	35(1)	28(1)	−2(1)	−1(1)	1(1)
C(8)	31(1)	35(1)	33(1)	−1(1)	−2(1)	−4(1)
C(9)	42(1)	28(1)	25(1)	−2(1)	−7(1)	1(1)
C(10)	53(1)	36(1)	38(1)	−2(1)	−3(1)	9(1)
C(11)	76(2)	35(1)	47(1)	−3(1)	−12(1)	15(1)
C(12)	94(2)	28(1)	56(1)	5(1)	−29(1)	−7(1)
C(13)	63(1)	42(1)	57(1)	10(1)	−25(1)	−18(1)
C(14)	45(1)	34(1)	37(1)	3(1)	−15(1)	−4(1)
C(15)	32(1)	33(1)	32(1)	−4(1)	−3(1)	1(1)
C(16)	38(1)	55(1)	37(1)	−1(1)	−10(1)	8(1)
C(17)	58(1)	58(1)	55(1)	0(1)	−7(1)	16(1)
C(18)	56(1)	62(1)	40(1)	−6(1)	−11(1)	3(1)
C(19)	41(1)	81(2)	53(1)	−8(1)	−11(1)	2(1)
C(20)	46(1)	40(1)	48(1)	−1(1)	−13(1)	−10(1)

Table 72. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for compound **180**.

	x	y	z	U(eq)
H(2)	4289	−843	11062	37
H(3)	5000	−1551	12500	38
H(5)	4711	1797	11014	34
H(10)	2968	3128	9424	51
H(11)	3206	4478	9119	63
H(12)	4477	4931	8890	71
H(13)	5515	4041	8947	65
H(14)	5290	2687	9267	46
H(17A)	1636	3109	7526	86
H(17B)	1408	3038	6153	86
H(17C)	2306	3045	6560	86
H(18A)	2538	1734	5546	79
H(18B)	1645	1662	5126	79
H(18C)	2032	977	5922	79
H(19A)	1006	1109	7395	88
H(19B)	586	1809	6666	88
H(19C)	844	1948	8016	88
H(20A)	2881	−419	8637	67
H(20B)	2912	214	7582	67
H(20C)	2247	278	8554	67

APPENDIX – C

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A new mild method for the one-pot synthesis of pyridines

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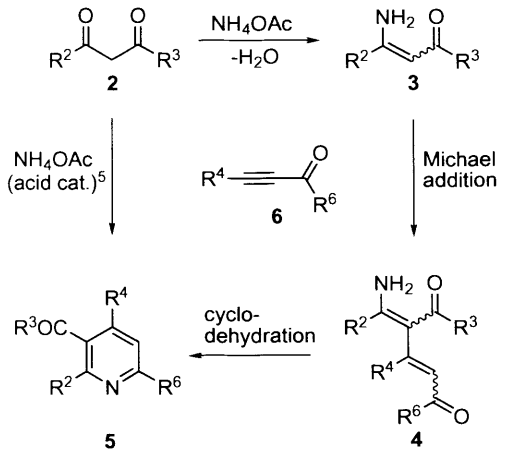
Abstract—Polysubstituted pyridines are prepared in good yield and with total regiocontrol by the one-pot reaction of an alkynone, 1,3-dicarbonyl compound and ammonium acetate in alcoholic solvents. This new three-component heteroannulation reaction proceeds under mild conditions in the absence of an additional acid catalyst and has been used in the synthesis of dimethyl sulfomycinamate, the acidic methanolysis degradation product of the sulfomycin family of thiopeptide antibiotics.

In our recent synthesis of dimethyl sulfomycinamate **1**,[1] the acidic methanolysis degradation product of the thiopeptide antibiotic sulfomycin I,[2] we described a Bohlmann–Rahtz[3] strategy (Scheme 1) for the preparation of the oxazole–thiazole–pyridine central domain (Scheme 2). This heteroannulation of an enamine **3**, often derived from a 1,3-dicarbonyl compound **2** by reaction with ammonium acetate, and alkynone **6** proceeds by Michael addition, typically at 50 °C, to give an aminodienone intermediate **4** that is cyclodehydrated at high temperature or under acidic conditions to tetrasubstituted pyridine **5**.[4] Our 13 step total synthesis of dimethyl sulfomycinamate **1**, which proceeded in 8% overall yield, used 1-(oxazol-4-yl)enamine **3a**, obtained from the corresponding β-ketoamide **2a**, and methyl 4-(trimethylsilyl)-2-oxobut-3-ynoate **6a** in a multistep heteroannulation reaction to give pyridine **5a** in 93% yield as a single regioisomer (Scheme 2). Curiously, this reaction occurred at room temperature in alcoholic solvent and did not give any trace of the Bohlmann–Rahtz intermediate **4a**; conditions, which appeared remarkably facile for spontaneous cyclodehydration to the pyridine.



Scheme 1. Bohlmann–Rahtz and three-component pyridine **5** synthesis.

We recently reported a one-pot method for the synthesis of pyridines from a β-ketoester, ammonia and an alkynone using a Brønsted or Lewis acid catalyst (Scheme 1)[5] and wanted to apply this methodology to the synthesis of dimethyl sulfomycinamate **1** in order to shorten the number of steps to this target. However, in all of the three-component reactions that we investigated acid-catalyzed degradation of the highly sensitive 2-(2-propenyl)oxazole unit prevented the isolation of the oxazole–pyridine product **5a**. In view of the facility of the Bohlmann–Rahtz pyridine synthesis in alcoholic solvent,[6,7] and the surprising ease with which the heteroannulation of enamine **3a** and alkynone **6a** gave the required pyridine **5a**, we set out to explore a new multistep three-component condensation process for the synthesis of pyridine heterocycles that would be compatible with these precursors and that avoided the use of an acid catalyst (Scheme 1).

Keywords: Pyridines; Multicomponent reactions; Heterocycles; Sulfomycin; Bohlmann–Rahtz.
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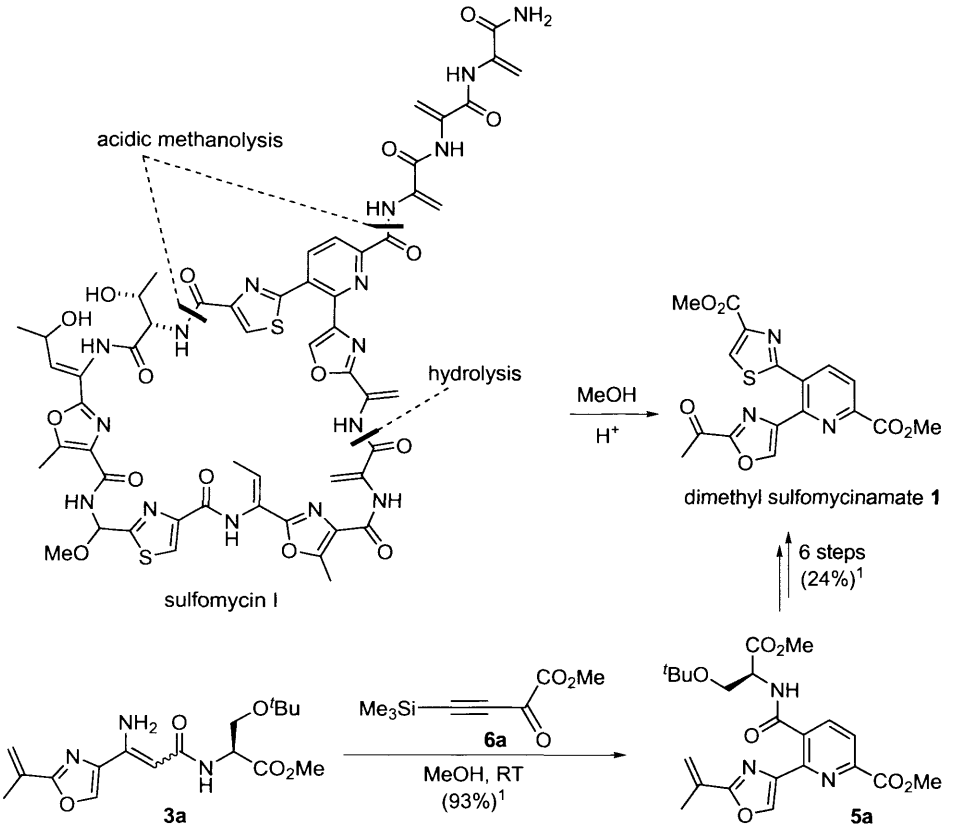
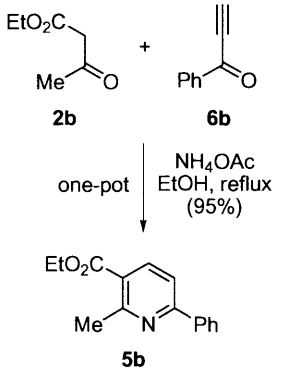


Scheme 2. Degradation of sulfomycin I and synthesis of dimethyl sulfomycinamate **1** via a Bohlmann–Rahtz heteroannulation strategy.

In order to examine if a one-step three-component heteroannulation reaction was possible under mild conditions without an acid catalyst, a mixture of ethyl acetoacetate **2b**, 1-phenylprop-2-yn-1-one **6b**, and ammonium acetate was stirred in ethanol for up to 3 days (Scheme 3). Reactions conducted at room temperature or at reflux with up to 4 equiv of ammonium acetate did not go to completion, giving mixtures of pyridine **5b**, aminodienone **4b** and/or enamine **3b** (Table 1). However, when the reaction was carried out at reflux with a large excess of ammonium acetate, pyridine **5b** was isolated as the only product in excellent yield, cyclodehydration occurring spontaneously under the reaction conditions without the use of an acid catalyst. Optimally, heating an excess of ethyl acetoacetate **2b** (1.7 equiv) and ammonium acetate (10 equiv with respect to **2b**) with **6b** for 24 h gave pyridine **5b** as a single regioisomer in 95% yield after purification on silica (Table 1, entry 5).[8]



Scheme 3. One-pot synthesis of pyridine **5b** under mild conditions.

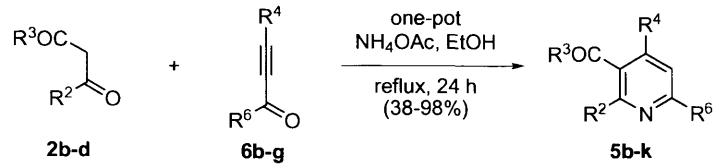
In order to investigate the scope of this reaction, a range of different 1,3-dicarbonyl compounds **2b–e** and alky-

Table 1. Optimizing the one-pot synthesis of ethyl 2-methyl-6-phenylpyridine-3-carboxylate **5b**

Entry	Ratio of **6b/2b**	NH_4OAc equivalents[a]	Temperature	Time (h)	Product (Yield[b] %)
1	0.6	5	Room temperature	72	**4b** (70) and **5b** (23)
2	1.0	2	Reflux	24	**3b** and **5b** (1:1)
3	1.0	4	Reflux	24	**3b** and **5b** (1.4:1)
4	1.0	10	Reflux	24	**5b** (89)
5	0.6	10	Reflux	24	**5b** (95)
6	1.7	10	Reflux	24	**5b** (91)

[a] Equivalents of NH_4OAc with respect to β-ketoester **2b**.
[b] Isolated yield after purification on silica.

Table 2. Examining the scope of a one-pot three-component reaction for the synthesis of pyridines **5b–k**



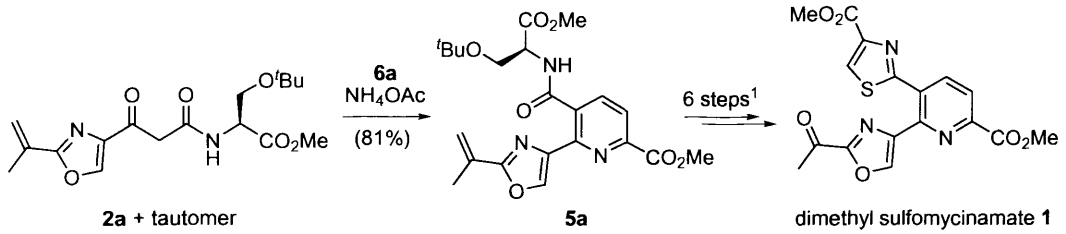
Entry	1,3-Dicarbonyl compound **2**	Alkynone **6**	R^2	R^3	R^4	R^6	NH_4OAc equivalents[a]	Product	Yield[b] (%)
1	**2b**	**6b**	Me	OEt	H	Ph	10	**5b**	95[c]
2	**2b**	**6c**	Me	OEt	H	4′-C_6H_4Cl	10	**5c**	84[c]
3	**2b**	**6d**	Me	OEt	H	4′-C_6H_4OMe	10	**5d**	90[c]
4	**2b**	**6e**	Me	OEt	Et	Me	10	**5e**	38
5	**2b**	**6f**	Me	OEt	TMS	Me	1	**5f**	90[d]
6	**2b**	**6f**	Me	OEt	TMS	Me	10	**5f**	90[d]
7	**2b**	**6g**	Me	OEt	Ph	Me	1	**5g**	51
8	**2c**	**6b**	Me	O^{t}Bu	H	Ph	10	**5h**	89
9	**2c**	**6e**	Me	O^{t}Bu	Et	Me	1	**5i**	71
10	**2c**	**6e**	Me	O^{t}Bu	Et	Me	10	**5i**	63
11	**2c**	**6f**	Me	O^{t}Bu	TMS	Me	1	**5j**	98[d]
12	**2d**	**6b**	Me	NH_2	H	Ph	1	**5k**	98

[a] Equivalents of NH_4OAc with respect to 1,3-dicarbonyl compound **2**.
[b] Isolated yield of pyridine **5** after purification on silica.
[c] An excess (1.7 equiv) of the β-ketoester **2** was employed.
[d] Only protodesilylated pyridine ($R^4 = H$) was produced.

nones **6b–g** were heated in ethanol at reflux in the presence of one or 10 equiv of ammonium acetate. In most experiments (Table 2), pyridine **5b–k** was generated in moderate to excellent yield (entries 1–12, 38–98% yield) as the only regioisomeric product. When 4-(trimethylsilyl)but-3-yn-2-one **6f** was used, only protodesilylated pyridines **5f** and **5j** were obtained. Unfortunately, reactions carried out using a mixture of ethyl benzoylacetate **2e** ($R^2 = Ph$), ammonium acetate and 1-arylprop-2-ynones **6b–d** did not give the desired pyridines and instead produced the corresponding enamine, ethyl 3-amino-3-phenylpropenoate, and a number of side products with degradation of the alkynone. In spite of this limitation, the reaction was successful for a wide variety of substrates (entries 1–12), and constitutes a mild method for the synthesis of polysubstituted pyridines **5b–k**.

Having established a one-pot three-component condensation method that operates under mild conditions, this methodology was applied to the synthesis of pyridine **5a**, the acid-sensitive intermediate in our total synthesis of dimethyl sulfomycinamate **1**. Although the three-component reaction had failed for ethyl benzoylacetate **2e**, the reaction of β-ketoamide **2a** (in equilibrium with its enol tautomer) prepared by our established route[1] with methyl 4-(trimethylsilyl)-2-oxobut-3-ynoate **6a** in the presence of 10 equiv of ammonium acetate was successful and gave pyridine **5a** in 81% yield (Scheme 4).[9] Employing this new multistep process, the total synthesis of dimethyl sulfomycinamate **1** is now complete in only 12 preparative steps and proceeds in 9% overall yield.

In conclusion, we have developed a novel one-pot three-component condensation for the synthesis of pyridines that combines a 1,3-dicarbonyl compound, ammonia and an alkynone without the use of an additional acid catalyst. The resulting polysubstituted pyridines are isolated in modest to excellent yield and as single regioisomers. The advantages that this methodology offers, in particular for the synthesis of acid-sensitive targets, have been highlighted by its application in the total synthesis of dimethyl sulfomycinamate **1** and now will be extended to prepare components of other thiopeptide antibiotics.



Scheme 4. Synthesis of pyridines **5a** under mild conditions by a one-pot three-component condensation reaction.[9]

Acknowledgements

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References and notes

1. Bagley, M. C.; Dale, J. W.; Xiong, X.; Bower, J. *Org. Lett.* **2003**, *5*, 4421–4424.
2. Abe, H.; Takaishi, T.; Okuda, T. *Tetrahedron Lett.* **1978**, *19*, 2791–2794.
3. Bohlmann, F.; Rahtz, D. *Chem. Ber.* **1957**, *90*, 2265–2272.
4. Bagley, M. C.; Brace, C.; Dale, J. W.; Ohnesorge, M.; Phillips, N. G.; Xiong, X.; Bower, J. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1663–1671.
5. Bagley, M. C.; Dale, J. W.; Bower, J. *Chem. Commun.* **2002**, *1*, 1682–1683.
6. Adlington, R. M.; Baldwin, J. E.; Catterick, D.; Pritchard, G. J.; Tang, L. T. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2311–2316.
7. Bashford, K. E.; Burton, M. B.; Cameron, S.; Cooper, A. L.; Hogg, R. D.; Kane, P. D.; MacManus, D. A.; Matrunola, C. A.; Moody, C. J.; Robertson, A. A. B.; Warne, M. R. *Tetrahedron Lett.* **2003**, 1627–1629.
8. In a typical procedure, a solution of ethyl acetoacetate **2b** (0.13 g, 1.0 mmol), 1-phenylprop-2-yn-1-one **6b** (80 mg, 0.6 mmol) and ammonium acetate (0.77 g, 10.0 mmol) in ethanol (10 mL) was stirred at reflux for 24 h, allowed to cool and evaporated in vacuo. The residue was partitioned between saturated aqueous sodium hydrogencarbonate solution (30 mL) and ethyl acetate (30 mL) and the aqueous layer was further extracted with ethyl acetate (20 mL). The combined organic extracts were washed sequentially with saturated aqueous sodium hydrogencarbonate solution (20 mL) and brine (20 mL), dried (Na_2SO_4) and evaporated in vacuo. Purification by column chromatography on silica, eluting with dichloromethane–light petroleum (1:1) gave pyridine **5b** (0.14 g, 95%), as a pale yellow solid whose characterization data agreed with literature reports (Ref. 4).
9. A solution of β-ketoamide **2a** (35 mg, 0.1 mmol), methyl 4-(trimethylsilyl)-2-oxobut-3-ynoate **6a** (49 mg, 0.25 mmol) and ammonium acetate (77 mg, 1.0 mmol) in methanol (10 mL) was stirred at reflux for 5 h, allowed to cool and evaporated in vacuo. The residue was partitioned between saturated aqueous sodium hydrogencarbonate solution (5 mL) and ethyl acetate (8 mL) and the aqueous layer was further extracted with ethyl acetate (5 mL). The combined organic extracts were washed sequentially with saturated aqueous sodium hydrogencarbonate solution (5 mL) and brine (5 mL), dried (Na_2SO_4) and evaporated in vacuo. Purification by column chromatography on silica, eluting with ethyl acetate–light petroleum (2:1) gave pyridine **5a** (36 mg, 81%), as a pale yellow oil whose characterization data agreed with the literature (Ref. 1).

APPENDIX – D

Simple Microwave-Assisted Method for the Synthesis of Primary Thioamides from Nitriles

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Abstract: Primary thioamides are prepared in excellent yield from the corresponding nitrile by treatment with ammonium sulfide in methanol, at room temperature for electron-deficient aromatic nitriles or under microwave irradiation at 80 °C or 130 °C in 15–30 minutes for other aromatic and aliphatic nitriles. This procedure avoids the use of gaseous H_2S under high pressure, proceeds in the absence of base and provides thioamides usually without the need for chromatographic purification.

Key words: thioamides, nitriles, microwaves

The use of thioamides as building blocks in the Hantzsch thiazole synthesis has found broad applicability in many areas of chemistry.[1] In general, two strategies may be adopted for the synthesis of thioamides: the thionation of the corresponding amide with an electrophilic reagent,[2] such as Lawesson's reagent[3] or phosphorus pentasulfide,[4] or reaction with a nucleophilic thionating reagent, by electrophilic activation of either an amide[5] or, more simply, by using the corresponding nitrile.[6] The latter conversion, which requires the use of hydrogen sulfide with triethylamine or pyridine as a catalyst at atmospheric pressure, proceeds well for aromatic nitriles but is highly problematic for the synthesis of aliphatic thioamides and inevitably, with a toxic gaseous reagent, experimentally can be somewhat involved.[7] The use of alkali-metal hydrogen sulfides or ammonium sulfide can simplify the procedure considerably,[8] but usually requires high pressures[9] and is restricted to very electron-deficient aromatic nitriles.[10] More convenient sources of hydrogen sulfide, such as thioacids[11] and thioacetamide,[12] and alternative reagents, such as Dowex SH^-,[13] $(P_4S_{11})Na_2$[14] or sodium trimethylsilanethiolate,[15] all of which require initial preparation, have been explored. However, the challenge of establishing a simple method that is successful for a wide range of different substrates and proceeds under straightforward experimental conditions using commercially available non-gaseous reagents remains.

Microwave dielectric heating has emerged as a valuable alternative to conventional conductive heating methods in recent years[16] and has been used in the three-component combinatorial Kindler synthesis of thioamides from aldehydes, amines and elemental sulfur[17] and to accelerate amide thionations using Lawesson's reagent.[18] Having used microwave-assisted methods in the synthesis of the sulfur-containing heterocyclic domain of the cyclic thiazolylpeptide amythiamicin[19] and the acidic methanolysis product of the sulfomycins, dimethyl sulfomycinamate,[20] we set out to establish a predictable method for the conversion of both aliphatic and aromatic nitriles to primary thioamides using microwave irradiation.

Initially, an electron-deficient aromatic substrate, 2-cyanopyridine (**1a**), was reacted with either sodium hydrosulfide or ammonium sulfide under a range of different conditions (Table 1). Although reactions with sodium hydrosulfide, the less unpleasant-smelling of the two sulfides, failed to give appreciable yields of the product even under microwave irradiation (entries 1–4), all reactions conducted with ammonium sulfide on the highly reactive electron-deficient aromatic nitrile **1a** provided thioamide **2a** in essentially quantitative yield after an aqueous work up without any need for further purification (entries 5–8).

The facile nature of this transformation, which proceeded at room temperature without the use of high pressures, was at first surprising, even though the precursor was an

Table 1 Synthesis of Pyridine-2-thiocarboxamide (**2a**)

	Sulfide	Conditions	Yield (%)
1	NaSH	Et_3N, MeOH–H_2O (3:2), r.t., 18 h	26[b]
2	NaSH	MeOH, r.t., 18 h	24
3	NaSH	MeOH, MW[a] (80 °C, 100 W), 30 min	46
4	NaSH	MeOH, MW[a] (130 °C, 130 W), 30 min	30
5	$(NH_4)_2S$	Et_3N, MeOH–H_2O (3:2), r.t., 18 h	>98
6	$(NH_4)_2S$	MeOH, r.t., 18 h	>98
7	$(NH_4)_2S$	MeOH, MW[a] (80 °C, 100 W), 15 min	>98
8	$(NH_4)_2S$	MeOH, MW[a] (130 °C, 130 W), 30 min	>98

[a] MW = microwave irradiation (hold temperature, initial power) conducted in a sealed tube in a CEM Discover synthesizer.
[b] Purification by column chromatography was required.

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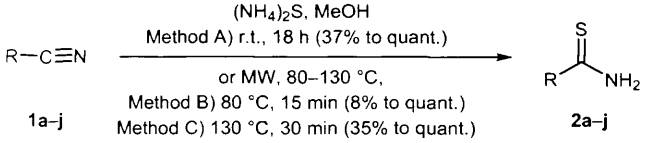
electron-deficient aromatic substrate, and represents a simple experimental procedure for the synthesis of primary thioamides that avoids the use of hydrogen sulfide gas.

In order to establish the scope of these new methods, a range of aliphatic and aromatic nitriles **1a–j** was reacted with ammonium sulfide in methanolic solvent at room temperature (method A)[21] and under microwave-assisted conditions at either 80 °C (method B)[22] or 130 °C (method C, Scheme 1, Table 2). With electron-deficient aromatic nitriles, the thionation reaction proceeded in essentially quantitative yield without heating, additional base or any subsequent purification, although microwave irradiation did dramatically accelerate these transformations. Most aliphatic and electron-rich aromatic nitriles failed to give any yield of the product at room temperature, but when irradiated generated the corresponding thioamide **2** in poor or near quantitative yield.



Scheme 1 Facile methods for synthesis of primary thioamides **2a–j**

Although this simple procedure often generates the primary thioamides in excellent yield, in particular for electron-deficient nitriles, a number of substrates performed poorly under these conditions. The thionation of 4-cyanophenol (**1e**) did not go to completion even under microwave irradiation (entries 11–13) and a number of nitriles failed to give any of the required thioamide product under all of the conditions investigated (Figure 1).[26,27] In spite of these restrictions on substrate tolerance, this method does provide facile access to primary thioamides without the use of base or gaseous reagents.

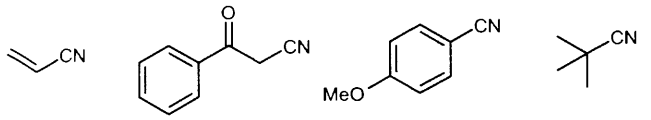


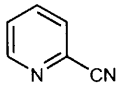
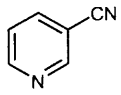
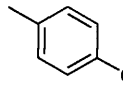
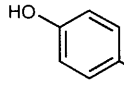
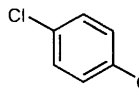
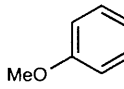
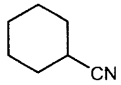
Figure 1 Nitriles that failed to give the corresponding thioamide **2** when reacted with ammonium sulfide both at ambient temperature and under microwave irradiation.

In conclusion, ammonium sulfide in methanol either at room temperature or under microwave irradiation represents an extremely simple method for the synthesis of primary thioamides from nitriles that is effective for both electron-deficient[27] and some electron-rich aliphatic and aromatic substrates, giving the product without any need for purification[28] and, often, in quantitative yield.

Acknowledgment

We thank CEM (Microwave Technology) Ltd and Chris J. Mason for valuable assistance.

Table 2 Reaction of Nitriles **1a–j** and Ammonium Sulfide

Entry	Substrate	Product	Mp (°C)[a]	Yield (%)[b]
1		**2a**	137–138	>98 (A)
2			(138–139)	>98 (B)
3				>98 (C)
4		**2b**	186–189	>98 (A)
5			191–192	>98 (B)
			(190–192)	
6	MeCN	**2c**	121–122	0 (A)
7	MeCN		113–114	53 (B)
8	MeCN		(108–109)[6]	39 (C)
9		**2d**	171–172	0 (A)
10			(169–170)	>98 (B)
11		**2e**		0 (A)
12				8 (B)[c]
13				40 (C)[c]
14		**2f**	116–117	>98 (A)
15			129–130	>98 (B)
			(129–130)	
16		**2g**	111–112	0 (A)
17			98–99	21 (B)[c]
18			(145–147)[23]	93 (C)[c]
19		**2h**	114–116	0 (A)
20			110–115	35 (B)
21			(116)[24]	35 (C)[d]
22	PhCN	**2i**	112–114	0 (A)
23	PhCN		(117–118)	90 (B)
24	PhCN			82 (C)[d]
25	$(EtO)_2CHCN$	**2j**	94–95	37 (A)
26	$(EtO)_2CHCN$		(81–82)[25]	>98 (B)

[a] The range in parentheses refers to literature melting points (ref.[13], unless stated otherwise).

[b] Isolated yield of pure product. The letter in parentheses refers to reaction conditions. Method A: r.t., 18 h. Method B: microwave irradiation at 80 °C (100 W) for 15 min. Method C: microwave irradiation at 130 °C (130 W) for 30 min.

[c] Not isolated yield but based on ^1H NMR analysis of crude reaction mixture.

[d] Purification by column chromatography on silica was required.

References

(1) (a) Takahata, H.; Yamazaki, T. *Heterocycles* **1988**, *27*, 1953. (b) Hurd, R. N.; Delamater, G. T. *Chem. Rev.* **1961**, *61*, 45.
(2) Brillon, D. *Sulfur Rep.* **1992**, *12*, 297.
(3) Cava, M. P.; Levinson, M. I. *Tetrahedron* **1985**, *41*, 5061.
(4) Hartke, K.; Gerber, H.-D. *J. Prakt. Chem.* **1996**, *338*, 763.
(5) Charette, A. B.; Grenon, M. *J. Org. Chem.* **2003**, *68*, 5792.
(6) Walter, W.; Bode, K. D. *Angew. Chem., Int. Ed. Engl.* **1996**, *5*, 447.
(7) Fairfull, A. E. S.; Lowe, J. L.; Peak, D. A. *J. Chem. Soc.* **1952**, 742.

(8) (a) Kindler, K. *Liebigs Ann. Chem.* **1923**, *431*, 187. (b) Wang, C.-H.; Hwang, F.-Y.; Horng, J.-M.; Chen, C.-T. *Heterocycles* **1979**, *12*, 1191.
(9) Gabriel, S.; Heymann, P. *Ber. Dtsch. Chem. Ges.* **1890**, *23*, 157.
(10) Erlenmeyer, H.; Degen, K. *Helv. Chim. Acta* **1946**, *29*, 1080.
(11) Albert, A. *Ber. Dtsch. Chem. Ges.* **1915**, *48*, 470.
(12) Taylor, E. C.; Zoltewicz, J. A. *J. Am. Chem. Soc.* **1960**, *82*, 2656.
(13) Liboska, R.; Zyka, D.; Bobek, M. *Synthesis* **2002**, 1649.
(14) Brillon, D. *Synth. Commun.* **1992**, *22*, 1397.
(15) Shiao, M. J.; Lai, L. L.; Ku, W. S.; Lin, P. Y.; Hwu, J. R. *J. Org. Chem.* **1993**, *58*, 4742.
(16) Reviews on microwave chemistry include: (a) Gabriel, C.; Gabriel, S.; Grant, E. H.; Halstead, B. S. J.; Mingos, D. M. P. *Chem. Soc. Rev.* **1998**, *27*, 213. (b) Kuhnert, N. *Angew. Chem. Int. Ed.* **2002**, *41*, 1863. (c) Lidström, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225. (d) Loupy, A.; Petit, A.; Hamelin, J.; Texier-Boullet, F.; Jacquault, P.; Mathé, D. *Synthesis* **1998**, 1213. (e) Galema, S. A. *Chem. Soc. Rev.* **1997**, *26*, 233. (f) Caddick, S. *Tetrahedron* **1995**, *51*, 10403. (g) Strauss, C. R.; Trainor, R. W. *Aust. J. Chem.* **1995**, *48*, 1665. (h) *Microwaves in Organic Synthesis*; Loupy, A., Ed.; Wiley VCH: Weinheim, **2002**.
(17) Zbruyev, O. I.; Stiasni, N.; Kappe, C. O. *J. Comb. Chem.* **2003**, *5*, 145.
(18) Varma, R. S.; Kumar, D. *Org. Lett.* **1999**, *1*, 697.
(19) Bagley, M. C.; Dale, J. W.; Jenkins, R. L.; Bower, J. *Chem. Commun.* **2004**, 102.
(20) Bagley, M. C.; Dale, J. W.; Xiong, X.; Bower, J. *Org. Lett.* **2003**, *5*, 4421.
(21) **General Procedure for Reaction of Nitriles 1 and Ammonium Sulfide at Room Temperature (Method A).** A solution of nitrile **1** (0.5 mmol, 1 equiv) and $(NH_4)_2S$ (0.5 mmol, 1 equiv; 50 wt.% in H_2O) in MeOH (5 mL) was stirred at r.t. for 18 h, evaporated in vacuo and partitioned between EtOAc (10 mL) and H_2O (10 mL). The aqueous layer was further extracted with EtOAc (2 × 5 mL) and the organic extracts were combined, washed with brine (10 mL), dried (Na_2SO_4) and evaporated in vacuo to give thioamide **2**.
(22) **General Procedure for Microwave-Assisted Reaction of Nitriles 1 and Ammonium Sulfide (Method B).** A solution of nitrile **1** (0.5 mmol, 1 equiv) and $(NH_4)_2S$ (0.5 mmol, 1 equiv; 50 wt.% in H_2O) in MeOH (5 mL) was irradiated for 15 min in a self-tunable CEM microwave Discover synthesizer at 80 °C (initial power 100 W) and then cooled using a flow of compressed air, evaporated in vacuo and partitioned between EtOAc and H_2O. The aqueous layer was further extracted with EtOAc (2 × 5 mL) and the organic extracts were combined, washed with brine (10 mL), dried (Na_2SO_4) and evaporated in vacuo to give thioamide **2**.
(23) Feiring, A. E. *J. Org. Chem.* **1976**, *41*, 148.
(24) Walter, W.; Curts, J. *Chem. Ber.* **1960**, *93*, 1511.
(25) Inami, K.; Shiba, T. *Bull Chem. Soc. Jpn.* **1985**, *58*, 352.
(26) The nitriles depicted in Figure 1 gave only unreacted starting material under ambient and microwave-assisted conditions, according to methods A and B, respectively, except for acrylonitrile which instead reacted by conjugate addition with ammonium sulfide.
(27) The reaction of 2-cyanopyridine(**1a**) with ammonium sulfide according to method A has been conducted on a larger scale (10 mmol) to give thioamide **2a** without any reduction in yield.
(28) With a volatile aliphatic nitrile, such as **1c**, evaporation in vacuo after an aqueous work-up removed unreacted starting material. For reactions that were not quantitative, purification by column chromatography on silica was usually required. For experiments that gave >98% yield (Table 2, entries 1–5, 10, 14, 15, and 26), no purification on silica or recrystallisation of the product was necessary.

APPENDIX – E

JOC Article

One-Pot Multistep Bohlmann–Rahtz Heteroannulation Reactions: Synthesis of Dimethyl Sulfomycinamate

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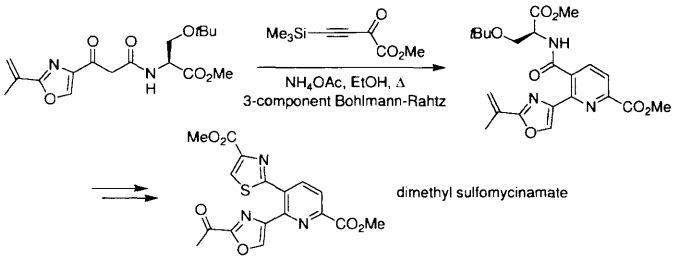

The synthesis of dimethyl sulfomycinamate, the acidic methanolysis product of the sulfomycin family of thiopeptide antibiotics, from methyl 2-oxo-4-(trimethylsilyl)but-3-ynoate is achieved in a 2,3,6-trisubstituted pyridine synthesis that proceeds with total regiocontrol in 13 steps by the Bohlmann–Rahtz heteroannulation of a 1-(oxazol-4-yl)enamine or in 12 steps and 9% yield by three-component cyclocondensation with *N*-[3-oxo-3-(oxazol-4-yl)propanoyl]serine and ammonia in ethanol.

Introduction

The sulfomycins (**1a–c**) are a family of three cyclic peptides isolated from actinomycetes that are members of the thiopeptide or thiazolyl peptide group of antibiotics.[1] This ever-expanding collection of compounds classifies 29 different families of natural products isolated from the mycelial cake of Gram-positive sporulating bacteria and encompasses 76 structurally distinct sulfur-containing secondary metabolites, including a number of well-known antibiotics such as thiostrepton (**2**), nosiheptide (**3**), and the micrococcins (Bycroft–Gowland structure, **4a,b**).

Sulfomycin I (**1a**) was isolated from *Streptomyces viridochromogenes* subsp. *sulfomycini* ATCC 29776 and exhibits strong inhibitory activity against Gram-positive bacteria,[2] whereas all of the sulfomycins, I–III, have been isolated from *Streptomyces viridochromogenes* MCRL-0368.[3] An investigation of sulfomycin hydrolysates, combined with FAB mass spectrometric data and ^{1}H and ^{13}C NMR spectroscopic analyses, elucidated the structure of these natural products. In these studies, the acidic methanolysis of sulfomycin I (**1a**) provided vital evidence and generated a number of different fragments including dimethyl sulfomycinamate (**5**),[4] produced on heating at reflux in methanol for 20 h in the presence of Amberlyst 15 ion-exchange resin, the structure of which was confirmed by X-ray crystallographic data (Scheme 1). Sulfomycin I (**1a**) is structurally distinct from sulfomycin II (**1b**) and III (**1c**) only in the identity of one side chain located on a 2-(2-aminoalkenyl)oxazole residue in the peptide backbone.[5] All of the sulfomycins contain an oxazole–thiazole–pyridine central heterocyclic domain that is common with a number of other thiopeptide antibiotics,[1] including the A10255 factors,[6] berninamycins,[4,7] geninthiocin,[8] methylsulfomycin,[9] promoinducin,[10]

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(1) Bagley, M. C.; Dale, J. W.; Merritt, E. A.; Xiong, X. *Chem. Rev.* **2005**, *105*, 685–714.

(2) Egawa, Y.; Umino, K.; Tamura, Y.; Shimizu, M.; Kaneko, K.; Sakurazawa, M.; Awataguchi, S.; Okuda, T. *J. Antibiot.* **1969**, *22*, 12.

(3) Konno, J.; Kameda, N.; Nishio, M.; Kinumaki, A.; Komatsubara, S. *J. Antibiot.* **1996**, *49*, 1063.

(4) Abe, H.; Takaishi, T.; Okuda, T.; Aoe, K.; Date, T. *Tetrahedron Lett.* **1978**, 2791.

(5) Abe, H.; Kushida, K.; Shiobara, Y.; Kodama, M. *Tetrahedron Lett.* **1988**, *29*, 1401.

(6) Debono, M.; Molloy, R. M.; Occolowitz, J. L.; Paschal, J. W.; Hunt, A. H.; Michel, K. H.; Martin, J. W. *J. Org. Chem.* **1992**, *57*, 5200.

(7) Lau, R. C. M.; Rinehart, K. L. *J. Antibiot.* **1994**, *47*, 1466.

(8) Yun, B.-S.; Hidaka, T.; Furihata, K.; Seto, H. *J. Antibiot.* **1994**, *47*, 969.

(9) Kumar, E. K. S. V.; Kenia, J.; Mukhopadhyay, T.; Nadkarni, S. R. *J. Nat. Prod.* **1999**, *62*, 1562.

10.1021/jo048106q CCC: $30.25
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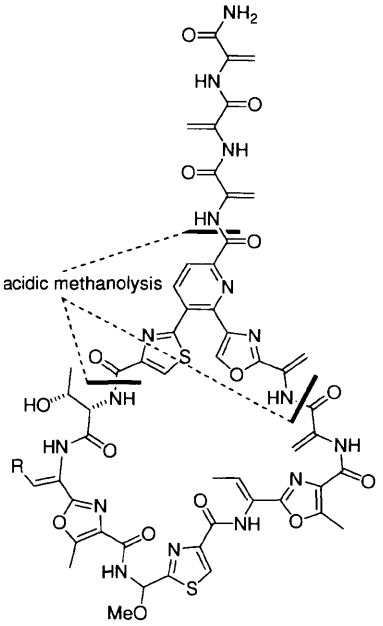
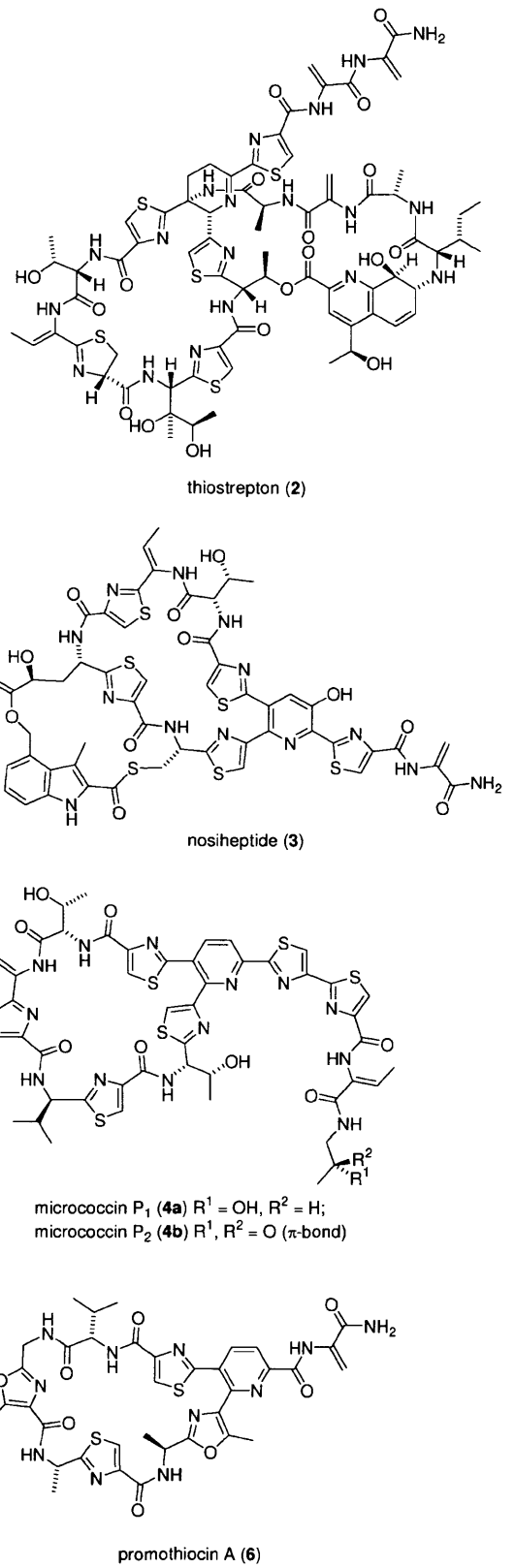
SCHEME 1. Acidic Methanolysis of Sulfomycin I



promothiocins (**A**, **6**),[11] radamycin,[12] thioactin,[13] thioxamycin,[14] and thiotipin.[15] The biological properties of the thiopeptide antibiotics have attracted considerable attention as inhibitors of bacterial protein synthesis with a novel mode of action. The parent of the family, thiostrepton, inhibits the binding of the aminoacyl-tRNA-containing ternary complex to the ribosomal A site[16] at the L11 binding domain on 23S rRNA,[17] and prevents peptide elongation by impeding a conformational change within protein L11 critical for stimulating the GTPase action of the elongation factors.[18] Autoimmunity in thiostrepton producers is achieved by the action of an RNA-pentose methylase enzyme[19] produced constitutively from its own promoter that introduces a single methyl group into the A1067 residue of the 23S rRNA in *Escherichia*

CHART 1

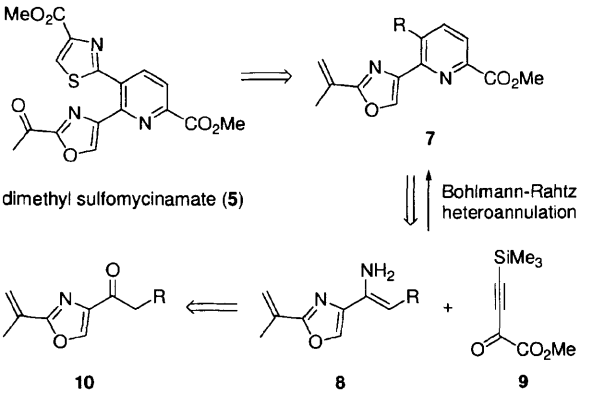


(10) Yun, B.-S.; Seto, H. *Biosci. Biotechnol. Biochem.* **1995**, *59*, 876.
(11) Yun, B.-S.; Hidaka, T.; Furihata, K.; Seto, H. *J. Antibiot.* **1994**, *47*, 510.
(12) Rodríguez, J. C.; Holgado, G. G.; Sánchez, R. I. S.; Cañedo, L. M. *J. Antibiot.* **2002**, *55*, 391.
(13) Yun, B.-S.; Hidaka, T.; Furihata, K.; Seto, H. *J. Antibiot.* **1994**, *47*, 1541.
(14) Matsumoto, M.; Kawamura, Y.; Yasuda, Y.; Tanimoto, T.; Matsumoto, K.; Yoshida, T.; Shoji, J. *J. Antibiot.* **1989**, *42*, 1465.
(15) Yun, B.-S.; Hidaka, T.; Furihata, K.; Seto, H. *Tetrahedron* **1994**, *50*, 11659.
(16) Cundliffe, E. *Biochem. Biophys. Res. Commun.* **1971**, 44, 912.
(17) (a) Xing, Y.; Draper, D. E. *Biochemistry* **1996**, *35*, 1581. (b) Conn, G. L.; Draper, D. E.; Lattman, E. E.; Gittis, A. G. *Science* **1999**, *284*, 1171. (c) Wimberly, B. T.; Guymon, R.; McCutcheon, J. P.; White, S. W.; Ramakrishnan, V. *Cell* **1999**, *97*, 491.
(18) (a) Porse, B. T.; Leviev, I.; Mankin, A. S.; Garrett, R. A. *J. Mol. Biol.* **1998**, 276, 391. (b) Lentzen, G.; Klinck, R.; Matassova, N.; Aboul-ela, F.; Murchie, A. I. H. *Chem. Biol.* **2003**, *10*, 769.

coli to give a modified 2′-*O*-methyladenosine-containing ribosome that is completely resistant to the antibiotic,[20] a phenomenon also observed in 23S rRNA mutants of *Halobacterium halobium*.[21] Many of these natural products have also been shown to activate transcription through binding to thiostrepton-induced proteins in bacteria in an autogenously controlled antibiotic resistance system.[22] Furthermore, the biosynthesis of these antibiotics has also emerged as an interesting area of study. The origin of many of the structural motifs in sulfomycin has been investigated by following the incorporation of isotopically labeled amino acids[23] and, based upon related studies on micrococcin P_1 (**4a**),[24] would appear to proceed by a template-directed nonribosomal enzymatic process[25] on nonribosomal peptide synthetase (NRPS) multimodular templates.

In view of the biological properties and considerable interest in the thiopeptide antibiotics, we set out to validate a synthetic route to the sulfomycin family that used an heteroannulation approach to establish the central oxazole–thiazole–pyridine domain and apply this in the synthesis of dimethyl sulfomycinamate (**5**). The synthesis of thiopeptide natural products has attracted much interest, with recent reports on the total synthesis of thiostrepton (**2**),[26] promothiocin A (**6**),[27] and amythiamicin D[28] and significant progress made toward a number of other targets, including the micrococcins (**4a,b**),[29] nosiheptide,[30,31] glycothiohexide α,[31] the A10255 factors,[32] cyclothiazomycin,[33] the berninamycins,[34] and the sulfomycins (**1a–c**).[35] Prior to our work in this area, the synthesis of the related thiopeptide hydrolysates berninamycinic acid[36] and micrococcinic acid,[37] the latter a derivative of micrococcin P_1 (**4a**), had been reported, contributing significantly to structure elucidation studies into their respective thiopeptide families. Furthermore, Kelly and Lang had described an elegant synthesis of dimethyl sulfomycinamate (**5**), using palladium-catalyzed coupling reactions to form the biaryl bonds and so establish the central tris-heterocyclic unit.[38] We now report a new approach to dimethyl sulfomycinamate (**5**) that complements this earlier work, avoids the use of palladium catalysts, and constructs the heterocyclic components from acyclic precursors.[39]

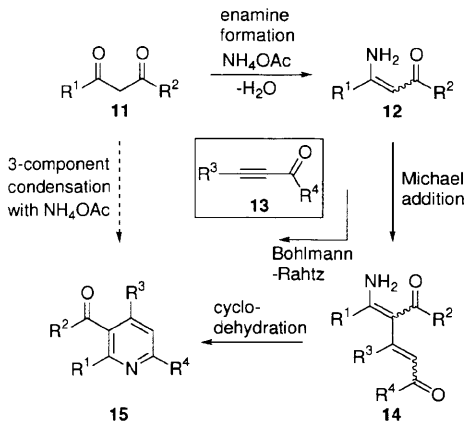
SCHEME 2. Dimethyl Sulfomycinamate (5) Disconnective Scheme



Our disconnective scheme for accessing dimethyl sulfomycinamate (**5**) hoped to establish oxazole–pyridine **7** by the Bohlmann–Rahtz heteroannulation[40] of methyl 2-oxo-4-(trimethylsilyl)but-3-ynoate (**9**) and a suitable enamine **8**, bearing a substituent (R) for later elaboration to the thiazole and prepared from oxazolyl ketone **10** by reaction with ammonia (Scheme 2). This two-step pyridine synthesis, for example, proceeds by Michael addition of a 2-aminopropenoate **12**, prepared from the corresponding β-ketoester **11**, and alkynone **13** at 50 °C to give an aminodienone intermediate **14** that is cyclodehydrated at high temperature to give tri- or tetrasubstituted pyridines **15** with total regiocontrol (Scheme 3). In recent years it has found a number of applications in the synthesis of unusual amino acids,[41] pyridine libraries,[42] and nonsteroidal antiinflammatory agents.[43] We have shown that this process is much more facile under acidic

(19) (a) Cundliffe, E.; Thompson, J. *Nature* **1979**, *278*, 859. (b) Cundliffe, E. *Nature* **1978**, *272*, 792.
(20) Thompson, J.; Schmidt, F.; Cundliffe, E. *J. Biol. Chem.* **1982**, *257*, 7915.
(21) Mankin, A. S.; Leviev, I.; Garrett, R. A. *J. Mol. Biol.* **1994**, *244*, 151.
(22) (a) Holmes, D. J.; Caso, J. L.; Thompson, C. J. *EMBO J.* **1993**, *12*, 3183. (b) Chiu, M. L.; Folcher, M.; Griffin, P.; Holt, T.; Klatt, T.; Thompson, C. J. *Biochemistry* **1996**, *35*, 2332. (c) Chiu, M. L.; Viollier, P. H.; Katoh, T.; Ramsden, J. J.; Thompson, C. J. *Biochemistry* **2001**, *40*, 12950. (d) Kahmann, J. D.; Sass, H.-J.; Allan, M. G.; Seto, H.; Thompson, C. J.; Grzesiek, S. *EMBO J.* **2003**, *22*, 1824.
(23) Fate, G. D.; Benner, C. P.; Grode, S. H.; Gilbertson, T. J. *J. Am. Chem. Soc.* **1996**, *118*, 11363.
(24) Carnio, M. C.; Stachelhaus, T.; Francis, K. P.; Scherer, S. *Eur. J. Biochem.* **2001**, 268, 6390.
(25) Mocek, U.; Zeng, Z.; O'Hagan, D.; Zhou, P.; Fan, L.-D. G.; Beale, J. M.; Floss, H. G. *J. Am. Chem. Soc.* **1993**, *115*, 7992.
(26) (a) Nicolaou, K. C.; Nevalainen, M.; Safina, B. S.; Zak, M.; Bulat, S. *Angew. Chem., Int. Ed.* **2002**, *41*, 1941. (b) Nicolaou, K. C.; Safina, B. S.; Funke, C.; Zak, M.; Zécri, F. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 1937. (c) Nicolaou, K. C.; Nevalainen, M.; Zak, M.; Bulat, S.; Bella, M.; Safina, B. S. *Angew. Chem., Int. Ed.* **2003**, *42*, 3418. (d) Nicolaou, K. C.; Safina, B. S.; Zak, M.; Estrada, A. A.; Lee, S. H. *Angew. Chem., Int. Ed.* **2004**, *43*, 5087. (e) Nicolaou, K. C.; Zak, M.; Safina, B. S.; Lee, S. H.; Estrada, A. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 5092.
(27) (a) Bagley, M. C.; Bashford, K. E.; Hesketh, C. L.; Moody, C. J. *J. Am. Chem. Soc.* **2000**, *122*, 3301. (b) Moody, C. J.; Bagley, M. C. *Chem. Commun.* **1998**, 2049.
(28) Hughes, R. A.; Thompson, S. P.; Alcaraz, L.; Moody, C. J. *Chem. Commun.* **2004**, 946.
(29) (a) Ciufolini, M. A.; Shen, Y.-C. *Org. Lett.* **1999**, *1*, 1843. (b) Okumura, K.; Ito, A.; Yoshioka, D.; Shin, C. *Heterocycles* **1998**, *48*, 1319.
(30) (a) Koerber-Plé, K.; Massiot, G. *Synlett* **1994**, 759. (b) Umemura, K.; Tate, T.; Yamaura, M.; Yoshimura, J.; Yonezawa, Y.; Shin, C. *Synthesis* **1995**, 1423. (c) Umemura, K.; Noda, H.; Yoshimura, J.; Konn, A.; Yonezawa, Y.; Shin, C. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 1391.
(31) Bentley, D. J.; Fairhurst, J.; Gallagher, P. T.; Manteuffel, A. K.; Moody, C. J.; Pinder, J. L. *Org. Biomol. Chem.* **2004**, *2*, 701.
(32) Umemura, K.; Ikeda, S.; Yoshimura, J.; Okumura, K.; Saito, H.; Shin, C. *Chem. Lett.* **1997**, 1203.
(33) (a) Shin, C.; Okabe, A.; Ito, A.; Ito, A.; Yonezawa, Y. *Bull. Chem. Soc. Jpn.* **2002**, *75*, 1583. (b) Endoh, N.; Yonezawa, Y.; Shin, C. *Bull. Chem. Soc. Jpn.* **2003**, *76*, 643. (c) Bagley, M. C.; Xiong, X. *Org. Lett.* **2004**, *6*, 3401.
(34) Yamada, T.; Okumura, K.; Yonezawa, Y.; Shin, C. *Chem. Lett.* **2001**, 102.
(35) Kayano, T.; Yonezawa, Y.; Shin, C. *Chem. Lett.* **2004**, *33*, 72.
(36) Kelly, T. R.; Echavarren, A.; Chandrakumar, N. S.; Köksal, Y. *Tetrahedron Lett.* **1984**, *25*, 2127.
(37) Kelly, T. R.; Jagoe, C. T.; Gu, Z. *Tetrahedron Lett.* **1991**, *32*, 4263.
(38) (a) Kelly, T. R.; Lang, F. *Tetrahedron Lett.* **1995**, *36*, 5319. (b) Kelly, T. R.; Lang, F. *J. Org. Chem.* **1996**, *61*, 4623.
(39) For preliminary reports, see: (a) Bagley, M. C.; Dale, J. W.; Xiong, X.; Bower, J. *Org. Lett.* **2003**, *5*, 4421. (b) Bagley, M. C.; Dale, J. W.; Bower, J. *Chem. Commun.* **2002**, 1682. (c) Bagley, M. C.; Chapaneri, K.; Xiong, X. *Tetrahedron Lett.* **2004**, *45*, 6121.
(40) Bohlmann, F.; Rahtz, D. *Chem. Ber.* **1957**, *90*, 2265.
(41) (a) Adamo, M. F. A.; Adlington, R. M.; Baldwin, J. E.; Pritchard, G. J.; Rathmell, R. E. *Tetrahedron* **2003**, *59*, 2197. (b) Adlington, R. M.; Baldwin, J. E.; Catterick, D.; Pritchard, G. J.; Tang, L. T. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2311. (c) Baldwin, J. E.; Catterick, D.; Pritchard, G. J.; Tang, L. T. *J. Chem. Soc., Perkin Trans. 1* **2000**, 303. (d) Moody, C. J.; Bagley, M. C. *Synlett* **1998**, 361.

SCHEME 3. Bohlmann–Rahtz and Related 3-Component Pyridine Synthesis

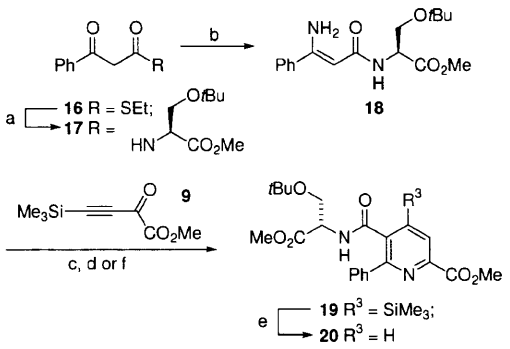


conditions,[44] either with a Brønsted[45] or Lewis acid catalyst,[46] is promoted by microwave irradiation,[47] and can be applied in solution-phase combinatorial chemistry[48] and for the synthesis of pyrido[2,3-*d*]pyrimidines[46,49] and heterocyclic natural products.[50] Yet as both the enamine formation[51] and two-step Bohlmann–Rahtz pyridine synthesis[44] are promoted under acidic conditions, it was proposed that the 3-component condensation of a 1,3-dicarbonylcompound **11**, alkynone **13**, and ammonia should provide a much more direct and efficient approach toward pyridines **15**. This new tandem process would be related to the Hantzsch dihydropyridine synthesis, but would not need subsequent oxidation and could generate the pyridine with total control of regiochemistry. This would constitute a rapid and facile method for the synthesis of pyridines of biological interest that was suitable for the preparation of oxazole–pyridine **7**, containing an acid-sensitive 2-(2-propenyl) group, for elaboration to the 2-acetyloxazole of dimethyl sulfomycinimate (**5**).

Results and Discussion

We embarked upon our approach to dimethyl sulfomycinamate (**5**) using a model study to establish the substituent (R) required for Bohlmann–Rahtz synthesis of the thiazole–pyridine domain. Starting from *S*-ethyl benzoylthioacetate (**16**) (Scheme 4), copper(I) iodide-promoted thiolate displacement with *O-tert*-butyl-L-serine

SCHEME 4. Bohlmann–Rahtz Synthesis of Pyridine 20[a]



[a] Reagents and conditions: (a) H-L-Ser(*t*Bu)-OMe.HCl, Et_3N, CuI, CH_2Cl_2, rt, 18 h (91%); (b) NH_4OAc, PhMe–AcOH (5:1), reflux, 20 h (58%); (c) **9**, PhMe–AcOH (5:1), 50 °C, 6 h, gave **19** (25%); (d) **9**, $ZnBr_2$ (20 mol %), PhMe, reflux, 6 h, gave **19** (64%); (e) TBAF, THF, rt, 2 h (81%); (f) **9**, MeOH, rt, 60 h, gave **20** (95%).

methyl ester according to a modified procedure of Olsen gave *N*-acyl serine **17** (91%),[52] which was heated at reflux with ammonium acetate in toluene–acetic acid to give the Bohlmann–Rahtz precursor **18** (58%). Reaction with methyl 2-oxo-4-(trimethylsilyl)but-3-ynoate (**9**), prepared by the addition of lithium (trimethylsilyl)acetylide to the Weinreb amide derivative of oxalic acid monomethyl ester,[44] under modified Bohlmann–Rahtz conditions with either a Brønsted or Lewis acid catalyst gave the pyridine **19** but in only 25% or 64% yield, respectively. Although the yield of these heteroannulation reactions was disappointing, subsequent protodesilylation with tetrabutylammonium fluoride (TBAF) in THF gave 2,3,6-trisubstituted pyridine **20** with a serine residue in place for elaboration of the 3-thiazolyl substituent. However, when traditional Bohlmann–Rahtz conditions were investigated, the Michael addition appeared facile even at room temperature giving, with spontaneous cyclodehydration, pyridine **20** directly in excellent yield (95%). From pyridine **20**, very efficient introduction of the pyridine 3-substituent was verified for the model system by thionation with Lawesson's reagent (LR) in benzene (96%) followed by cleavage of the *tert*-butyl ether of **21** in trifluoroacetic acid (TFA) at reflux (>98%). Under these conditions, spontaneous cyclization occurred and the generated thiazoline **22** could be readily oxidized, using manganese dioxide in chloroform at 120 °C under microwave irradiation (>98%), to give thiazole–pyridine **23** in excellent overall yield (Scheme 5).

With the route to the model system established, we sought to validate a faster route to pyridine **7** by the 3-component heteroannulation of potentially acid-sensitive oxazolyl ketone **10**, methyl oxobutynoate **9**, and ammonia, under mild conditions with in situ generation of enamine **8**. Given the surprising facility of the Bohlmann–Rahtz heteroannulation reaction for the synthesis of pyridine **20** in ethanol, without using elevated temperatures or an acid catalyst, we decided to investigate a similar procedure for the 3-component reaction. To this end, a range of 1,3-dicarbonyl compounds **11a–d** and alkynones **13a–f** were heated at reflux with ammonium

(42) Bashford, K. E.; Burton, M. B.; Cameron, S.; Cooper, A. L.; Hogg, R. D.; Kane, P. D.; MacManus, D. A.; Matrunola, C. A.; Moody, C. J.; Robertson, A. A. B.; Warne, M. R. *Tetrahedron Lett.* **2003**, *44*, 1627.

(43) Schroeder, E.; Lehmann, M.; Boettcher, I. *Eur. J. Med. Chem.* **1979**, *14*, 309.

(44) Bagley, M. C.; Brace, C.; Dale, J. W.; Ohnesorge, M.; Phillips, N. G.; Xiong, X.; Bower, J. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1663.

(45) Bagley, M. C.; Dale, J. W.; Bower, J. *Synlett* **2001**, 1149.

(46) Bagley, M. C.; Dale, J. W.; Hughes, D. D.; Ohnesorge, M.; Phillips, N. G.; Bower, J. *Synlett* **2001**, 1523.

(47) Bagley, M. C.; Lunn, R.; Xiong, X. *Tetrahedron Lett.* **2002**, *43*, 8331.

(48) Bagley, M. C.; Dale, J. W.; Ohnesorge, M.; Xiong, X.; Bower, J. *J. Comb. Chem.* **2003**, *5*, 41.

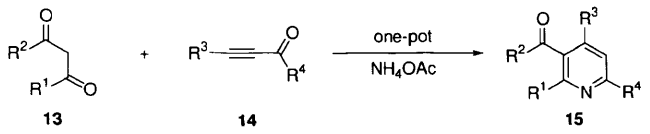
(49) (a) Hughes, D. D.; Bagley, M. C. *Synlett* **2002**, 1332. (b) Bagley, M. C.; Hughes, D. D.; Lloyd, R.; Powers, V. E. C. *Tetrahedron Lett.* **2001**, *42*, 6585.

(50) Bagley, M. C.; Dale, J. W.; Jenkins, R. L.; Bower, J. *Chem. Commun.* **2004**, 102.

(51) Baraldi, P. G.; Simoni, D.; Manfredini, S. *Synthesis* **1983**, 302.

(52) Kim, H.-O.; Olsen, R. K.; Choi, O.-S. *J. Org. Chem.* **1987**, *52*, 4531.

TABLE 1. One-Pot 3-Component Synthesis of Pyridines 15[a]

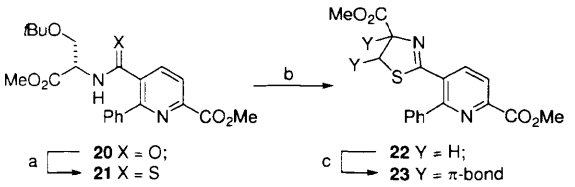


13 14 15

entry	11	R^1	R^2	13	R^3	R^4	15	yield (%) methods A–C	yield (%) method D
1	**a**	Me	EtO	**a**	Me_3Si	Me	**aa**	55A,[b] 75B[c]	90[c]
2	**a**	Me	EtO	**b**	Et	Me	**ab**	96A, 82B[d]	38
3	**a**	Me	EtO	**c**	Ph	Me	**ac**	80B	51[e]
4	**a**	Me	EtO	**d**	H	Ph	**ad**	84A,[f] 90B[f]	95[g]
5	**a**	Me	OEt	**e**	H	4′-C_6H_4Cl	**ae**	97B[f]	84[g]
6	**a**	Me	OEt	**f**	H	4′-C_6H_4OMe	**af**	98B[f]	90[g]
7	**b**	Ph	OEt	**c**	Ph	Me	**bc**	88A, 70B	<8[h]
8	**c**	Me	O*t*Bu	**a**	Me_3Si	Me	**ca**	0A	98[c,e]
9	**c**	Me	O*t*Bu	**b**	Et	Me	**cb**	49A, 55B	71[e]
10	**c**	Me	O*t*Bu	**c**	Ph	Me	**cc**	49A, 60C	33
11	**c**	Me	O*t*Bu	**d**	H	Ph	**cd**	93C[f]	89
12	**d**	Me	NH_2	**d**	H	Ph	**dd**	82A[f]	98[e]

[a] Reagents and conditions: (A) **13** (2 equiv), NH_4OAc (10 equiv), $ZnBr_2$ (20 mol %), toluene, reflux, 20 h; (B) **13** (2 equiv), NH_4OAc (10 equiv), toluene-acetic acid (5:1), reflux, 20 h; (C) **13** (3 equiv), NH_4OAc (10 equiv), Amberlyst 15, toluene, reflux, 20 h; (D) **13** (1.0 equiv), NH_4OAc (10 equiv), ethanol, reflux, 24 h. Yield refers to isolated yield of pyridine **15** after purification on silica. [b] A mixture of 4-(trimethylsilyl)pyridine and protodesilylated product was obtained (56:44). [c] Only protodesilylated pyridine (R^4 = H) was produced. [d] An excess of **13** (3 equiv) was used. [e] Only 1 equiv of NH_4OAc was used. [f] Only 1 equiv of **13** was used. [g] An excess of **14** (1.7 equiv) and NH_4OAc (17 equiv) was used. [h] Not isolated yield, but based upon ^1H NMR analysis of the crude product.

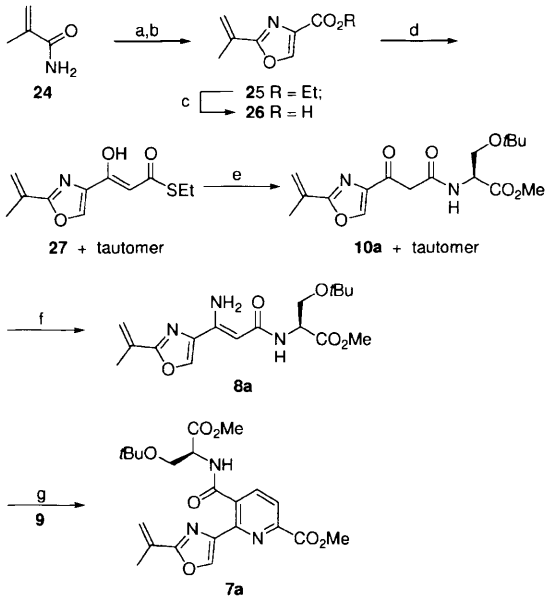
SCHEME 5. Synthesis of Model Thiazole-Pyridine 23[a]



[a] Reagents and conditions: (a) LR, benzene, reflux, 66 h (96%); (b) TFA, reflux, 48 h (>98%); (c) MnO_2, $CHCl_3$, microwave, 100 °C, 10 min (>98%).

acetate in ethanol and the results compared to a selection of acid-catalyzed 3-component processes, either in toluene in the presence of a Lewis acid catalyst (20 mol % $ZnBr_2$), with acetic acid as a Brønsted acid catalyst, or over Amberlyst 15 acidic ion-exchange resin (Table 1). For the most part, pyridine **15** was generated in higher yield when there was no acid catalyst, except for reactions with less reactive terminally substituted alkynones such as hex-3-yn-2-one **13b** and phenylbutynone **13c**, but was always isolated as a single regioisomeric product. Reactions with 4-(trimethylsilyl)but-3-yn-2-one **13a** in ethanol gave only the protodesilylated pyridines **15aa** and **15ca**. Unfortunately, reactions carried out with a mixture of ethyl benzoyl acetate **11b**, ammonium acetate, and 1-arylprop-2-ynones **13d–f** did not give the desired pyridines and instead produced the corresponding enamine, ethyl 3-amino-3-phenylpropenoate, and a number of side products with degradation of the alkynone. Similarly, the reaction of β-ketoester **11b** with phenylbutynone **13c** gave only a trace of the desired pyridine product **15ca** in the absence of added catalyst (entry 7). However, despite these limitations, the reaction was successful in a number of cases for a wide variety of substrates and thus constitutes a mild method for the regiospecific synthesis of polysubstituted pyridines **15** that would appear to proceed, based upon the isolation

SCHEME 6. B-R Synthesis of Pyridine 7a[a]

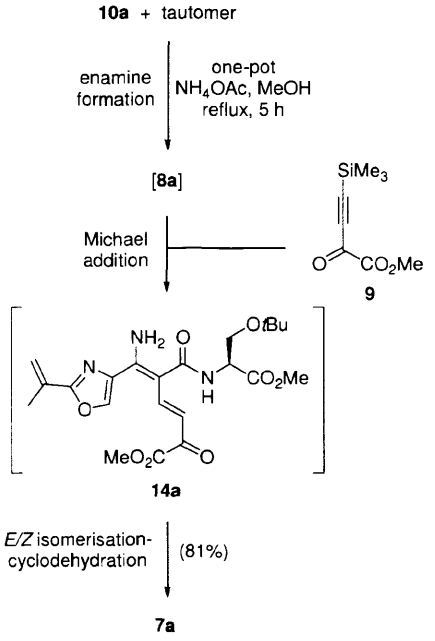


[a] Reagents and conditions: (a) ethyl bromopyruvate, $NaHCO_3$, THF (80%); (b) TFAA, 2,6-lutidine, THF (94%); (c) LiOH, MeOH, H_2O (94%); (d) EtO_2CCl, Et_3N, THF; LDA, *S*-ethyl thioacetate, THF, −78 °C (75%); (e) HCl.H-L-Ser(*t*Bu)-OMe, Et_3N, CuI, CH_2Cl_2 (83%); (f) NH_4OAc, MeOH (80%); (g) MeOH, rt, 24 h (93%).

of intermediates **12** and **14** (Scheme 3) from reactions halted prior to completion, via enamine formation and subsequent Bohlmann–Rahtz heteroannulation all in one pot.

With all of the model studies established, synthesis of dimethyl sulfomycinamate according to our disconnective scheme (Scheme 2) started from 2-methacrylamide (**24**) (Scheme 6). Oxazole **25** was produced in excellent yield via a two-step modified Hantzsch reaction with ethyl bromopyruvate, in which the condensation was per-

SCHEME 7. One-Pot Synthesis of Pyridine 7a

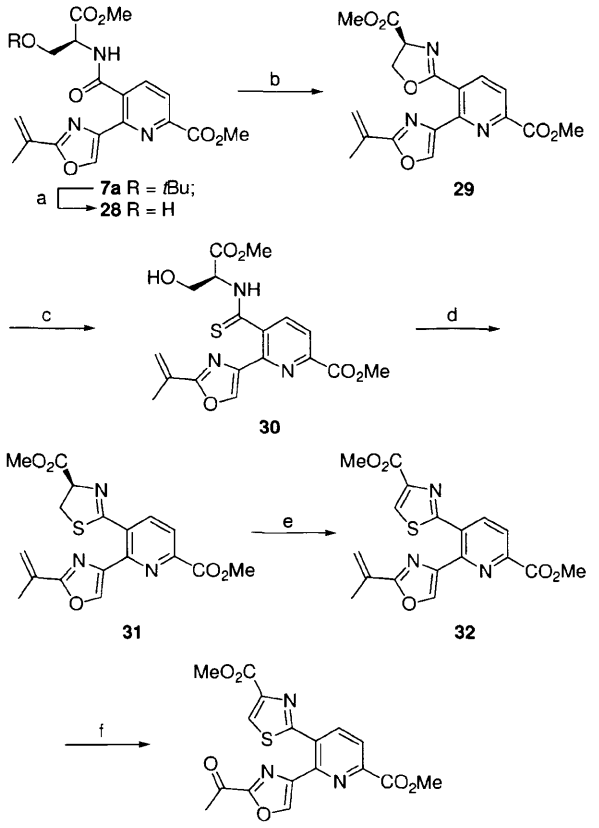


formed under basic conditions with subsequent hydroxythiazoline dehydration, using a mixture of trifluoroacetic anhydride (TFAA) and 2,6-lutidine. Saponification with lithium hydroxide in methanol–water gave carboxylic acid **26**, which was treated with ethyl chloroformate under basic conditions and homologated by reaction with the lithium enolate of *S*-ethyl thioacetate to give *S*-ethyl 3-hydroxypropenoate **27** in equilibrium with its keto tautomer. Reaction with *O*-*tert*-butyl-L-serine methyl ester hydrochloride in dichloromethane in the presence of copper(I) iodide and triethylamine generated amide **10a** as a mixture of tautomers that was heated at reflux overnight in methanol in the presence of ammonium acetate to give the Bohlmann–Rahtz precursor, enamine **8a**, in a single tautomeric form (80% yield).

The key heteroannulation reaction was first tried for comparison, using enamine **8a** in a standard Bohlmann–Rahtz reaction on the basis of the model study. Stirring a solution of enamine **8a** and methyl oxobutynoate **9** in methanol at room temperature facilitated Michael addition and spontaneous cyclodehydration even under ambient conditions to give pyridine **7a** in excellent yield (93%), as a single regioisomer. However, despite the failure of reactions of ethyl benzoyl acetate **11b** in the absence of an additional acid catalyst (Table 1, entry 7), the pyridine synthesis was improved overall by a one-pot 3-component process. Heating β-ketoamide **10a**, used as a tautomeric mixture, 2-oxobutynoate **9**, and ammonium acetate (10 equiv) at reflux in methanol for 5 h gave pyridine **7a** directly in 81% yield, presumably via enamine **8a** in a one-pot Bohlmann–Rahtz heteroannulation reaction (Scheme 7).

Elaboration of oxazole–pyridine **7a** to dimethyl sulfomycinamate (**5**) by introduction of the 3-thiazolyl substituent was first investigated in accordance with the model route. Thionation by treatment with Lawesson's reagent failed even under forcing conditions and so an alternative strategy (Scheme 8) was adopted according

SCHEME 8. Synthesis of Dimethyl Sulfomycinamate (5)[a]



[a] Reagents and conditions: (a) TFA–CH_2Cl_2 (1:1), 20 min (96%); (b) Burgess reagent, THF, 70 °C, 1 h (63%); (c) H_2S, MeOH, Et_3N (71%); (d) Burgess reagent, THF, 70 °C, 30 min (87%); (e) MnO_2, microwave, 100 °C, CH_2Cl_2, 150 min (79%); (f) OsO_4, $NaIO_4$, MeCN, dioxane, H_2O, rt, 12 h (80%).

to good literature precedent.[53] Deprotection of the *tert*-butyl ether **7a** under acidic conditions gave alcohol **28** in excellent yield (96%). Subsequent cyclization to oxazoline **29**, using Burgess reagent, was followed by thionation with hydrogen sulfide in methanol under basic conditions, to give thioamide **30**. Thiazoline **31** formation by cyclization, once again using Burgess reagent, at 70 °C and oxidation by the microwave-assisted procedure, using activated manganese dioxide at 100 °C, in accordance with the model study, gave thiazole **32**. Finally, oxidation with osmium tetroxide/sodium periodate cleaved the isopropenyl unit to give dimethyl sulfomycinamate (**5**), mp 159–161 °C (lit.[4] mp 160.5–161.0 °C) whose spectroscopic and physical properties were in agreement with literature data.[4,38]

In conclusion, methods for the totally regioselective synthesis of 2,3,6-trisubstituted and 2,3,4,6-tetrasubstituted pyridines from β-ketoesters and amides have been developed with use of a one-pot 3-component Bohlmann–Rahtz heteroannulation reaction. This facile transformation proceeds in the presence of zinc(II) bromide, acetic acid, or an immobilized sulfonic acid resin and, in some

(53) Wipf, P.; Miller, C. P.; Venkatraman, S.; Fritch, P. C. *Tetrahedron Lett.* **1995**, *36*, 6395.

cases, is effective in alcoholic solvents at reflux in the absence of any added acid catalyst. Application of this mild procedure to the heteroannulation of an acid-sensitive precursor has established the synthesis of dimethyl sulfomycinamate (**5**), the acidic methanolysis degradation product of the sulfomycin thiopeptide antibiotics, in 12 steps and 9% overall yield to complement the cross-coupling methodology of Kelly and demonstrate an alternative method to access the tris-heterocyclic core of the parent actinomycete metabolites.

Experimental Section

Lithium Enolate of *S*-Ethyl Thioacetate. To a stirred solution of DIPA (1.40 mL, 10.0 mmol) in dry THF (10 mL) was added *n*BuLi in hexanes (2.5 M; 4.00 mL, 10.0 mmol) at 0 °C. The mixture was stirred for 10 min and cooled to −65 to −70 °C. Freshly distilled *S*-ethyl thioacetate (0.53 mL, 5.0 mmol) was added and the solution was stirred for 30 min.

***S*-Ethyl Benzoylthioacetate (16) and *S*-Ethyl 3-Hydroxy-3-phenylthiopropenoate.** To a stirred solution of $PhCO_2H$ (0.61 g, 5.0 mmol) in dry THF (10 mL) was added Et_3N (1.39 mL, 10.0 mmol) followed by EtO_2CCl (0.96 mL, 10.0 mmol) at 0 °C. After the mixture was stirred for 30 min at 0 °C, the mixture was filtered and the filtrate added dropwise to a solution of the lithium enolate of *S*-ethyl thioacetate at −68 °C. The mixture was stirred for 20 min and saturated aqueous NH_4Cl solution (50 mL) was added. The resulting mixture was warmed to room temperature and extracted with EtOAc (50 mL). The organic extract was washed with brine, dried (Na_2SO_4), and evaporated in vacuo. Purification by flash chromatography on SiO_2, eluting with light petroleum−$CHCl_3$ (2:1), gave a mixture of the title compounds[54] (0.73 g, 70%) as a pale yellow oil (found: M^-, 208.0557; $C_{11}H_{12}O_2S$ requires M^-, 200.0917); IR (film) ν_{max} 3062, 2970, 2931, 2874, 1698, 1672, 1611, 1574, 1451, 1381, 1266, 1096, 1054, 911, 757, 688; ^1H NMR (400 MHz, $CDCl_3$) δ 13.16 (0.47H, s, OH), 7.88 (1.06H, m), 7.70 (0.94H, m), 7.51 (0.53H, m), 7.39 (1.41H), 7.33 (1.06H, m), 6.00 (0.47H, s), 4.13 (1.06H, s), 2.91 (0.94H, q, J = 7.4 Hz), 2.85 (1.06H, q, J = 7.4 Hz), 1.25 (1.41H, t, J = 7.4 Hz), 1.18 (1.59H, t, J = 7.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.5 (C), 193.1 (C), 192.5 (C), 169.1 (C), 136.4 (C), 134.2 (CH), 133.3 (C), 132.1 (CH), 129.3 (CH), 129.2 (CH), 129.0 (CH), 126.8 (CH), 97.7 (CH), 54.4 (CH_2), 24.5 (CH_2), 23.4 (CH_2), 15.4 (Me), 14.9 (Me); MS (APcI) *m/z* (rel intensity) 209 (MH^-, 2%), 147 (9), 105 (100).

General Procedure for CuI-Mediated Condensation of β-Keto Thioesters with H-Ser(*t*Bu)-OMe. A solution of the β-keto thioester (2.0 mmol) in dry CH_2Cl_2 (5 mL) was added to a stirred solution of Et_3N (0.56 mL, 4.0 mmol) and HCl.H-Ser(*t*Bu)-OMe (0.42 g, 2.0 mmol) in dry CH_2Cl_2 (15 mL). CuI (0.76 g, 4.0 mmol) was added and the mixture was stirred at room temperature overnight. CH_2Cl_2 (5 mL) and dilute hydrochloric acid (1 N; 5 mL) were added and the mixture was filtered. The organic filtrate was washed sequentially with dilute hydrochloric acid (1 N; 10 mL), saturated aqueous sodium hydrogen carbonate solution, and brine, dried (Na_2SO_4), and evaporated in vacuo to give the crude product.

(*S*)-β-Ketoamide 17. *S*-Ethyl benzoylthioacetate (**16**) (0.42 g, 2.0 mmol) was reacted according to the general procedure for CuI-mediated condensation with H-Ser(*t*Bu)-OMe. Purification by flash chromatography on SiO_2, eluting with CH_2Cl_2−ether (3:1), gave the title compound (0.58 g, 91%) as a colorless solid, mp 48−50 °C (methanol) (found: MH^-, 322.1652; $C_{17}H_{23}NO_5$ requires MH^-, 322.1649); $[\alpha]^{22}_D$ +28.3 (*c* 2.00, $CHCl_3$); IR (KBr) ν_{max} 2968, 1752, 1691, 1669, 1639, 1534, 1450, 1364, 1209, 1100, 1051, 1021, 774, 760, 691; ^1H NMR (400 MHz, $CDCl_3$) δ 13.89 (0.18H, s, OH), 7.94 (1.64H, m), 7.69 (0.36H, m), 7.59 (0.82H, d, J = 7.8 Hz, NH), 7.54 (0.82H, m), 7.42 (1.64H, m), 7.35 (0.54H), 6.19 (0.18H, d, J = 8.3 Hz, NH), 5.56 (0.18H, s), 4.75 (0.18H, m), 4.67 (0.82H, m), 3.97 (0.82H, d, J = 16.4 Hz), 3.91 (0.82H, d, J = 16.4 Hz), 3.80 (0.18H, dd, J = 9.1, 2.8 Hz), 3.76 (0.82H, dd, J = 9.1, 3.1 Hz), 3.70 (0.54H, s), 3.66 (2.46H, s), 3.56 (0.18H, dd, J = 9.1, 3.1 Hz), 3.51 (0.82H, dd, J = 9.1, 3.3 Hz), 1.08 (1.62H, s), 1.07 (7.38H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.0 (C), 171.6 (C), 171.0 (C), 170.7 (C), 170.0 (C), 165.8 (C), 136.2 (C), 134.1 (C), 133.9 (CH), 130.8 (CH), 128.8 (CH), 128.6 (CH), 128.4 (CH), 125.8 (CH), 88.5 (CH), 73.6 (C), 73.5 (C), 62.1 (CH_2), 61.8 (CH_2), 53.1 (CH), 52.5 (Me), 52.4 (CH), 52.4 (Me), 45.6 (CH_2), 27.3 (Me), 27.3 (Me); MS (APcI) *m/z* (rel intensity) 322 (MH^+, 23%), 266 (100).

(*S*)-Enamine 18. NH_4OAc (2.52 g, 32.7 mmol) was added to a solution of (*S*)-β-ketoamide **17** (1.05 g, 3.27 mmol) in PhMe-AcOH (5:1) (30 mL) under nitrogen and the reaction was heated at reflux overnight, using a Dean−Stark trap. After cooling to room temperature, the mixture was partitioned between EtOAc (50 mL) and saturated aqueous $NaHCO_3$ solution (50 mL) and the aqueous layer was further extracted twice with EtOAc. The combined organic extracts were washed sequentially with saturated aqueous $NaHCO_3$ solution and brine, dried (Na_2SO_4), and evaporated in vacuo. Purification by flash chromatography on SiO_2, eluting with light petroleum−EtOAc (2:1), gave the title compound (0.61 g, 58%) as a pale yellow oil (Found: MH^+, 321.1809; $C_{17}H_{24}N_2O_4$ requires MH^+, 321.1809); $[\alpha]^{23}_D$ +27.2 (*c* 1.39, $CHCl_3$); IR (KBr) ν_{max} 3433, 3307, 2972, 1747, 1627, 1554, 1499, 1364, 1343, 1196, 1090, 771, 700; ^1H NMR (400 MHz, $CDCl_3$) δ 7.47 (2H, m), 7.34 (3H), 6.52 (2H, br s), 5.90 (1H, d, J = 8.1 Hz), 4.83 (1H, s), 4.74 (1H, m), 3.78 (1H, dd, J = 8.9, 2.9 Hz), 3.68 (3H, s), 3.52 (1H, dd, J = 8.9, 3.4 Hz), 1.07 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8 (C), 169.8 (C), 158.3 (C), 138.3 (C), 129.9 (CH), 128.8 (CH), 126.1 (CH), 87.1 (CH), 73.4 (C), 62.4 (CH_2), 52.4 (CH), 52.3 (CH_3), 27.3(Me); MS (APcI) *m/z* (rel intensity) 321 (MH^+, 100%), 265 (14).

Monomethyloxalic Acid *N*-Methoxy-*N*-methylamide. Et_3N (11.4 mL, 81.6 mmol) was added dropwise over a 10-min period to a stirred solution of MeONHMe·HCl (3.98 g, 40.8 mmol) and MeO_2CCOCl (3.75 mL, 40.8 mmol) in dry CH_2Cl_2 (270 mL) at 0 °C. The mixture was stirred for 3.5 h, diluted with MeOH (5 mL), and evaporated in vacuo. THF (100 mL) was added and the solution was filtered under suction, washing with THF (2 × 100 mL), and evaporated in vacuo. Purification by distillation gave the title compound (6.47 g, 94%) as a colorless oil, bp 114−120 °C (2−3 Torr) (Found: MNH_4^-, 165.0870; $C_5H_9NO_4$ requires MNH_4^-, 165.0870); IR (film) ν_{max} 2945, 1748, 1680, 1394, 1257, 1175, 1092, 999, 962, 784; ^1H NMR (400 MHz, $CDCl_3$) δ 3.83 (3H, s), 3.70 (3H, s), 3.18 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.8 (C), 161.8 (C), 62.3 (Me), 52.6 (Me), 31.4 (Me); MS (APcI) *m/z* (rel intensity) 148 (MH^+, 57%), 147 (100), 120 (23), 88 (69).

Methyl 2-Oxo-4-(trimethylsilyl)but-3-ynoate (9). A solution of *n*BuLi in hexanes (2.5 M; 3.1 mL, 7.82 mmol) was added dropwise over 10 min to a stirred solution of TMSCCH (0.7 mL, 6.8 mmol) in dry THF (30 mL) at −78 °C. The solution was stirred for 30 min and added dropwise to a solution of monomethyloxalic acid *N*-methoxy-*N*-methylamide (1.0 g, 6.8 mmol) in dry THF (60 mL) at −78 °C. The mixture was stirred for 30 min, warmed to room temperature, and poured over ice (20 g). Aqueous orthophosphoric acid solution (20%; 30 mL) was added. The mixture was concentrated in vacuo and partitioned between H_2O (20 mL) and ether (50 mL), further extracting the aqueous layer twice with ether. The combined organic extracts were washed sequentially with aqueous orthophosphoric acid solution (10%; 20 mL), saturated aqueous sodium hydrogen carbonate solution, and brine, dried (Na_2SO_4), and evaporated in vacuo. Purification by flash chromatography on SiO_2, eluting with light petroleum−ether (5:1), gave the title compound (0.61 g, 49%) as a yellow oil (Found: M^-, 184.0545; $C_8H_{12}O_3Si$ requires M, 184.0550); IR (film) ν_{max} 2960, 2150, 1746, 1685, 1438, 1254, 1103, 850, 763; ^1H NMR

(54) Hayashi, Y.; Miyamoto, Y.; Shoji, M. *Tetrahedron Lett.* **2002**, *43*, 4079.

(400 MHz, $CDCl_3$) δ 3.71 (3H, s), 0.08 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8 (C), 159.3 (C), 107.0 (C), 100.0 (C), 53.7 (Me), −1.0 (Me); MS (EI) *m/z* (rel intensity) 184 (M^+, 3%), 169 (20), 158 (100).

(*S*)-Pyridine-3-carboxamide 20. A solution of (*S*)-enamine **18** (26 mg, 0.08 mmol) and methyl 2-oxo-4-(trimethylsilyl)but-3-ynoate (**9**) (19 mg, 0.10 mmol) in MeOH (15 mL) was stirred at room temperature for 60 h and evaporated in vacuo. Purification by flash chromatography on SiO_2, eluting with light petroleum−EtOAc (1:1), gave the title compound (32 mg, 95%) as a pale yellow oil (Found: MH^+, 415.1863; $C_{22}H_{26}N_2O_6$ requires MH^+, 415.1864); $[\alpha]^{23}_D$ +48.3 (*c* 2.83, $CHCl_3$); IR (KBr) ν_{max} 3428, 3341, 2976, 1750, 1654, 1522, 1433, 1392, 1364, 1321, 1228, 1192, 1168, 1096, 972, 859, 740, 699; ^1H NMR (400 MHz, $CDCl_3$) δ 8.09 (2H, app s), 7.66 (2H, m), 7.37 (3H), 6.28 (1H, d, J = 8.3 Hz), 4.66 (1H, m), 3.95 (3H, s), 3.64 (1H, dd, J = 9.0, 2.9 Hz), 3.63 (3H, s), 3.18 (1H, dd, J = 9.0, 3.2 Hz), 0.91 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3 (C), 167.4 (C), 165.2 (C), 156.7 (C), 148.7 (C), 138.4 (CH), 138.2 (C), 133.6 (C), 129.5 (CH), 129.2 (CH), 128.7 (CH), 123.2 (CH), 73.4 (C), 61.3 (CH_2), 53.2 (CH), 53.1 (Me), 52.5 (Me), 27.1 (Me); MS (APcI) *m/z* (rel intensity) 415 (MH^+, 100%).

General Procedure for One-Step Bohlmann−Rahtz Reactions Catalyzed by AcOH. A solution of the enamine (~1 mmol) and alkynone (1.2−2.4 equiv) in PhMe−AcOH (5:1) (5 mL) was stirred at 50 °C for 6 h. The mixture was partitioned between PhMe (30 mL) and saturated aqueous $NaHCO_3$ solution (30 mL). The aqueous layer was twice further extracted with PhMe and the combined organic extracts were washed sequentially with saturated aqueous $NaHCO_3$ solution and brine, dried (Na_2SO_4), and evaporated in vacuo to give the crude pyridine product.

General Procedure for One-Step Bohlmann−Rahtz Reactions Catalyzed by $ZnBr_2$. A solution of the enamine (~1 mmol, 1 equiv), alkynone (1.2−2.4 equiv), and $ZnBr_2$ (15−20 mol %) in PhMe (6 mL) was heated at reflux for 6 h and then allowed to cool. After the addition of H_2O (6 mL), the mixture was stirred for 20 min and extracted with EtOAc (2 × 10 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), and evaporated in vacuo to give the crude pyridine product.

(*S*)-4-(Trimethylsilyl)pyridine 19. (*S*)-Enamine **18** (65 mg, 0.20 mmol) and methyl 2-oxo-4-(trimethylsilyl)but-3-ynoate (**9**) (74 mg, 0.40 mmol) were reacted according to the general procedure for one-step Bohlmann−Rahtz reactions catalyzed by AcOH or $ZnBr_2$. Purification by flash chromatography on SiO_2, eluting with light petroleum−EtOAc (2:1), gave the title compound [24 mg, 25% for AcOH (reaction time 80 min); 62 mg, 64% for $ZnBr_2$ (reaction time 70 min)] as a pale yellow oil (Found: MH^-, 487.2257; $C_{25}H_{34}N_2O_6Si$ requires MH^-, 487.2259); $[\alpha]^{22}_D$ +51.0 (*c* 2.91, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3431, 2960, 1742, 1664, 1508, 1439, 1365, 1261, 1213, 1096, 1020, 846, 807; ^1H NMR (400 MHz, $CDCl_3$) δ 8.20 (1H, s), 7.62 (2H, m), 7.32 (3H, m), 6.12 (1H, d, J = 8.5 Hz), 4.62 (1H, m), 3.94 (3H, s), 3.55 (3H, s), 3.50 (1H, dd, J = 8.9, 2.8 Hz), 2.90 (1H, dd, J = 8.9, 3.2 Hz), 0.87 (9H, s), 0.33 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2 (C), 168.7 (C), 165.9 (C), 155.6 (C), 151.9 (C), 146.8 (C), 139.2 (C), 139.1 (C), 129.1 (CH), 129.0 (CH), 128.6 (CH), 128.5 (CH), 73.2 (C), 61.6 (CH_2), 53.1 (CH), 53.0 (Me), 52.3 (Me), 27.1 (Me), −0.6 (Me); MS (APcI) *m/z* (rel intensity) 487 (MH^-, 100%), 431 (11).

(*S*)-Pyridine 20 from Silyl Ether 19. A solution of TBAF in THF (1 M; 0.06 mL, 0.06 mmol) was added to a solution of silyl ether **19** (26 mg, 0.05 mmol) in THF (10 mL) at 0 °C. The mixture was stirred at this temperature for 2 h, concentrated in vacuo, and partitioned between H_2O (10 mL) and $CHCl_3$ (10 mL). The aqueous layer was twice further extracted with chloroform and the combined organic extracts were dried (Na_2SO_4) and evaporated in vacuo. Purification by flash chromatography on silica, eluting with light petroleum−EtOAc (1:1), gave the title compound (17 mg, 81%) as a pale yellow oil with identical physical and spectroscopic properties.

(*S*)-Thioamide 21. A solution of (*S*)-amide **20** (67 mg, 0.16 mmol) and Lawesson's reagent (52 mg, 0.13 mmol) in PhH (25 mL) was heated under reflux for 66 h. The mixture was allowed to cool, evaporated in vacuo, and purified by flash chromatography on SiO_2, eluting with light petroleum−EtOAc (4:3), to give the title compound (66 mg, 96%) as a pale yellow oil (Found: MH^+, 431.1637; $C_{22}H_{26}N_2O_5S$ requires MH^+, 431.1635); $[\alpha]^{28}_D$ +99.7 (*c* 1.52, $CHCl_3$); IR (KBr) ν_{max} 3294, 2973, 1744, 1512, 1432, 1392, 1364, 1321, 1223, 1153, 1095, 915, 848, 802, 743, 700; ^1H NMR (400 MHz, $CDCl_3$) δ 8.13 (1H, d, J = 8.0 Hz), 8.04 (1H, d, J = 8.0 Hz), 7.72 (1H, d, J = 7.9 Hz), 7.71 (2H, m), 7.35 (3H), 5.12 (1H, m), 3.95 (3H, s), 3.64 (1H, dd, J = 9.2, 2.5 Hz), 3.62 (3H, s), 3.14 (1H, dd, J = 9.2, 3.1 Hz), 0.89 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.3 (C), 169.1 (C), 165.2 (C), 154.0 (C), 148.3 (C), 140.1 (C), 139.5 (CH), 138.1 (C), 129.3 (CH), 129.0 (CH), 128.6 (CH), 123.1 (CH), 73.7 (C), 60.5 (CH_2), 58.8 (CH), 53.1 (Me), 52.7 (Me), 27.1 (Me); MS (EI) *m/z* (rel intensity) 430 (M^+, 100%).

Thiazoline 22. A solution of (*S*)-thioamide **21** (61 mg, 0.14 mmol) in TFA (10 mL) was heated under reflux for 48 h. The solution was allowed to cool and evaporated in vacuo. Purification by flash chromatography on SiO_2, eluting with light petroleum−EtOAc (2:3), gave the title compound (50 mg, 99%) as a colorless solid, mp 121−122.5 °C (MeOH); (Found: MH^+, 357.0904; $C_{18}H_{16}N_2O_4S$ requires MH^+, 357.0904); $[\alpha]^{28}_D$ +3.8 (*c* 1.05, $CHCl_3$); IR (KBr) ν_{max} 2955, 1740, 1723, 1584, 1440, 1426, 1320, 1227, 1177, 1130, 1104, 1027, 804, 749, 701; ^1H NMR (400 MHz, $CDCl_3$) δ 8.07 (2H, app s), 7.57 (2 H, m), 7.35 (3H), 5.15 (1H, app t, J = 9.1 Hz), 3.94 (3H, s), 3.73 (3H, s), 3.62 (1H, dd, J = 11.2, 8.5 Hz), 3.52 (1H, dd, J = 11.2, 9.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2 (C), 170.4 (C), 165.2 (C), 158.1 (C), 148.8 (C), 138.8 (CH), 138.1 (C), 131.4 (C), 129.6 (CH), 129.4 (CH), 128.3 (CH), 123.0 (CH), 77.8 (CH), 53.2 (Me), 53.0 (Me), 36.9 (CH_2); MS (APcI) *m/z* (rel intensity) 357 (MH^+, 100%).

Thiazole 23. A mixture of thiazoline **22** (36 mg, 0.10 mmol) and activated MnO_2 (174 mg, 2.0 mmol) in CH_2Cl_2 (3 mL) was irradiated at 100 °C (initial power 300 W) for 10 min in a sealed pressure-rated reaction tube (10 mL), using a CEM Discover Microwave Synthesizer. The mixture was cooled rapidly to room temperature in a flow of compressed air for 5 min, filtered through Celite, washed with CH_2Cl_2 (2 × 10 mL), and evaporated in vacuo to give the title compound (35 mg, 100%) as a pale yellow solid, mp 173−175 °C (MeOH) (Found: MH^+, 355.0747; $C_{18}H_{14}N_2O_4S$ requires MH^+, 355.0747); IR (KBr) ν_{max} 2962, 1719, 1262, 1096, 1023, 801; ^1H NMR (400 MHz, $CDCl_3$) δ 8.53 (1H, d, J = 8.1 Hz), 8.15 (1H, d, J = 8.1 Hz), 8.06 (1H, s), 7.41−7.32 (5H), 3.95 (3H, s), 3.91 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.3 (C), 165.1 (C), 161.7 (C), 158.2 (C), 148.2 (C), 146.8 (C), 139.3 (CH), 138.1 (C), 130.9 (C), 130.2 (CH), 130.0 (CH), 129.6 (CH), 128.9 (CH), 123.7 (CH), 53.2 (Me), 52.6 (Me); MS (APcI) *m/z* (rel intensity) 355 (MH^+, 100%).

General Procedure for Traditional Two-Step Bohlmann−Rahtz Reactions. A solution of the enamine (~1 mmol, 1 equiv) and alkynone (1.2−2.4 equiv) in EtOH (5 mL) was stirred at 50 °C for 5 h, cooled, and then evaporated in vacuo to give the dienone intermediate. The residue was heated at 140−160 °C in a flask fitted with a drying tube for 1−2 h and allowed to cool to give the crude pyridine product.

General Procedure for One-Pot 3-Component Bohlmann−Rahtz Pyridine Synthesis with Acetic Acid. NH_4OAc (10 equiv) was added to a solution of the β-ketoester **11** (~2.2 mmol, 1 equiv) and alkynone **13** (~2 equiv) in PhMe−AcOH (5:1) (12 mL). The mixture was heated at reflux for 20 h and partitioned between saturated aqueous $NaHCO_3$ solution (20 mL) and EtOAc (20 mL). The aqueous layer was twice further extracted with EtOAc and the combined organic extracts were washed sequentially with saturated aqueous $NaHCO_3$ solution and brine, dried ($MgSO_4$), and evaporated in vacuo to give the crude pyridine **15**.

General Procedure for One-Pot 3-Component Bohlmann–Rahtz Pyridine Synthesis with Zinc(II) Bromide. NH_4OAc (10 equiv) was added to a stirred solution of the β-ketoester **11** (~2.2 mmol, 1 equiv) and alkynone **13** (~2 equiv) in PhMe (12 mL) with zinc(II) bromide (20 mol %). The mixture was heated at reflux for 20 h then cooled and H_2O (6 mL) was added. After heating at reflux for a further 20 min, the solution was allowed to cool and partitioned between H_2O (20 mL) and EtOAc (20 mL). The aqueous layer was twice further extracted with EtOAc and the combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated in vacuo to give the crude pyridine **15**.

General Procedure for One-Pot 3-Component Bohlmann–Rahtz Pyridine Synthesis with Amberlyst 15 Ion-Exchange Resin. NH_4OAc (10 equiv) was added to a stirred solution of the β-ketoester **11** (~2.2 mmol, 1 equiv) and alkynone **13** (~2 equiv) in the presence of Amberlyst 15 ion-exchange resin (0.20 g). The mixture was heated at reflux for 20 h and partitioned between H_2O (20 mL) and EtOAc (20 mL). The aqueous layer was twice further extracted with EtOAc and the combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated in vacuo to give the crude pyridine **15**.

General Procedure for One-Pot 3-Component Bohlmann–Rahtz Pyridine Synthesis in Alcoholic Solvent. A solution of the β-ketoester **11** (1 mmol), alkynone **13** (0.6–3.0 mmol), and NH_4OAc (1–10 mmol) in EtOH (10 mL) was stirred at reflux for 24 h, allowed to coo, and evaporated in vacuo. The residue was partitioned between saturated aqueous $NaHCO_3$ solution (30 mL) and EtOAc (30 mL) and the aqueous layer was further extracted with EtOAc. The combined organic extracts were washed sequentially with saturated aqueous $NaHCO_3$ solution and brine, dried (Na_2SO_4), and evaporated in vacuo. Purification by column chromatography on SiO_2, eluting either with CH_2Cl_2–light petroleum (1:1) or EtOAc–light petroleum (1:3), gave pyridine **15**.

Ethyl 4-Hydroxy-2-(2-propenyl)-2-oxazoline-4-carboxylate. Ethyl bromopyruvate (0.9 mL, 7.17 mmol) was added to a stirred solution of methacrylamide (**24**) (0.5 g, 6.02 mmol) and dry $NaHCO_3$ (ground and dried in an oven at 115 °C for 2 d prior to use) (2.5 g, 29.76 mmol) in dry THF (60 mL). The mixture was heated at reflux for 18 h, filtered through Celite, and evaporated in vacuo. Purification by recrystallization (light petroleum–ether) gave the title compound as a colorless solid (0.96 g, 80%), mp 80–81 °C (EtOAc) (Found: C, 54.0; H, 6.4; N, 6.7. Calcd for $C_9H_{13}NO_4$: C, 54.3; H, 6.6; N, 7.0) (Found: MH^-, 200.0916; $C_9H_{13}NO_4$ requires *MH*, 200.0917); IR (Nujol) ν_{max} 1749, 1654, 1602, 1459, 1376, 1224, 1154, 1083, 1016, 954; ^1H NMR (400 MHz; d_4-methanol) δ 5.89 (1H, m), 5.52 (1H, m), 4.59 (1H, d, J = 10.0 Hz), 4.15 (2H, q, J = 7.1 Hz), 4.12 (1H, d, J = 10.0 Hz), 1.86 (3H, m), 1.21 (3H, t, J = 7.1 Hz); ^{13}C NMR (100 MHz; d_4-methanol) δ 170.6 (C), 168.6 (C), 132.2 (C), 123,8 (CH_2), 97.1 (C), 76.1 (CH_2), 62.0 (CH_2), 17.9 (Me), 13.0 (Me); MS (APcI) *m/z* 200 (MH^+, 100%), 182 (32).

Oxazole 25. A solution of 2,6-lutidine (8.12 mL, 77.12 mmol) and TFAA (4.73 mL, 33.49 mmol) in dry THF (10 mL) was added to a solution of ethyl 4-hydroxy-2-(2-propenyl)-2-oxazoline-4-carboxylate (5.55 g, 27.86 mmol) at 0 °C. After the solution was stirred for 30 min, H_2O (50 mL) was added and the mixture was evaporated in vacuo. Purification by flash chromatography on SiO_2, gradient eluting with light petroleum to light petroleum–EtOAc (3:1), gave the title compound as a colorless oil (5.06 g, 94%) (Found: MH^+, 182.0810; $C_9H_{11}NO_3$ requires *MH*, 182.0817); IR (film) ν_{max} 3155, 2984, 1744, 1575, 1543, 1448, 1391, 1315, 1254, 1176, 115, 982, 916, 763; ^1H NMR (400 MHz; $CDCl_3$) δ 8.12 (1H, s), 6.15 (1H, d, J = 1.4 Hz), 5.39 (1H, dd, J = 1.4, 0.9 Hz), 4.32 (2H, q, J = 7.1 Hz), 2.12 (3H, s), 1.30 (3H, t, J = 7.1 Hz); ^{13}C NMR (100 MHz; $CDCl_3$) δ 163.1 (C), 161.3 (C), 143.5 (CH), 134.2 (C), 131.1 (C), 119.9 (CH_2), 61.2 (CH_2), 19.0 (Me), 14.3 (Me); MS (EI) *m/z* 181 (M^-, 100%).

Carboxylic Acid 26. LiOH monohydrate (6.49 g, 0.155 M) was added to a solution of ethyl ester **25** (4.76 g, 26.44 mmol) in MeOH–H_2O (1:1) (100 mL). The mixture was stirred at room temperature for 2 h, concentrated in vacuo, and partitioned between H_2O (100 mL) and $CHCl_3$ (50 mL). The aqueous layer was twice further extracted with $CHCl_3$, acidified to pH 2–3 with dilute hydrochloric acid (3 N), and thrice extracted with $CHCl_3$. The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated in vacuo to give the title compound as a colorless solid (3.14 g, 78%), mp 121.5–122 °C (EtOAc) (Found: C, 54.6; H, 4.6; N, 8.9. Calcd for $C_9H_{13}NO_4$: C, 54.9; H, 4.6; N, 9.2) (Found: MH^+, 154.0498; $C_7H_7NO_3$ requires *MH*, 154.0499); IR (Nujol) ν_{max} 3136, 1691, 1562, 1462, 1377, 1260, 1186, 1124, 984, 910, 853, 766, 665; ^1H NMR (400 MHz; $CDCl_3$) δ 10.26 (1H, br s), 8.23 (1H, s), 6.00 (1H, s), 5.44 (1H, s), 2.14 (3H, s); ^{13}C NMR (100 MHz; $CDCl_3$) δ 166.1 (C), 163.5 (C), 145.0 (CH), 133.4 (C), 130.9 (C), 120.6 (CH_2), 19.0 (Me); MS (APcI) *m/z* 154 (MH^+, 100%), 136 (80).

***S*-Ethyl Thioester 27.** EtO_2CCl (0.54 mL, 5.7 mmol) was added dropwise to a stirred solution of carboxylic acid **26** (800 mg, 5.22 mmol) and Et_3N (0.80 mL, 5.7 mmol) in dry THF (11 mL) at 0 °C. After being stirred for 30 min, the mixture was filtered and cooled to −78 °C and a solution of the lithium enolate of *S*-ethyl thioacetate (0.83 mL, 7.8 mmol) in THF (16 mL) was added dropwise. The mixture was stirred at −78 °C for 30 min and partitioned between saturated aqueous NH_4Cl solution (60 mL) and EtOAc (60 mL). The organic extract was washed with brine, dried (Na_2SO_4), and evaporated in vacuo. Purification by flash chromatography on SiO_2, eluting with CH_2Cl_2, gave a mixture of the title compounds (0.94 g, 75%) as a pale yellow oil (Found: MH^+, 240.0688; $C_{11}H_{13}NO_3S$ requires MH^-, 240.0689); IR (KBr) ν_{max} 2966, 2925, 1704, 1648, 1589, 1538, 1452, 1408, 1330, 1246, 1120, 1080, 775, 722; ^1H NMR (400 MHz; $CDCl_3$) δ 12.54 (0.65H, s, OH), 8.15 (0.35H, s), 7.93 (0.65H, s), 6.20 (0.65H, s), 5.94 (0.35H, s), 5.91 (0.65H, s), 5.40 (0.35H, s), 5.37 (0.65H, s), 4.10 (0.70H, s), 2.90 (1.30H, q, J = 7.4 Hz), 2.86 (0.70H, q, J = 7.4 Hz), 2.09 (3H, s), 1.24 (1.95H, t, J = 7.4 Hz), 1.19 (1.05H, t, J = 7.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.5 (C), 192.0 (C), 186.9 (C), 163.0 (C), 162.8 (C), 161.0 (C), 142.8 (CH), 140.7 (C), 139.7 (CH), 136.6 (C), 131.2 (C), 131.0 (C), 120.1 (CH_2), 119.6 (CH_2), 98.3 (CH), 54.5 (CH_2), 24.0 (CH_2), 22.9 (CH_2), 18.91 (Me), 18.88 (Me), 14.8 (Me), 14.5 (Me); MS (APcI) *m/z* 240 (MH^+, 100%), 210 (44).

(*S*)-Serine Methyl Ester 10a. A solution of *S*-ethyl thioester **27** (274 mg, 1.14 mmol) in dry CH_2Cl_2 (5 mL) was added to a stirred solution of Et_3N (0.32 mL, 2.29 mmol) and HCl·H-L-Ser(*t*Bu)-OMe (242 mg, 1.14 mmol) in dry CH_2Cl_2 (15 mL). CuI (485 mg, 2.29 mmol) was added and the mixture was stirred at room temperature overnight. After being partitioned between CH_2Cl_2 (5 mL) and dilute hydrochloric acid (1 N; 5 mL), the mixture was filtered. The organic extract was washed sequentially with dilute hydrochloric acid (1 N), saturated aqueous $NaHCO_3$ solution, and brine, dried (Na_2SO_4), and evaporated in vacuo. Purification by flash column chromatography on SiO_2, eluting with light petroleum–EtOAc (4:1), gave a mixture of the title compounds (0.33 g, 83%) as a pale yellow oil (Found: MH^+, 353.1701; $C_{17}H_{24}N_2O_6$ requires MH^+, 353.1707); $[\alpha]^{24}_D$ +41.7 (*c* 1.1, $CHCl_3$); IR (KBr) ν_{max} 3366, 2971, 1750, 1694, 1661, 1609, 1549, 1438, 1364, 1248, 1204, 1093, 1054, 1020, 915, 812, 780, 737; ^1H NMR (400 MHz; $CDCl_3$) δ 13.36 (0.36H, s, OH), 8.24 (0.64H, s), 7.87 (0.36H, s), 7.72 (0.64H, d, J = 8.2 Hz), 6.42 (0.36H, d, J = 8.5 Hz), 5.95 (0.64H, s), 5.90 (0.36H, s), 5.79 (0.36H, s), 5.42 (0.64H, s), 5.35 (0.36H, s), 4.71 (0.36H, m), 4.66 (0.64H, m), 3.93 (0.64H, d, J = 15.6 Hz), 3.89 (0.64H, d, J = 15.6 Hz), 3.78 (0.36H, dd, J = 8.9, 2.9 Hz), 3.74 (0.64H, dd, J = 9.1, 3.0 Hz), 3.68 (1.08H, s), 3.65 (1.92H, s), 3.54 (0.36H, dd, J = 8.9, 3.2 Hz), 3.49 (0.64H, dd, J = 9.1, 3.2 Hz), 2.11 (1.92H, s), 2.08 (1.08H, s), 1.06 (1.08H, s), 1.04 (1.92H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.8 (C), 171.3 (C), 170.8 (C), 170.6 (C), 165.2 (C), 162.8 (C), 162.7 (C), 162.2 (C), 143.2 (CH), 140.7 (C), 138.1 (CH), 137.4 (C), 131.2 (C), 130.9 (C), 120.2 (CH_2), 119.2 (CH_2), 89.9 (CH), 73.4 (C),

73.3 (C), 61.9 (CH_2), 61.8 (CH_2), 53.1 (CH), 52.4 (Me), 52.3 (Me), 52.3 (CH), 47.0 (CH_2), 27.2 (Me), 27.2 (Me), 18.9 (Me), 18.8 (Me); MS (APcI) *m/z* 353 (MH^+, 44%), 297 (100), 279 (12), 120 (37).

(*S*)-Enamine 8a. NH_4OAc (293 mg, 3.8 mmol) was added to a stirred solution of **10a** (269 mg, 0.76 mmol) in dry MeOH (15 mL) under N_2. After being heated at reflux overnight, the reaction mixture was cooled to room temperature and evaporated in vacuo. The residue was partitioned between EtOAc (30 mL) and H_2O (30 mL) and the aqueous layer further extracted with EtOAc. The combined organic extracts were washed sequentially with saturated aqueous $NaHCO_3$ solution and brine, dried (Na_2SO_4), and evaporated in vacuo. Purification by flash chromatography on SiO_2, eluting with light petroleum–EtOAc (1:1), gave the title compound (214 mg, 80%) as a pale yellow oil (Found: MH^+, 352.1871; $C_{17}H_{25}N_3O_5$ requires MH^+, 352.1867); $[\alpha]^{24}_D$ +51.2 (*c* 1.0, $CHCl_3$); IR (KBr) ν_{max} 3452, 3324, 2974, 1748, 1644, 1598, 1540, 1363, 1198, 1098, 1050, 1021, 976, 913, 778; ^1H NMR (400 MHz; $CDCl_3$) δ 7.79 (1H, s), 6.82 (2H, br s), 5.90 (1H, s), 5.89 (1H, d, J = 8.5 Hz), 5.36 (1H, s), 5.00 (1H, s), 4.72 (1H, m), 3.78 (1H, dd, J = 8.9, 2.9 Hz), 3.68 (3H, s), 3.51 (1H, dd, J = 8.9, 3.2 Hz), 2.10 (3H, s), 1.08 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8 (C), 169.8 (C), 162.6 (C), 147.8 (C), 138.6 (C), 135.5 (CH), 131.3 (C), 119.1 (CH_2), 84.2 (CH), 73.4 (C), 62.4 (CH_2), 52.34 (CH), 52.30 (Me), 27.3 (Me), 19.0 (Me); MS (APcI) *m/z* 353 (100%), 352 (MH^+, 67).

(*S*)-Pyridine 7a from Enamine 8a. A solution of (*S*)-enamine **8a** (88 mg, 0.25 mmol) and methyl 2-oxo-4-(trimethylsilyl)but-3-ynoate (**9**) (61 mg, 0.33 mmol) in MeOH (10 mL) was stirred at room temperature for 24 h and evaporated in vacuo. Purification by flash chromatography on SiO_2, eluting with light petroleum–EtOAc (1:2), gave the title compound (104 mg, 93%) as a pale yellow oil (Found: MH^+, 446.1925; $C_{22}H_{27}N_3O_7$ requires MH^+, 446.1927); $[\alpha]^{29}_D$ +12.0 (*c* 1.8, $CHCl_3$); IR (KBr) ν_{max} 2966, 1751, 1670, 1540, 1436, 1364, 1323, 1262, 1099, 801, 760; ^1H NMR (400 MHz; $CDCl_3$) δ 8.18 (1H, s), 8.05 (1H, d, J = 8.0 Hz), 8.01 (1H, d, J = 8.0 Hz), 7.00 (1H, d, J = 8.0 Hz), 5.93 (1H, s), 5.35 (1H, s), 4.85 (1H, m), 3.95 (3H, s), 3.80 (1H, dd, J = 9.1, 3.0 Hz), 3.69 (3H, s), 3.57 (1H, dd, J = 9.1, 3.2 Hz), 2.10 (3H, s), 1.01 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5 (C), 167.0 (C), 165.0 (C), 162.6 (C), 148.5 (C), 147.5 (C), 139.5 (C), 139.0 (CH), 138.1 (CH), 133.3 (C), 131.4 (C), 123.6 (CH), 119.0 (CH_2), 73.6 (C), 61.8 (CH_2), 53.5 (CH), 53.1 (Me), 52.5 (Me), 27.2 (Me), 19.0 (Me); MS (APcI) *m/z* 446 (MH^+, 100%).

(*S*)-Pyridine 7a from β-Ketoester 10a. A solution of (*S*)-β-ketoester **10a** (35 mg, 0.1 mmol), methyl 2-oxo-4-(trimethylsilyl)but-3-ynoate (**9**) (49 mg, 0.25 mmol), and NH_4OAc (77 mg, 1.0 mmol) in MeOH (10 mL) was stirred at reflux for 5 h. After cooling, the mixture was evaporated in vacuo. The residue was partitioned between saturated aqueous $NaHCO_3$ solution (5 mL) and EtOAc (8 mL) and the aqueous layer was further extracted with EtOAc. The combined organic extracts were washed sequentially with saturated aqueous $NaHCO_3$ solution and brine, dried (Na_2SO_4), and evaporated in vacuo. Purification by column chromatography on SiO_2, eluting with EtOAc–light petroleum (2:1), gave the title compound (36 mg, 81%) as a pale yellow oil with identical physical and spectroscopic properties.

(*S*)-Alcohol 28. A solution of pyridine **7a** (60 mg, 0.14 mmol) in TFA–CH_2Cl_2 (1:1) (20 mL) was stirred at room temperature for 20 min and evaporated in vacuo. Purification by flash column chromatography on SiO_2, eluting with EtOAc, gave the title compound (50 mg, 96%) as colorless crystals, mp 74–76 °C (aqueous EtOH) (Found: MH^+, 390.1301; $C_{18}H_{19}N_3O_7$ requires MH^+, 390.1296); $[\alpha]^{25}_D$ −8.8 (*c* 0.5, $CHCl_3$); IR (KBr) ν_{max} 3439, 2954, 1734, 1654, 1542, 1438, 1323, 1293, 1234, 1174, 1140, 760; ^1H NMR (400 MHz; $CDCl_3$) δ 8.22 (1H, s), 7.89 (1H, d, J = 7.9 Hz), 7.84 (1H, d, J = 7.9 Hz), 7.50 (1H, d, J = 7.1 Hz), 5.89 (1H, s), 5.35 (1H, s), 4.70 (1H, m), 4.32 (1H, br s), 4.01 (1H, dd, J = 8.2, 3.1 Hz), 3.94 (1H, dd, J = 8.2, 3.7 Hz), 3.91 (3H, s), 3.68 (3H, s), 2.05 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5 (C), 167.6 (C), 164.9 (C), 162.8 (C), 148.0 (C), 147.2 (C), 142.2 (C), 139.7 (CH), 137.8 (CH), 132.8 (C), 131.0 (C), 123.5 (CH), 119.9 (CH_2), 62.2 (CH_2), 55.6 (CH), 53.2 (Me), 52.8 (Me), 18.9 (Me); MS (APcI) *m/z* 390 (MH^+, 100%).

(*S*)-Oxazoline 29. A solution of (*S*)-alcohol **28** (41 mg, 0.10 mmol) and Burgess reagent (28 mg, 0.11 mmol) in dry THF (5 mL) was stirred at 70 °C for 1 h and evaporated in vacuo. Purification by flash chromatography on SiO_2, eluting with EtOAc–light petroleum (2:1), gave the title compound (24 mg, 63%) as a pale yellow oil (Found: MH^+, 372.1191; $C_{18}H_{17}N_3O_6$ requires MH^+, 372.1191); $[\alpha]^{29}_D$ +29.1 (*c* 0.87, $CHCl_3$); IR (KBr) ν_{max} 2956, 1741, 1654, 1437, 1325, 1286, 1228, 1139, 1052, 958, 762; ^1H NMR (400 MHz, $CDCl_3$) δ 8.25 (1H, s), 8.06 (1H, d, J = 8.0 Hz), 8.01 (1H, d, J = 8.0 Hz), 5.93 (1H, s), 5.36 (1H, s), 4.94 (1 H, dd, J = 10.7, 8.6 Hz), 4.64 (1H, app t, J = 8.6 Hz), 4.57 (1H, dd, J = 10.7, 8.6 Hz), 3.95 (3H, s), 3.77 (3H, s), 2.11 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2 (C), 165.9 (C), 164.9 (C), 162.3 (C), 149.6 (C), 149.0 (C), 140.2 (C), 139.8 (CH), 139.1 (CH), 131.3 (C), 124.9 (C), 123.1 (CH), 118.8 (CH_2), 70.3 (CH_2), 68.8 (CH), 53.1 (Me), 52.8 (Me), 19.0 (Me); MS (APcI) *m/z* (rel intensity) 372 (MH^+, 100%).

(*S*)-Thioamide 30. A solution of oxazoline **29** (23 mg, 0.06 mmol) in MeOH–Et_3N (2:1) (3 mL) was saturated with H_2S, stirred at room temperature for 3.5 h, and evaporated in vacuo. Purification by flash chromatography on SiO_2, eluting with ether–acetone (5:1), gave the title compound (17 mg, 71%) as a pale yellow oil (Found: MH^+, 406.1062; $C_{18}H_{19}N_3O_6S$ requires MH^+, 406.1067); $[\alpha]^{20}_D$ −29.6 (*c* 0.90, $CHCl_3$); IR (KBr) ν_{max} 3400, 2956, 1736, 1542, 1437, 1388, 1293, 1262, 1232, 1140, 1087, 1027, 802, 761; ^1H NMR (400 MHz, $CDCl_3$) δ 9.18 (1H, d, J = 6.1 Hz), 8.31 (1H, s), 7.91 (1H, d, J = 8.0 Hz), 7.81 (1H, d, J = 8.0 Hz), 5.89 (1H, s), 5.37 (1H, s), 5.18 (1H, m), 4.34 (1H, dd, J = 11.9, 3.2 Hz), 4.05 (1H, dd, J = 11.9, 2.9 Hz), 3.93 (3H, s), 3.83 (1H, br s), 3.77 (3H, s), 2.04 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.9 (C), 169.6 (C), 164.9 (C), 162.7 (C), 146.7 (C), 144.8 (C), 140.2 (CH), 139.7 (C), 138.5 (C), 137.7 (CH), 130.8 (C), 123.3 (CH), 120.1 (CH_2), 61.2 (CH_2), 61.0 (CH), 53.2 (Me), 52.9 (Me), 18.9 (Me); MS (APcI) *m/z* (rel intensity) 406 (MH^+, 87%), 181 (68), 130 (100).

(*R*)-Thiazoline 31. A solution of thioamide **30** (33 mg, 0.08 mmol) and Burgess reagent (24 mg, 0.10 mmol) in dry THF (5 mL) was stirred at 70 °C for 30 min and evaporated in vacuo. Purification by flash chromatography on SiO_2, eluting with EtOAc, gave the title compound (27 mg, 87%) as a pale yellow oil (Found: MH^+, 388.0962; $C_{18}H_{17}N_3O_5S$ requires MH^+, 388.0962); $[\alpha]^{23}_D$ +18.4 (*c* 1.06, $CHCl_3$); IR (KBr) ν_{max} 2952, 1742, 1618, 1436, 1323, 1281, 1227, 1137, 931, 851, 759; ^1H NMR (400 MHz, $CDCl_3$) δ 8.16 (1H, s), 8.02 (1H, d, J = 8.0 Hz), 7.91 (1H, d, J = 8.0 Hz), 5.92 (1H, s), 5.35 (1H, s), 5.21 (1H, app t, J = 9.7 Hz), 3.95 (3H, s), 3.77 (3H, s), 3.77 (1H, dd, J = 11.2, 9.7 Hz), 3.67 (1H, dd, J = 11.2, 9.7 Hz), 2.12 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8 (C), 169.6 (C), 165.0 (C), 162.4 (C), 148.6 (C), 148.5 (C), 139.4 (C), 139.3 (CH), 138.6 (CH), 131.4 (C), 130.8 (C), 123.2 (CH), 78.6 (CH), 53.1 (Me), 53.0 (Me), 37.0 (CH_2), 19.1 (Me); MS (APcI) *m/z* (rel intensity) 388 (MH^+, 100%).

Thiazole 32. A mixture of thiazoline **31** (27 mg, 0.07 mmol) and activated MnO_2 (121 mg, 1.39 mmol) in CH_2Cl_2 (3 mL) was irradiated at 100 °C (initial power 300 W) for 150 min in a sealed pressure-rated reaction tube (10 mL), using a CEM Discover Microwave Synthesizer. The mixture was cooled rapidly to room temperature in a flow of compressed air for 5 min, filtered through Celite, washed with CH_2Cl_2 (2 × 10 mL), and evaporated in vacuo. Purification by flash chromatography on SiO_2, eluting with EtOAc–light petroleum (2:1), gave the title compound (21 mg, 79%) as a pale yellow oil (Found: MH^+, 386.0812; $C_{18}H_{15}N_3O_5S$ requires MH^+, 386.0805); IR (KBr) ν_{max} 2956, 2919, 1724, 1560, 1542, 1438, 1322, 1229, 1139, 1087, 761; ^1H NMR (400 MHz, $CDCl_3$) δ 8.27 (1H, s), 8.20 (1H, d, J = 8.0 Hz), 8.10 (1H, d, J = 8.0 Hz), 7.96 (1H, s), 5.83 (1H, s),

5.30 (1H, s), 3.97 (3H, s), 3.91 (3H, s), 1.95 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.0 (C), 164.6 (C), 162.3 (C), 161.7 (C), 149.2 (C), 148.6 (C), 146.9 (C), 140.0 (CH), 139.3 (C), 139.1 (CH), 131.3 (C), 130.7 (C), 129.8 (CH), 123.6 (CH), 118.8 (CH_2), 53.2 (Me), 52.7 (Me), 18.9 (Me); MS (APcI) *m/z* (rel intensity) 386 (MH^-, 100%).

Dimethyl Sulfomycinamate (5). A solution of OsO_4 (1.2 mg, 4.7 μmol) in MeCN (60 μL) was added to a solution of alkene **32** (16 mg, 0.04 mmol) in dioxane–H_2O (1:1) (8 mL). Sodium periodate (17 mg, 0.08 mmol) was added and the mixture was stirred at room temperature overnight. After extracting twice with CH_2Cl_2, the combined organic extracts were washed sequentially with saturated aqueous $NaHCO_3$ solution, H_2O, and brine, dried (Na_2SO_4), and evaporated in vacuo. Purification by flash chromatography on SiO_2, eluting with EtOAc–light petroleum (2:1), gave the title compound (12 mg, 80%) as colorless crystals, mp 159.0–161.0 °C (ether–hexane) (lit.[4] mp 160.5–161.0 °C) (lit.[38] mp 157.3–160.2 °C) (Found: MH^-, 388.0604; $C_{17}H_{13}N_3O_6S$ requires MH^-, 388.0595); IR (KBr) ν_{max} 3150, 2954, 1728, 1702, 1573, 1534, 1477, 1435, 1373, 1338, 1316, 1219, 1128, 1096, 1005, 963, 869, 842, 768; ^{1}H NMR (400 MHz; $CDCl_3$) δ 8.33 (1H, s), 8.31 (1H, s), 8.16 (2H, app s), 3.98 (3H, s), 3.91 (3H, s), 2.41 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 185.6 (C), 164.7 (C), 164.2 (C), 161.6 (C), 157.0 (C), 148.8 (C), 148.0 (C), 147.2 (C), 142.7 (CH), 140.4 (CH), 140.3 (C), 130.7 (C), 129.7 (CH), 124.2 (CH), 53.3 (Me), 52.8 (Me), 26.6 (Me); MS (APcI) *m/z* 388 (MH^+, 100%).

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Supporting Information Available: Experimental procedures, characterization data for pyridines **15**, and ^{1}H NMR spectra for the synthesis of dimethyl sulfomycinamate (**5**). This material is available free of charge via the Internet at http://pubs.acs.org.

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REFERENCES

REFERENCES

[1] Anderson, T. *Trans. R. Soc. Edinb. I* **1849**, 16, 123.

[2] Dobbin, L, *J. Chem. Educ.*, **1934**, *11*, 596.

[3] Baeyer, *Ber.*, **1869**, *2*, 398.

[4] Baeyer, *Ann.*, **1870**, *155*, 281.

[5] Ramsey W, *Philos. Mag.*, **1876**, *2*, 269.

[6] Koehn C. J.; Elvehjem C.A. **1937**, *J. Bio. Chem.*, **118**, *3*: 693.

[7] Fahanullah; Agatwal, N.; Goel, A.; Ram, V. J. *J. Org. Chem.*, **2003**, *68*, 2983.

[8] Matocsy, G. *Pesticide Chemistry*; Elsevier Scientific; Amsterdam Oxford, **1998**, 427.

[9] Henkel, T.; Brunne, R. M.; Müller, H.; Reichel, F. *Angew. Chem., Int. Ed. Engl.*, **1999**, *38*, 643.

[10] Petrich, S. A.; Hicks. F. A.; Wilkinson, D. R.; Tarrant J. G.; Bruno, S. M. ; Vargas, M. ; Hosein, K. N.; Gupton, J. T.; Sikorski, J. *Tetrahedron.* **1995**, *51*, 1575.

[11] Alvares–Insúla, A. S.; Lora–Tamayo, M.; Soto, J. L. *Synthesis of Organic Compounds II*, **1970**, 1308.

[12] Shi, F.; Tu, S.; Fang, F.; Li, T. *ARKIVOC*, **2005**, 137.

[13] Zhou, W. J.; Ji, S. J.; Shen, Z. L. *J. Organomet. Chem.*, **2006**, 1356.

[14] Roth, H. J.; Kleemann, A. In *Pharmaceutical Chemistry. Volume 1: Drug Synthesis*; John Wiley & Sons: New York, **1988**.

[15] (a) Meyer. *J. prakt. Chem.*, **1908**, *78*, 497. (b) Meyer. *J. prakt. Chem.*, **1915**, *90*, 1. (c) Meyer. *J. prakt. Chem.*, **1915**, *92*, 174.

[16] Harris; Stiller; Folkers. *J. Am. Chem. Soc.*, **1939**, *61*, 1242.

[17] Wenner; Platti. *J. Org. Chem.*, **1946**, *11*, 751.

[18] (a) Little. E. L.; Middleton, W. J.; Coffman, D. D.; Englehardt, V. A.; Sausen, G. N. *J. Am. Chem Soc.* **1958**, *80*, 3832. (b) Cottis, S. G.; Tieckelmann, H. *J. Org. Chem.*, **1961**, *26*, 79.

[19] Alvares–Insúla; Lora–Tamayo; Soto. *Synthesis of Heterocyclics II.* **1970**, *7*, 1305.

[20] (a) Gupton, J.; Krolikowski. D.; Yu, R.; Riesinger, S.; Sikorski, J. *J. Org. Chem.*, **1990**, 55, 4735. (b) Gupton, J.; Krolikowski. D.; Yu, R.; Sikorski, J.; Dahl. M.; Jones, C. *J. Org. Chem.* **1992**, 57, 5480.

[21] Jutz, C.; Lobering, H.–G.; Trinkl, K.–H. *Synthesis*, **1977**, 326.

[22] Chatterjea, J. N. *J. Indian. Chem. Soc.*, **1952**, 29, 323.

[23] Matsui, M.; Oji, A.; Hiramatsu, K.; Shibata, K.; Maramatsu, H. *J. Chem. Soc., Perkin Trans. 2.* **1992**, *2*, 201.

[24] Reviews on microwave chemistry include: (a) Gabriel, C.; Gabriel, S.; Grant, E. H.; Halstead, B. S. J.; Mingos, D. M. P. *Chem. Soc. Rev.,* **1998**, *27*, 213; (b) Kuhnert, N. *Angew. Chem. Int. Ed.*, **2002**, *41*, 1863; (c) Lidström, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron.* **2001**, *57*, 9225; (d) Loupy, A.; Petit, A.; Hamelin, J.; Texier-Boullet, F.; Jacquault, P.; Mathé, D. *Synthesis.* **1998**, 1213; (e) Galema, S. A. *Chem. Soc. Rev.*, **1997**, *26*, 233; (f) Caddick, S. *Tetrahedron.* **1995**, *51*, 10403; (g) Strauss, C. R.; Trainor, R. W. *Aust. J. Chem.*, **1995**, *48*, 1665.

[25] Paul, S.; Gupta, R.; Loupy, A. *J. Chem. Research.* **1998**, S, 330.

[26] Dombrowski. K. E.; Baldwin, W.; Sheats, J. *J. Organomet. Chem.*, **1986**, 302, 281.

[27] Zhou, W. J.; Ji, S. J.; Shen, Z. L. *J. Organomet. Chem.*, **2006**, 691, 1356.

[28] (a) Pandya, S.; Yu, J.; Parker, D. *Dalton Trans.*, **2006**, 2757. (b) Gunnlaugsson, T.; Stomeo, F. *Org. Biomol. Chem.*, **2007**, *5*, 1999. (c) Bunzli, J-C.G.; Piguet, C. *Chem. Soc. Rev.*, **2005**, *34*, 1048. (d) Gunnlaugsson, T.; Leonard, J.P. *Chem. Commun.*, **2005**, 3114. (e) Chauvin, A-S.; Vandevyer, C.; Comby S.; Bunzli, J-C. G. *Chem. Commun.*, **2007**, 1716. (f) Parker, D.; Pal, R. *Chem. Commun.,* **2007**, 474. (g) Faulkner S.; Pope, S.J.A.; Burton-Pye, B.P. *Appl. Spectrosc. Rev.*, **2005**, *40*, 1.

[29] Bowman, M. D.; Jacobsen, M. M.; Blackwell, H. E. *Org. Lett.*, **2006**, 8, 1645.

[30] Raghukumar, V.; Thirumalai, D.; Ramakrishnan, V. T.; Karunakara, V.; Ramamurthy, P. *Tetrahedron.* **2003**, *59*, 3761.

[31] Bowman, M. D.; Neill, J. O.; Sringer, J. S.; Blackwell, H. E.*Chem. & Biol.*, **2007**, 14, 351.

[32] Bashkin, J. K.; Xie, J.; Daniher, A. T. ; Sampath, U. ; Kao, J. L.-F. *J. Org. Chem.*, **1996**, *61*, 2314.

[33] Sun, L. C.; Hammarstrom, L.; Åkermark, B.; Styring, S. *Chem. Soc. Rev.*, **2001**, *30*, 36; (b) Kleverlaan. C. J.; Indelli, M. T.; Bignozzi, C. A.; Pavanin, L.; Scandola, F.; Hasselman, G. M.; Meyer, G. J. *J. Am. Chem. Soc.*, **2001**, *122*, 2840.

[34] Kleverlaan. C. J.; Indelli, M. T.; Bignozzi, C. A.; Pavanin, L.; Scandola, F.; Hasselman, G. M.; Meyer, G. J. *J. Am. Chem. Soc.,* **2001**, *122*, 2840.

[35] Demas, J. M.; DeGra, B. A. *Coord. Chem. Rev.,* **2001**, *211*, 317.

[36] Sauvage, J. P.; Collin, J. P.; Chambron, J.C.; Guillerez, S.; Coudret, C.; Balzani, V.; Barigelletti, F.; De Cola, L.; Flamigni, L. *Chem. Rev.,* **1994**, *94*, 993.

[37] Kozhevnikov, V. N.; Kozhevnikov , D. N.; Nikitina, T. V.; Rusinov, V. L.; Chupakhin, O. L.; Zabel, M.; Konig, B. *J. Org. Chem.,* **2003**, *68*, 2882.

[38] (a) Morgan, G. T.; Burstall, F. H. *J. Chem. Soc.*, **1932**, 20. (b) Burstall, F. H. *J. Chem. Soc.*, **1938**, 1662.

[39] Blau, F. *Monatsh. Chem.,* **1888**, *10*, 375.

[40] Hein; Schwelder. *Ber.*, **1935**, *68*, 681.

[41] Krönke, F.; *Synthesis*. **1976**, 1.

[42] Cordaro, J. G.; McCusker J. K.; Bergmann, R. G. *Chem. Comm.*, **2002**, 1496.

[43] Cave, G. W. V.; Raston, C. L. *J. Chem. Soc., Perkin Trans. 1* **2001**, 3258.

[44] Hedge, V.; Jahng, Y.; Thummel, R. P. *Tetrahedron Lett.* **1987**, 4023.

[45] Wang, J; Hanan, G. S. *Synlett.* **2005**, 8, 1251.

[46] Wang, J; Hanan, G. S. *Chem. Comm.*, **2002**, 3931.

[47] Tu, S.; Jia, R.; Jiang, B.; Zhang, J.; Zhang, Y.; Yao, C.; Ji, S. *Tetrahedron.* **2007**, 63, 381.

[48] Christopoulus, T. K. *Anal. Chem.* **1990**, 62, 1149A.

[49] Kozhevnikov, V. N.; Kozhevnikov, D. N.; Rusinov, V. L.; Chupakhin, O. N.; König, B. *Synthesis*. **2003**, 15, 2400.

[50] (a) Bashkin, J. K.; Xie, J.; Daniher, A. T.; Sampath, U.; Kao, J. L. –F. *J. Chem. Soc.*, **1996**, *61*, 2314. (b) Putman, W. C.; Daniher, A. T.; Tranwick, B. N.; Bashkin, J. K. *Nucleic Acids Res.,* **2001**, *29*, 2199. (c) Tranwick, B. N.; Osiek, T. A.; Bashkin, J. K. *Bioconjugate Chem*, **2001**, *12*, 900

[51] Hantzsch, A, *Liebigs Ann. Chem.*, **1882**, *215*, 1.

[52] Katritzky, A. R.; Rees, C. W. *Comp. Heterocycl. Chem.*, **1984**, 398.

[53] Joule, J.; Smith, G.; Mills, K. *Heterocyclic Chemistry.*3rd Ed. Chapman and Hall **1995**, 72.

[54] Nozaki, H.; Fujita, S.; Mori, T. *Bull. Chem. Soc. Jpn.*, **1969,** *42*, 1163.

[55] Bohlmann, F.; Rahtz, D, *Chem. Ber.* **1957**, 90, 2265.

[56] Bagley, M. C.; Brace, C.; Dale, J. W.; Ohnesorge, M.; Phillips, N. G.; Xiong, X.; Bower, J. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1663.

[57] Bagley, M. C.; Dale, J. W.; Bower, J. *Synlett.* **2001**, 1149.

[58] Baraldi, P. G.; Simoni, D.; Manfredini, S. *Synthesis.* **1983**, 902.

[59] Bagley, M. C.; Dale, J. W.; Bower, J. *J. Chem. Comm.*, **2002**, 1682.

[60] Bagley, M. C.; Hughes, D. D.; Sabo, H. M.; Taylor, P. H.; Xiong, X. *Synlett.* **2003**, 1443.

[61] Agami, C.; Dechoux, L.; Hebbe, S. *Synlett.* **2001**, 1440.

[62] Agami, C.; Dechoux, L.; Hamon, L.; Hebbe, S. *Synthesis*. **2003**, 859.

[63] Agami, C.; Dechoux, L.; Hebbe, S.; Moulinas, J. *Synlett.* **2002**, 79.

[64] Bagley, M. C.; Glover, C.; Merrit, E.; Xiong, X. *Synlett.* **2004**, 811.

[65] Bagley, C. M.; Glover, C.; Chevis, D. *Synlett.* **2005**, 649.

[66] Gabriel, C.; Gabriel, S.; Grant, E. H.; Halstead, B. S. J.; Mingos, D. M. P. *Chem. Soc. Rev.*, **1998**, *27*, 213.

[67] Collins, J. M.; Leadbeater, N. E. *Org. Biomol. Chem.*, **2007,** *5*, 1141.

[68] Bagley, M. C.; Lunn, R.; Xiong, X.; *Tetrahedron Lett.*, **2002**, *43*, 8331.

[69] Raner, K. D.; Strauss, C. R.; Trainor, R. W.; Thorn. J. S. *J. Org. Chem.*, **1995**, *60*, 2456.

[70] http://www.cemsynthesis.com.

[71] Bagley, M. C.; Jenkins, R. L.; Lubinu, M. C.; Mason, C.; Wood, R. *J. Org. Chem.*, **2005**, *70*, 7003.

[72] Bagley, M. C.; Dale, J. W.; Ohnesroge, M.; Xiong, X.; Bower, J. *J. Chem. Comm.*, **2003**, *5*, 41.

[73] (a) Gilchrist, T. L. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2849; (b) Gilchrist, T. L. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2491.

[74] (a) Bouras, A.; Boggetto, N.; Benatalah, Z.; de Rosny, E.; Sicsic, S.; Reboud–Ravaux, M. *J. Med. Chem.,* **1999**, *42*, 957; (b) Phillips, G.; Davey, D. D.; Eagen, K. A.; Koovakkat, S. E.; Liang, A.; Ng, H. P.; Pinkerton, M.; Trinh, L.; Whitlow, M,; Beatty, A. M.; Morrissey, M. M.; *J. Med. Chem.,* **1999**, *42*, 1749.

[75] SU, T. L.: Micrococcin. An antibacterial substance formed by a strain of Micrococcus. Brit. J Exptl. Path. 1948, *29*, 473.

[76] Vandeputte, J.; Dutcher, J. D. *Antibiot. Ann.*, **1956**, 560.

[77] Steinberg, B. A.; Jambor, W. P.; Snydam, L. O. *Antibiot. Ann.*, **1956**, 562.

[78] Bagley, M. C.; Dale, J. W.; Jenkins. R. L.; Bower, J. *Chem. Commun.*, **2004**, 192.

[79] Yun, B. S.; Hidaka, T.; Furihata, K.; Seto, H. *J. Antibiot.*, **1994**, *47*, 510.

[80] Moody, C. J.; Bagley, M. C. *Chem. Comm.*, **1998**, 2049.

[81] Bagley, M. C.; Bashford, K. E.; Hesketh, C. L.; Moody, C. J. *J. Am. Chem. Soc.*, **2000**, *122*, 3301.

[82] Yun, B. S.; Hidaka, T.; Furihata, K.; Seto, H. *Tetrahedron Lett.*, **2001**, 57, 9683.

[83] Aoki, M.; Ohtshka, T.; Yamada, K. *J. Antibiot.*, **1991**, *44*, 582–588.

[84] Aoki, M.; Ohtshka, T.; Itezono, Y.; Yokose, K.; Furihata, K.; Seto, H. . *Tetrahedron Lett.*, **1991**, *32*, 221.

[85] (a) Shin, C.; Okabe, A.; Ito, A.; Ito, A.; Yonezawa, Y. *Bull. Chem. Soc. Jpn.*, **2002**, *75*, 1583; (b) Endoh, N.; Yonezawa, Y.; Shin, C. *Bull. Chem. Soc. Jpn.*, **2003**, *76*, 643.

[86] Bagley. M. C.; Xiong, X. *Org. Lett.*, **2004**, *6*, 3401.

[87] Honore, T.; Hjeds, H.; Krogsgaard–Larsen, P.; Christiansen, T. R. *Eur. J. Med. Chem.*, **1978**, 13, 429.

[88] Bagley, M. C.; Lunn, R.; Xiong, X.; *Tetrahedron Lett.*, **2002**, *43*, 8331.

[89] Abe, H.; Takaishi, T.; Okuda, T. *Tetrahedron Lett.*, **1978**, 2791.

[90] Bagley, M. C.; Dale, J. W.; Xiong, X.; Bower, J. *Org. Lett.*, **2003,** *5*, 4421.

[91] Xiong, X.; Bagley, M. C.; Chapaneri, K. *Tetrahedron Lett.*, **2004**, *45,* 6124.

[92] Bagley, M. C.; Chapaneri, K.; Dale, J. W.; Xiong, X.; Bower, J. *J. Org. Chem.*, **2005**, *70*, 1389.

[93] Alonso, D. D.; Nájera, C.; Pacheco, M. C. *J. Org. Chem.*, **2004**, *5,* 1615.

[94] Chowdhury, C.; Kundu, N. G. *Tetrahedron*. **1999**, *55*, 7011.

[95] Baraldi, P. G.; Simoni, D.; Manfredini, S. *Synthesis*. **1983**, 902.

[96] (a) Takahata, H.; Yamazaki, T. *Heterocycles* **1988**, *27*, 1953. (b) Hurd, R. N.; Delamater, G. T, ; *Chem Rev.*

[97] Brillon, D. *Sulpfur Rep*. **1992**, *12*, 297.

[98] Cava, M. P.; Levinson, M. I. *Tetrahedron* **1985**, *41*, 5061.

[99] Hartke, K.; Gerber, H.–D. *J. Prakt. Chem.* **1996**, *338*, 763.

[100] Charette, A. B.; Grenon, M. *J. Org. Chem.* **2003**, *68*, 5792

[101] Walter, W.; Bode, K. D. *Angew. Chem., Int. Ed. Engl.* **1996**, *5*, 447.

[102] Fairfull, A. E. S.; Lowe, J. L.; Peak, D. A. *J. Chem. Soc.* **1952**, 742.

[103] (a) Kindler, K. *Liebigs Ann. Chem.* **1923**, *431*, 187. (b) Wang, C. –H.; Hwang, F. –Y.; Chen, C. –T. *Herterocycles*.**1979**, *12*, 1191.

[104] Gabriel, S.; Heymann, P. *Ber. Dtsch. Chem. Ges.* **1890**, *23*, 157.

[105] Erlenmeyer, H.; Degen, K. *Helv. Chim. Acta* **1946**, *29*, 1080.

[106] Albert, A. *Ber. Dtsch. Chem. Ges.* **1915**, *48*, 470.

[107] Taylor, E. C.; Zoltewicz, J. A. *J. Am. Chem. Soc.* **1960**, *82*, 2656.

[108] Brillon, D. *Synth. Commun.* **1992**, *22*, 1397.

[109] Shiao, M. J.; Lai, L. L.; Ku, W. S.; Lin, P. Y.; Hwu, J. R. *J. Org. Chem.* **1993**, *58*, 4742.

[110] Liboska, R.; Zyka, D.; Bobek, M. *Synthesis* **2002**, 1649.

[111] Reviews on microwave chemistry include: (a) Gabriel, C.; Gabriel, S.; Grant, E. H.; Halstead, B. S. J.; Mingos, D. M. P. *Chem. Soc. Rev.* **1998**, *27*, 213; (b) Kuhnert, N. *Angew.*

Chem. Int. Ed. **2002**, *41*, 1863; (c) Lidström, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225; (d) Loupy, A.; Petit, A.; Hamelin, J.; Texier-Boullet, F.; Jacquault, P.; Mathé, D. *Synthesis* **1998**, 1213; (e) Galema, S. A. *Chem. Soc. Rev.* **1997**, *26*, 233; (f) Caddick, S. *Tetrahedron* **1995**, *51*, 10403; (g) Strauss, C. R.; Trainor, R. W. *Aust. J. Chem.* **1995**, *48*, 1665.

[112] Zbruyev, O. I.; Stiasni, N.; Kappe, C. O. *J. Comb. Chem.* **2003**, *5*, 102.

[113] Varma, R. S.; Kumar, D. *Org. Lett.* **1999**, *1*, 697.

[114] Bagley, M. C.; Dale, J. W.; Jenkins, R. L.; Bower, J. *Chem. Commun.* **2004**, 102.

[115] Bagley, M. C.; Dale, J. W.; Xiong, X.; Bower, J. *Org. Lett.* **2003**, *5*, 4421.

[116] Inami, K.; Shiba, T. Bull. *Chem. Soc. Jpn.* **1985**, *58*, 352–360.

[117] Bagley, M. C.; Chapaneri, K.; Glover, C.; Merritt, E. *Synlett*. **2004**, *14*. 2615.

[118] Blessing, R. H. *Acta. Crysrallography.* Sect. A. **1995**, *51*, 33.

[119] Beurskens, P. T.; Beurskens, G.; de Gelder, R.; Gracia–Granda, S.; Gould, R. O.; Israel, R.; Smith, J. M. M. Crystallography Laboratory, University of Nijmegen, The Netherlands. **1999**.

[120] Sheldrick, G. M. Shelex–97, Program for the refinement of Crystal Structures, University of Göttinggen, Germany. **1992**.

[121] Bagley, M. C.; Dale, J. W.; Glover, C.; Ohnesorge, M.; Phillips, N. G.; Xiong X.; Bower, J. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1663.

[123] Ameer, F.; Drewes, S. E.; Drewes M.W.; Watson, M.C. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1425.

[124] Pigge, F.; Ghasedi, F.; Zheng, Z.; Rath, N. P.; Nichols, G.; Chickos, J. S. *J. Chem. Soc., Perkin Trans. 2* **2000**, 2458.

[124] Bagley, M. C.; Glover, C.; Merrit, E. A.; Xiong, X. *Synlett* **2005**, 649–651

[126] Julia, M. *Bulletin de la Societe Chimique de France.* **1966**, *7*, 2381.

[127] Bagley, M. C.; Glover, C.; Merrit, E. A.; Xiong, X. *Synlett*. **2005**, 649.

[128] Petrich, S. A.; Hicks. F. A.; Wilkinson, D. R.; Tarrant J. G.; Bruno, S. M. ; Vargas, M. ; Hosein, K. N.; Gupton, J. T.; Sikorski, J. *Tetrahedron.* **1995**, *51*, 1575.

[129] Shibata, K. *Bull. Chem. Soc. Jpn.,* **1988**, *61* , 199.

[130] Jacobs, J. *Tetrahedron.* **2008**, *64* (32), 7545.

[131] Hiyama, T.; Kobayashi, K.; Nishide, K. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 2127.

[132] Buckler, R. T.; Hartzler, H. E. *J. Med. Chem.*, **1975**, *18*, 509.

[133] Feiring, A. E. *J. Org. Chem.*, **1976,** *41*, 146.