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DEVELOPMENT OF NOVEL ROUTES TO

PYRIDINES

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DEVELOPMENT OF NOVEL ROUTES TO PYRIDINES

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For my family

Zum Werke, das wir ernst bereiten,
Geziemt sich wohl ein ernstes Wort;
Wenn gute Reden sie begleiten,
Dann fließt die Arbeit munter fort.
So laßt uns jetzt mit Fleiß betrachten,
Was durch schwache Kraft entspringt;
Den schlechten Mann muß man verachten,
Der nie bedacht, was er vollbringt.
Das ist's ja, was den Menschen zieret,
Und dazu ward ihm der Verstand,
Daß er im Herzen spüret,
Was er erschaffen mit seiner Hand.

„Das Lied von der Glocke"
Johann Christoph Friedrich von Schiller

— — — — —

An earnest word doth well betide
When we prepare for earnest deeds,
By good discourse accompanied
Then labour cheerfully proceeds.
So let us carefully now scan
Of feeble strength what are the fruits;
One must despise the wretched man,
Who, unreflecting, executes.
For this it is that Man doth grace,
Hereto he hath power to understand,
That he, in his heart's core, may trace
The type of his creative hand.

"The Song of the Bell"
Johann Christoph Friedrich von Schiller

ABSTRACT

Pyridines occupy a central part in modern day organic chemistry. Recent studies in various fields of chemistry, biology and physics have featured numerous examples and applications of these compounds. The purpose of this study was to produce a library of polysubstituted pyridines, 2,2'-bipyridines and 2,2':6',2"-terpyridines *via* pathways that allowed unusual or even unique substitution patterns. To achieve a generic pyridine synthesis that delivers a diversity of products tailored to different industrial needs, a strategy by which the target molecule is constructed in a [2+2+2]-manner was chosen, i.e. the six atoms of the pyridine ring and their pendant functionalities are traced back to three building blocks, each delivering two atoms to the pyridine ring.

A range of α-acetoxy-α-chloro-β-keto esters were prepared in three steps from commercially available β-keto esters through α-chlorination with sulfuryl chloride, α-acetoxylation with acetic acid and triethylamine and a second α-chlorination in good overall yields (69 – 89 %) without the need for chromatographic purification. These α-acetoxy-α-chloro-β-keto esters served as equivalents for α,β-diketo esters (building block 1) in the synthesis of various 1,2,4-triazines through condensation with picolinohydrazonamides or thiosemicarbazides (building block 2). A subsequent aza Diels-Alder reaction of these 1,2,4-triazines with electron-rich dienophiles (building block 3) such as 2,5-norbornadiene, 1-pyrrolidino-1-cyclopentene and 2,3-dihydrofuran furnished an array of novel polysubstitued (bi)pyridines. The two-step sequence of condensation and aza Diels-Alder reaction could be advanced into a 'one-pot' synthesis on several occasions.

Furthermore, we devised a feasible synthetic alternative towards α,β-diketo esters. Alpha-picolinoyl-β-keto esters were prepared from the same starting materials as the α-acetoxy-α-chloro-β-keto esters in a shortened two-step sequence of α-chlorination of β-keto esters with sulfuryl chloride and replacement of the chloro group by a picolinoyl group using picolinic acid and KHCO$_3$. The overall yields of α-picolinoyl-β-keto esters (55 – 91 %) were comparable to those of the α-acetoxy-α-chloro-β-keto esters. Copper(II) acetate-facilitated methanolysis of α-picolinoyl-β-keto esters and immediate oxidation of the *in situ* generated α-hydroxy-β-keto esters by excess copper(II) acetate afforded α,β-diketo esters which reacted with hydrazonamides in the same manner as the α-chloro-α-acetoxy-β-keto esters. However, in terms of product purity and yield the 'chloroacetate route' remains the superior strategy.

Ultimately, our methodologies were applied to the related substance classes of 2,2':6',2"-terpyridines and imidazoles and, hence, novel representatives thereof were synthesised.

ACKNOWLEDGEMENTS

DECLARATION

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I hereby declare that the work contained in this thesis has not been submitted for any other award and that it is all my own work. The work was conducted in collaboration with Vertellus Specialties UK Ltd., Seal Sands.

Alexander Gehre

Signature:

Date:

ABBREVIATIONS

abs.	absolute
Ac (AcOH)	acetyl (acetic acid)
ar	aromatic
Bzl	benzyl
b.p.	boiling point
bpy	2,2':6',2"-bipyridine
BTP	2,6-bis(1,2,4-triazin-3-yl)pyridine
cat.	catalytic (amounts)
conc.	concentrated
DA	Diels-Alder
DCB	1,2-Dichlorobenzene
(2,3-)DHF	2,3-Dihydrofuran
DMAP	4-(Dimethylamino)pyridine
DMD	dimethyl dioxirane
DMF	*N,N*-Dimethylformamide
DMFDMA	*N,N*-Dimethylformamide dimethylacetal
equiv.	equivalent(s)
EDCI	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
EtOH	ethanol
HRMS	high resolution mass spectrometry
IR	infrared
LDA	Lithium diisopropylamide
LHMDS	Lithium hexamethyldisilazide; Lithium bis(trimethylsilyl)amide
mCPBA	*meta*-Chloroperbenzoic acid
MIBK	methylisobutylketone; 4-methyl-2-pentanone
m.p.	melting point
Na$_2$EDTA	sodium ethylenediaminetetraacetate
NBS/NCS	*N*-bromosuccinimide, *N*-chlorosuccinimide
NMR	nuclear magnetic resonance
Ns	nosyl; 4-nitrobenzenesulfonyl
Oxone®	2KHSO$_5$·KHSO$_4$·K$_2$SO$_4$
	active component: potassium peroxomonosulfate (KHSO$_5$)
PHT	pyrrolidone hydrotribromide

Pnb	*para*-nitrobenzyl; (4-nitrophenyl)methyl
Np	*para*-nitrophenyl; 4-nitrophenyl
Py	2-pyridyl; 2-pyridinyl; pyridin-2-yl
RT	room temperature
sat.	saturated
THF	tetrahydrofuran
TLC	thin layer chromatography
tpy	2,2':6',2"-terpyridine
Ts	tosyl; 4-toluenesulfonyl

INTRODUCTION

1 Introduction

Heterocycles occupy a central part in modern day organic chemistry. Studies in various fields of chemistry, biology and physics have featured numerous examples of these compounds over the last centuries – and due to the continuous discovery and development of new and improved synthetic methods many more of these structurally diverse compounds will become target molecules or at least play a key role as intermediates in future syntheses.

Pyridine (**1**) (Figure 1), one of the simplest heterocyclic compounds, is encountered as a building block or – on many occasions – even as the central element in ubiquitous chemical structures.

1
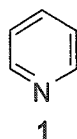
Figure 1. Pyridine.

Pyridine owes its name (*pyr*, Greek for fire) to the way in which it and a small range of its simple alkyl derivatives were first found and isolated, namely by pyrolysis of bone and the distillation of the freed oils. The ending *idine* classified it as an 'aromatic base'. Until the end of the 19th century it was solely obtained from coal tar distillation and even into the first half of the 20th century, coal tar was the main source of pyridines for early industrial applications.[1]

1.1 Pyridines – nature and industry

At the beginning of the 20th century, as the commercial interest in specific pyridines such as 2-picoline and niacine (**2**) grew, their demand rapidly outstretched the quantities of pyridines available from coal tar. This marked the beginning of the uprising of pyridine chemistry to become a field of major industrial significance.

There are only a small number of natural pyridine sources, most of them being classed as either (co)enzymes or precursors thereof or alkaloids.[2] However, the effects those compounds have on the human body are significant and the roles they play in biochemical processes are vital.

Niacine (2) – or vitamin B_3 – is converted by the human body into nicotinamide adenine dinucleotide (NAD^+) (3) and its phosphate $NADP^+$, two coenzymes regulating oxidation-reduction processes in cellular respiration and in various anabolic (fatty acid and nucleic acid synthesis) as well as catabolic processes (glycolysis). Pyridoxin (4) or vitamin B_6 forms a coenzyme in the human body, which is involved in a number of processes in the amino acid metabolism (Figure 2).[3]
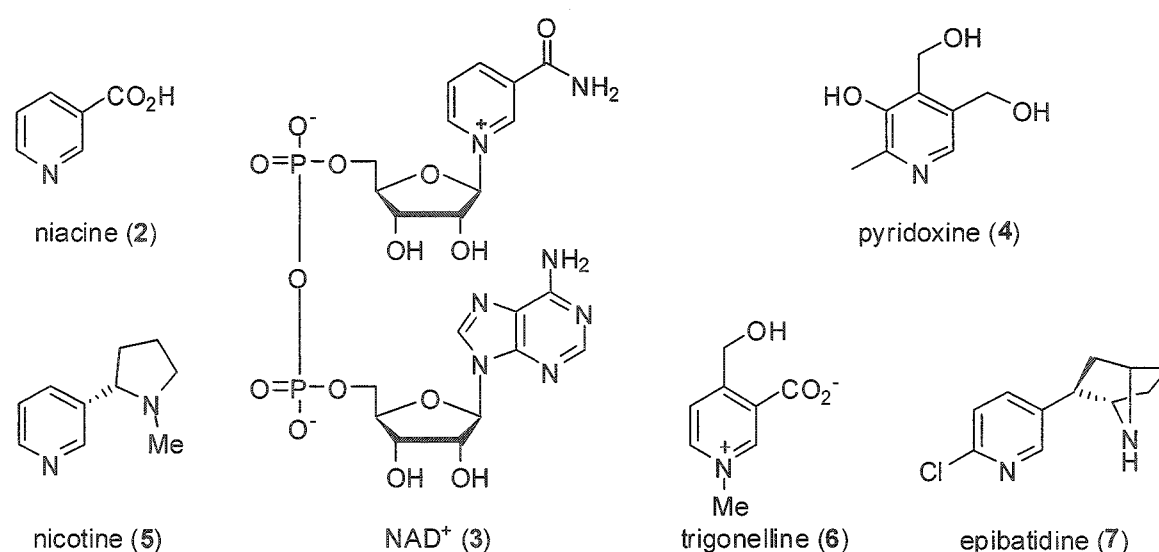
Figure 2. Naturally occurring pyridines.

The highly potent neurotoxin nicotine (5), predominantly found in tobacco, is undoubtedly the best-known pyridine worldwide. However, it is not the toxicity, it is the stimulating effects it exerts in low concentrations that brought nicotine its fame. Other pyridine-based alkaloids are trigonelline (6), which is found in coffee and shows antitumour- and antiseptic activity, and epibatidine (7),[4] a highly potent painkiller which is 200 to 500 times more effective than morphine without showing the addictive side-effects of the former (Figure 2).

With a vast number of diverse industrial applications, pyridines have attracted much attention amongst preparative organic chemists and manufacturers alike. And with more than 7000 drugs containing a pyridine subunit,[1] the pharmaceutical sector appears to be the most lucrative market in chemical industry. The three proton pump inhibitors

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Esomeprazole, Lansoprazole and Pantoprazole (**10a-c**) all range amongst the top twenty bestselling drugs worldwide for the year 2006 with combined sales of more than US$5,100 million.[5] Other pyridine-based drugs show activity against tumours (**8**) or HIV (**9**), tuberculosis (**11**), depression (**12**), inflammation and asthma (**13**, **14**), hypo-/hypertension (**14/15**), heart-failure (**15**) etc. (Figure 3).[1]

Streptonigrin (**8**)
(antitumour antibiotic)

L-754,394 (**9**)
(HIV protease inhibitor)

Esomeprazole (**10a**): $R^1 = R^3 = OMe$, $R^2 = R^4 = Me$
Lansoprazole (**10b**): $R^1 = R^4 = H$, $R^2 = Me$, $R^3 = OCH_2CF_3$
Pantoprazole (**10c**): $R^1 = OCHF_2$, $R^2 = R^3 = OMe$, $R^4 = H$
(proton pump inhibitors)

isoniazide (**11**)
(antituberculosis)

5-HT$_{1A}$ receptor antagonist (**12**)
(antidepressant)

A3 adenosine receptor antagonist (**13**)
(antiinflammatory, antiasthmatic)

FR173657
bradykinin (BK) B2 receptor antagonist (**14**)
(pain, inflammation, asthma, hypotension)

endothelin receptor agonist (**15**)
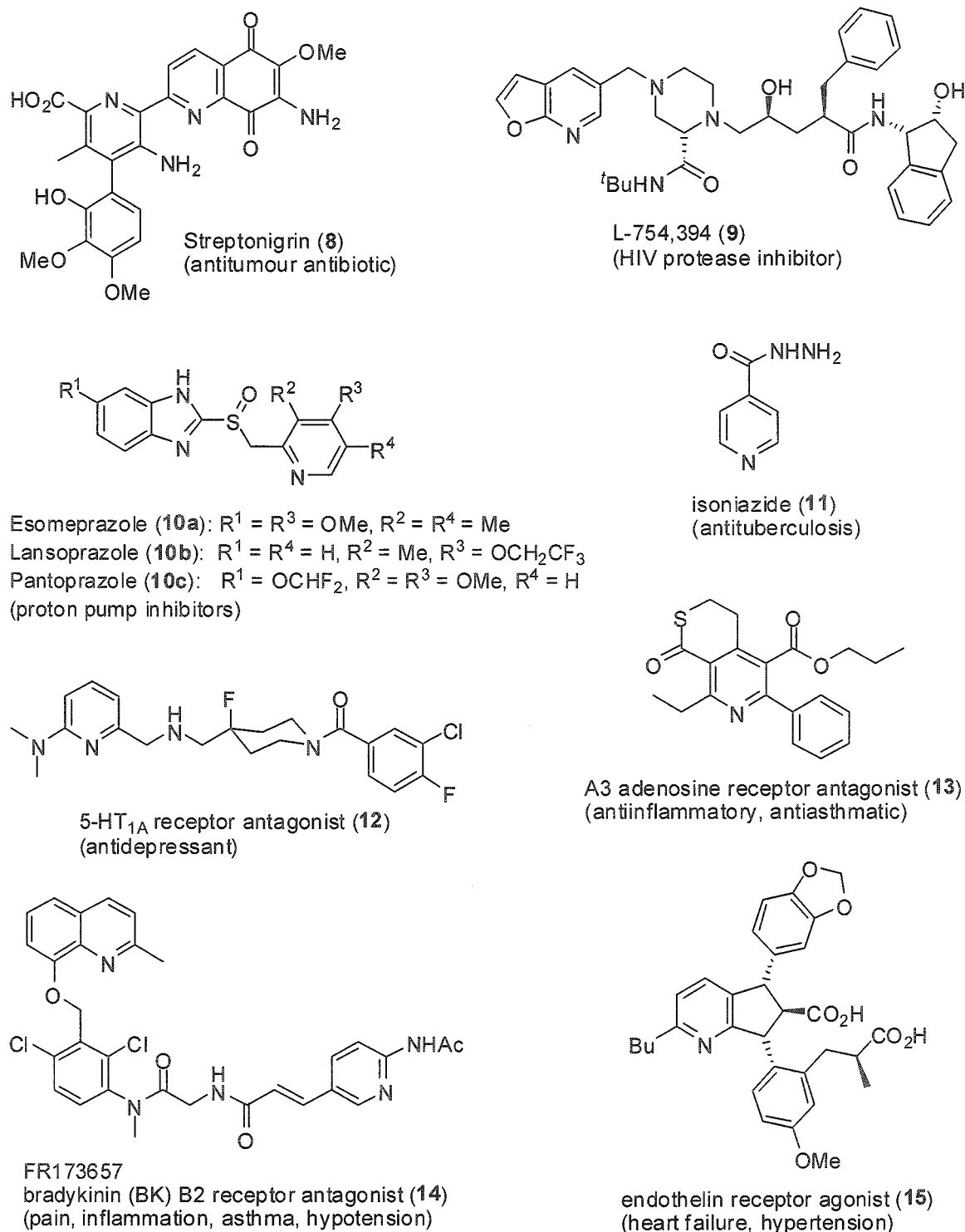(heart failure, hypertension)

Figure 3. Pyridine-based pharmaceuticals.

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Further applications which are of interest to industry are, for example, pyridines as agrochemicals, food supplements (niacine; Figure 2), starting material for polymers (2-vinylpyridine) or bases to catalyse synthetic reactions (DMAP, 2,6-lutidine).[1] The pyridines used as agrochemicals are usually small, polychlorinated molecules such as the herbicides paraquat (16) and picloram (17), the bactericide nitrapyrin (18) and the fungicide pyroxychlor (19) (Figure 4).

paraquat (16)
(herbicide)

picloram (17)
(herbicide)

nitrapyrin (18)
(bactericide)

pyroxychlor (19)
(fungicide)
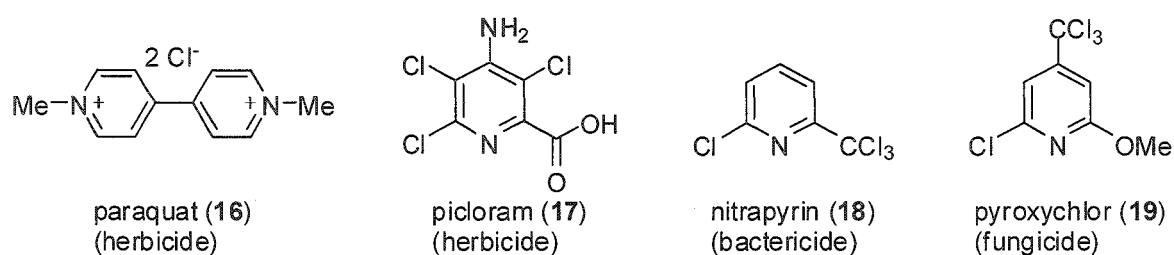
Figure 4. Pyridine-based agrochemicals.

By virtue of their ability to bind to a wide variety of transition metal ions, molecules containing two, three or more pyridine moieties in relative proximity to each other such as 2,2'-bipyridine (bipy) (20), 2,2';6'2"-terpyridine (tpy) (21) or phenanthroline (phen) (21) can serve as chelating ligands (Figure 5).[6] This physico-chemical property has been exploited in purification processes,[7] catalysis[8] and to an increasing degree in asymmetric catalysis.[9-12] Other areas where polypyridine complexes find application are the closely linked fields of redox- and photochemistry,[13] macro- and supramolecular chemistry[14,15] and high-sensitivity analytical chemistry and sensor techniques.[16]

20

21

22

Figure 5. Pyridine-based ligands: bipy (20), tpy (21), phen (22).

1.2 Past and present studies and established approaches

Over the last two centuries the synthesis of pyridines has been studied extensively to create ever new substitution patterns around the azabenzene ring. Therefore, it is not – and cannot be – our intention to give a detailed and complete overview of all the existing pyridine syntheses. We simply want to outl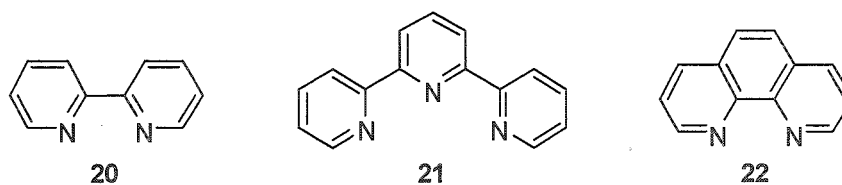ine the 'evolution' from early groundbreaking approaches *via* syntheses which are still of major importance up to some of the most recent methodologies. We will start out with an overview of the possible strategies, then focus on the one which has proven to be the most diverse and successful, discuss likely retrosynthetic disconnection approaches back to commercially available starting materials, again focussing on methods that seemed to be most promising to us.

Pyridines are usually prepared using one of the two following basic reaction types: condensation or cycloaddition reactions.

1.2.1 Condensation reactions

Early syntheses of simple pyridine derivatives such as compound **27** involved a [5+1]-type reaction of a 1,5-dicarbonyl compound (**23** or **24**) with ammonia or hydroxylamine (Scheme 1) where the dicarbonyl contributes all five carbon atoms to the ring.[2] Depending on the nature of the 1,5-dicarbonyl these reactions proceed through dihydropyridines **25** or **26**. These simple reactions, however, do not tolerate the presence of most functional groups due to their harsh reaction conditions.
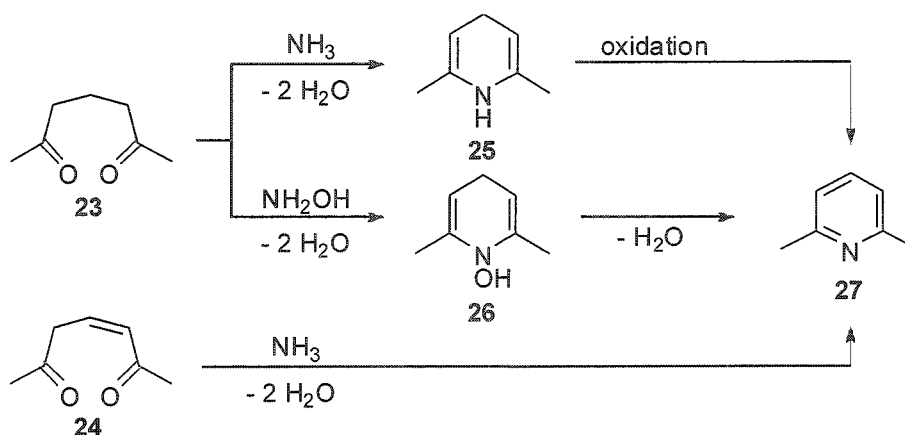
Scheme 1. Simple condensation reactions.

The HANTZSCH-Synthesis[17] (Scheme 2), a condensation of one mole of aldehyde **28** with two moles of a 1,3-dicarbonyl compound **29** and a source of nitrogen such as ammonia or ammonium acetate, is an efficient [2+2+1+1]-type 'one-pot' synthesis to generate symmetrical, carbonyl- or ester-substituted pyridines **30** which form the basis of a range of present-day pharmaceuticals. However, the symmetry of the products is a limitation of the HANTZSCH-Synthesis.
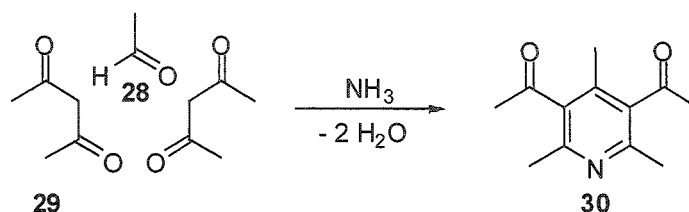
Scheme 2. Example of a HANTZSCH-Synthesis.

The [3+3]-type approach is very versatile and of great importance since it allows the synthesis of unsymmetric pyridines from readily available starting materials. Two well-known examples of a [3+3]-type construction are the BOHLMANN-RATZ-Synthesis[18] (Scheme 3), in which an ynone **31** and an enamine **32** react through an intermediate **33** under high temperature or acidic conditions to give pyridine **34**, and the GUARESCHI-Synthesis[19] (Scheme 4), in which a 1,3-dicarbonyl compound **35** reacts either with a cyanoacetate **36** and ammonia or directly with cyanoacetamide to give pyridine **37**.
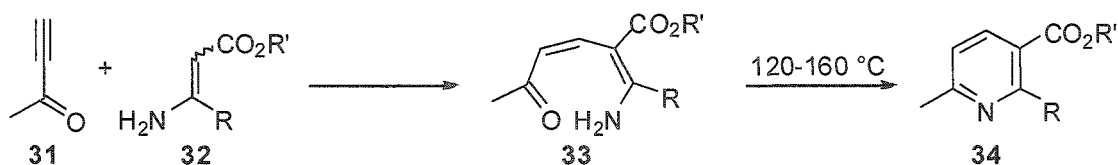
Scheme 3. Example of a BOHLMANN-RATZ-Synthesis.
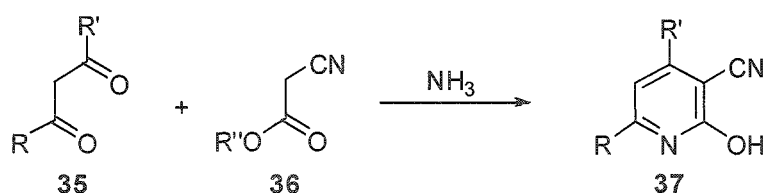
Scheme 4. Example of a GUARESCHI-Synthesis.

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Probably the most frequently used strategy for constructing pyridines is the [3+2+1]-disconnection, in particular the one applying a base-promoted Michael addition of an α-substituted ketone **39** to an α,β-unsaturated ketone **40** as the key step in order to form pyridine **41**. An early example is the KRÖHNKE-Synthesis[20] (Scheme 5) in which **39** is a pyridinium salt that is easily prepared from compound **38** and pyridine.
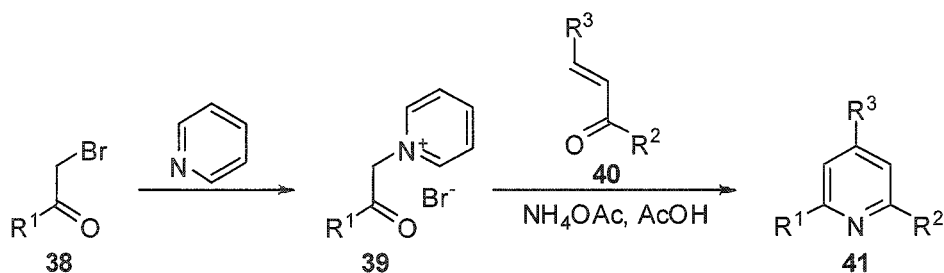
Scheme 5. Example of a KRÖHNKE-Synthesis.

1.2.2 Cycloaddition reactions

Cycloadditions are generally pericyclic reactions in which two σ-bonds are formed between the two substrates at the expense of two π-bonds (one of each substrate). Pyridines can be sythesised *via* cycloadditions from other heterocycles such as oxazoles[21,22] as well as *via* the rather atypical [2+2+2] cyclocotrimerisation.[23] However, the most intriguing pyridine synthesis involves the use of 1,2,4-triazines (**42**) (Figure 6). Their conversion into pyridines is one example of a so-called Diels-Alder reaction.

42
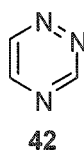
Figure 6. 1,2,4-Triazine (**42**).

2 Diels-Alder reactions

The Diels-Alder (DA) reaction[24] is one of the cornerstones in organic chemistry – even to such an extent that when discovered in 1928 it was already anticipated to be the basis of numerous organic syntheses, including those of various natural products[25] that had not been accessible before.

The DA reaction is a specific type of a cycloaddition, in which a conjugated diene adds to an olefinic or acetylenic dienophile through its 1- and 4-position – making it a [4+2]-cycloaddition – in order to generate a six-membered ring with up to four new stereocentres (Scheme 6). The participating π-bonded electron pairs are shifted as a whole with the bond breaking and bond formation occurring in a concerted fashion. Therefore, the reaction proceeds through a cyclic transition state.
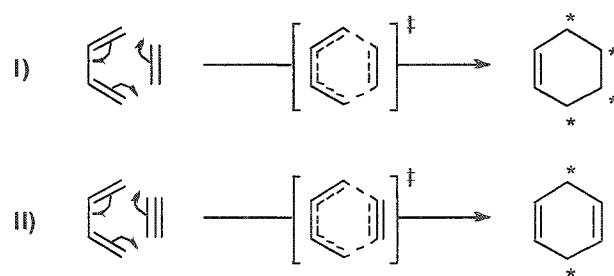
Scheme 6. Diels-Alder mechanism. Possible stereocentres (*).

In contrast to the majority of chemical reactions which are charge controlled, the DA reaction is orbital controlled. In order to understand and predict the reactivity and selectivity of different DA reactions one can apply the Frontier Molecular Orbital (FMO) theory, which focuses on the interactions between the reactants' highest occupied molecular orbitals (HOMOs) and the lowest unoccupied molecular orbitals (LUMOs) – the two orbital types that are closest to each other in energy and, therefore, interact the strongest.[26]

The structurally simplest DA reaction, the addition of butadiene to ethylene (Figure 7, centre) will not proceed under mild reaction conditions (low temperature, atmospheric pressure) by virtue of the electronic nature of its reactants. Both $HOMO_{butadiene}$–$LUMO_{ethylene}$ and $LUMO_{butadiene}$–$HOMO_{ethylene}$ show little interaction.

By choosing reactants bearing electron donating groups (EDGs), which will raise the energy levels of all π-type MOs, and/or electron withdrawing groups (EWGs), which will lower the energy levels of those MOs, one can decrease the energetic difference between the HOMO of one reactant and the LUMO of the other (Figure 7, left and right). This will result in a stronger interaction between those two orbitals and, therefore, in a stabilisation of the transition state – or in other words: in an increased reactivity.[27]
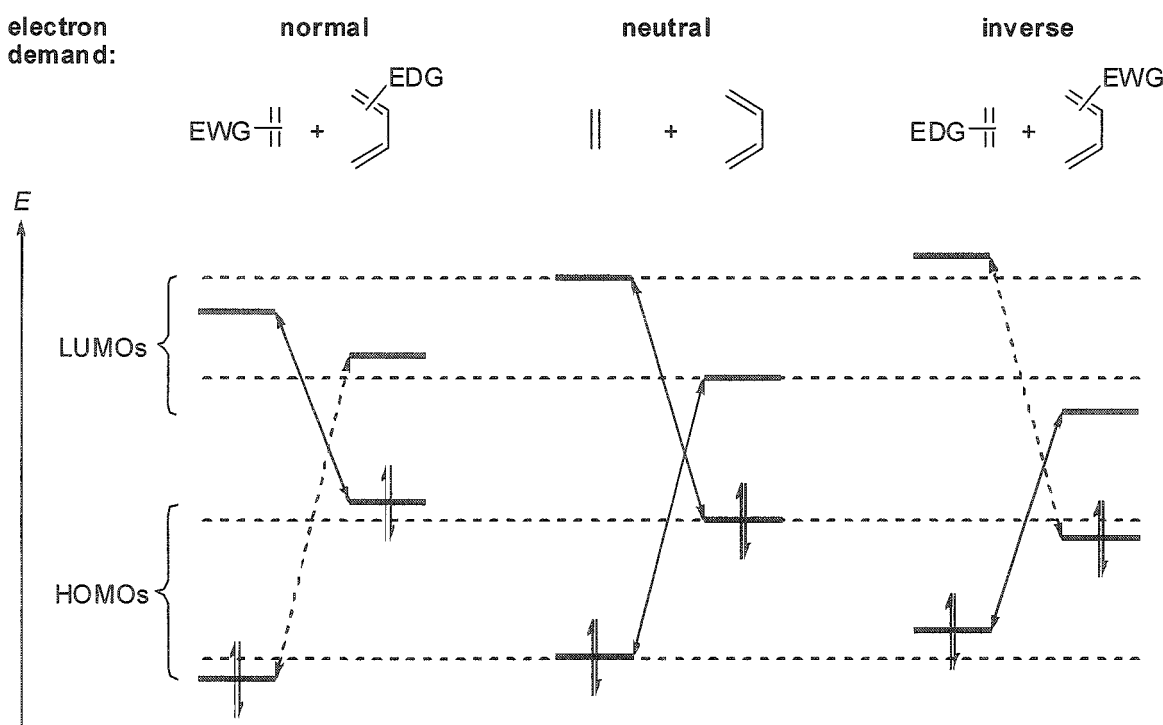

Figure 7. FMO interactions for different electron demands.

The most common type of DA reaction sees an electron-rich diene adding onto an electron-deficient dienophile. This $HOMO_{diene}$–$LUMO_{dienophile}$ interaction occurs in the majority of the all-carbon DA reactions and is referred to as "normal electron demand" DA reaction (Figure 7, left).

However, the concept of DA reactions is not limited to all-carbon systems – with C=O,[28] N=O,[29] S=O or C=S functionalities (amongst many others) being suitable olefin substitutes both in dienes and dienophiles – making the DA reaction a versatile tool for organic synthesis.

If one or more nitrogen atoms, e.g. in the shape of nitriles, imines,[28] azadienes,[30] di-, tri- or tetrazines, are involved in this cycloaddition it is referred to as an aza Diels-Alder reaction (Scheme 7). Comprehensive overviews of these hetero Diels-Alder reactions including the aza variant were compiled by BOGER and WEINREB[31] and TIETZE and KETTSCHAU.[32]
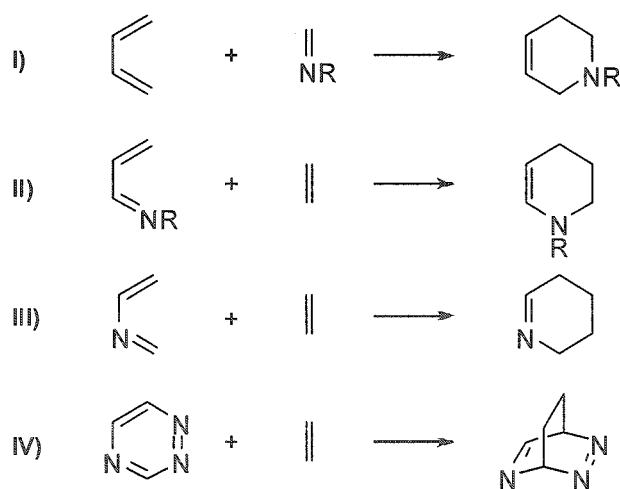
Scheme 7. Aza Diels-Alder reactions.

Using an imine-based diene (Scheme 7, II to IV) will – in most cases – make it electron deficient and, therefore, require an electron-rich dienophile. This is referred to as a DA reaction with "inverse electron demand" (Figure 7, right). A comprehensive review of both nitrogen-containing dienes and suitable dienophiles (which will be mentioned in the following sections) has been published by BOGER.[30]

Out of the four options in Scheme 7 the one involving the 1,2,4-triazine seems to be the most attractive. They are relatively easy to prepare, stable and the nitrogen extrusion from the triazines' azo group is a strong driving force for the re-aromatisation of the DA adduct in order to furnish pyridines where reactions I to III may form stable di- or tetrahydropyridines.

Before we discuss how the triazines are disconnected into readily available materials, we should take a look at the sort of dienophiles it will react with and which functional groups will thereby be introduced.

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2.1 Dienophiles

The number of suitable dienophiles for the reaction with 1,2,4-triazines is vast and new variations are frequently being published. Furthermore, regioselectivity varies depending on the nature (i.e. pattern and bulkiness of substitution) of the diene. Therefore, only the most popular examples shall feature prominently here.

In order to yield pyridines the DA adduct of 1,2,4-triazines and their dienophiles has to undergo a retro-DA (cycloreversion) reaction. The initial step of this elimination sees a loss of nitrogen, which is a considerable driving force. Depending on the nature of the dienophile, two scenarios are possible: in the case of the dienophile being acetylene or an equivalent thereof, the elimination of nitrogen leads directly to re-aromatisation (Scheme 8). If the dienophile is an olefin, then it needs to possess a suitable leaving group X (Scheme 9 – Scheme 11) which is labile under the chosen reaction conditions and eliminates as XH subsequent to the extrusion of nitrogen.

2.1.1 Acetylenic dienophiles

The partcipation of alkynes such as ethynyl- (**43b**) or 1-propynylbenzene (**43a**) (Scheme 8) in aza DA reactions requires high temperatures and/or pressure and is generally not very regioselective.[33] In intramolecular[34,35] reactions of this type the orientation of the cycloaddition can be determined by the length of the tether. For intermolecular reactions where an ester functionality is present in the diene, selectivity can be enhanced using ethynyltributylstannane (**43c**) since repulsion of the two groups strongly favours one of the cycloadducts **44** or **45** and, hence, one of the outcomes **46** or **47** in Scheme 8 over the other. Moreover, the tributylstannyl functionality is easily transformable into a variety of electron-withdrawing groups, not accessible directly through inverse electron demand DA reactions.[36] The toxicity and moisture sensitivity of the stannane, however, limits its application.
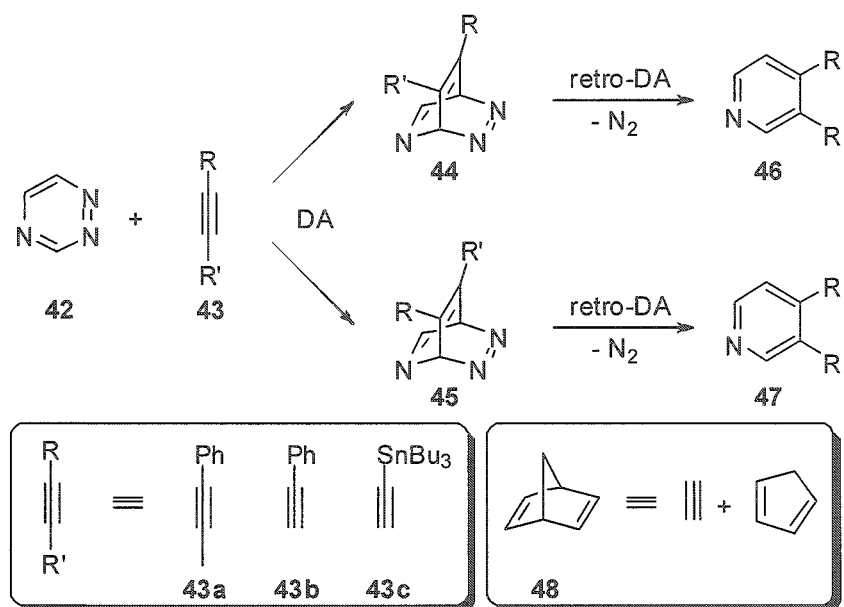
Scheme 8. Acetylenes in aza Diels-Alder reactions.

Despite not adding any functional groups to the product, 2,5-norbornadiene (**48**) is the most utilised dienophile in aza DA methodology. Although 2,5-norbornadiene (**48**) is technically not an acetylene, the decomposion of its strained bicyclic ring system into acetylene and cyclopentadiene upon cycloreversion of the DA adduct constitutes the driving force for the spontaneous reaction right through to the pyridine even under comparably mild conditions.

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2.1.2 Olefinic dienophiles

2.1.2.1 Ketene acetals

One class of olefinic dienophiles through which alkoxy-, amine- or alkylthio-bearing pyridines are easily prepared are 1,1-heterodisubstituted olefins such as ketene acetals **49a** and their nitrogen or sulfur equivalents **49b,c**, conveniently referred to as ketene-*O,N*-, -*N,N*-, -*S,N*-acetals etc. (Scheme 9). The total synthesis of the antibiotic streptonigrin[37] (Figure 3, p. 4) is a popular example featuring a DA reaction with a ketene acetal.

As shown by BURG *et al.*[38] ketene acetals possess high regioselectivity as well as high reactivity towards electron-deficient dienes since both strong electron donors, which are also excellent leaving groups, are attached to the same ethylene carbon. In fact, their reactivity is of such scale that most ketene acetals will proceed through a sequence of cycloaddition and cycloreversion directly to pyridines **54/55** at ambient temperatures without isolatable DA adducts **50/51** or dihyhydropyridines **52/53**. In mixed ketene acetals functional groups on the diene as well as solvent selection may influence which one of the heteroalkyl substituents acts as the leaving group.

Like the alkynylstannanes, ketene acetals are highly moisture sensitve. Therefore, they have to be prepared freshly or generated *in situ*.
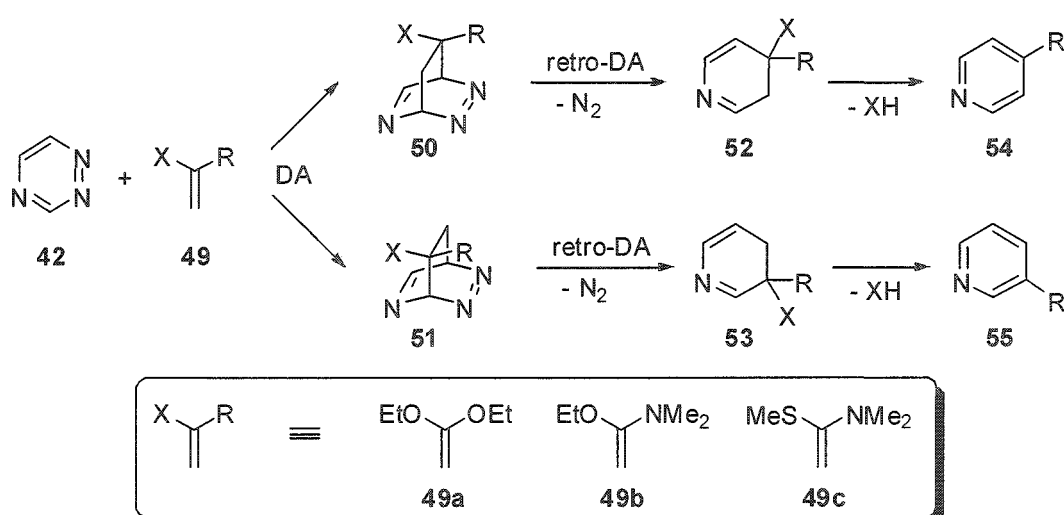
Scheme 9. Ketene acetals in aza Diels-Alder reaction.

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2.1.2.2 Enamines

A simple means of introducing alkyl groups or even forming annulated pyridines is by the reaction of triazines **42** with enamines,[39] pyrroles/indoles[40] and imidazoles[41] **56** through cycloadducts **57** or **58** (Scheme 10). Reactivities and, therefore, reaction temperatures range between those of alkynes and ketene acetals. Enamines can also be generated *in situ*[42] for convenience. Re-aromatisation of dihydropyridines **59/60** to pyridines **61/62** results from elimination of the synperiplanar orientated bridgehead hydrogen and amine (for **56a-c**) or from elimination of H_2 in the case of pyrroles/indoles (**56d**) and imidazoles (**56e**). Intramolecular versions have been utilised to get access to Aspidosperma alkaloids[43] and (tetrahydro)naphthyridines.[41]
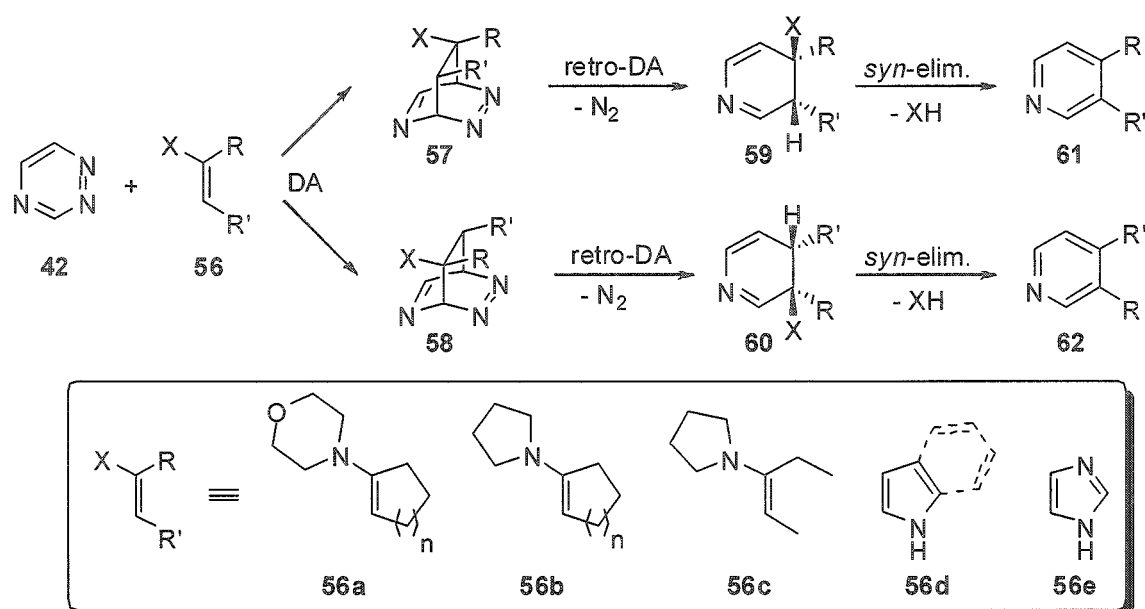
Scheme 10. Enamines in aza Diels-Alder reaction.

2.1.2.3 Cyclic vinyl ethers

Similar to ketene acetals, vinyl ethers like the dihydrofurans **63a** exhibit good regioselectivity to furnish either cycloadduct **64a** or **65a** upon reaction with triazine **42** (Scheme 11); as with any other dienophile the more electrophilic of the two unsaturated centres will generally react with the more nucleophilic position (1- or 4-position) of the diene and *vice versa* unless this interaction is inhibited by steric constraints.

Reactivity varies strongly between the different ethers and only the most electron-deficient dienes react smoothly with all of them. In some instances, sidestepping this with harsher reaction conditions (higher temperature; sealed tube) brings about 2:1 cycloadducts as the major products.

Mechanistically, the dihydropyridines **66a/67a** re-aromatise spontaneously through the opening of the furan ring which corresponds to an antiperiplanar elimination of ROH. This ring opening leads to pyridines **68a/69a** containing a side chain with a terminal hydroxy group. These hydroxy groups tend to either lactonise with nearby esters (Section 3, Scheme 23, p. 25) or add to excess vinyl ether forming acetals (Section 6.3.2.3, Scheme 49, p. 54). Examples of both ot these reactions will be shown in the work at hand. Deprotection of the hydroxy groups from the acetals is easily achieved by acidic workup.
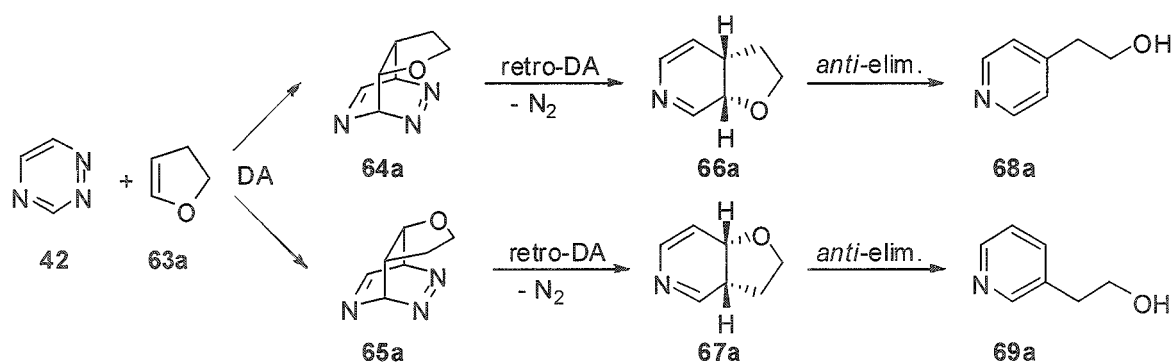
Scheme 11. Cyclic vinyl ethers in aza Diels-Alder reactions.

Reactions of triazines **42** with ethoxy-substituted vinyl ethers like **63b** result in the formation of pyridines **68b/69b** bearing a side chain with an aldehyde group instead of a hydroxy group (Scheme 12). A good account of the reaction of 1,2,4-triazines with both substituted and unsubstituted dihydrofurans and -pyrans was given by ROCHA GONSALVES *et al.*.[44]
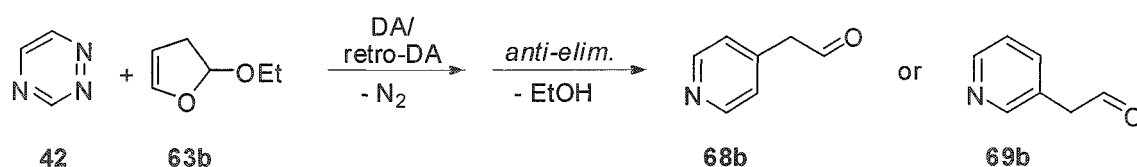
Scheme 12. Cyclic vinyl ethers in aza Diels-Alder reactions.

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2.2 Dienes

An obvious choice for the diene is a 1,2,4-triazine **70** because of the ease and variety of routes for its preparation. Ways of disconnecting the heterocycle include the condensation of a vicinal dicarbonyl compound **71** with a hydrazide **72** following a double condensation with a nitrogen source such as ammonia or ammonium acetate[45] (Scheme 13) or the double condensation of the said dicarbonyl with a hydrazonamide **73**.[46] For reactions with otherwise poor regioselectivity, disconnection into hydrazones **74** and acid derivatives such as acid anhydrides **75** can be used as an alternative.[45]
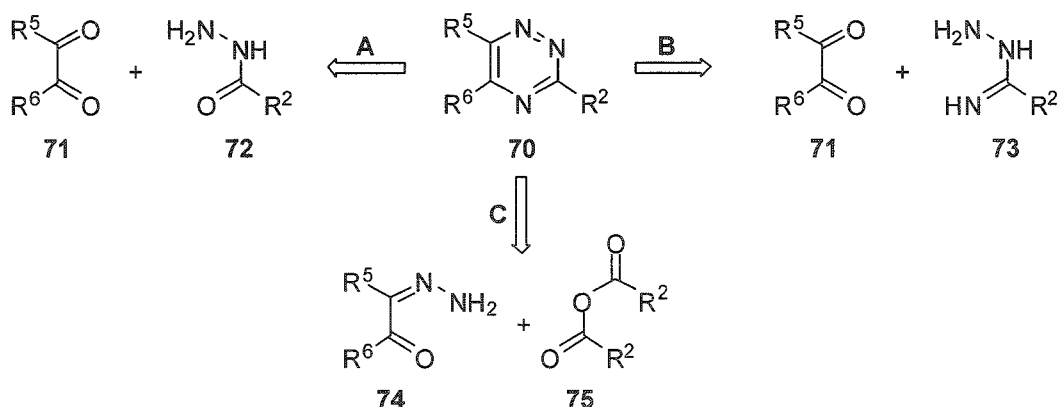
Scheme 13. Retrosynthetic disconnection of triazines.

2.3 Di- and tricarbonyls

In Scheme 13 it becomes apparent that for routes A and B there are two possible stereochemical outcomes: one being the triazine **70** depicted; the other being its regioisomer (R^5 in the place of R^6 and *vice versa*). The position of the first nucleophilic attack by the hydrazide/hydrazonamide, i.e. the regioselectivity, is mainly determined by steric factors. Vicinal tricarbonyls (VTCs) **76** (Scheme 14), e.g. α,β-diketo esters, have often been used as asymmetric dicarbonyls owing to the fact that generally the first attack occurs exclusively on the central carbonyl group. Though most VTCs are not commercially available manifold preparations have been developed.[47]

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It has to be mentioned that, depending on reaction media and workup conditions, VTCs **76** will exist largely as their monohydrates **77** but can be dehydrated by distillation, sublimation and heating over desiccants such as phosphorous pentoxide. They are generally shown in their water-free form for simplicity.
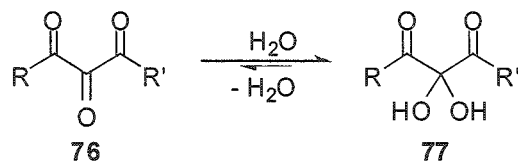
Scheme 14. General structure of a VTC (**76**) and its monohydrate form (**77**).

2.3.1 From 1,3-diketones

Several two-step syntheses of vicinal tricarbonyl compounds **81** from their corresponding 1,3-dicarbonyls **78** have been developed throughout the last century. To our knowledge, SACHS et al.[48] presented the first examples (between 1901 and 1907) using N,N-dimethyl-4-nitrosoaniline (toxic!) at ambient temperature to form the arylimide **79** which furnishes the desired tricarbonyl on strongly acidic workup. Nitrous acid acts in the same fashion as the nitrosoaniline to form oxime **80** which yields the target compounds on reaction with nitrogen peroxide (Scheme 15).[49]
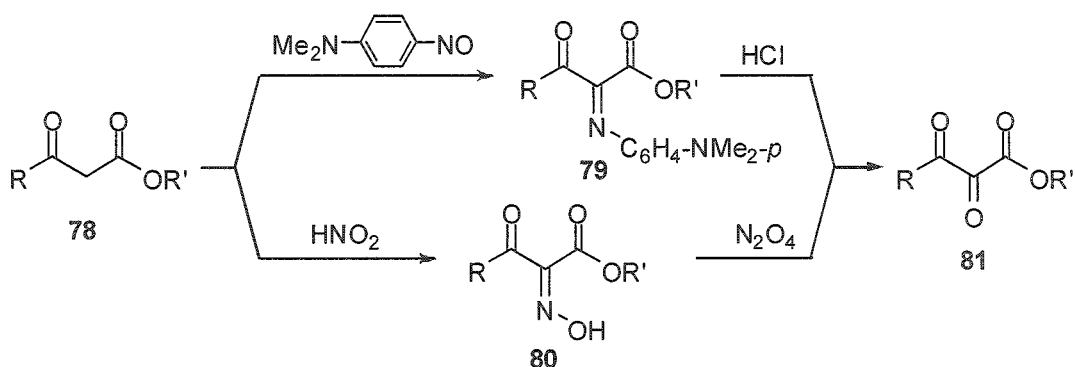
Scheme 15. Early oxidations of β-keto esters **78**.

The sensitive monobromo compound **82** (Figure 8) – prepared with NBS or PHT – reacts with DMSO presumably forming the dimethylalkoxysulfonium bromide intermediate **83**, which collapses into the target compound and dimethylsulfide under aqueous workup.[50,51] Other preparations involved intermediates such as **84**[52] (from reaction with DMFDMA), the dihalo compound **85**[53] or the nosylate **86**[54] (prepared with 4-nitrobenzenesulfonyl

peroxide). Compounds **84** and **85** were converted into tricarbonyls using singlet oxygen or ozone; compound **86** was decomposed with triethylamine.
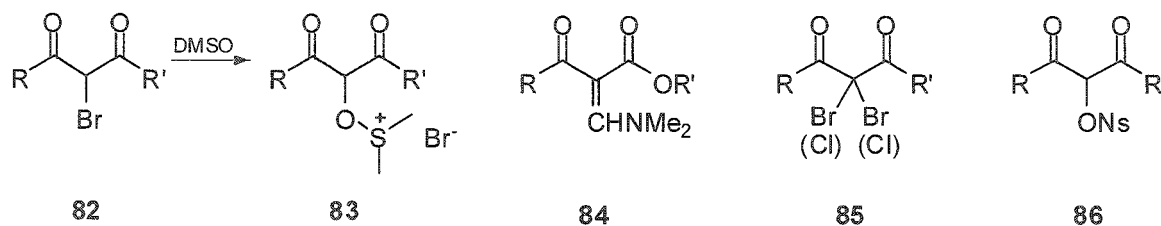
Figure 8. Intermediates of diverse oxidation methods of 1,3-diketo to 1,2,3-triketo compounds.

2.3.2 Direct synthesis

Considering the elimination of a synthetic step and the respective purification, a direct oxidation of 1,3-dicarbonyls **78** to their corresponding vicinal tricarbonyls **81** (Scheme 16) *via* labile intermediates such as **87** or **88** is desirable. However, only when this economisation outweighes other possible drawbacks such as toxicity or cost of reagents, will it be feasible for large scale use.
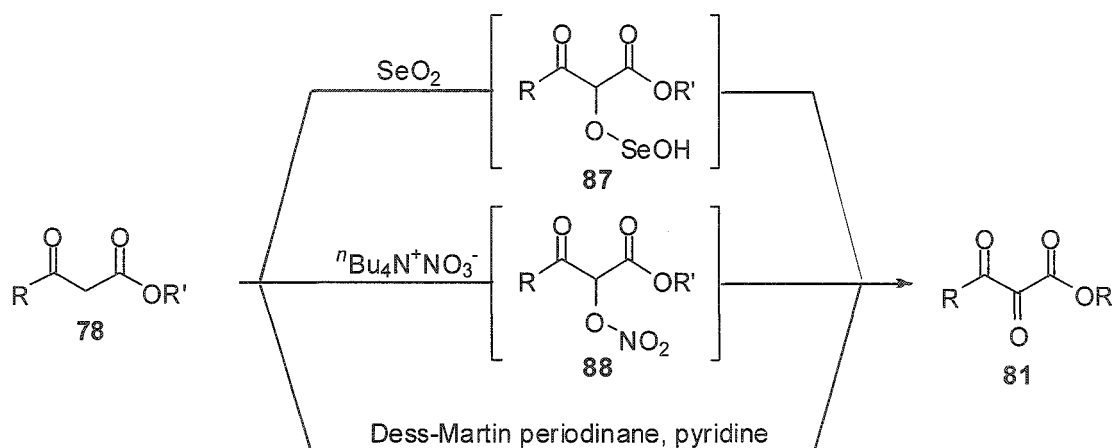
Scheme 16. Direct oxidation methods of β-keto esters.

Having come to fame through the RILEY oxidation[55] selenium dioxide was first used on 1,3-dicarbonyls by DAYER *et al.*[51] in 1974. However, complex product mixtures and contamination with the toxic oxidant posed problems. A much superior method was presented by CAINELLI *et al.*[56] (1986) who reacted tetrabutylammonium nitrates with 1,3-dicarbonyls at ambient temperatures. The nitrate ester intermediates **88** decomposed easily.

BATCHELOR et al.[57] (1993) reported an unorthodox application of Dess-Martin periodinane in the presence of two equivalents of pyridine (presumably to reduce I^V to I^{III}). The main advantage of this method over other oxidations is its selectivity in the presence of N-heterocycles. On the other hand, the high cost of the Dess-Martin reagent is a concern in terms of industrial application.

2.3.3 *Via* ylides

Alternatively, vicinal tricarbonyl compounds **76** can be prepared from their 1,3-dicarbonyl equivalents **89** by formation of an ylide in the 2-position and ozonolytic cleavage of said zwitterion (Scheme 17). SCHANK et al.[58-60] (1982/83) developed procedures involving sulfonium **90**,[59] pyridinium **91**[58] and iodonium ylides **92**[60] with the latter having the added advantage that they can also derive from the reaction of an acid chloride with a pre-formed ylide **39** where 1,3-dicarbonyls are rather complex and not commercially available. The same applies for the procedure described by BESTMANN and KLOETERS[61] (1978) involving a phosphonium ylide **93** generated by the reaction of an acid or acid chloride with a pre-formed ylide **94**.
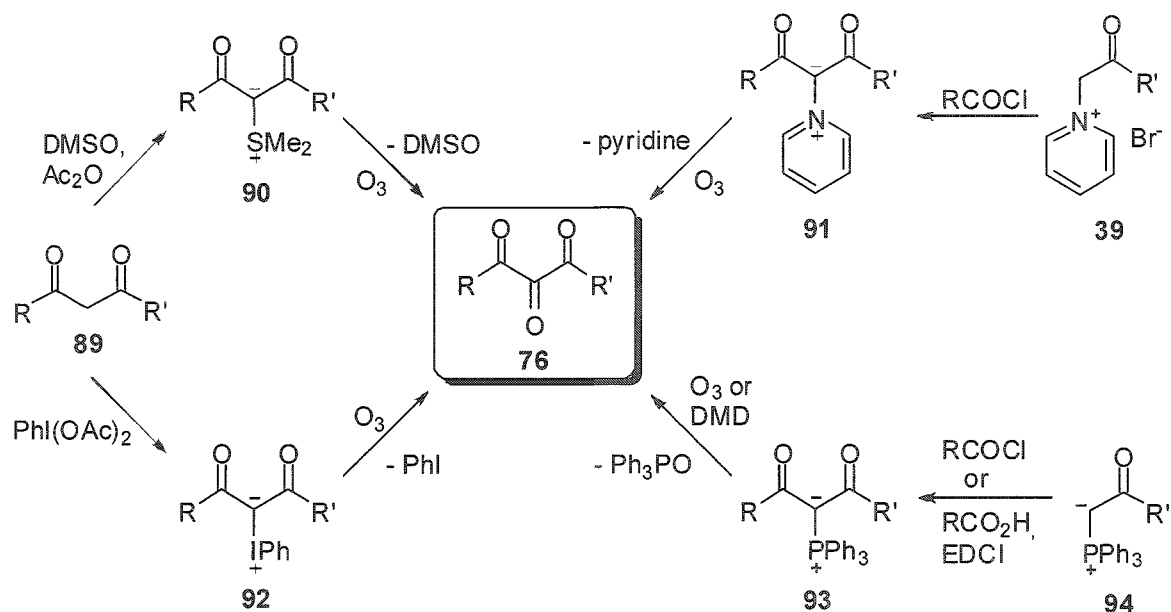
Scheme 17. Oxidations *via* ylides.

Negative aspects of this type of reaction are the low temperatures (-70 to -40 °C) needed for the oxidation, the potential formation of peroxides and the lack of selectivity in the presence of other oxidisable functionalities (e.g. double bonds).

These problems were overcome in an inproved method by WASSERMAN *et al.*[62] who used dimethyldioxirane (DMD) – a much milder oxidant which in most cases allowed for oxidation at ambient temperatures – on phosphonium ylides. Consequently, this method is still proving to be a very popular choice for the formation of tricarbonyls.[63]

Shortcomings of this method are the intolerance of *N*-heterocycles and – even more importantly – the generation of triphenylphosphine oxide which, generally, is difficult to remove since it is likely to be soluble in the same solvents as the desired products. By-products of the other ylides (i.e. iodobenzene, pyridine, DMSO), though easier to remove, would still require a high vacuum.

3 Past developments within the STANFORTH group

As the foregoing line of argument suggests, when our research group set out to do the retrosynthetic analysis to our pyridine syntheses, we opted for the disconnection shown in Scheme 18. The rationale was that this convergent approach will allow for the synthesis of highly substituted pyridines in a few reaction steps and will enable us to create a library of pyridines by variation of either of the three building blocks **A**, **B** and **C**. This would have been more intricate with the linear approaches mentioned in Section 1.2.1 (p. 6).
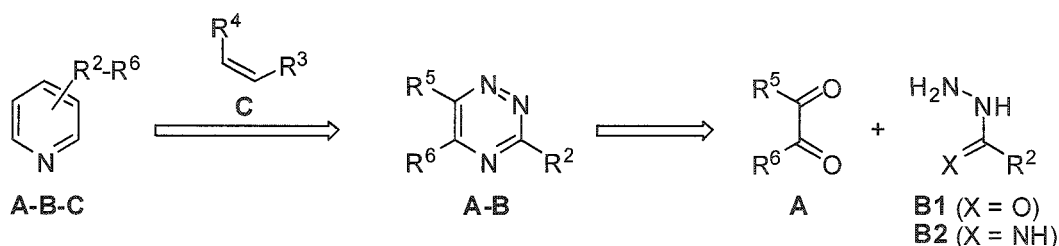
Scheme 18. Retrosynthetic disconnection of pyridines.

The possibilities for the olefin building block **C** have already been discussed and through building block **B** we were aiming to introduce a selection of aliphatic, aromatic and heteroatom substituents. As representatives for the dicarbonyl building block **A** we were mainly interested in α,β-diketo esters for a number of reasons. Besides the already mentioned selective attack of hydrazides/hydrazonamides **B** in order to avoid regioisomeric mixtures during the triazine formation, the ester group also accounts for the directing effect on the cycloaddition of said triazines across the C-3/C-6 axis (Scheme 19; reaction **I**) as opposed to the N-2/C-5 axis (reaction **II**) which would eliminate R_5CN instead of N_2 to form a pyrimidine.
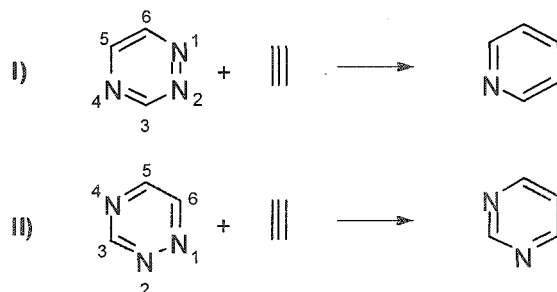
Scheme 19. Possible cycloadditions of 1,2,4-triazines.

In addition to the directing effects, using a dicarbonyl building block **A** bearing an ester group would allow for attachment to a solid support.[64] This would simplify workup procedures as a purification of the final products by column chromatography could be circumvented. Intramolecular aza DA reactions where a dienophile-bearing tether was introduced by attachment to a triazine's ester group have also been reported.[65] Another interesting aspect is that only a few examples are reported in the literature[40,41,66] where α,β-diketo esters are used as building blocks for the triazine or pyridine synthesis.

Initial preparations of these α,β-diketo esters **81** by WATSON *et al.* utilised a sequence of a diazo transfer from 4-acetamidobenzenesulfonyl azide (**97**) onto β-keto esters **78** followed by the hypochlorite-facilitated scission of the α-diazo-β-keto esters **95** that proceeded through intermediates **96** (Scheme 20).[67] Recent modifications saw the use of milder, more stable hypochlorite substitutes such as DMD[68] and Oxone®.[69]
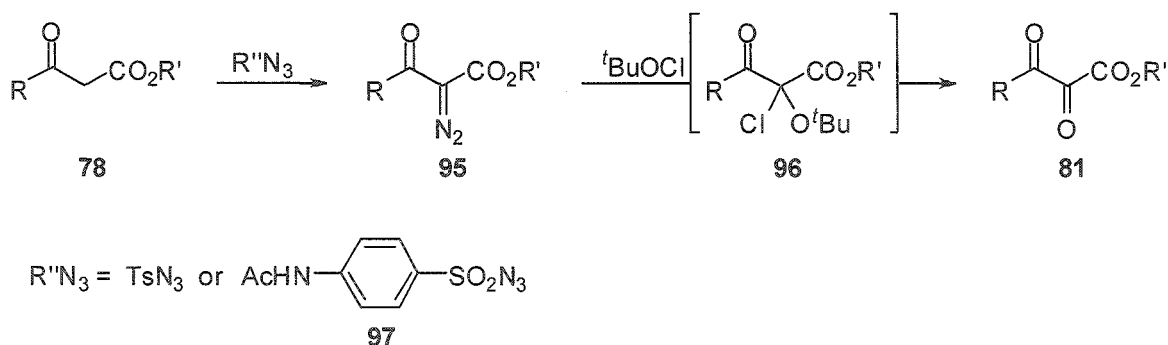
Scheme 20. General tricarbonyl synthesis as featured in our group's early work.

However, the problem remained that from a manufacturing point of view the use of diazo compounds is not attractive. In view of these limitations, ALTUNA-URQUIJO *et al.*[70,71] screened for novel preparations of α,β-diketo esters or equivalents thereof identifying α-hydroxy- **98** and α-hydroximino esters **99** (Figure 9) as tricarbonyl precursors and finally α-chloro-α-acetoxy esters **102** (Scheme 21) as tricarbonyl equivalents, with the latter compounds proving to be most suitable in terms of accessibility and yield from starting material, purification issues and product yield when converted into their corresponding triazines/pyridines.[71,72]
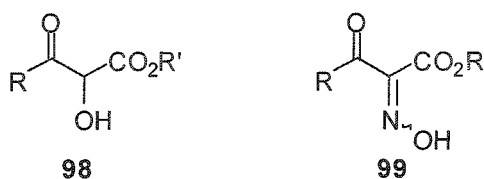

Figure 9. Tricarbonyl precursors/eqivalents.

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These α-chloro-α-acetoxy esters **102** were obtained through a reaction sequence of α-chlorination of β-keto esters **78** with sulfuryl chloride,[73] replacement of the chloro by an acetoxy group, followed by a second chlorination in the α-position (Scheme 21) liberating the gaseous by-products SO_2 and HCl, which significantly simplifies the workup.
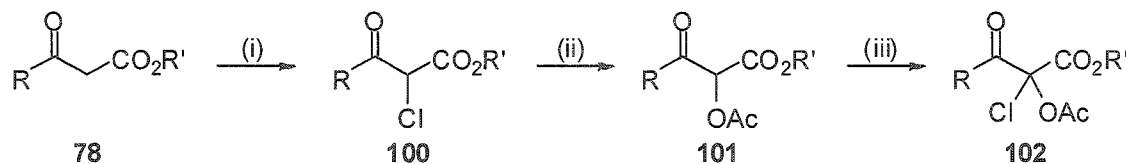
Scheme 21. A novel tricarbonyl equivalent **102**. Reagents and conditions: (i) and (iii) SO_2Cl_2, CH_2Cl_2, 0 °C to RT; (ii) AcOH, NEt_3, DMF, RT.

The α-acetoxylation, which utilised acetic acid and triethylamine, was adapted from a method by PASSAROTTI et al.;[74] similar methods use potassium acetate.[75] Mechanistic details on how chloroacetates act as tricarbonyl equivalents will be described at a later stage of this thesis (cf. Section 6, p. 34 f.).

Direct preparations of the α-acetoxy compounds **101** from **78** with lead(IV) acetate[76] and more recently with an AcOH/*m*CPBA/iodobenzene-mix[77] have been reported. However, the neurotoxicity of the by-product lead(II) acetate in the former and the purification issues in the latter synthesis are again major shortcomings.

With the tricarbonyls **81** (or their equivalents) in hand WATSON et al.[78-80] and later ALTUNA-URQUIJO et al.[70,71] synthesised a library of 1,2,4-triazines **103-107** (occasionally showing traces of regioisomers **108-112**), pyridines and 2,2'-bipyridines **113-117** as outlined in Scheme 22, some of which later underwent functional group interconversion (R = SMe to SOMe, OEt). In some cases the triazine and pyridine formation advanced into 'one-pot' reactions (R = Py). Again, a mechanistic view as well as discussions about reaction conditions will follow at later stages of this thesis.
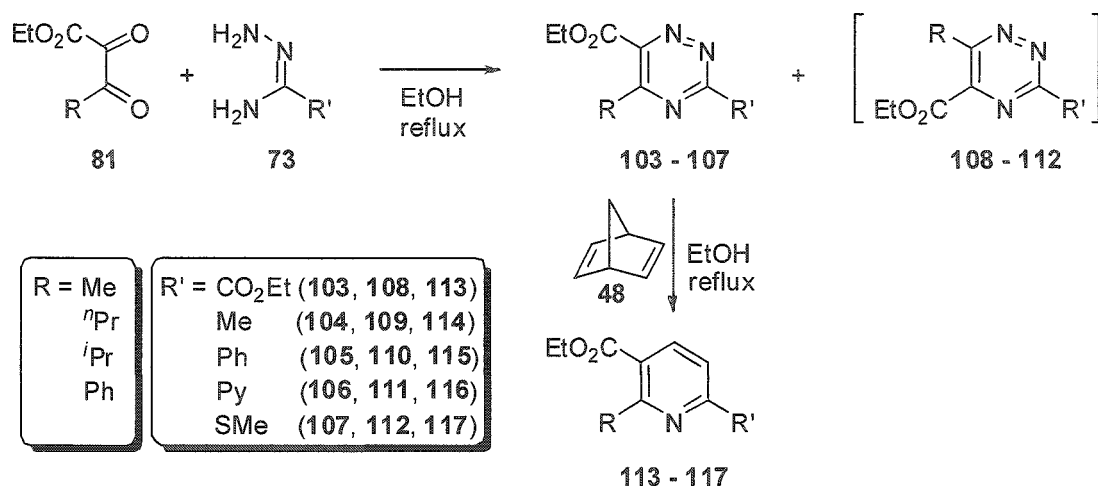
Scheme 22. Overview of early (bi)pyridine syntheses in our research group.

Preliminary studies have been carried out using dienophiles other than 2,5-norbornadiene (**48**). Noteworthy examples of annulated pyridines **120** have been obtained from the reaction of triazines **103** with DHF (**63a**) after re-aromatisation of their DA adducts **118** and spontaneous lactonisation of their intermediates **119** (Scheme 23). Reactions with this and other dienophiles have been investigated in more detail in the work at hand.
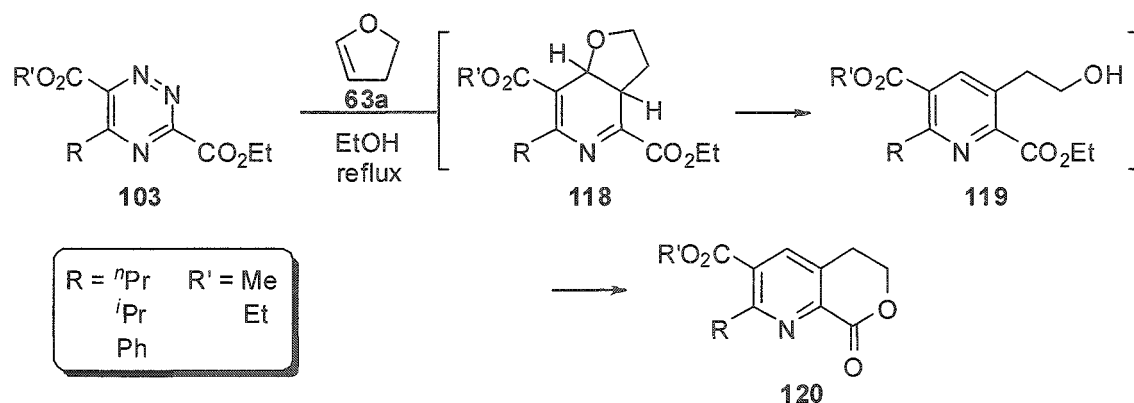
Scheme 23. Synthesis of an annulated pyridine by WATSON *et al.*

Despite our interest in α,β-diketo esters **81** in pyridine/triazine syntheses our group has also prepared a number of triazines **123** from the reaction of amidrazone **73a** with the symmetric vicinal diketones **121** as well as triazine **124** from phenylglyoxal **122** and semicarbazide **73b** (Scheme 24). Dicarbonyls **121** and **122** have also featured heavily in the research of the group by TAYLOR[35] amongst others.[41,81]
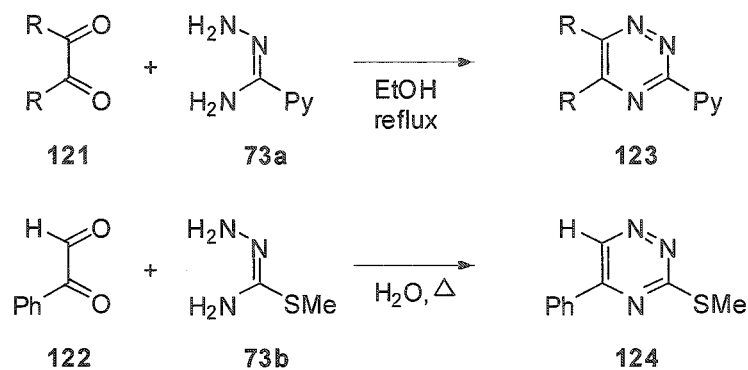
Scheme 24. Triazine syntheses from symmetric and asymmetric dicarbonyls in our research group.

4 Aims and objectives

The purpose of this study, which was conducted in collaboration with *Vertellus Specialties UK Ltd.*, was to produce a library of polysubstituted (bi)pyridines and (pyridyl)triazines *via* pathways that allowed unusual or even unique substitution patterns.

It was hoped that these types of compounds would be of great interest to the chemical and pharmaceutical industry – be it as ready-to-use target compounds or as readily available building blocks – in a variety of applications.

To achieve a generic pyridine synthesis that delivers a diversity of products tailored to different industrial needs, we opted for a combination of condensation and cycloaddition steps by which the target molecule is effectively connected in a [2+2+2]-manner, i.e. the six atoms of the pyridine ring and their appendant functionalities are traced back to three building blocks, each delivering two atoms to the pyridine ring (Scheme 25).
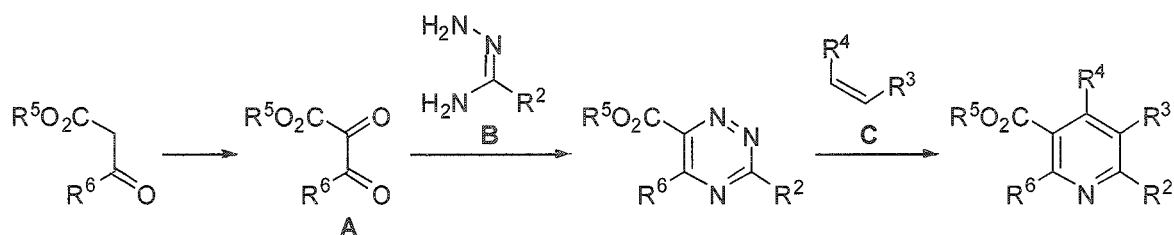
Scheme 25. Synthesis of highly substituted pyridines.

Variation of either of the three building blocks **A** - **C** would give us a fair amount of control over all functional groups attached to the pyridine core without having to sacrifice the simplicity of the synthetic route.

To put the aforementioned aims into practise, we applied synthetic strategies that have been developed by former co-workers of our group to add a series of novel representatives to an already existing library of polysubstituted (bi)pyridines and (pyridyl-)triazines.

Alongside, we aimed to establish more efficient ways towards pyridines and triazines – both known and novel derivatives. This included a shortened preparation of the tricarbonyl building block A from the same commercially available starting materials (Scheme 26) as well as diverse optimised experimental procedures such as 'one-pot' or 'telescoping' reactions.
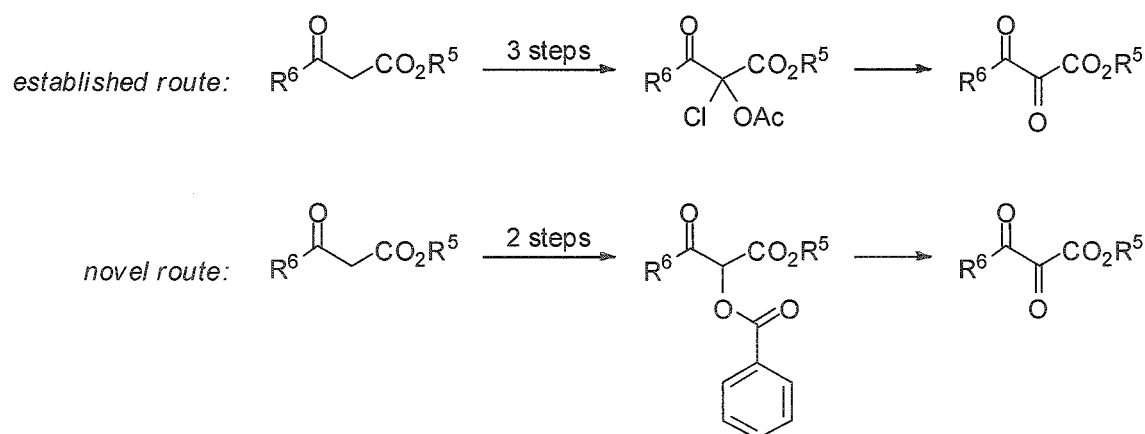
Scheme 26. Established and novel routes towards pyridine building block A.

During the course of this study we also intended to widen the application of our methodologies to the related families of 2,2':6',2"-terpyridines and imidazoles.

Although this project was University-based and the reactions were mainly carried out on a gram-scale, our approaches were governed by the transferability of the procedures to a plant-scale. Various factors had to be taken into consideration for a potential scale-up: starting materials had to be readily available, inexpensive and preferably easy to handle; the synthesis itself needed to be efficient in terms of reaction time, yield, number of steps and cost; by-products and chemical waste had to be kept to a minimum and needed to be safe and inexpensive to dispose of.

DISCUSSION

5 Starting materials

5.1 Commercially unavailable β-keto esters

β-Keto esters **78** represent excellent starting materials for the synthesis of vicinal tricarbonyls as a wide range of these compounds is commercially available. Where the β-keto esters **78** were not readily available they were prepared by condensation of ketones **125** with an excess (2.8 equivalents) of diethyl carbonate (**126**) using a modified literature method[82,83] (Scheme 27). Ethyl 5-methyl-3-oxohexanoate (**78f**) was obtained in good yield (76 %) upon distillation. In the case of **125k** competative condensation at both the methyl and methylene position afforded an inseparable mixture of the desired product **78k** and its skeletal isomer **127k** in very low overall yield (23 %). Although other preparation methods[84] are known, they did not seem viable and the follow-up chemistry for **78k** was abandoned.
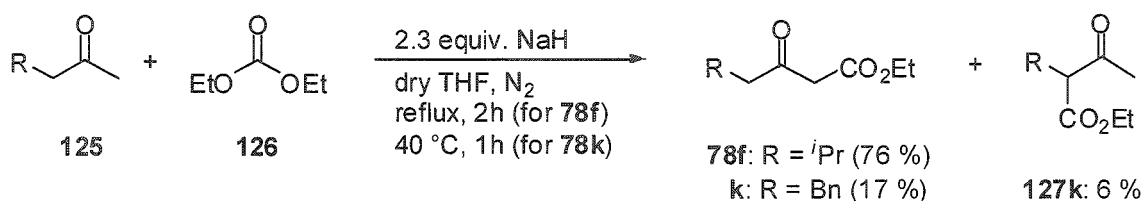
Scheme 27. β-Keto esters **78** from ester condensation. Keto:enol ratios of **78f** 92:8, **78k** 97:3 (in CDCl₃).

5.2 β-Keto esters as starting materials

With the exception of compounds **78a** and **78j** where the α-chloro-β-keto esters **100a** and **100j** are commercially available, the β-keto esters **78** were chlorinated in the α-position using a slight excess of sulfuryl chloride to furnish α-chloro-β-keto esters **100** (Scheme 28) including the previously uncharacterised **100c** (R = Et, R' = Me) and the novel compound **100f** (R = ^{i}Bu, R' = Et).
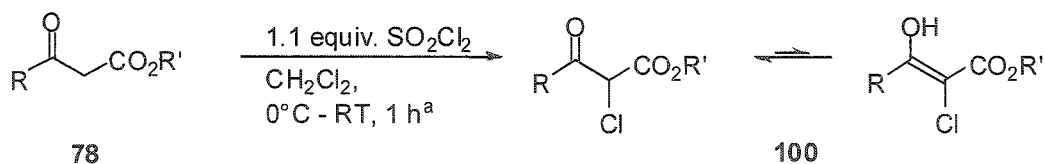
Scheme 28. α-Chloro-β-keto esters **100**. [a] Reaction time for **78d** (R = ^{n}Pr, R' = Et), **78e** (R = ^{i}Pr, R' = Et): overnight.

The products **100** – existing predominantly in their keto forms – were obtained in good to excellent yields throughout (Table 1) without any need for further purification. They were easily identified by ^{1}H-NMR spectroscopy; the signal of the α-proton(s) shifted downfield from around 3 to 4 ppm for compounds **78** towards 4.7 (**100b**) to 5.6 (**100h**) ppm (in CDCl$_3$ relative to TMS). Not surprisingly, the acid labile *tert*-butyl ester **100b** showed a dramatic decrease in yield when left in the reaction mixture for longer (overnight) than the usual reaction time of one hour; all other esters **100** were stable under these conditions.

Table 1. Yields of α-chloro-β-keto esters **100**.

ester 100	R	R'	yield	keto:enol ratio[a]
a	Me	Et	available	n/a
b	Me	^{t}Bu	71 %	93:7
c	Et	Me	99 %	92:8
d	^{n}Pr	Et	98 %	93:7
e	^{i}Pr	Et	94 %	92:8
f	^{t}Bu	Et	100 %	86:14
g	^{i}Bu	Et	100 %	91:9
h	Ph	Et	100 %	> 99:1
i	Np	Et	77 %	100:0
j	CF$_3$	Et	available	n/a

[a] in CDCl$_3$.

The otherwise straightforward chlorination had its limitations with compounds containing other 'activated' positions than the desired α-methylene group. In particular, reaction of benzyl 3-oxobutanoate (**78m**) under the usual conditions resulted in a complex mixture of the desired product **100m** and at least two by-products. An AB spin system of CH_2Cl in the ^1H-NMR spectrum indicated the presence of **128m**;[85] two additional singlets in the aliphatic region were ascribed to **129m** when comparing the spectrum to those of similar compounds (Scheme 29).
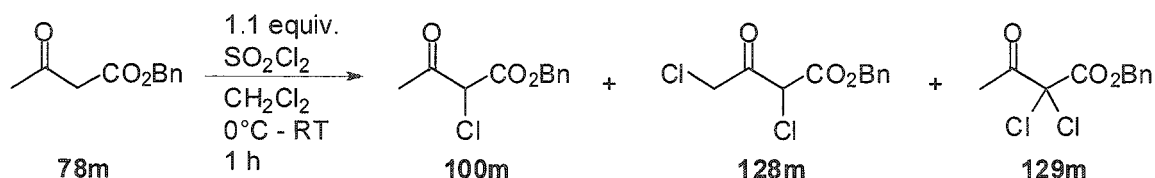
Scheme 29. Product mixture from α-chlorination of **78m**.

Equally unsatisfactory results were obtained when we attempted the mono-chlorination of the symmetrical diester **78n** which led to an inseparable mixture of product **100n**, overchlorinated side-product **128n** and unreacted substrate (Scheme 30). Therefore, the product could not be fully characterised.
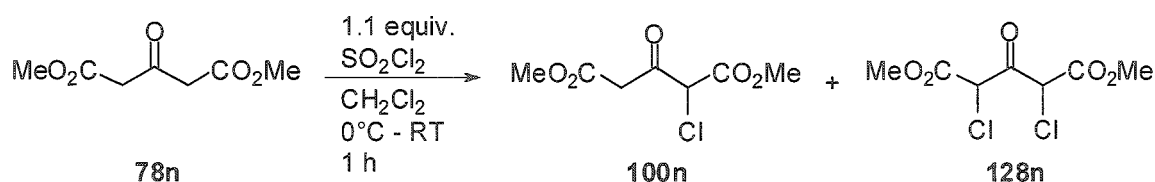
Scheme 30. Attempted single chlorination of the symmetrical diester **78n**.

Getting hold of a (2-pyridinyl)-substituted α,β-diketo ester **81o** would mean easy access to bipyridines **131** and terpyridines **131** (R = Py) through a novel methodology (Scheme 31).
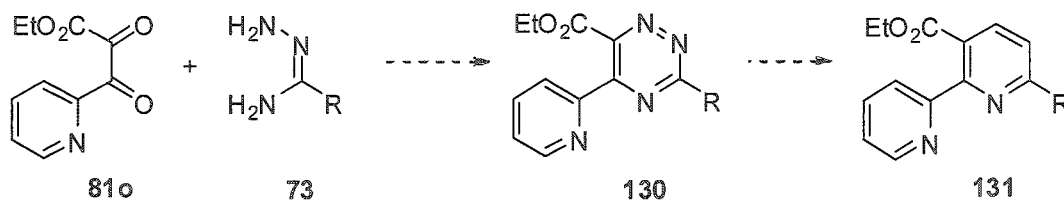
Scheme 31. Possible route towards bi-/terpyridines **131** *via* triazines **130**.

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To achieve this, the β-keto-β-(2-pyridyl) ester **78o** was prepared through ester condensation of readily available ethyl picolinate (**132**) and ethyl acetate with sodium ethoxide as a base (Scheme 32).[86,87] But despite adopting various literature methods (Table 2), halogenation of β-keto ester **78o** did not produce the pure product **100o**.

Compound **78o** remained indifferent when subjected to the routine procedure (entry 1) or NCS as the chlorinating agent (entries 3, 4); it decomposed giving ethyl picolinate (**132**) when treated with 2.2 equivalents of sulfuryl chloride in boiling dichloromethane (entry 2). A combination of sulfuryl chloride and hydrogen chloride (entries 5, 6) saw partial conversion to the product alongside decompositon into **132**. Though α-chloro-β-keto esters have been purified by column chromatography in the literature,[88] from a manufacturing point of view this did not seem desirable to us at such an early stage in the pyridine synthesis.
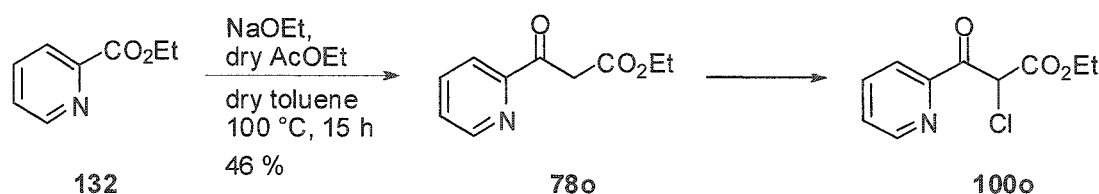
Scheme 32. Preparation and attempted α-chlorination of β-keto-β-(2-pyridyl) ester **78o**.

Table 2. Attempted preparations of α-chloro-β-keto ester **100o** from **78o**.

entry	reactant	conditions	remarks	lit.
1	1.1 equiv. SO_2Cl_2	0 °C to RT, CH_2Cl_2	no conversion	70
2	2.2 equiv. SO_2Cl_2	0 to 40 °C, CH_2Cl_2	decomposition to **132**	89
3	1.05 equiv. NCS, Amberlyst® 15	RT, ethyl acetate	no product	90
4	1.5 equiv. NaH, 2.0 equiv. NCS	0 °C to RT, dry THF	no conversion	8
5	1.1 equiv. SO_2Cl_2, excess conc. HCl	0 °C to RT, CH_2Cl_2	mixture of **132**, **78o** and **100o**	
6	1.1 equiv. SO_2Cl_2, $HCl_{(g)}$	0 °C to RT, CH_2Cl_2	mixture of **132**, **78o** and **100o**	

The attempt to prepare compound **100o** *via* ester condensation of ethyl picolinate (**132**) and ethyl chloroacetate (**133**) also failed and only **132** could be re-isolated (Scheme 33). Thus, the synthesis of bi- and terpyridines was pursued using alternative approaches which will be discussed at a later stage.

Scheme 33. Attempted preparation of α-chloro-β-(2-pyridyl)-β-keto ester **100o**. Reagents and conditions: (i) 1.3 equiv. ^{i}Pr$_2$NH, 1.3 equiv. BuLi, dry THF, 0 °C, 1 h; (ii) **133**, - 78 °C; (iii) 1.0 equiv. **132**, 0 °C to RT, overnight.

6 Chloroacetate route

6.1 Acetates and chloroacetates

This route encompasses the conversion of α-chloro-β-keto esters **100** into the α-acetoxy-α-chloro-substituted tricarbonyl equivalents **102** in two steps (Scheme 34). The generation of tricarbonyl equivalents has been studied extensively by our research group for several years and this route was found to be a short, industrially feasible and high-yielding method for the generation of pyridine building blocks from readily available β-keto esters **78** in only three steps.
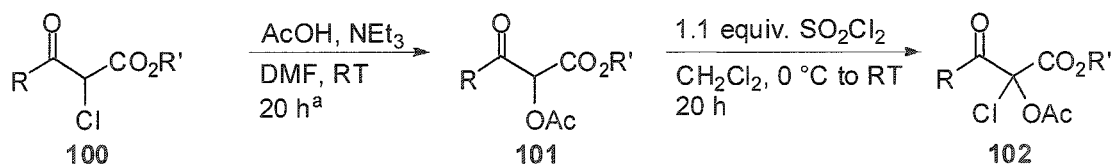
Scheme 34. Preparation of chloroacetates **102** from α-chloro compounds **100**. [a] **101e** (R = ^{i}Pr, R' = Et): 2 d, **101h** (R = Ph, R' = Et): 3 d.

In an initial nucleophilic substitution reaction between α-chloro compounds **100** and acetic acid in the presence of triethylamine as a base, the chloride in **100** was replaced by an acetoxy group to form acetates **101** in moderate to excellent yields (Table 3). This exchange of α-substituents was reflected by a downfield shift of the signal for the α-proton (5.5...6.3 ppm for compounds **101** compared to 4.7...5.6 ppm for compounds **100**) as well as by the presence of an additional acetoxy singlet at 2.2 ppm in the ^{1}H-NMR spectra which was in accordance with literature data. The novel derivative **101g** was fully characterised.

Table 3. Yields of α-acetoxy-β-keto esters **101** and α-acetoxy-α-chloro-β-keto esters **102**.

ester	R	R'	yield of 101	yield of 102 [a]
a	Me	Et	85 %	81 % (69 %)
c	Et	Me	90 %	92 % (82 %)
e	^{i}Pr	Et	55 %	
f	^{i}Bu	Et	100 %	95 % (72 %)
g	^{t}Bu	Et	70 %	mixture
h	Ph	Et	93 %	96 % (89 %)
j	CF$_3$	Et	0 %	n/a

[a] from compound **101** and (overall yield from commercially available starting material).

The reaction of the trifluoromethylated α-chloro-β-keto ester **100j** was carried out in dry toluene under a nitrogen atmosphere due to its moisture sensitive nature. Unfortunately, no product **101j** was isolated. An explanation could be that the target compound **101j** is likely to be as sensitive as the substrate and that it is labile under the conditions of the workup, i.e. washing with an aqueous solution of sodium bicarbonate to neutralise.

The chloroacetates **102** were subsequently prepared from acetates **101** in the same manner as the α-chloro compounds **100** have been produced from β-keto esters **78** before (Section 5.2, p. 30). However, yields of chloroacetates **102** were generally slightly lower than those of the corresponding α-chloro compounds **100**; chloroacetate **102g** could not be obtained in its pure form.

Complete disappearance of the signal for the α-proton in the products' ^{1}H-NMR spectra indicated full conversions. The structures of the novel chloroacetates **102c** and **102f** (Figure 10) were confirmed by a combination of ^{1}H-NMR (Table 4, Table 5), ^{13}C-NMR, HRMS and IR spectrometry (Table 6).

Figure 10. Chloroacetates **102c** and **102f**.

Table 4. ^{1}H-NMR spectral data of chloroacetate **102c**.

chemical shift (ppm)	multiplicity	integral	coupling constants (Hz)	assignment
3.87	s	3		ester-CH$_3$
2.92	q	2	7.2	-CH$_2$-
2.24	s	3		acetoxy-CH$_3$
1.15	t	3	7.2	-CH$_3$

Table 5. ^{1}H-NMR spectral data of chloroacetate **102f**.

chemical shift (ppm)	multiplicity	integral	coupling constants (Hz)	assignment
4.37 and 4.32	2q	2	7.2	ester-CH$_2$-
2.77 – 2.70	m	2		-CH$_2$-
2.24	s	3		acetoxy-CH$_3$
2.30 – 2.15	m	1		-CH(CH$_3$)$_2$
1.35 and 1.31	2t	3	7.2	ester-CH$_3$
0.97 and 0.96	2t	6	6.7	-CH$_3$

Table 6. HRMS data of chloroacetates **102c,f**.

ester	mass calculated for [M+NH$_4$]$^+$	mass measured
102c	240.0633	240.0633
102f	282.1103	282.1104

6.2 Triazine formation

As this study was a continuation / expansion of earlier work[70,71,78-80] with the intentions of adding novel derivatives to a library of triazines and pyridines as well as optimising established reactions, the results obtained during the course of this study have to be viewed as such. Consequently, overviews and tables may feature results gained from both this and earlier studies in order to draw sound conclusions.
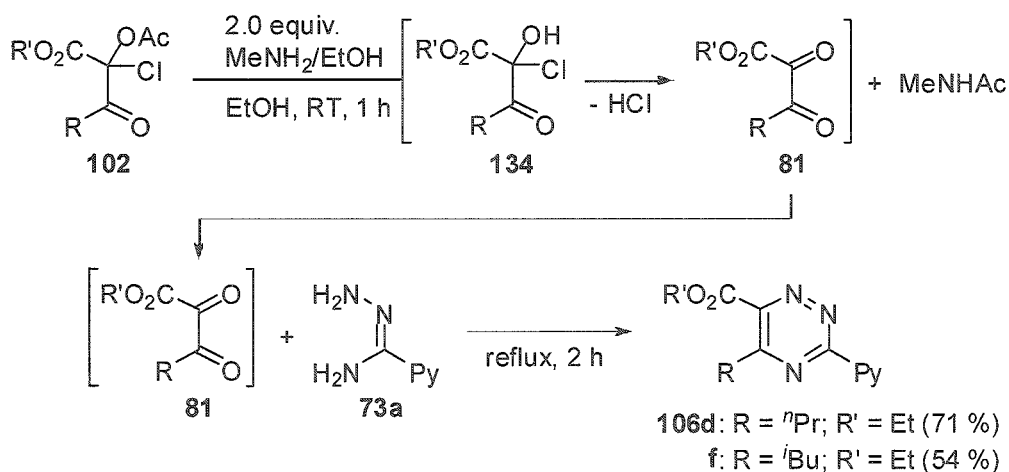
6.2.1 (2-Pyridyl)triazines

Triazines **106** were generated from the reaction of chloroacetates **102** and 2.5 equivalents of amidrazone **73a** in boiling ethanol (Scheme 35; Table 7, method A). Amidrazone **73a**, in turn, can be obtained from 2-cyanopyridine (**136**) by reaction with hydrazine monohydrate. It was available in quantity from prior research and did not have to be prepared freshly. The use of excess amidrazone was based on earlier experiments in our group which showed that these reactions only gave satisfactory yields when at least two equivalents of the amidrazone **73a** were used.[70,71] However, even under these conditions the reactions of chloroacetates **102** bearing small substituents (R = Me, Et) showed unsatisfactory yields of triazines **106a** (36 %) and **106c** (22 %) respectively.
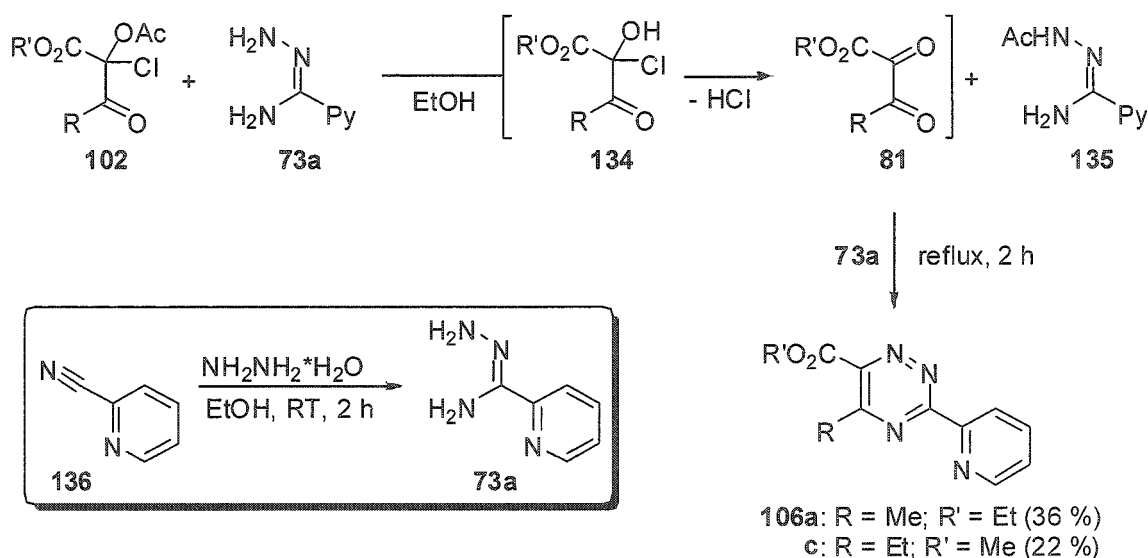
Scheme 35. Preparation of 3-(2'-pyridyl)-triazines **106** from chloroacetates **102**. Method A: 2.5 equiv. **73a**.

Mechanistically, we proposed that an initial decomposition was brought about by the reaction of one equivalent of amidrazone with the acetoxy group of compound **102**, thus forming amide **135** and the de-acylated intermediate **134** which, under release of hydrogen chloride, formed the α,β-diketo ester **81**. Condensation of a second equivalent of **73a** with **81** subsequently furnished triazines **106**.

A refinement of this method where no amidrazone had to be sacrificed used two equivalents methylamine to transform the chloroacetates **102** into their corresponding α,β-diketo esters **81** (Scheme 36). The two compounds were stirred in ethanol at room temperature for around one hour. The condensation step then required reflux again to furnish triazines **106** in moderate to good yields (Table 7, method B). Alternatively a saturated ethanolic hydrogen chloride solution has been used for the pre-treatment of chloroacetates **102** with great success in earlier studies (Table 7, method C).[71]

Scheme 36. Preparation of 3-(2'-pyridyl)-triazines **106** from chloroacetates **102**. Method B.

Table 7. Yields of 3-(2'-pyridyl)-triazines **106** from chloroacetates **102**.

triazine 106	R	R'	method A	method B	method C
a	Me	Et	36 % (*79 %*)	*mixture*	
c	Et	Me	22 %		
d	*n*Pr	Et	*98 %*	71 % (*61 %*)	*79 %*
f	*i*Bu	Et		54 %	
h	Ph	Et	*97 %*	*65 %*	*95 %*
i	Np	Et	*32 %*		

Method A: no pre-treatment of chloroacetates **102**; method B: pre-treatment of **102** with MeNH₂; method C: pre-treatment of chloroacetates **102** with EtOH/HCl; results from former co-workers in *italics*.

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All triazines **106** were purified by column chromatography. The ^{1}H-NMR spectral data of the known representatives **106a** and **106d** was consistent with that found in the literature;[71] novel triazines **106c** and **106f** (Figure 11) gave comparable patterns (Table 8) and their structures could be confirmed by HRMS (Table 9).
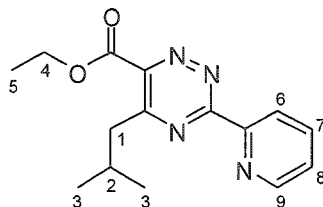

Figure 11. Triazine **106f**.

**Table 8.** ^{1}H-NMR spectral data of triazine **106f**.

chemical shift (ppm)	multiplicity	integral	coupling constants (Hz)	assignment
8.94	ddd	1	1.0, 1.7, 4.7	9-H
8.72	ddd	1	1.0, 1.2, 7.9	6-H
7.95	ddd	1	1.7, 7.7, 7.9	7-H
7.51	ddd	1	1.2, 4.7, 7.7	8-H
4.57	q	2	7.2	4-H
3.15	d	2	7.2	1-H
2.36 – 2.21	m	1		2-H
1.50	t	3	7.2	5-H
0.99	d	6	6.7	3-H

Table 9. HRMS data of triazines **106c,f**.

triazine	mass calculated for [M+H]$^+$	mass measured
106c	245.1033	245.1031
102f	287.1503	287.1504

6.2.1.1 Test for the reaction rate of the chloroacetate decomposition

To a solution of chloroacetate **102d** in ethanol was added 2-phenylethylamine (Scheme 37) and samples of the reaction mixture were taken after 1, 7, 15, 30 and 60 min. The ethanol was evaporated under reduced pressure and ^{1}H-NMR spectra were recorded (in CDCl$_3$). The significant changes, i.e. complete disappearance of the acetoxy singlet (2.2 ppm) of chloroacetate **102d** and appearance of the acetamide singlet (1.8 ppm) of compound **137**, were observed already after 1 min. The spectra taken at 7, 15, 30 and 60 min showed no further changes.
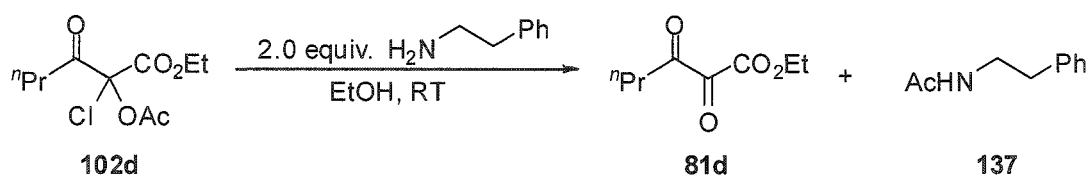
Scheme 37. Test for the reaction rate of the decomposition of chloroacetate **102d** into α,β-diketo esters **81d**.

6.2.1.2 Reactions at ambient temperatures

As we have constantly striven to optimise reaction conditions, we attempted a triazine synthesis at ambient temperatures. The usual preparation methods for polysubstituted 1,2,4-triazines used ethanol or, where necessary, a higher boiling solvent under reflux. In one instance where the carbonyl component was thermolabile and only available in aqueous solution, PABST and SAUER switched to an ethanol/water system at room temperature.[91] However, heating at 100 °C in DMF was necessary to complete the condensation. Using chloroacetate **102d** as an example we performed a series of test reactions at room temperature (Table 10), none of which showed complete conversion even after extended reaction times.

Table 10. Synthesis of triazine **106d** from chloroacetate **102d** with amidrazone **73a** at room temperature.

entry	chloro-acetate	solvent	equivalents of amidrazone 73a	time	conversion to 106d
1	**102d**	methanol-d_4	2.5	4 d	40…46 %
2	**102d**	toluene-d_8	2.5	4 d	39 %
3	**102d**	CDCl$_3$	2.5	4 d	35…45 %
4	**102d** [a]	CDCl$_3$	1.0	2 d	50 %

[a] pre-treated with excess methylamine

6.2.2 Sulfur-containing triazines

The rather labile thiosemicarbazide **73b** was prepared by *S*-alkylation of its parent compound **138** with iodomethane in boiling absolute ethanol and isolated in moderate yield (59 %) simply by filtration of the precipitating product from the cooled and concentrated reaction mixture. Reactions of chloroacetates **102d,h** with 2.5 equivalents of *S*-methyl-thiosemicarbazide **73b** in boiling ethanol afforded products **107d,h** as easy-to-handle liquids in quantitative yields (Scheme 38). Not surprisingly, the yield dropped drastically (25 % of **107b**) when only one equivalent of **73b** was used. Following a basic workup procedure consisting of extraction into dichloromethane and washing with water, the products **107** did not require any further purification. The analytical data was consistent with that found in the literature.[71]
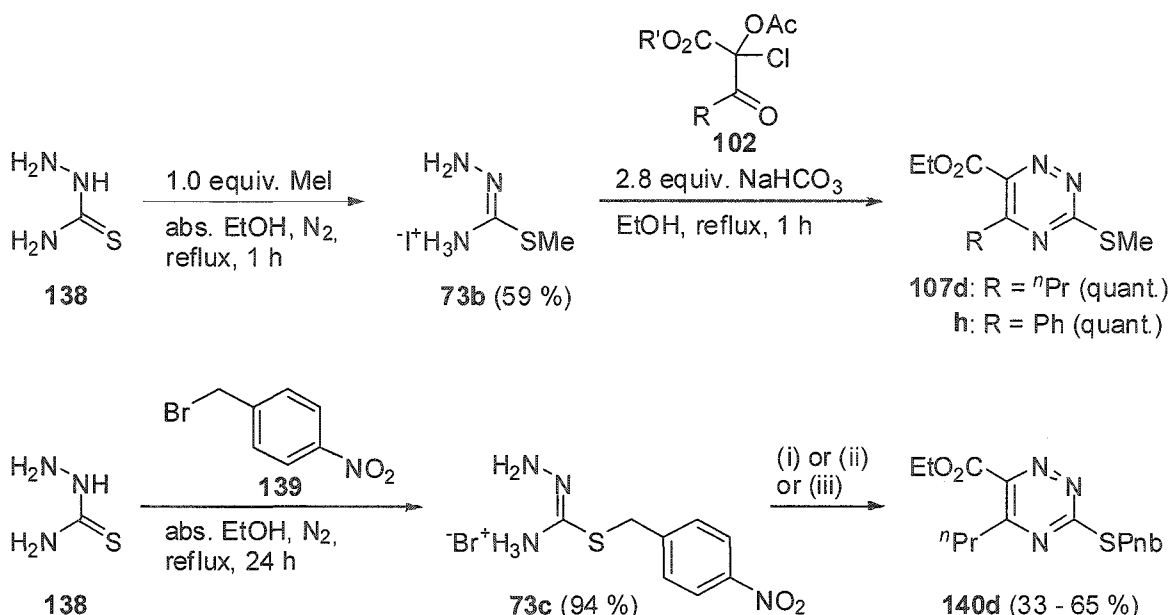
Scheme 38. Preparation of 3-methylthiotriazines **107d,h** and 3-(4-nitrobenzylthio)triazine **140d**. Reagents and conditions: (i) **102d**, 2.5 equiv. **73c**, 2.8 equiv. NaHCO$_3$, EtOH, reflux, 1 h; 33 %; (ii) **102d**, 2.0 equiv. MeNH$_2$, EtOH, RT, 1 h; then 1.0 equiv. **73c**, 1.0 equiv. NaHCO$_3$, EtOH, reflux, 2 h; 65 %. (iii) 'telescoping synthesis': same as (ii) but with *in situ*-generated **73c** (from **138** and **139**); 63 % overall yield.

The yield of *S*-(4-nitrobenzyl)triazine **140d**, which derived from the reaction of chloroacetate **102d** with thiosemicarbazide **73c**, was poor (33 %) when prepared according to **107d** but could be improved to 65 % when pre-treating **102d** with two equivalents of methylamine (Scheme 38). The thiosemicarbazide **73c**, in turn, was prepared in excellent yield (94 %) from an equimolar mixture of its parent compound **138** and 4-nitrobenzyl bromide (**139**). In a simplified method chloroacetate **102d** was pre-treated with

methylamine and then reacted with the *in situ*-generated thiosemicarbazide **73c** (from **138** and **139**) to furnish triazine **140d** in good yield (63 %).

In all of the above mentioned triazine formations stoichiometric amounts of sodium bicarbonate were added as a scavenger for the HI and HBr liberated from the thiosemicarbazide hydrogenhalide salts **73b** and **73c** respectively.

### 6.2.2.1 Eschenmoser sulfide contraction

The purpose of the preparation of thiosemicarbazide **73c** and, in turn, triazine **140d** was to test the applicability of the Eschenmoser sulfide contraction[92] to triazines or pyridines. The fact that this type of conversion has been observed in structurally related 2-pyrimidones[93] sparked our interest in this reaction.

The original Eschenmoser sulfide contraction (Scheme 39) saw an initial *S*-alkylation of a secondary thioamide or thiolactam **141** by an α-halogenated carbonyl compound **142**. Addition of a base to the newly-formed compound **143** induced a sequence of deprotonation (**144**), enolisation (**145**), episulfide formation (**146**) and opening (**147**) and elimination which resulted in the formation of vinylogous amide (**148**). The extruded sulfur was taken up by a thiophile such as triphenylphosphine.
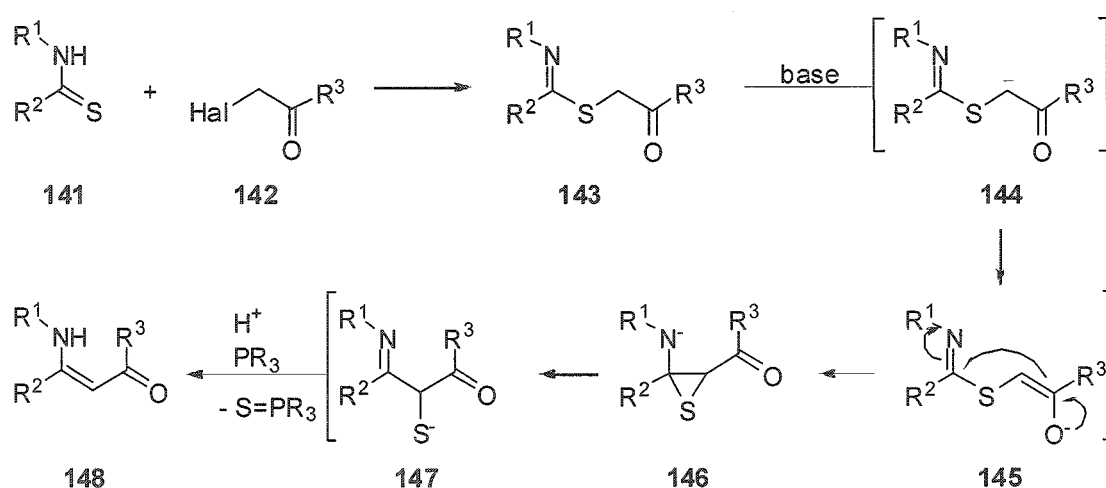
Scheme 39. Mechanism of the Eschenmoser sulfide contraction.

Preliminary work within the group remained unsuccessful and the reaction was re-investigated on the model of the SPnb-substituted triazine **140d** (Scheme 40). In this case – given that no α-carbonyl group was present – the carbanion in structure **149** was hoped to nucleophilically attack the triazine's 3-position directly. The negative charge could be easily delocalised through the triazine ring and stabilised by the ester group. But despite testing different bases (NaH, KO^{t}Bu, NaOEt) and solvents (DMF, THF, toluene), the expected 3-(4-nitrobenzyl)-triazine **150** was not observed. Instead, the starting material was partly re-isolated (42 - 70 %).
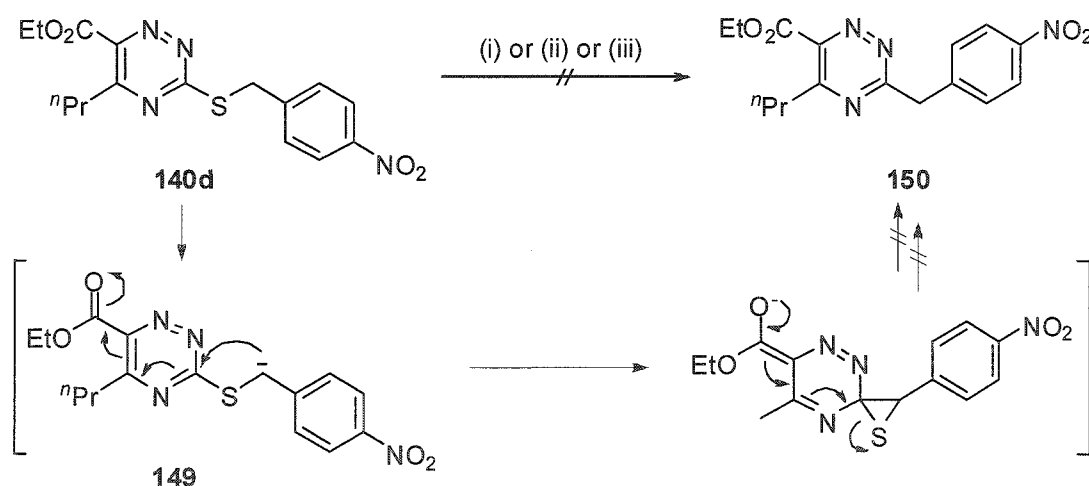
Scheme 40. Attempted sulfide contraction reaction. Reagents and conditions: (i) 1.0 equiv. NaH, 1.0 equiv. PPh$_3$, N$_2$, DMF or dry THF, -15 °C, 2 h; (ii) 1.1 equiv. KO^{t}Bu, 1.0 equiv. PPh$_3$, toluene, -30 °C, 90 min; (iii) 1.0 equiv. NaOEt, DMF, -15 °C, 2 h.

6.3 Pyridine formation

6.3.1 Alkylthio-, sulfinyl- and sulfonylpyridines

6.3.1.1 Reactions of triazines and 2,5-norbornadiene

The 3-methylthio-1,2,4-triazines **107** were prepared with the prospect of having the *S*-methyl functionality replaced by other groups such as trichloromethyl at a later stage of the pyridine synthesis. On various occasions SMe and SO$_2$Me[34,35] substituents have shown to be excellent leaving groups.

There are two possible strategies to convert the 3-methylthio-1,2,4-triazines **107** into the desired methylsulfinyl- and methylsulfonyl-pyridines **153** and **154** respectively: oxidation to *SO*-methyl- and *SO₂*-methyl-triazines **151** and **152** followed by cycloaddition (Scheme 41, route **A**) or the cycloaddition to *S*-methyl-pyridines **117** followed by oxidation (route **B**).
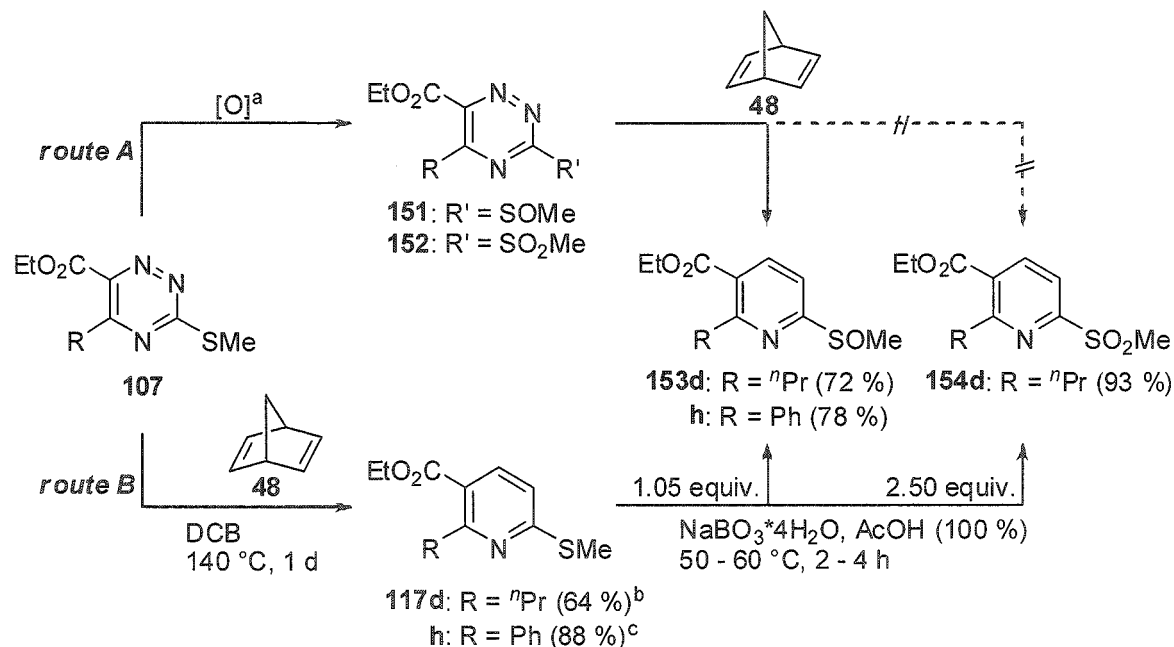
Scheme 41. Two possible preparations of SOMe- and SO₂Me-pyridines from SMe-triazines. [a] mCPBA or NaIO₄ or NaBO₃·4H₂O; [b] 10.0 equiv. **48**; [c] 35.0 equiv. **48**.

Both routes have been investigated in our research group's earlier studies and route **A** was favoured due to initial conversion problems from triazines **107** to pyridines **117** in the first step of route **B**, that is to say no reaction in ethanol, very little conversion in toluene and slow conversion in xylene (product/substrate = 1:1 after 12 h of reflux).

However, when attempting to reproduce the syntheses of route **A**, the oxidation reaction from *S*-methyl compound **107** to *SO*-methyl compound **151** using mCPBA showed a lack of selectivity giving mixtures of substrate, product and in one case over-oxidised side product **152**. Other oxidants such as NaIO₄ and NaBO₃·4H₂O also proved unsuccessful.

Moreover, despite showing that sulfoxy-triazine **151** successfully underwent DA/retro-DA reaction with 2,5-norbornadiene to furnish **153**, ALTUNA-URQUIJO and co-workers[71] found that the same could not be said about the conversion of their sulfonyl equivalents **152** into compounds **154**. Failure to isolate pyridines **154** could be ascribed to ethanolysis of the sulfonyl group. This, however, would have led to presumably easily identifiable products.

A reasoning by ROCHA GONSALVES et al.[44] (in reference to CHENARD et al.[94]) stating that 'In the cycloaddition of 3-(methylsulfonyl)-1,2,4-triazine with some enamines dihydropyridines were also isolated and this was ascribed to conformational factors which made the elimination step unfavourable.' seems more likely. In that case a second successive DA reaction gave the 2:1 adduct as the predominant or even the only product.

Faced with the shortcomings of both the oxidation and the retro-DA step of route A, our focus now turned back to route B. The conversion of 107h to 117h in xylene was re-visited using a longer reaction time (1 day) giving an only slightly improved product/substrate mixture of around 3:2. Reactions in neat 2,5-norbornadiene at an extended reaction time (2 days) showed more promise giving good yields of the products 117d (66 %) and 117h (64 %), each with 8 % of the substrate 107 remaining unconverted. Full conversion was finally achieved in 1,2-dichlorobenzene at 140 °C. The higher yield of 117h (88 %) compared to 117d (64 %) was a result of optimisation, namely the use of a greater excess of dienophile 48 (35 instead of 10 equivalents).

The subsequent oxidation was initially carried out with mCPBA, the reagent of choice for conversions of this type in numerous publications. However, in this instance 1.1 equivalents of mCPBA afforded a separable mixture of the desired sulfoxy compound 153h (22 %) and the over-oxidised sulfonyl compound 154h (56 %); the use of 1.1 equivalents of sodium periodate resulted in an inseparable mixture of 153h (25 %) and starting material 117h (25%). Eventually, single pure products 153 and 154 were obtained in good yields (72 – 93 %) using sodium perborate (1.05 and 2.5 equivalents respectively) which, compared to mCPBA, is a relatively mild and stable oxidant. Only on one occasion was a mixture of 153h (49 %) and over-oxidised 154h (29 %) observed when aiming for the sulfoxy compound 153h.

A comparison of ^{1}H-NMR spectral data for the methylthio- **117d**, sulfinyl- **153d** and sulfonyl-pyridines **154d** (Figure 12) can be found in Table 11. The structures were verified by HRMS (Table 12).
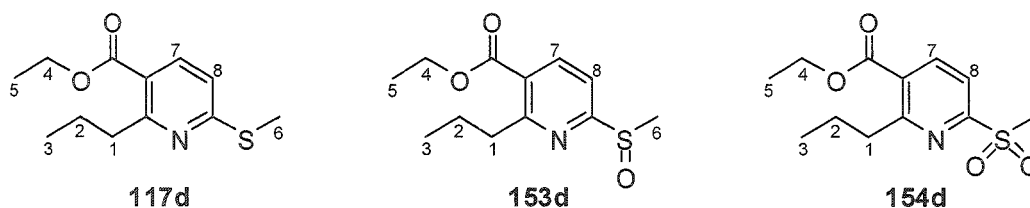

Figure 12. Sulfur-containing pyridines.

Table 11. ^{1}H-NMR spectral data of SMe-pyridine **117d**, SOMe-pyridine **153d** and SO$_2$Me-pyridine **154d**.

chemical shift (ppm)			multiplicity,	coupling	assignment
117d	**153d**	**154d**	integral	const. (Hz)	
7.97	8.35	8.37	d, 1	8.2	7-H
7.04	7.89	7.96	d, 1	8.2	8-H
4.34	4.37	4.43	q, 2	7.2	4-H
3.15 – 3.09	3.15 – 3.09	3.22 – 3.16	m, 3		1-H
2.59	2.83	3.27	s, 3		6-H
1.84 – 1.70	1.71	1.79	m / tq, 2	n/a / 7.4	2-H
1.39	1.38	1.43	t, 3	7.2	5-H
1.00	0.95	1.01	t, 3	7.2 / 7.4	3-H

Table 12. HRMS data of SMe-pyridine **117d**, SOMe-pyridine **153d** and SO$_2$Me-pyridine **154d**.

pyridine	mass calculated for [M+H]$^+$	mass measured
117d	240.1053	240.1052
153d	256.1002	256.1002
154d	272.0951	272.0951

The same methodology of cycloaddition in dichlorobenzene followed by perborate oxidation was applied to (4-nitrobenzylthio)triazine **140d** resulting in moderate yields of pyridine **155d** (50 %), sulfinyl-pyridine **156d** (43 %) and sulfonyl-pyridine **157d** (73 %) which did not quite compare to the ones of the respective methylthio equivalents but, nevertheless, furnished pure products (Scheme 42). On this occasion, the DA reaction in neat 2,5-norbornadiene (**48**) showed full conversion of **140d** but produced only 35 % of pyridine **155d**.
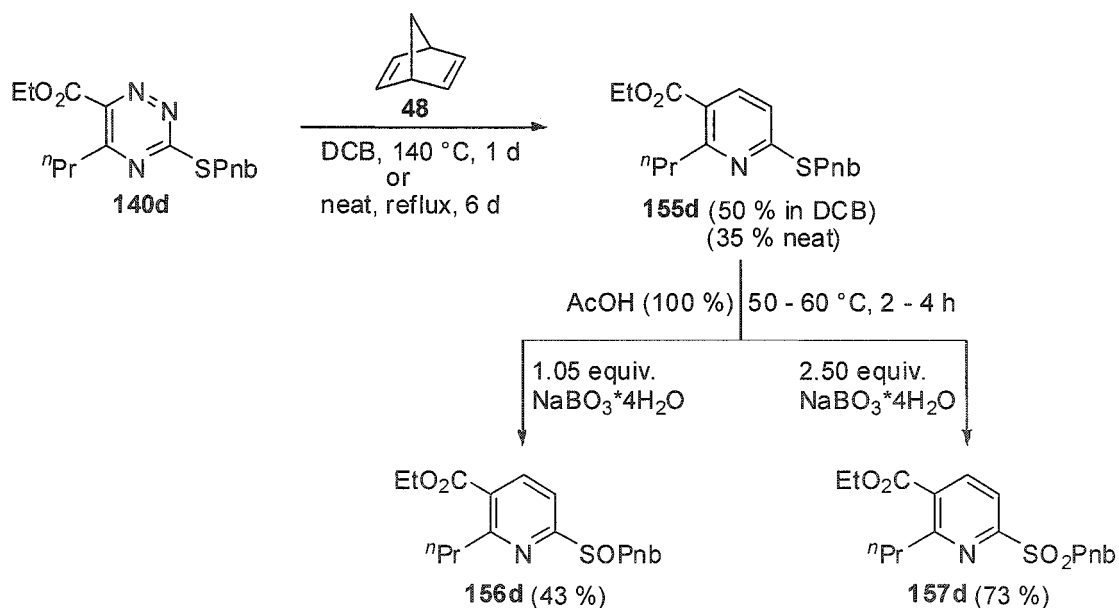
Scheme 42. Preparation of sulfinyl- and sulfonyl-pyridines **156d** and **157d** from triazine **140d**.

The ^{1}H-NMR spectra of SPnb-pyridines **155d** showed downfield shifts similar to those of the SMe-pyridine **117d** when oxidised. Again, structures were assured by HRMS (Table 13).

Table 13. HRMS data of SPnb-pyridine **155d**, SOPnb-pyridine **156d** and SO$_2$Pnb-pyridine **157d**.

pyridine	mass calculated for [M+H]$^+$	mass measured
155d	361.1217	361.1219
156d	377.1166	377.1168
157d	393.1115	393.1119

6.3.1.2 Reactions of chloroacetates and thiosemicarbazides – 'one-pot' reaction

The 'one-pot' synthesis of the sulfur-containing pyridine **155d** from chloroacetate **102d**, thiosemicarbazide **73c** and 2,5-norbornadiene (**48**) (Scheme 43) was carried out in a bid to optimise the yield of the two-step procedure. However, with only 24 % of isolated target compound this method was far inferior to the stepwise approach where triazine **140d** was isolated in quantitative yield and converted into the pyridine **155d** in 50 % yield.
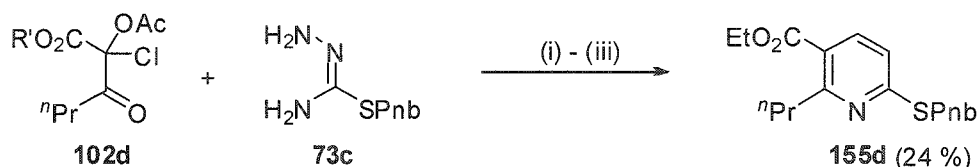
Scheme 43. 'One-pot' synthesis of pyridine **155d**. Reagents and conditions: (i) **102d**, 2.0 equiv. $MeNH_2$, EtOH, RT, 1 h; (ii) 1.0 equiv. **73c**, 1.0 equiv. $NaHCO_3$, EtOH, reflux, 2 h; (iii) 32 equiv. 2,5-norbornadiene (**48**), DCB, 140 °C, 3 d.

6.3.2 Bipyridines

6.3.2.1 Reactions of (2-pyridyl)triazines and norbornadiene

The straightforward conversion of (2-pyridyl)triazines **106** into their corresponding bipyridines **116** with 2,5-norbornadiene (**48**) in boiling ethanol (Scheme 44) has already been explored by WATSON et al.[78] showing a low yield of compound **116a** (R = Me; 36 %) but generally good results for bipyridines **116d** (R = ^{n}Pr; 81 %), **116e** (R = ^{i}Pr; 81%) and **116h** (R = Ph; 87 %) with larger substituents, a trend that was recurring for various DA reactions in our study.
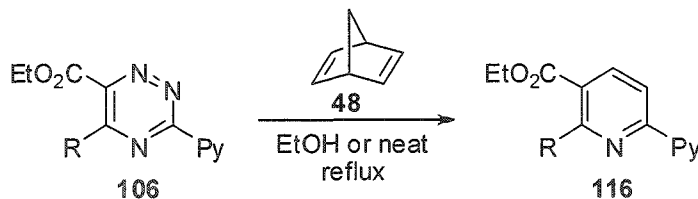

Scheme 44. DA reaction of **116d** in neat 2,5-norbornadiene (**48**).

We attempted an optimisation of this conversion by means of a solvent-free reaction of triazine **106d** with 2,5-norbornadiene (**48**) which proceeded smoothly to full conversion but resulted in a reduced yield of bipyridine **116d** (65 %).

6.3.2.2 Reactions of chloroacetates and amidrazones – 'one-pot' reaction

Earlier work by ALTUNA-URQUIJO *et al.* has shown that a 'one-pot' synthesis of bipyridines 116 from chloroacetates 102, amidrazones 73a and 2,5-norbornadiene (48) is a superior method to the two-step-process with isolation of triazines 106. Similarly to the preparation of triazines 106 (cf. Section 6.2) these syntheses have been investigated in much detail and the examples presented in Scheme 45 are an extension to the work of past co-workers.
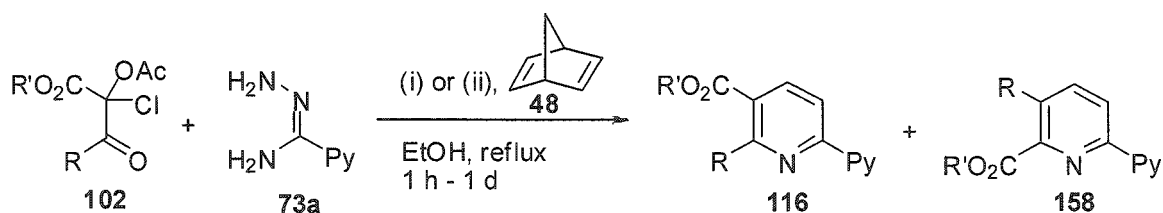
Scheme 45. 'One-pot' syntheses of bipyridines. Reagents and conditions: (i) 2.5 equiv. 73a; (ii) 102, 2.0 equiv. MeNH$_2$, RT, 1 h; then 1.0 equiv. 73a.

Bipyridines 116 were initially prepared from the reaction of their corresponding chloroacetates 102 using 2.0 – 2.5 equivalents of amidrazone 73a (Table 14, method A) and ten equivalents of 2,5-norbornadiene (48) in boiling ethanol. In context with earlier results it is noticable that chloroacetates 102 with small substituents (R = Me, Et) gave unsatisfactory yields (22 %) whereas those with larger substituents (R = ^{n}Pr, ^{i}Bu, Ph) showed moderate yields (49 – 63 %).

Table 14. Yields of bipyridines 116 (results in *italics* are from former co-workers).

pyridine 116	R	R'	method A	method B	method C
a	Me	Et	22 % (*18 %*)		
c	Et	Me	22 %		
d	^{n}Pr	Et	*63 %*	56 % (*80 %*)	*96 %*
f	^{i}Bu	Et	49 % [a]	61 % [b]	
h	Ph	Et	*50 %*	*68 %*	*80 %*
i	Np	Et	*14 %*		

Methods: A: no pre-treatment of chloroacetates 102; B: pre-treatment of 102 with MeNH$_2$;

C: pre-treatment of 102 with EtOH/HCl; [a] 2:1 mixture with regioisomer 158f; [b] 3:1 mixture with 158f.

Alternatively, chloroacetates **102** were subjected to two equivalents of methylamine prior to reaction with one equivalent of amidrazone **73a** (method B) generally improving the yields of bipyridines **116**. Reaction of chloroacetate **102f** resulted in a product mixture of regioisomers **116f** (Figure 13; Table 15) and **158f** (Figure 14; Table 16).

On the two occasions where pre-treatment of chloroacetates by ethanolic hydrogen chloride solution (method C) was applied in earlier studies, the yields (of **116d,h**) were superior to those of methods A and B.

While the conversion of triazine **106d** to pyridine **116d** in neat 2,5-norbornadiene (**48**) proceded smoothly (Scheme 44, p. 48), this was not the case for the 'neat one-pot' reaction from chloroacetate **102d** (Scheme 45) where at best an inseparable mixture of **116d** (35 %) and **102d** (35 %) was obtained (after 2 days at reflux).
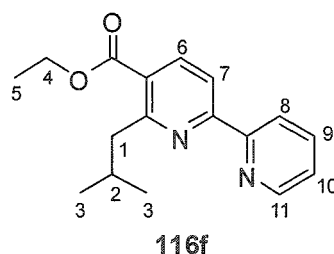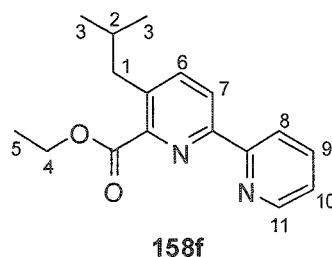

116f

Figure 13. Bipyridine **116f**.

Table 15. ^{1}H-NMR spectral data of bipyridine **116f**.

chemical shift (ppm)	multiplicity	integral	coupling constants (Hz)	assignment
8.70	ddd	1	1.0, 1.7, 4.7	11-H
8.52	ddd	1	1.0, 1.2, 7.9	8-H
8.30 and 8.27	2d	2	8.2	6-H, 7-H
7.84	ddd	1	1.7, 7.7, 7.9	9-H
7.34	ddd	1	1.2, 4.7, 7.7	10-H
4.40	q	2	7.2	4-H
3.16	d	2	6.7	1-H
2.26	nonet	1	6.7	2-H
1.43	t	3	7.2	5-H
0.99	t	3	6.7	3-H

Figure 14. Bipyridine **158f.**

Table 16. ^{1}H-NMR spectral data of bipyridine **158f.**

chemical shift (ppm)	multiplicity	integral	coupling constants (Hz)	assignment
8.70	ddd	1	1.0, 1.7, 4.7	11-H
8.58	ddd	1	1.0, 1.2, 7.9	8-H
8.42	d	1	8.2	7-H
8.33	d	1	8.2	6-H
7.85	ddd	1	1.7, 7.7, 7.9	9-H
7.36	ddd	1	1.2, 4.7, 7.7	10-H
4.43	q	2	7.2	4-H
2.54	d	2	6.9	1-H
2.30 – 2.15	m	1		2-H
1.31	t	3	7.2	5-H
0.89	t	3	6.7	3-H

Correct assignment of the regioisomers 116 and 158:

The initial assignment of the products (or product mixtures) obtained from the DA reaction in Scheme 45 to the two regioisomers **116** and **158** was based upon a structure determination of the DA products **113** carried out by WATSON *et al.*[78] (Scheme 46).

Treatment of the diesters **113d,h** with 0.5M NaOH resulted in hydrolysis of the ester group in the 2-position whilst the one in 5-position remained stable under these conditions. Compound **159** was then decarboxylated and the NMR spectral data of the resulting nicotinate **160** was found to be identical to an authentic sample of **160** verifying the regioselectivity of the DA reaction leading to pyridines **113**.
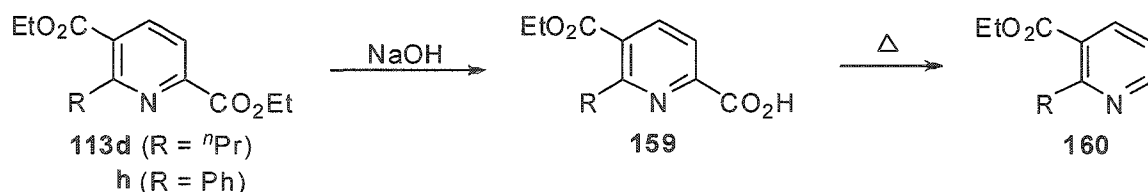
Scheme 46. Confirmation of structure **113** by defunctionalisation and comparison to authentic samples of **160** (WATSON et al.[78]).

We then hydrolysed the ester **116d** using aqueous KOH for the cleavage and acidic conditions for the precipitation of the nicotinate **161d** obtaining the crystalline acid **161d** in good yield (Scheme 47). Subsequently, we subjected compound **161d** to several decarboxylation regimes in order to determine its regioisomeric constitution through comparison of the NMR spectral data of the decarboxylation product **162d** to that of an authentic sample.
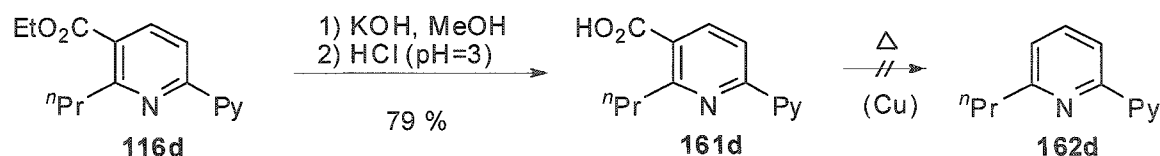
Scheme 47. (Attempted) FGI of the ester group in pyridine **116d**.

Although – and possibly because – failing to obtain the literature-known nicotinate **162d**, we were confident that our assignment was correct as only a *meta*-substituted ester/acid group would be stable under the hereinafter described conditions. Heating of a sample of **161d** to 200 °C for 10 minutes showed no conversion; heating to 150 °C for 2 h resulted in sublimation of the crystals and deposition of fine white needles which turned out to be still substrate. Heating the highly stable compound **161d** in the presence of one equivalent of copper powder melted the solid at 80 °C, a temperature at which the product would be expected to melt. However, NMR analysis could not be performed due to the formation of an insoluble copper-bipyridine complex.

A determination of the regioselectivity of DA reactions on the example of triazine **106d** (Scheme 48) was unsuccessful as the ester did not hydrolyse under the standard reaction conditions.
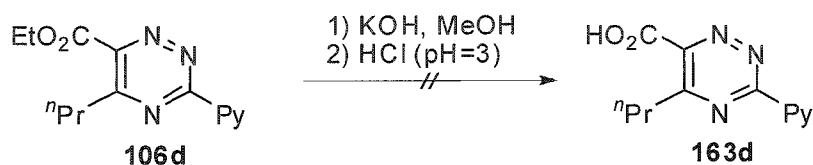
Scheme 48. Attempted FGI of the ester group in triazine **106d**.

6.3.2.3 Reactions of (2-pyridyl)triazines and 2,3-dihydrofuran

As 2,5-norbornadiene (48) had already been used extensively as a dienophile on various triazines in our group's earlier work, we went on to test further dienophiles for DA reactions, namely 2,3-dihydrofuran (63a) and 1-pyrrolidino-1-cyclopentene (56b), on the example of (2-pyridyl)triazines 106d.

Whilst needing a similar activation energy (i.e. temperatures of around 80 °C) as 2,5-norbornadiene (48) for reactions with most aza-dienes, DHF (63a) has a much lower boiling point (54 °C as opposed to 89 °C) which posed a considerable challenge in terms of experimental setup. A closed system would, by virtue of the building pressure, suppress the spontaneous extrusion of nitrogen from the DA adduct and favour the formation of 2:1-adducts.[44] Hence, DHF had to be used in an open system and in large excess in order to compensate for its volatility.

Reasonably good yields of pyridine 164d (62 – 64 %) were obtained from triazine 106d after comparably[44] short reaction times (20 h) at vigorous reflux in high-boiling solvents (Scheme 49; Table 17, entries 3 and 4). Unlike with 2,5-norbornadiene (48) as the dienophile/solvent, this reaction could not be performed in neat DHF (63a) since it is very susceptible to polymerisation and other side reactions at elevated temperatures.

Table 17. DA reaction of triazine 106d using cyclic vinyl ether 63a in various solvents.

entry	solvent	equiv. of DHF (63a)	temp.	time	yield of 164d
1	CH_2Cl_2	7	RT	3.5 d	-
2	CH_2Cl_2	12	40 °C	5 d	22 %
3	ethanol	32	80 °C [a]	20 h	64 %
4	toluene	32	80 °C [a]	20 h	62 %

[a] vigorous reflux (b.p. of DHF is 54 °C)

It can be said with confidence that the regioselectivity of the cycloaddition of DHF (**63a**) onto triazine **106d** is as depicted in Scheme 49. Had the dienophile **63a** reacted with opposite regioselectivity, the ring-opening of the added DHF would have resulted in reaction with the adjacent ester, thus, lactonisation (cf. Scheme 23, p. 25) instead of reaction with another equivalent of DHF (**63a**). This was ruled out as NMR spectroscopy (Table 18) and HRMS confirmed the target structure to be **164d** (Figure 15).
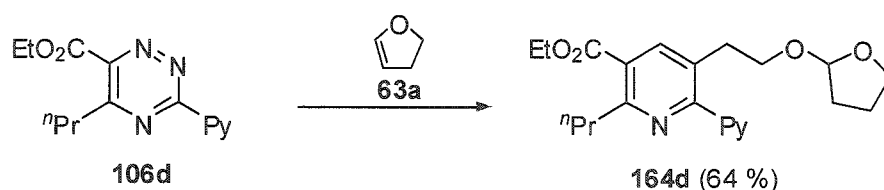
Scheme 49. DA reaction using cyclic vinyl ether **63a**.
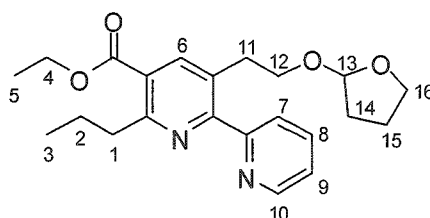
Figure 15. Bipyridine **164d**.

Table 18. ^{1}H-NMR spectral data of bipyridine **164d**.

chemical shift (ppm)	multiplicity	integral	coupling constants (Hz)	assignment
8.68	ddd	1	1.0, 1.7, 4.7	10-H
8.17	s	1		6-H
7.88	ddd	1	1.0, 1.5, 7.9	7-H
7.82	ddd	1	1.7, 7.7, 7.9	8-H
7.31	ddd	1	1.5, 4.7, 7.7	9-H
5.10 – 5.03	m	1		13-H
4.40	q	2	7.2	7-H
3.82 – 3.74	m	2		16-H
3.19	t	2	6.7	11-H
3.18 – 3.13	m	2		4-H
2.04 – 1.70	m	6		5-H, 20-H, 21-H
1.43	t	3	7.2	8-H
1.01	t	3	7.4	6-H

54

6.3.2.4 Reactions of (2-pyridyl)triazines and 1-pyrrolidino-1-cyclopentene

For the reaction of triazines with 1-pyrrolidino-1-cyclopentene (56b) (Scheme 50) a method by KOZHEVNIKOV et al.[95] was adapted. Unlike with DHF (63a) as the dienophile (cf. Scheme 49, p. 54) the regioselectivity of the addition of enamine 56b onto triazine 106d is irrelevant because whether the reaction proceeds through cycloadduct 165d or rather through 166d, the outcome is always pyridine 167d.
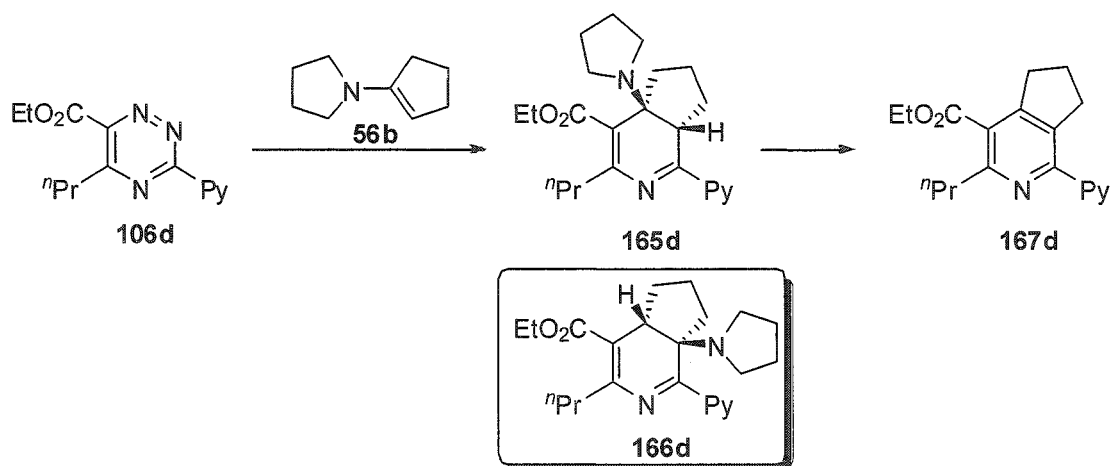
Scheme 50. DA reaction using enamine 56b; only additions from top-face shown for simplicity.

Table 19. ^{1}H-NMR spectral data of bipyridine 167d.

chemical shift (ppm)	multiplicity	integral	coupling constants (Hz)	assignment
8.68	ddd	1	1.0, 1.7, 4.7	Py-H
8.25	ddd	1	1.0, 1.2, 7.9	Py-H
7.80	ddd	1	1.7, 7.7, 7.9	Py-H
7.27	ddd	1	1.2, 4.7, 7.7	Py-H
4.42	q	2	7.2	ester-CH$_2$
3.38 and 3.06	2t	4	7.7	-CH_2-CH$_2$-CH_2-
3.01 – 2.95	m	2		-CH_2-CH$_2$-CH$_3$
2.16 – 2.02	m	2		-CH$_2$-CH_2-CH$_2$-
1.82	tq	2	7.4	-CH$_2$-CH_2-CH$_3$
1.42	t	3	7.2	ester-CH$_3$
1.01	t	3	7.4	-CH$_2$-CH$_2$-CH_3

Several reaction conditions (solvent, amount of 56b, temperature) and workup procedures were tested to optimise the initially low yield (Table 20; entry 1) but the crucial step seemed to be the elimination of the DA adduct 165d, thus depending on the workup rather than the reaction conditions and in particular the addition of acetic acid. We were then especially pleased to see that upon acid-facilitated re-aromatisation of 165d followed by workup in basic medium (entry 7) the product 167d was obtained in good yield (84 %) without need for column chromatography or recrystallisation. Furthermore, the reaction proceeded smoothly at ambient temperature without external heating.

Table 20. Preparation of annulated pyridine 167d from triazine 106d and enamine 56b.

entry	dienophile 56b	solvent	temp.	time	workup [a]	yield of 167d
1	1.12 equiv.	dioxane	reflux	1 h	B, C	49 %
2	1.12 equiv.	ethanol	reflux	1 h	B, C	49 %
3	2.24 equiv.	ethanol	reflux	1 h	B, C	45 %
4	1.12 equiv.	ethanol	reflux	1 h	C	52 %
5	large excess	neat	reflux	1 h	C	-
6	1.11 equiv.	ethanol	RT	1 h	C	45 %
7	1.11 equiv.	ethanol	RT	1 h	A, B	84 %

[a] A: acidic workup (stir with excess glacial acetic acid for 1 h at RT);
B: basic workup (make basic with excess 1M NaOH and then extract with dichloromethane);
C: column chromatography.

The literature showed that utilising a microwave improved the yield of similar aza DA reactions using the same dienophile.[96] On an industrial scale, however, such a procedure would not be feasible.

6.3.2.5 'One-pot' reaction with 1-pyrrolidino-1-cyclopentene

A 'one-pot' reaction involving enamines as dienophiles required a slightly modified procedure to the one involving 2,5-norbornadiene (48) that was discussed earlier. As enamines are prone to undergo side reactions with the chloroacetates or the *in situ*-generated tricarbonyls they would interfere with the condensation of tricarbonyls and amidrazones. In fact, when adding both amidrazone 73a and enamine 56b to the solution of chloroacetate 102d in ethanol at once no bipyridine 167d was formed.

Addition of the enamine **56b** two hours into the reaction of chloroacetate **102** with amidrazone **73a** furnished 41 % of the desired pyridine **167d** (Scheme 51). As already shown (Table 20), this yield could theoretically be further increased by means of an acidic workup but this has not been investigated.
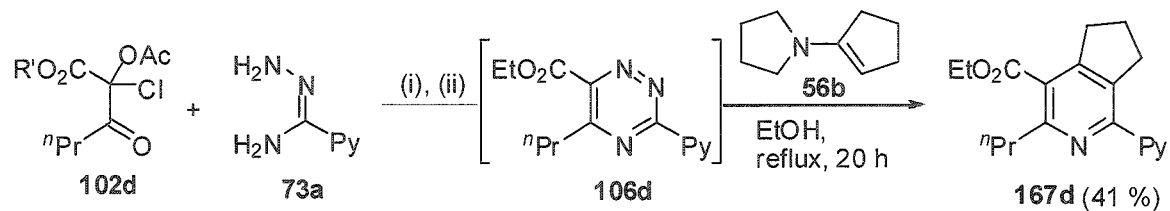

Scheme 51. DA reaction using enamine **56b**. Reagents and conditions: (i) **102**, 2.0 equiv. MeNH$_2$, EtOH, RT, 1 h; (ii) 1.0 equiv. **73a**, reflux, 1 h.

7 Picolinate route

7.1 Rationale

Alongside the improvements on, and modifications to, the existing methodology we developed and optimised a very promising novel route towards pyridines. In this alternative to the chloroacetate route the tricarbonyl precursors that were reacted with amidrazones to triazines/pyridines were picolinic acid esters **168**.

The rationale was that picolinic acid esters **168** are capable of forming complexes **169** with metal salts such as copper(II) acetate. This complexation would facilitate the cleavage of the ester bond by methanol resulting in the formation of α-hydroxy-β-keto esters **98** and methyl picolinate (**170**) as a by-product. The presence of excess copper(II) acetate would ultimately result in immediate oxidation of the *in situ* generated α-hydroxy-β-keto esters **98** to the desired α,β-diketo esters **81** (Scheme 52). Related transformations, i.e. the scission of picolinate esters[97] and the oxidation[98] of alcohols to ketones, have independently been reported before.
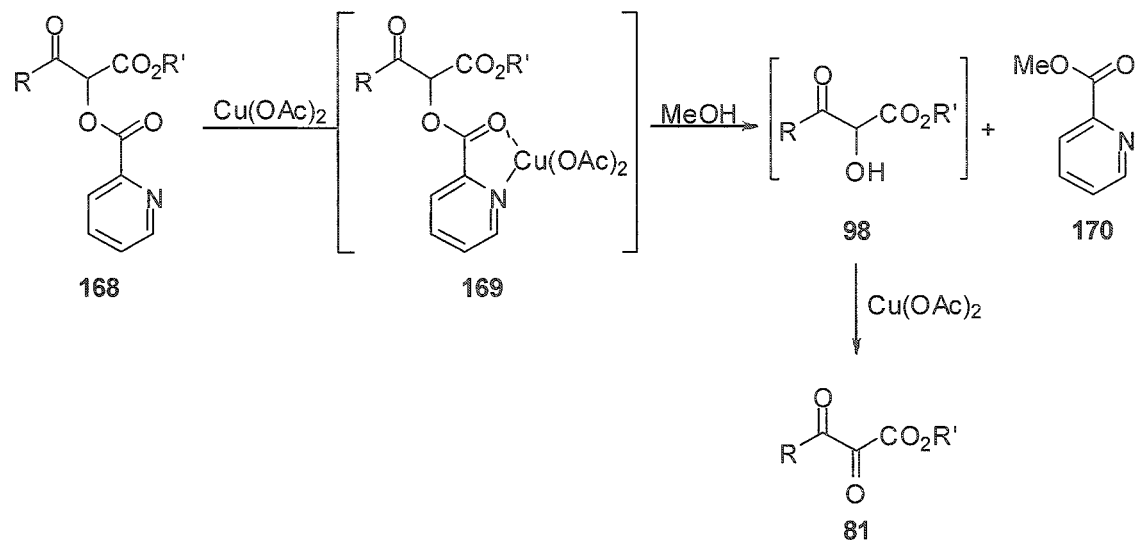
Scheme 52. A novel route to α,β-diketo esters **81**.

7.2 Picolinates

In the first step (Scheme 53) of this route we simply adapted the experimental procedure for the preparation of the α-acetoxy compounds **101** from the chloroacetate route (Section 6.1, p. 34): α-chloro compounds **100** were added to a solution of picolinic acid and KHCO$_3$ in DMF.
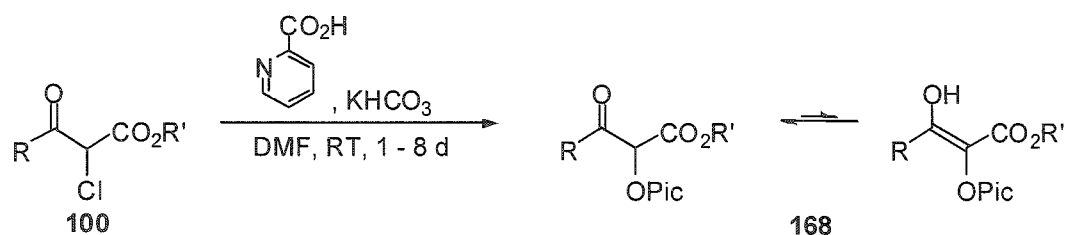
Scheme 53. Preparation of picolinates **168** from α-chloro compounds **100**.

Table 21. Yields of α-chloro-β-keto esters **100**.

picolinate 168	R	R'	yield [a]
a	Me	Et	77 % [b] (77 %)
b	Me	^{t}Bu	69 % [c] (49 %)
c	Et	Me	81 % (80 %)
d	^{n}Pr	Et	91 % (89 %)
e	^{i}Pr	Et	59 % (55 %)
f	^{t}Bu	Et	80 % (61 %)
g	^{t}Bu	Et	64 % (64 %)
h	Ph	Et	92 % (92 %)
i	Np	Et	77 % [d] (59 %)
j	CF$_3$	Et	0 %

[a] from α-chloro-β-keto ester **100** and (from commercially available starting material);

[b] keto:enol form = 93:7; [c] keto:enol form = 90:10; [d] containing small amounts of impurities.

Reaction rates of the picolinate **168** formation were generally slower (1 to 8 days) than those for the acetoxy equivalents **101** (20 h to 3 days) of the chloroacetate route but the products **168** were obtained in the same good to excellent yields (Table 21) as the chloroacetates **102** from the same substrates **100**. The only exception was the trifluoromethyl derivative **168j** which, as in the chloroacetate route (Section 6.1, p. 34 f.), could not be obtained from its α-chloro-β-keto ester **100j**. In the synthesis of derivative **168g** 3 % of substrate **100** remained unreacted. Reactions at elevated temperatures were

not carried out but it is imaginable that this would increase reaction rates and drive the reaction of **100g** to completion.

The structures **168** were confirmed by ^{1}H- and ^{13}C-NMR spectroscopy and HRMS. The ^{1}H-NMR spectra (Table 22 for **168d**) contained the four characteristic picolinate signals at 8.8, 8.2, 7.9 and 7.5 ppm as well as the signal for the α-proton which showed a downfield shift (5.7…6.6 ppm) compared to the substrates **100** (4.7…5.6 ppm).
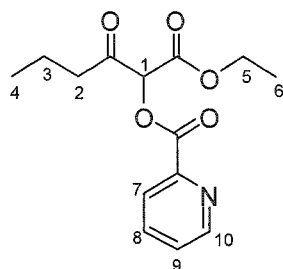
Figure 16. Picolinate **168d**.

Table 22. ^{1}H-NMR spectral data of picolinate **168d**.

chemical shift (ppm)	multiplicity	integral	coupling constants (Hz)	assignment
8.82	ddd	1	1.0, 1.7, 4.7	10-H
8.23	ddd	1	1.0, 1.2, 7.9	7-H
7.89	ddd	1	1.7, 7.7, 7.9	8-H
7.54	ddd	1	1.2, 4.7, 7.7	9-H
5.81	s	1		1-H
4.33	q	2	7.2	5-H
2.77	t	2	7.2	2-H
1.70	tq	2	7.2	3-H
1.33	t	3	7.2	6-H
0.96	t	3	7.2	4-H

Compared to the already short chloroacetate route described in Section 6.1 (p. 34 f.) this route saved an additional reaction step as the second chlorination step that was necessary in the chloroacetate route could be omitted here.

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7.3 Triazine and pyridine formation

7.3.1 (2-Pyridyl)triazines and 2,2'-bipyridines

For the synthesis of triazines **106** and pyridines **116** (Scheme 54), suspensions of picolinates **168**, 2.0 - 2.5 equivalents of copper(II) acetate and excess methanol in dichloromethane were stirred at ambient temperatures and monitored by TLC for disappearance of the starting material (generally one day). The copper salts were filtered off and remaining traces were removed from the organic solution by washing with an aqueous solution of the strong complexating agent Na_2EDTA. It was essential that the copper was fully removed as it would have interfered with the subsequent condensation of α,β-diketo esters **81** and amidrazone **73a** by means of complexing the amidrazone. From this stage on the procedure was identical to that of the chloroacetate route. The tricarbonyls **81** and amidrazone **73a** were converted into triazines **106** in boiling ethanol or optionally transformed directly into pyridines **116** adding 2,5-norbornadiene (**48**) together with the amidrazone **73a**.
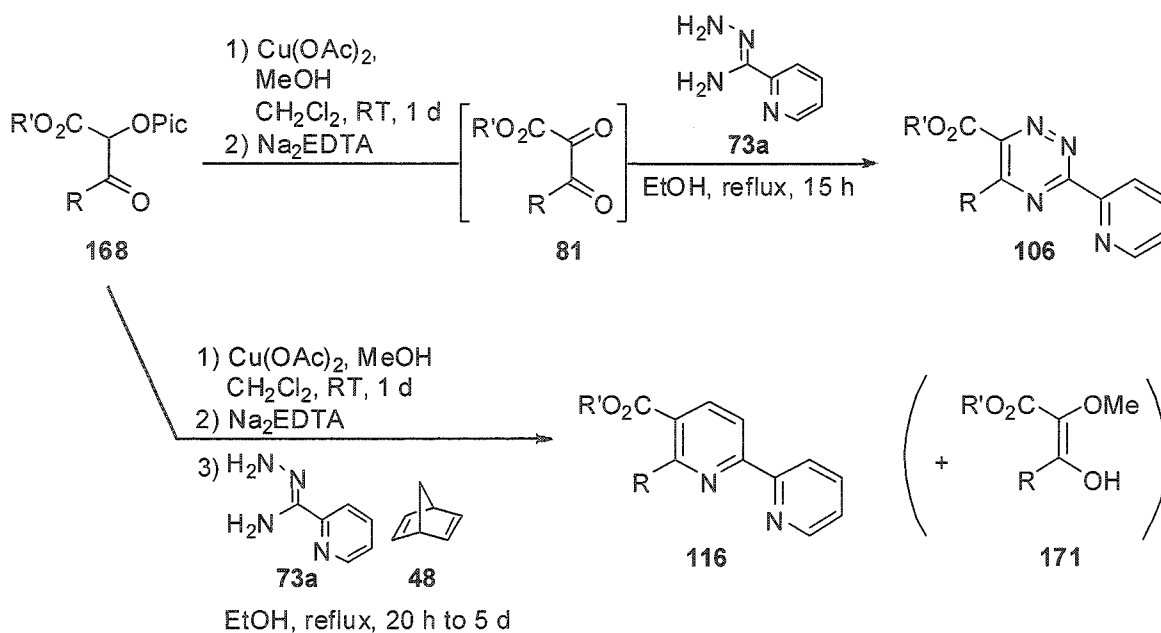
Scheme 54. (2-Pyridyl)triazine and 2,2'-bipyridine syntheses from picolinates **168**.

When analysing the yields and purities of the various triazines **106** and bipyridines **116** (Table 23) it becomes apparent once more that reactions of tricarbonyl equivalents (here picolinates **168**) bearing small 6-substituents (R = Me, Et) tend to result in lower yields and/or products of lesser purity (despite purification by column chromatography)

compared to those with larger substituents (R = ^{n}Pr, ^{i}Bu, ^{t}Bu, Ph). The 6-isobutyl pyridine **116f**, which could only ever be obtained in a mixture with its regioisomer **158f** *via* the chloroacetate route, was obtained as the single regioisomer from its picolinate **168f**.

Table 23. Yields of (2-Pyridyl)triazines **106** and 2,2'-bipyridines **116**.

ester	R	R'	triazine 106	pyridine 116
a	Me	Et		complex mixture
b	Me	^{t}Bu		23 % [a]
c	Et	Me	22 %	24 %
d	^{n}Pr	Et	43 %	59 %
e	^{i}Pr	Et		13 % [b]
f	^{i}Bu	Et	58 %	45 %
g	^{t}Bu	Et		68 %
h	Ph	Et	63 %	71 %
i	Np	Et		7 % [c]

[a-c] inseparable mixtures with **171**: [a] 16 %; [b] 20 %; [c] 16 % of **171**.

The reactions of picolinates **168b,e** and **i** afforded low-yielding, inseparable mixtures of the corresponding bipyridines **116** and by-products which we suggested to be compounds **171** according to interpretation of the ^{1}H-NMR spectral data (Table 24 for **171e**).
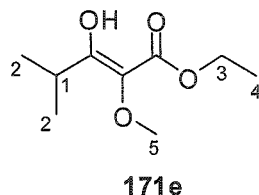
171e

Figure 17. Suggested by-product **171e** from conversion of picolinate **168e** into bipyridine **116e**.

Table 24. ^{1}H-NMR spectral data of picolinate by-product **171e**.

chemical shift (ppm)	multiplicity	integral	coupling constants (Hz)	Assignment
4.29 and 4.27	2q	2	7.2	3-H
3.81	s	3		5-H
2.65	septet	1	6.9	1-H
1.31	t	3	7.2	4-H
0.93 and 0.92	2t	3	6.9	2-H

7.3.1.1 Optimisation I: catalytic use of copper salts

At the outset of this method we used around two equivalents of copper(II) acetate in order to obtain α,β-diketo esters **81** from their precursors **168** – one for the picolinic ester cleavage and another to oxidise the α-hydroxy-β-keto intermediates **98** (Table 25, entry 1). However, in a time where chemical processes are not only assessed by economical but also by ecological criteria the use of stoichiometric quantities of heavy metals is simply not acceptable from an industrial point of view.

A series of optimisation tests was carried out on the example of picolinate **168h**. The first of which was to reduce the load of metal salts to 1.2 equivalents (entries 2 and 3). The reasoning was that the copper(II) acetate that complexes and cleaves the picolinate **168** might not actually be consumed and, therefore, would be available to the oxidation of the freed alcohol of compound **98**. As this resulted in a dramatic decrease in yield we assumed that the copper(II) acetate was indeed consumed by the complexation. Thus, we screened various catalytic $Cu(OAc)_2$/co-oxidant systems for their applicability (entries 4 to 7).

Table 25. Preparation of **116h** from **154h**.

entry	oxidant, (co-oxidant) [a]	conditions for ester cleavage	conditions for aza DA	yield of 116h [b]
1	2.0 equiv. $Cu(OAc)_2$	CH_2Cl_2, 1 d	ethanol, reflux, 2 d	71 %
2	1.2 equiv. $Cu(OAc)_2$	CH_2Cl_2, 4 d	ethanol, reflux, 2 d	32 %
3	1.2 equiv. $Cu(OAc)_2$	toluene, 4 d	toluene, reflux, 2 d	28 %
4	5 mol% $Cu(OAc)_2$, 3.0 equiv. NH_4NO_3	$AcOH/H_2O$, 7 d	ethanol, reflux, 1 d	- [b]
5	6 mol% $Cu(OAc)_2$, 3.2 equiv. $N^nBu_4NO_3$	$AcOH/H_2O$, 7 d	ethanol, reflux, 1 d	47 %
6	5 mol% $Cu(OAc)_2$, air	toluene, 3d	toluene, reflux, 2 d	49 %
7	5 mol% $Pd(OAc)_2$, air	DMSO, 1d	toluene, reflux, 2 d	-

[a] based on picolinate **168h**; [b] based on amidrazone **73a**; [b] 41 % α-hydroxy compound **98h** (Scheme 55).

Catalytic systems for the oxidation of alcohols to ketones are diverse and plentiful. $Cu(OAc)_2/NH_4NO_3$ in acetic acid/water (5:1) seemed promising since an oxidiation similar to the one discussed here had been carried out.[98] Unfortunately, instead of the desired product 116h the α-hydroxy-β-keto ester 98h was isolated (Table 25, entry 4; Scheme 55).
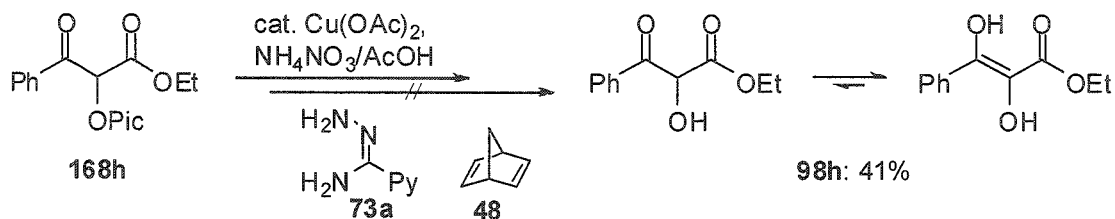
Scheme 55. Incomplete ester cleavage/oxidation reaction.

Replacing NH_4NO_3 by $N^nBu_4NO_3$ under retention of the reaction medium and reaction conditions yielded 47 % of the product (entry 5). Incidentally, $N^nBu_4NO_3$ has also been used before to convert α-halo-β-carbonyl esters into α,β-diketo esters *via* the nitrate esters.[56] Therefore, it cannot be said for certain whether $N^nBu_4NO_3$ re-oxidised the copper(II) acetate or functioned as the sole oxidant. But either way, the use of three equivalents of ammonium salt in combination with a considerable loss in yield did not represent the desired optimisation.

Stimulated by our observation that, no matter if a co-oxidant was used or not, the distinctive turquoise copper(II) acetate colour was always restored after an initial change to green indicating the presence of Cu^I, we succesfully tested a $Cu(OAc)_2/air$ system in the absence of acetic acid and ammonium salts (entry 6) which gave 49 % of the product 116h with a mere 5 mol% of oxidant. This seemingly inconsistent result in comparison with entry 3 (100 mol% oxidant; 23 % product) can easily be explained. Regeneration of Cu^I to Cu^{II} depends largely on the availability of oxygen, i.e. the rate of stirring and the reaction in an open system as opposed to a closed system in entry 3.

The literature suggests that a) both the use of oxygen instead of air and elevated temperatures will increase reaction rates, b) polar solvents inhibit the reaction whereas especially toluene has proven useful and c) yields are likely to be improved by the addition of either stoichiometric amounts of bases such as $NaHCO_3$ or catalytic amounts of non-oxidisable bases with molecular sieves.[99] The finding under point b) was consistent with our results (entries 6 and 7).

Systems simply using oxygen as the stoichiometric and sole co-oxidant have been reported for various metals, e.g. Co, Cu, Ru, Rh, Pd or Pt.[99-102] However, the active catalysts of those systems are transition metal-centered complexes such as $Cu(pyr)_4L_2$ (**A**),[100] $Cu(bpy)_2L_2$ (**B**)[101] or $Pd(OAc)_2$/pyridine[103] (Figure 18), which makes our finding that 5 mol% of $Cu(OAc)_2$ facilitated a picolinate cleavage plus subsequent oxidation of the freed alcohol – apparently without any catalytic complex – all the more interesting. But an oxidative system composed of $Cu(OAc)_2$ and air is not known and seems highly unlikely.
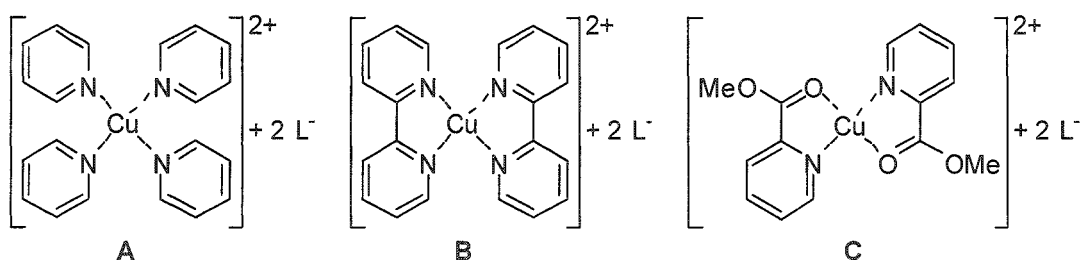
Figure 18. Identified oxidation catalysts (**A**, **B**) and our proposed catalyst (**C**).

We, therefore, propose that the copper-picolinate complex **169** (Scheme 52, p. 58) which is key to the methanolysis of picolinate **168**, subsequently forms a $Cu(PicOMe)_2L_2$ complex **C** (Figure 18) catalysing the oxidation of the *in situ* formed alcohol **98** to the corresponding ketone **81**. According to literature[100,101] the full catalytic system may be depicted as $Cu(PicOMe)_2{}^{2+}/2MeO^-/98/O_2$. Intriguingly, with the picolinate moiety of the substrate acting as a surrogate for additives such as pyridine or bpy in other syntheses, this may be the first example of an aerobic oxidation which requires solely the addition of catalytic amounts of metal salts.

Proposed mechanism II:

Since the presence of the above mentioned oxidative system is purely hypothetical and the good yield in Table 25, entry 6 (p. 63) was rather unexpected, we also considered a second possible reaction mechanism. If the α-hydroxy-β-keto esters **98** that were generated from the cleavage of picolinates **168** were not capable of being oxidised by the catalytic amounts of copper(II) salts, then the reactions had to proceed through just a single condensation of the β-keto group of the compounds **98** with the amidrazone **73a** and a S_N reaction of the the amidrazone's second amine group to form dihydrotriazine **172**, followed either by dehydrogenation/aromatisation to the triazine or DA reaction of **172** to form the pyridine **116** (Scheme 56).
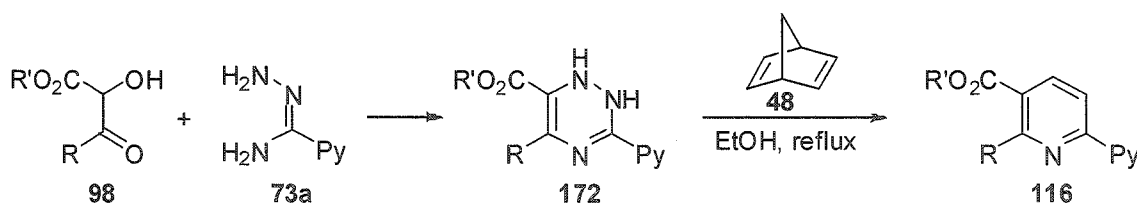
Scheme 56. A second proposed mechanism for the conversion of picolinates **168** into pyridines **116**.

To clarify this, α-acetoxy compound **101h** was de-acylated by treatment with a saturated solution of ethanolic hydrogen chloride and subsequently amidrazone **73a** and 2,5-norbornadiene (**48**) were added to the newly formed α-hydroxy-β-keto ester **98h** (Scheme 57).
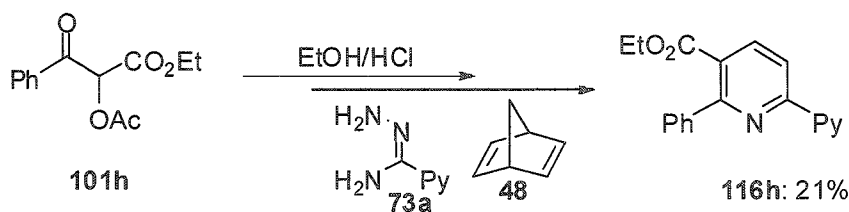
Scheme 57. From acetates to pyridines. Reagents and conditions: (i) excess sat. EtOH/HCl, RT, 1 d; (ii) 1.1 equiv. **73a**, 10 equiv. **48**, N_2, EtOH, reflux, 2 d.

Although the yield was very low, the fact that this novel type of reaction proceeded through to the target compound **116h** gives reason to believe that the conversion of picolinates **168** into pyridines **116** with catalytic amounts of oxidant also proceeded at least partly *via* mechanism II.

7.3.1.2 Optimisation II: improving yields of pyridines with small 6-substituents

Since pyridines with a small substituent in 6-position (R = Me, Et) were obtained in poor yields *via* both the chloroacetate and the picolinate route, we decided to re-examine the pyridine synthesis as carried out by WATSON *et al*. Ethyl 3-oxobutanoate (**78a**) was converted into the tricarbonyl precursor **95a** by diazo transfer from 4-acetamidobenzenesulfonyl azide (**97**) in 27 % yield (Scheme 58). Decomposition of diazo compond **95a** with *tert*-butyl hypochlorite furnished the α,β-diketo ester **81a** which was reacted with amidrazone **73a** and 2,5-norbornadiene (**48**). Unfortunately, **106a** was isolated in very low yield (16 %) again. Additionally, 5 % of the regioisomer **158a** was obtained after column chromatography.
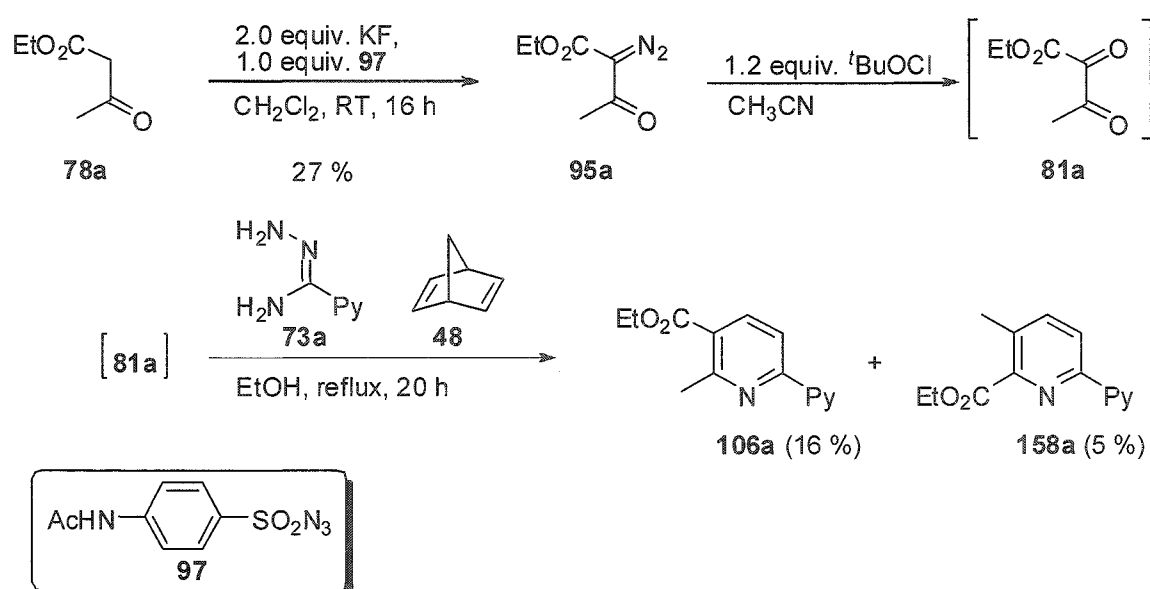
Scheme 58. Synthesis of pyridine **106** *via* its diazo compound **95a** using 1.0 equiv. **73a** and 10 equiv. **48**.

7.3.2 Sulfur-containing triazines

Triazines **107** were prepared from their corresponding picolinates **168** and thiosemicarbazide **73b** as outlined in Scheme 59. Similarly to the chloroacetate route, triazines **107** prepared from thiosemicarbazide **73b** generally gave better yields than their 2-pyridyl substituted equivalents **106**.
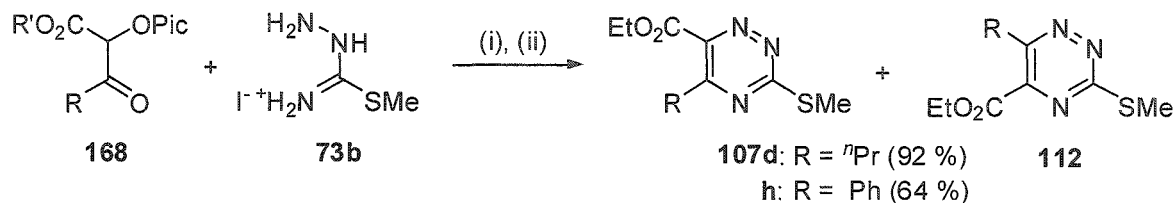
Scheme 59. Preparation of 3-(S-methyl)-triazines **107**. Reagents and conditions: (i) **154**, 2.1 equiv. $Cu(OAc)_2$, excess MeOH, CH_2Cl_2, RT, 1 h; (ii) 2.6 equiv. **73b**, 2.9 equiv. $NaHCO_3$, EtOH, reflux, 2 h.

However, the S-methyl triazines **107** synthesised from chloroacetates **102** were found to be superior to the the ones synthesised from picolinates **168** in terms of purity as the the latter showed slight contamination by their inseparable regioisomers **112** – and in the case of **107d** contamination by methyl picolinate as well.

The corresponding pyridines could then be prepared from triazines **107** as discussed earlier (cf. Section 6.3.1.1, p. 43 f.).

8 Further functional group interconversion

8.1 Lactone formation

As already mentioned, pyridines are very useful tools in asymmetric catalysis. The chirality, essential for this type of application, can be introduced into pyridines either by coupling to the (bi)pyridine core or by incorporation into the (bi)pyridine skeleton. It can arise from various sources[10,11] but to a large extent stems from the pinene pool.[9,15]

With the preparation of lactone **173** (Scheme 60) we envisioned a synthesis of a chiral target molecule from the reaction of **116f** with benzaldehyde. It was hoped for that due to steric hindrance generation of the two *syn*-isomers of lactone **173** would be disfavoured. Consequently, a racemic mixture of the two *anti*-isomers would be the outcome and could be shifted towards one of the two enantiomers by using a chiral base to deprotonate **116f**.
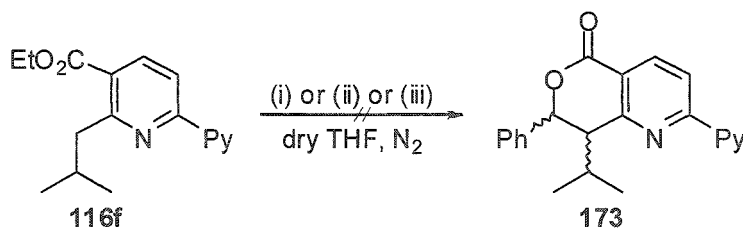
Scheme 60. Attempted lactone synthesis. Reagents and conditions: (i) **116f**, 1.2 equiv. LDA, -78 °C, 30 min; then 1.2 equiv. PhCHO, -78 °C to RT, 1 h (ii) **116f**, 1.2 equiv. LHMDS, -72 °C, 80 min; then 2.5 equiv. PhCHO, -72 °C, 30 min, RT, 1 h; (iii) 1.5 equiv. NaOEt, 0 °C, 30 min; then 2.4 equiv. PhCHO, 0 °C, 30 min, then RT, 30 min.

When LDA (generated *in situ* from diisopropylamine and *n*-butyllithium) was used as the base no conversion of **116f** was observed; LHMDS and sodium ethanolate under similar conditions gave a crude mixture within which no product **173** was identified.

8.2 Halogenated pyridines

A great deal of pyridine-based pharmaceuticals and agrochemicals are fluorinated and chlorinated derivatives. However, halogenated moieties in the target molecules are usually derived either from substitution of suitable leaving groups by halogen-bearing sidechains or from coupling reactions of the pre-formed pyridine with readily available aromatic or aliphatic halogen-bearing reactants.[104] A conversion of 3-methyl-1,2,4-triazines with chlorine gas to furnish their 3-trichloromethyl equivalents has also been reported[105] but this approach would not be attractive to our work due to the lack of selectivity and functional group tolerance. The number of syntheses where triazines[106] or pyridines[21,23,107] are assembled from halogenated building blocks is very scarce.

In addition to the reactions of halogen-bearing β-keto esters mentioned earlier on, attempts have been made to replace the methylsulfonyl group in pyridine **154h**. Introduction of a fluorine substituent by means of excess potassium fluoride (and catalytic amounts of benzo-18-crown-6)[86] showed mainly recovered starting material and traces of an unidentified compound but no product **174** (Scheme 61).
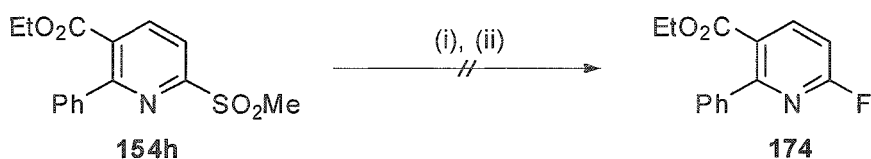
Scheme 61. Attempted fluorination of **154h**. Reagents and conditions: (i) 2.0 equiv. KF, DMF, N_2-atmosphere, 120 - 140 °C, 1 d; (ii) 1.5 equiv. KF, 10 mol% benzo-18-crown-6, MeCN, reflux, 1 d.

Attempts to functionalise the pyridine ring with a trifluoromethyl functionality included the reaction of the methylsulfinyl or methylsulfonyl pyridines **153d** and **154d** respectively with a trifluoromethyl anion (generated from reaction of methyl chlorodifluoroacetate, KF and CuI upon heating in DMF) (Scheme 62). In literature, a replacement of this type has been successful with Cl as the leaving group.[108] The preparation of compound **175**, however, remained without success.

2.0 equiv. F_2ClCCO_2Me,
2.0 equiv. KF
1.5 equiv. CuI

DMF, N_2, 115 °C, 5 h

153d: R = SOMe
154d: R = SO$_2$Me

175
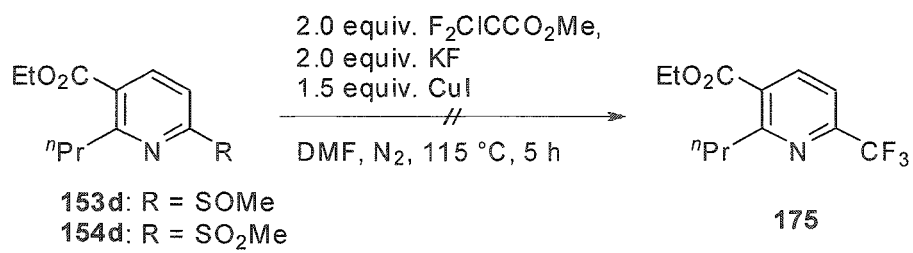
Scheme 62. Attempted trifluoromethylation of **153d/154d**.

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9   Terpyridines

2,2':6',2''-Terpyridines (tpys) are one of the most widely used classes of ligands in coordination and supramolecular chemistry.[11,109] This is largely due to their ability to form stable complexes with a range of transition metal ions. Certain representatives also show excellent electro-/photochemical and -physical properties[110] and over the last couple of years there has been an ever increasing interest in other fields such as catalysis[111] and polymer chemistry.[112] However, the vast majority of tpys featured in the literature are not highly substituted; in most cases they only possess a spacer group in the 4'-position linking them – depending on their use – to a solid support, a polymer backbone or anchoring them within a supramolecular assembly.

9.1   Established approaches

Terpyridines are largely prepared either by the coupling of the pyridine units or construction of the central pyridine ring. The former strategy suffers from low yields and often involves the separation of intractable mixtures of different oligomers and regioisomers. The latter strategy, although more rational, is fairly lengthy and the reaction steps are often inconvenient.[113]

A strategy much less exploited, but very useful for the synthesis of highly substituted tpys, is to start off with the central pyridine unit and to construct the two lateral/peripheral pyridine rings. One example is a route deploying a bpy and tpy synthesis first described by JAMESON and GUISE[113] which was then used by BRUNNER and SCHECK,[114] PLEIER et. al.,[115] BEJAN et al.[116] and HASSANIEN[117] to prepare a series of polyaza heterocycles with the latter author being the only one to report a tpy synthesis of this kind. His target compounds, for example **180a**, are obtained in KRÖHNKE-type sequence of Michael addition, condensation and aromatisation from enaminone **178** and compounds such as β-keto ester **78a** via intermediates **179a** (Scheme 63). Enaminone **178** is prepared from the reaction of DMFDMA (**177**) with 2,6-diacetylpyridine (**176**) which is commercially available, though costly, and is best prepared from dipicolinic acid in two steps.[118] Unfortunately this route does not allow for substitution in the 3/3''- or 4/4''-positions of the products **180**.
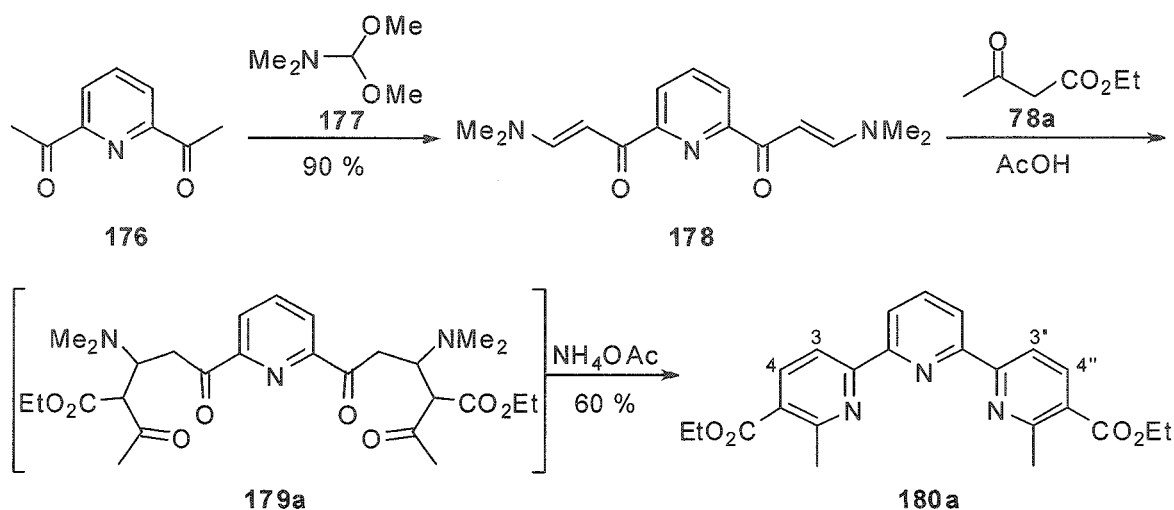
Scheme 63. Example of a tpy synthesis by HASSANIEN.

A rather unusual approach was chosen by KOZHEVNIKOV et. al.[95] 2,6-Pyridinedicarbox-aldehyde (**182**) was reacted with 1-aryl-1-hydrazono-2-oximinoethane (**181**), forming a series of 2,6-bis(6-aryl-1,2,4-triazin-3-yl)pyridines (**183**) which are transformed into the respective tpys **184** in a common aza DA reaction (Scheme 64). This approach, however, is limited to aryl substituents in the 5/5"-position of the products **184**.
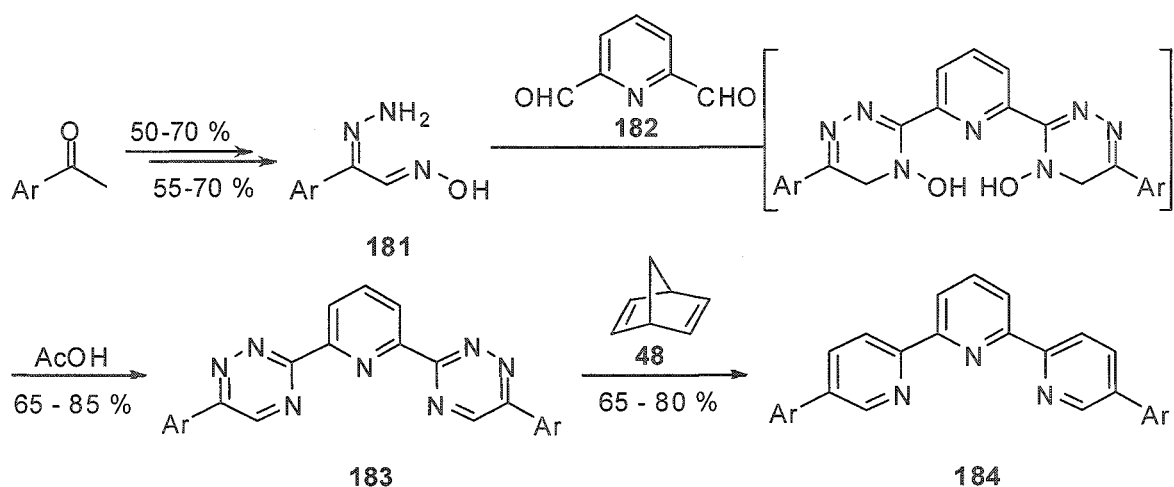
Scheme 64. General BTP/tpy synthesis by KOZHEVNIKOV et. al.

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9.2 STANFORTH terpyridine synthesis

In keeping with our pyridine and bipyridine research we opted for a strategy similar to KOZHEVNIKOV *et al.* where we proceeded via 2,6-bis(1,2,4-triazin-3-yl)pyridines (BTPs). This not only allows for substituents in the 3/3"- and/or the 4/4"-positions of the target compounds but BTPs are of great interest to the chemical industry in their own right as they show potential in nuclear reprocessing (SANEX process – Selective ActiNide Extraction process).[81,119]

9.2.1 Central building block

For our BTP/tpy synthesis we used pyridine 2,6-bis(carbohydrazonamide) (**189**) – prepared from 2,6-pyridinedicarbonitrile (**188**) according to a method by CASE[120] – as the central building block (Scheme 65). Though carbonitrile **188** is commercially available, from a manufacturing point of view it is too expensive. The 2,6-bis(amidrazone) **189** was instead prepared from 2,6-pyridinedicarboxylic acid (**185**) in four steps in an overall yield of 64 %.
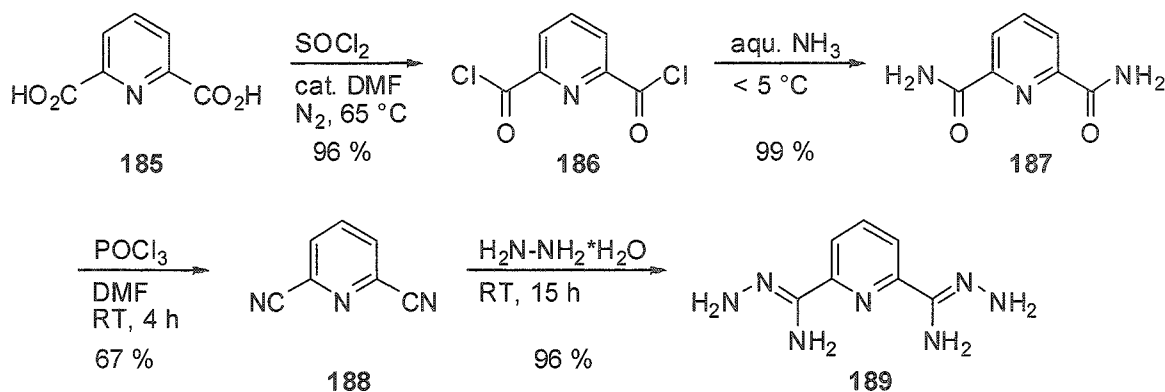
Scheme 65. Preparation of the tpy's central building block 189.

The diacid **185** was converted into acid chloride **186** using an excess of thionyl chloride acting both as solvent and reagent. Catalytic amounts of DMF were added, forming a formidinium chloride salt (Vilsmeier reagent) which shows enhanced reactivity towards the acid compared to the thionyl chloride. The moisture-sensitive acid chloride **186** was treated very carefully with ice-cold aqueous ammonia forming amide **187** which, in turn, was dehydrated to the carbonitrile **188** under mild conditions utilising yet another Vilsmeier complex (POCl₃/DMF).[121] Eventually, reaction of carbonitrile **188** with

hydrazine monohydrate at ambient temperatures afforded the 2,6-bis(amidrazone) **189**. The NMR spectral data and melting points of all intermediates were consistent with those in the literature.

9.2.2 Construction of lateral triazines/pyridines

As we have already discussed, there are two different options for the decomposition of chloroacetates in our pyridine and bipyridine syntheses: a) the use of either ethanolic HCl or methylamine prior to condensation with the amidrazone and b) the use of two equivalents of amidrazone. In the tpy synthesis, however, only option a) is applicable because if the 2,6-bis(amidrazone) **189** were to be used for decomposition of chloro-acetates **102** then not only would we sacrifice a much more expensive substrate but we would also suffer a loss of product since the 'hemitriazine' intermediate **190** (Figure 19) will compete with 2,6-bis(amidrazone) **189** for the decomposition of the chloroacetate **102**.
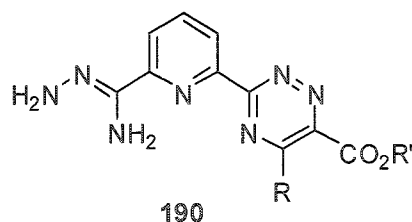
Figure 19. 'Hemitriazine'.

The 2,6-bis(1,2,4-triazin-3-yl)pyridines **191d,h** were synthesised from reaction of 2,6-bis-(amidrazone) **189** with two equivalents of the methylamine-pre-treated chloroacetates **102d,h** (Scheme 66) according to the usual method described in Section 6.2 (p. 37 f.). However, the yields were unsatisfactory and remained so when the reaction time was extended (**191d**: 4 h of reflux instead of 2 h; same yield).
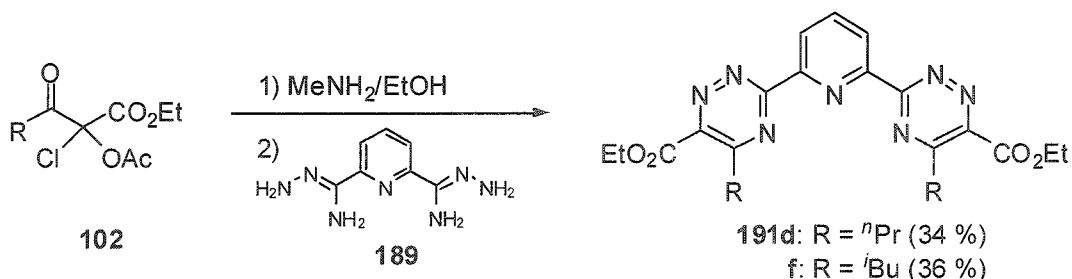
Scheme 66. Preparation of BTPs **191**. Reagents and conditions: 2.0 equiv. **102**, 4.0 equiv. $MeNH_2$, EtOH, RT, 1 h; then **191**, reflux, 2 h.

The structures were verified by full characterisation. A representative set of ^{1}H-NMR spectral data for BTP **191d** (Table 26) and HRMS results for both BTPs **191d,f** (Table 27) can be found below.

Table 26. ^{1}H-NMR spectral data of BTP **191d**.

chemical shift (ppm)	multiplicity	integral	coupling constants (Hz)	assignment
8.85	d	2	7.9	Py-H
8.19	t	1	7.9	Py-H
4.56	q	4	7.2	ester-CH_2
3.23 – 3.17	m	4		-CH_2-CH_2-CH_3
1.98 – 1.85	m	4		-CH_2-CH_2-CH_3
1.48	t	6	7.2	ester-CH_3
1.07	t	6	7.2	-CH_2-CH_2-CH_3

Table 27. HRMS data of BTPs **191**.

BTP	mass calculated for $[M+H]^+$	mass measured
191d	466.2197	466.2192
191f	494.2510	494.2512

The 'one-pot' reaction of 2,6-bis(amidrazone) **189** with two equivalents of chloroacetates **102d,f** and **h** respectively and 20 equivalents of 2,5-norbornadiene (**48**) (Scheme 67) furnished the corresponding terpyridines **192** in moderate to good yields.
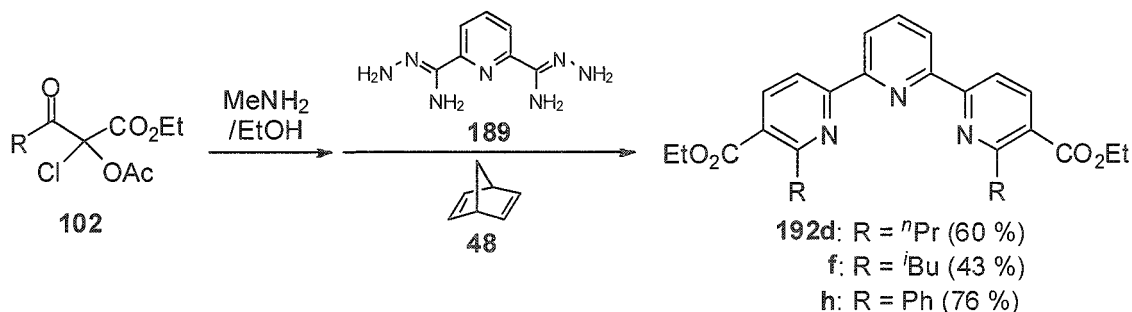
Scheme 67. 'One-pot' synthesis of tpys **192**. Reagents and conditions: 2.0 equiv. **102**, 4.0 equiv. MeNH$_2$, EtOH, RT, 1 h; then **189**, 20 equiv. **48**, reflux, 20 h.

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Addition of 2,5-norbornadiene (48) to the reaction mixture of compounds 102 and 189 after two hours of heating at reflux – as it has proved to be successful for reactions with enamines as the dienophile (cf. Section 6.3.2.5, p. 56) – did not improve the yield. Results by SAUER and co-workers suggest that a better yield may be obtained by switching to a higher boiling solvent.[122]

Again, structures were verified by full characterisation. The ^{1}H-NMR spectral data for tpy 192d (Table 28) and all HRMS (Table 29) are given below.

Table 28. ^{1}H-NMR spectral data of tpy 192d.

chemical shift (ppm)	multiplicity	integral	coupling constants (Hz)	assignment
8.59	d	2	7.9	central Py-H
8.47 and 8.30	2d	4	8.3	lateral Py-H
7.91	t	1	7.9	central Py-H
4.42	q	4	7.2	ester-CH_2
3.26 – 3.20	m	4		-CH_2-CH_2-CH_3
1.94 – 1.80	m	4		-CH_2-CH_2-CH_3
1.44	t	6	7.2	ester-CH_3
1.06	t	6	7.2	-CH_2-CH_2-CH_3

Table 29. HRMS data of tpys 192.

terpyridine	mass calculated for [M+H]$^+$	mass measured
192d	462.2387	462.2394
192f	490.2700	490.2699
192h	530.2074	530.2079

The 'one-pot' synthesis of the annulated tpys 193 (Scheme 68) from 2,6-bis(amidrazone) 189 with two equivalents of chloroacetates 102d and h respectively and 2.1 equivalents of enamine 56b showed moderate yields (40 – 50 %). The chloroacetates 102 were pre-treated with methylamine in the usual manner. The 2,6-bis(amidrazone) 189 was added and the mixture was refluxed for 2 h in order to form the BTPs 191 *in situ*. Then two different experimental procedures were applied. Initially, enamine 56b was added to the boiling

mixture and it was kept under reflux for further 20 h before purification by column chromatography yielded tpy **193d** (48 %). Alternatively, the mixture was left to cool to room temperature, enamine **56b** was added and it was stirred for 1 h followed by treatment with excess glacial acetic acid (1 h at room temperature) and basic workup (excess NaOH). Column chromatography furnished the pure tpys **193d** (40 %) and **193f** (50 %). The ^{1}H-NMR spectral data for tpy **193d** (Table 30) and both HRMS (Table 31) are given below.
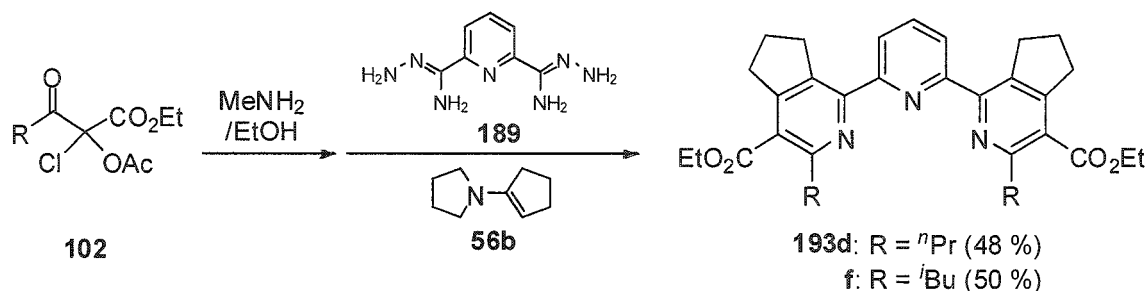
Scheme 68. 'One-pot'synthesis of annulated tpys **193**. Reagents and conditions: 2.0 equiv. **102**, 4.0 equiv. MeNH$_2$, EtOH, RT, 1 h; then **191**, reflux, 2 h; then 2.1 equiv. **56b**, RT...reflux, 1h...20 h.

Table 30. ^{1}H-NMR spectral data of tpy **193d**.

chemical shift (ppm)	multiplicity	integral	coupling constants (Hz)	assignment
8.18	d	2	7.9	Py-H
7.92	t	1	7.9	Py-H
4.41	q	4	7.2	ester-CH$_2$
3.29 and 3.06	2t	8	7.4	-CH_2-CH$_2$-CH_2-
3.02 – 2.96	m	4		-CH_2-CH$_2$-CH$_3$
2.04	tt	4	7.4	-CH$_2$-CH_2-CH$_2$-
1.84	tq	4	7.4	-CH$_2$-CH_2-CH$_3$
1.41	t	6	7.2	ester-CH$_3$
1.03	t	6	7.2	-CH$_2$-CH$_2$-CH_3

Table 31. HRMS data of tpys **193**.

terpyridine	mass calculated for [M+H]$^+$	mass measured
193d	542.3013	542.3014
193f	570.3326	570.3324

10 Application to imidazole synthesis

Not only are vicinal tricarbonyls and, therefore, chloroacetates and picolinates useful building blocks of triazines and pyridines but they also find application in the synthesis of various other heterocycles such as pyrroles and furans.[47,63]

Imidazoles (**194**) (Figure 20) are another class of heterocycles which are of industrial interest, especially to the pharmaceutical industry. A miniproject alongside our studies on pyridines focussed on whether the methodologies we developed to synthesise triazines could be transferred to the synthesis of imidazoles.

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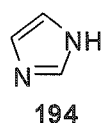
Figure 20. Imidazole (**194**).

The simple replacement of an amidrazone or thiosemicarbazide by an amidine such as **195** in the reaction with chloroacetate **102d** did not result in the formation of product **196d** (Scheme 69).
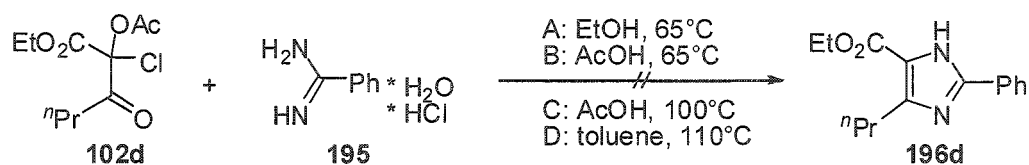
Scheme 69. Attempted imidazole synthesis.

Based on the experimental procedure of BRACKEEN *et al.*,[123] in which imidazoles are prepared *via* a KRÖHNKE-type reaction sequence from vicinal tricarbonyls with benzaldehyde and ammonium acetate in acetic acid, we synthesised the novel imidazole **196d** from both tricarbonyl equivalents, chloroacetate **102d** and picolinate **168d** (Scheme 70). The benzaldehyde was used without purification. This may (partly) account for the low yields.

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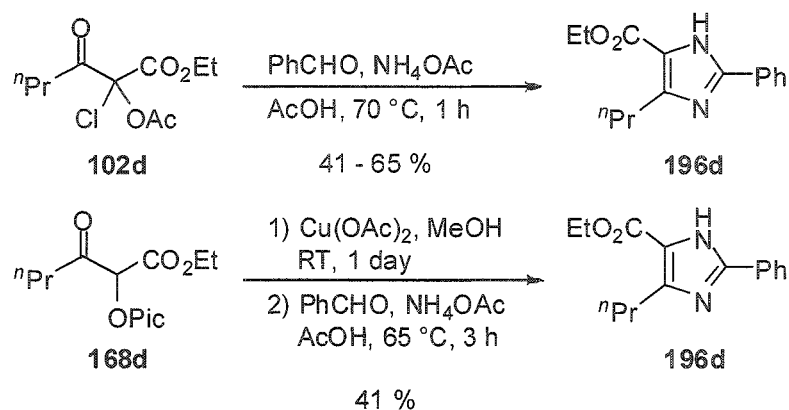
Scheme 70. Preparation of imidazole 196d from chloroacetate 102d and picolinate 154d.

Treatment of chloroacetate 102d with a saturated ethanolic hydrogen chloride solution prior to reaction with benzaldehyde and ammonium acetate resulted in an identical yield (41 %). Treatment with methylamine showed an improved yield (65 %) of the pure imidazole 196d with no need for column chromatography. Full characterisation including ^{1}H-NMR (Table 32) and HRMS (calculated for [M+H]$^+$: 570.3326; measured: 570.3324) confirmed the structure of the target compound.

Table 32. ^{1}H-NMR spectral data of imidazole 196d.

chemical shift (ppm)	multiplicity	integral	coupling constants (Hz)	assignment
7.90 – 7.86	m	2		Ph-H
7.49 – 7.40	m	3		Ph-H
4.38	q	4	7.2	ester-CH$_2$
2.98 – 2.89	m	8	7.4	-CH_2-CH$_2$- CH$_3$
1.75	tq	4	7.4	-CH$_2$-CH_2-CH$_3$
1.40	t	6	7.2	ester-CH$_3$
1.00	t	6	7.4	-CH$_2$-CH$_2$-CH_3

The diphenyl-substituted imidazole **196h** has also been prepared from its corresponding picolinate **168h** (Scheme 71) using the same method as for the synthesis of imidazole **196d**. An advantage of the imidazole synthesis in acetic acid over the pyridine synthesis in ethanol or toluene is that the product precipitated on cooling of the reaction mixture to room temperature.
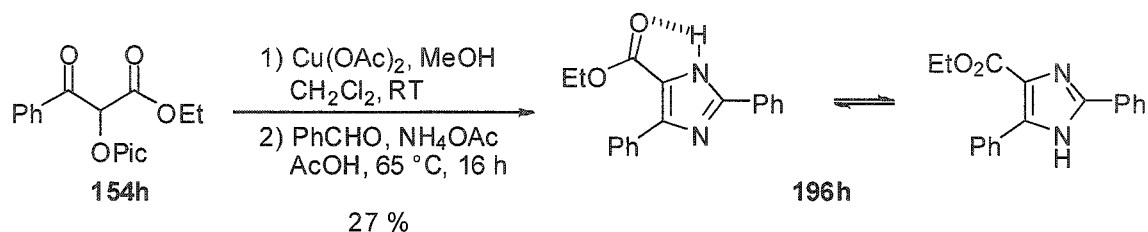
Scheme 71. Preparation of imidazole **196h** from picolinate **168h**.

The ^{1}H-NMR spectral data is consistent with that in the literature. Although a ratio of the two tautomers of imidazole **196h** could not be determined, we reason that the predominant tautomer was the one forming an intramolecular hydrogen bond.

11 Summary

We prepared a range of α-chloro-α-acetoxy-β-keto esters **102** in three straightforward and generally high-yielding steps from commercially available starting materials. These chloroacetates **102** served as equivalents for vicinal tricarbonyls **81** in the synthesis of various 1,2,4-triazines through condensation with hydrazonamides **73** (Scheme 72).

R^5 = Me, Et
R^6 = alkyl, aryl

R^2 = Py,
SMe
SPnb

3 steps
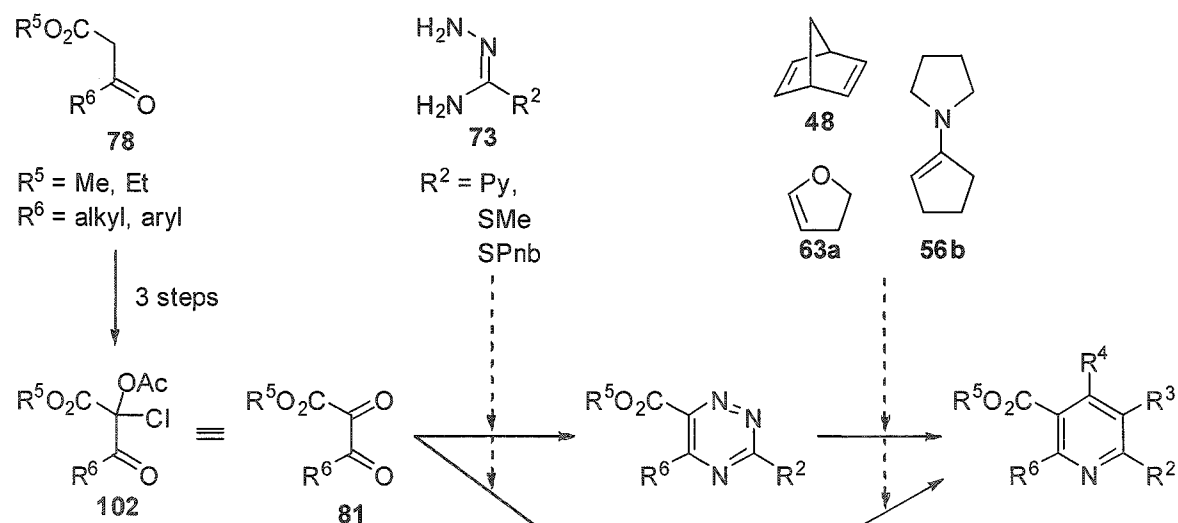
Scheme 72. Synthesis of polysubstituted pyridines.

Subsequent (or 'one-pot') aza Diels-Alder reactions of (*in situ* generated) 1,2,4-triazines with electron-rich dienophiles such as 2,5-norbornadiene (**48**), 1-pyrrolidino-1-cyclopentene (**56b**) and 2,3-DHF (**63a**) (Scheme 72) and in some case functional group interconversion (oxidation, ester hydrolysis) furnished an array of novel polysubstitued pyridines (Figure 21).

116c: R^6 = Et, R^5 = Me
f: R^6 = ^{i}Bu, R^5 = Et
g: R^6 = ^{t}Bu, R^5 = Et
161d: R^6 = ^{n}Pr, R^5 = H

167d

164d

153d: R^6 = ^{n}Pr
h: R^6 = Ph

155d: X = S
156d: X = SO
157d: X = SO$_2$
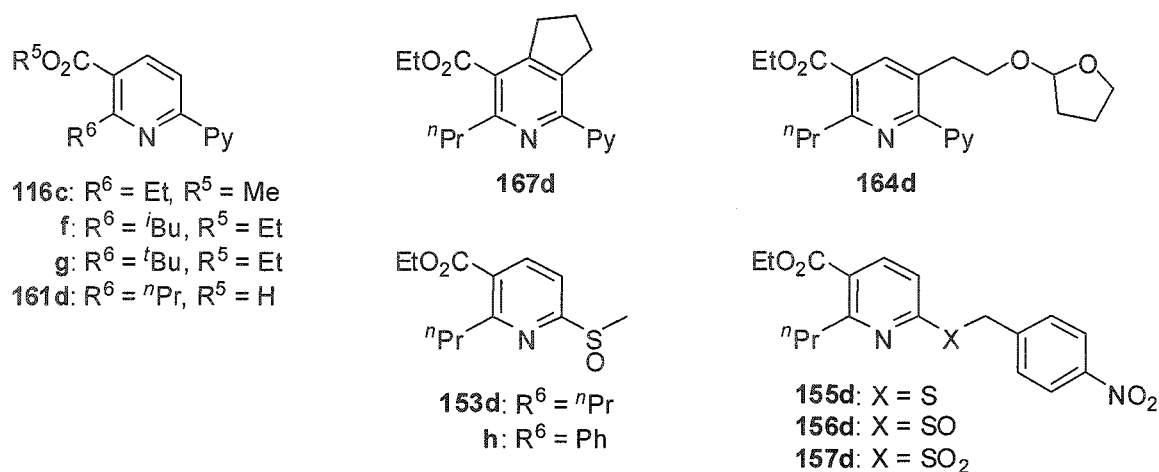
Figure 21. Novel (bi)pyridines.

We also devised a feasible alternative route towards vicinal tricarbonyls **81**. Picolinates **168** were prepared from the same starting materials **78** as their chloroacetate counterparts in a shortened two-step sequence (Scheme 73) also showing high purities and generally good to excellent overall yields. Copper(II) acetate-facilitated methanolysis of **168** and immediate oxidation of α-hydroxy-β-keto esters **98** by excess copper(II) acetate afforded tricarbonyls **81** which reacted with hydrazonamides **73** in the same manner as the chloroacetates.
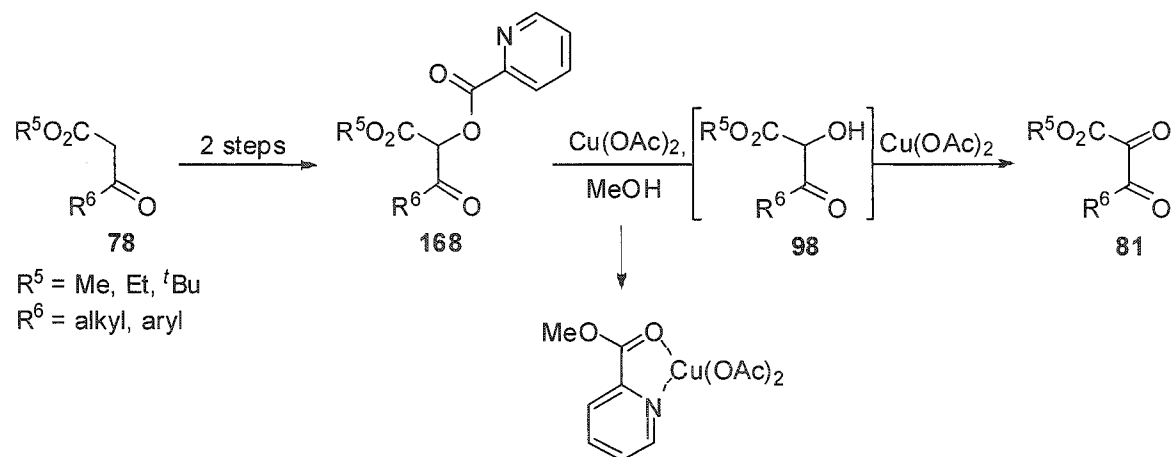
Scheme 73. Picolinate route.

As the oxidation of *sec*-alcohols **98** to their corresponding ketones **81** proceeded with catalytic amounts of copper(II) acetate in the absense of a co-oxidant (other than air), we believe to have identified a novel oxidation system in $Cu[PicOMe]_n/O_2$. This, however, will have to be tested in more depth to be verified.

Irrespective of the route chosen, tricarbonyl equivalents with small substituents R^6 (Me, Et) generally gave lower yields of triazines or pyridines than those with larger aliphatic (^nPr, ^iPr, ^tBu, ^tBu) or aromatic substituents (Ph, Np).

Both the chloroacetate and the picolinate methodology could be applied to the synthesis of novel 2,6-bis(1,2,4-triazin-3-yl)pyridines and, hence, 2,2':6',2"-terpyridines from 2,6-bis-(carbohydrazonamide) (**189**) (Figure 22) as well to the synthesis of imidazoles.

189

191d: R = ^{n}Pr
f: R = ^{i}Bu

192d: R = ^{n}Pr
f: R = ^{i}Bu
h: R = Ph

193d: R = ^{n}Pr
f: R = ^{i}Bu
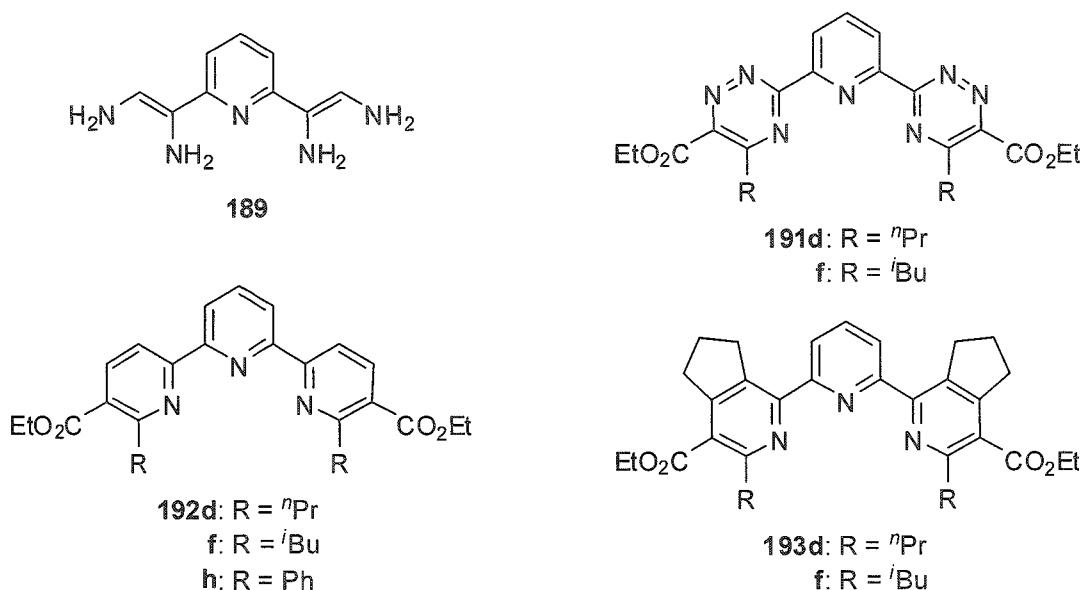
Figure 22. Novel BTPs **191** and tpys **192/193**.

The four-step synthetic sequence (Scheme 74) leading up to 2,6-bis(carbohydrazonamide) (**189**) (Figure 22) was part of an upscaling project at multi-100-g scale.

70 % over
2 steps

185: X = OH
186: X = Cl (96 %)
187: X = NH$_2$

188

189
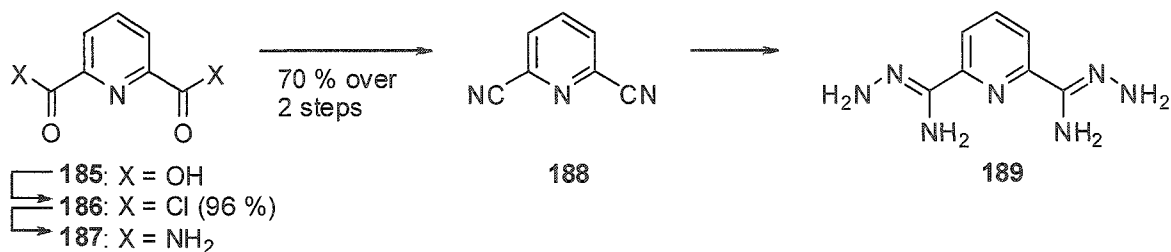
Scheme 74. Preparation of the tpy's central building block **189**.

84

The other two preparations that were successfully upscaled to +100 g of starting material were the four-step synthesis of ethyl 2-acetoxy-2-chloro-5-methyl-3-oxo-hexanoate (**102f**) in 61 % overall yield (Scheme 75) and the three-step synthesis of ethyl 2-acetoxy-2-chloro-3-oxo-3-phenylpropanoate (**102g**) in 82 % overall yield (Scheme 76).
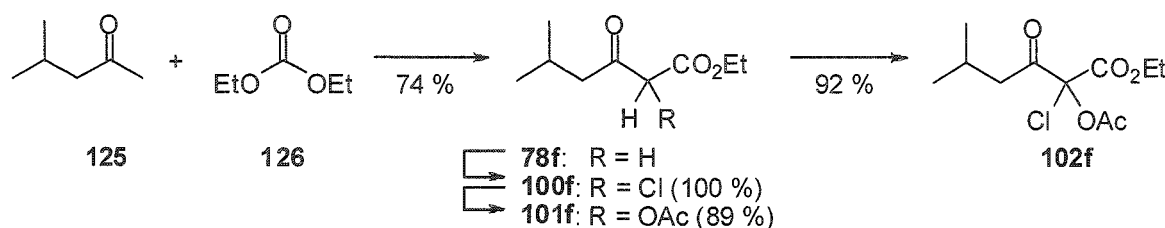
Scheme 75. Large scale synthesis of chloroacetate **102f**.
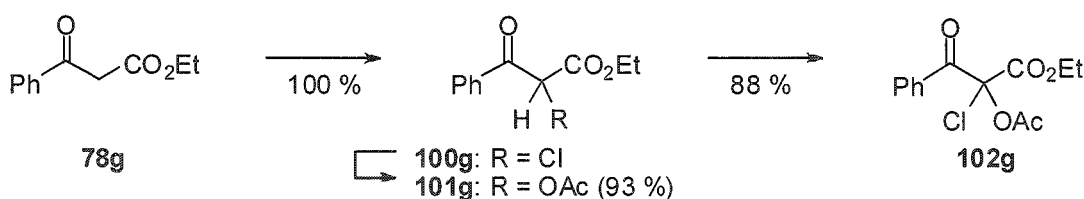
Scheme 76. Large scale synthesis of chloroacetate **102g**.

12 Outlook

As far as triazine, pyridine and bipyridine syntheses are concerned, several preparative methods have been investigated and experimental procedures have been optimised to a point where a numer of target compounds showed good overall yield. However, for those substrates and intermediates that gave poor product yields or product mixtures, a well-known method involving the reaction of tricarbonyls **81** (or their equivalents) with hydrazides **72** and a source of ammonia such as ammonium acetate (Scheme 77) may prove successful.
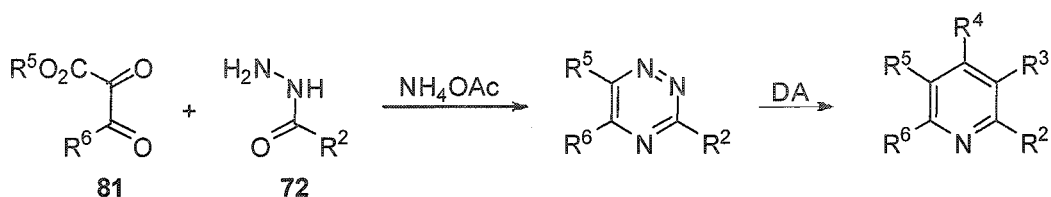
Scheme 77. Alternative triazine/pyridine synthesis.

Access to chiral terpyridines could be gained from the reaction of the central tpy building block **189** with cyclohexane-1,2-dione (**197**) and 2,5-norbornadiene (**48**) (Scheme 78). The resulting 2,6-bis(5,6,7,8-tetrahydroquinolin-2-yl)pyridine (**198**) would then have to be deprotonated on its cyclohexyl rings followed by an alkylation which hopefully selectively furnishes a single stereoisomer, e.g. **199**.
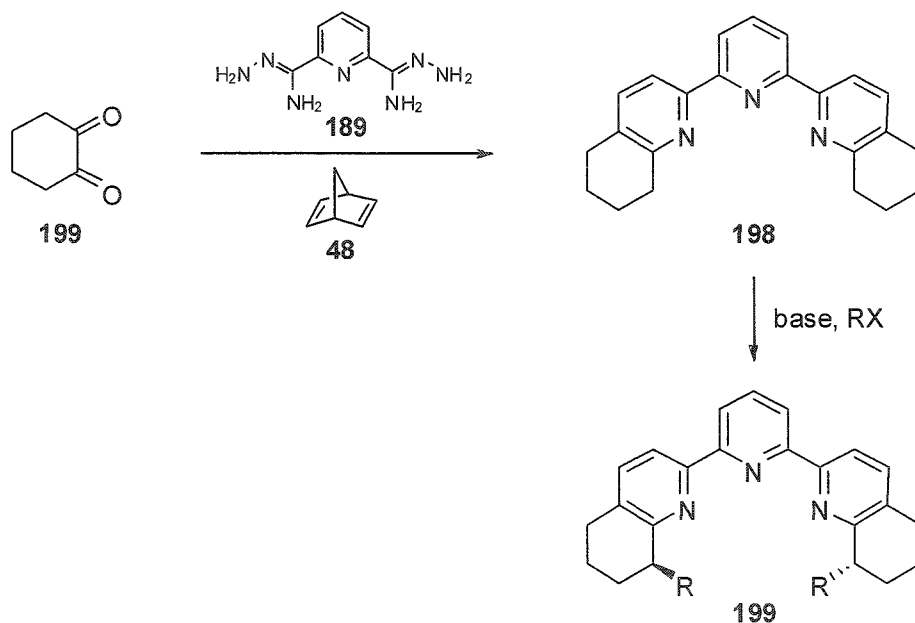
Scheme 78. Possible synthesis of a chiral tpy **199**.

We have shown that our methodologies for the synthesis of triazines and pyridines from two different types of tricarbonyl equivalents – chloroacetates **102** and picolinates **168** – were, in principle, transferable to the synthesis of imidazoles. An extension of this work in terms of widening the range of products by derivatives such as **200** – **202** (Figure 23) as well as optimisation of experimental procedures is an undertaking worth pursuing.
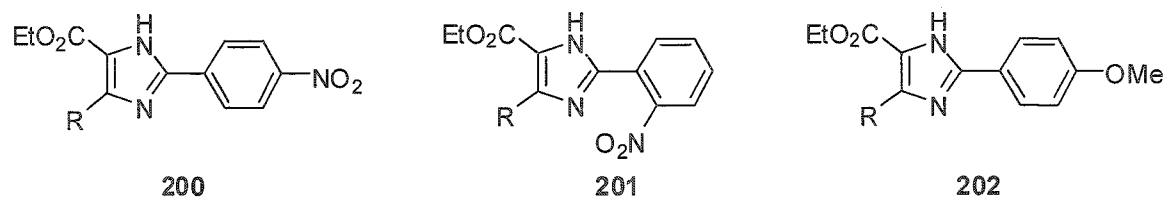
Figure 23. Future imidazole represantatives.

EXPERIMENTAL PART

1 General information

The **nomenclature** of the compounds was assigned according to the nomenclature program CS CHEMDRAW ULTRA®, Version 10.0 by CAMBRIDGESOFT. The numbering of atoms within the chemical structures is not necessarily according to IUPAC nomenclature. They are derived from the numbering in their respective substrates and rather reflect the chronology of the syntheses of the compounds.

Percentages and yields of products or product mixtures are relative to the number of moles. Yields of product mixtures or products in solution were calculated by the ratio of peak intensities in the ^{1}H-NMR spectrum. Percentages of reagents in solution are relative to mass; percentages of solvent mixture are relative to volume.

The identity of products prepared by different methods was checked by comparison of their NMR spectra. Hence, corresponding NMR spectral data for multiple synthetic methods is only stated for the first method.

1.1 Methods

Melting points were measured with a BÜCHI *510* and are corrected.

Thin layer chromatography (TLC) was performed on plastic or aluminium sheets pre-coated with silica gel 60 F_{254} obtained from MERCK. The detection of products was carried out with UV light of the wavelenght 254 nm. If necessary, TLC plates were stained with a potassium permanganate solution (made up of 3 g $KMnO_4$, 20 g K_2CO_3, 5 mL 5 % aqueous NaOH and 300 mL water).[124]

Column chromatography was performed using silica gel 60 (0.060 – 0.200 mm) purchased from MERCK and ReagentGrade solvents purchased from FISCHER SCIENTIFIC.

NMR spectra were recorded on a JEOL *JNM-EX270* FT NMR system at frequencies of 270.17 MHz (^{1}H) or 67.93 MHz (^{13}C). Chemical shifts are noted in ppm relative to tetramethylsilane (TMS) as internal standard. The multiplicities of the ^{1}H-NMR signals are as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad.

High resolution mass spectrometry was carried out by the EPSRC's National Mass Spectrometry Service Centre at the University of Wales, Swansea and was performed on a FINNIGAN *MAT900 XLT* using electrospray ionisation (ESI).

IR spectra were obtained using a SENSIR TECHNOLOGIES diamond anvil cell on a PERKIN ELMER *Paragon 1000FT-IR* spectrometer. The shapes and intensities of the bands are as follows: s = strong, m = medium, w = weak, br = broad.

1.2 Chemicals

Starting materials and **reagents** were purchased from ACROS, FLUKA, LANCASTER, MERCK and SIGMA-ALDRICH and used without further purification unless noted otherwise. Picolinohydrazonamide (**73a**) and 2-acetoxy-2-chloro-3-oxo-3-hexanoate (**102d**) were readily available from prior research in our group.[71] Where benzaldehyde is stated as being purified it was washed with a 10 % aqueous solution of Na_2CO_3, a saturated solution of Na_2SO_3, dried over $MgSO_4$ and vacuum distilled.[125]
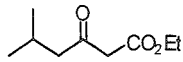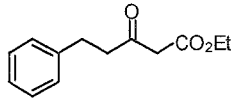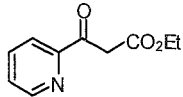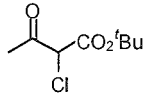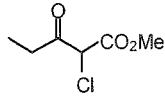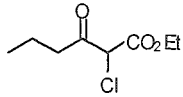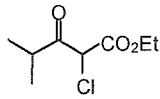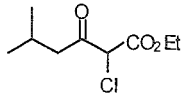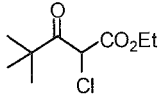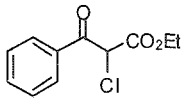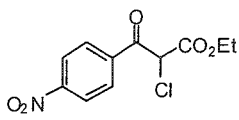
Solvents were purchased from FISCHER SCIENTIFIC and were generally of ReagentGrade. Absolute ethanol was bought as such. Where solvents are stated as being "dry" they were purified as follows:
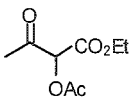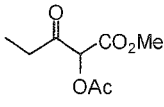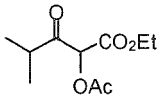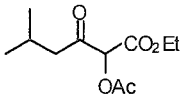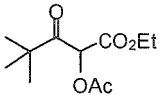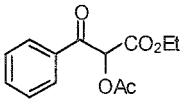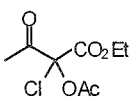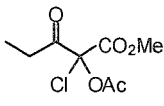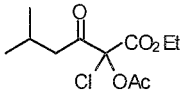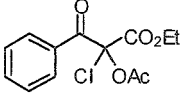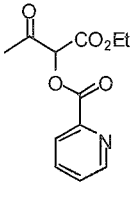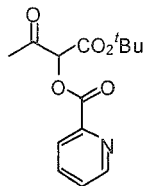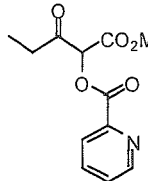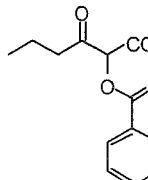
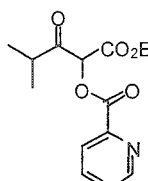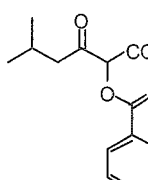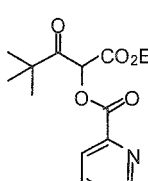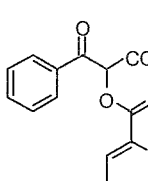Ethyl acetate was dried over 4Å molecular sieves.[125]

Tetrahydrofuran was pre-dried with sodium wire and then passed through a column of alumina. Where absolutely 'dry' THF was needed it was refluxed over / distilled from either sodium hydride or sodium/potassium alloy.[125]
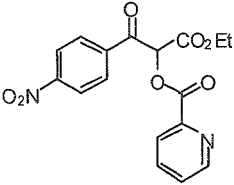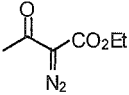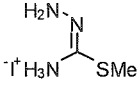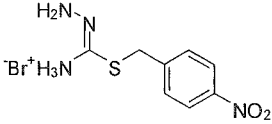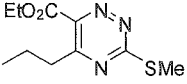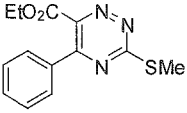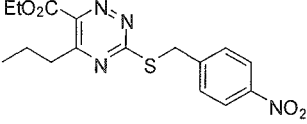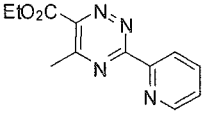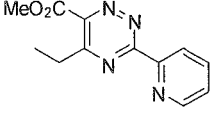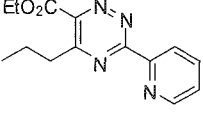
Toluene was dried over 4Å molecular sieves.[125]

1.3   List of products
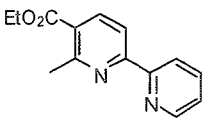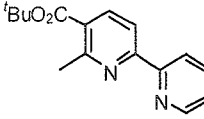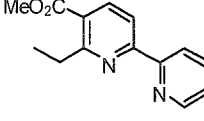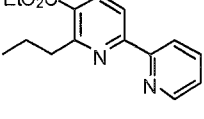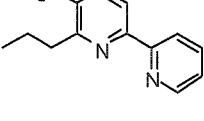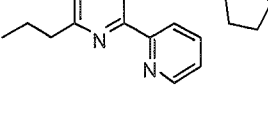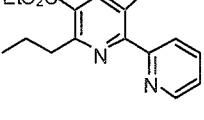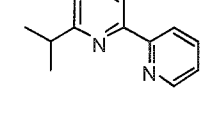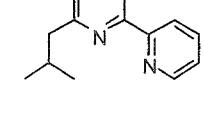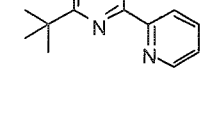
structure	name	page
	Ethyl 5-methyl-3-oxohexanoate (**78f**)	98
	Ethyl 3-oxo-5-phenylpentanoate (**78k**)	99
	Ethyl 3-oxo-3-(pyridin-2-yl)propanoate (**78o**)	100
	tert-Butyl 2-chloro-3-oxobutanoate (**100b**)	101
	Methyl 2-chloro-3-oxopentanoate (**100c**)	102
	Ethyl 2-chloro-3-oxohexanoate (**100d**)	103
	Ethyl 2-chloro-4-methyl-3-oxopentanoate (**100e**)	103
	Ethyl 2-chloro-5-methyl-3-oxohexanoate (**100f**)	104
	Ethyl 2-chloro-4,4-dimethyl-3-oxopentanoate (**100g**)	105
	Ethyl 2-chloro-3-oxo-3-phenylpropanoate (**100h**)	105
	Ethyl 2-chloro-3-(4-nitrophenyl)-3-oxopropanoate (**100i**)	106
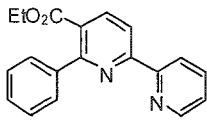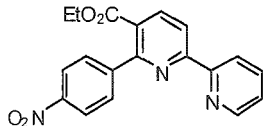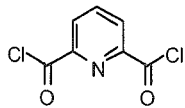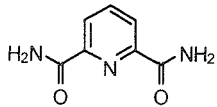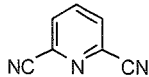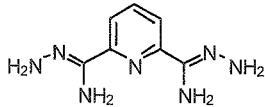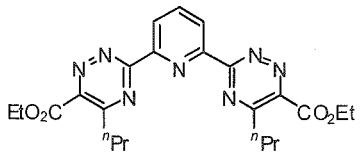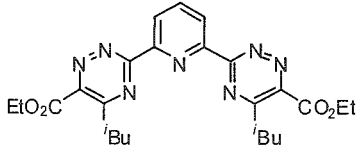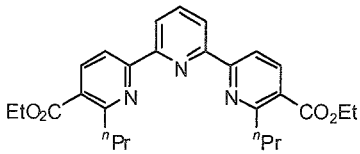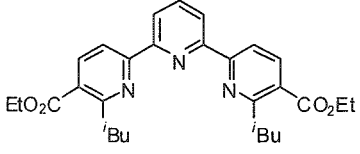
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structure	name	page
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structure	name	page
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structure	name	page
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EtO₂C, with propyl and pyridine	Ethyl 6-propyl-[2,2']-bipyridine-5-carboxylate (**116d**)	147
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structure	name	page
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structure	name	page

Diethyl 2,2'-(pyridine-2,6-diyl)bis(6-phenyl-pyridine-5-carboxylate) (**192h**)

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Diethyl 1,1'-(pyridine-2,6-diyl)bis(3-propyl-6,7-dihydro-5H-cyclopenta[c]pyridine-4-carboxylate) (**193d**)

168

Diethyl 1,1'-(pyridine-2,6-diyl)bis(3-isobutyl-6,7-dihydro-5H-cyclopenta[c]pyridine-4-carboxylate) (**193f**)

169

Ethyl 2-phenyl-4-(*n*-propyl)-1*H*-imidazole-5-carboxylate (**196d**)

170

Ethyl 2,4-diphenyl-1*H*-imidazole-5-carboxylate (**196h**)

172

8-Isopropyl-7-phenyl-2-(pyridin-2-yl)-7,8-dihydro-5H-pyrano-[4,3-b]pyridin-5-one (**173**) (unsuccessful)

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2 β-Keto esters

2.1 Ethyl 5-methyl-3-oxohexanoate (78f)

To a suspension of sodium hydride (9.31 g; 60 % w/w dispersion in mineral oil; 233 mmol; 2.33 equiv.) in dry tetrahydrofuran (60 mL) was added diethyl carbonate (126) (33.8 mL; 279 mmol; 2.79 equiv.) and then dropwise 4-methyl-2-pentanone (125f) (10 g; 100 mmol) in dry tetrahydrofuran (15 mL) under a nitrogen atmosphere and the mixture was heated under reflux for 2 h. After cooling to room temperature, the mixture was quenched with water, neutralised with dilute HCl and extracted with diethyl ether. The organic phase was washed with water, a saturated solution of $NaHCO_3$ and brine, dried over $MgSO_4$ and the solvents were evaporated under reduced pressure. The residue was distilled under vacuum yielding 78f (13.1 g; 76.1 mmol; 76 %) as a colourless liquid. The ratio of keto to enol form was 92:8.

The reaction was scaled up to 200 g (2.00 mol) of 4-methyl-2-pentanone and 680 mL (5.61 mol; 2.81 equiv.) of diethyl carbonate yielding 254 g (1.47 mol; 74 %) of 78f as a colourless liquid (b.p. 74 – 75 °C / 1 mbar). At this scale the reaction was carried out in two batches and the 4-methyl-2-pentanone was added at such a rate (over 1.5 h) that the mixture remained refluxing without external heating once the exothermic reaction set in. Complete reaction was indicated by the formation of a clear orange solution. Dilute HCl was replaced by concentrated HCl.

$C_9H_{16}O_3$ (M = 172.22 g/mol)
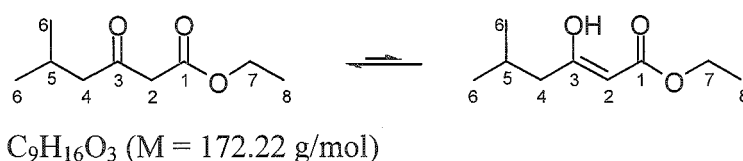
^{1}H-NMR (CDCl$_3$): δ = 12.09 (s, 1H, OH enol form), 4.96 (s, 1H, 2-H enol form), 4.20 (q, 2H, 7-H keto form, $J_{7/8}$ = 7.2 Hz), 4.19 (q, 2H, 7-H enol form, $J_{7/8}$ = 7.2 Hz), 3.41 (s, 2H, 2-H keto form), 2.42 (d, 2H, 4-H, $J_{4/5}$ = 6.6 Hz) 2.16 (nonet, 1H, 5-H, $J_{5/4}$ = $J_{5/6}$ = 6.6 Hz), 2.08 – 1.96 (m, 3H, 4-H, 5-H enol form), 1.29 (t, 3H, 8-H enol form, $J_{8/7}$ = 7.2 Hz), 1.28 (t, 3H, 8-H keto form, $J_{8/7}$ = 7.2 Hz), 0.94 (2d, 12H, 6-H enol and keto form,

$J_{6/5}$ = 6.6 Hz) ppm. The ^{1}H-NMR spectral data is consistent with that found in the literature.[83]

2.2 Ethyl 3-oxo-5-phenylpentanoate (78k)

To a suspension of sodium hydride (8.00 g of 60 % dispersion in mineral oil; washed free from oil with petroleum ether; 200 mmol; 2.00 equiv.) in tetrahydrofuran (50 mL) was added diethyl carbonate (126) (23.6 g; 200 mmol; 2.00 equiv.) and the mixture was heated to 40 °C. 4-Phenyl-2-butanone (125k) (14.8 g; 100 mmol) was then added dropwise over 5 h. After complete addition the mixture was heated for another hour. It was cooled to 0 °C and glacial acetic acid (12.5 mL) was added dropwise along with tetrahydrofuran (200 mL) in order to keep the mixture liquid. After addition of water (250 mL) in order to dissolve the generated sodium acetate, the aqueous phase was extracted with diethyl ether, the combined organic phases were washed with a saturated solution of $NaHCO_3$, dried over $MgSO_4$ and the ether evaporated under reduced pressure. Vacuum distillation of the residue afforded an inseparable mixture (4.99 g; 22.7 mmol; 23 %) of 78k and ethyl 2-benzyl-3-oxobutanoate (127k) as a colourless liquid (b.p. 168 – 174 °C / 1 mBar). The ratio of 78k to 127k was 72:28. The ratio of keto to enol form of 78k was 97:3.

$C_{13}H_{16}O_3$ (M = 220.27 g/mol)
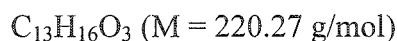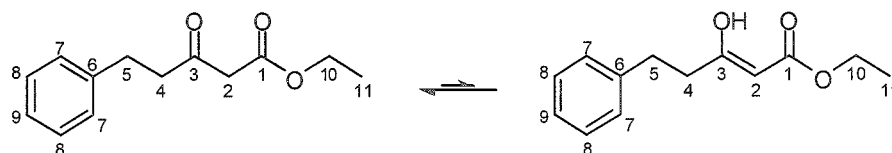
Analytical data for 78k:

^{1}H-NMR (CDCl$_3$) of the keto form: δ = 7.31 – 7.14 (m, 5H, 7-H to 9-H), 4.17 (q, 2H, 10-H, $J_{10/11}$ = 7.2 Hz), 3.41 (s, 2H, 2-H), 2.96 – 2.82 (m, 4H, 4-H, 5-H), 1.25 (t, 3H, 11-H, $J_{11/10}$ = 7.2 Hz) ppm. The ^{1}H-NMR spectral data is consistent with that found in the literature.[126]

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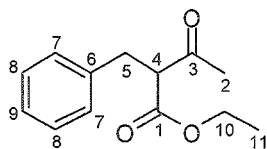
$C_{13}H_{16}O_3$ (M = 220.27 g/mol)

Analytical data for ethyl 2-benzyl-3-oxobutanoate (127k):

^{1}H-NMR (CDCl$_3$): δ = 7.31 − 7.14 (m, 5H, 7-H to 9-H), 4.14 (q, 2H, 10-H, $J_{10/11}$ = 7.2 Hz), 3.76 (t, 1H, 4-H, $J_{4/5}$ = 7.6 Hz), 3.15 (d, 2H, 5-H, $J_{5/4}$ = 7.6 Hz), 2.18 (s, 3H, 2-H), 1.19 (t, 3H, 11-H, $J_{11/10}$ = 7.2 Hz) ppm. The ^{1}H-NMR spectral data is consistent with that found in the literature.[127]

2.3 Ethyl 3-oxo-3-(pyridin-2-yl)propanoate (78o)

Under a nitrogen atmosphere and without stirring sodium (1.38 g; 60.0 mmol; 1.51 equiv.) was heated in dry toluene (30 mL) until just boiling. It was then vigorously stirred until a grey suspension formed, stirring was discontinued and it was left to cool to room temperature. Under vigorous stirring absolute ethanol (20 mL) was added at such a rate that the temperature remained below 85 °C (gentle reflux).[86] After complete addition of the ethanol the mixture was heated to 100 °C for 1 h. A solution of ethyl picolinate (132) (6.05 g; 40.0 mmol) in dry ethyl acetate (7.05 g; 80.0 mmol; 2.00 equiv.) was then added dropwise and the mixture was heated for 15 h. Water (350 mL) was added to the cooled reaction mixture followed by glacial acetic acid (5mL). The organic phase was separated, the aqueous phase extracted with diethyl ether, the combined organic phases washed with water and dried over MgSO$_4$. The solvents were evaporated under reduced pressure yielding 78o (3.59 g; 18.6 mmol; 46 %) as a red liquid (b.p. 108 °C / 1 mBar) which faded to straw colour on standing. The ratio of keto to enol form was 85:15.

$C_{10}H_{11}NO_3$ (M = 193.20 g/mol)

100

^{1}H-NMR (CDCl$_3$): δ = 12.40 (s, 1H, OH enol form), 8.67 (ddd, 1H, 8-H keto form, $J_{8/5}$ = 1.0 Hz, $J_{8/6}$ = 1.7 Hz, $J_{8/7}$ = 4.7 Hz), 8.63 (ddd, 1H, 8-H enol form, $J_{8/5}$ = 1.0 Hz, $J_{8/6}$ = 1.7 Hz, $J_{8/7}$ = 4.7 Hz), 8.08 (ddd, appearance similar to dt, 1H, 5-H keto form, $J_{5/8}$ = 1.0 Hz, $J_{5/7}$ = 1.2 Hz, $J_{5/6}$ = 7.9 Hz), 7.92 (ddd, appearance similar to dt, 1H, 5-H enol form, $J_{5/8}$ = 1.0 Hz, $J_{5/7}$ = 1.2 Hz, $J_{5/6}$ = 7.9 Hz), 7.85 (ddd, appearance similar to dt, 1H, 6-H keto form, $J_{6/8}$ = 1.7 Hz, $J_{6/7}$ = 7.7 Hz, $J_{6/5}$ = 7.9 Hz), 7.79 (ddd, appearance similar to dt, 1H, 6-H enol form, $J_{6/8}$ = 1.7 Hz, $J_{6/7}$ = 7.7 Hz, $J_{6/5}$ = 7.9 Hz), 7.49 (ddd, 1H, 7-H keto form, $J_{7/5}$ = 1.2 Hz, $J_{7/8}$ = 4.7 Hz, $J_{7/6}$ = 7.7 Hz), 7.35 (ddd, 1H, 7-H enol form, $J_{7/5}$ = 1.2 Hz, $J_{7/8}$ = 4.7 Hz, $J_{7/6}$ = 7.7 Hz), 6.32 (s, 1H, 2-H enol form), 4.28 (q, 2H, 9-H enol form, $J_{9/10}$ = 7.2 Hz), 4.20 (q, 2H, 9-H keto form, $J_{9/10}$ = 7.2 Hz), 4.19 (s, 2H, 2-H keto form), 1.33 (t, 3H, 10-H enol form, $J_{10/9}$ = 7.2 Hz), 1.24 (t, 3H, 10-H keto form, $J_{10/9}$ = 7.2 Hz) ppm. The ^{1}H-NMR spectral data is consistent with that found in the literature.[128]

3 α-Chloro-β-keto esters

3.1 *tert*-Butyl 2-chloro-3-oxobutanoate (100b)

To a stirred ice-cold solution of *tert*-butyl acetoacetate (78b) (5.00 g; 31.6 mmol) in dichloromethane (30 mL) was added dropwise over 5 min sulfuryl chloride (4.69 g; 34.7 mmol; 1.10 equiv.). After warming to room temperature, the solution was left stirring for 1 h, then washed with a saturated solution of NaHCO$_3$ (60 mL) and water (30 mL). The organic phase was separated, dried over MgSO$_4$ and the solvent evaporated under reduced pressure yielding 100b (4.34 g; 22.5 mmol; 71 %) as a colourless liquid. The ratio of keto to enol form was 93:7.

C$_8$H$_{13}$ClO$_3$ (M = 192.64 g/mol)
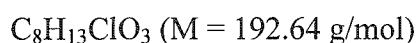
^{1}H-NMR (CDCl$_3$): δ = 12.45 (s, 1H, OH enol form), 4.66 (s, 1H, 2-H keto form), 2.36 (s, 3H, 4-H keto form), 2.13 (s, 3H, 4-H enol form), 1.51 (s, 9H, 6-H enol form), 1.49 (s, 9H, 6-H keto form) ppm. The ^{1}H-NMR spectral data is consistent with that found in the literature.[129]

3.2 Methyl 2-chloro-3-oxopentanoate (100c)

Following the procedure in Section 3.1, methyl 3-oxopentanoate (**78c**) (1.00 g; 7.68 mmol) and sulfuryl chloride (1.14 g; 8.45 mmol; 1.10 equiv.) were converted into **100c** (1.25 g; 7.59 mmol; 99 %) which was obtained as a pale yellow liquid. The ratio of keto to enol form was 92:8.

This reaction was scaled up to 40 g (307 mmol) of starting material resulting in a slightly reduced yield (47.2 g; 287 mmol; 93 %).

$C_6H_9ClO_3$ (M = 164.59 g/mol)

^{1}H-NMR (CDCl$_3$): δ = 12.33 (s, 1H, OH enol form), 4.81 (s, 1H, 2-H keto form), 3.92 (s, 3H, 6-H enol form), 3.85 (s, 3H, 6-H keto form), 2.88 (2q, 2H, 4-H enol form, two non-identical H, 1H *syn* and 1H *anti* to Cl, $J_{4/5}$ = 7.2 Hz), 2.75 (2q, 2H, 4-H keto form, two non-identical H, 1H *syn* and 1H *anti* to Cl, $J_{4/5}$ = 7.2 Hz), 1.19 (t, 3H, 5-H enol form, $J_{5/4}$ = 7.2 Hz), 1.12 (t, 3H, 5-H keto form, $J_{5/4}$ = 7.2 Hz) ppm.

^{13}C-NMR (CDCl$_3$) of the keto form: δ = 199.74 (C-3), 165.72 (C-1), 60.59 (C-2), 53.82 (C-6), 32.57 (C-4), 7.71 (C-5) ppm.

The HRMS spectrum was not recorded.

IR: v_{max}/cm^{-1} = 2960 (w, CH$_{alkyl}$), 1726 (s, C=O), 1263 + 1167 (m, C-O).

3.3 Ethyl 2-chloro-3-oxohexanoate (100d)

Following the procedure in Section 3.1 (reaction time overnight), ethyl 3-oxohexanoate (78d) (20.0 g; 126 mmol) and sulfuryl chloride (18.8 g; 139 mmol; 1.10 equiv.) were converted into 100d (23.9 g; 124 mmol; 98 %) which was obtained as a pale yellow liquid. The ratio of keto to enol form was 93:7.

$C_8H_{13}ClO_3$ (M = 192.64 g/mol)
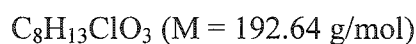
^{1}H-NMR (CDCl$_3$): δ = 12.40 (s, 1H, OH enol form), 4.77 (s, 1H, 2-H keto form), 4.28 (2q, 4H, 7-H enol and keto form, $J_{7/8}$ = 7.2 Hz), 2.68 and 2.67 (2t, appearance similar to dt, 2H, 4-H keto form, two non-identical H, 1H *syn* and 1H *anti* to Cl, $J_{4/5}$ = 7.2 Hz), 2.48 (t, 2H, 4-H enol form, $J_{4/5}$ = 7.2 Hz), 1.68 (tq, appearance similar to sextet, 2H, 5-H enol form, $J_{5/4}$ = $J_{5/6}$ = 7.2 Hz), 1.65 (tq, appearance similar to sextet, 2H, 5-H keto form, $J_{5/4}$ = $J_{5/6}$ = 7.2 Hz), 1.30 (t, 6H, 8-H enol and keto form completely overlapped, $J_{8/7}$ = 7.2 Hz), 0.97 (t, 3H, 6-H enol form, $J_{6/5}$ = 7.2 Hz), 0.92 (t, 3H, 6-H keto form , $J_{6/5}$ = 7.2 Hz) ppm. The ^{1}H-NMR spectral data is consistent with that found in the literature.[130]

3.4 Ethyl 2-chloro-4-methyl-3-oxopentanoate (100e)

Following the procedure in Section 3.1 (reaction time overnight), ethyl 4-methyl-3-oxopentanoate (78e) (3.00 g; 19.0 mmol) and sulfuryl chloride (1.68 mL; 20.9 mmol; 1.10 equiv.) were converted into 100e (3.43 g; 17.8 mmol; 94 %) which was obtained as a pale yellow liquid. The ratio of keto to enol form was 92:8.

$C_8H_{13}ClO_3$ (M = 192.64 g/mol)
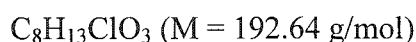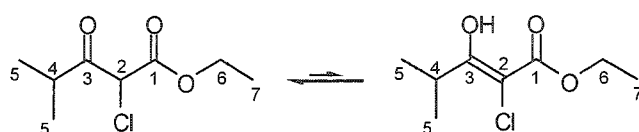
^{1}H-NMR (CDCl$_3$): δ = 12.53 (s, 1H, OH enol form), 4.93 (s, 1H, 2-H keto form), 4.29 (q, 4H, 6-H enol and keto form completely overlapped, $J_{6/7}$ = 7.2 Hz), 3.09 (septet, 2H, 4-H enol and keto form completely overlapped, $J_{4/5}$ = 6.9 Hz), 1.30 (t, 6H, 7-H enol and keto form completely overlapped, $J_{7/6}$ = 7.2 Hz), 1.26 (d, 3H, 5-H enol form, $J_{5/4}$ = 6.9 Hz), 1.18 and 1.16 (2d, appearance similar to t, 6H, 5-H keto form, $J_{5/4}$ = 6.9 Hz) 1.15 (d, 3H, 5-H enol form, $J_{5/4}$ = 6.9 Hz) ppm. The ^{1}H-NMR spectral data is consistent with that found in the literature.[130]

3.5 Ethyl 2-chloro-5-methyl-3-oxohexanoate (100f)

Following the procedure in Section 3.1 (reaction time overnight), ethyl 5-methyl-3-oxohexanoate (78f) (12.0 g; 69.7 mmol) and sulfuryl chloride (6.16 mL; 76.7 mmol; 1.10 equiv.) were converted into 100f (14.6 g; quantitative yield) which was obtained as a pale yellow liquid. The ratio of keto to enol form was 86:14.

This reaction was scaled up to 254 g (1.47 mol) of starting material also resulting in a quantitative yield (306 g).

C$_9$H$_{15}$ClO$_3$ (M = 206.67 g/mol)
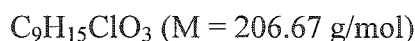
^{1}H-NMR (CDCl$_3$) : δ = 12.43 (s, 1H, OH enol form), 4.75 (s, 1H, 2-H), 4.29 (q, 2H, 7-H enol form, $J_{7/8}$ = 7.2 Hz), 4.28 (q, 2H, 7-H keto form, $J_{6/7}$ = 7.2 Hz), 2.70 (d, 2H, 4-H enol form, $J_{4/5}$ = 7.2 Hz), 2.59 and 2.56 (2d, 2H, 4-H keto form, two non-identical H, 1H *syn* and 1H *anti* to Cl, $J_{4/5}$ = 7.2 Hz), 2.19 (nonet, 2H, 5-H enol and keto form completely overlapped, $J_{5/4}$ = $J_{5/6}$ = 6.7 Hz), 1.31 (t, 6H, 8-H enol and keto form completely overlapped, $J_{8/7}$ = 7.2 Hz), 0.99 +0.96 (2d, 6H, 6-H enol form, $J_{6/5}$ = 7.2 Hz), 0.94 and 0.93 (2d, 6H, 6-H keto form, $J_{6/5}$ = 7.2 Hz) ppm.

^{13}C-NMR (CDCl$_3$) of the keto form: δ = 198.46 (C-3), 165.09 (C-1), 63.20 (C-7), 61.30 (C-2), 47.71 (C-4), 24.32 (C-5), 22.41 and 22.31 (C-6), 14.04 (C-8) ppm.

HRMS (ESI) for C$_9$H$_{16}$ClO$_3$ [M+H]$^+$: calculated: 207.0782; measured: 207.0781.

IR: v_{max}/cm^{-1} = 2962 (w, CH$_{alkyl}$), 1729 (m, C=O), 1252 + 1181 (m, C-O), 1022 (m).

3.6 Ethyl 2-chloro-4,4-dimethyl-3-oxopentanoate (100g)

Following the procedure in Section 3.1, ethyl 4,4-dimethyl-3-oxopentanoate (**78g**) (10.0 g; 58.1 mmol) and sulfuryl chloride (5.13 mL; 63.9 mmol; 1.10 equiv.) were converted into **100g** (12.2 g; quantitative yield) which was obtained as a pale yellow liquid. The ratio of keto to enol form was 91:9.


$C_9H_{15}ClO_3$ (M = 206.67 g/mol)
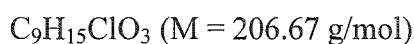
^{1}H-NMR (CDCl$_3$): δ = 5.22 (s, 1H, 2-H keto form), 4.36 (2H, 6-H enol form, $J_{6/7}$ = 7.2 Hz), 4.26 (q, 2H, 6-H keto form, $J_{6/7}$ = 7.2 Hz), 1.36 (s, 9H, 5-H enol form), 1.28 (t, 6H, 7-H enol and keto form completely overlapped, $J_{7/6}$ = 7.2 Hz), 1.26 (s, 9H, 5-H keto form) ppm. The OH signal of the enol form was not detected. The ^{1}H-NMR spectral data is consistent with that found in the literature.[130]

3.7 Ethyl 2-chloro-3-oxo-3-phenylpropanoate (100h)

Following the procedure in Section 3.1, ethyl 3-oxo-3-phenylpropanoate (**78h**) (18.0 g; 93.6 mmol) and sulfuryl chloride (13.9 g; 103 mmol; 1.10 equiv.) were converted into **100h** (21.5 g; quantitative yield) which was obtained as an orange oil. The ratio of keto to enol form was > 99:1.

This reaction was scaled up to 115 g (598 mmol) of starting material also resulting in a quantitative yield (136 g).

$C_{11}H_{11}ClO_3$ (M = 226.66 g/mol)
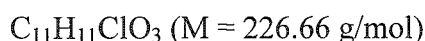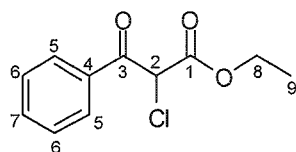
^{1}H-NMR (CDCl$_3$): δ = 12.87 (s, trace, OH enol form), 8.01 (dd, 2H, 5-H, $J_{5/7}$ = 1.7 Hz, $J_{5/6}$ = 7.2 Hz), 7.64 (tt, 1H, 7-H, $J_{7/5}$ = 1.7 Hz, $J_{7/6}$ = 7.2 Hz), 7.51 (dd, 2H, 6-H, $J_{6/5}$ = $J_{6/7}$ = 7.2 Hz), 5.61 (s, 1H, 2-H), 4.29 (q, 2H, 8-H, $J_{8/9}$ = 7.2 Hz), 1.25 (t, 3H, 9-H, $J_{9/8}$ = 7.2 Hz) ppm. The ^{1}H-NMR spectral data is consistent with that found in the literature.[130]

3.8 Ethyl 2-chloro-3-(4-nitrophenyl)-3-oxopropanoate (100i)

Following the procedure in Section 3.1 (reaction time: overnight), ethyl 3-(4-nitrophenyl)-3-oxopropanoate (78i) (3.00 g; 12.6 mmol) and sulfuryl chloride (1.12 mL; 13.9 mmol; 1.10 equiv.) were converted into 100i (2.64 g; 9.72 mmol; 77 %) which was obtained as an orange oil. The product exists solely in its keto form.
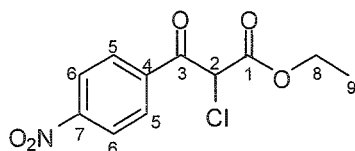
C$_{11}$H$_{10}$ClNO$_5$ (M = 271.66 g/mol)

^{1}H-NMR (CDCl$_3$): δ = 8.36 (d, 2H, 6-H, $J_{6/5}$ = 8.7 Hz), 8.18 (d, 2H, 5-H, $J_{5/6}$ = 8.7 Hz), 5.57 (s, 1H, 2-H), 4.32 (q, 2H, 8-H, $J_{8/9}$ = 7.2 Hz), 1.27 (t, 3H, 9-H, $J_{9/8}$ = 7.2 Hz) ppm. The ^{1}H-NMR spectral data is consistent with that found in the literature.[71]

4   α-Acetoxy-β-keto esters

4.1 Ethyl 2-acetoxy-3-oxobutanoate (101a)

To a stirred ice-cold solution of glacial acetic acid (20 mL; 349 mmol; 5.75 equiv.) in DMF (100 mL) was dropwise added triethylamine (20 mL; 143 mmol; 2.36 equiv.). After warming to room temperature, ethyl 2-chloro-3-oxobutanoate (100a) (10.0 g; 60.8 mmol)

was added and the solution was left stirring for 20 h. The solution was then washed with water (100 mL), extracted with dichloromethane (100 mL), washed again with water (5x 50 mL), dried over $MgSO_4$ and the solvent evaporated under reduced pressure yielding **101a** (9.67 g; 51.4 mmol; 85 %) which was obtained as an orange liquid. The product exists solely in its keto form.

$C_8H_{12}O_5$ (M = 188.18 g/mol)
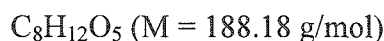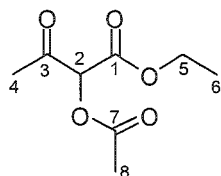
^{1}H-NMR (CDCl$_3$): δ = 5.50 (s, 1H, 2-H), 4.29 (q, 3H, 5-H, $J_{5/6}$ = 7.2 Hz), 2.36 (s, 3H, 4-H), 2.24 (s, 3H, 8-H), 1.32 (t, 3H, 6-H, $J_{6/5}$ = 7.2 Hz) ppm. The 1H-NMR spectral data is consistent with that found in the literature.[74]

4.2 Methyl 2-acetoxy-3-oxopentanoate (101c)

Following the procedure in Section 4.1 and using triethylamine (30 mL; 215 mmol; 3.54 equiv.), methyl 2-chloro-3-oxopentanoate (**100c**) (10.0 g; 60.8 mmol) and glacial acetic acid (30 mL; 524 mmol; 8.63 equiv.) were converted into **101c** (10.3 g; 54.7 mmol; 90 %) which was obtained as a yellow liquid. The product exists solely in its keto form.

$C_8H_{12}O_5$ (M = 188.18 g/mol)
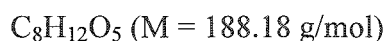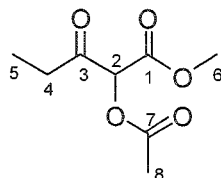
^{1}H-NMR (CDCl$_3$): δ = 5.53 (s, 1H, 2-H), 3.83 (s, 3H, 6-H), 2.71 and 2.70 (2q, appearance similar to dq, 2H, 4-H keto form, two non-identical H, 1H *syn* and 1H *anti* to Cl, $J_{4/5}$ = 7.2 Hz), 2.24 (s, 3H, 8-H), 1.11 (t, 3H, 5-H, $J_{5/4}$ = 7.2 Hz) ppm. The ^{1}H-NMR spectral data is consistent with that found in the literature.[131]

4.3 Ethyl 2-acetoxy-4-methyl-3-oxopentanoate (101e)

Following the procedure in Section 4.1 (reaction time 2 days) and using triethylamine (2 mL; 14.3 mmol; 2.76 equiv.), ethyl 2-chloro-4-methyl-3-oxopentanoate (**100e**) (1.00 g; 5.19 mmol) and glacial acetic acid (2 mL; 34.9 mmol; 6.73 equiv.) were converted into **101e** (617 mg; 2.85 mmol; 55 %) which was obtained as a yellow liquid. The product exists solely in its keto form.

$C_{10}H_{16}O_5$ (M = 216.23 g/mol)
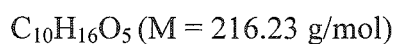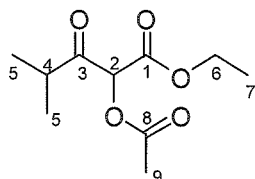
^{1}H-NMR (CDCl$_3$): δ = 5.64 (s, 1H, 2-H), 4.26 (q, 2H, 6-H, $J_{6/7}$ = 7.2 Hz), 3.03 (septet, 1H, 4-H, $J_{4/5}$ = 6.9 Hz), 2.21 (s, 3H, 9-H), 1.29 (t, 3H, 7-H, $J_{7/6}$ = 7.2 Hz), 1.16 and 1.11 (2d, 6H, 5-H, $J_{5/4}$ = 6.9 Hz) ppm. The ^{1}H-NMR spectral data is consistent with that found in the literature.[132]

4.4 Ethyl 2-acetoxy-5-methyl-3-oxohexanoate (101f)

Following the procedure in Section 4.1 and using triethylamine (10 mL; 71.7 mmol; 2.97 equiv.), ethyl 2-chloro-5-methyl-3-oxohexanoate (**100f**) (5.00 g; 24.2 mmol) and glacial acetic acid (10 mL; 175 mmol; 7.22 equiv.) were converted into **101f** (5.67 g; quantitative yield) which was obtained as a yellow liquid. The product exists solely in its keto form.

This reaction was scaled up to 306 g (1.48 mol) of starting material resulting in a yield of 304 g (1.32 mol; 89 %).
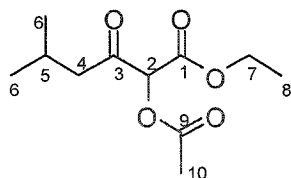
$C_{11}H_{18}O_5$ (M = 230.26 g/mol)

^{1}H-NMR (CDCl$_3$): δ = 5.46 (s, 1H, 2-H), 4.27 (q, 2H, 7-H, $J_{7/8}$ = 7.2 Hz), 2.53 (d, 2H, 4-H, $J_{4/5}$ = 6.7 Hz), 2.22 (s, 3H, 10-H), 2.19 (nonet, 1H, 5-H, $J_{5/4}$ = $J_{5/6}$ = 6.7 Hz), 1.30 (t, 3H, 8-H, $J_{8/7}$ = 7.2 Hz), 0.93 and 0.90 (2d, 6H, 6-H, $J_{6/5}$ = 6.7 Hz) ppm. The ^{1}H-NMR spectral data is consistent with that found in the literature.[132]

4.5 Ethyl 2-acetoxy-4,4-dimethyl-3-oxopentanoate (101g)

Following the procedure in Section 4.1 and using triethylamine (11 mL; 78.9 mmol; 8.16 equiv.), ethyl 2-chloro-4,4-dimethyl-3-oxopentanoate (100g) (2.00 g; 9.68 mmol) and glacial acetic acid (11 mL; 192 mmol; 19.9 equiv.) were converted into 101g (1.56 g; 6.77 mmol; 70 %) which was obtained as a yellow liquid. The product exists solely in its keto form.
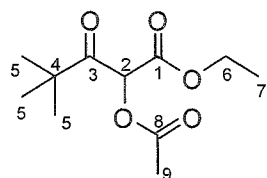
$C_{11}H_{18}O_5$ (M = 230.26 g/mol)

^{1}H-NMR (CDCl$_3$): δ =5.92 (s, 1H, 2-H), 4.26 (q, 2H, 6-H keto form, $J_{6/7}$ = 7.2 Hz), 2.21 (s, 3H, 9-H), 1.28 (t, 3H, 7-H, $J_{7/6}$ = 7.2 Hz), 1.24 (s, 9H, 5-H) ppm.

^{13}C-NMR (CDCl$_3$): δ = 205.19 (C-3), 169.58 and 165.47 (C-1, C-8), 72.21 (C-2), 62.38 (C-6), 44.76 (C-4), 26.24 (C-5), 20.52 (C-9), 14.04 (C-7) ppm.

HRMS (ESI) for $C_{11}H_{19}O_5$ [M+H]$^+$: calculated: 231.1227; measured: 231.1226.

IR: v_{max}/cm^{-1} = 2970 (w, CH$_{alkyl}$), 1752 + 1719 (s, C=O), 1370 (m, CH$_{alkyl}$), 1197 (s, C-O), 1085 (m, C-O).

4.6 Ethyl 2-acetoxy-3-oxo-3-phenylpropanoate (101h)

Following the procedure in Section 4.1 (reaction time 3 days) and using triethylamine (12.9 mL; 92.6 mmol; 1.00 equiv.), ethyl 2-chloro-3-oxo-3-phenylpropanoate (100h) (20.9 g; 92.2 mmol; 1.00 equiv.) and glacial acetic acid (7.44 mL; 130 mmol; 1.41 equiv.) were converted into 101h (21.1 g; 84.3 mmol; 91 %) which was obtained as a brown liquid. The product exists solely in its keto form.

This reaction was scaled up to 136 g (600 mmol) of starting material resulting in a slightly improved yield of 140 g (559 mmol; 93 %). At this large scale the considerable amounts of triethylamine hydrochloride salts that precipitated during the reaction were filtered off before continuing the workup.

$C_{13}H_{14}O_5$ (M = 250.25 g/mol)
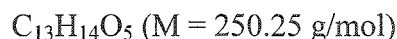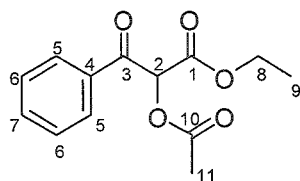
^{1}H-NMR (CDCl$_3$): δ = 8.01 (dd, 2H, 5-H, $J_{5/7}$ = 1.7 Hz, $J_{5/6}$ = 7.2 Hz), 7.63 (tt, 1H, 7-H, $J_{7/5}$ = 1.7 Hz, $J_{7/6}$ = 7.2 Hz), 7.50 (dd, 2H, 6-H, $J_{6/5}$ = $J_{6/7}$ = 7.2 Hz), 6.33 (s, 1H, 2-H), 4.25 (q, 2H, 8-H, $J_{8/9}$ = 7.2 Hz), 2.23 (s, 3H, 11-H), 1.22 (t, 3H, 9-H, $J_{9/8}$ = 7.2 Hz) ppm. The ^{1}H-NMR spectral data is consistent with that found in the literature.[77]

5 α-Chloro-α-acetoxy-β-keto esters

5.1 Ethyl 2-acetoxy-2-chloro-3-oxobutanoate (102a)

To a stirred ice-cold solution of ethyl 2-acetoxy-3-oxobutanoate (101a) (4.00 g; 21.3 mmol) in dichloromethane (50 mL) was added dropwise over 1 min sulfuryl chloride (1.88 mL; 23.4 mmol; 1.10 equiv.). After stirring at room temperature for 20 h, the solution was washed with a saturated solution of $NaHCO_3$, dried over $MgSO_4$ and the solvent evaporated under reduced pressure yielding 102a (3.83 g; 17.2 mmol; 81 %) which was obtained as a yellow liquid.

$C_8H_{11}ClO_5$ (M = 222.63 g/mol)
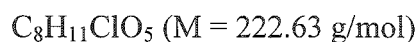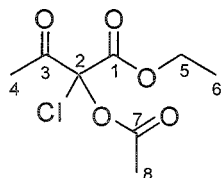
^{1}H-NMR (CDCl$_3$): δ = 4.33 (q, 2H, 5-H, $J_{5/6}$ = 7.2 Hz), 2.50 (s, 3H, 4-H), 2.24 (s, 3H, 8-H), 1.32 (t, 3H, 6-H, $J_{6/5}$ = 7.2 Hz) ppm.

^{13}C-NMR (CDCl$_3$): δ = 194.50 (C-3), 167.70 and 163.32 (C-1, C-7), 89.98 (C-2), 63.96 (C-5), 24.81 (C-4), 20.80 (C-8), 13.87 (C-6) ppm.

HRMS data can be found in the literature.[71]

IR: v_{max}/cm^{-1} = 2987 (w, CH$_{alkyl}$), 1733 (s, C=O), 1370 (m, CH$_{alkyl}$), 1252 + 1199 + 1086 (s, C-O), 1042 (s), 1011 (s).

5.2 Methyl 2-acetoxy-2-chloro-3-oxopentanoate (102c)

Following the procedure in Section 5.1, methyl 2-acetoxy-3-oxopentanoate (101c) (10.3 g; 54.7 mmol) and sulfuryl chloride (4.84 mL; 60.2 mmol; 1.10 equiv.) were converted into 102c (11.2 g; 50.3 mmol; 92 %) which was obtained as a yellow liquid.
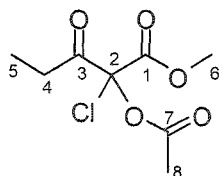
$C_8H_{11}ClO_5$ (M = 222.63 g/mol)

^{1}H-NMR (CDCl$_3$): δ = 3.87 (s, 3H, 6-H), 2.92 (q, 2H, 4-H, $J_{4/5}$ = 7.2 Hz), 2.24 (s, 3H, 8-H), 1.15 (t, 3H, 5-H, $J_{5/4}$ = 7.2 Hz) ppm.

^{13}C-NMR (CDCl$_3$): δ = 197.88 (C-3), 167.73 and 164.12 (C-1, C-7), 89.87 (C-2), 54.38 (C-6), 30.48 (C-4), 20.83 (C-8), 7.74 (C-5) ppm.

HRMS (ESI) for $C_8H_{15}ClNO_5$ [M+NH$_4$]$^+$: calculated: 240.0633; measured: 240.0633.

IR: v_{max}/cm^{-1} = 2960 (w, CH$_{alkyl}$), 1779 + 1736 (s, C=O), 1262 (m, C-O), 1200 (s, C-O), 1095 (s, C-O), 1071 (m, C-O).

5.3 Ethyl 2-acetoxy-2-chloro-5-methyl-3-oxo-hexanoate (102f)

Following the procedure in Section 5.1, ethyl 2-acetoxy-5-methyl-3-oxohexanoate (101f) (4.97 g; 21.6 mmol) and sulfuryl chloride (1.91 mL; 23.8 mmol; 1.10 equiv.) were converted into 102f (5.45 g; 20.6 mmol; 95 %) which was obtained as a yellow liquid.
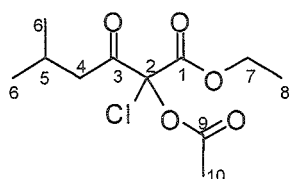
$C_{11}H_{17}ClO_5$ (M = 264.71 g/mol)

^{1}H-NMR (CDCl$_3$): δ = 4.37 and 4.32 (2q, 2H, 7-H, $J_{7/8}$ = 7.2 Hz), 2.77 – 2.70 (m, 2H, 4-H), 2.30 – 2.15 (m, 1H, 5-H), 2.24 (s, 3H, 10-H), 1.35 and 1.31 (t, 3H, 8-H, $J_{8/7}$ = 7.2 Hz), 0.97 and 0.96 (2t, 6H, 6-H, $J_{6/5}$ = 6.7 Hz) ppm.

^{13}C-NMR (CDCl$_3$): δ = 196.16 (C-3), 167.67 and 163.46 (C-1, C-9), 63.89 (C-7), 45.51 (C-4), 24.06 (C-5), 22.43 and 22.20 (C-6), 20.86 (C-10), 13.89 (C-8) ppm. The signal for C-2 was not detected.

HRMS (ESI) for $C_{11}H_{21}ClNO_5$ [M+NH$_4$]$^+$: calculated: 282.1103; measured: 282.1104.

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IR: v_{max}/cm^{-1} = 2965 (w, CH_{alkyl}), 1735 (m, C=O), 1247 + 1200 + 1090 (m, C-O), 1021.

5.4 Ethyl 2-acetoxy-2-chloro-3-oxo-3-phenylpropanoate (102g)

Following the procedure in Section 5.1, ethyl 2-acetoxy-3-oxo-3-phenylpropanoate (**101g**) (21.1 g; 84.3 mmol) and sulfuryl chloride (7.44 mL; 92.6 mmol; 1.10 equiv.) were converted into **102g** (23.1 g; 81.1 mmol; 96 %) which was obtained as an orange oil.

This reaction was scaled up to 140 g (559 mmol) of starting material resulting in a yield of 140 g (492 mmol, 88 %) of **102g** which was obtained as yellow crystals (m.p. 44 – 46 °C from diethyl ether / hexanes).
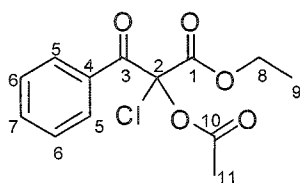
$C_{13}H_{13}ClO_5$ (M = 284.70 g/mol)

^{1}H-NMR (CDCl$_3$): δ = 8.10 (dd, 2H, 5-H, $J_{5/6}$ = 7.2 Hz, $J_{5/7}$ = 1.7 Hz), 7.63 (tt, 1H, 7-H, $J_{7/5}$ = 1.7 Hz, $J_{7/6}$ = 7.2 Hz), 7.49 (dd, 2H, 6-H, $J_{6/5}$ = $J_{6/7}$ = 7.2 Hz), 4.36 (q, 2H, 8-H, $J_{8/9}$ = 7.2 Hz), 2.21 (s, 3H, 11-H), 1.29 (t, 3H, 9-H, $J_{9/8}$ = 7.2 Hz) ppm. The ^{1}H-NMR spectral data is consistent with that found in the literature.[133]

6 Picolinates

6.1 1-Ethoxy-1,3-dioxobutan-2-yl picolinate (168a)

To a stirred ice-cold solution of picolinic acid (17.8 g; 145 mmol; 2.50 equiv.) in DMF (100 mL) was added $KHCO_3$ (8.57 g; 85.6 mmol; 1.48 equiv.). After warming to room temperature, ethyl 2-chloro-3-oxobutanoate (100a) (9.50 g; 57.7 mmol) was added and the solution was left stirring for 2 days. The solution was poured onto water (100 mL), extracted with dichloromethane (2x 100 mL), washed with water (4x 50 mL) to remove the DMF from the organic phase, dried over $MgSO_4$ and the solvent evaporated under reduced pressure yielding 168a (11.1 g; 44.2 mmol; 77 %) which was obtained as a viscous orange liquid. The ratio of keto to enol form was 93:7.

$C_{12}H_{13}NO_5$ (M = 251.24 g/mol)
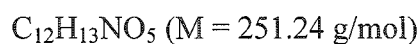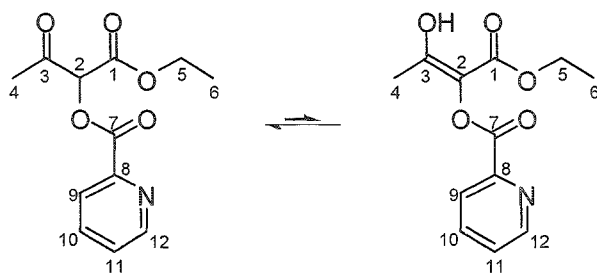
^{1}H-NMR (CDCl$_3$): δ = 12.35 (s, 1H, OH enol form), 8.82 (ddd, 2H, 12-H keto and enol form completely overlapped, $J_{12/9}$ = 1.0 Hz, $J_{12/10}$ = 1.7 Hz, $J_{12/11}$ = 4.7 Hz), 8.23 (ddd, appearance similar to dt, 2H, 9-H keto and enol form completely overlapped, $J_{9/12}$ = 1.0 Hz, $J_{9/11}$ = 1.2 Hz, $J_{9/10}$ = 7.9 Hz), 7.90 (ddd, appearance similar to dt, 2H, 10-H keto and enol form completely overlapped, $J_{10/12}$ = 1.7 Hz, $J_{10/11}$ = 7.7 Hz, $J_{10/9}$ = 7.9 Hz), 7.55 (ddd, 2H, 11-H keto and enol form completely overlapped, $J_{11/9}$ = 1.2 Hz, $J_{11/12}$ = 4.7 Hz, $J_{11/10}$ = 7.7 Hz), 5.81 (s, 1H, 2-H keto form), 4.34 (q, 2H, 5-H keto form, $J_{5/6}$ = 7.2 Hz), 4.33 (q, 2H, 5-H enol form, $J_{5/6}$ = 7.2 Hz), 2.47 (s, 3H, 4-H keto form), 2.39 (s, 3H, 4-H enol form), 1.34 (t, 3H, 6-H keto form, $J_{6/5}$ = 7.2 Hz), 1.33 (t, 3H, 6-H enol form, $J_{6/5}$ = 7.2 Hz) ppm.

^{13}C-NMR (CDCl$_3$) of the keto form: δ = 197.19 (C-3), 164.28 and 163.61 (C-1, C-7), 150.39

(C-12), 146.63 (C-8), 137.22 (C-10), 127.63 (C-11), 125.88 (C-9), 78.61 (C-2), 62.78 (C-5), 27.48 (C-4), 14.08 (C-6) ppm.

HRMS (ESI) for $C_{12}H_{14}NO_5$ $[M+H]^+$: calculated: 252.0866; measured: 252.0866.

IR: v_{max}/cm^{-1} = 2986 (w, CH_{alkyl}), 1727 (s, C=O), 1290 (m), 1244 + 1215 (m, C-O), 1126 + 1092 (s, C-O), 749 + 700 (s, CH_{ar}).

6.2   1-*Tert*-butoxy-1,3-dioxobutan-2-yl picolinate (168b)

Following the procedure in Section 6.1 and using 12.0 g $KHCO_3$ (120 mmol; 3.99 equiv.), *tert*-butyl 2-chloro-3-oxobutanoate (100b) (5.78 g; 30.0 mmol) and picolinic acid (14.8 g; 120 mmol; 4.01 equiv.) were converted into 168b (5.80 g; 20.8 mmol; 69 %) which was obtained as an orange liquid. The ratio of keto to enol form was ≈ 90:10.
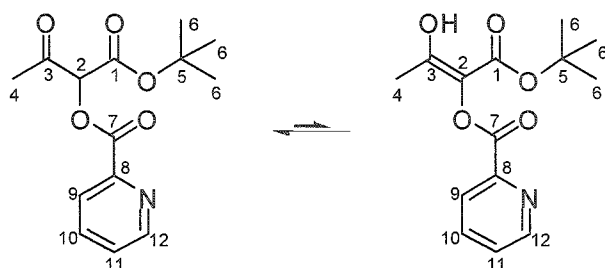
$C_{14}H_{17}NO_5$ (M = 279.29 g/mol)

^{1}H-NMR (CDCl$_3$): δ = 8.82 (ddd, 1H, 12-H, keto form, $J_{12/9-H}$ = 1.0 Hz, $J_{12/10}$ = 1.7 Hz, $J_{12/11}$ = 4.7 Hz), 8.81 -8.78 (m, 1H, 12-H, enol form), 8.23 (ddd, appearance similar to dt, 1H, 9-H, keto form, $J_{9/12}$ = 1.0 Hz, $J_{9/11}$ = 1.2 Hz, $J_{9/10}$ = 7.9 Hz), 8.22 – 8.18 (m, 1H, 9-H, enol form), 7.92 – 7.86 (m, 1H, 10-H, enol form), 7.88 (ddd, appearance similar to dt, 1H, 10-H, keto form, $J_{10/12}$ = 1.7 Hz, $J_{10/11}$ = 7.7 Hz, $J_{10/9}$ = 7.9 Hz), 7.53 (ddd, 2H, 11-H, keto and enol form completely overlapped, $J_{11/9}$ = 1.2 Hz, $J_{11/12}$ = 4.7 Hz, $J_{11/10}$ = 7.7 Hz) 5.72 (s, 1H, 2-H, keto), 2.45 (s, 3H, 4-H, keto form), 2.36 (s, 3H, 4-H, enol form), 1.52 (t, 9H, 6-H, keto form), 1.50 (s, 9H, 6-H, enol form) ppm.

^{13}C-NMR (CDCl$_3$) of the keto form: δ = 197.42 (C-3), 163.60 + 163.05 (C-1, C-7), 150.42 (C-12), 146.82 (C-8), 137.18 (C-10), 127.53 (C-11), 125.82 (C-9), 84.42 (C-5), 79.04 (C-2), 27.97 (C-6), 27.63 (C-4) ppm.

HRMS: The expected ion was not observed due to decomposition/hydrolysis of the ester.

IR: ν_{max}/cm^{-1} = 2984 (w, CH_{alkyl}), 1726 (s, C=O), 1308 (m), 1244 (m, C-O), 1123 (s, C-O), 1091 (m, C-O), 748 + 704 (s, CH_{ar}).

6.3 1-Methoxy-1,3-dioxopropan-2-yl picolinate (168c)

Following the procedure in Section 6.1 and using $KHCO_3$ (0.61 g; 6.09 mmol; 1.00 equiv.), methyl 2-chloro-3-oxopropanoate (100c) (1.00 g; 6.08 mmol) and picolinic acid (2.99 g; 24.3 mmol; 4.00 equiv.) were converted into 168c (1.24 g; 4.94 mmol; 81 %) which was obtained as a viscous orange liquid. The product exists solely in its keto form.
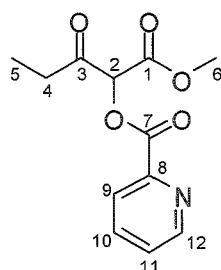
$C_{12}H_{13}NO_5$ (M = 251.24 g/mol)

^{1}H-NMR (CDCl$_3$): δ = 8.82 (ddd, 1H, 12-H, $J_{12/9}$ = 1.0 Hz, $J_{12/10}$ = 1.7 Hz, $J_{12/11}$ = 4.7 Hz), 8.23 (ddd, appearance similar to dt, 1H, 9-H, $J_{9/12}$ = 1.0 Hz, $J_{9/11}$ = 1.2 Hz, $J_{9/10}$ = 7.9 Hz), 7.90 (ddd, appearance similar to dt, 1H, 10-H, $J_{10/12}$ = 1.7 Hz, $J_{10/11}$ = 7.7 Hz, $J_{10/9}$ = 7.9 Hz), 7.55 (ddd, 1H, 11-H, $J_{11/9}$ = 1.2 Hz, $J_{11/12}$ = 4.7 Hz, $J_{11/10}$ = 7.7 Hz), 5.84 (s, 1H, 2-H), 3.87 (s, 3H, 6-H), 2.84 (q, 2H, 4-H, $J_{4/5}$ = 7.2 Hz), 1.15 (t, 3H, 5-H, $J_{5/4}$ = 7.2 Hz) ppm.
^{13}C-NMR (CDCl$_3$): δ = 200.17 (C-3), 165.05 and 163.69 (C-1, C-7), 150.39 (C-12), 146.60 (C-8), 137.24 (C-10), 127.66 (C-11), 125.91 (C-9), 78.02 (C-2), 53.38 (C-6), 33.49 (C-4), 7.23 (C-5) ppm.
HRMS (ESI) for $C_{12}H_{14}NO_5$ [M+H]$^+$: calculated: 252.0866; measured: 252.0865.
IR: ν_{max}/cm^{-1} = 2917 (w, CH_{alkyl}), 1725 (s, C=O), 1307 (m), 1290 (m), 1234 (m, C-O), 1127 (s, C-O), 1090 (m, C-O), 748 + 703 (s, CH_{ar}).

6.4 1-Ethoxy-1,3-dioxohexan-2-yl picolinate (168d)

Following the procedure in Section 6.1 (reaction time 3 days) and using $KHCO_3$ (1.56 g; 15.6 mmol), ethyl 2-chloro-3-oxohexanoate (100d) (3.00 g; 15.6 mmol) and picolinic acid (3.84 g; 31.2 mmol; 2.00 equiv.) were converted into 168d (3.94 g; 14.1 mmol; 91 %) which was obtained as a viscous orange liquid. The product exists solely in its keto form.

$C_{14}H_{17}NO_5$ (M = 279.29 g/mol)
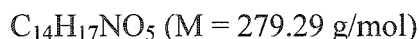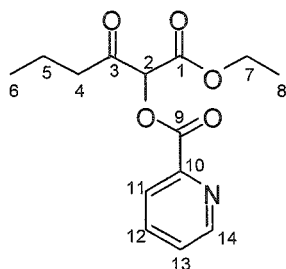
^{1}H-NMR (CDCl$_3$): δ = 8.82 (ddd, 1H, 14-H, $J_{14/11}$ = 1.0 Hz, $J_{14/12}$ = 1.7 Hz, $J_{14/13}$ = 4.7 Hz), 8.23 (ddd, appearance similar to dt, 1H, 11-H, $J_{11/14}$ = 1.0 Hz, $J_{11/13}$ = 1.2 Hz, $J_{11/12}$ = 7.9 Hz), 7.89 (ddd, appearance similar to dt, 1H, 12-H, $J_{12/14}$ = 1.7 Hz, $J_{12/13}$ = 7.7 Hz, $J_{12/11}$ = 7.9 Hz), 7.54 (ddd, 1H, 13-H, $J_{13/11}$ = 1.2 Hz, $J_{13/14}$ = 4.7 Hz, $J_{13/12}$ = 7.7 Hz) 5.81 (s, 1H, 2-H), 4.33 (q, 2H, 7-H, $J_{7/8}$ = 7.2 Hz), 2.77 (t, 2H, 4-H, $J_{4/5}$ = 7.2 Hz), 1.70 (tq, appearance similar to sextet, 2H, 5-H, $J_{5/4}$ = $J_{5/6}$ 7.2 Hz), 1.33 (t, 3H, 8-H, $J_{8/7}$ = 7.2 Hz), 0.96 (t, 3H, 6-H, $J_{6/5}$ = 7.2 Hz) ppm.

^{13}C-NMR (CDCl$_3$): δ = 199.55 (C-3), 164.48 and 163.66 (C-1, C-9), 150.41 (C-14), 146.73 (C-10), 137.21 (C-12), 127.60 (C-13), 125.88 (C-11), 78.33 (C-2), 62.72 (C-7), 41.84 (C-4), 16.70 (C-5), 14.13 (C-8), 13.58 (C-6) ppm.

HRMS (ESI) for $C_{14}H_{18}NO_5$ [M+H]$^+$: calculated: 280.1179; measured: 280.1180.

IR: v_{max}/cm^{-1} = 2978 (m, CH$_{alkyl}$), 1729 (s, C=O), 1306 (m), 1244 + 1134 (s, C-O), 749 + 705 (m, CH$_{ar}$).

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6.5 1-Ethoxy-4-methyl-1,3-dioxopentan-2-yl picolinate (168e)

Following the procedure in Section 6.1 (reaction time 6 days) and using $KHCO_3$ (2.60 g; 26.0 mmol; 5.00 equiv.), ethyl 2-chloro-4-methyl-3-oxopentanoate (**100e**) (1.00 g; 5.19 mmol) and picolinic acid (3.20 g; 26.0 mmol; 5.01 equiv.) were converted into **168e** (859 mg; 3.08 mmol; 59 %) which was obtained as a yellow liquid. The product exists solely in its keto form.

$C_{14}H_{17}NO_5$ (M = 279.29 g/mol)
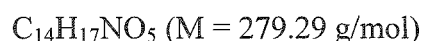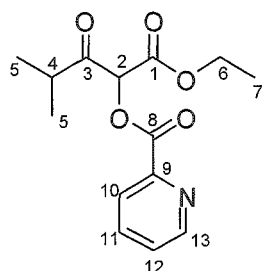
^{1}H-NMR (CDCl$_3$): δ = 8.82 (ddd, 1H, 13-H, $J_{13/10}$ = 1.0 Hz, $J_{13/11}$ = 1.7 Hz, $J_{13/12}$ = 4.7 Hz), 8.23 (ddd, appearance similar to dt, 1H, 10-H, $J_{10/13}$ = 1.0 Hz, $J_{10/12}$ = 1.2 Hz, $J_{10/11}$ = 7.9 Hz), 7.89 (ddd, appearance similar to dt, 1H, 11-H, $J_{11/13}$ = 1.7 Hz, $J_{11/12}$ = 7.7 Hz, $J_{11/10}$ = 7.9 Hz), 7.54 (ddd, 1H, 12-H, $J_{12/10}$ = 1.2 Hz, $J_{12/13}$ = 4.7 Hz, $J_{12/11}$ = 7.7 Hz) 5.97 (s, 1H, 2-H), 4.33 (q, 2H, 6-H, $J_{6/7}$ = 7.2 Hz), 3.19 (septet, 1H, 4-H, $J_{4/5}$ = 6.9 Hz), 1.33 (t, 3H, 7-H, $J_{7/6}$ = 7.2 Hz), 1.26 and 1.18 (2d, 6H, 5-H, $J_{5/4}$ = 6.9 Hz) ppm.

^{13}C-NMR (CDCl$_3$): δ = 203.44 (C-3), 164.63 and 163.60 (C-1, C-8), 150.42 (C-13), 146.74 (C-9), 137.18 (C-11), 127.56 (C-12), 125.85 (C-10), 76.89 (C-2), 62.70 (C-6), 38.36 (C-4), 18.54 and 17.82 (C-5), 14.12 (C-7) ppm.

HRMS (ESI) for $C_{14}H_{18}NO_5$ [M+H]$^+$: calculated: 280.1179; measured: 280.1180.

IR: v_{max}/cm^{-1} = 2924 (w, CH$_{alkyl}$), 1725 (s, C=O), 1248 + 1194 (s, C-O), 744 + 709 (s, CH$_{ar}$).

6.6 1-Ethoxy-5-methyl-1,3-dioxohexan-2-yl picolinate (168f)

Following the procedure in Section 6.1 (reaction time 7 days) and using KHCO$_3$ (969 mg; 9.68 mmol; 2.00 equiv.), ethyl 2-chloro-5-methyl-3-oxohexanoate (100f) (1.00 g; 4.84 mmol) and picolinic acid (1.19 g; 9.67 mmol; 2.00 equiv.) were converted into 168f (1.14g; 3.89 mmol; 80 %) which was obtained as a green liquid. The product exists solely in its keto form.
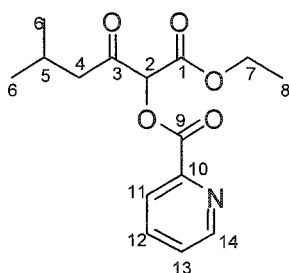
C$_{15}$H$_{19}$NO$_5$ (M = 293.32 g/mol)

^{1}H-NMR (CDCl$_3$): δ = 8.82 (ddd, 1H, 14-H, $J_{14/11}$ = 1.0 Hz, $J_{14/12}$ = 1.7 Hz, $J_{14/13}$ = 4.7 Hz), 8.23 (ddd, appearance similar to dt, 1H, 11-H, $J_{11/14}$ = 1.0 Hz, $J_{11/13}$ = 1.2 Hz, $J_{11/12}$ = 7.9 Hz), 7.89 (ddd, appearance similar to dt, 1H, 12-H, $J_{12/14}$ = 1.7 Hz, $J_{12/13}$ = 7.7 Hz, $J_{12/11}$ = 7.9 Hz), 7.54 (ddd, 1H, 13-H, $J_{13/11}$ = 1.2 Hz, $J_{13/14}$ = 4.7 Hz, $J_{13/12}$ = 7.7 Hz) 5.79 (s, 1H, 2-H), 4.33 (q, 2H, 7-H, $J_{7/8}$ = 7.2 Hz), 2.67 and 2.66 (2d, 2H, 4-H, $J_{4/5}$ = 6.7 Hz), 2.26 (nonet, 1H, 5-H, $J_{5/4}$ = $J_{5/6}$ 6.7 Hz), 1.33 (t, 3H, 8-H, $J_{8/7}$ = 7.2 Hz), 0.98 and 0.96 (2d, 6H, 6-H, $J_{6/5}$ = 6.7 Hz) ppm.

^{13}C-NMR (CDCl$_3$): δ = 199.02 (C-3), 164.40 and 163.63 (C-1, C-9), 150.42 (C-14), 146.73 (C-10), 137.20 (C-12), 127.58 (C-13), 125.86 (C-11), 78.55 (C-2), 62.72 (C-7), 48.69 (C-4), 24.16 (C-5), 22.54 and 22.44 (C-6), 14.13 (C-8) ppm.

HRMS (ESI) for C$_{15}$H$_{20}$NO$_5$ [M+H]$^+$: calculated: 294.1336; measured: 294.1332.

IR: v$_{max}$/cm^{-1} = 2961 (w, CH$_{alkyl}$), 1725 (s, C=O), 1308 (m), 1290 (m), 1245 + 1192 (m, C-O), 1130 (s, C-O), 1092 (m, C-O), 749 + 702 (m, CH$_{ar}$).

6.7 1-Ethoxy-4,4-dimethyl-1,3-dioxopentan-2-yl picolinate (168g)

Following the procedure in Section 6.1 (reaction time 3 days) and using $KHCO_3$ (1.45 g; 14.5 mmol; 2.99 equiv.), the reaction of ethyl 2-chloro-4,4-dimethyl-3-oxopentanoate (100g) (1.00 g; 4.84 mmol) and picolinic acid (1.79 g; 14.5 mmol; 3.00 equiv.) afforded 0.94 g of a mixture of 168g (3.10 mmol; 64 %) and unconverted 100g (145 μmol; 3 %) which was obtained as a viscous orange liquid. The product exists solely in its keto form.

$C_{15}H_{19}NO_5$ (M = 293.32 g/mol)
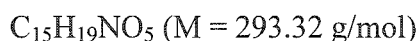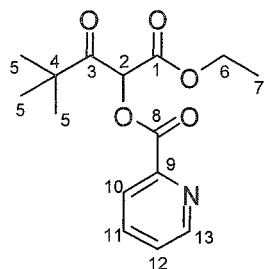
^{1}H-NMR (CDCl$_3$): δ = 8.81 (ddd, 1H, 13-H, $J_{13/10}$ = 1.0 Hz, $J_{13/11}$ = 1.7 Hz, $J_{13/12}$ = 4.7 Hz), 8.20 (ddd, appearance similar to dt, 1H, 10-H, $J_{10/13}$ = 1.0 Hz, $J_{10/12}$ = 1.2 Hz, $J_{10/11}$ = 7.9 Hz), 7.87 (ddd, appearance similar to dt, 1H, 11-H, $J_{11/13}$ = 1.7 Hz, $J_{11/12}$ = 7.7 Hz, $J_{11/10}$ = 7.9 Hz), 7.52 (ddd, 1H, 12-H, $J_{12/10}$ = 1.2 Hz, $J_{12/13}$ = 4.7 Hz, $J_{12/11}$ = 7.7 Hz) 6.23 (s, 1H, 2-H), 4.30 (q, 2H, 6-H, $J_{6/7}$ = 7.2 Hz), 1.31 (t, 3H, 7-H, $J_{7/6}$ = 7.2 Hz), 1.31 (s, 9H, 5-H) ppm.

^{13}C-NMR (CDCl$_3$): δ = 204.87 (C-3), 165.22 and 163.56 (C-1, C-8), 150.42 (C-13), 146.70 (C-9), 137.17 (C-11), 127.54 (C-12), 125.88 (C-10), 73.02 (C-2), 62.55 (C-6), 44.89 (C-4), 26.35 (C-5), 14.07 (C-7) ppm.

HRMS (ESI) for $C_{15}H_{20}NO_5$ [M+H]$^+$: calculated: 294.1336; measured: 294.1336.

IR: v_{max}/cm^{-1} = 2974 (w, CH$_{alkyl}$), 1750 (m, C=O), 1725 (s, C=O), 1305 (m), 1291 (m), 1242 + 1206 (m, C-O), 1122 (s, C-O), 1091 (m, C-O), 746 + 699 (m, CH$_{ar}$).

6.8 1-Ethoxy-1,3-dioxo-3-phenylpropan-2-yl picolinate (168h)

Following the procedure in Section 6.1 (reaction time 8 days; until judged complete by TLC) and using KHCO$_3$ (8.84 g; 88.3 mmol; 2.0 equiv.), ethyl 2-chloro-3-oxo-3-phenylpropanoate (100h) (10.0 g; 44.1 mmol) and picolinic acid (13.6 g; 110 mmol; 2.5 equiv.) were converted into 168h (12.7 g; 40.5 mmol; 92 %) which was obtained as a viscous orange liquid. The product exists solely in its keto form.
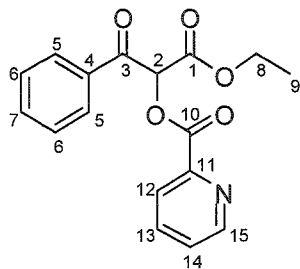
C$_{17}$H$_{15}$NO$_5$ (M = 313.31 g/mol)

^{1}H-NMR (CDCl$_3$): δ = 8.81 (ddd, 1H, 15-H, $J_{15/12}$ = 1.0 Hz, $J_{15/13}$ = 1.7 Hz, $J_{15/14}$ = 4.7 Hz), 8.20 (ddd, appearance similar to dt, 1H, 12-H, $J_{12/15}$ = 1.0 Hz, $J_{12/14}$ = 1.2 Hz, $J_{12/13}$ = 7.9 Hz), 8.09 (m, 2H, 5-H), 7.86 (ddd, appearance similar to dt, 1H, 13-H, $J_{13/15}$ = 1.7 Hz, $J_{13/14}$ = 7.7 Hz, $J_{13/12}$ = 7.9 Hz), 7.64 (tt, 1H, 7-H, $J_{7/5}$ = 1.4 Hz, $J_{7/6}$ = 7.3 Hz), 7.55-7.48 (m, 3H, 14-H and 6-H), 6.64 (s, 1H, 2-H), 4.30 (q, 2H, 8-H, $J_{8/9}$ = 7.2 Hz), 1.24 (t, 3H, 9-H, $J_{9/8}$ = 7.2 Hz) ppm.

^{13}C-NMR (CDCl$_3$): δ = 189.30 (C-3), 164.95 and 163.58 (C-1, C-10), 150.43 (C-15), 146.67 (C-11), 137.21 (C-13), 134.41 (C-7), 134.26 (C-4), 129.42 (C-5), 128.92 (C-6), 127.60 (C-14), 125.97 (C-12), 75.31 (C-2), 62.77 (C-8), 14.01 (C-9) ppm.

HRMS (ESI) for C$_{17}$H$_{16}$NO$_5$ [M+H]$^+$: calculated: 314.1023; measured: 314.1021.

IR: v_{max}/cm^{-1} = 2984 (w, CH$_{ar}$), 1748 + 1694 (s, C=O), 1598 + 1583 (m, C=C$_{ar}$), 1450, 1372 + 1237 + 1128 + 1023 (s, C-O), 748 + 703 (s, CH$_{ar}$).

6.9 1-Ethoxy-3-(4-nitrophenyl)-1,3-dioxopropan-2-yl picolinate (168i)

Following the procedure in Section 6.1 (reaction time 1 day) and using $KHCO_3$ (1.80 g; 18.0 mmol; 2.00 equiv.), ethyl 2-chloro-3-(4-nitrophenyl)-3-oxopropanoate (**100i**) (2.44 g; 8.98 mmol) and picolinic acid (2.21 g; 18.0 mmol; 2.00 equiv.) were converted into **168i** (2.49 g; 6.95 mmol; 77 % including small amounts of impurities) which was obtained as an orange solid (decomposition > 154 °C). The ratio of keto to enol form was not determined.
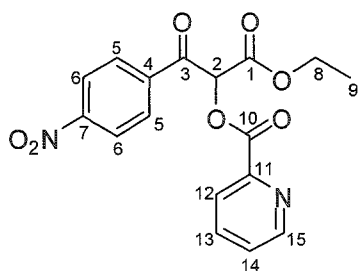
$C_{17}H_{14}N_2O_7$ (M = 358.31 g/mol)

^{1}H-NMR (CDCl$_3$): δ = 8.82 (ddd, 1H, 15-H, $J_{15/12}$ = 1.0 Hz, $J_{15/13}$ = 1.7 Hz, $J_{15/14}$ = 4.7 Hz), 8.36 (d, 2H, 6-H, $J_{6/5}$ = 8.9 Hz), 8.28 (d, 2H, 5-H, $J_{5/6}$ = 8.9 Hz), 8.20 (ddd, appearance similar to dt, 1H, 12-H, $J_{12/15}$ = 1.0 Hz, $J_{12/14}$ = 1.2 Hz, $J_{12/13}$ = 7.9 Hz), 7.90 (ddd, appearance similar to dt, 1H, 13-H, $J_{13/15}$ = 1.7 Hz, $J_{13/14}$ = 7.7 Hz, $J_{13/12}$ = 7.9 Hz), 7.56 (ddd, 1H, 14-H, $J_{14/12}$ = 1.2 Hz, $J_{14/15}$ = 4.7 Hz, $J_{14/13}$ = 7.7 Hz), 6.56 (s, 1H, 2-H), 4.32 (q, 2H, 8-H, $J_{8/9}$ = 7.2 Hz), 1.26 (t, 3H, 9-H, $J_{9/8}$ = 7.2 Hz) ppm.

^{13}C-NMR (CDCl$_3$): δ = 188.42 (C-3), 164.27 and 163.55 (C-1, C-10), 150.87 (C-7), 150.46 (C-15), 146.27 (C-11), 138.83 (C-4), 137.37 (C-13), 130.53 (C-5), 124.04 (C-6), 127.89 (C-14), 126.04 (C-12), 75.84 (C-2), 63.22 (C-8), 14.04 (C-9) ppm.

The HRMS spectrum was not recorded.

IR: v_{max}/cm^{-1} = 3117 (w, CH$_{ar}$), 2839 (w, CH$_{alkyl}$), 1686 (s, C=O), 1601 (m, C=C$_{ar}$), 1539 (m, NO$_2$), 1426 (m, CH$_{alkyl}$), 1349 (s, NO$_2$), 1310 + 1291 + 1278 (s, C-O) + 1109 (m, C-O), 1014 (m), 930 (m), 878 + 860 + 800 + 788 + 715 (s, CH$_{ar}$).

7 Other compounds

7.1 Ethyl 2-diazo-3-oxobutanoate (95a)

To a stirred solution of ethyl acetoacetate (**78a**) (2.60 g; 20.0 mmol) and potassium fluoride (2.32 g; 40.0 mmol; 2.00 equiv.) in dichloromethane (50 mL) was added 4-acetamidobenzenesulfonyl azide (**97**) (4.80 g; 20.0 mmol). The solution was protected from the light and stirred at room temperature for 16 h. After filtering the mixture through a layer of silica gel (2 – 3 cm) the filtrate was washed with 5 % KOH solution (50 mL), water (3x 10 mL), dried over MgSO₄ and the solvent was evaporated under reduced pressure yielding **95a** (0.84 g; 5.38 mmol; 27 %) which was obtained as an orange liquid.

$C_6H_8N_2O_3$ (M = 156.14 g/mol)
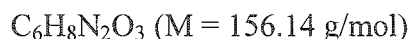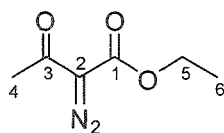
^{1}H-NMR (CDCl₃): δ = 4.31 (q, 2H, 5-H, $J_{5/6}$ = 7.2 Hz), 2.49 (s, 3H, 4-H), 1.34 (t, 3H, 6-H, $J_{6/5}$ = 7.2 Hz) ppm.

A full characterisation was not carried out; the structure of **AG95a** was confirmed by analysis of the product of its follow-up chemistry (Section 10.1, p. 143).

7.2 *S*-Methylthiosemicarbazide hydrogen iodide (73b)

To a solution of thiosemicarbazide (**138**) (2.00 g, 21.9 mmol) in absolute ethanol (20 mL) was added iodomethane (1.4 mL; 21.9 mmol) and the solution heated under reflux and a nitrogen atmosphere for 1 h. The solvent was evaporated to half volume and the precipitate filtered yielding **73b** (3.00 g; 12.9 mmol; 59 %) which was obtained as a yellow solid (m.p. 134 - 136 °C; lit. [134]: 140 °C).

$$\text{H}_2\text{N} - \text{N} = \overset{\displaystyle}{\text{C}}(\text{SMe})(\text{N}^+\text{H}_3\ \text{I}^-)$$
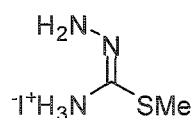
C$_2$H$_8$IN$_3$S (M = 233.08 g/mol)

The ^{1}H- and ^{13}C-NMR spectra were not recorded; the structure of **AG73b** was confirmed by analysis of the products of its follow-up chemistry (Sections 8.1 and 8.2, p. 125 f.)

IR: v_{max}/cm^{-1} = 3336 – 3136 (m, multiple peaks, N-H), 1644 + 1608 (m, C=N and N-H), 1450 (m), 962 (m).

7.3 *S*-(4-Nitrobenzyl)thiosemicarbazide hydrogen bromide (73c)

A solution of thiosemicarbazide (**138**) (1.50 g, 16.5 mmol) and 4-nitrobenzyl bromide (**139**) (3.56 g; 16.5 mmol) in absolute ethanol (45 mL) was heated under reflux and a nitrogen atmosphere for 24 h. The solvent was evaporated under reduced pressure and the residue washed with dichloromethane yielding **73c** (4.75 g; 15.5 mmol; 94 %) which was obtained as an off-white solid (m.p. 143 – 144 °C).
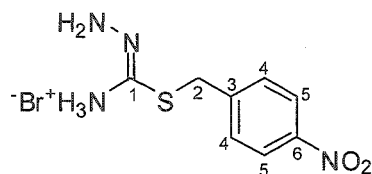
C$_8$H$_{11}$BrN$_4$O$_2$S (M = 307.17 g/mol)

^{1}H-NMR (CD$_3$OD): δ = 8.24 (d, 2H, 5-H, $J_{5/4}$ = 8.9 Hz), 7.66 (d, 2H, 4-H, $J_{4/5}$ = 8.9 Hz), 4.90 (s, 2H, 2-H) ppm.

^{13}C-NMR (CD$_3$OD): δ = 147.61 (C-6), 129.93 (C-4), 123.69 (C-5), 34.40 (C-2) ppm. The signals for C-1 and C-3 were not detected.

HRMS (ESI) for C$_8$H$_{11}$N$_4$O$_2$S [M-Br]$^+$: calculated: 227.0597; measured: 225.0599.

IR: v_{max}/cm^{-1} = 3296 + 3136 (w, N-H), 2909 (w, CH$_{alkyl}$), 1662 + 1615 (m, C=N and N-H), 1508 (m, C=C$_{ar}$), 1350 (m), 699 (m, CH$_{ar}$).

8 Triazines

8.1 Ethyl 3-methylthio-5-propyl-1,2,4-triazine-6-carboxylate (107d)

Method A – From the chloroacetate

To a stirred solution of ethyl 2-acetoxy-2-chloro-3-oxohexanoate (**102d**) (5.00 g; 19.9 mmol) and $NaHCO_3$ (4.70 g; 55.9 mmol; 2.80 equiv.) in ethanol (200 mL) was added S-methyl thiosemicarbazide hydroiodide (**73b**) (11.7 g; 50.2 mmol; 2.52 equiv.) and the mixture was heated under reflux for 1 h. After cooling down to room temperature, the mixture was poured into water (200 mL), extracted with dichloromethane (2x 100 mL), washed with water (200 mL), dried over $MgSO_4$ and the solvent evaporated under reduced pressure yielding **107d** (4.92 g; quantitative yield) which was obtained as a brown liquid.

$C_{10}H_{15}N_3O_2S$ (M = 241.31 g/mol)
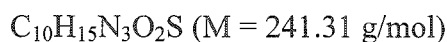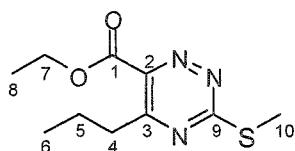
^{1}H-NMR ($CDCl_3$): δ = 4.50 (q, 2H, 7-H, $J_{7/8}$ = 7.2 Hz), 3.06-3.00 (m, 2H, 4-H), 2.70 (s, 3H, 10-H), 1.79 (tq, 2H, 5-H, $J_{5/4} = J_{5/6}$ = 7.4 Hz), 1.46 (t, 3H, 8-H, $J_{8/7}$ = 7.2 Hz), 1.02 (t, 3H, 6-H, $J_{6/5}$ = 7.4 Hz) ppm. The ^{1}H-NMR spectral data is consistent with that found in the literature.[71]

Method B – From the picolinate

A mixture of 1-ethoxy-1,3-dioxohexan-2-yl picolinate (**168d**) (500 mg; 1.79 mmol), $Cu(OAc)_2 \cdot H_2O$ (746 mg; 3.74 mmol; 2.09 equiv.) and methanol (1 mL) in dichloromethane (25 mL) was stirred at room temperature for one day. The reaction was diluted with hexanes (10 mL) and washed with a saturated aqueous solution of Na_2EDTA until the aqueous phase remained colourless. The organic phase was dried over $MgSO_4$ and the solvents evaporated. The resulting oil was taken up in ethanol (25 mL), $NaHCO_3$ (440 mg; 5.24 mmol; 2.93 equiv.) and S-methyl thiosemicarbazide hydrogen iodide (**73b**) (1.09 g; 4.68 mmol; 2.61 equiv.) were added and the solution was heated under reflux for 2 h. After cooling down to room temperature, the mixture was poured onto water (20 mL), extracted

with dichloromethane (2x 10 mL), washed with water (20 mL), dried over $MgSO_4$ and the solvent evaporated under reduced pressure. The residue was purified by column chromatography (dichloromethane / ethyl acetate = 49:1; R_f = 0.37) yielding **107d** (398 mg; 1.65 mmol; 92 %) which was obtained as an orange oil.

8.2 Ethyl 3-methylthio-5-phenyl-1,2,4-triazine-6-carboxylate (107h)

From the chloroacetate

Following method A in Section 8.1 and using $NaHCO_3$ (4.12 g; 49.0 mmol; 2.79 equiv.), ethyl 2-acetoxy-2-chloro-3-oxo-3-phenylpropanoate (**102h**) (5.00 g; 17.6 mmol) and *S*-methyl thiosemicarbazide hydroiodide (**73b**) (10.2 g; 43.8 mmol; 2.49 equiv.) were converted into **107h** (5.06 g; quantitative yield) which was obtained as a brown liquid.

$C_{13}H_{13}N_3O_2S$ (M = 275.33 g/mol)
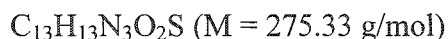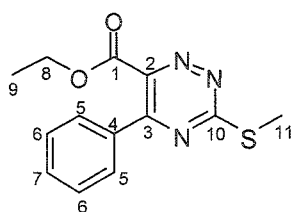
^{1}H-NMR ($CDCl_3$): δ = 7.77 – 7.47 (m, 5H, 5-H to 7-H), 4.39 (q, 2H, 8-H, $J_{8/9}$ = 7.2 Hz), 2.75 (s, 3H, 11-H), 1.27 (t, 3H, 9-H, $J_{9/8}$ = 7.2 Hz) ppm. The ^{1}H-NMR spectral data is consistent with that found in the literature.[71]

From the picolinate

Following method B in Section 8.1 and using $Cu(OAc)_2 \cdot H_2O$ (662 mg; 3.32 mmol; 2.08 equiv.) and $NaHCO_3$ (390 mg; 4.64 mmol; 2.91 equiv.), 1-ethoxy-1,3-dioxo-3-phenylpropan-2-yl picolinate (**168h**) (500 mg; 1.60 mmol) and *S*-methyl thiosemicarbazide hydrogen iodide (**73b**) (966 mg; 4.14 mmol; 2.60 equiv.) were converted into **107h**. Purification by column chromatography (dichloromethane / ethyl acetate = 49:1; R_f = 0.40) afforded the product (294 mg; 1.07 mmol; 64 %) as a yellow wax.

8.3 Ethyl 3-(4-nitrobenzylthio)-5-propyl-1,2,4-triazine-6-carboxylate (140d)

Method C – From the chloroacetate with methylamine

To a stirred solution of ethyl 2-acetoxy-2-chloro-3-oxohexanoate (**102d**) (500 mg; 1.99 mmol) in ethanol (20 mL) was added methylamine (372 mg; 33 % w/w in ethanol; 3.99 mmol; 2.0 equiv.) and the mixture was stirred at room temperature for 1 h. A solution of *S*-(4-nitrobenzyl)-thiosemicarbazide hydrobromide (**73c**) (613 mg; 2.00 mmol; 1.00 equiv.) and $NaHCO_3$ (168 mg; 2.00 mmol; 1.00 equiv.) in ethanol (20 mL) was added to the mixture and it was heated under reflux for 2 h. After cooling down to room temperature, the mixture was poured onto water (400 mL), extracted with dichloromethane (2x 200 mL), dried over $MgSO_4$ and the solvent evaporated under reduced pressure. The residue was purified by column chromatography (dichloromethane / ethyl acetate = 49:1; R_f = 0.52) yielding **140d** (472 mg; 1.30 mmol; 65 %) which was obtained as a yellow solid (m.p. 86 – 89 °C).

$C_{16}H_{18}N_4O_4S$ (M = 362.41 g/mol)
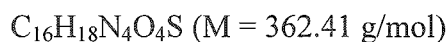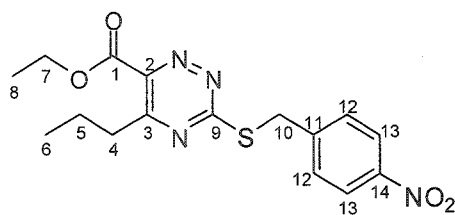
^{1}H-NMR (CDCl$_3$): δ = 8.17 (d, 2H, 13-H, $J_{13/12}$ = 8.7 Hz), 7.67 (d, 2H, 12-H, $J_{12/13}$ = 8.7 Hz), 4.59 (s, 2H, 10-H), 4.51 (q, 2H, 7-H, $J_{7/8}$ = 7.2 Hz), 3.05 – 2.98 (m, 2H, 4-H), 1.74 (tq, appearance similar to sextet, 2H, 5-H, $J_{5/4}$ = $J_{5/6}$ = 7.4 Hz), 1.46 (t, 3H, 8-H $J_{8/7}$ = 7.2 Hz), 1.00 (t, 3H, 6-H, $J_{6/5}$ = 7.4 Hz) ppm.

^{13}C-NMR (CDCl$_3$): δ = 172.92 (C-9), 163.84, 163.29, 147.34, 146.96 and 144.65 (C-1, C-2, C-3, C-11, C-14), 130.11 (C-12), 123.85 (C-13), 62.77 (C-7), 36.89 (C-4), 34.26 (C-10), 21.40 (C-5), 14.24 and 14.02 (C-6, C-8) ppm.

HRMS (ESI) for $C_{16}H_{19}N_4O_4S$ [M+]$^+$: calculated: 363.1122; measured: 363.1121.

IR: v_{max}/cm^{-1} = 2966 + 2938 + 2874 (w, CH$_{alkyl}$), 1715 (s, C=O), 1526 (s, NO$_2$), 1507 (s, C=C$_{ar}$), 1341 (s, NO$_2$), 1186 + 1169 (s, C-O), 1043 (s), 860 + 802 (m, CH$_{ar}$), 711 (s, CH$_{ar}$).

From the chloroacetate

Following method A in Section 8.1 and using NaHCO₃ (94 mg; 1.12 mmol; 2.80 equiv.), ethyl 2-acetoxy-2-chloro-3-oxohexanoate (**102d**) (100 mg; 399 μmol) and S-(4-nitrobenzyl)-thiosemicarbazide hydroiodide (**73c**) (306 mg; 996 μmol; 2.50 equiv.) were converted into **140d**. Purification by column chromatography (dichloromethane; $R_f = 0.12$) afforded the product (47 mg; 130 μmol; 33 %) as an orange oil.

'One pot' reaction

A solution of thiosemicarbazide (**138**) (911 mg, 10.0 mmol) and 4-nitrobenzyl bromide (**139**) (2.16 g; 10.0 mmol) in absolute ethanol (30 mL) was heated under reflux and a nitrogen atmosphere for 24 h. To a second solution of ethyl 2-acetoxy-2-chloro-3-oxohexanoate (**102d**) (2.51 g; 10.0 mmol) in ethanol (100 mL) was added methylamine (1.86 g; 33 % w/w in ethanol; 20.0 mmol; 2.0 equiv.) and the mixture was stirred at room temperature for 1 h. The two solutions were combined, NaHCO₃ (840 mg; 10.0 mmol) was added and the mixture was stirred under reflux for 2 h. After cooling down to room temperature, the mixture was poured onto water (200 mL), extracted with dichloromethane (200 mL), dried over MgSO₄ and the solvent evaporated under reduced pressure. The residue was purified by column chromatography (dichloromethane / ethyl acetate = 99:1; $R_f = 0.21$) yielding **140d** (2.29 g; 6.32 mmol; 63 %) which was obtained as a yellow solid.

8.4 Ethyl 5-methyl-3-(pyridin-2-yl)-1,2,4-triazine-6-carboxylate (106a)

Method A – From the chloroacetate

A stirred solution of picolinohydrazonamide (**73a**) (3.06 g; 22.5 mmol; 2.50 equiv.) and ethyl 2-acetoxy-2-chloro-3-oxo-3-butanoate (**102a**) (2.00 g; 8.98 mmol) in ethanol (100 mL) was heated under reflux for 2 h. After cooling down to room temperature, the mixture was poured into water (100 mL), extracted with dichloromethane (100 mL), washed with water (100 mL), dried over MgSO₄ and the solvent evaporated under reduced pressure. The residue was purified by column chromatography (ethyl acetate; $R_f = 0.15$) yielding **106a** (786 mg; 3.22 mmol; 36 %) which was obtained as an orange wax which turned brown on standing.
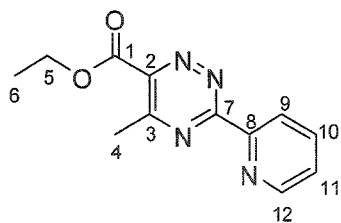
$C_{12}H_{12}N_4O_2$ (M = 244.25 g/mol)

^{1}H-NMR: (CDCl$_3$) δ = 8.94 (ddd, 1H, 12-H, $J_{12/9}$ = 1.0 Hz, $J_{12/10}$ = 1.7 Hz, $J_{12/11}$ = 4.7 Hz), 8.77 (ddd, appearance similar to dt, 1H, 9-H, $J_{9/12}$ = 1.0 Hz, $J_{9/11}$ = 1.2 Hz, $J_{9/10}$ = 7.9 Hz), 7.96 (ddd, appearance similar to dt, 1H, 10-H, $J_{10/12}$ = 1.7 Hz, $J_{10/11}$ = 7.7 Hz, $J_{10/9}$ = 7.9 Hz), 7.52 (ddd, 1H, 11-H, $J_{11/9}$ = 1.2 Hz, $J_{11/12}$ = 4.7 Hz, $J_{11/10}$ = 7.7 Hz), 4.58 (q, 2H, 5-H, $J_{5/6}$ = 7.2 Hz), 2.98 (s, 3H, 4-H), 1.51 (t, 3H, 6-H, $J_{6/5}$ = 7.2 Hz) ppm. The ^{1}H-NMR spectral data is consistent with that found in the literature.[71]

8.5 Methyl 5-ethyl-3-(pyridin-2-yl)-1,2,4-triazine-6-carboxylate (106c)

From the chloroacetate

Following method A in Section 8.4, methyl 2-acetoxy-2-chloro-3-oxo-3-pentanoate (**AG75**) (5.00 g; 22.5 mmol) and picolinohydrazonamide (**73a**) (7.65 g; 56.2 mmol; 2.50 equiv.) were converted into **106c**. Purification by column chromatography (ethyl acetate; R$_f$ = 0.24) afforded the product (1.21 g; 4.95 mmol; 22 %) as a brown solid (m.p. 55 – 57 °C).
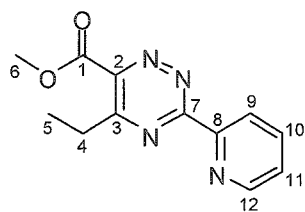
$C_{12}H_{12}N_4O_2$ (M = 244.25 g/mol)

^{1}H-NMR (CDCl$_3$): δ = 8.95 (ddd, 1H, 12-H, $J_{12/9}$ = 1.0 Hz, $J_{12/10}$ = 1.7 Hz, $J_{12/11}$ = 4.7 Hz), 8.73 (ddd, appearance similar to dt, 1H, 9-H, $J_{9/12}$ = 1.0 Hz, $J_{9/11}$ = 1.2 Hz, $J_{9/10}$ = 7.9 Hz), 7.96 (ddd, appearance similar to dt, 1H, 10-H, $J_{10/12}$ = 1.7 Hz, $J_{10/11}$ = 7.7 Hz, $J_{10/9}$ =

7.9 Hz), 7.52 (ddd, 1H, 11-H, $J_{11/9}$ = 1.2 Hz, $J_{11/12}$ = 4.7 Hz, $J_{11/10}$ = 7.7 Hz), 4.11 (s, 3H, 6-H), 3.28 (q, 2H, 4-H, $J_{4/5}$ = 7.4 Hz), 1.15 (t, 3H, 5-H, $J_{5/4}$ = 7.4 Hz) ppm.

^{13}C-NMR (CDCl$_3$): δ = 165.02, 164.51, 162.75, 152.17 and 149.32 (C-1, C-2, C-3, C-7, C-8), 150.81 (C-12), 137.34 (C-10), 126.14 (C-11), 125.07 (C-9), 53.56 (C-6), 28.85 (C-4), 12.77 (C-5) ppm.

HRMS (ESI) for C$_{12}$H$_{13}$N$_4$O$_2$ [M+H]$^+$: calculated: 245.1033; measured: 245.1031.

IR: ν_{max}/cm^{-1} = 3059 + 3001 (w, CH$_{ar}$), 2953 (w, CH$_{alkyl}$), 1732 (s, C=O), 1513 (m, C=C$_{ar}$), 1384 (m, CH$_{alkyl}$), 1332 (m), 1221 + 1126 (s, C-O), 813 (s, CH$_{ar}$), 767 + 743 (m, CH$_{ar}$).

Method B – From the picolinate

A mixture of 1-methoxy-1,3-dioxopropan-2-yl picolinate (**168c**) (500 mg; 1.99 mmol; 1.19 equiv.), Cu(OAc)$_2$·H$_2$O (834 mg; 4.18 mmol; 2.51 equiv.) and ethanol (1.0 mL) in dichloromethane (25 mL) was stirred at room temperature for one day. The reaction was diluted with hexanes (10 mL) and washed with Na$_2$EDTA (10 mL; 0.1M aqueous solution) until the aqueous phase remained colourless. The organic phase was dried over MgSO$_4$ and the solvent evaporated. The resulting oil was taken up in ethanol (25 mL), picolinohydrazonamide (**73a**) (227 mg; 1.67 mmol) was added and the solution was heated under reflux for 15 h. After cooling down to room temperature, the mixture was poured onto water, extracted with dichloromethane, washed with water, dried over MgSO$_4$ and the solvent evaporated under reduced pressure. The residue was purified by column chromatography (ethyl acetate / diethyl ether = 1:1; R$_f$ = 0.17) yielding **106c** (91 mg; 373 μmol; 22 %) which was obtained as a brown solid (m.p. 45 – 54 °C).

8.6   Ethyl 5-propyl-3-(pyridin-2-yl)-1,2,4-triazine-6-carboxylate (106d)

Method C – From the chloroacetate with methylamine

A solution of ethyl 2-acetoxy-2-chloro-3-oxo-3-hexanoate (**102d**) (10.0 g; 39.9 mmol; 1.01 equiv.) and methylamine (9.80 mL; 33 % w/w in ethanol; 80.0 mmol; 2.0 equiv.) in ethanol (60 mL) was stirred at room temperature for 1 h. Then picolinohydrazonamide (**73a**) (5.40 g; 39.7 mmol) was added and the solution was heated under reflux for 2 h. After cooling down to room temperature, the mixture was poured onto water, extracted with dichloromethane (3x 100 mL), washed with water (3x 150 mL), dried over MgSO$_4$

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and the solvent evaporated under reduced pressure. The residue was recrystallised from ethyl acetate / petroleum ether (1:4; 20 mL) yielding **106d** (7.71 g; 28.3 mmol; 71 %) which was obtained as a brown solid (m.p. 61 – 65 °C; lit.[78]: 68 – 70 °C).


$C_{14}H_{16}N_4O_2$ (M = 272.31 g/mol)
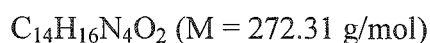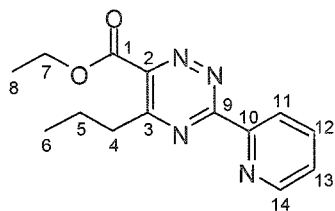
^{1}H-NMR (CDCl$_3$): δ = 8.94 (ddd, 1H, 14-H, $J_{14/11}$ = 1.0 Hz, $J_{14/12}$ = 1.7 Hz, $J_{14/13}$ = 4.7 Hz), 8.73 (ddd, appearance similar to dt, 1H, 11-H, $J_{11/14}$ = 1.0 Hz, $J_{11/13}$ = 1.2 Hz, $J_{11/12}$ = 7.9 Hz), 7.95 (ddd, appearance similar to dt, 1H, 12-H, $J_{12/14}$ = 1.7 Hz, $J_{12/13}$ = 7.7 Hz, $J_{12/11}$ = 7.9 Hz), 7.51 (ddd, 1H, 13-H, $J_{13/11}$ = 1.2 Hz, $J_{13/14}$ = 4.7 Hz, $J_{13/12}$ = 7.7 Hz), 4.57 (q, 2H, 7-H, $J_{7/8}$ = 7.2 Hz), 3.24 – 3.17 (m, 2H, 4-H), 1.94 – 1.80 (m, 2H, 5-H), 1.50 (t, 3H, 8-H, $J_{8/7}$ = 7.2 Hz), 1.07 (t, 3H, 6-H, $J_{6/5}$ = 7.4 Hz) ppm. The ^{1}H-NMR spectral data is consistent with that found in the literature.[71]

From the picolinate

Following method B in Section 8.5 and using Cu(OAc)$_2$·H$_2$O (500 mg; 2.50 mmol; 2.10 equiv.) 1-ethoxy-1,3-dioxohexan-2-yl picolinate (**168d**) (333 mg; 1.19 mmol) and picolinohydrazonamide (**73a**) (170 mg; 1.25 mmol; 1.05 equiv.) were converted into **106d**. Purification by column chromatography (ethyl acetate / diethyl ether = 1:1; R$_f$ = 0.25) afforded the product (138 mg; 507 μmol; 43 %) as a brown solid.

8.7 Ethyl 5-isobutyl-3-(pyridin-2-yl)-1,2,4-triazine-6-carboxylate (106f)

From the picolinate

Following method B in Section 8.5 and using Cu(OAc)$_2$·H$_2$O (340 mg; 1.70 mmol; 2.00 equiv.), 1-ethoxy-5-methyl-1,3-dioxohexan-2-yl picolinate (**168f**) (250 mg; 852 μmol), and picolinohydrazonamide (**73a**) (116 mg; 852 μmol) were converted into **106f**. Purification by column chromatography (ethyl acetate / petroleum ether (b.p. 40 –

60 °C) = 2:1; R_f = 0.29) afforded the product (142 mg; 496 μmol; 58 %) as orange crystals (m.p. 80 – 83 °C).
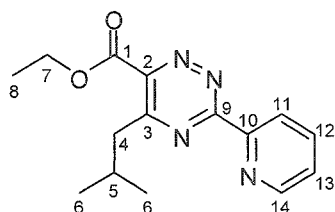
$C_{15}H_{18}N_4O_2$ (M = 286.33 g/mol)

^{1}H-NMR (CDCl$_3$): δ = 8.94 (ddd, 1H, 14-H, $J_{14/11}$ = 1.0 Hz, $J_{14/12}$ = 1.7 Hz, $J_{14/13}$ = 4.7 Hz), 8.72 (ddd, appearance similar to dt, 1H, 11-H, $J_{11/14}$ = 1.0 Hz, $J_{11/13}$ = 1.2 Hz, $J_{11/12}$ = 7.9 Hz), 7.95 (ddd, appearance similar to dt, 1H, 12-H, $J_{12/14}$ = 1.7 Hz, $J_{12/13}$ = 7.7 Hz, $J_{12/11}$ = 7.9 Hz), 7.51 (ddd, 1H, 13-H, $J_{13/11}$ = 1.2 Hz, $J_{13/14}$ = 4.7 Hz, $J_{13/12}$ = 7.7 Hz), 4.57 (q, 2H, 7-H, $J_{7/8}$ = 7.2 Hz), 3.15 (d, 2H, 4-H, $J_{4/5}$ = 7.2 Hz), 2.36 – 2.21 (m, 1H, 5-H), 1.50 (t, 3H, 8-H, $J_{8/7}$ = 7.2 Hz), 0.99 (d, 6H, 6-H, $J_{6/5}$ = 6.7 Hz) ppm.

^{13}C-NMR (CDCl$_3$): δ = 164.34 (C-1), 163.09, 162.52, 152.27 and 150.42 (C-2, C-3, C-9, C-10), 150.77 (C-14), 137.32 (C-12), 126.04 (C-13), 124.98 (C-11), 62.92 (C-7), 43.25 (C-4), 29.12 (C-5), 22.49 (C-6), 14.25 (C-8) ppm.

HRMS (ESI) for $C_{15}H_{19}N_4O_2$ [M+H]$^+$: calculated: 287.1503; measured: 287.1504.

IR: v_{max}/cm^{-1} = 2955 + 2928 + 2868 (w, CH$_{alkyl}$), 1723 (s, C=O), 1505 (s, C=C$_{ar}$), 1248 + 1137 (s, C-O), 1051 (s), 785 + 744 (s, CH$_{ar}$).

From the chloroacetate with methylamine

Following method C in Section 8.6 (reflux time 1 day) and using methylamine (1.85 mL; 33 % w/w in ethanol; 15.0 mmol; 2.0 equiv.) ethyl 2-acetoxy-2-chloro-5-methyl-3-oxohexanoate (**102f**) (2.00 g; 7.56 mmol; 1.01 equiv.) and picolinohydrazonamide (**73a**) (1.02 g; 7.49 mmol) were converted into **106f**. Purification by column chromatography (ethyl acetate / petroleum ether (b.p. 40 – 60 °C) = 2:1; R_f = 0.31) afforded the product (1.15 g; 4.02 mmol; 54 %) as orange crystals.

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8.8 Ethyl 5-phenyl-3-(pyridin-2-yl)-1,2,4-triazine-6-carboxylate (106h)

From the picolinate

Following method B in Section 8.5 and using $Cu(OAc)_2 \cdot H_2O$ (1.32 g; 6.61 mmol; 2.49 equiv.) 1-ethoxy-1,3-dioxo-3-phenylpropan-2-yl picolinate (**168h**) (1.00 g; 3.19 mmol; 1.20 equiv.) and picolinohydrazonamide (**73a**) (361 mg; 2.65 mmol) were converted into **106h**. Purification by column chromatography (ethyl acetate / diethyl ether = 1:1; R_f = 0.25) afforded the product (513 mg; 1.67 mmol; 63 %) as yellow crystals (m.p. 99 – 108 °C).

$C_{17}H_{14}N_4O_2$ (M = 306.32 g/mol)
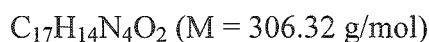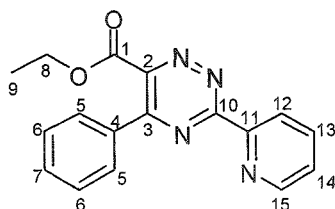
^{1}H-NMR (CDCl$_3$): δ = 8.95 (ddd, 1H, 15-H, $J_{15/12}$ = 1.0 Hz, $J_{15/13}$ = 1.7 Hz, $J_{15/14}$ = 4.7 Hz), 8.73 (ddd, appearance similar to dt, 1H, 12-H, $J_{12/15}$ = 1.0 Hz, $J_{12/14}$ = 1.2 Hz, $J_{12/13}$ = 7.9 Hz), 7.96 (ddd, appearance similar to dt, 1H, 13-H, $J_{13/15}$ = 1.7 Hz, $J_{13/14}$ = 7.7 Hz, $J_{13/12}$ = 7.9 Hz), 7.91 – 7.86 (m, 2H, 5-H), 7.61 – 7.50 (m, 4H, 6-H, 7-H, 14-H), 4.44 (q, 2H, 8-H, $J_{8/9}$ = 7.2 Hz), 1.29 (t, 3H, 9-H, $J_{9/8}$ = 7.2 Hz) ppm. The ^{1}H-NMR spectral data is consistent with that found in the literature.[71]

9 Pyridines

9.1 Ethyl 6-methylthio-2-propylnicotinate (117d)

Method E – From the triazine in DCB

A stirred solution of ethyl 3-methylthio-5-propyl-1,2,4-triazine-6-carboxylate (**107d**) (100 mg; 414 μmol) and 2,5-norbornadiene (**48**) (0.45 mL; 4.17 mmol; 10.1 equiv.) in 1,2-dichlorobenzene (5 mL) was heated to 140 °C under a nitrogen atmosphere for 1 day. After cooling to room temperature, the solvent was evaporated and the residue purified by column chromatography (ethyl acetate / hexanes = 1:4; R_f = 0.55) yielding **117d** (63 mg; 263 μmol; 64 %) which was obtained as a yellow liquid.

$C_{12}H_{17}NO_2S$ (M = 239.34 g/mol)
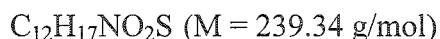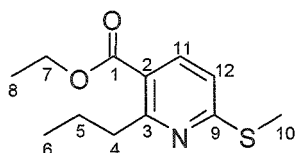
^{1}H-NMR (CDCl$_3$): δ = 7.97 (d, 1H, 11-H, $J_{11/12}$ = 8.2 Hz), 7.04 (d, 1H, 12-H, $J_{12/11}$ = 8.2 Hz), 4.34 (q, 2H, 7-H, $J_{7/8}$ = 7.2 Hz), 3.15 – 3.09 (m, 2H, 4-H), 2.59 (s, 3H, 10-H), 1.84-1.70 (m, 2H, 5-H), 1.39 (t, 3H, 8-H, $J_{8/7}$ = 7.2 Hz), 1.00 (t, 3H, 6-H, $J_{6/5}$ = 7.2 Hz) ppm.

^{13}C-NMR (CDCl$_3$): δ = 166.76 (C-1), 163.63 (C-3), 162.98 (C-9), 138.10 (C-11), 120.57 (C-2), 118.05 (C-12), 61.04 (C-7), 38.95 (C-4), 22.78 (C-5), 14.35 (C-6), 14.28 (C-8), 13.22 (C-10) ppm.

HRMS (ESI) for $C_{12}H_{18}NO_2S$ [M+H]$^+$: calculated: 240.1053; measured: 240.1052.

IR: v_{max}/cm^{-1} = 2962 + 2931 + 2872 (w, CH$_{alkyl}$), 1718 (s, C=O), 1575 (s, C=C$_{ar}$), 1441 + 1375 (m, CH$_{alkyl}$), 1260 + 1144 + 1094 (s, C-O).

Method F – From the triazine in neat 2,5-norbornadiene

Under a nitrogen atmosphere a stirred solution of ethyl 3-methylthio-5-propyl-1,2,4-triazine-6-carboxylate (**107d**) (100 mg; 414 μmol) in 2,5-norbornadiene (**48**) (2.00 mL; 18.5 mmol; 44.7 equiv.) was heated under reflux for 2 days. After cooling to room temperature, the solvent was evaporated and the residue purified by column

chromatography (ethyl acetate / hexanes = 1:4; R_f = 0.56) yielding **117d** (65 mg; 272 µmol; 66 %) which was obtained as a yellow oil plus recovered starting material **107d** (8 mg; 33 µmol; 8 %).

9.2 Ethyl 6-methylthio-2-phenylnicotinate (117h)

From the triazine in DCB

Following method E in Section 9.1, 3-methylthio-5-phenyl-1,2,4-triazine-6-carboxylate (**107h**) (2.00 g; 7.26 mmol) and 2,5-norbornadiene (**48**) (27.4 mL; 254 mmol; 35.0 equiv.) were converted into **117h**. Purification by column chromatography (ethyl acetate / hexanes = 1:4; R_f = 0.32) afforded the product (1.75 g; 6.40 mmol; 88 %) as an orange liquid.

$C_{15}H_{15}NO_2S$ (M = 273.36 g/mol)
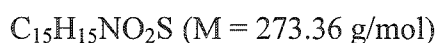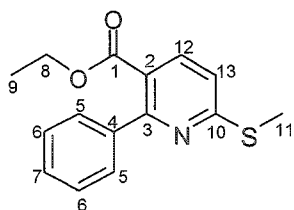
^{1}H-NMR (CDCl$_3$): δ = 7.92 (d, 1H, 12-H, $J_{12/13}$ = 8.2 Hz), 7.58 – 7.40 (m, 5H, 5-H to 7-H), 7.18 (d, 1H, 13-H, $J_{13/12}$ = 8.2 Hz), 4.13 (q, 2H, 8-H, $J_{8/9}$ = 7.2 Hz), 2.61 (s, 3H, 11-H), 1.05 (t, 3H, 9-H, $J_{9/8}$ = 7.2 Hz) ppm.

^{13}C-NMR (CDCl$_3$): δ = 168.19 (C-1), 162.64 (C-10), 158.89 (C-3), 140.32 (C-4), 137.73 (C-12), 128.89 (C-6), 128.73 (C-7), 127.99 (C-5), 122.26 (C-2), 119.18 (C-13), 61.31 (C-8), 13.77 (C-9), 13.29 (C-11) ppm.

HRMS (ESI) for $C_{15}H_{16}NO_2S$ [M+H]$^+$: calculated: 274.0896; measured: 274.0894.

IR: v_{max}/cm^{-1} = 2982 + 2928 (w, CH$_{alkyl}$), 1710 (s, C=O), 1567 (s, C=C$_{ar}$), 1427 + 1385 (m, CH$_{alkyl}$), 1281 + 1265 + 1152 + 1130 (s, C-O), 1046 (s), 764 + 697 (CH$_{ar}$).

From the triazine in neat 2,5-norbornadiene

Following method F in Section 9.1, 3-methylthio-5-phenyl-1,2,4-triazine-6-carboxylate (**107h**) (100 mg; 363 µmol) and 2,5-norbornadiene (**48**) (2.00 mL; 18.5 mmol; 51.0 equiv.) were converted into **117h**. Purification by column chromatography (ethyl acetate / hexanes

= 1:4; R_f = 0.38) afforded the product (64 mg; 234 µmol; 64 %) as an orange liquid as well as small amounts of recovered starting material **107h** (8 mg; 29 µmol; 8 %).

9.3 Ethyl 6-(4-nitrobenzylthio)-2-propylnicotinate (155d)

From the triazine in DCB

Following method E in Section 9.1 (reaction time 1 day; complete conversion according to TLC), 3-(4-nitrobenzylthio)-5-propyl-1,2,4-triazine-6-carboxylate **(140d)** (100 mg; 276 µmol) and 2,5-norbornadiene **(48)** (0.89 mL; 8.25 mmol; 29.9 equiv.) were converted into **155d**. Purification by column chromatography (dichloromethane; R_f = 0.58) afforded the product (50 mg; 139 µmol; 50 %) as a yellow oil.

$C_{18}H_{20}N_2O_4S$ (M = 360.43 g/mol)
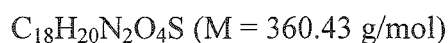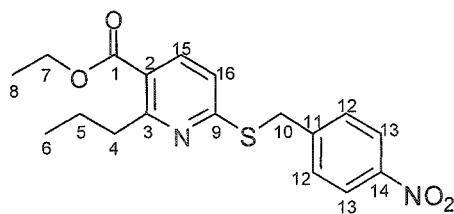
^{1}H-NMR (CDCl$_3$): δ = 8.14 (d, 2H, 13-H, $J_{13/12}$ = 8.9 Hz), 7.98 (d, 1H, 15-H, $J_{15/16}$ = 8.4 Hz), 7.59 (d, 2H, 12-H, $J_{12/13}$ = 8.9 Hz), 7.04 (d, 1H, 16-H, $J_{16/15}$ = 8.4 Hz), 4.56 (s, 2H, 10-H), 4.35 (q, 2H, 7-H, $J_{7/8}$ = 7.2 Hz), 3.16 – 3.09 (m, 2H, 4-H), 1.72 (tq, appearance similar to sextet, 2H, 5-H, $J_{5/4}$ = $J_{5/6}$ = 7.4 Hz), 1.38 (t, 3H, 8-H $J_{8/7}$ = 7.2 Hz), 0.99 (t, 3H, 6-H, $J_{6/5}$ = 7.4 Hz) ppm.

^{13}C-NMR (CDCl$_3$): δ = 166.49 (C-1), 163.74 (C-3), 159.98 (C-9), 147.02 (C-14), 146.63 (C-11), 138.55 (C-15), 129.83 (C-12), 123.71 (C-13), 121.60 (C-2), 118.87 (C-16), 61.22 (C-7), 38.96 (C-4), 33.11 (C-10), 22.95 (C-5), 14.34 and 14.31 (C-6, C-8) ppm.

HRMS (ESI) for $C_{18}H_{21}N_2O_4S$ [M+H]$^+$: calculated: 361.1217; measured: 361.1219.

IR: ν_{max}/cm^{-1} = 2963 (w, CH$_{alkyl}$), 1717 (s, C=O), 1573 (s, C=C$_{ar}$), 1520 + 1350 (s, NO$_2$), 1259 + 1143 + 1094 (s, C-O), 858 + 788 + 719 (CH$_{ar}$).

From the triazine in neat 2,5-norbornadiene

Following method F in Section 9.1 (reaction time 6 days; complete conversion according to TLC), 3-(4-nitrobenzylthio)-5-propyl-1,2,4-triazine-6-carboxylate (**140d**) (100 mg; 276 μmol) and 2,5-norbornadiene (**48**) (2.00 mL; 18.5 mmol; 67.1 equiv.) were converted into **155d**. Purification by column chromatography (dichloromethane; R_f = 0.58) afforded the product (35 mg; 97 μmol; 35 %) as a yellow oil.

From the chloroacetate in DCB

A solution of ethyl 2-acetoxy-2-chloro-3-oxo-3-hexanoate (**102d**) (4.13 g; 16.5 mmol; 1.07 equiv.) and methylamine (3.07 g; 33 % w/w in ethanol; 32.9 mmol; 2.13 equiv.) in ethanol (150 mL) was stirred at room temperature for 1 h and then added to a solution of S-(4-nitrobenzyl)-thiosemicarbazide hydrogen bromide (**73c**) (4.75 g; 15.5 mmol) and NaHCO$_3$ (1.38 g; 16.4 mmol; 1.06 equiv.) in ethanol (150 mL) and heated under reflux for another 2 h. After cooling down to room temperature, water (200 mL) was added and the product was extracted with dichloromethane (2x 100 mL). The combined organic extracts were dried over MgSO$_4$ and the solvent evaporated under reduced pressure. The residue was taken up in 1,2-dichlorobenzene (100 mL), 2,5-norbornadiene (**48**) (53.3 mL; 494 mmol; 31.9 equiv.) was added and the solution was stirred at 140 °C until judged complete according to TLC (3 days). The solvent was then evaporated and the residue purified by column chromatography (diethyl ether / hexanes (b.p. 40 – 60 °C) = 1:3; R_f = 0.48) yielding **155d** (1.32 g; 3.66 mmol; 24 %) which was obtained as an orange liquid.

9.4 Ethyl 6-methylsulfinyl-2-propylnicotinate (153d)

Method G - With NaBO$_3$·4H$_2$O

A suspension of NaBO$_3$·4H$_2$O (68 mg; 442 μmol; 1.06 equiv.) in glacial acetic acid (2.5 mL) was heated to 50 – 60 °C and ethyl 6-methylthio-2-propylnicotinate (**117d**) (100 mg; 418 μmol) was added. It was stirred for 4 h. After cooling down to room temperature, the precipitated Na$_3$BO$_3$ was filtered off and the solvent evaporated under reduced pressure yielding **153d** (77 mg; 302 μmol; 72 %) which was obtained as a brown oil.
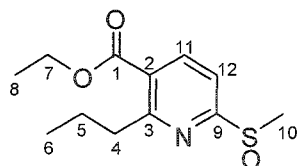
$C_{12}H_{17}NO_3S$ (M = 255.34 g/mol)

^{1}H-NMR (CDCl$_3$): δ = 8.35 (d, 1H, 11-H, $J_{11/12}$ = 8.2 Hz), 7.89 (d, 1H, 12-H, $J_{12/11}$ = 8.2 Hz), 4.37 (q, 2H, 7-H, $J_{7/8}$ = 7.2 Hz), 3.15 – 3.07 (m, 2H, 4-H), 2.83 (s, 3H, 10-H), 1.71 (tq, appearance similar to sextet, 2H, 5-H, $J_{5/4}$ = $J_{5/6}$ = 7.4 Hz), 1.38 (t, 3H, 8-H, $J_{8/7}$ = 7.2 Hz), 0.95 (t, 3H, 6-H, $J_{6/5}$ = 7.4 Hz) ppm.

^{13}C-NMR (CDCl$_3$): δ = 168.23 (C-9), 166.00 (C-1), 163.66 (C-3), 140.37 (C-11), 126.66 (C-2), 116.33 (C-12), 61.81 (C-7), 41.20 (C-10), 38.54 (C-4), 22.89 (C-5), 14.28 (C-8), 14.11 (C-6) ppm.

HRMS (ESI) for $C_{12}H_{18}NO_3S$ [M+H]$^+$: calculated: 256.1002; measured: 256.1002.

IR: v_{max}/cm^{-1} = 1721 (C=O), 1262 + 1095 (C-O), 1065 (S=O).[71]

9.5 Ethyl 6-methylsulfinyl-2-phenylnicotinate (153h)

With NaBO$_3$·4H$_2$O

Following method G in Section 9.4 and using NaBO$_3$·4H$_2$O (59 mg; 383 µmol; 1.05 equiv.), ethyl 6-methylthio-2-phenylnicotinate (**117h**) (100 mg; 366 µmol) was converted into 83 mg (287 µmol; 78 %) of **153h** which was obtained as a yellow oil.
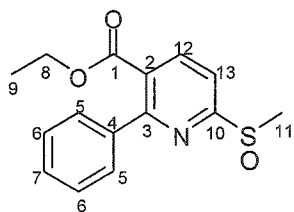
$C_{15}H_{15}NO_3S$ (M = 289.36 g/mol)

^{1}H-NMR (CDCl$_3$): δ = 8.33 (d, 1H, 12-H, $J_{12/13}$ = 8.2 Hz), 8.09 (d, 1H, 13-H, $J_{13/12}$ = 8.2 Hz), 7.57 – 7.44 (m, 5H, 5-H to 7-H), 4.20 (q, 2H, 8-H, $J_{8/9}$ = 7.2 Hz), 2.93 (s, 3H, 11-H), 1.09 (t, 3H, 9-H, $J_{9/8}$ = 7.2 Hz) ppm.

^{13}C-NMR (CDCl$_3$): δ = 168.06 (C-1), 167.45 (C-10), 158.73 (C-3), 139.92 (C-12), 138.80 (C-4), 129.42 (C-7), 128.74 (C-6), 128.34 (C-5), 117.26 (C-13), 62.02 (C-8), 41.33 (C-11), 13.73 (C-9) ppm. The signal for C-2 was not detected.

HRMS (ESI) for C$_{15}$H$_{16}$NO$_3$S [M+H]$^+$: calculated: 290.0845; measured: 290.0846.

IR: v_{max}/cm^{-1} = 1718 (C=O), 1281 + 1085 (C-O), 1047 (S=O), 698 (CH$_{ar}$).[71]

With mCPBA

To a stirred ice-cold solution of ethyl 6-methylthio-2-phenylnicotinate (**117h**) (100 mg; 366 μmol) in dichloromethane (10 mL) was added mCPBA (99 mg; 70 % w/w; 402 μmol; 1.10 equiv.) and it was stirred at 0 °C for 1 h, warmed to room temperature and stirred for another hour. The mixture was poured onto water (10 mL), washed with a saturated aqueous solution of NaHCO$_3$ (2x 10 mL), dried over MgSO$_4$ and the solvent evaporated under reduced pressure. The residue was purified by column chromatography (dichloromethane / methanol = 19:1) yielding **153h** (23 mg; 79 μmol; 22 %; R$_f$ = 0.13) which was obtained as a yellow solid (m.p. 65 – 69 °C) and the over-oxidised side product ethyl 6-sulfonyl-2-propylnicotinate (**154h**) (63 mg; 206 μmol; 56 %; R$_f$ = 0.59) which was obtained as an off-white solid (m.p. not determined due to insufficient yield). The ^{1}H-NMR spectral data of **154h** can be found under Section 9.8 (p. 141).

With NaIO$_4$

To a stirred ice-cold solution of NaIO$_4$ (82 mg; 383 μmol; 1.05 equiv.) in water (2 mL) was added ethyl 6-methylthio-2-phenylnicotinate (**117h**) (100 mg; 366 μmol) in methanol (4 mL) and it was stirred at room temperature overnight. The product was then extracted with dichloromethane (4 mL), dried over MgSO$_4$ and the solvent evaporated to afford 103 mg of an inseparable 1:1 mixture of **153h** (183 μmol; 50 %) and unconverted starting material **117h** (183 μmol; 50 %).

9.6 Ethyl 6-(4-nitrobenzylsulfinyl)-2-propylnicotinate (156d)

Following method G in Section 9.4 and using $NaBO_3 \cdot 4H_2O$ (63 mg; 409 µmol; 1.05 equiv.), ethyl 6-(4-nitrobenzylthio)-2-propylnicotinate (155d) (140 mg; 388 µmol) was converted into 156d (63 mg; 167 µmol; 43 %) which was obtained as an orange solid (m.p. 88 – 91 °C).

$C_{18}H_{20}N_2O_5S$ (M = 376.43 g/mol)
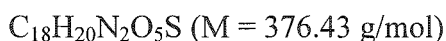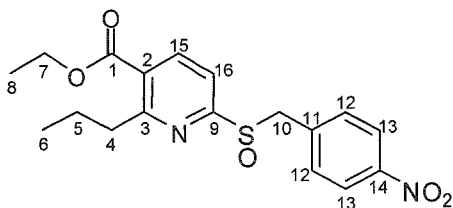
^{1}H-NMR (CDCl$_3$): δ = 8.23 (d, 1H, 15-H, $J_{15/16}$ = 8.2 Hz), 8.08 (d, 2H, 13-H, $J_{13/12}$ = 8.7 Hz), 7.44 (d, 1H, 16-H, $J_{16/15}$ = 8.2 Hz), 7.14 (d, 2H, 12-H, $J_{12/13}$ = 8.7 Hz), 4.45 (d, 1H, 10-H, J_{gem} = 13.1 Hz), 4.41 (q, 2H, 7-H, $J_{7/8}$ = 7.2 Hz), 4.22 (d, 1H, 10-H, J_{gem} = 13.1 Hz), 3.28 – 3.16 (m, 2H, 4-H), 1.81 (tq, appearance similar to sextet, 2H, 5-H, $J_{5/4}$ = $J_{5/6}$ = 7.4 Hz), 1.42 (t, 3H, 8-H = 7.2 Hz), 1.06 (t, 3H, 6-H, $J_{6/5}$ = 7.4 Hz) ppm.

^{13}C-NMR (CDCl$_3$): δ = 131.16 (C-12), 123.42 (C-13), 117.88 (C-16), 61.98 (C-7), 58.13 (C-10), 38.57 (C-4), 23.20 (C-5), 14.27 and 14.23 (C-6, C-8) ppm. The atoms C-1, C-2, C-3, C-9, C-11, C-14 and C-15 could not be assigned.

HRMS (ESI) for : calculated: 377.1166; measured: 377.1168.

IR: v_{max}/cm^{-1} = 2960 + 2932 + 2872 (w, CH$_{alkyl}$), 1725 (s, C=O), 1520 + 1343 (s, NO$_2$), 1259 + 1098 (s, C-O), 1034 (s, S=O), 852 + 695 (s, CH$_{ar}$).

9.7 Ethyl 6-methylsulfonyl-2-propylnicotinate (154d)

Method G - With $NaBO_3 \cdot 4H_2O$

A suspension of $NaBO_3 \cdot 4H_2O$ (1.61 g; 10.5 mmol; 2.50 equiv.) in glacial acetic acid (50 mL) was heated to 50 – 60 °C and ethyl 6-methylthio-2-propylnicotinate (117d) (1.00 g; 4.18 mmol) was added. The mixture was stirred for 2 h at that temperature. After cooling down to room temperature, the precipitated Na$_3$BO$_3$ was filtered off, a saturated

aqueous solution of NaHCO$_3$ (200 mL) was added to the solution and it was extracted with dichloromethane (200 mL). The organic solution was then washed with a saturated aqueous solution of NaHCO$_3$ and water (200 mL each), dried over MgSO$_4$ and the solvent evaporated under reduced pressure yielding **154d** (1.06 g; 3.91 mmol; 93 %) which was obtained as a yellow oil.
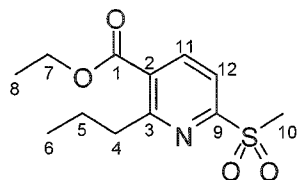
C$_{12}$H$_{17}$NO$_4$S (M = 271.34 g/mol)

^{1}H-NMR (CDCl$_3$): δ = 8.37 (d, 1H, 11-H, $J_{11/12}$ = 8.2 Hz), 7.96 (d, 1H, 12-H, $J_{12/11}$ = 8.2 Hz), 4.43 (q, 2H, 7-H, $J_{7/8}$ = 7.2 Hz), 3.27 (s, 3H, 10-H), 3.22 – 3.16 (m, 2H, 4-H), 1.79 (tq, appearance similar to sextet, 2H, 5-H, $J_{5/4}$ = $J_{5/6}$ = 7.4 Hz), 1.43 (t, 3H, 8-H, $J_{8/7}$ = 7.2 Hz), 1.01 (t, 3H, 6-H, $J_{6/5}$ = 7.4 Hz) ppm.

^{13}C-NMR (CDCl$_3$): δ = 165.48 (C-1), 164.21 (C-3), 159.06 (C-9), 140.58 (C-11), 129.43 (C-2), 117.66 (C-12), 62.15 (C-7), 39.56 (C-10), 38.45 (C-4), 22.72 (C-5), 14.25 (C-8), 14.07 (C-6) ppm.

HRMS (ESI) for C$_{12}$H$_{18}$NO$_4$S [M+H]$^+$: calculated: 272.0951; measured: 272.0951.

IR: ν$_{max}$/cm^{-1} = 2964 + 2935 + 2875 (w, CH$_{alkyl}$), 1724 (s, C=O), 1309 (s, SO$_2$), 1265 (s, C-O), 1128 (s, SO$_2$), 1095 (s, C-O), 758 (s, CH$_{ar}$).

9.8 Ethyl 6-methylsulfonyl-2-phenylnicotinate (154h)

This compound was isolated as a side product of the oxidation reaction of ethyl 6-methylthio-2-phenylnicotinate (**117h**) with mCPBA (cf. Section 9.5, p. 138 f.).
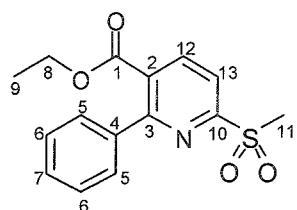
C$_{15}$H$_{15}$NO$_4$S (M = 305.35 g/mol)

^{1}H-NMR (CDCl$_3$): δ = 8.31 (d, 1H, 12-H, $J_{12/13}$ = 8.2 Hz), 8.09 (d, 1H, 13-H, $J_{13/12}$ = 8.2 Hz), 7.62 – 7.46 (m, 5H, 5-H to 7-H), 4.21 (q, 2H, 8-H, $J_{8/9}$ = 7.2 Hz), 3.30 (s, 3H, 11-H), 1.08 (t, 3H, 9-H, $J_{9/8}$ = 7.2 Hz) ppm.

^{13}C-NMR (CDCl$_3$): δ = 167.08 (C-1), 159.05, 158.86 (C-3, C-10), 140.14 (C-12), 138.21 (C-4), 129.76 (C-7), 128.89 and 128.44 (C-5, C-6), 128.33 (C-2), 118.40 (C-13), 62.31 (C-8), 39.65 (C-11), 13.69 (C-9) ppm.

HRMS (ESI) for C$_{15}$H$_{16}$NO$_4$S [M+H]$^+$: calculated: 306.0795; measured: 306.0792.

The IR spectrum was not recorded due to insufficient yield.

9.9 Ethyl 6-(4-nitrobenzylsulfonyl)-2-propylnicotinate (157d)

Following method G in Section 9.7 and using NaBO$_3$·4H$_2$O (107 mg; 695 μmol; 2.51 equiv.), ethyl 6-(4-nitrobenzylthio)-2-propylnicotinate (155d) (100 mg; 277 μmol) was converted into 157d (80 mg; 204 μmol; 73 %) which was obtained as yellow needles (m.p. 74 – 76 °C).
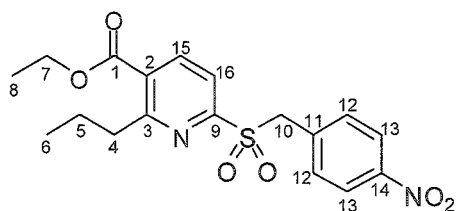
C$_{18}$H$_{20}$N$_2$O$_6$S (M = 392.43 g/mol)

^{1}H-NMR (CDCl$_3$): δ = 8.29 (d, 1H, 15-H, $J_{15/16}$ = 8.2 Hz), 8.15 (d, 2H, 13-H, $J_{13/12}$ = 8.7 Hz), 7.77 (d, 1H, 16-H, $J_{16/15}$ = 8.2 Hz), 7.47 (d, 2H, 12-H, $J_{12/13}$ = 8.7 Hz), 4.81 (s, 2H, 10-H), 4.43 (q, 2H, 7-H, $J_{7/8}$ = 7.2 Hz), 3.28 – 3.21 (m, 2H, 4-H), 1.84 (tq, appearance similar to sextet, 2H, 5-H, $J_{5/4}$ = $J_{5/6}$ = 7.4 Hz), 1.42 (t, 3H, 8-H = 7.2 Hz), 1.07 (t, 3H, 6-H, $J_{6/5}$ = 7.4 Hz) ppm.

^{13}C-NMR (CDCl$_3$): δ = 165.24 (C-1), 164.50 (C-3), 157.16 (C-9), 148.22 (C-14), 140.61 (C-15), 134.62 (C-11), 132.15 (C-12), 129.76 (C-2), 123.89 (C-13), 119.47 (C-16), 62.31 (C-7), 56.94 (C-10), 38.56 (C-4), 23.06 (C-5), 14.23 (C-6, C-8 completely overlapped) ppm.

HRMS (ESI) for $C_{18}H_{21}N_2O_6S$ $[M+H]^+$: calculated: 393.1115; measured: 393.1119.

IR: v_{max}/cm^{-1} = 3059 (w, CH_{ar}), 2965 + 2930 + 2872 (w, CH_{alkyl}), 1732 (s, C=O), 1528 + 1348 (s, NO_2), 1309 (m, SO_2), 1260 (s, C-O), 1112 (s, SO_2), 1097 (s, C-O), 1043 (m), 858 + 706 + 694 + 652 (s, CH_{ar}).

10 Bipyridines

10.1 Ethyl 6-methyl-[2,2']-bipyridine-5-carboxylate (116a)

Method A – From the chloroacetate

To an ice-cold stirred solution of picolinohydrazonamide (73a) (272 mg; 2.00 mmol; 2.00 equiv.) in ethanol (3 mL) was added a solution of ethyl 2-acetoxy-2-chloro-3-oxo-3-butanoate (102a) (223 mg; 1.00 mmol) in ethanol (2 mL). After 5 min. 2,5-norbornadiene (48) (1.1 mL; 10.2 mmol; 10.2 equiv.) was added and it was heated under reflux for 2 h. After cooling down to room temperature, the solvent was evaporated under reduced pressure and the residue was purified by column chromatography (diethyl ether / hexanes = 4:1; R_f = 0.41) yielding 116a (54 mg; 223 μmol; 22 %) which was obtained as white needles (m.p. 77 – 79 °C; lit.[135]: 80 °C from ethanol).
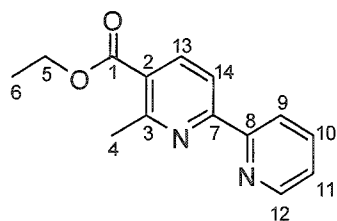
$C_{14}H_{14}N_2O_2$ (M = 242.28 g/mol)

^{1}H-NMR (CDCl$_3$): δ = 8.71 (ddd, 1H, 12-H, $J_{12/9}$ = 1.0 Hz, $J_{12/10}$ = 1.7 Hz, $J_{12/11}$ = 4.7 Hz), 8.51 (ddd, appearance similar to dt, 1H, 9-H, $J_{9/12}$ = 1.0 Hz, $J_{9/11}$ = 1.2 Hz, $J_{9/10}$ = 7.9 Hz), 8.34 (d, 1H, 14-H, $J_{14/13}$ = 8.2 Hz), 8.29 (d, 1H, 13-H, $J_{13/14}$ = 8.2 Hz), 7.84 (ddd, appearance similar to dt, 1H, 10-H, $J_{10/12}$ = 1.7 Hz, $J_{10/11}$ = 7.7 Hz, $J_{10/9}$ = 7.9 Hz), 7.35 (ddd, 1H, 11-H, $J_{11/9}$ = 1.2 Hz, $J_{11/12}$ = 4.7 Hz, $J_{11/10}$ = 7.7 Hz), 4.41 (q, 2H, 5-H, $J_{5/6}$ =

7.2 Hz), 2.93 (s, 3H, 4-H), 1.43 (t, 3H, 6-H, $J_{6/5}$ = 7.2 Hz) ppm. The ^{1}H-NMR spectral data is consistent with that found in the literature.[71]

From the diazo compound

To a stirred ice-cold solution of ethyl 2-diazo-3-oxobutanoate (**95a**) (0.84 g, 5.38 mmol) in acetonitrile (11mL) and water (1.0 mL) was added slowly *tert*-butylhypochlorite (0.70 g; 6.45 mmol; 1.20 equiv.). After 30 min. the solution was poured onto water (50 mL), extracted with dichloromethane (2x 10 mL), dried over $MgSO_4$ and most of the solvent was evaporated under reduced pressure. The remainder was added to a solution of picolinohydrazonamide (**73a**) (733 mg; 5.38 mmol) and 2,5-norbornadiene (**48**) (5.80 mL; 53.8 mmol; 10.0 equiv.) in ethanol (50 mL) and heated under reflux for 20 h. The solvent was evaporated again and the residue purified by column chromatography (diethyl ether / hexanes = 4:1) yielding **116a** (207 mg; 854 µmol; 16 %; R_f = 0.51) which was obtained as an orange solid and its regioisomer **158a** (66 mg; 272 µmol; 5 %; R_f = 0.39) which was obtained as an orange oil. Compound **158a** decarboxylated/ decomposed on standing.

$C_{14}H_{14}N_2O_2$ (M = 242.28 g/mol)

Analytical data for ethyl 5-methyl-[2,2']-bipyridine-6-carboxylate (**158a**):

^{1}H-NMR (CDCl$_3$): δ = 8.67 (ddd, 1H, 12-H, $J_{12/9}$ = 1.0 Hz, $J_{12/10}$ = 1.7 Hz, $J_{12/11}$ = 4.7 Hz), 8.46 (ddd, appearance similar to dt, 1H, 9-H, $J_{9/12}$ = 1.0 Hz, $J_{9/11}$ = 1.2 Hz, $J_{9/10}$ = 7.9 Hz), 8.41 (d, 1H, 14-H, $J_{14/13}$ = 8.2 Hz), 7.82 (ddd, appearance similar to dt, 1H, 10-H, $J_{10/12}$ = 1.7 Hz, $J_{10/11}$ = 7.7 Hz, $J_{10/9}$ = 7.9 Hz), 7.73 (d, 1H, 13-H, $J_{13/14}$ = 8.2 Hz), 7.32 (ddd, 1H, 11-H, $J_{11/9}$ = 1.2 Hz, $J_{11/12}$ = 4.7 Hz, $J_{11/10}$ = 7.7 Hz), 4.49 (q, 2H, 5-H, $J_{5/6}$ = 7.2 Hz), 2.59 (s, 3H, 4-H), 1.47 (t, 3H, 6-H, $J_{6/5}$ = 7.2 Hz) ppm.

Due to decarboxylation/decomposition the ^{13}C-NMR spectra was not obtained.

HRMS (ESI) for $C_{14}H_{15}N_2O_2$ [M+H]$^+$: calculated: 243.1128; measured: 243.1127.

IR: v_{max}/cm^{-1} = 2980 + 2932 (w, CH$_{alkyl}$), 1719 (m, C=O), 1433 (m, CH$_{alkyl}$), 1214 + 1091 + 1088 (s, C-O), 789 + 745 (s, CH$_{ar}$).

10.2 *Tert*-butyl 6-methyl-[2,2']-bipyridine-5-carboxylate (116b)

Method B – From the picolinate

A mixture of 1-*tert*-butoxy-1,3-dioxobutan-2-yl picolinate (**168b**) (500 g; 1.79 mmol; 1.19 equiv.), Cu(OAc)$_2$·H$_2$O (746 mg; 3.74 mmol; 2.49 equiv.) and methanol (1.0 mL) in dichloromethane (25 mL) was stirred at room temperature for 5 days. The reaction was diluted with hexanes (10 mL) and washed with an aqueous solution of Na$_2$EDTA until the aqueous phase remained colourless. The organic phase was dried over MgSO$_4$ and the solvent evaporated. The resulting oil was taken up in ethanol (25 mL), picolinohydrazonamide (**73a**) (204 mg; 1.50 mmol) and 2,5-norbornadiene (**48**) (1.61 mL; 14.9 mmol; 9.96 equiv.) were added and the solution heated under reflux for 2 days. After cooling down to room temperature, the solvent was evaporated under reduced pressure. Column chromatography (diethyl ether / hexanes = 1:1; R$_f$ = 0.51) afforded 139 mg of an inseparable 3:2-mixture of **116b** (351 μmol; 23 %) and *tert*-butyl 3-hydroxy-2-methoxybut-2-enoate (**171b**) (234 μmol; 16 %).

C$_{16}$H$_{18}$N$_2$O$_2$ (M = 270.33 g/mol)
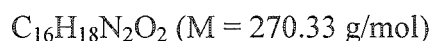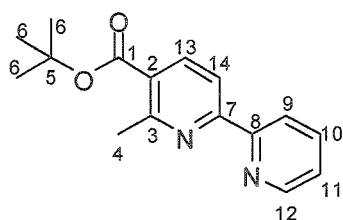
Analytical data for **116b**:

^{1}H-NMR (CDCl$_3$): δ = 8.70 (ddd, 1H, 12-H, $J_{12/9}$ = 1.0 Hz, $J_{12/10}$ = 1.7 Hz, $J_{12/11}$ = 4.7 Hz), 8.49 (ddd, appearance similar to dt, 1H, 9-H, $J_{9/12}$ = 1.0 Hz, $J_{9/11}$ = 1.2 Hz, $J_{9/10}$ = 7.9 Hz), 8.27 (d, 1H, 14-H, $J_{14/13}$ = 8.2 Hz), 8.23 (d, 1H, 13-H, $J_{13/14}$ = 8.2 Hz), 7.83 (ddd, appearance similar to dt, 1H, 10-H, $J_{10/12}$ = 1.7 Hz, $J_{10/11}$ = 7.7 Hz, $J_{10/9}$ = 7.9 Hz), 7.34 (ddd, 1H, 11-H, $J_{11/9}$ = 1.2 Hz, $J_{11/12}$ = 4.7 Hz, $J_{11/10}$ = 7.7 Hz), 2.89 (s, 3H, 4-H), 1.63 (s, 9H, 6-H) ppm.
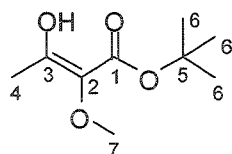
$C_9H_{16}O_4$ (M = 188.22 g/mol)

Analytical data for *tert*-butyl 3-hydroxy-2-methoxybut-2-enoate (**171b**):

^{1}H-NMR (CDCl$_3$): δ = 3.79 (s, 3H, 7-H), 1.59 (s, 3H, 4-H), 1.48 (s, 9H, 6-H) ppm.

10.3 Methyl 6-ethyl-[2,2']-bipyridine-5-carboxylate (116c)

From the picolinate

Following method B in Section 10.2 (reaction times: 1st step: overnight; reflux: overnight) and using Cu(OAc)$_2$·H$_2$O (783 mg; 3.92 mmol; 2.10 equiv.), 1-methoxy-1,3-dioxopentan-2-yl picolinate (**168c**) (470 mg; 1.87 mmol), picolinohydrazonamide (**73a**) (267 mg; 1.96 mmol; 1.05 equiv.) and 2,5-norbornadiene (**48**) (4.23 mL; 39.2 mmol; 21.0 equiv.) were converted into **116c**. Purification by column chromatography (diethyl ether / hexanes = 4:1; R$_f$ = 0.45) afforded the product (110 mg; 454 µmol; 24 %) as orange crystals (m.p. 58 – 61 °C).

This reaction was repeated using toluene in the second reaction step resulting in a comparable yield of **116c** (89 mg; 367 µmol; 20 %) which was obtained as light yellow needles.
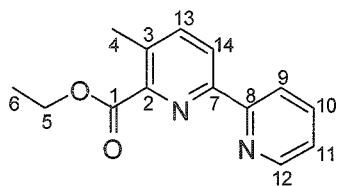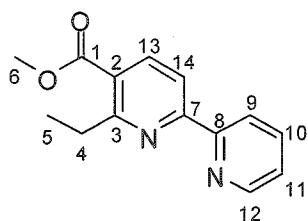

$C_{14}H_{14}N_2O_2$ (M = 242.28 g/mol)

^{1}H-NMR (CDCl$_3$): δ = 8.70 (ddd, 1H, 12-H, $J_{12/9}$ = 1.0 Hz, $J_{12/10}$ = 1.7 Hz, $J_{12/11}$ = 4.7 Hz), 8.55 (ddd, appearance similar to dt, 1H, 9-H, $J_{9/12}$ = 1.0 Hz, $J_{9/11}$ = 1.2 Hz, $J_{9/10}$ = 7.9 Hz), 8.30 (s, 2H, 13-H, 14-H), 7.84 (ddd, appearance similar to dt, 1H, 10-H, $J_{10/12}$ = 1.7 Hz, $J_{10/11}$ = 7.7 Hz, $J_{10/9}$ = 7.9 Hz), 7.34 (ddd, 1H, 11-H, $J_{11/9}$ = 1.2 Hz, $J_{11/12}$ = 4.7 Hz, $J_{11/10}$ =

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7.7 Hz), 3.94 (s, 3H, 6-H), 3.27 (q, 2H, 4-H, $J_{4/5}$ = 7.4 Hz), 1.39 (t, 3H, 5-H, $J_{5/4}$ = 7.4 Hz) ppm.

^{13}C-NMR (CDCl$_3$): δ = 167.19 (C-1), 164.05 (C-3), 157.70 (C-7), 155.57 (C-8), 149.32 (C-12), 139.57 (C-10), 137.03 (C-13), 124.60 (C-2), 124.32 (C-11), 121.96 (C-9), 117.79 (C-14), 52.32 (C-6), 30.32 (C-4), 13.66 (C-5) ppm.

HRMS (ESI) for C$_{14}$H$_{15}$N$_2$O$_2$ [M+H]$^+$: calculated: 243.1128; measured: 243.1129.

IR: v_{max}/cm^{-1} = 2976 + 2934 (w, CH$_{alkyl}$), 1723 (s, C=O), 1582 + 1557 (m, C=C$_{ar}$), 1450 (m), 1430 (s), 1282 (s), 1250 (s, C-O), 1200 (s), 1138 (s), 1099 (s), 1083 (s, C-O), 791 + 759 (s, CH$_{ar}$).

10.4 Ethyl 6-propyl-[2,2']-bipyridine-5-carboxylate (116d)

From the triazine in neat 2,5-norbornadiene

Under a nitrogen atmosphere a solution of ethyl 5-propyl-3-(pyridin-2-yl)-1,2,4-triazine-6-carboxylate (**106d**) (100 mg; 367 µmol) in 2,5-norbornadiene (**48**) (2.0 mL; 18.5 mmol; 50.5 equiv.) was heated under reflux until judged complete by TLC. After evaporation of the 2,5-norbornadiene under reduced pressure the residue was purified by column chromatography (diethyl ether; R$_f$ = 0.65) yielding **116d** (65 mg; 240 µmol; 65 %) which was obtained as colourless needles (m.p. 55 – 57 °C).
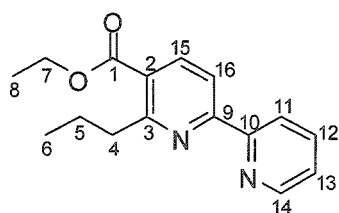
C$_{16}$H$_{18}$N$_2$O$_2$ (M = 270.33 g/mol)

^{1}H-NMR (CDCl$_3$): δ = 8.70 (ddd, 1H, 14-H, $J_{14/11}$ = 1.0 Hz, $J_{14/12}$ = 1.7 Hz, $J_{14/13}$ = 4.7 Hz), 8.53 (ddd, appearance similar to dt, 1H, 11-H, $J_{11/14}$ = 1.0 Hz, $J_{11/13}$ = 1.2 Hz, $J_{11/12}$ = 7.9 Hz), 8.28 (s, 2H, 15-H, 16-H), 7.84 (ddd, appearance similar to dt, 1H, 12-H, $J_{12/14}$ = 1.7 Hz, $J_{12/13}$ = 7.7 Hz, $J_{12/11}$ = 7.9 Hz), 7.34 (ddd, 1H, 13-H, $J_{13/11}$ = 1.2 Hz, $J_{13/14}$ = 4.7 Hz, $J_{13/12}$ = 7.7 Hz), 4.40 (q, 2H, 7-H, $J_{7/8}$ = 7.2 Hz), 3.25 – 3.19 (m, 2H, 4-H), 1.85 (tq, appearance similar to sextet, 2H, 5-H, $J_{5/4}$ = $J_{5/6}$ = 7.4 Hz) , 1.43 (t, 3H, 8-H, $J_{8/7}$ = 7.2 Hz),

1.05 (t, 3H, 6-H, $J_{6/5}$ = 7.4 Hz) ppm. The ^{1}H-NMR spectral data is consistent with that found in the literature.[80]

From the picolinate

Following method B in Section 10.2 (reaction times: 1st step: 1 day; reflux: 20 h) and using Cu(OAc)$_2$·H$_2$O (500 mg; 2.50 mmol; 2.10 equiv.), 1-ethoxy-1,3-dioxohexan-2-yl picolinate (**168d**) (333 mg; 1.19 mmol), picolinohydrazonamide (**73a**) (170 mg; 1.25 mmol; 1.05 equiv.) and 2,5-norbornadiene (**48**) (135 µL; 1.25 mmol; 1.05 equiv.) were converted into **116d**. Purification by column chromatography (diethyl ether; R$_f$ = 0.54) afforded the product (187 mg; 741 µmol; 59 %) as an orange solid.

Method C – From the chloroacetate with methylamine

A solution of ethyl 2-acetoxy-2-chloro-3-oxohexanoate (**102d**) (5.01 g; 20.0 mmol; 1.01 equiv.) and methylamine (4.93 mL; 33 % w/w in ethanol; 40.0 mmol; 2.02 equiv.) in ethanol (20 mL) was stirred at room temperature for 1 h. Then picolinohydrazonamide (**73a**) (2.70 g; 19.8 mmol) and 2,5-norbornadiene (**48**) (18.4 g; 200 mmol; 10.1 equiv.) were added and the solution was heated under reflux for 20 h. After cooling down to room temperature, the solvent was evaporated under reduced pressure and the viscous brown residue purified by column chromatography (ethyl acetate / petroleum ether (b.p. 40 – 60 °C) = 1:2; R$_f$ = 0.38) yielding **116d** (3.02 g; 11.2 mmol; 56 %) which was obtained as orange crystals.

From the chloroacetate in neat 2,5-norbornadiene

Under a nitrogen atmosphere a mixture of ethyl 2-acetoxy-2-chloro-3-oxohexanoate (**102d**) (100 mg; 399 µmol) and picolinohydrazonamide (**73d**) (136 mg; 999 µmol; 2.50 equiv.) in 2,5-norbornadiene (**48**) (5.0 mL; 46.3 mmol; 116 equiv.) was heated under reflux for 2 days. The 2,5-norbornadiene was then evaporated under reduced pressure. Column chromatography (diethyl ether; R$_f$ = 0.63) of the residue afforded 72 mg of an inseparable mixture of **116d** (138 µmol; 35 %) and unconverted starting material **102d** (138 µmol; 35 %) which was obtained as a brown oil.

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10.5 6-Propyl-[2,2']-bipyridine-5-carboxylic acid (161d)

A solution of ethyl 6-propyl-[2,2']-bipyridine-5-carboxylate (116d) (360 mg; 1.33 mmol) in methanol (2 mL) and 1M KOH (2 mL) was stirred at room temperature overnight. The solvent was evaporated, the residue dissolved in a minimal amount of water and washed with dichloromethane. The aqueous phase was acidified with concentrated HCl to pH = 3 and left to crystalise yielding 161d (254 mg; 1.05 mmol; 79 %) which was obtained as colourless crystals (decomposition at 206 °C).

$C_{14}H_{14}N_2O_2$ (M = 242.28 g/mol)
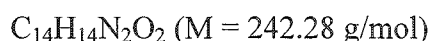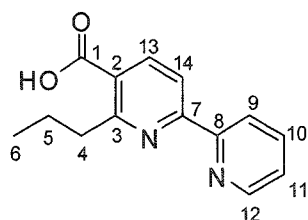
^{1}H-NMR (DMSO-d_6): δ = 8.86 (ddd, 1H, 12-H, $J_{12/9}$ = 1.0 Hz, $J_{12/10}$ = 1.7 Hz, $J_{12/11}$ = 4.7 Hz), 8.64 (ddd, appearance similar to dt, 1H, 9-H, $J_{9/12}$ = 1.0 Hz, $J_{9/11}$ = 1.2 Hz, $J_{9/10}$ = 7.9 Hz), 8.41 and 8.37 (2d, 2H, 13-H, 14-H, $J_{13/14}$ = 7.8 Hz), 8.33 (ddd, appearance similar to dt, 1H, 10-H, $J_{10/12}$ = 1.7 Hz, $J_{10/11}$ = 7.7 Hz, $J_{10/9}$ = 7.9 Hz), 7.80 (ddd, 1H, 11-H, $J_{11/9}$ = 1.2 Hz, $J_{11/12}$ = 4.7 Hz, $J_{11/10}$ = 7.7 Hz), 3.22 – 3.17 (m, 2H, 4-H), 1.80 (tq, appearance similar to sextet, 2H, 5-H, $J_{5/4}$ = $J_{5/6}$ = 7.4 Hz), 0.98 (t, 3H, 6-H, $J_{6/5}$ = 7.4 Hz) ppm. The OH signal was not detected.

^{13}C-NMR (DMSO-d_6): δ = 168.06 C-1), 162.40 (C-3), 153.36 (C-7), 151.80 (C-8), 147.44 (C-12), 142.00 (C-13), 140.51 (C-10), 127.87 (C-2), 126.56 (C-11), 123.41 (C-9), 119.44 (C-14), 38.34 (C-4), 23.00 (C-5), 14.57 (C-6) ppm.

HRMS (ESI) for $C_{14}H_{15}N_2O_2$ [M+H]$^+$: calculated: 243.1128; measured: 243.1125.

IR: v_{max}/cm^{-1} = 3370 (br, OH), 2866 (br, CH$_{alkyl}$), 1716 (s, C=O), 1579 + 1530 + 1460 (m, C=C$_{ar}$), 1219 + 1090 (s, C-O), 839 (m, CH$_{ar}$), 783 + 764 (s, CH$_{ar}$), 731 (m, CH$_{ar}$).

10.6 Ethyl 6-propyl-3-(2-(tetrahydrofuran-2-yloxy)ethyl)-[2,2']-bipyridine-5-carboxylate (164d)

From the triazine

Under a nitrogen atmosphere a solution of ethyl 5-propyl-3-(pyridin-2-yl)-1,2,4-triazine-6-carboxylate (**106d**) (256 mg; 940 μmol) in 2,3-dihydrofuran (**63a**) (2.11 g; 30.1 mmol; 32.0 equiv.) and ethanol was heated under reflux for 20 h. After evaporation of most of the solvent under reduced pressure the residue was purified by column chromatography (diethyl ether / hexanes = 9:1; R_f = 0.33) yielding **164d** (233 mg; 606 μmol; 64 %) which was obtained as a brown oil.

The reaction was repeated a) replacing ethanol by toluene giving an almost identical yield (223 mg; 580 mmol; 62 %) and b) using 2,3-dihydrofuran as the sole solvent giving no identifiable product.

$C_{22}H_{28}N_2O_4$ (M = 384.48 g/mol)
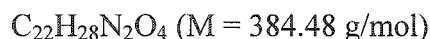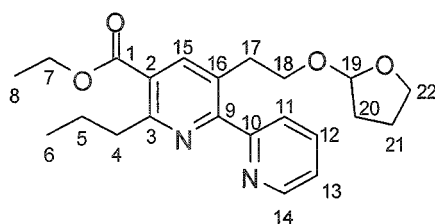
^{1}H-NMR (CDCl$_3$): δ = 8.66 (ddd, 1H, 14-H, $J_{14/11}$ = 1.0 Hz, $J_{14/12}$ = 1.7 Hz, $J_{14/13}$ = 4.7 Hz), 8.17 (s, 1H, 15-H), 7.88 (ddd, appearance similar to dt, 1H, 11-H, $J_{11/14}$ = 1.0 Hz, $J_{11/13}$ = 1.5 Hz, $J_{11/12}$ = 7.9 Hz), 7.82 (ddd, appearance similar to dt, 1H, 12-H, $J_{12/14}$ = 1.7 Hz, $J_{12/13}$ = 7.7 Hz, $J_{12/11}$ = 7.9 Hz), 7.31 (ddd, 1H, 13-H, $J_{13/11}$ = 1.5 Hz, $J_{13/14}$ = 4.7 Hz, $J_{13/12}$ = 7.7 Hz), 5.10 – 5.03 (m, 1H, 19-H), 4.40 (q, 2H, 7-H, $J_{7/8}$ = 7.2 Hz), 3.85 and 3.65 (2dt, 2H, 18-H, $J_{18/17}$ = 6.7 Hz, J_{gem} = 9.0 Hz), 3.82 – 3.74 (m, 2H, 22-H), 3.19 (t, 2H, 17-H, $J_{17/18}$ = 6.7 Hz), 3.18 – 3.13 (m, 2H, 4-H), 2.04 – 1.70 (m, 6H, 5-H, 20-H, 21-H), 1.43 (t, 3H, 8-H, $J_{8/7}$ = 7.2 Hz), 1.01 (t, 3H, 6-H, $J_{6/5}$ = 7.4 Hz) ppm.

^{13}C-NMR (CDCl$_3$): δ = 166.95 (C-1), 160.42 (C-3), 158.43 (C-9), 157.83 (C-10), 148.48 (C-14), 141.74 (C-15), 136.76 (C-12), 130.74 (C-16), 124.67 (C-11), 123.10 (C-13), 103.74 (C-19), 67.07 and 66.89 (C-18, C-22), 61.30 (C-7), 38.70 (C-4), 32.41 and 32.36 (C-17, C-20), 23.43 (C-5), 14.38 and 14.31 (C-6, C-8) ppm. The signals for C-2 and C-21 were not detected. This may be due to overlap with other signals.

HRMS (ESI) for $C_{22}H_{29}N_2O_4$ [M+H]$^+$: calculated: 385.2122; measured: 385.2118.

IR: v_{max}/cm^{-1} = 2960 + 2873 (w, CH_{alkyl}), 1718 (s, C=O), 1252(s, C-O), 1184 (m, C-O), 1091 (s, C-O), 1034 (s, C-O).

10.7 Ethyl 3-propyl-1-(pyridin-2-yl)-6,7-dihydro-5H-cyclopenta[c]-pyridine-4-carboxylate (167d)

From the triazine

A solution of ethyl 5-propyl-3-(pyridin-2-yl)-1,2,4-triazine-6-carboxylate (**106d**) (128 mg; 470 μmol) and 1-cyclopentenylpyrrolidine (**56b**) (76 μL; 521 μmol; 1.11 equiv.) in ethanol (5 mL) was stirred at room temperature for 1 h. Glacial acetic acid (0.5 mL) was added and it was stirred for another hour. It was then made basic with 1M NaOH (15 mL), the organic layer separated and the aqueous layer extracted with dichloromethane (2x 5 mL). The combined organic extracts were dried over $MgSO_4$ and the solvent evaporated yielding **167d** (122 mg; 393 μmol; 84 %) which was obtained as a brown oil.

For the sake of optimisation this reaction was carried out several times varying parameters such as solvent, temperature and workup. Details thereof can be found under Section 6.3.2.4 (p. 55).
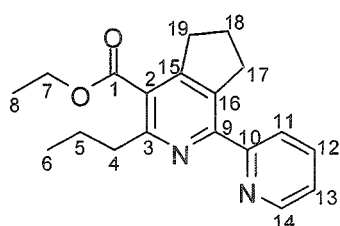
$C_{19}H_{22}N_2O_2$ (M = 310.40 g/mol)

^{1}H-NMR (CDCl$_3$): δ = 8.68 (ddd, 1H, 14-H, $J_{14/11}$ = 1.0 Hz, $J_{14/12}$ = 1.7 Hz, $J_{14/13}$ = 4.7 Hz), 8.25 (ddd, appearance similar to dt, 1H, 11-H, $J_{11/14}$ = 1.0 Hz, $J_{11/13}$ = 1.2 Hz, $J_{11/12}$ = 7.9 Hz), 7.80 (ddd, appearance similar to dt, 1H, 12-H, $J_{12/14}$ = 1.7 Hz, $J_{12/13}$ = 7.7 Hz, $J_{12/11}$ = 7.9 Hz), 7.27 (ddd, 1H, 13-H, $J_{13/11}$ = 1.2 Hz, $J_{13/14}$ = 4.7 Hz, $J_{13/12}$ = 7.7 Hz), 4.42 (q, 2H, 7-H, $J_{7/8}$ = 7.2 Hz), 3.38 and 3.06 (2t, 4H, 17-H, 19-H, $J_{17/18}$ = $J_{19/18}$ = 7.7 Hz), 3.01 – 2.95 (m, 2H, 4-H), 2.16 – 2.02 (m, 2H, 18-H), 1.82 (tq, appearance similar to sextet,

2H, 5-H, $J_{5/4} = J_{5/6} = 7.4$ Hz) , 1.42 (t, 3H, 8-H, $J_{8/7} = 7.2$ Hz), 1.01 (t, 3H, 6-H, $J_{6/5} = 7.4$ Hz) ppm.

^{13}C-NMR (CDCl$_3$): δ = 168.47 (C-1), 158.16 and 157.90 (C-3 and C-9), 155.94 (C-10), 152.02 (C-15), 148.64 (C-14), 136.97 (C-16), 136.50 (C-12), 124.29 (C-2), 123.52 (C-11), 123.01 (C-13), 61.20 (C-7), 38.37 (C-4), 32.95 and 32.89 (C-17, C-19), 25.08 (C-18), 23.41 (C-5), 14.39 (C-8), 14.26 (C-6) ppm.

HRMS (ESI) for C$_{19}$H$_{23}$N$_2$O$_2$ [M+H]$^+$: calculated: 311.1754; measured: 311.1750.

IR: v_{max}/cm^{-1} = 2961 + 2873 (w, CH$_{alkyl}$), 1717 (s, C=O), 1568 + 1555 (m, C=C$_{ar}$), 1255 (m, C-O), 1231 + 1116 (s, C-O), 1093 (m, C-O), 1024 (m), 743 (s, CH$_{ar}$).

From the chloroacetate with methylamine

A solution of ethyl 2-acetoxy-2-chloro-3-oxohexanoate (**102d**) (251 mg; 1.00 mmol) and methylamine (0.25 mL; 33 % w/w in ethanol; 2.03 mmol; 2.03 equiv.) in ethanol was stirred at room temperature for 1 h. Picolinohydrazonamide (**73a**) (136 mg; 1.00 mmol) and ethanol (10 mL) were added and the solution was heated under reflux for 2 h. Then 1-cyclopentenylpyrrolidine (**56b**) (153 µL; 1.05 mmol; 1.05 equiv.) was added and the solution was heated under reflux for another 20 h. After cooling down to room temperature, the solution was made basic with 1M NaOH (30 mL), the organic layer separated, the aqueous layer extracted with diethyl ether and the combined organic phases dried over MgSO$_4$. The solvent was then evaporated and the residue purified by column chromatography (diethyl ether / hexanes = 1:1; R$_f$ = 0.50) yielding **167d** (128 mg; 412 µmol; 41 %) which was obtained as a yellow liquid.

10.8 Ethyl 6-isopropyl-[2,2']-bipyridine-5-carboxylate (116e)

From the picolinate

Following method B in Section 10.2 (reaction times: 1st step: overnight; reflux: 2 d) and using Cu(OAc)$_2$·H$_2$O (746 mg; 3.74 mmol; 2.49 equiv.), the reaction of 1-methoxy-1,3-dioxopentan-2-yl picolinate (**168e**) (500 mg; 1.79 mmol; 1.19 equiv.), picolinohydrazonamide (**73a**) (204 mg; 1.50 mmol) and 2,5-norbornadiene (**48**) (1.61 mL; 14.9 mmol; 10.0 equiv.) afforded 110 mg of an inseparable 2:3-mixture of **116c** (199 µmol; 13 %) and ethyl 3-hydroxy-2-methoxy-4-methylpent-2-enoate (**171e**)

(299 µmol; 20 %) which was obtained as orange crystals after column chromatography (diethyl ether / hexanes = 2:1).

$C_{16}H_{18}N_2O_2$ (M = 270.33 g/mol)
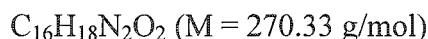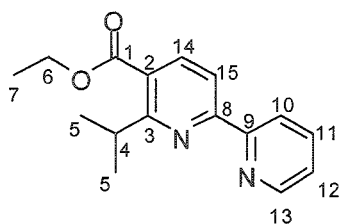
Analytical data for 116e:

^{1}H-NMR (CDCl$_3$): δ = 8.69 (ddd, 1H, 13-H, $J_{13/10}$ = 1.0 Hz, $J_{13/11}$ = 1.7 Hz, $J_{13/12}$ = 4.7 Hz), 8.59 (ddd, appearance similar to dt, 1H, 10-H, $J_{10/13}$ = 1.0 Hz, $J_{10/12}$ = 1.2 Hz, $J_{10/11}$ = 7.9 Hz), 8.28 (d, 1H, 15-H, $J_{15/14}$ = 8.2 Hz), 8.20 (d, 1H, 14-H, $J_{14/15}$ = 8.2 Hz), 7.85 (ddd, appearance similar to dt, 1H, 11-H, $J_{11/13}$ = 1.7 Hz, $J_{11/12}$ = 7.7 Hz, $J_{11/10}$ = 7.9 Hz), 7.34 (ddd, 1H, 12-H, $J_{12/10}$ = 1.2 Hz, $J_{12/13}$ = 4.7 Hz, $J_{12/11}$ = 7.7 Hz), 4.40 (q, 2H, 6-H, $J_{6/7}$ = 7.2 Hz), 3.99 – 3.89 (m, 1H, 4-H), 1.43 (t, 3H, 7-H, $J_{7/6}$ = 7.2 Hz), 1.38 (d, 6H, 5-H, $J_{5/4}$ = 6.7 Hz) ppm. The ^{1}H-NMR spectral data is consistent with that found in the literature.[80]

$C_9H_{16}O_4$ (M = 188.22 g/mol)
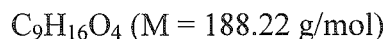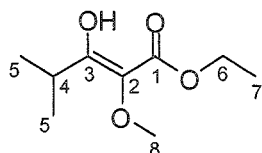
Analytical data for ethyl 3-hydroxy-2-methoxy-4-methylpent-2-enoate (171e):

^{1}H-NMR (CDCl$_3$): δ = 4.29 and 4.27 (2q, 2H, 6-H $J_{6/7}$ = 7.2 Hz), 3.81 (s, 3H, 8-H), 2.65 (septet, 1H, 4-H, $J_{4/5}$ = 6.9 Hz), 1.31 (t, 3H, 7-H $J_{7/6}$ = 7.2 Hz), 0.93 and 0.92 (2d, 6H, 5-H, $J_{5/4}$ = 6.9 Hz) ppm.

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10.9 Ethyl 6-isobutyl-[2,2']-bipyridine-5-carboxylate (116f)

From the chloroacetate with methylamine

Following method C in Section 10.4 (reaction times: 1 st step: 1 h; reflux: 20 h) and using methylamine (4.93 mL; 33 % w/w in ethanol; 40.0 mmol; 2.0 equiv.), the reaction of ethyl 2-acetoxy-2-chloro-5-methyl-3-oxohexanoate (**102f**) (5.29 g; 20.0 mmol; 1.01 equiv.), Picolinohydrazonamide (**73a**) (2.70 g; 19.8 mmol) and 2,5-norbornadiene (**48**) (18.4 g; 200 mmol; 10.1 equiv.) afforded an inseparable 3:1-mixture of regioisomers **116f** and **158f** (3.42 g; 12.0 mmol; 61 %) which was obtained as a yellow liquid after purification by column chromatography (ethyl acetate / petroleum ether (b.p. 40 – 60 °C) = 1:4; R_f = 0.29).

$C_{17}H_{20}N_2O_2$ (M = 284.36 g/mol)
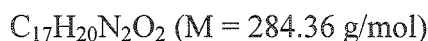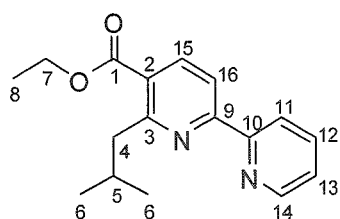
^{1}H-NMR (CDCl$_3$): δ = 8.70 (ddd, 1H, 14-H, $J_{14/11}$ = 1.0 Hz, $J_{14/12}$ = 1.7 Hz, $J_{14/13}$ = 4.7 Hz), 8.52 (ddd, appearance similar to dt, 1H, 11-H, $J_{11/14}$ = 1.0 Hz, $J_{11/13}$ = 1.2 Hz, $J_{11/12}$ = 7.9 Hz), 8.30 and 8.27 (2d, very strong *roofing* effect, 2H, 15-H, 16-H, $J_{15/16}$ = 8.2 Hz), 7.84 (ddd, appearance similar to dt, 1H, 12-H, $J_{12/14}$ = 1.7 Hz, $J_{12/13}$ = 7.7 Hz, $J_{12/11}$ = 7.9 Hz), 7.34 (ddd, 1H, 13-H, $J_{13/11}$ = 1.2 Hz, $J_{13/14}$ = 4.7 Hz, $J_{13/12}$ = 7.7 Hz), 4.40 (q, 2H, 7-H, $J_{7/8}$ = 7.2 Hz), 3.16 (d, 2H, 4-H, $J_{4/5}$ = 6.7 Hz), 2.26 (nonet, 1H, 5-H, $J_{5/4}$ = $J_{5/6}$ = 6.7 Hz), 1.43 (t, 3H, 8-H, $J_{8/7}$ = 7.2 Hz), 0.99 (d, 6H, 6-H, $J_{6/5}$ = 6.7 Hz) ppm.

^{13}C-NMR (CDCl$_3$): δ = 167.09 (C-1), 162.07 (C-3), 157.25 (C-9), 155.66 (C-10), 149.29 (C-14), 139.42 (C-15), 137.05 (C-12), 125.82 (C-2), 124.26 (C-13), 121.94 (C-11), 117.69 (C-16), 61.34 (C-7), 45.25 (C-4), 29.13 (C-5), 22.67 (C-6), 14.34 (C-8) ppm.

HRMS (ESI) for $C_{17}H_{21}N_2O_2$ [M+H]$^+$: calculated: 285.1598; measured: 285.1598.

IR: v_{max}/cm^{-1} = 3057 (w, CH$_{ar}$), 2957 + 2930 + 2870 (w, CH$_{alkyl}$), 1719 (s, C=O), 1583 + 1555 (m, C=C$_{ar}$), 1254 + 1093 (s, C-O), 1052 (m), 770 (s, CH$_{ar}$), 744 (m, CH$_{ar}$).

From the picolinate

Following method B in Section 10.2 (reaction times: 1st step: 1 day; reflux: 1 day) and using $Cu(OAc)_2 \cdot H_2O$ (340 mg; 1.70 mmol; 2.0 equiv.), 1-ethoxy-5-methyl-1,3-dioxohexan-2-yl picolinate (**168f**) (250 mg; 0.852 mmol), picolinohydrazonamide (**73a**) (116 mg; 0.852 mmol) and 2,5-norbornadiene (**48**) (0.92 mL; 8.52 mmol; 10.0 equiv.) were converted into **116f**. Purification by column chromatography (diethyl ether / hexanes = 1:2; R_f = 0.14) afforded the product (109 mg; 383 μmol; 45 %) as a brown liquid.

From the chloroacetate

Following method A in Section 10.1 (reaction time: 20 h), the reaction of 2-acetoxy-2-chloro-5-methyl-3-oxohexanoate (**102f**) (2.00 g; 7.56 mmol), picolinohydrazonamide (**73a**) (2.55 g; 18.7 mmol; 2.48 equiv.) and 2,5-norbornadiene (**48**) (8.15 mL;75.5 mmol; 10.0 equiv.) afforded an inseparable 2:1-mixture of regioisomers **116f** and **158f** (1.05 g; 3.69 mmol; 49 %) which was obtained as a yellow liquid after column chromatography (diethyl ether / hexanes = 1:2; R_f = 0.23).

$C_{17}H_{20}N_2O_2$ (M = 284.36 g/mol)
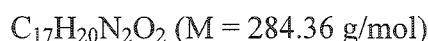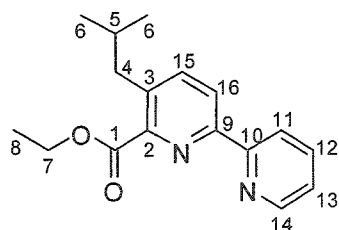
Analytical data for ethyl 5-isobutyl-[2,2']-bipyridine-6-carboxylate (**158f**):

^{1}H-NMR (CDCl$_3$): δ = 8.70 (ddd, 1H, 14-H, $J_{14/11}$ = 1.0 Hz, $J_{14/12}$ = 1.7 Hz, $J_{14/13}$ = 4.7 Hz), 8.58 (ddd, appearance similar to dt, 1H, 11-H, $J_{11/14}$ = 1.0 Hz, $J_{11/13}$ = 1.2 Hz, $J_{11/12}$ = 7.9 Hz), 8.42 (d, 1H, 16-H, $J_{16/15}$ = 8.2 Hz), 8.33 (d, 1H, 15-H, $J_{15/16}$ = 8.2 Hz), 7.85 (ddd, appearance similar to dt, 1H, 12-H, $J_{12/14}$ = 1.7 Hz, $J_{12/13}$ = 7.7 Hz, $J_{12/11}$ = 7.9 Hz), 7.36 (ddd, 1H, 13-H, $J_{13/11}$ = 1.2 Hz, $J_{13/14}$ = 4.7 Hz, $J_{13/12}$ = 7.7 Hz), 4.43 (q, 2H, 7-H, $J_{7/8}$ = 7.2 Hz), 2.54 (d, 2H, 4-H, $J_{4/5}$ = 6.9 Hz), 2.30 – 2.15 (m, 1H, 5-H) , 1.31 (t, 3H, 8-H, $J_{8/7}$ = 7.2 Hz), 0.89 (d, 6H, 6-H, $J_{6/5}$ = 6.7 Hz) ppm.

10.10 Ethyl 6-*tert*-butyl-[2,2']-bipyridine-5-carboxylate (116g)

From the picolinate

Following method B in Section 10.2 (reaction times: 1st step: 2 days; reflux: 5 days) and using Cu(OAc)$_2$·H$_2$O (709 mg; 3.55 mmol; 2.51 equiv.), 1-ethoxy-4,4-dimethyl-1,3-dioxopentan-2-yl picolinate (**168g**) (500 mg; 1.70 mmol; 1.20 equiv.), picolinohydrazonamide (**73a**) (193 mg; 1.42 mmol) and 2,5-norbornadiene (**48**) (1.53 mL; 14.2 mmol; 10.0 equiv.) were converted into **116g**. Purification by column chromatography (diethyl ether / hexanes = 1:1; R$_f$ = 0.35) afforded the product (273 mg; 960 μmol; 68 %) as a yellow liquid.

C$_{17}$H$_{20}$N$_2$O$_2$ (M = 284.36 g/mol)
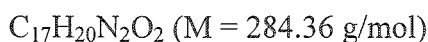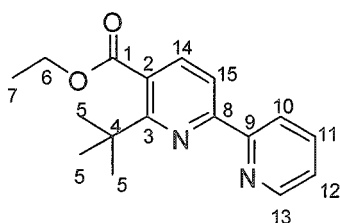
^{1}H-NMR (CDCl$_3$): δ = 8.68 (ddd, 1H, 13-H, $J_{13/10}$ = 1.0 Hz, $J_{13/11}$ = 1.7 Hz, $J_{13/12}$ = 4.7 Hz), 8.52 (ddd, appearance similar to dt, 1H, 10-H, $J_{10/13}$ = 1.0 Hz, $J_{10/12}$ = 1.2 Hz, $J_{10/11}$ = 7.9 Hz), 8.26 (d, 1H, 15-H, $J_{15/14}$ = 8.2 Hz), 7.83 (ddd, appearance similar to dt, 1H, 11-H, $J_{11/13}$ = 1.7 Hz, $J_{11/12}$ = 7.7 Hz, $J_{11/10}$ = 7.9 Hz), 7.78 (d, 1H, 14-H, $J_{14/15}$ = 8.2 Hz), 7.33 (ddd, 1H, 12-H, $J_{12/10}$ = 1.2 Hz, $J_{12/13}$ = 4.7 Hz, $J_{12/11}$ = 7.7 Hz), 4.40 (q, 2H, 6-H, $J_{6/7}$ = 7.2 Hz), 1.51 (s, 9H, 5-H) , 1.27 (t, 3H, 8-H, $J_{8/7}$ = 7.2 Hz) ppm.

^{13}C-NMR (CDCl$_3$): δ = 148.41 (C-13), 138.07 and 137.89 (C-11, C-14), 124.26 (C-12), 122.22 (C-10), 117.40 (C-15), 61.85 (C-6), 30.13 (C-5), 14.14 (C-7) ppm. The signals for the quaternary carbons C-1 to C-4, C-8 and C-9 were not detected.

The HRMS spectrum was not recorded.

IR: v$_{max}$/cm^{-1} = 2981 (w, CH$_{alkyl}$), 1723 (s, C=O), 1259 + 1064 (s, C-O), 779 (s, CH$_{ar}$).

10.11 Ethyl 6-phenyl-[2,2']-bipyridine-5-carboxylate (116h)

From the picolinate

Following method B in Section 10.2 (reaction times: 1st step: 1 day; reflux: 2 days) and using Cu(OAc)$_2$·H$_2$O (1.32 g; 6.61 mmol; 2.49 equiv.), 1-ethoxy-1,3-dioxo-3-phenylpropan-2-yl picolinate (168h) (1.00 g; 3.19 mmol; 1.20 equiv.), picolinohydrazonamide (73a) (361 mg; 2.65 mmol) and 2,5-norbornadiene (48) (2.9 mL; 26.9 mmol; 10.1 equiv.) were converted into 116h. Purification by column chromatography (diethyl ether; R$_f$ = 0.65) afforded the product (570 mg; 1.87 mmol; 71 %) as colourless crystals (80.5 – 83.5 °C).

For the sake of optimisation this reaction was carried out several times varying parameters such as solvent and number of equivalents of Cu(OAc)$_2$·H$_2$O. Details thereof can be found under Section 7.3.1.1, Table 25 (p. 63).

C$_{19}$H$_{16}$N$_2$O$_2$ (M = 304.35 g/mol)
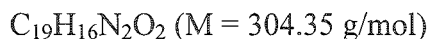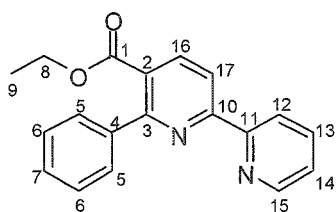
^{1}H-NMR (CDCl$_3$): δ = 8.71 (ddd, 1H, 15-H, $J_{15/12}$ = 1.0 Hz, $J_{15/13}$ = 1.7 Hz, $J_{15/14}$ = 4.7 Hz), 8.57 (ddd, appearance similar to dt, 1H, 12-H, $J_{12/15}$ = 1.0 Hz, $J_{12/14}$ = 1.2 Hz, $J_{12/13}$ = 7.9 Hz), 8.46 (d, 1H, 17-H, $J_{17/16}$ = 8.2 Hz), 8.24 (d, 1H, 16-H, $J_{16/17}$ = 8.2 Hz), 7.82 (ddd, appearance similar to dt, 1H, 13-H, $J_{13/15}$ = 1.7 Hz, $J_{13/14}$ = 7.7 Hz, $J_{13/12}$ = 7.9 Hz), 7.68 – 7.63 (m, 2H, 5-H), 7.49 – 7.45 (m, 3H, 6-H, 7-H), 7.35 (ddd, 1H, 14-H, $J_{14/12}$ = 1.2 Hz, $J_{14/15}$ = 4.7 Hz, $J_{14/13}$ = 7.7 Hz), 4.19 (q, 2H, 8-H, $J_{8/9}$ = 7.2 Hz), 1.09 (t, 3H, 9-H, $J_{9/8}$ = 7.2 Hz) ppm. The ^{1}H-NMR spectral data is consistent with that found in the literature.[80]

With catalytic amounts of Cu(OAc)$_2$·H$_2$O and co-oxidant

A mixture of 1-ethoxy-1,3-dioxo-3-phenylpropan-2-yl picolinate (168h) (448 mg; 1.43 mmol; 1.08 equiv.), Cu(OAc)$_2$·H$_2$O (18 mg; 90 μmol; 0.06 equiv.) and N^{n}Bu$_4$NO$_3$ (1.38 g; 4.53 mmol; 3.41 equiv.) in aqueous acetic acid (5 mL; 80 % v/v) was stirred at

room temperature for 7 days. Then Na₂EDTA (0.1M aqueous solution) was added, the product was extracted with dichloromethane, the solution washed with water and the dichloromethane evaporated. The resulting oil was taken up in ethanol, picolinohydrazonamide (73a) (181 mg; 1.33 mmol) and 2,5-norbornadiene (48) (1.45 mL; 13.4 mmol; 10.1 equiv.) were added and the solution was refluxed under a nitrogen atmosphere for 1 day. The solvent was evaporated again and the residue purified by column chromatography (diethyl ether / hexanes; R_f = 0.37) yielding 116h (192 mg; 631 µmol; 47 %) which was obtained as a brown wax.

With catalytic amounts of Cu(OAc)₂·H₂O and without co-oxidant

A mixture of 1-ethoxy-1,3-dioxo-3-phenylpropan-2-yl picolinate (168h) (448 mg; 1.43 mmol; 1.08 equiv.), Cu(OAc)₂·H₂O (33 mg; 165 µmol; 0.12 equiv.) and methanol (1 mL) in toluene (5 mL) was stirred at room temperature for 3 days. The reaction mixture was washed with an aqueous solution of Na₂EDTA (1 g per 10 mL) until the aqueous phase remained colourless, the organic phase dried over MgSO₄ and taken up in more toluene (20 mL). Picolinohydrazonamide (73a) (181 mg; 1.33 mmol) and 2,5-norbornadiene (48) (1.45 mL; 13.4 mmol; 10.1 equiv.) were added and the solution was refluxed under a nitrogen atmosphere for 2 days. The solvent was evaporated again and the residue purified by column chromatography (diethyl ether / hexanes = 1:1; R_f = 0.23) yielding 116h (198 mg; 651 µmol; 49 %) which was obtained as a yellow wax.

From its corresponding acetate

A solution of 2-acetoxy-3-oxo-3-phenylpropanoate (101h) (1.00 g; 4.00 mmol) in saturated ethanolic HCl (5 mL) was stirred at room temperature for 1 day. Then water (10 mL) was added, it was extracted with diethyl ether (10 mL), the organic phase was washed with a saturated solution of NaHCO₃, dried over MgSO₄ and the solvent evaporated under reduced pressure. The residue was taken up in ethanol (30 mL), picolinohydrazonamide (73a) (592 mg; 4.35 mmol; 1.09 equiv.) and 2,5-norbornadiene (48) (4.32 mL; 40.0 mmol; 10.0 equiv.) were added and the solution was refluxed under a nitrogen atmosphere for 2 days. The solvent was evaporated again and the residue purified by column chromatography (diethyl ether / hexanes = 1:1; R_f = 0.21) yielding 116h (258 mg; 848 µmol; 21 %) which was obtained as orange crystals.

10.12 Ethyl 6-(4-nitrophenyl)-[2,2']-bipyridine-5-carboxylate (116i)

From the picolinate

Following method B in Section 10.2 (reaction times: 1st step: 1 day; reflux: 1 day) and using 576 mg Cu(OAc)$_2$·H$_2$O (2.89 mmol; 2.5 equiv.), the reaction of 1-ethoxy-3-(4-nitrophenyl)-1,3-dioxopropan-2-yl picolinate (**168i**) (500 mg; 1.44 mmol; 1.25 equiv.), picolinohydrazonamide (**73a**) (157 mg; 1.15 mmol) and 2,5-norbornadiene (**48**) (1.25 mL; 11.5 mmol; 8.0 equiv.) afforded 77 mg of an inseparable 3:7-mixture of **116i** (79 µmol; 7 %) and ethyl 3-hydroxy-2-methoxy-3-(4-nitrophenyl)acrylate (**171i**) (185 µmol; 16 %) which was obtained as a brown solid after column chromatography (diethyl ether / hexanes = 1:1; R$_f$ = 0.25).

C$_{19}$H$_{15}$N$_3$O$_4$ (M = 349.35 g/mol)
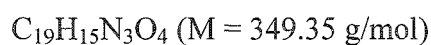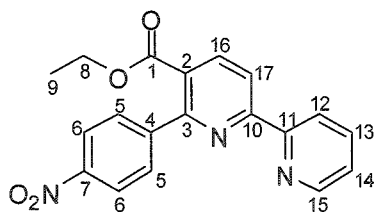
Analytical data for **116i**:

^{1}H-NMR (CDCl$_3$): δ = 8.73 (ddd, 1H, 15-H, $J_{15/12}$ = 1.0 Hz, $J_{15/13}$ = 1.7 Hz, $J_{15/14}$ = 4.7 Hz), 8.56 (d, 1H, 17-H, $J_{17/16}$ = 8.2 Hz), 8.51 (ddd, appearance similar to dt, 1H, 12-H, $J_{12/15}$ = 1.0 Hz, $J_{12/14}$ = 1.2 Hz, $J_{12/13}$ = 7.9 Hz), 8.36 (d, 1H, 16-H, $J_{16/17}$ = 8.2 Hz), 8.34 (d, 2H, 5-H, $J_{5/6}$ = 8.9 Hz), 7.86 – 7.81 (m, 1H, 13-H), 7.80 (d, 2H, 6-H, $J_{6/5}$ = 8.9 Hz), 7.39 (ddd,1H, 14-H, $J_{14/12}$ = 1.2 Hz, $J_{14/15}$ = 4.7 Hz, $J_{14/13}$ = 7.7 Hz), 4.24 (q, 2H, 8-H, $J_{8/9}$ = 7.2 Hz), 1.17 (t, 3H, 9-H, $J_{9/8}$ = 7.2 Hz) ppm.

C$_{12}$H$_{13}$NO$_6$ (M = 267.24 g/mol)

^{1}H-NMR (CDCl$_3$): δ = 8.23 (d, 2H, 6-H, $J_{6/5}$ = 8.9 Hz), 7.90 (d, 2H, 5-H, $J_{5/6}$ = 8.9 Hz), 4.34 and 4.32 (2q, 2H, 8-H, $J_{8/9}$ = 7.2 Hz), 3.87 (s, 3H, 10-H), 1.31 (t, 3H, 9-H, $J_{9/8}$ = 7.2 Hz) ppm.

11 Terpyridines and precursors

11.1 2,6-Pyridinedicarbonyl dichloride (186)

Under a nitrogen atmosphere and with mechanical stirring thionyl chloride (2.0 L; 27.4 mol; 9.16 equiv.) was added at once to 2,6-pyridinedicarboxylic acid (185) (500 g; 2.99 mol) in two 250 g batches. The mixtures were heated to 65 °C at which point the reaction set in. Catalytic amounts of DMF were added and it was heated at 65 °C until the release of gas had ceased (5 h). The batches were combined and the majority of the excess thionyl chloride distilled off. On cooling to 0 °C the product crystallised out and was was filtered off under reduced pressure yielding 186 (583 g; 2.86 mol; 96 %) which was obtained as a moisture sensitive off-white solid (m.p. 57 – 60 °C; lit.[136]: 60 – 60.5 °C).
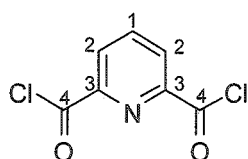
C$_7$H$_3$Cl$_2$NO$_2$ (M = 204.01 g/mol)

^{1}H-NMR (CDCl$_3$): δ = 8.40 – 8.36 (m, 2H, 2-H), 8.21 – 8.15 (m, 1H, 1-H) ppm.
^{13}C-NMR (CDCl$_3$): δ = 169.55 (C-4), 149.32 (C-3), 139.51 (C-1), 129.10 (C-2) ppm.
The ^{1}H- and ^{13}C-NMR spectral data is consistent with that found in the literature.[137]

11.2 2,6-Pyridinedicarboxamide (187)

To a large excess of ice-cold aqueous ammonia (30 % v/v) was carefully added 2,6-pyridinedicarbonyl dichloride (186) (6.00 g; 29.4 mmol) under vigorous stirring. After complete addition the mixture was stirred for another hour, the solid was filtered off and dried under a stream of air yielding 187 (4.81 g; 29.1 mmol; 99 %) which was obtained as a white powder (m.p. > 250 °C; lit.[138]: decomposition at 305 – 306 °C)

The reaction was scaled up to 234 g (1.15 mol) of starting material. The product which still contained water and/or ammonia was used for the subsequent reaction (Section 11.3, p. 161) without further purification and assuming quantitative yield of pure product 187. At this scale the reaction was performed in two batches using ice-cold ammonia (15.2 equiv.) plus external cooling and a mechanical stirrer; 2,6-pyridinedicarbonyl dichloride (186) was added at such rate (3 h) that the temperature did not rise above 5 °C.

$C_7H_7N_3O_2$ (M = 165.15 g/mol)
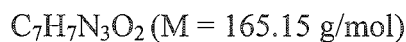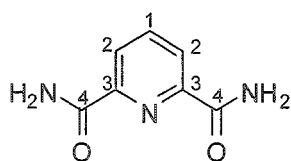
^{1}H-NMR (DMSO-d_6): δ = 8.88 (br, 2H, NH$_2$), 8.20 – 8.09 (m, 3H, 1-H and 2-H), 7.72 (br, 2H, NH$_2$) ppm. The ^{1}H-NMR spectral data is consistent with that found in the literature.[139]
^{13}C-NMR (DMSO-d_6): δ = 165.91 (C-4), 149.63 (C-3), 139.71 (C-1), 124.71 (C-2) ppm.

11.3 2,6-Pyridinedicarbonitrile (188)

Under gentle heating 2,6-pyridinedicarboxamide (187) (4.50 g; 27.2 mmol) was dissolved in DMF (70 mL) and allowed to cool to room temperature. POCl$_3$ (12.5 g; 81.5 mmol; 2.99 equiv.) was added in one portion and the mixture was stirred for 4 h. The mixture was diluted with dichloromethane (75 mL), washed with water (5x 75 mL) and the dichloromethane fraction was evaporated under reduced pressure. The residue was washed

again with water (75 mL) and dried yielding **188** (2.37 g; 18.4 mmol; 67 %) which was obtained as shiny platelets (m.p. 124 – 125 °C; lit.[140]: 126 °C).

The reaction was scaled up to 190 g (1.15 mol) of starting material yielding 103 g (798 mmol; 70 %) product. At this scale the reaction was performed in 3 batches and the POCl$_3$ had to be added slowly under cooling with an ice-bath.

C$_7$H$_3$N$_3$ (M = 129.12 g/mol)
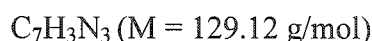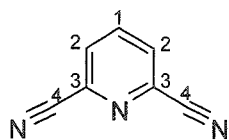
^{1}H-NMR (CDCl$_3$): δ = 8.13 – 8.06 (m, 1H, 1-H), 7.97 – 7.93 (m, 2H, 2-H) ppm.

^{1}H-NMR (DMSO-d_6): δ = 8.41 – 8.30 (m, 3H, 1-H and 2-H) ppm.

^{13}C-NMR (CDCl$_3$): δ = 138.96 (C-1), 135.42 (C-3), 131.21 (C-2), 115.52 (C-4) ppm.

^{13}C-NMR (DMSO-d_6): δ = 140.90 (C-1), 134.45 (C-3), 133.15 (C-2), 116.69 (C-4) ppm.

The ^{1}H-NMR spectral data is consistent with that found in the literature.[141]

11.4 Pyridine 2,6-bis(carbohydrazonamide) (189)

To 2,6-pyridinedicarbonitrile (**188**) (2.00 g; 15.5 mmol) was added hydrazine monohydrate (10 mL; 206 mmol; 13.3 eq.) at room temperature. The mixture was briefly stirred and then left to stand overnight. The crude product was filtered off, slurried with water and oven-dried yielding **189** (2.86 g; 14.8 mmol; 96 %) which was obtained as a pale yellow powder (decomposition > 200 °C; lit.[120]: m.p. 228 °C).

C$_7$H$_{11}$N$_7$ (M = 193.21 g/mol)
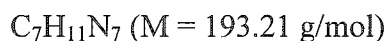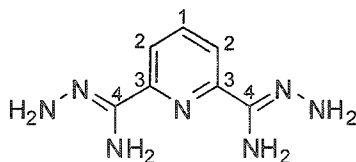
^{1}H-NMR (DMSO-d_6): δ = 7.80 (d, 2H, 2-H, $J_{2/1}$ = 7.4 Hz), 7.64 (t, 1H, 1-H, $J_{1/2}$ = 7.4 Hz) ppm. The ^{1}H-NMR spectral data is consistent with that found in the literature.[120]

11.5 Diethyl 3,3'-(pyridine-2,6-diyl)bis(5-propyl-1,2,4-triazine-6-carboxylate) (191d)

Method C - From the chloroacetate with methylamine

To a stirred solution of 2-chloro-2-acetoxy-3-oxohexanoate (**102d**) (501 mg; 2.00 mmol; 2.00 equiv.) in ethanol (3 mL) was added methylamine (0.49 mL; 33 % w/w in ethanol; 3.98 mmol; 3.98 equiv.). The mixture was stirred at room temperature for 1 h. Pyridine 2,6-bis(carbohydrazonamide) (**189**) (193 mg; 1.00 mmol) was added and the mixture was heated under reflux for 2 h. After cooling to room temperature, the solvent was evaporated under reduced pressure and the residue purified by column chromatography (ethyl acetate / petroleum ether (b.p. 40 – 60 °C) = 3:1; R_f = 0.27) yielding **191d** (157 mg; 337 µmol; 34 %) which was obtained as a brown solid (m.p. 105 – 107 °C).

$C_{23}H_{27}N_7O_4$ (M = 465.51 g/mol)
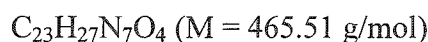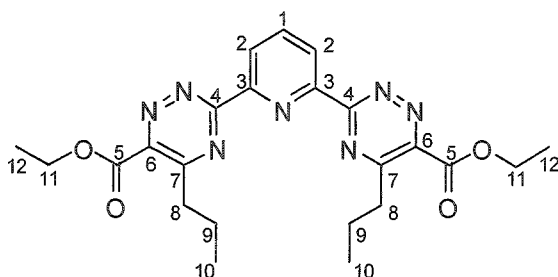
^{1}H-NMR (CDCl$_3$): δ = 8.85 (d, 2H, 2-H, $J_{2/1}$ = 7.9 Hz), 8.19 (t, 1H, 1-H, $J_{1/2}$ = 7.9 Hz), 4.56 (q, 4H, 11-H, $J_{11/12}$ = 7.2 Hz), 3.23 – 3.17 (m, 4H, 8-H), 1.98 – 1.85 (m, 4H, 9-H), 1.48 (t, 6H, 12-H, $J_{12/11}$ = 7.2 Hz), 1.07 (t, 6H, 10-H, $J_{10/9}$ = 7.2 Hz) ppm.

^{13}C-NMR (CDCl$_3$): δ = 164.10, 163.97, 162.42, 153.23, 150.00 (C-3 to C-7), 138.74 (C-1), 126.98 (C-2), 63.01 (C-11), 37.12 (C-8), 21.96 (C-9), 14.26 and 14.20 (C-10, C-12) ppm.

HRMS (ESI) for $C_{23}H_{28}N_7O_4$ [M+H]$^+$: calculated: 466.2197; measured: 466.2192.

IR: v_{max}/cm^{-1} = 2964 + 2934 + 2874 (w, CH$_{alkyl}$), 1721 (s, C=O), 1512 (m, C=C$_{ar}$), 1255 + 1081 (s, C-O), 1045 (s), 815 + 743 + 668 (m, CH$_{ar}$).

11.6 Diethyl 3,3'-(pyridine-2,6-diyl)bis(5-isobutyl-1,2,4-triazine-6-carboxylate) (191f)

Following method C in Section 11.5 and using methylamine (0.49 mL; 33 % w/w in ethanol; 3.98 mmol; 3.98 equiv.), 2-acetoxy-2-chloro-5-methyl-3-oxohexanoate (102f) (461 mg; 1.74 mmol; 1.74 equiv.) and pyridine 2,6-bis(carbohydrazonamide) (189) (193 mg; 1.00 mmol) were converted into 191f. Purification by column chromatography (ethyl acetate / petroleum ether (b.p. 40 – 60 °C) = 3:1; R_f = 0.39) afforded the product (156 mg; 316 µmol; 36 % based on 102f) as a yellow solid (m.p. 99 – 102 °C).

$C_{25}H_{31}N_7O_4$ (M = 493.57 g/mol)
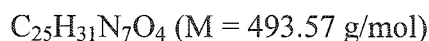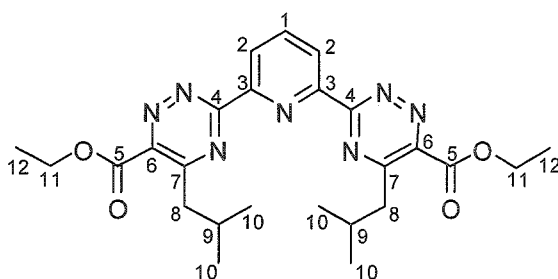
^{1}H-NMR (CDCl$_3$): δ = 8.84 (d, 2H, 2-H, $J_{2/1}$ = 7.9 Hz), 8.19 (t, 1H, 1-H, $J_{1/2}$ = 7.9 Hz), 4.57 (q, 4H, 11-H, $J_{11/12}$ = 7.2 Hz), 3.13 (d, 4H, 8-H, $J_{8/9}$ = 7.2 Hz), 2.45 – 2.30 (m, 2H, 9-H), 1.50 (t, 6H, 12-H, $J_{12/11}$ = 7.2 Hz), 1.03 (d, 12H, 10-H, $J_{10/9}$ = 6.7 Hz) ppm.

^{13}C-NMR (CDCl$_3$): δ = 164.24 (C-5), 163.24 (C-3), 162.37 (C-1), 153.29 (C-2), 150.45 (C-4), 138.65 (C-6), 126.90 (C-7), 62.99 (C-11), 43.23 (C-8), 28.83 (C-9), 22.62 (C-10), 14.26 (C-12) ppm.

HRMS (ESI) for $C_{25}H_{32}N_7O_4$ [M+H]$^+$: calculated: 494.2510; measured: 494.2512.

IR: v_{max}/cm^{-1} = 2960 2871 (w, CH$_{alkyl}$), 1720 (s, C=O), 1510 (m, C=C$_{ar}$), 1256 + 1085 (s, C-O), 1047 (s), 798 + 744 + 669 (m, CH$_{ar}$).

11.7 Diethyl 2,2'-(pyridine-2,6-diyl)bis(6-propylpyridine-5-carboxylate) (192d)

Method C - From the chloroacetate with methylamine

To a solution of 2-chloro-2-acetoxy-3-oxohexanoate (**102d**) (501 mg; 2.00 mmol; 2.00 equiv.) in ethanol (3 mL) was added methylamine (0.49 mL; 33 % w/w in ethanol; 3.98 mmol; 3.98 equiv.) and left stirring at room temperature for 1 h. Pyridine 2,6-bis-(carbohydrazonamide) (**189**) (193 mg; 1.00 mmol) and 2,5-norbornadiene (**48**) (2.15 mL; 19.9 mmol; 19.9 equiv.) were added and the mixture was heated under reflux for 20 h. The solvent was evaporated under reduced pressure and the residue purified by column chromatography (ethyl acetate / petroleum ether (b.p. 40 – 60 °C) = 1:4; R_f = 0.42) yielding **192d** (279 mg; 604 µmol; 60 %) which was obtained as a white solid (m.p. 105 – 106 °C from ethanol).

$C_{27}H_{31}N_3O_4$ (M = 461.56 g/mol)
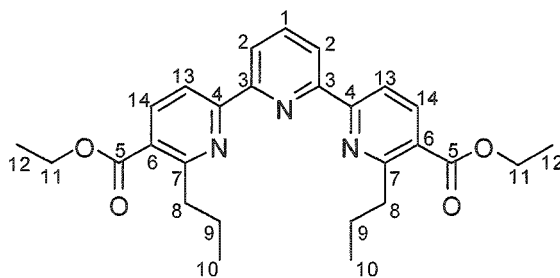
^{1}H-NMR (CDCl$_3$): δ = 8.59 (d, 2H, 2-H, $J_{2/1}$ = 7.9 Hz), 8.47 and 8.30 (2d, 4H, 13-H, 14-H, $J_{13/14}$ = $J_{14/13}$ = 8.3 Hz), 7.91 (t, 1H, 1-H, $J_{1/2}$ = 7.9 Hz), 4.42 (q, 4H, 11-H, $J_{11/12}$ = 7.2 Hz), 3.26 - 3.20 (m, 4H, 8-H), 1.94 – 1.80 (m, 4H, 9-H), 1.44 (t, 6H, 12-H, $J_{12/11}$ = 7.2 Hz), 1.06 (t, 6H, 10-H, $J_{10/9}$ = 7.4 Hz) ppm.

^{13}C-NMR (CDCl$_3$): δ = 167.01 (C-5), 162.79 (C-7), 157.48 (C-4), 154.94 (C-3), 139.42 (C-14), 137.95 (C-1), 125.41 (C-6), 122.31 (C-2), 117.85 (C-13), 61.34 (C-11), 39.05 (C-8), 23.02 (C-9), 14.37 and 14.30 (C-10, C-12) ppm.

HRMS (ESI) for $C_{27}H_{32}N_3O_4$ [M+H]$^+$: calculated: 462.2387; measured: 462.2394.

IR: v_{max}/cm^{-1} = 2960 + 2933 + 2871 (w, CH$_{alkyl}$), 1721 (s, C=O), 1582 (s, C=C$_{ar}$), 1553 (m), 1436 (m), 1247 (s, C-O), 1141 (m), 1091 (s, C-O), 1040 (m), 1018 (m), 828 (m, CH$_{ar}$), 786 (s, CH$_{ar}$), 745 + 736 (m, CH$_{ar}$).

11.8 Diethyl 2,2'-(pyridine-2,6-diyl)bis(6-isobutylpyridine-5-carboxylate) (192f)

Following method C in Section 11.7 and using methylamine (0.49 mL; 33 % w/w in ethanol; 3.98 mmol; 3.98 equiv.), 2-acetoxy-2-chloro-5-methyl-3-oxohexanoate (102f) (461 mg; 1.74 mmol; 1.74 equiv.), pyridine 2,6-bis(carbohydrazonamide) (189) (193 mg; 1.00 mmol) and 2,5-norbornadiene (48) (2.15 mL; 19.9 mmol; 19.9 equiv.) were converted into 192f. Purification by column chromatography (ethyl acetate / petroleum ether (b.p. 40 – 60 °C) = 1:9; R_f = 0.35) afforded the product (182 mg; 372 µmol; 43 % based on 102f) as colourless crystals (m.p. 109 – 112 °C).

$C_{29}H_{35}N_3O_4$ (M = 489.61 g/mol)
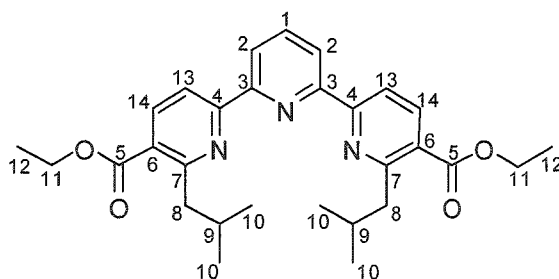
^{1}H-NMR (CDCl$_3$): δ = 8.58 (d, 2H, 2-H, $J_{2/1}$ = 7.9 Hz), 8.49 and 8.31 (2d, 4H, 13-H, 14-H, $J_{13/14}$ = $J_{14/13}$ = 8.3 Hz), 7.91 (t, 1H, 1-H, $J_{1/2}$ = 7.9 Hz), 4.42 (q, 4H, 11-H, $J_{11/12}$ = 7.2 Hz), 3.17 (d, 4H, 8-H, $J_{8/9}$ = 7.2 Hz), 2.36 – 2.21 (m, 2H, 9-H), 1.44 (t, 6H, 12-H, $J_{12/11}$ = 7.2 Hz), 1.00 (d, 12H, 10-H, $J_{10/9}$ = 6.7 Hz) ppm.

^{13}C-NMR (CDCl$_3$): δ = 167.13 (C-5), 162.05 (C-7), 157.24 (C-4), 154.94 (C-3), 139.38 (C-14), 137.99 (C-1), 125.91 (C-6), 122.30 (C-2), 117.76 (C-13), 61.36 (C-11), 45.28 (C-8), 29.16 (C-9), 22.68 (C-10), 14.39 (C-12) ppm.

HRMS (ESI) for $C_{29}H_{36}N_3O_4$ [M+H]$^+$: calculated: 490.2700; measured: 490.2699.

IR: v_{max}/cm^{-1} = 2957 (m, CH$_{alkyl}$), 1721 (s, C=O), 1581 (s, C=C$_{ar}$), 1552 (m), 1438 (m), 1254 (s, C-O), 1099 (s, C-O), 1073 (m), 822 (m, CH$_{ar}$), 784 + 764 (s, CH$_{ar}$), 731 (m, CH$_{ar}$).

11.9 Diethyl 2,2'-(pyridine-2,6-diyl)bis(6-phenylpyridine-5-carboxylate) (192h)

Following method C in Section 11.7 and using methylamine (0.49 mL; 33 % w/w in ethanol; 3.98 mmol; 3.98 equiv.), 2-chloro-2-acetoxy-3-oxo-3-phenylpropanoate (102h) (569 mg; 2.00 mmol; 2.0 equiv.), pyridine 2,6-bis(carbohydrazonamide) (189) (193 mg; 1.00 mmol) and 2,5-norbornadiene (48) (2.15 mL; 19.9 mmol; 19.9 equiv.) were converted into 192h. Purification by column chromatography (ethyl acetate / petroleum ether (b.p. 40 – 60 °C) = 1:4; R_f = 0.32) afforded the product (403 mg; 761 μmol; 76 %) as fine white needles (m.p. 156 – 157 °C from ethanol).

$C_{33}H_{27}N_3O_4$ (M = 529.60 g/mol)
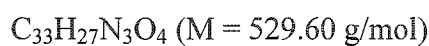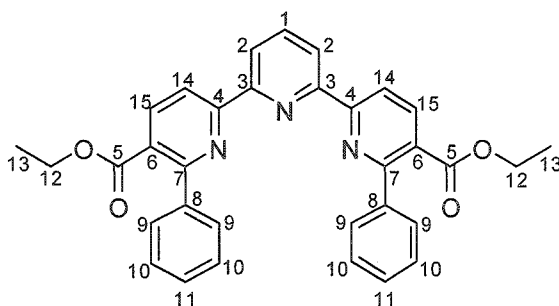
^{1}H-NMR (CDCl$_3$): δ = 8.67 (d, 2H, 14-H or 15-H, $J_{14/15}$ = 8.2 Hz), 8.62 (d, 2H, 2-H, $J_{2/1}$ = 7.9 Hz), 8.27 (d, 2H, 14-H or 15-H, $J_{14/15}$ = 8.2 Hz), 7.93 (t, 1H, 1-H, $J_{1/2}$ = 7.9 Hz), 7.69 – 7.63 (m, 4H, 9-H), 7.51 – 7.43 (m, 6H, 10-H, 11-H), 4.19 (q, 4H, 12-H, $J_{12/13}$ = 7.2 Hz), 1.07 (t, 6H, 13-H, $J_{13/12}$ = 7.2 Hz) ppm.

^{13}C-NMR (CDCl$_3$): δ = 168.42 (C-5), 158.35, 157.17 and 154.60 (C-3, C-4, C-7), 140.49 (C-1), 139.04 (C-15), 138.01 (C-8), 128.92 and 128.15 (C-9, C-10), 128.76 (C-11), 127.13 (C-6), 122.57 (C-2), 118.76 (C-14), 61.57 (C-12), 13.78 (C-13) ppm.

HRMS (ESI) for $C_{33}H_{28}N_3O_4$ [M+H]$^+$: calculated: 530.2074; measured: 530.2079.

IR: v_{max}/cm^{-1} = 2981 (w, CH$_{alkyl}$), 1705 (s, C=O), 1573 (m, C=C$_{ar}$), 1278 + 1117 (s, C-O), 1085 (m), 1046 (m), 1018 (m), 796 + 766 + 699 (s, CH$_{ar}$).

11.10 Diethyl 1,1'-(pyridine-2,6-diyl)bis(3-propyl-6,7-dihydro-5H-cyclopenta[c]pyridine-4-carboxylate) (193d)

From the chloroacetate with methylamine

A solution of ethyl 2-acetoxy-2-chloro-3-oxohexanoate (**102d**) (501 mg; 2.00 mmol; 2.0 equiv.) and methylamine (0.49 mL; 33 % w/w in ethanol; 3.98 mmol; 3.98 equiv.) in ethanol (5 mL) was stirred at room temperature for 1 h. Pyridine 2,6-bis-(carbohydrazonamide) (**189**) (193 mg; 1.00 mmol) was added and the solution was heated under reflux for 2 h. Then 1-cyclopentenylpyrrolidine (**56b**) (306 μL; 2.10 mmol; 2.10 equiv.) was added and the solution was refluxed for another 20 h. After cooling down to room temperature, the solvent was evaporated and the residue purified by column chromatography (diethyl ether / hexanes = 4:1; R_f = 0.41) yielding **193d** (261 mg; 482 μmol; 48 %) which was obtained as a yellow solid (m.p. 61 – 63 °C).

$C_{33}H_{39}N_3O_4$ (M = 541.69 g/mol)
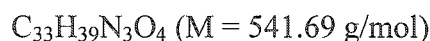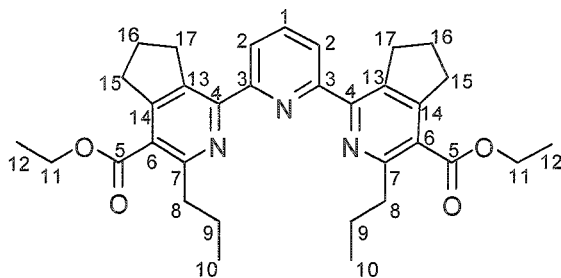
^{1}H-NMR (CDCl$_3$): δ = 8.18 (d, 2H, 2-H, $J_{2/1}$ = 7.9 Hz), 7.92 (t, 1H, 1-H, $J_{1/2}$ = 7.9 Hz), 4.41 (q, 4H, 11-H, $J_{11/12}$ = 7.2 Hz), 3.29 and 3.06 (2t, 8H, 15-H, 17-H, $J_{15/16}$ = $J_{17/16}$ = 7.4 Hz), 3.02 – 2.96 (m, 4H, 8-H), 2.04 (tt, appearance similar to quintet, 4H, 16-H, $J_{16/15}$ = $J_{16/17}$ = 7.4 Hz), 1.84 (tq, appearance similar to sextet, 4H, 9-H, $J_{9/8}$ = $J_{9/10}$ = 7.4 Hz), 1.41 (t, 6H, 12-H, $J_{12/11}$ = 7.2 Hz), 1.03 (t, 6H, 10-H, $J_{10/9}$ = 7.4 Hz) ppm.

^{13}C-NMR (CDCl$_3$): δ = 168.44 (C-5), 157.88 and 157.02 (C-4, C-7), 155.79 (C-3), 152.61 (C-14), 137.12 (C-13), 136.94 (C-1), 124.26 (C-6), 123.24 (C-2), 61.23 (C-11), 38.39 (C-8), 33.01 and 32.90 (C-15, C-17), 25.24 (C-16), 23.44 (C-9), 14.39 and 14.31 (C-10, C-12) ppm.

HRMS (ESI) for $C_{33}H_{40}N_3O_4$ [M+H]$^+$: calculated: 542.3013; measured: 542.3014.

IR: v_{max}/cm^{-1} = 2962 + 2935 + 2872 (w, CH$_{alkyl}$), 1717 (s, C=O), 1557 (m, C=C$_{ar}$), 1256 + 1237 + 1122 (s, C-O), 1031 (m), 826 + 737 (m, CH$_{ar}$).

Method I – From the chloroacetate with methylamine and acidic workup

A solution of ethyl 2-acetoxy-2-chloro-3-oxohexanoate (**102d**) (501 mg; 2.00 mmol; 2.0 equiv.) and methylamine (0.49 mL; 33 % w/w in ethanol; 3.98 mmol; 3.98 equiv.) in ethanol (5 mL) was stirred at room temperature for 1 h. Pyridine 2,6-bis-(carbohydrazonamide) (**189**) (193 mg; 1.00 mmol) and ethanol (5 mL) were added and the solution was heated under reflux for 1 h. After cooling down to room temperature, 1-cyclopentenylpyrrolidine (**56b**) (306 µL; 2.10 mmol; 2.10 equiv.) was added and the solution was stirred for 1 h, glacial acetic acid (1 mL) was added and it was stirred for another hour. It was then made basic with 1M NaOH (60 mL), the organic layer was separated, the aqueous phase extracted with dichloromethane (2x 10 mL) and the combined organic extracts dried over $MgSO_4$. The solvent was evaporated and the residue purified by column chromatography (diethyl ether / hexanes = 1:1; R_f = 0.58) yielding **193d** (219 mg; 404 µmol; 40 %) which was obtained as a pale yellow solid.

11.11 Diethyl 1,1'-(pyridine-2,6-diyl)bis(3-isobutyl-6,7-dihydro-5H-cyclopenta[c]pyridine-4-carboxylate) (193f)

Following method I in Section 11.10 and using methylamine (0.49 mL; 33 % w/w in ethanol; 3.98 mmol; 3.98 equiv.), ethyl 2-acetoxy-2-chloro-5-methyl-3-oxohexanoate (**102f**) (529 mg; 2.00 mmol; 2.00 equiv.), pyridine 2,6-bis(carbohydrazonamide) (**189**) (193 mg; 1.00 mmol) and 1-cyclopentenylpyrrolidine (**56b**) (306 µL; 2.10 mmol; 2.10 equiv.) were converted into **193f**. Purification by column chromatography (diethyl ether / hexanes = 4:1; R_f = 0.81) afforded the product (268 mg; 495 µmol; 50 %) as a yellow wax.

$C_{35}H_{43}N_3O_4$ (M = 569.74 g/mol)
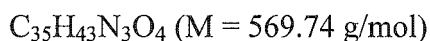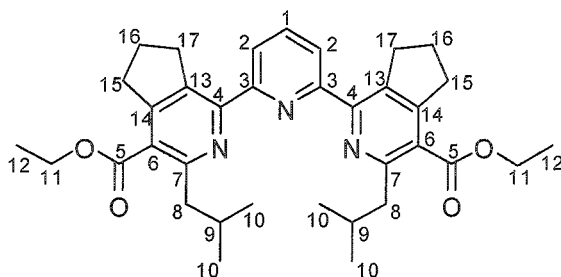
^{1}H-NMR (CDCl$_3$): δ = 8.18 (d, 2H, 2-H, $J_{2/1}$ = 7.9 Hz), 7.93 (t, 1H, 1-H, $J_{1/2}$ = 7.9 Hz), 4.42 (q, 4H, 11-H, $J_{11/12}$ = 7.2 Hz), 3.30 and 3.06 (2t, 8H, 15-H, 17-H, $J_{15/16}$ = $J_{17/16}$ = 7.4 Hz), 2.89 (d, 4H, 8-H, $J_{8/9}$ = 7.2 Hz), 2.34 – 2.18 (m, 2H, 9-H), 2.05 (tt, appearance similar to quintet, 4H, 16-H, $J_{16/15}$ = $J_{16/17}$ = 7.4 Hz), 1.42 (t, 6H, 12-H, $J_{12/11}$ = 7.2 Hz), 0.99 (d, 12H, 10-H, $J_{10/9}$ = 6.7 Hz) ppm.

^{13}C-NMR (CDCl$_3$): δ = 168.53 (C-5), 157.09 and 156.98 (C-4, C-7), 155.51 (C-3), 152.46 (C-14), 137.05 (C-13), 136.76 (C-1), 124.83 (C-6), 123.23 (C-2), 61.18 (C-11), 44.71 (C-8), 32.93 (C-15, C-17), 29.27 (C-9), 25.18 (C-16), 22.69 (C-10), 14.39 (C-12) ppm.

HRMS (ESI) for C$_{35}$H$_{44}$N$_3$O$_4$ [M+H]$^+$: calculated: 570.3326; measured: 570.3324.

IR: v_{max}/cm^{-1} = 2955 (m, CH$_{alkyl}$), 2869 (w, CH$_{alkyl}$), 1718 (s, C=O), 1557 (m, C=C$_{ar}$), 1256 + 1233 + 1119 + 1095 (s, C-O), 1039 (m), 828 + 744 (m, CH$_{ar}$).

12 Imidazoles

12.1 Ethyl 2-phenyl-4-(*n*-propyl)-1*H*-imidazole-5-carboxylate (196d)

From the chloroacetate with methylamine

To a stirred solution of 2-acetoxy-2-chloro-3-oxohexanoate (**102d**) (500 mg; 1.99 mmol) in ethanol (5 mL) was added methylamine (0.49 mL; 33 % w/w in ethanol; 3.98 mmol; 2.00 equiv.) and it was left stirring at room temperature for 1 h. After evaporation of the solvent benzaldehyde (423 mg; 3.99 mmol; 2.00 equiv.) and a solution of ammonium acetate (1.53 g; 19.8 mmol; 9.95 equiv.) in acetic acid (6 mL) were added to the residue and the mixture was heated to 80 °C for 3 h. The solvent was evaporated, the residue taken up in ethyl acetate (12 mL), washed with NaHCO$_3$ (12 mL), water (12 mL) and brine (12 mL) and dried over MgSO$_4$. Evaporation of the ethyl acetate afforded **196d** (335 mg; 1.30 mmol; 65 %) which was obtained as orange solid (decomposition >140 °C) without need for column chromatography.
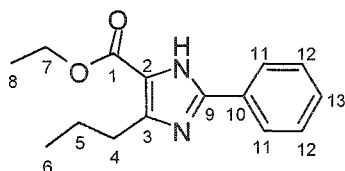
$C_{15}H_{18}N_2O_2$ (M = 258.32 g/mol)

^{1}H-NMR (CDCl$_3$): δ = 7.90 – 7.86 (m, 2H, 11-H), 7.49 – 7.40 (m, 3H, 12-H, 13-H), 4.38 (q, 2H, 7-H, $J_{7/8}$ = 7.2 Hz), 2.98 – 2.89 (m, 2H, 4-H), 1.75 (tq, appearance similar to sextet, 2H, 5-H, $J_{5/4} = J_{5/6}$ = 7.4 Hz), 1.40 (t, 3H, 8-H, $J_{8/7}$ = 7.2 Hz), 1.00 (t, 3H, 6-H, $J_{6/5}$ = 7.4 Hz) ppm.

^{13}C-NMR (CDCl$_3$): δ = 128.99 (C-12), 125.88 (C-11), 60.72 (C-7), 23.06 (C-5), 14.49 and 14.05 (C-6, C-8) ppm. The atoms C-1 to C-4, C-9, C-10 and C-13 could not be assigned.

HRMS (ESI) for $C_{15}H_{19}N_2O_2$ [M+H]$^+$: calculated: 259.1441; measured: 259.1441.

IR: v_{max}/cm^{-1} = 2964 (w, CH$_{alkyl}$), 1702 (s, C=O), 1323 (s), 1215 (s), 1113 (s, C-O), 714 + 694 (s, CH$_{ar}$).

From the chloroacetate

To a stirred solution of ammonium acetate (1.53 g; 19.8 mmol; 9.95 equiv.) in acetic acid (6 mL) at room temperature were added 2-acetoxy-2-chloro-3-oxohexanoate (**102d**) (500 mg; 1.99 mmol) and benzaldehyde (423 mg; 3.99 mmol; 2.00 equiv.) and the mixture was heated to 65 °C for 1 h. The solvent was evaporated, the residue taken up in ethyl acetate, washed with NaHCO$_3$, water and brine and dried over MgSO$_4$. After evaporation of the ethyl acetate the residue was purified by column chromatography (ethyl acetate / hexanes = 3:2; R$_f$ = 0.54) yielding **196d** (211 mg; 817 µmol; 41 %) which was obtained as yellow needles (decomposition >140 °C).

From the chloroacetate with EtOH/HCl

A solution of 2-acetoxy-2-chloro-3-oxohexanoate (**102d**) (500 mg; 1.99 mmol) in saturated ethanolic HCl (6 mL) was stirred at room temperature for 20 h. After evaporation of the solvent benzaldehyde (423 mg; 3.99 mmol; 2.00 equiv.) and a solution of ammonium acetate (1.53 g; 19.8 mmol; 9.95 equiv.) in acetic acid (6 mL) were added to the residue and the mixture was heated to 70 °C for 3 h. The solvent was evaporated, the residue taken up in ethyl acetate (12 mL), washed with NaHCO$_3$ (12 mL), water (12 mL) and brine (12 mL) and dried over MgSO$_4$. After evaporation of the ethyl acetate the crude product was

purified by column chromatography (ethyl acetate / hexanes = 3:2; R_f = 0.40) yielding **196d** (209 mg; 809 µmol; 41 %) which was obtained as yellow needles.

From the picolinate

A mixture of 1-ethoxy-1,3-dioxohexan-2-yl picolinate (**168d**) (888 mg; 3.18 mmol), Cu(OAc)$_2$·H$_2$O (1.32 mg; 6.61 mmol; 2.08 equiv.) and methanol (2.0 mL) in dichloromethane (50 mL) was stirred at room temperature for 1 day. The reaction was diluted with hexanes (20 mL) and washed with an aqueous solution of Na$_2$EDTA (1 g per 10 mL) until the aqueous phase remained colourless. The organic phase was dried over MgSO$_4$ and the solvent evaporated. The resulting oil and benzaldehyde (704 mg; 6.63 mmol; 2.09 equiv.) were then added to a solution of NH$_4$OAc (2.56 g; 33.2 mmol; 10.4 equiv.) in acetic acid (12 mL) and stirred at 65 °C for 3 h. The acetic acid was evaporated, the residue was taken up in ethyl acetate (25 mL), washed with NaHCO$_3$ (2x 25 mL), water (25 mL), brine (25 mL), dried over MgSO$_4$ and the solvent evaporated under reduced pressure. The crude product was purified by column chromatography (ethyl acetate / hexane = 3:2; R_f = 0.40) yielding **196d** (335 mg; 1.30 mmol; 41 %) which was obtained as yellow needles.

12.2 Ethyl 2,4-diphenyl-1*H*-imidazole-5-carboxylate (196h)

From the picolinate

A mixture of 1-ethoxy-1,3-dioxo-3-phenylpropan-2-yl picolinate (**168h**) (1.00 g; 3.19 mmol), Cu(OAc)$_2$·H$_2$O (1.32 mg; 6.61 mmol; 2.08 equiv.) and methanol (2.0 mL) in dichloromethane (50 mL) was stirred at room temperature until judged complete by TLC. The reaction was diluted with hexanes (20 mL) and washed with with an aqueous solution of Na$_2$EDTA (1 g per 10 mL) until the aqueous phase remained colourless. The organic phase was dried over MgSO$_4$ and the solvent evaporated. The resulting oil and benzaldehyde (707 mg; 6.66 mmol; 2.09 equiv.) were then added to a solution of NH$_4$OAc (2.56 g; 33.2 mmol; 10.4 equiv.) in acetic acid (12 mL) and stirred at 65 °C for 16 h. The acetic acid was evaporated, the residue was taken up in ethyl acetate (25 mL), washed with NaHCO$_3$ (2x 25 mL), water (25 mL), brine (25 mL), dried over MgSO$_4$ and the solvent evaporated under reduced pressure. The crude product was purified by column

chromatography (ethyl acetate / hexane = 3:2; R_f = 0.55) yielding **196h** (255 mg; 872 µmol; 27 %) as a yellow solid (m.p. 167 °C; lit.[123]: 165 – 167 °C).

$C_{18}H_{16}N_2O_2$ (M = 292.34 g/mol)
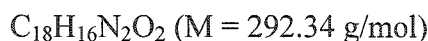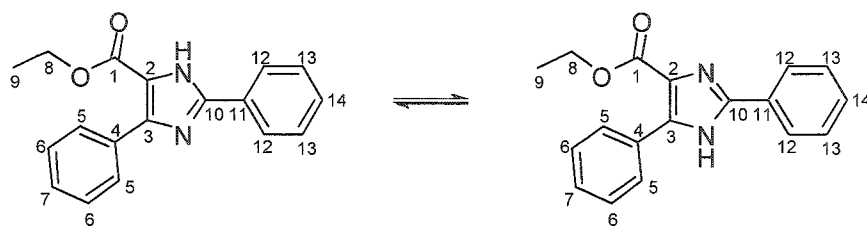
^{1}H-NMR (CDCl$_3$) of both tautomeric forms: δ = 8.03 – 7.90 (br s, 6H) and 7.52 – 7.34 (m, 14H) (5-H to 7-H, 12-H to 14-H), 4.34 (q, 4H, 8-H, $J_{8/9}$ = 7.2 Hz), 1.32 and 1.29 (2t, 6H, 9-H, $J_{9/8}$ = 7.2 Hz) ppm. The ^{1}H-NMR spectral data is consistent with that found in the literature.[123]

13 Attempted synthesis of 8-isopropyl-7-phenyl-2-(pyridin-2-yl)-7,8-dihydro-5H-pyrano-[4,3-b]pyridin-5-one (173)
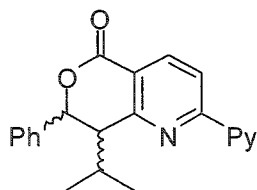
With *n*-BuLi

To a solution of diisopopylamine (0.24 mL; 1.70 mmol; 1.20 equiv.) in dry THF (5 mL, distilled from NaH) at -40 °C under a nitrogen atmoshere was added *n*-butyllithium (0.65 mL; 2.5M in hexanes; 1.62 mmol; 1.15 eq.) and the mixture was stirred for 30 min. After cooling down to -78 °C a solution of ethyl 6-isobutyl-[2,2']-bipyridine-5-carboxylate (**116f**) (400 mg; 1.41 mmol) in dry THF (5 mL) was added upon which the mixture turned dark immediately. After another 30 min of stirring, benzaldehyde (0.165 mL; 1.62 mmol; 1.15 equiv.) was added and the mixture was allowed to warm to RT. The mixture was

washed with aqueous Na_2CO_3 (5 mL), the aqueous phase was extracted with diethyl ether (2x 5 mL), the combined organic extracts were dried over K_2CO_3 and the solvent was evaporated. ^{1}H-NMR spectroscopy of the crude product showed only unconverted ethyl 6-isobutyl-[2,2']-bipyridine-5-carboxylate (116f).

With lithium hexamethyldisilazide (LHMDS)

Note: all glassware was dried at >100 °C under vacuum and flushed with nitrogen prior to the experiment.

A solution of LHMDS (1.08 mL; 1.06M in THF/ethylbenzene; 1.15 mmol; 1.15 equiv.) in anhydrous THF (2.5 mL) was cooled to -72 °C and a solution of ethyl 6-isobutyl-[2,2']-bipyridine-5-carboxylate (116f) (270 mg; 1.00 mmol) in anhydrous THF (5 mL) was added upon which the mixture turned dark immediately. After stirring for 80 min purified benzaldehyde (0.25 mL; 2.46 mmol; 2.46 equiv.) was added and the stirring was continued for another 30 min before warming to room temperature. The mixture was washed with an aqueous solution of Na_2CO_3 (5 mL) and the aqueous phase was extracted with diethyl ether (2x 2.5 mL). The combined organic extracts were dried over K_2CO_3 and the solvent was evaporated. ^{1}H-NMR spectroscopy of the crude mixture showed no identifiable product.

With sodium ethanolate

Note: all glassware was dried at >100 °C under vacuum and flushed with nitrogen prior to the experiment.

A solution of sodium ethanolate (102 mg; 1.50 mmol; 1.50 equiv.) in anhydrous THF (5 mL) was cooled to 0 °C and a solution of ethyl 6-isobutyl-[2,2']-bipyridine-5-carboxylate (116f) (270 mg; 1.00 mmol) in anhydrous THF (5 mL) was and the mixture was stirred for 30 min after which purified benzaldehyde (0.24 mL; 2.36 mmol; 2.36 equiv.) was added. After warming to room temperature and stirring for another 30 min the mixture was washed with an aqueous solution of Na_2CO_3 (5 mL) and the aqueous phase was extracted with diethyl ether (2x 2.5 mL). The combined organic extracts were dried over K_2CO_3 and the solvent was evaporated. ^{1}H-NMR spectroscopy of the crude mixture showed no identifiable product.

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A convenient synthesis of 2,2'-bipyridine derivatives

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Abstract—Picolinates **7** were prepared from the corresponding α-chloro-β-keto-esters **6**. Esters **7** were converted into 2,2'-bipyridine derivatives **10** via triazines **9** using an aza Diels–Alder reaction.
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In a series of previous Letters,[1–4] we have described the synthesis of triazines **3** from readily available amidrazones **1** and hydrated α,β-diketo-esters **2** or their equivalents (Scheme 1). These triazines **3** reacted with 2,5-norbornadiene **5** affording pyridine derivatives **4** in an inverse electron-demand aza Diels–Alder reaction. Alternatively, pyridines **4** could be prepared directly from a mixture of amidrazones **1**, α,β-diketo-esters **2** and 2,5-norbornadiene **5** in a convenient 'one-pot' reaction.

In our preliminary work,[1–3] α,β-diketo-esters **2** were prepared by a diazo-transfer reaction between commercially available β-keto-esters and tosyl azide giving the corresponding diazo-compounds [$R^2COC(N_2)CO_2Et$]. These diazo-compounds were subsequently treated with 'BuOCl affording α,β-diketo-esters **2**.[5] From a manufacturing perspective, the large scale use of these diazo-compounds would not be attractive and their replacement by other α,β-diketo-ester equivalents would be highly desirable. Alternative methods of preparing α,β-diketo-esters **2** similarly have other drawbacks: for example, α,β-diketo-esters are commonly prepared by ozonolysis of phosphorane precursors [$R^2COC(=PPh_3)$-CO_2Et][6], which generates large quantities of triphenylphosphine oxide as an unwanted by-product. In view of these limitations, the preparation of α-acetoxy-α-chloro-β-keto-esters as α,β-diketo-ester **2** equivalents was developed and published in a preliminary form.[4]

In this Letter we describe an alternative synthesis of α,β-diketo-esters **2** and their application to the preparation of 2,2'-bipyridine derivatives. 2,2'-Bipyridine derivatives were chosen as targets because of their current interest as ligands in a wide range of contemporary metal-catalysed processes.[7]

The oxidation of α-hydroxy-β-keto-esters **8** (Scheme 2) was envisaged as a suitable method for the synthesis of compounds **2** and picolinate esters **7** were chosen as suitable precursors of compounds **8**. Picolinates **7** were readily prepared from picolinic acid and α-chloro-β-keto-esters **6** under basic conditions in good overall yield.[8] Furthermore, compounds **7** did not require purification and could be used directly in subsequent reactions. The facile cleavage of picolinate esters in the presence of copper salts is well known[9] and this reaction was used to generate α-hydroxy-β-keto-esters **8** in situ. Thus, when picolinates **7** were treated with copper(II) acetate, compounds **8** were initially formed and were subsequently oxidised by the excess copper(II) acetate yielding the required α,β-diketo-esters **2**. After washing the reaction mixture with Na_2EDTA to remove copper salts, solutions of compounds **2** could then be reacted with amidrazone **1** (R^1 = 2-pyridyl) giving triazines **9**. Triazines **9** have been converted into the corresponding 2,2'-bipyridines **10** by an aza Diels–Alder reaction but it is more convenient to transform α,β-diketo-esters **2** directly into 2,2'-bipyridines **10**.[10] Thus, after reacting picolinates **7** with copper(II) acetate, the resulting α,β-diketo-esters **2** were dissolved in ethanol and amidrazone **1** (R^1 = 2-pyridyl) and 2,5-norbornadiene **5** were added. After heating at reflux the required 2,2'-bipyridines **10** were obtained.
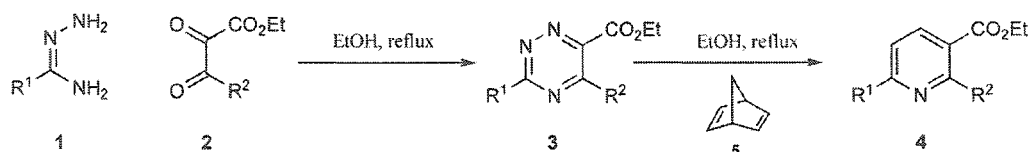
Scheme 1. Synthesis of pyridines **4**.
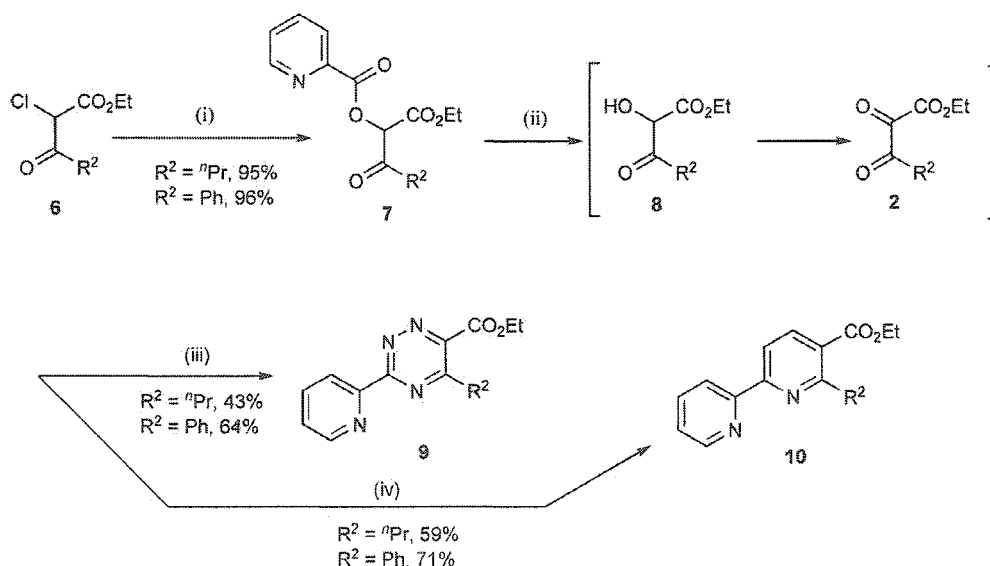
Scheme 2. Synthesis of bipyridines **10**. Reagents and conditions: (i) picolinic acid, $KHCO_3$, DMF, rt; (ii) $Cu(OAc)_2$, MeOH, CH_2Cl_2 then Na_2EDTA; (iii) amidrazone **1** (R^1 = 2-pyridyl), EtOH, reflux; (iv) amidrazone **1** (R^1 = 2-pyridyl), **5**, EtOH, reflux.

In summary, picolinates **7** are readily prepared and can be used as convenient sources of α,β-diketo-esters **2**. 2,2′-Bipyridines **10** can be prepared from the reaction of compounds **2**, amidrazone **1** (R^1 = 2-pyridyl) and 2,5-norbornadiene **5**. This methodology compliments our other studies directed at the preparation and application of readily available α,β-diketo-esters **2** equivalents.[4]

Acknowledgements

References and notes

1. Stanforth, S. P.; Tarbit, B.; Watson, M. D. *Tetrahedron Lett.* **2002**, *43*, 6015–6017.

2. Stanforth, S. P.; Tarbit, B.; Watson, M. D. *Tetrahedron Lett.* **2003**, *44*, 693–694.

3. Stanforth, S. P.; Tarbit, B.; Watson, M. D. *Tetrahedron* **2004**, *60*, 8893–8897.

4. Altuna-Urquijo, M.; Stanforth, S. P.; Tarbit, B. *Tetrahedron Lett.* **2005**, *46*, 6111–6113.

5. Detering, J.; Martin, H.-D. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 695–698.

6. Wasserman, H. H.; Parr, J. *Acc. Chem. Res.* **2004**, *37*, 687–701.

7. See, for example: (a) Malkov, A. V.; Baxendale, I. R.; Bella, M.; Langer, V.; Fawcett, J.; Russell, D. R.; Mansfield, D. J.; Valko, M.; Kočovský, P. *Organometallics* **2001**, *20*, 673–690; (b) Puglisi, A.; Benaglia, M.; Annunziata, R.; Bologna, A. *Tetrahedron Lett.* **2003**, *44*, 2947–2951; (c) Fletcher, N. C. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1831–1842; (d) Malkov, A. V.; Pernazza, D.; Bell, M.; Bella, M.; Massa, A.; Teply, F.; Meghani, P.; Kočovský, P. *J. Org. Chem.* **2003**, *68*, 4727–4742; (e) Bouet, A.; Heller, B.; Papamicaël, C.; Dupas, G.; Oudeyer, S.; Marsais, F.; Levacher, V. *Org. Biomol. Chem.* **2007**, 1397–1404.

8. *Ethyl 2-picolinoyl-3-oxo-3-phenylpropanoate* **7** (R^2 = Ph): To a stirred ice-cold solution of picolinic acid (13.6 g; 110 mmol) in DMF (150 mL) was added $KHCO_3$ (8.84 g, 88.3 mmol). After warming to room temperature, compound **6** (R^2 = Ph) (10.0 g; 44.1 mmol) was added and the solution was left stirring at room temperature until the reaction was judged complete by TLC (8 days). The solution was poured into water (100 mL), extracted with CH_2Cl_2 and the combined organic fractions were washed with water (4 × 200 mL), dried ($MgSO_4$) and evaporated giving the product (12.7 g, 96%) as a viscous orange liquid. IR: ν_{max}/cm^{-1} 2984, 1748 (C=O), 1694 (C=O), 1598, 1583, 1450, 1372, 1237, 1128, 1023, 748, 703. ^{1}H NMR: (270 MHz, $CDCl_3$) δ = 8.81 (ddd, 1H, J = 1.0, 1.7 and 4.7 Hz, Py–*H*), 8.20 (ddd, 1H, J = 1.0, 1.2 and 7.9 Hz, Py–*H*), 8.09 (m, 2H, Ph–*H*), 7.86 (ddd, 1H, J = 1.7, 7.7 and 7.9 Hz, Py–*H*), 7.64 (tt, 1 H, J = 1.4 and 7.3 Hz, Ph–*H*), 7.55–7.48 (m, 3H, Py–*H* and Ph–*H*), 6.64 (s, 1H,

CHOPic), 4.30 (q, 2H, $J = 7.2$ Hz, ester–CH_2–), 1.24 (t, 3H, $J = 7.2$ Hz, ester–CH_3) ppm. ^{13}C NMR: (68 MHz, CDCl$_3$) $\delta = 189.30$ (CO), 164.95 (CO), 163.58 (CO), 150.43 (CH), 146.67 (CH), 137.21 (CH), 134.41 (CH), 134.26 (C), 129.42 (CH), 128.92 (CH), 127.60 (CH), 125.97 (CH), 75.31 (CH), 62.77 (CH$_2$), 14.01 (CH$_3$) ppm. HRMS (EI): calcd for C$_{17}$H$_{15}$NO$_5$ (M+H)$^+$: 314.1023. Found: 314.1021. *Ethyl 2-picolinoyl-3-oxo-3-hexanoate* **7** (R^2 = ^{n}Pr): Using a similar procedure to that described above compound **7** (R^2 = ^{n}Pr) (95%) was obtained as a viscous orange liquid. IR: v_{max}/cm^{-1} 2968, 1732 (C=O), 1128. ^{1}H NMR: (270 MHz, CDCl$_3$) $\delta = 8.82$ (ddd, 1H, $J = 1.0$, 1.7 and 4.7 Hz, Py–H), 8.23 (ddd, 1H, $J = 1.0$, 1.2 and 7.9 Hz, Py–H), 7.89 (ddd, 1H, $J = 1.7$, 7.7 and 7.9 Hz, Py–H), 7.54 (ddd, 1H, $J = 1.2$, 4.7 and 7.7 Hz, Py–H) 5.81 (s, 1H, CHOPy), 4.33 (q, 2H, $J = 7.2$ Hz, ester–CH_2–), 2.77 (t, 2 H, $J = 7.2$ Hz, CH$_3$–CH$_2$–CH_2–), 1.70 (sextet, 2H, $J = 7.2$ Hz, CH$_3$–CH_2–CH$_2$–), 1.33 (t, 3H, $J = 7.2$ Hz, ester–CH_3), 0.96 (t, 3H, $J = 7.2$ Hz, propyl–CH_3) ppm. ^{13}C NMR: (68 MHz, CDCl$_3$) $\delta = 199.55$ (CO), 164.48 (CO), 163.66 (CO), 150.41 (CH), 146.73 (C), 137.21 (CH), 127.60 (CH), 125.88 (CH), 78.33 (CH), 62.72 (CH$_2$), 41.84 (CH$_2$), 16.70 (CH$_2$), 14.13 (CH$_3$), 13.58 (CH$_3$) ppm. HRMS (EI): calcd for C$_{14}$H$_{17}$NO$_5$ (M+H)$^+$: 280.1179. Found: 280.1180.

9. Sammakia, T.; Jacobs, J. S. *Tetrahedron Lett.* **1999**, *40*, 2685–2688.

10. *Typical procedures: Ethyl 6-phenyl-[2,2']-bipyridine-5-carboxylate* **10** (R^2 = Ph): A mixture of compound **7** (R^2 = Ph) (1.00 g; 3.32 mmol), Cu(OAc)$_2$ (1.32 g; 6.63 mmol; 2.0 equiv) and ethanol (2 mL) in DCM (50 mL) was stirred at room temperature for one day. The reaction was diluted with hexanes (20 mL) and washed with Na$_2$EDTA (0.1 M aqueous solution) until the aqueous phase remained colourless. The organic phase was dried over MgSO$_4$, filtered and evaporated. The resulting oil was taken up in ethanol (50 mL), compound **1** (R^1 = 2-pyridyl) (361 mg; 2.65 mmol; 0.8 equiv) and 2,5-norbornadiene **5** (2.9 mL; 26.5 mmol; 8.0 equiv) were added and the solution was heated at reflux under a nitrogen atmosphere for 2 days. After cooling to room temperature the mixture was poured onto water and extracted with CH$_2$Cl$_2$. The organic layer was washed with water, dried (MgSO$_4$) and evaporated. The crude mixture was purified by column chromatography (silica gel: diethyl ether) giving the product (570 mg; 71%) identical with an authentic sample.[3] *Ethyl 6-propyl-[2,2']-bipyridine-5-carboxylate* **10** (R^2 = ^{n}Pr): Using a similar procedure to that described above, compound **10** (R^2 = ^{n}Pr) (59%) was obtained, identical with an authentic sample.[3]

A convenient synthesis of substituted 2,2':6',2"-terpyridines

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ABSTRACT

The 2,2':6',2"-terpyridines 8a and 8b were prepared in good yield by reacting α-acetoxy-α-chloro-β-keto-esters 1 (R^1 = ^{n}Pr and Ph) with the bis-amidrazone 7 and 2,5-norbornadiene 5 in ethanol at reflux.

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2,2':6',2"-Terpyridines have found extensive use in both coordination chemistry and supramolecular chemistry, and consequently synthetic approaches to this important class of ligand have attracted considerable attention.[1] We have previously described a convenient methodology that has enabled the preparation of 2,2'-bipyridine derivatives,[2–6] and in this Letter we disclose how this work has been extended and adapted to allow the synthesis of 2,2':6',2"-terpyridines.

We have demonstrated that readily available α-acetoxy-α-chloro-β-keto-esters 1 are synthetic equivalents of α,β-diketo-es-

ters 2,[5] which reacted with amidrazones 3 yielding triazines 4. An aza Diels–Alder reaction of these triazines using 2,5-norbornadiene 5 as an acetylene equivalent (or with other aza dienophiles)[5,6] furnished pyridine derivatives 6 (Scheme 1). The substituted pyridines 6 could also be produced in a 'one-pot' reaction directly from compounds 1, amidrazones 3 and 2,5-norbornadiene 5 in ethanol solution at reflux without isolating the triazines 4. When the amidrazone 3 had R^2 = 2-pyridyl, then 2,2'-bipyridines were formed.

When the bis-amidrazone 7 (available from the reaction of 2,6-dicyanopyridine with hydrazine)[7] was reacted with
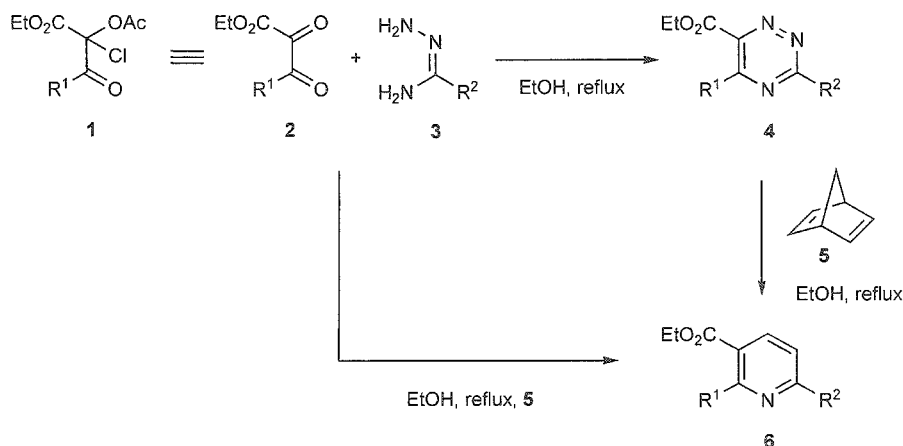
Scheme 1. Synthesis of substituted pyridines.[5]

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7

8a R = ^{n}Pr
8b R = Ph

9a R = ^{n}Pr
9b R = Ph
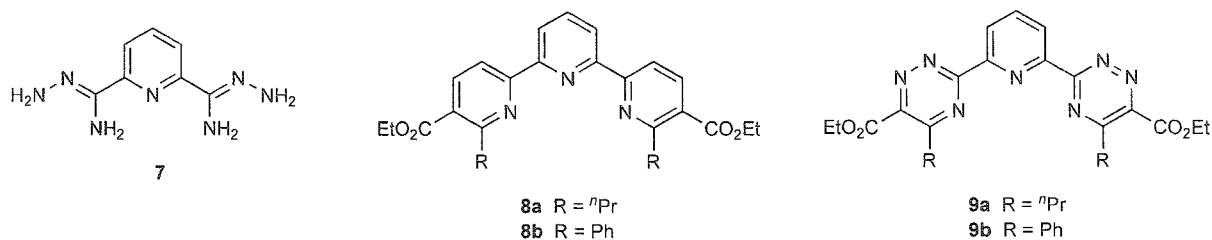
α-acetoxy-α-chloro-β-keto-esters **1** (R^1 = ^{n}Pr or Ph) in the presence of an excess of 2,5-norbornadiene **5** in ethanol at reflux, the 2,2′: 6′,2″-terpyridine derivatives **8a** (60%) and **8b** (76%) were obtained following the general sequence outlined above in Scheme 1 without isolation of the corresponding triazine intermediates **9a** and **9b**.[8,9] The structures of the products **8a** and **8b** were fully supported by their spectroscopic data.[8] This method of constructing the 2,2′:6′,2″-terpyridine nucleus is versatile in view of the availability of compounds **1** (from β-keto-esters)[5] and 2,6-dicyanopyridine (commercially available or readily prepared from the inexpensive pyridine-2,6-dicarboxylic acid). Additionally, the reactivity of 1,2,4-triazines towards aza dienophiles other than 2,5-norbornadiene **5** is well known (e.g., enamines)[10] and hence the introduction of additional substituents in the lateral pyridine rings of the 2,2′:6′,2″-terpyridine system should be feasible.

We have therefore demonstrated that our general route to pyridine derivatives depicted in Scheme 1 can be conveniently applied to 2,2′:6′,2″-terpyridine synthesis.

Acknowledgement

References and notes

1. Constable, E. C. Chem. Soc. Rev. **2007**, 36, 246–253.
2. Stanforth, S. P.; Tarbit, B.; Watson, M. D. Tetrahedron Lett. **2002**, 43, 6015–6017.
3. Stanforth, S. P.; Tarbit, B.; Watson, M. D. Tetrahedron Lett. **2003**, 44, 693–694.
4. Stanforth, S. P.; Tarbit, B.; Watson, M. D. Tetrahedron **2004**, 60, 8893–8897.
5. Altuna-Urquijo, M.; Stanforth, S. P.; Tarbit, B. Tetrahedron Lett. **2005**, 46, 6111–6113.
6. Gehre, A.; Stanforth, S. P.; Tarbit, B. Tetrahedron Lett. **2007**, 48, 6974–6976.
7. Case, F. H. J. Heterocycl. Chem. **1971**, 8, 1043–1046.
8. Compound **8a**: To a solution of compound **1** (R^1 = ^{n}Pr) (501 mg; 2.00 mmol; 2.0 equiv) in EtOH (3 mL) was added MeNH$_2^9$ (0.49 mL; 33% w/w in EtOH; 4.00 mmol; 4.0 equiv) and the mixture was stirred at room temperature for 1 h. The bis-amidrazone **7** (193 mg; 1.00 mmol) and 2,5-norbornadiene **5** (2.15 mL; 20.0 mmol; 20.0 equiv) were added and the mixture was heated under reflux for 20 h. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography [ethyl acetate/petroleum ether (bp 40–60 °C) (1:4)] giving compound **8a** as an off-white solid (279 mg; 60%), mp 105–106 °C (from EtOH). IR (diamond anvil): ν 1721 cm^{-1}. ^{1}H NMR: (270 MHz, CDCl$_3$) δ 8.59 (d, 2H, J = 7.9 Hz), 8.47 (d, 2H, J = 8.3 Hz), 8.30 (d, 2H, J = 8.3 Hz), 7.91 (t, 1H, J = 7.9 Hz), 4.42 (q, 4H, J = 7.2 Hz), 3.26–3.20 (m, 4H), 1.94–1.80 (m, 4 H), 1.44 (t, 6H, J = 7.2 Hz), 1.06 (t, 6H, J = 7.2 Hz) ppm. ^{13}C NMR: (65 MHz, CDCl$_3$) δ 167.01, 162.79, 157.48, 154.94, 139.42, 137.95, 125.41, 122.31, 117.85, 61.34, 39.05, 23.02, 14.37, 14.30 ppm. HRMS (ES) for C$_{27}$H$_{32}$N$_3$O$_4$ [M+H]$^+$: calcd: 462.2387; measured: 462.2394. Compound **8b** (76%) was prepared using a similar procedure to that described above, mp 156–157 °C (from EtOH). IR (diamond anvil) ν 1704 cm^{-1}. ^{1}H NMR: (270 MHz, CDCl$_3$) δ 8.67 (d, 2H, J = 8.2 Hz), 8.62 (d, 2H, J = 7.9 Hz), 8.27 (d, 2H, J = 8.2 Hz), 7.93 (t, 1H, J = 7.9 Hz), 7.69–7.63 (m, 4H), 7.51–7.43 (m, 6H), 4.19 (q, 4H, J = 7.2 Hz), 1.07 (t, 6H, J = 7.2 Hz) ppm. ^{13}C NMR: (65 MHz, CDCl$_3$) δ 168.42, 158.35, 157.17, 154.60, 140.49, 139.04, 138.01, 128.92, 128.76, 128.15, 127.13, 122.57, 118.76, 61.57, 13.78 ppm. HRMS (EI) for C$_{33}$H$_{28}$N$_3$O$_4$ [M+H]$^+$: calcd: 530.2074; measured: 530.2079.
9. Methylamine is added to compounds **1** prior to their reactions with amidrazones. We believe that the methylamine reacts at the acetoxy carbonyl group generating compounds **2** by de-acylation followed by chloride elimination. If methylamine is not added, then we have found that 2 equiv of the chloroacetate **1** are required for each R(NH$_2$)C=NNH$_2$ functional group.
10. For a recent example in 2,2′:6′,2″-terpyridine chemistry see: Kozhevnikov, V. N.; Whitwood, A. C.; Bruce, D. W. Chem. Commun. **2007**, 3826–3828.

BIBLIOGRAPHY

1 Henry, G. D. 'De novo synthesis of substituted pyridines', *Tetrahedron* **2004**, *60*, 6043-6061.

2 Brody, F. and Ruby, P. R. Synthetic and Natural Sources of the Pyridines Ring, in E. Klingsberg (ed.) *The Chemistry of Heterocyclic Compounds. Pyridine and Its Derivatives*, London: Interscience Publishers, **1960**, pp. 102-113 and references therein.

3 Dyke, S. F. The Vitamins B_6, in *The chemistry of natural products Vol. 6: The chemistry of the vitamins*, London: Interscience Publishers, **1965**, pp. 75-96.

4 Spande, T. F., Garaffo, H. M., Edwards, M. W., Yeh, H. J. C., Pannell, L. and Daly, J. W. 'Epibatidine: A Novel (Chloropyridyl)azabicycloheptane with Potent Analgesic Activity from an Ecuadoran Poison Frog', *J. Am. Chem. Soc.* **1992**, *114*, 3475-3478; Broka, C. A. 'Total Synthesis of Epibatidine', *Tetrahedron Lett.* **1993**, *34*, 3251-3254.

5 Humphreys, A. 'Med Ad News 200 - World's Best-Selling Medicines' in *MedAdNews* July **2007**.

6 Kaes, C., Katz, A. and Howweini, M. W. 'Bipyridine: The Most Widely Used Ligand. A Review of Molecules Comprising at Least Two 2,2'-Bipyridine Units', *Chem. Rev.* **2000**, *100*, 3553-3590.

7 Hara, H. and Ohta, N. 'Synergistic Extraction of Manganese(II) in the Presence of Cobalt(II) with Benzoylacetone and 2,2'-Bipyridine', *Nippon Kagaku Kaishi* **1979**, *1979*, 1061-1065; Taguchi, S., Hojjatie, M. and Freiser, H. 'Extraction of Lanthanides with 8-Quinolinol in the Presence of 6-Amino-4,4'-(5-Nonyl)-2,2'-Bipyridine', *Anal. Chim. Acta* **1987**, *197*, 333-337; Nakamura, S. and Suzuki, N. 'Synergic Extraction of Lanthanide(III) Ions with 2-Thenoyltrifluoroacetone in the Presence of 2,2'-Bipyridine or Pyridine', *Polyhedron* **1988**, *7*, 155-159; Yamada, M., Kishii, N., Araki, K. and Shiraishi, S. 'Extraction and Release of Divalent Metal-Ions by 6,6'-Diamino-2,2'-Bipyridine Supported on Polymer Beads', *Nippon Kagaku Kaishi* **1989**, 988-992; Regnouf-de-Vains, J. B., Dalbavie, J. O., Lamartine, R. and Fenet, B. 'Quantitative solvent extraction from neutral aqueous nitrate media of silver(I) against lead(II) with a new calix[4]arene-based bipyridine podand', *Tetrahedron Lett.* **2001**, *42*, 2681-2684; Kavallieratos, K., Rosenberg, J. M. and Bryan, J. C. 'Pb(II) Coordination and Synergistic Ion-Exchange Extraction by Combinations of Sulfonamide Chelates and 2,2'-Bipyridine', *Inorg. Chem.* **2005**, *44*, 2573-2575; Bai, Y. and Yang, H. J. 'Metal Ion Extraction Using Newly-synthesized Bipyridine Derivative as a Chelating Reagent in Supercritical CO_2', *Anal. Sci.* **2006**, *22*, 1469-1471; Narbutt, J. and Krejzler, J. 'Neutral bidentate *N*-heterocyclic ligands - phase transfer reagents improving the kinetics of solvent extraction of Am(III) and Eu(III) ions with tetradentate 6,6'-bis-(diethyl-1,2,4-triazin-3-yl)-2,2'-bipyridine', *Radiochim. Acta* **2008**, *96*, 219-223.

8 Davies, D. T., Kapur, N. and Parsons, A. F. 'Preparation of *N*-Heterocycles by Radical Cyclisation of Enamides Mediated by Manganese(III) or Copper(I). A Comparison of Cyclisation Methods', *Tetrahedron* **2000**, *56*, 3941-3949.

9 Malkov, A. V., Baxendale, I. R., Bella, M., Langer, V., Fawcett, J., Russell, D. R., Mansfield, D. J., Valko, M. and Kocovsky, P. 'Synthesis of New Chiral 2,2'-Bipyridyl-Type Ligands, Their Coordination to Molybdenum(0), Copper(II), and Palladium(II), and Application in Asymmetric Allylic Substitution, Allylic Oxidation, and Cyclopropanation', *Organometallics* **2001**, *20*, 673-690; Malkov, A. V., Pernazza, D., Bell, M., Bella, M., Massa, A., Teply, F., Meghani, P. and

Kocovsky, P. 'Synthesis of New Chiral 2,2'-Bipyridine Ligands and Their Application in Copper-Catalyzed Asymmetric Allylic Oxidation and Cyclopropanation', *J. Org. Chem.* **2003**, *68*, 4727-4742.

10 Puglisi, A., Benaglia, M., Annuniziata, R. and Bologna, A. 'Enantiomerically pure phenanthroline or bipyridine containing macrocycles: a new class of ligands for asymmetric catalysis', *Tetrahedron Lett.* **2003**, *44*, 2947-2951; Fletcher, N. C. 'Chiral 2,2'-bipyridines: ligands for asymmetric induction', *J. Chem. Soc., Perkin Trans. 1* **2002**, *2002*, 1831-1842; Bouet, A., Heller, B., Papamicael, C., Dupas, G., Oudeyer, S., Marsais, F. and Levacher, V. 'Preparation of new axially chiral bridged 2,2'-bipyridines and pyridyl monooxazolines (pymox). Evaluation in copper(I)-catalyzed enantioselective cyclopropanation', *Org. Biomol. Chem.* **2007**, *5*, 1397-1404.

11 Chelucci, G. and Thummel, R. P. 'Chiral 2,2'-Bipyridines, 1,10-Phenanthrolines, and 2,2':6',2"-Terpyridines: Syntheses and Applications in Asymmetric Homogeneous Catalysis', *Chem. Rev.* **2002**, *102*, 3129-3170.

12 Chelucci, G., Murineddu, G. and Pinna, G. A. 'Chiral pyridine *N*-oxides: useful ligands for asymmetric catalysis', *Tetrahedron: Asymmetry* **2004**, *15*, 1373-1389; Chelucci, G. 'Synthesis and application in asymmetric catalysis of camphor-based pyridine ligands', *Chem. Soc. Rev.* **2006**, *35*, 1230-1243; Kwong, H. L., Yeung, H. L., Yeung, C. T., Lee, W. S., Lee, C. S. and Wong, W. L. 'Chiral pyridine-containing ligands in asymmetric catalysis', *Coord. Chem. Rev.* **2007**, *251*, 2188-2222.

13 Sun, L. C., Hammarstrom, L., Akermark, B. and Styring, S. 'Towards artificial photosynthesis: ruthenium-manganese chemistry for energy production', *Chem. Soc. Rev.* **2001**, *30*, 36-49; Herrmann, C., Neugebauer, J., Presselt, M., Uhlemann, U., Schmitt, M., Rau, S., Popp, J. and Reiher, M. 'The First Photoexcitation Step of Ruthenium-Based Models for Artificial Photosynthesis Highlighted by Resonance Raman Spectroscopy', *J. Phys. Chem. B* **2007**, *111*, 6078-6087; Chakraborty, S., Wadas, T. J., Hester, H., Schmehl, R. and Eisenberg, R. 'Platinum Chromophore-Based Systems for Photoinduced Charge Separation: A Molecular Design Approach for Artificial Photosynthesis', *Inorg. Chem.* **2005**, *44*, 6865-6878.

14 Lawrence, D. S., Jiang, T. and Levett, M. 'Self-Assembling Supramolecular Complexes', *Chem. Rev.* **1995**, *95*, 2229-2260; Newkome, G. R., Patri, A. K., Holder, E. and Schubert, U. S. 'Synthesis of 2,2'-Bipyridines: Versatile Building Blocks for Sexy Architectures and Functional Nanomaterials', *Eur. J. Org. Chem.* **2004**, *2004*, 235-254.

15 Mamula, O. and von Zelewsky, A. 'Supramolecular coordination compounds with chiral pyridine and polypyridine ligands derived from terpenes', *Coord. Chem. Rev.* **2003**, *242*, 87-95.

16 Song, Q. J., Greenway, G. M. and McCreedy, T. 'Tris(2,2'-bipyridine)ruthenium(II) electrogenerated chemiluminescence of alkaloid type drugs with solid phase extraction sample preparation', *Analyst* **2001**, *126*, 37-40; Keefe, M. H., Benkstein, K. D. and Hupp, J. T. 'Luminescent sensor molecules based on coordinated metals: a review of recent developments', *Coord. Chem. Rev.* **2000**, *205*, 201-228.

17 Hantzsch, A. 'Condensationsprodukte aus Aldehydammoniak und Ketonartigen Verbindungen', *Ber. Dtsch. Chem. Ges.* **1881**, *14*, 1637-1638.

18 Bohlmann, F. and Rahtz, D. 'Über eine neue Pyridinsynthese', *Chem. Ber.* **1957**, *90*, 2265-2272.

19 Guareschi, I. **1901**, 579; Guareschi, I. *Gazz. Chim. Ital.* **1919**, *49*, 126.

20 Kröhnke, F. 'The Specific Synthesis of Pyridines and Oligopyridines', *Synthesis* **1976**, *1976*, 1-24.

21 Sandford, G., Wilson, I. and Timperley, C. M. 'Diels-Alder reactions of trifluoromethyl alkenes with 5-ethoxyoxazoles: synthesis of trifluoromethylated pyridine derivatives', *J. Fluorine Chem.* **2004**, *125*, 1425-1430.

22 Bondock, S. 'One-Pot Synthesis of Pyridine Derivatives via Diels-Alder Reactions of 2,4-Dimethyl-5-methoxyoxazole', *Heteroatom Chem.* **2005**, *16*, 49-55; Bringmann, G. and Schneider, S. 'Rational synthesis of deuterium-labelled pyridoxal and pyridoxyl alkaloids', *Tetrahedron Lett.* **1986**, *27*, 175-180; Firestone, R. A., Harris, E. E. and Reuter, W. 'Synthesis of Pyridoxine by Diels-Alder Reactions with 4-Methyl-5-alkoxy Oxazoles', *Tetrahedron* **1967**, *23*, 943-955.

23 Yamamoto, Y., Kinpara, K., Nishiyama, H. and Itoh, K. 'Synthesis of 2-Haloalkylpyridines *via* Cp*RuCl-Catalyzed Cycloaddition of 1,6-Diynes with α-Halonitriles. Unusual Halide Effect in Catalytic Cyclocotrimerization', *Adv. Synth. Catal.* **2005**, *347*, 1913-1916; Yamamoto, Y., Kinpara, K., Saigoku, F., Takagishi, H., Okuda, S., Nishiyama, H. and Itoh, K. 'Cp*RuCl-Catalyzed [2 + 2 + 2] Cycloadditions of α,ω-Diynes with Electron-Deficient Carbon-Heteroatom Multiple Bonds Leading to Heterocycles', *J. Am. Chem. Soc.* **2005**, *127*, 605-613.

24 Diels, O. and Alder, K. 'Synthesen in der hydroaromatischen Reihe', *Liebigs Ann. Chem.* **1928**, *460*, 98-122.

25 Stocking, E. M. and Williams, R. M. 'Chemistry and Biology of Biosynthetic Diels-Alder Reactions', *Angew. Chem., Int. Ed. Engl.* **2003**, *42*, 3078-3115; Nicolaou, K. C., Snyder, S. A., Montagnon, T. and Vassilikogiannakis, G. 'The Diels-Alder Reaction in Total Synthesis', *Angew. Chem., Int. Ed. Engl.* **2002**, *41*, 1668-1698.

26 Ess, D. H., Jones, G. O. and Houk, K. N. 'Conceptual, Qualitative, and Quantitative Theories of 1,3-Dipolar and Diels-Alder Cycloadditions Used in Synthesis', *Adv. Synth. Catal.* **2006**, *348*, 2337-2361.

27 Brückner, R. *Reaktionsmechanismen: organische Reaktionen, Stereochemie, moderne Synthesemethoden.* 2nd edn., Heidelberg: Spektrum, 2003.

28 Jorgensen, K. A. 'Catalytic Asymmetric Hetero-Diels-Alder Reactions of Carbonyl Compounds and Imines', *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 3558-3588.

29 Vogt, P. F. and Miller, M. J. 'Development and applications of amino acid derived chiral acylnitroso hetero Diels-Alder reactions', *Tetrahedron* **1998**, *54*, 1317-1348.

30 Boger, D. L. 'Diels-Alder Reactions of Azadienes', *Tetrahedron* **1983**, *39*, 2869-2939.

31 Boger, D. L. in B. M. Trost and I. Fleming (ed.) *Comprehensive organic synthesis*, Oxford: Pergamon, **1991**, pp. 451 - 512; Weinreb, S. M. in B. M. Trost and I. Fleming (ed.) *Comprehensive organic synthesis*, Oxford: Pergamon, **1991**, pp. 401-449.

32 Tietze, L. F. and Kettschau, G. in P. Metz (ed.) *Stereoselective Heterocyclic Synthesis I*, Berlin Heidelberg: Springer, **1997**, pp. 1-120.

33 Boger, D. L. 'Diels-Alder reactions of heterocyclic aza dienes: scope and applications', *Chem. Rev.* **1986**, *86*, 781-793.

34 Hajbi, Y., Suzenet, F., Khouili, M., Lazar, S. and Guillaumet, G. 'Polysubstituted 2,3-dihydrofuro[2,3-*b*]pyridines and 3,4-dihydro-2*H*-pyrano[2,3-*b*]pyridines via microwave-activated inverse electron demand Diels-Alder reactions', *Tetrahedron* **2007**, *63*, 8286-8297.

35 Taylor, E. C. and Macor, J. E. 'Intramolecular Diels-Alder Reactions of 1,2,4-Triazines. A Facile Synthesis of Thieno[2,3-*b*]pyridines and 3,4-Dihydro-2*H*-thiopyrano[2,3-*b*]pyridines', *J. Org. Chem.* **1987**, *52*, 4280-4287; Taylor, E. C., Macor, J. E. and Pont, J. L. 'Intramolecular Diels-Alder Reactions of 1,2,4-Triazines. A General Synthesis of Furo[2,3-*b*]pyridines, 2,3-Dihydropyrano[2,3-*b*]pyridines, and Pyrrolo[2,3-*b*]pyridines', *Tetrahedron* **1987**, *43*, 5145-5158; Taylor, E. C., Pont,

J. L. and Warner, J. C. 'Heterodienophilic Intramolecular Diels-Alder Reactions of 1,2,4-Triazines - Synthesis of Novel Polycyclic Condensed Pyrazines and Lumazines', *Tetrahedron* **1987**, *43*, 5159-5168.

36 Sauer, J. and Heldmann, D. K. 'Ethynyltributyltin - a Synthetic Equivalent for Acetylene, Aryl, Acyl and Halogeno Alkynes in [4+2] Cycloadditions', *Tetrahedron Lett.* **1998**, *39*, 2549-2552.

37 Boger, D. L., Cassidy, K. C. and Nakahara, S. 'Total synthesis of streptonigrone', *J. Am. Chem. Soc.* **1993**, *115*, 10733-10741.

38 Burg, B., Dittmar, W., Reim, H., Steigel, A. and Sauer, J. 'Reaktionen sechsgliedriger Heterocyclen mit Ketenacetalen', *Tetrahedron Lett.* **1975**, *16*, 2897-2900.

39 Boger, D. L. and Panek, J. S. 'Pyridine Construction via Thermal Cycloaddition of 1,2,4-Triazines with Enamines: Studies on the Preparation of the Biaryl CD Rings of Streptonigrin', *J. Org. Chem.* **1982**, *47*, 3763-3765; Boger, D. L. and Panek, J. S. 'Diels-Alder Reaction of Heterocyclic Azadienes. 1. Thermal Cycloaddition of 1,2,4-Triazines with Enamines: Simple Preparation of Substituted Pyridines', *J. Org. Chem.* **1981**, *46*, 2179-2182; Dittmar, W., Sauer, J. and Steigel, A. '(4+2)-Cycloadditionen der 1.2.4-Triazine - ein neuer Weg zu 4-H-Azepinen', *Tetrahedron Lett.* **1969**, *10*, 5171-5174.

40 Benson, S. C., Gross, J. L. and Snyder, J. K. 'Indole as a Dienophile in Inverse Electron Demand Diels-Alder Reactions: Reactions with 1,2,4-Triazines and 1,2-Diazine', *J. Org. Chem.* **1990**, *55*, 3257-3269.

41 Lahue, B. R., Lo, S.-M., Wan, Z.-K., Who, G. H. C. and Snyder, J. K. 'Intramolecular Inverse-Electron-Demand Diels-Alder Reactions of Imidazoles with 1,2,4-Triazines: A New Route to 1,2,3,4-Tetrahydro-1,5-naphthyridines and Related Heterocycles', *J. Org. Chem.* **2004**, *69*, 7171-7182.

42 Boger, D. L., Panek, J. S. and Meier, M. M. 'Diels-Alder Reaction of Heterocyclic Azadienes. 2. "Catalytic" Diels-Alder Reaction of in Situ Generated Enamines with 1,2,4-Triazines. General Pyridine Annulation', *J. Org. Chem.* **1982**, *47*, 895-897.

43 Benson, S. C., Lee, L., Yang, L. and Snyder, J. K. 'Intramolecular Inverse Electron Demand Diels-Alder Reactions of Tryptamine with Tethered Heteroaromatic Azadienes', *Tetrahedron* **2000**, *56*, 1165-1180.

44 Gonsalves, A. M. d. A. R., Melo, T. M. V. D. P. e. and Gilchrist, T. L. 'Diels-Alder Reactions of 1,2,4-Triazines with Cyclic Vinyl Ethers', *Tetrahedron* **1993**, *49*, 5277-5290.

45 Ohsumi, T. and Neunhoeffer, H. 'Synthesis of 1,2,4-Triazines, XII. New Synthesis of 1,2,4-Triazines with a Functional-Group in the 6-Position', *Tetrahedron* **1992**, *48*, 651-662.

46 Paudler, W. W. and Chen, T. K. '1,2,4-Triazines. III. A Convenient Synthesis of 1,2,4-Triazines and Their Covalent Hydration', *J. Heterocyclic Chem.* **1970**, *7*, 767-771.

47 Rubin, M. B. and Gleiter, R. 'The Chemistry of Vicinal Polycarbonyl Compounds', *Chem. Rev.* **2000**, *100*, 1121-1164.

48 Sachs, F. and Barschall, H. 'Über das Triketopentan. I', *Ber. Dtsch. Chem. Ges.* **1901**, *34*, 3047-3054; Sachs, F. and Herold, V. 'Über Triketone. IV', *Ber. Dtsch. Chem. Ges.* **1907**, *40*, 2714-2730.

49 Dahn, H. and Hauth, H. 'Über die Synthese von Acetessigester-[1-^{14}C] und α,β-Diketobuttersäureester-[1-^{14}C]. 12. Mitteilung über Reduktone und 1,2,3-Tricarbonylverbindungen', *Helv. Chim. Acta* **1959**, *42*, 1214-1224.

50 Schipper, E., Cinnamon, M., Raschev, L., Chinng, Y. H. and Oroshnik, W. 'Oxidation of active methylenes by dimethyl sulfoxide: A new ninhydrin synthesis',

Tetrahedron Lett. **1968**, *9*, 6201-6204; Wolfe, S., Berry, J. E. and Peterson, M. R. 'Stereomutation of 1,2,3-triketone: an example of an asymmetric reaction', *Can. J. Chem.* **1976**, *54*, 210-217.

51 Dayer, F., Dao, H. L., Rodegowa.H, Dahn, H. and Gold, H. 'Zur Herstellung von 1,2,3-Tricarbonylverbindungen aus 1,3-Dicarbonylverbindungen. 27. Mitteilung über Reduktone und Tricarbonylverbindungen', *Helv. Chim. Acta* **1974**, *57*, 2201-2209.

52 Wasserman, H. H. and Han, W. T. 'Vicinal Tricarbonyl Products from Singlet Oxygen Reactions. Application to the Synthesis of Carbacephams', *Tetrahedron Lett.* **1984**, *25*, 3743-3746.

53 Neufville, R. d. and Pechmann, H. v. 'Ueber das Diphenyltriketon', *Ber. Dtsch. Chem. Ges.* **1890**, *23*, 3375-3387; Mahran, M. R., Abdou, W. M., Sidky, M. M. and Wamhoff, H. 'Singlet-Oxygen Photolysis of Dihaloketones. A Facile and Efficient Approach to Vicinal Triketones and Their Monohydrates', *Synthesis* **1987**, *1987*, 506-508.

54 Hoffman, R. V., Kim, H. O. and Wilson, A. L. '2-(((p -Nitrophenyl)sulfonyl)oxy)-3-keto Esters: Versatile Intermediates for the Preparation of 1,2,3-Tricarbonyl Compounds', *J. Org. Chem.* **1990**, *55*, 2820-2822; Hoffman, R. V., Wilson, A. L. and Kim, H. O. 'Synthesis of 2-[[(p-Nitrophenyl)sulfonyl]oxy] 3-Keto Esters from 3-Keto Esters and (p-Nitrophenyl)sulfonyl Peroxide', *J. Org. Chem.* **1990**, *55*, 1267-1270.

55 Riley, H. L., Morley, J. F. and Friend, N. A. C. 'Selenium dioxide, a new oxidising agent. Part I. Its reaction with aldehydes and ketones', *J. Chem. Soc.* **1932**, 1875-1883.

56 Cainelli, G., Manescalchi, F. and Plessi, L. 'The Use of Nitrate Esters in the Synthesis of Di-Carbonyl and Tri-Carbonyl Compounds', *Gazz. Chim. Ital.* **1986**, *116*, 163-164.

57 Batchelor, M. J., Gillespie, R. J., Golec, J. M. C. and Hedgecock, C. J. R. 'A Novel Application of the Dess-Martin Reagent to the Synthesis of an FK506 Analogue and other Tricarbonyl Compounds', *Tetrahedron Lett.* **1993**, *34*, 167-170.

58 Schank, K. and Lick, C. 'Einführung von Sauerstoff-Funktionen in die α-Stellung von β-Diketonen, 9. Ozonolytische Fragmentierung von Pyridinium-Yliden', *Chem. Ber.* **1982**, *115*, 3890-3893.

59 Schank, K. and Schuhknecht, C. 'Einführung von Sauerstoff-Funktionen in die α-Stellung von β-Diketonen, 8. Ozonspaltung von Sulfonium-Yliden', *Chem. Ber.* **1982**, *115*, 3032-3041; Schank, K. and Schuhknecht, C. 'Einführung von Sauerstoff-Funktionen in die α-Stellung von β-Diketonen, 7. Oxo-Meldrums Säuren durch Ozonspaltung von (Methoxymethylen)-Meldrums Säuren', *Chem. Ber.* **1982**, *115*, 2000-2002.

60 Schank, K. and Lick, C. 'Ozonolytic Fragmentation of Phenyliodonium β-Diketonates: A Convenient Synthesis of Unsolvated *vic*-Triketones', *Synthesis* **1983**, *1983*, 392-395.

61 Bestmann, H. J. and Kloeters, W. 'Über die Reaktion von Hexaphenylcarbodiphosphoran mit cyclischen aromatischen Carbonsäureanhydriden', *Tetrahedron Lett.* **1978**, *19*, 3343-3344.

62 Wasserman, H. H., Baldino, C. M. and Coats, S. J. 'Selective Oxidation of Phosphorus Ylides by Dimethyldioxirane. Application to the Formation of Vicinal Tricarbonyls', *J. Org. Chem.* **1995**, *60*, 8231-8235; Wasserman, H. H. and Vu, C. B. 'Formation of Vicinal Tricarbonyl Compounds by Selective Oxidation of Ylides Using Potassium Peroxymonosulfate', *Tetrahedron Lett.* **1990**, *31*, 5205-5208.

63 Wasserman, H. H. and Parr, J. 'The Chemistry of Vicinal Tricarbonyls and Related Systems', *Acc. Chem. Res.* **2004**, *37*, 687-701.

64 Tietze, L. F., Hippe, T. and Steinmetz, A. 'Solid-Phase Three-Component Domino Reactions: Combinatorial Approach to Substituted 3,4-Dihydro-2*H*-pyrans', *Synlett* **1996**, *1996*, 1043-1044.

65 Sagi, M., Wada, K., Konno, S. and Yamanaka, H. 'Studies on as-Triazine Derivatives .15. Intramolecular Reverse-Electron Demand Diels-Alder Reaction of 1,2,4-Triazine Derivatives', *Heterocycles* **1990**, *30*, 1009-1021.

66 Sagi, M., Wada, K., Konno, S. and Yamanaka, H. 'Studies of as-Triazine Derivatives. XV. Intramolecular Reverse-Electron Demand Diels-Alder Reaction of 1,2,4-Triazine Derivatives', **1990**, *30*, 1009-1021; Adlington, R. M., Baldwin, J. E., Catterick, D. and Pritchard, G. J. 'The efficient, enantioselective synthesis of quinoxaline, pyrazine and 1,2,4-triazine substituted α-amino acids from vicinal tricarbonyls', *J. Chem. Soc., Perkin Trans. 1* **2001**, *2001*, 668-679.

67 Regitz, M. and Adolph, H.-G. 'Untersuchungen an Diazoverbindungen, III. Neue Synthesemoglichkeiten fur Ninhydrin und benzokondesierte Derivate', *Chem. Ber.* **1968**, *101*, 3604-3611; Regitz, M. and Adolph, H.-G. 'Untersuchungen an Diazoverbindungen, IV. Vicinale Tricarbonylverbindungen aus 2-Diazo-1,3-dicarbonyl-verbindungen durch Sauerstoff-Halogen-Insertion', *Liebigs Ann. Chem.* **1969**, *723*, 47-60; Detering, J. and Martin, H. D. '4,6,6-Trimethyl-4-cyclohexene-1,2,3-trione, a Contribution to the Biogenesis of Norcarotinoids', *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 695-698.

68 Saba, A. 'Synthesis of Vicinal Trioxo Compounds by Dimethyl Dioxirane Oxidation of 2-Diazo-1,3-Dioxo Derivatives', *Synth. Commun.* **1994**, *24*, 695-699.

69 Ma, M., Li, C. K., Peng, L. L., Xie, F., Zhang, X. and Wang, J. B. 'An efficient synthesis of aryl α-keto esters', *Tetrahedron Lett.* **2005**, *46*, 3927-3929.

70 Altuna-Urquijo, M., Stanforth, S. P. and Tarbit, B. 'The preparation of 1,2,4-triazines from α,β-diketo-ester equivalents and their application in pyridine synthesis', *Tetrahedron Lett.* **2005**, *46*, 6111-6113.

71 Altuna-Urquijo, M. (**2005**), *Development of novel routes to pyridines*. PhD thesis, Northumbria University, Newcastle.

72 Altuna-Urquijo, M., Stanforth, S. P. and Tarbit, B. 'The preparation of 1,2,4-triazines from α,β-diketo-ester equivalents and their application in pyridine synthesis', **2005**, *46*, 6111-6113.

73 Cabon, O., Buisson, D., Larcheveque, M. and Azerad, R. 'The Microbial Reduction of 2-Chloro-3-oxoesters', *Tetrahedron: Asymmetry* **1995**, *6*, 2199-2210.

74 Passarotti, C., Resnati, G. and Doria, G. 'Synthesis of New 2-(2-Phenylethenyl)-4-Oxo-4h-Pyrido[1,2-a]Pyrimidine-7-Carboxylic Acids', *Farmaco* **1984**, *39*, 837-845.

75 Sugiyama, N., Yamamoto, M., Takano, T. and Kahima, C. 'Syntheses of Reductones. A New Method of Synthesizing 2-Acetoxy-1,3-dicarbonyl Compounds', *Bull. Chem. Soc. Japan* **1967**, *40*, 2909-2913; Valgimigli, L., Brigati, G., Pedulli, G. F., DiLabio, G. A., Mastragostino, M., Arbizzani, C. and Pratt, D. A. 'The Effect of Ring Nitrogen Atoms on the Homolytic Reactivity of Phenolic Compounds: Understanding the Radical-Scavenging Ability of 5-Pyrimidinols', *Chem-Eur. J.* **2003**, *9*, 4997-5010.

76 Russell, G. A. and Weiner, S. A. 'Aliphatic Semidiones. V. Radical Anions Derived from Vicinal Triketones', *J. Am. Chem. Soc.* **1967**, *89*, 6623-6628; Jucker, E. and Lindenmann, A. 'Oxydationsprodukte von substituierten 1-[N-alkyl-piperidyl-(4')]-pyrazolonen-(5)', *Helv. Chim. Acta* **1961**, *44*, 1249-1257.

77 Ochiai, M., Takeuchi, Y., Katayama, T., Sueda, T. and Miyamoto, K. 'Iodobenzene-Catalyzed α-Acetoxylation of Ketones. In Situ Generation of Hypervalent

(Diacyloxyiodo)benzenes Using *m*-Chloroperbenzoic Acid', *J. Am. Chem. Soc.* **2005**, *127*, 12244-12245.

78 Watson, M. D. (**2002**), *Novel methodologies in pyridine chemistry*. PhD thesis, Northumbria University, Newcastle.

79 Stanforth, S. P., Tarbit, B. and Watson, M. D. 'Synthesis of pyridine derivatives using aza Diels-Alder methodology', *Tetrahedron Lett.* **2002**, *43*, 6015-6017; Stanforth, S. P., Tarbit, B. and Watson, M. D. 'Synthesis of 2,2 '-bipyridyl derivatives using aza Diels-Alder methodology', *Tetrahedron Lett.* **2003**, *44*, 693-694.

80 Stanforth, S. P., Tarbit, B. and Watson, M. D. 'Synthesis of pyridine and 2,2 '-bipyridine derivatives from the aza Diels-Alder reaction of substituted 1,2,4-triazines', *Tetrahedron* **2004**, *60*, 8893-8897.

81 Hudson, M. J., Boucher, C. E., Braekers, D., Desreux, J. F., Drew, M. G. B., Foreman, M. R. S., Harwood, L. M., Hill, C., Madic, C., Marken, F. and Youngs, T. G. A. 'New bis(triazinyl) pyridines for selective extraction of americium(III)', *New. J. Chem.* **2006**, *30*, 1171-1183.

82 Domon, K. and Mori, K. 'Pheromone Synthesis, CXCIII Simple Synthesis of (+/-)-Stigmolone (8-Hydroxy-2,5,8-trimethyl-4-nonanone), the Pheromone of *Stigmatella aurantiaca*', *Eur. J. Org. Chem.* **1999**, *1999*, 979-980.

83 Mori, K. 'Synthesis of Optically-Active Forms of Ipsenol, Pheromone of *Ips* Bark Beetles', *Tetrahedron* **1976**, *32*, 1101-1106.

84 Zhou, C. M., Shao, Y. and Gibbs, R. A. 'Aromatic Farnesyl Diphosphate Analogues: Vinyl Triflate-Mediated Synthesis and Preliminary Enzymatic Evaluation', *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1417-1420; Sum, F. W. and Weiler, L. 'Stereoselective synthesis of β-substituted α,β-unsaturated esters by dialkylcuprate coupling to the enol phosphate of β-keto esters', *Can. J. Chem.* **1979**, *57*, 1431-1441; Balaji, B. S. and Chanda, B. M. 'Simple and High Yielding Syntheses of β-Keto esters Catalysed by Zeolites', *Tetrahedron* **1998**, *54*, 13237-13252; Giacomelli, G., Porcheddu, A., Salaris, M. and Taddei, M. 'Microwave-Assisted Solution-Phase Synthesis of 1,4,5-Trisubstituted Pyrazoles', *Eur. J. Org. Chem.* **2003**, *2003*, 537-541.

85 Hoff, B. H. and Anthonsen, T. 'Lipase-catalyzed resolution of esters of 4-chloro-3-hydroxybutanoic acid: effects of the alkoxy group and solvent on the enantiomeric ratio', *Tetrahedron: Asymmetry* **1999**, *10*, 1401-1412.

86 Becker, H. G. O., Beckert, R., Domschke, G., Fanghänel, E., Habicher, W. D., Metz, P., Pavel, D. and Schwetlick, K. *Organikum.* 21st ed., Weinheim: WILEY-VCH, 2001.

87 Gilman, H. and Broadbent, H. S. 'The Synthesis of Some Substituted 2-Thiouracils', *J. Am. Chem. Soc.* **1948**, *70*, 2755-2757.

88 Frantz, R., Hintermann, L., Perseghini, M., Broggini, D. and Togni, A. 'Titanium-Catalyzed Stereoselective Geminal Heterodihalogenation of β-Ketoesters', *Org. Lett.* **2003**, *5*, 1709-1712.

89 Hayashi, Y., Orikasa, S., Tanaka, K., Kanoh, K. and Kiso, Y. 'Total Synthesis of Anti-microtubule Diketopiperazine Derivatives: Phenylahistin and Aurantiamine', *J. Org. Chem.* **2000**, *65*, 8402-8405.

90 Meshram, H. M., Reddy, P. N., Sadashiv, K. and Yadav, J. S. 'Amberlyst-15[(R)]-promoted efficient 2-halogenation of 1,3-keto-esters and cyclic ketones using *N*-halosuccinimides', *Tetrahedron Lett.* **2005**, *46*, 623-626.

91 Pabst, G. R. and Sauer, J. 'A New and Simple 'LEGO' System for the Synthesis of 2,6-Oligopyridines', *Tetrahedron Lett.* **1998**, *39*, 6687-6690.

92 Roth, M., Dubs, P., Gotschi, E. and Eschenmoser, A. 'Sulfidkontraktion *via* alkylative Kupplung: eine Methode zur Darstellung von β-Dicarbonylderivaten', *Helv. Chim. Acta* **1971**, *54*, 710-734.

93 Roth, B., Laube, R., Tidwell, M. Y. and Rauckman, B. S. 'Extrusion of Sulfur from [(Acylmethyl)Thio]Pyrimidinones', *J. Org. Chem.* **1980**, *45*, 3651-3657.

94 Chenard, B. L., Ronau, R. T. and Schulte, G. K. 'The Inverse Electron Demand Diels-Alder Reaction of 3-(Methylsulfonyl)-1,2,4-triazine and Enamines. Isolation of Crystalline Intermediates and an Improved Synthesis of 1-(Methylsulfonyl)tetrahydroisoquinolines', *J. Org. Chem.* **1988**, *53*, 5175-5177.

95 Kozhevnikov, V. N., Kozhevnikov, D. N., Shabunina, O. V., Rusinov, V. L. and Chupakhin, O. N. 'An efficient route to 5-(hetero)aryl-2,4'- and 2,2'-bipyridines through readily available 3-pyridyl-1,2,4-triazines', *Tetrahedron Lett.* **2005**, *46*, 1791-1793.

96 Laphookhieo, S., Jones, S., Raw, S. A., Fernández Sainz, Y. and Taylor, R. J. K. 'Tandem oxidation process for the regioselective preparation of 5-substituted and 6-substituted 1,2,4-triazines', *Tetrahedron Lett.* **2006**, *47*, 3865-3870.

97 Sammakia, T. and Jacobs, J. S. 'Picolinic Acid as a Partner in the Mitsunobu Reaction: Subsequent Hydrolysis of Picolinate Esters under Essentially Neutral Conditions with Copper Acetate in Methanol', *Tetrahedron Lett.* **1999**, *40*, 2685-2688.

98 Ghosh, S., Banerjee, I. and Baul, S. 'Studies on oxygen heterocycles part 2: Synthesis of 2-arylcoumaranones and 2-phenylbenzofuran', *Tetrahedron* **1999**, *55*, 11537-11546.

99 Marko, I. E., Giles, P. R., Tsukazaki, M., Brown, S. M. and Urch, C. J. 'Copper-catalyzed oxidation of alcohols to aldehydes and ketones: An efficient, aerobic alternative', *Science* **1996**, *274*, 2044-2046; Peterson, K. P. and Larock, R. C. 'Palladium-Catalyzed Oxidation of Primary and Secondary Allylic and Benzylic Alcohols', *J. Org. Chem.* **1998**, *63*, 3185-3189.

100 Driscoll, J. J. and Kosman, D. J. 'Proton-Transfer in the Copper(II)-Tetrapyridine Catalyzed Oxidation of Acetol (Monohydroxyacetone)', *J. Am. Chem. Soc.* **1987**, *109*, 1765-1772.

101 Liu, X., Qiu, A. M. and Sawyer, D. T. 'The Bis(bipyridine)copper(II)-Induced Activation of Dioxygen for the Catalytic Dehydrogenation of Alcohols', *J. Am. Chem. Soc.* **1993**, *115*, 3239-3243.

102 Semmelhack, M. F., Schmid, C. R., Cortes, D. A. and Chou, C. S. 'Oxidation of Alcohols to Aldehydes with Oxygen and Cupric Ion, Mediated by Nitrosonium Ion', *J. Am. Chem. Soc.* **1984**, *106*, 3374-3376.

103 Nishimura, T., Onoue, T., Ohe, K. and Uemura, S. 'Pd(OAc)$_2$-Catalyzed Oxidation of Alcohols to Aldehydes and Ketones by Molecular Oxygen', *Tetrahedron Lett.* **1998**, *39*, 6011-6014.

104 Cottet, F. and Schlosser, M. 'Trifluoromethyl-Substituted Pyridines Through Displacement of Iodine by in situ Generated (Trifluoromethyl)copper', *Eur. J. Org. Chem.* **2002**, *2002*, 327-330.

105 Konno, S., Sagi, M., Takaharu, E., Fujimura, S., Hayashi, K. and Yamanaka, H. 'Studies on *as*-Triazine Derivatives. XII. Synthesis of Alkenyl-1,2,4-triazine Derivatives', *Chem. Pharm. Bull.* **1988**, *36*, 1721-1726.

106 Kozhevnikov, D. N., Kataeva, N. N., Rusinov, V. L. and Chupakhin, O. N. 'Chloromethyl-, dichloromethyl-, and trichloromethyl-1,2,4-triazines and their 4-oxides: method for the synthesis and *tele*-substitution reactions with C-nucleophiles', *Russ. Chem. Bull.* **2004**, *53*, 1295-1300.

107 Volle, J. N. and Schlosser, M. '1-Ethoxy-3-trifluoromethyl-1,3-butadiene and Congeners as Diels-Alder Components Opening an Entry to Functionalized (Trifluoromethyl)benzenes and -pyridines', *Eur. J. Org. Chem.* **2002**, *2002*, 1490-1492; Evariste, F., Janousek, Z., Maliverney, C., Merenyi, R. and Viehe, H. G.

'Reactivity in [4+2] cycloadditions of new 4-trifluoromethyl-1,3-oxazin-6-ones: Access to functionalized 2-trifluoromethyl pyridines', *J Prak Chem./Chem-Ztg.* **1993**, *335*, 35-41.

108 Goodman, A. J., Stanforth, S. P. and Tarbit, B. 'Desymmetrization of Dichloroazaheterocycles', *Tetrahedron* **1999**, *55*, 15067-15070.

109 Constable, E. C. '2,2 ': 6 ',2 "-Terpyridines: From chemical obscurity to common supramolecular motifs', *Chem. Soc. Rev.* **2007**, *36*, 246-253.

110 Flamigni, L., Collin, J. P. and Sauvage, J. P. 'Iridium Terpyridine Complexes as Functional Assembling Units in Arrays for the Conversion of Light Energy', *Acc. Chem. Res.* **2008**, *41*, 857-871.

111 Liu, P., Wong, E. L. M., Yuen, A. W. H. and Che, C. M. 'Highly Efficient Alkene Epoxidation and Aziridination Catalyzed by Iron(II) Salt + 4,4',4"-Trichloro-2,2':6',2"-terpyridine/4,4"-Dichloro-4'-*O*-PEG-OCH$_3$-2,2':6',2"-terpyridine', *Org. Lett.* **2008**, *10*, 3275-3278.

112 Schubert, U. S. and Eschbaumer, C. 'Macromolecules Containing Bipyridine and Terpyridine Metal Complexes: Towards Metallosupramolecular Polymers', *Angew. Chem., Int. Ed. Engl.* **2002**, *41*, 2893-2926.

113 Jameson, D. L. and Guise, L. E. 'An Improved, 2-Step Synthesis of 2,2'-6',2"-Terpyridine', *Tetrahedron Lett.* **1991**, *32*, 1999-2002.

114 Brunner, H. and Scheck, T. 'Neue optisch aktive Pyrazolderivate für die enantioselektive Katalyse', *Chem. Ber.* **1992**, *125*, 701-709.

115 Pleier, A. K., Glas, H., Grosche, M., Sirsch, P. and Thiel, W. R. 'Microwave Assisted Synthesis of 1-Aryl-3-dimethylaminoprop-2-enones: A Simple and Rapid Access to 3(5)-Arylpyrazoles', *Synthesis* **2001**, *2001*, 55-62.

116 Bejan, E., Haddou, H. A., Daran, J. C. and Balavoine, G. G. A. 'The Reaction of Enaminones with Carboxamidines: A Convenient Route for the Synthesis of Polyaza Heterocycles', *Synthesis* **1996**, *1996*, 1012-1018.

117 Hassanien, A. Z. A. '2, 6-Bis [3-N,N-dimethylamino-1-oxopropen-1-yl]pyridine as a building block in heterocyclic synthesis: synthesis of 2,2':6',2"-terpyridines and 2,6-bis [pyrazolyl, isoxazolyl, diazepinyl, pyrazolo[5,1-a]pyrimidinyl and pyrazolo-[4,3-d]pyridazinyl pyridines', *J. Chem. Res.* **2004**, *2004*, 536-540.

118 Su, B. Y., Zhao, J. S., Cui, Y., Liang, Y. Q. and Sun, W. H. 'Controlled Synthesis of 2-Acetyl-6-carbethoxypyridine and 2,6-Diacetylpyridine from 2,6 - Dimethylpyridine', *Synth. Commun.* **2005**, *35*, 2317-2324.

119 Kolarik, Z., Mullich, U. and Gassner, F. 'Extraction of Am(III) and Eu(III) nitrates by 2,6-di-(5,6-dipropyl-1,2,4-triazin-3-yl)pyridines', *Solvent Extr. Ion Exch.* **1999**, *17*, 1155-1170; Kolarik, Z., Mullich, U. and Gassner, F. 'Selective extraction of Am(III) over Eu(III) by 2,6-ditriazolyl- and 2,6-ditriazinylpyridines', *Solvent Extr. Ion Exch.* **1999**, *17*, 23-32; Hill, C., Berthon, L., Bros, P., Dancausse, J.-P. and Guillaneux, D., *SANEX-BTP Process Development Studies* Seventh Information Exchange Meeting on Actinide and Fission Product Partitioning and Transmutation. Session II: Progress in Partitioning and Waste Forms, (Jeju (Republic of Korea)) **2002**, pp. 453-461, Available at: http://www.nea.fr/html/pt/docs/iem/jeju02/session2/Session%20II-19.pdf; Geist, A., Weigl, M., Müllich, U. and Gompper, K., *Actinide(III)/Lanthanide(III) Partitioning using n-Pr-BTP as Extractant: Extraction Kinetics and Extraction Test in a Hollow Fibre Module* Sixth Information Exchange Meeting on Actinide and Fission Product Partitioning and Transmutation, (Madrid (Spain)) **2000**, pp. 641-647, Available at: http://www.nea.fr/html/pt/docs/iem/madrid00/Proceedings/Paper14.pdf.

120 Case, F. H. 'The Preparation of 2,4-Bis-Triazinyl and 2,6-Bis-Triazinyl and Triazolinyl Derivatives of Pyridine', *J. Heterocyclic Chem.* **1971**, *8*, 1043-1046.

121 Gorbyleva, O. I., Yevstratova, M. I. and Yakhontov, L. N. 'The vilsmeier complex as a dehydrating agent in the synthesis of 2,6-dicyanopyridine', *Chem. Heterocycl. Compd. Engl. Transl.* **1983**, *19*, 1133.

122 Pabst, G. R., Schmid, K. and Sauer, J. 'A New and Simple 'LEGO' System for the Synthesis of Branched Oligopyridines', *Tetrahedron Lett.* **1998**, *39*, 6691-6694.

123 Brackeen, M. F., Stafford, J. A., Feldman, P. L. and Karanewsky, D. S. 'An Efficient and Mild Synthesis of Highly Substituted Imidazoles', *Tetrahedron Lett.* **1994**, *35*, 1635-1638.

124 Rizzo, C. J. (unknown year), *TLC Stain Recipes*. Available at: http://www.vanderbilt.edu/AnS/Chemistry/Rizzo/stuff/TLCstains.pdf, (Accessed: 22 September 2005)

125 Perrin, D. D. and Armarego, W. L. F. *Purification of Laboratory Chemicals*. 3rd edn., Oxford: Pergamon Press, 1998.

126 Fang, X., Yang, X. Y., Yang, X. J., Zhao, M., Chen, G. R. and Wu, F. H. 'Palladium-catalyzed arylation of α,α-difluoro-allylic-β-hydroxyester', *Tetrahedron Lett.* **2006**, *47*, 8231-8234.

127 Lee, H. S., Park, J. S., Kim, B. M. and Gellman, S. H. 'Efficient Synthesis of Enantiomerically Pure β^2-Amino Acids via Chiral Isoxazolidinones', *J. Org. Chem.* **2003**, *68*, 1575-1578.

128 Yadav, J. S., Reddy, B. V. S., Eeschwaraiah, B. and Reddy, P. N. 'Niobium(V) chloride-catalyzed C-H insertion reactions of α-diazoesters: synthesis of β-keto esters', *Tetrahedron* **2005**, *61*, 875-878; Helbling, A. M. and Viscontini, M. 'Synthese von racemischen Proferrorosamin and Ferrorosamin', *Helv. Chim. Acta* **1976**, *59*, 938-940.

129 Burdett, J. L. and Rogers, M. T. 'Keto-Enol Tautomerism in β-Dicarbonyls Studied by Nuclear Magnetic Resonance Spectroscopy. I. Proton Chemical Shifts and Equilibrium Constants of Pure Compounds', *J. Am. Chem. Soc.* **1964**, *86*, 2105 - 2109.

130 Perrone, M. G., Santandrea, E., Dell'Uomo, N., Giannessi, F., Milazzo, F. M., Sciarroni, A. F., Scilimati, A. and Tortorella, V. 'Synthesis and biological evaluation of new clofibrate analogues as potential PPARα agonists', *Eur. J. Med. Chem.* **2005**, *40*, 143-154.

131 Cornwall, P., Dell, C. P. and Knight, D. W. 'Regioselectivity in the Lithiation of Methyl-Substituted Thiazole- and Oxazole-Carboxylic Acids and Carboxamides: General-Methods for the Elaboration of Trisubstituted Thiazoles and Oxazoles', *J. Chem. Soc., Perkin Trans. 1* **1991**, *1991*, 2417-2428.

132 Komiyama, T., Takaguchi, Y. and Tsuboi, S. 'Novel and Effective Synthesis of 2-Acyloxy-3-keto Esters', *Synthesis* **2006**, *2006*, 1767-1770.

133 Altuna-Urquijo, M., Stanforth, S. P. and Tarbit, B. 'The preparation of 1,2,4-triazines from alpha,beta-diketo-ester equivalents and their application in pyridine synthesis', **2005**, *46*, 6111-6113.

134 Freund, M., and Paradies, T. 'Zur Kenntniss des Tetrazols', **1901**, *34*, 3110-3115.

135 Agamy, S. M., Abdel-Khalik, M. M., Mohamed, M. H. and Elnagdi, M. H. 'Enaminones as Building Blocks In Heterocyclic Synthesis: A New One Pot Synthesis of Polyfunctional Substituted Pyridines', *Z. Naturforsch. B* **2001**, *56*, 1074-1078.

136 Oae, S. and Kozuka, S. 'Rearrangement of tertiary amine N-oxides—XIV: The mechanism of the reaction of pyridine N-oxide with acetic anhydride', *Tetrahedron* **1965**, *21*, 1971-1975.

137 Comelles, J., Pericas, A., Moreno-Manas, M., Vallribera, A., Drudis-Sole, G., Lledos, A., Parella, T., Roglans, A., Garcia-Granda, S. and Roces-Fernandez, L.

'Highly Enantioselective Electrophilic Amination and Michael Addition of Cyclic α-Ketoesters Induced by Lanthanides and (S,S)-ip-pybox. The Mechanism', *J. Org. Chem.* **2007**, *72*, 2077-2087.

138 Evstratova, M. I., Prokopov, A. A., Ivanova, I. L., Markova, I. G., Tubina, I. S., Anisimova, O. S., Skvirskaya, N. V., Kan, I. I., Suvorov, B. V. and Yakhontov, L. N. 'Study of hydrolysis processes of 2,6-dicyanopyridine', *Pharm. Chem. J.* **1985**, *19*, 126-129.

139 Marlin, D. S., Olmstead, M. M. and Mascharak, P. K. 'Extended structures controlled by intramolecular and intermolecular hydrogen bonding: a case study with pyridine-2,6-dicarboxamide, 1,3-benzenedicarboxamide and *N,N* '-dimethyl-2,6-pyridinedicarboxamide', *J. Mol. Struct.* **2000**, *554*, 211-223.

140 Lukes, R. and Pergal, M. 'Homologues of Pyridine. II. Synthesis and Reactions of Some α,α'-Disubstituted Pyridines', *Collect. Czech. Chem. Commun.* **1959**, *24*, 36-43.

141 Sakamoto, T., Kaneda, S., Nishimura, S. and Yamanaka, H. 'Site-Selectivity in the Cyanation of 3-Substituted Pyridine 1-Oxides with Trimethylsilanecarbonitrile', *Chem. Pharm. Bull.* **1985**, *33*, 565-571.