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NEW ROUTES TO FUNCTIONALISED PYRIDINES

Marta Altuna-Urquijo

Ph.D **September 2005**

New routes to functionalised pyridines

Marta Altuna-Urquijo, MChem

A thesis submitted in partial fulfilment of the requirements of the University of Northumbria for the degree of Doctor of Philosophy

September 2005

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Finally, I would like to thank David for being by my side all these years, for being so understanding and for keeping me sane and happy. Thank you for everything, I don't think I would have managed without you.

Abstract

A novel method of preparing substituted pyridines has been developed. This method uses readily available β-ketoesters and amidrazone as starting materials. The pyridines obtained do not require purification and different substitution patterns, not available by known methods, can be obtained.

The formation of 1,2,3-tricarbonyl compounds was achieved by oxidation of the alcohol precursors, following two different methods. α-Chloro-α-acetoxy-β-dicarbonyls were prepared in excellent yields and were shown to react as tricarbonyl equivalents in the formation of 1,2,4-triazines.

Regioselective condensation reactions were observed between different amidrazones with tricarbonyl and tricarbonyl equivalents to produce a series of novel 1,2,4-triazines in good yields with no contamination by any regioisomer. When 1,2,4-triazines were obtained from α-chloro-α-acetoxy-β-dicarbonyls, 2.5 equivalents of amidrazone were required. However, decomposition of α-chloro-α-acetoxy-β-dicarbonyls *prior to* reaction with 1 equivalent of amidrazone yielded the 1,2,4-triazines in good yields.

These 1,2,4-triazines underwent aza Diels-Alder cycloaddition reactions with 2,5-norbornadiene to give a series of novel 2,3,6-trisubstituted pyridines. The pyridines bearing electron withdrawing groups as substituents could also be obtained in a 'one-pot' reaction from their corresponding tricarbonyls or tricarbonyl derivatives. The 1,2,4-triazines bearing electron donating groups could be converted to their corresponding pyridines either by changing the reaction conditions or, when possible, by conversion of the electron donating group into a more electron withdrawing substituent by oxidation (e.g. sulphoxide substituent).

Pyridines bearing a sulphoxide substituent undergo nucleophilic substitutions, giving great scope to introduce different functionality in the C-6 of the pyridines.

Contents

Abbreviation list

THF: tetrahydrofuran

DCM: dichloromethane

DMF: dimethylformamide

DMSO: dimethyl sulphoxide

MCPBA: *m*-chloroperbenzoic acid

DMD: dimethyldioxirane

EDCI: 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride

TEMPO: 2,2,6,6-tetramethyl piperidinyloxy

NBS: *N*-bromosuccinimide

"Oxone": commercial name for potassium peroxymonosulphate

RT: room temperature

NMR: nuclear magnetic resonance

EIMS: electron impact mass spectrometry

IR: infrared

INTRODUCTION

1. Introduction

1.1. Pyridines

Pyridine is the simplest and best-known azaheterocycle, consisting in a six membered aromatic ring, where one of the carbons is substituted with nitrogen. Pyridine was first isolated from bone pyrolysates and its name is constructed from the Greek for fire, 'pyr' and the suffix 'idine', which was used for all aromatic bases at that time.

Heterocycles such as pyridine derivatives are the basic building blocks of many important natural products, pharmaceuticals, agrochemicals, polymers and bipyridyl catalysts.

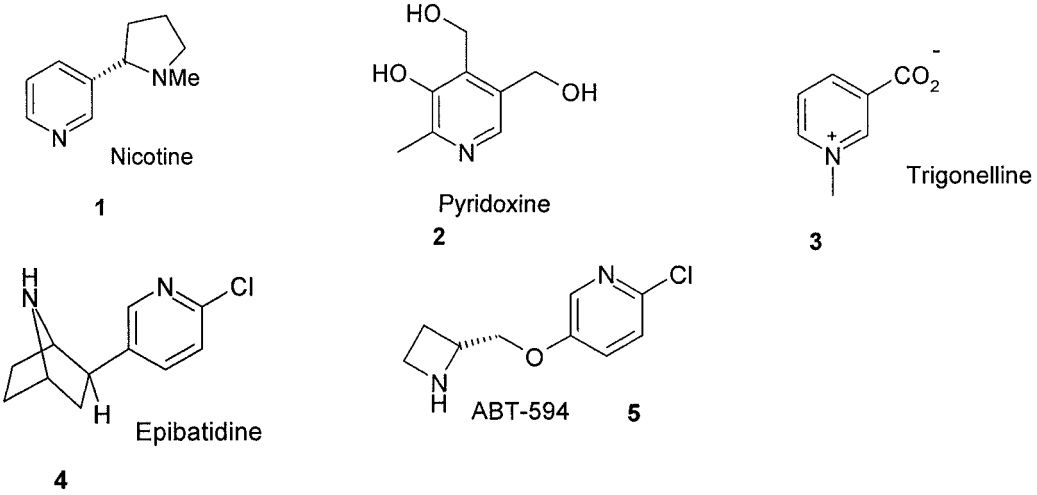
1.1.1. Pyridines in nature

One of the best-known natural occurring pyridines is the tobacco alkaloid nicotine **1**. It is the major active component in tobacco and has proven to be highly addictive and highly toxic; it has therefore been used as a pesticide for centuries.

Pyridoxine (vitamin B_6) **2** occurs in yeast and wheatgerm and it is a biologically important compound. It is involved in the synthesis of amino acids, which is based on the fact that in many biological systems α-ketocarboxylic acids are transformed to α-amino acids by a process known as transamination[1]. It also participates in the process of making neurotransmitters and controls the blood levels of homocysteine, so it is widely used in the treatment of heart diseases.

Trigonelline **3** is found in Fenugreek seeds and in coffea Arabica and it is biologically active as a potent antiseptic and anticancer agent.

Epibatidine **4** has been isolated from poisonous frogs found in tropical forests. It has been shown to provide pain relief 200 times higher than morphine acting through a non-opioid mechanism; however, it is highly toxic. Investigations have been carried out with similar alkaloids to reduce its toxicity, maintaining the analgesic and non-addictive qualities of epibatidine and a new compound ABT-594 **5** has been successfully synthesised [2].

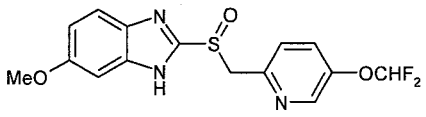


1.1.2. Synthetic pyridines

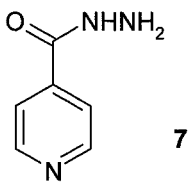
In the pharmaceutical industry, pyridine forms the nucleus of over 7000 existing drugs[3]. Among the many pyridines which have been developed as pharmaceuticals are pantoprazole **6**, effective for the treatment of peptic ulcers, isoniazide **7**, a major antituberculosis agent and nifedipine **8**, a cardiovascular drug.

The pyridine ring also appears in many agrochemicals[4] such as davicil **9**, a fungicide, nitrapyrin **10**, a potent bactericide and paraquat **11**, a well known herbicide. Pyridine derivatives have wide applications in polymer synthesis[5]; 2-vinylpyridine **12** is a constituent in latex.

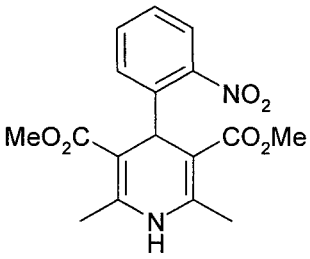
N-Alkylpyridinium salts, for example compound **13**, are ionic liquids[6,7] which can dissolve organic and inorganic compounds and are highly polar but non-coordinating. They have potential in 'green' industrial applications and they can even dissolve spent nuclear fuels.



6 Pantoprazole
(used for peptic ulcers)



7
Isoniazide
(antituberculosis agent)



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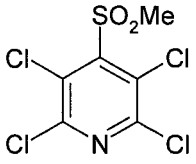
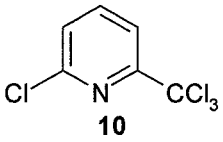
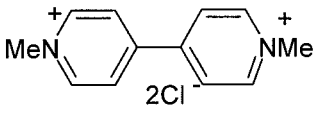
Nifedipine
(cardiovascular drug)



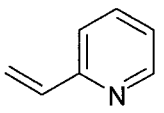
9
Davicil



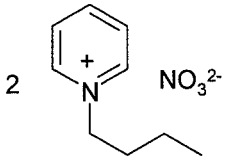
10
Nitrapyrin



11 Paraquat
(herbicide)



12
2-Vinylpyridine

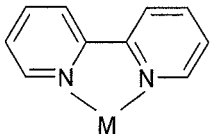


13
N-Alkylpyridinium salt

1.1.3. Bipyridyls

Other analogues of pyridines, such as bipyridyls and terpyridyls have found extensive use in many areas of chemistry. They are attractive blocks for supramolecular chemistry[8]. Bipyridyls **14** have a geometry favourable for accepting various metal centres, they are therefore widely used in coordination chemistry[9]. This unique family of ligands also possesses accessible redox chemistry as a consequence of the π-conjugation. One area of extensive research that has developed as a consequence of this has been their use in photo-activated species[10,11], by coordination to an appropriate transition metal such as ruthenium

(II), osmium (II) or rhenium (I). In such complexes an electron can be excited from the metal to the ligand. In particular, the transition metal bipyridyl complexes have found various applications: from catalysis and photocatalysis to chemosensors and luminescent probes for biomolecular systems[12].



14

Among bipyridines, 5-aryl-2,2'-bipyridines exhibit the best luminescent properties, due to the effect of the aromatic substituents making bipyridines attractive as chromophores and antennae[13]. They have also shown strong fungicidal activity against different plant diseases[14].

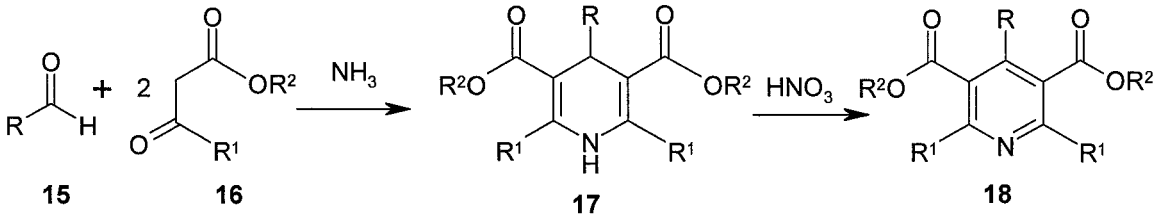
Over the last decade metal centred stereochemistry has become a major research topic driven by the potential application in such diverse fields of research as nanoscale technology, materials chemistry and asymmetric catalysis[15]. The most frequent method of controlling the stereochemistry of a metal centre is by using chiral ligands of known configuration. These transfer the chiral information stored in the ligand's structure to the metal centre.

Advances in the non-racemic chiral functionalization of 2,2'-bipyridine over the last decade have opened new and exciting opportunities to influence both the metal centred stereochemistry and the chirality of other species coordinated to the same metal centre. Consequently, the familiar 2,2'-bipyridine structure is finding new applications in such areas as enantiomerically pure supramolecular lattices and homogeneous asymmetric catalysis[16,17].

1.2. Synthesis of pyridines

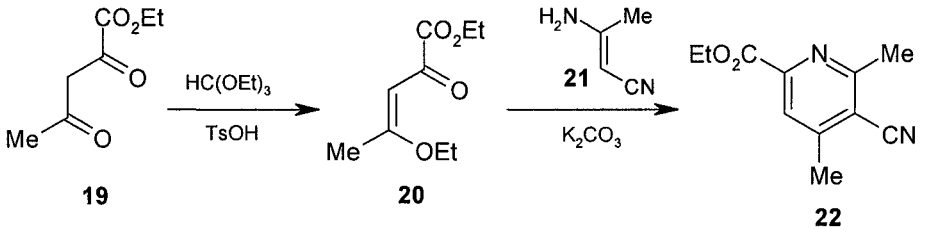
Pyridine and its simple alkyl derivatives were for a long time produced by isolation from coal tar, in which they occur in quantity. However, synthetic processes have displaced this source. Many diverse methods have been developed to synthesize substituted pyridines from other compounds and this has been recently reviewed by Henry[18].

The best known route to pyridines is the Hantzsch synthesis (1882). Although numerous variations are known, the simplest consists of the condensation of 2 equivalents of a 1,3-dicarbonyl compound **16** with an aldehyde **15** and ammonia. At the end of the reaction the dihydropyridine **17** is aromatized to the corresponding pyridine **18** by oxidation with nitric acid (Scheme 1). The normal Hantzsch procedure leads to symmetrical dihydropyridines, and is commonly limited to carboxyl substituents at the 3- and 5- positions and an aryl substituent at the 4-position.



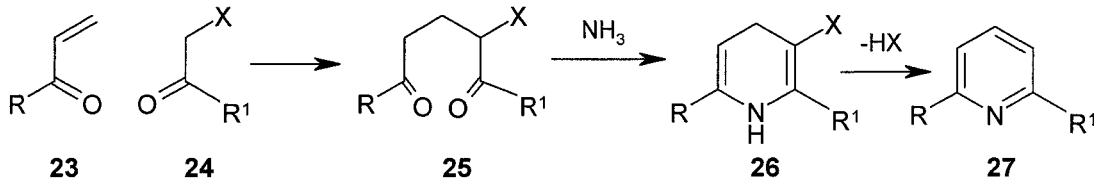
Scheme 1 Hantzsch synthesis of pyridines

A versatile and useful route to unsymmetrically substituted pyridines from relatively simple precursors is the Guareschi synthesis. It involves the reaction of a 1,3-dicarbonyl compound **19** with triethyl orthoformate to give an ester enol ether **20**, before Michael addition of a 3-amino nitrile **21**, as shown in Scheme 2.



Scheme 2 Guareschi synthesis of pyridines

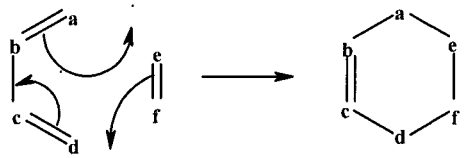
The Kröhnke synthesis consists on the formation of a 1,5-dicarbonyl intermediate **25**, by a base-promoted Michael addition of α-substituted ketones **24** (X= leaving group) with α,β-unsaturated compounds **23**. Further treatment of compound **25** with ammonia and a final aromatisation process yields the substituted pyridines **27**. (Scheme 3)



Scheme 3 Kröhnke synthesis of pyridines

1.2.1. The aza Diels-Alder reaction

By virtue of its excellent chemo-, regio- and diastereoselectivity, the Diels-Alder reaction is one of the most important methods for the construction of six-membered ring systems. In this pericyclic [4+2]π cycloaddition reaction, the concerted reaction (one single step) between a diene and a dienophile produces a six-membered ring with up to four new stereo-centres (Scheme 4). The synthetic, mechanistic, and theoretical aspects of this reaction have all been extensively studied[19,20].

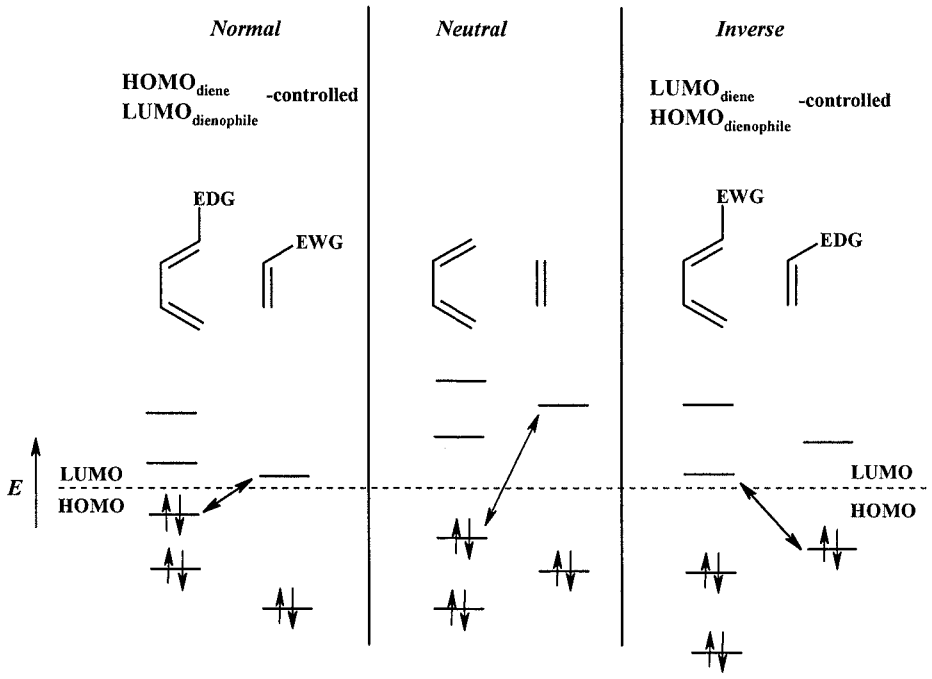


Scheme 4 The general form of the Diels-Alder reaction

The Diels-Alder reactions can be classified into three types based on the descriptions of both pairs of frontier orbitals in the molecular orbital model: normal, neutral and inverse.

In these reactions, the interaction of the highest occupied molecular orbitals of one reactant (HOMO) with the lowest unoccupied molecular orbitals of the other (LUMO) controls the formation of a cycloadduct (Scheme 5). The efficiency of the two frontier molecular orbitals interaction is increased if the energy separation is decreased.

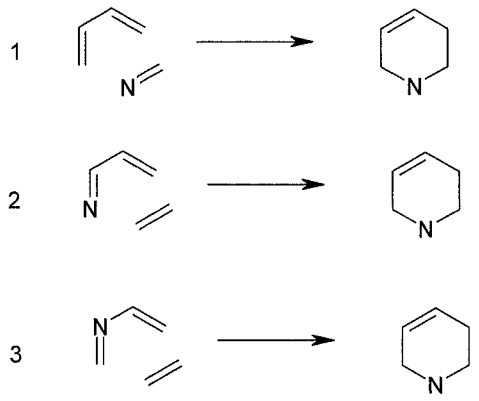
In the normal Diels-Alder reaction (the most common one), electron-donating groups (EDG) on the diene and electron-withdrawing groups (EWG) on the dienophile decrease the energy separation and therefore increase the reaction rate. In the inverse electron demand Diels-Alder reaction the electronic effect of the substituents is the reverse to that of the normal reaction.



Scheme 5 Frontier orbitals in the Diels-Alder reaction

The Diels-Alder reaction is not just limited to the formation of all-carbon systems. It has also become a very important method for the synthesis of six membered nitrogen containing heterocycles.

Scheme 6 shows three basic variants of the aza Diels-Alder reaction. In the first and most common method the imine function appears as the dienophile. In the second and third variants the imine is found in the diene as either 1-azadienes or 2-azadienes.

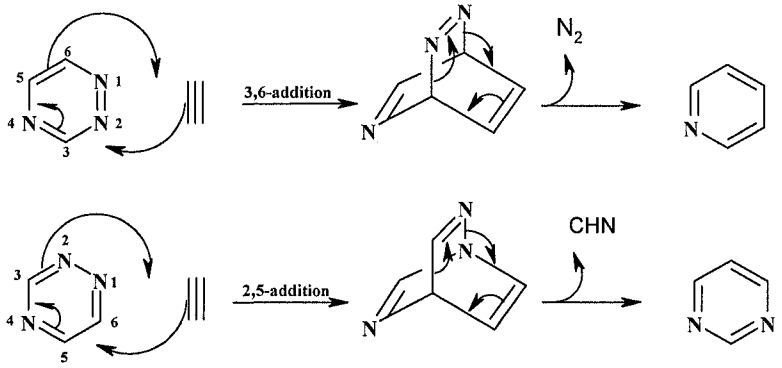


Scheme 6 The three basic variants of the aza Diels-Alder reaction

The recent advances in the azadiene Diels-Alder reaction as a general synthetic method owe much to the development of methods to activate the azadiene system. Both azadienes appropriately substituted can react as either electron-rich or electron-deficient dienes in the corresponding normal or inverse electron demand Diels-Alder reaction. In recent years several reviews have been published on the synthetic utility of azadienes in the Diels-Alder reaction[21-23], showing the current interest in this reaction.

1.2.1.1. The intermolecular aza Diels-Alder reaction of 1,2,4-triazines.

The inverse electron demand aza Diels-Alder cycloaddition of substituted 1,2,4-triazines constitute the most thoroughly investigated heteroaromatic azadiene system capable of 4π diene participation. Two potential modes of cycloaddition are open to 1,2,4-triazines: cycloaddition across C-3/C-6 or C-5/N-2 of the triazine; further loss of nitrogen and aromatisation yields pyridines or pyrimidines respectively as shown in Scheme 7.



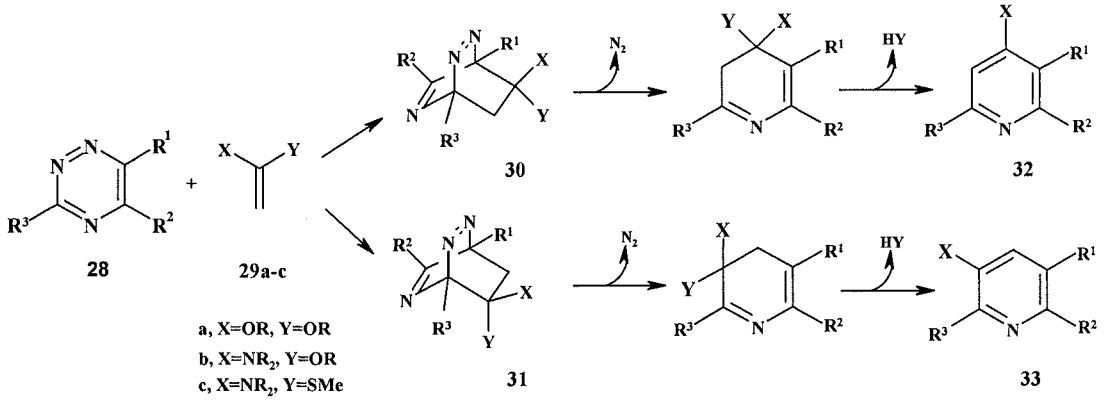
Scheme 7 The aza Diels-Alder reaction of 1,2,4-triazines

The addition of electron-withdrawing substituents to the 1,2,4-triazine nucleus generally increases its rate of participation in the inverse electron demand aza Diels-Alder reaction, influencing the mode of cycloaddition (3,6-addition is preferred) and controlling the observed regioselectivity. In addition, the reactivity of the dienophile, as well as the reaction conditions have a pronounced effect on the observed course of the [4+2]π cycloaddition reactions.

Most electron-rich dienophiles cycloadd exclusively across C-3/C-6 of the triazine. The regioselectivity of this cycloaddition process is subject to control by the electronic and steric parameters of the triazine and the dienophile. The exception to this generalization is the cycloaddition reactions of ynamines where C-5/N-2 cycloaddition process is generally observed.

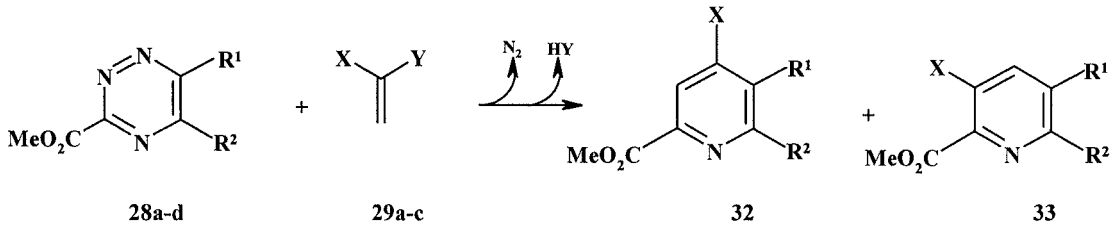
1.2.1.1.1. Ketene acetals and related compounds

1,2,4-Triazine derivatives **28** have been shown to react with a variety of dienophiles **29a-c**. Scheme 8 shows the general form of this reaction. The first step of this reaction involves cycloaddition giving one of the two possible regioisomers **30** or **31**, followed by loss of nitrogen to give a dihydropyridine and subsequent elimination of HY to produce the corresponding substituted pyridine **32** or **33**.



Scheme 8 The general reaction pathway of 1,2,4-triazines with compounds **29a-c**

Sauer and colleagues[24] investigated the cycloaddition reactions of the compounds **29a-c** with a range of 1,2,4-triazines **28a-d** (Scheme 9). The yields and regioselectivity overall were good to excellent (Tables 1-3).



Scheme 9 Reaction conditions: see Tables 1-3

1,2,4-Triazine-3-carboxylic acid methyl ester **28a** and 5-phenyl-1,2,4-triazine-3-carboxylic acid methyl ester **28b** reacted with dienophiles **29a, 29b** and **29c** to selectively yield (57-90 %) their corresponding pyridines **33** with little or no formation of regioisomers. With 5,6-diphenyl-1,2,4-triazine-3-carboxylic acid methyl ester **28c** and 1,2,4-triazine-3,5,6-tricarboxylic acid trimethyl ester **28d** the regioselectivity was reversed and pyridines **32** were formed in good yields.

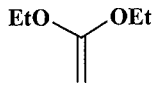
Dienophile 29a	Triazine 28	R^1	R^2	Yield (%)	Ratio 32 : 33	
	**a**	H	H	57	0	100
	b	H	Ph	85	0	100
	c	Ph	Ph	100	95	5
	d	CO_2Me	CO_2Me	19-48	100	0

Table 1 Reaction conditions: acetonitrile, 40°C

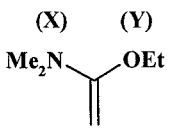
Dienophile 29b	Triazine 28	R^1	R^2	Yield (%)	Ratio 32 : 33	
	**a**	H	H	74	0	100
	b	H	Ph	63	8	92
	c	Ph	Ph	99	97	3
	d	CO_2Me	CO_2Me	21	98	2

Table 2 Reaction conditions: benzene, 40°C

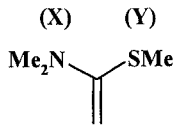
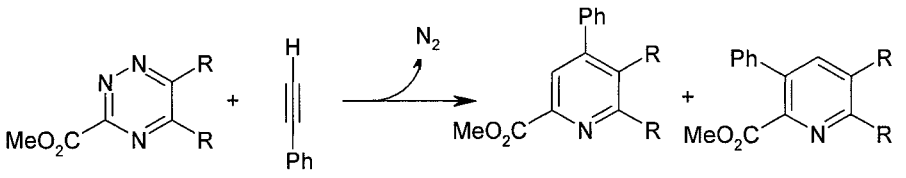
Dienophile 29c	Triazine 28	R^1	R^2	Yield (%)	Ratio 32 : 33	
	**a**	H	H	82	0	100
	b	H	Ph	90	4	96
	c	Ph	Ph	84	92	8
	d	CO_2Me	CO_2Me	91	98	2

Table 3 Reaction conditions: dioxane, 100°C

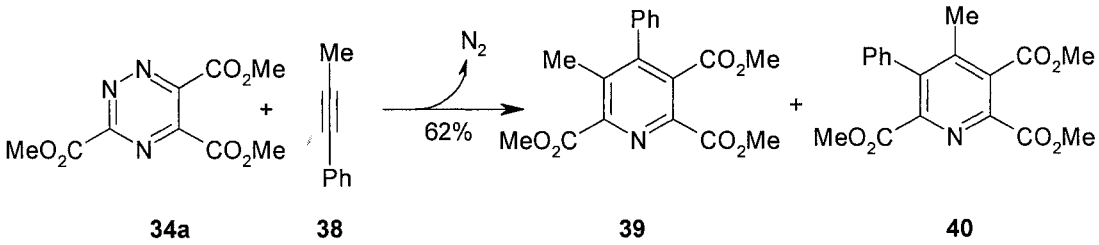
1.2.1.1.2. Acetylenes

The cycloaddition of 1,2,4-triazines **34a** and **34b** (**a** R=CO_2Me and **b** R=Me) with ethynylbenzene **35**[21] was not particularly regioselective and gave mixtures of their respective pyridines **36** and **37** (Scheme 10). With 1,2,4-triazine-3,5,6-tricarboxylic acid trimethyl ester **34a**, pyridines **36a** and **37a** were formed in a ratio of approximately 1:1.3 (84 %) and with 5,6-dimethyl-1,2,4-triazine-3-carboxylic acid methyl ester **34b**, pyridines **36b** and **37b** were formed in a ratio of 1:4 (28 %).



Scheme 10 Reaction conditions: xylene, 145°C, 20 h

Boger and colleagues[25] utilised the reaction of 1,2,4-triazine-3,5,6-tricarboxylic acid trimethyl ester **34a** with prop-1-ynylbenzene **38** in the key step in model studies of the synthesis of Streptonigrin, an anti-tumour antibiotic (Scheme 11). Triazine **34a** was reacted with an excess of **38** in a Parr bomb for 12 hours to give a 3:2 mixture of pyridines **39** and **40**, thus showing little regioselectivity. Fortunately the desired pyridine **39** could be crystallised from this mixture in 18 % yield.

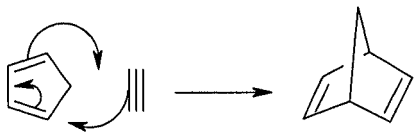


Scheme 11 Reaction conditions: 200°C, in a Parr bomb, 12 h

1.2.1.1.3. Acetylene equivalents:

1.2.1.1.3.1. 2,5-Norbornadiene

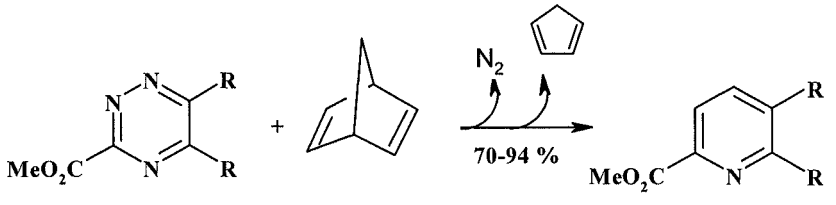
2,5-Norbornadiene **41** is the Diels-Alder product of acetylene and cyclopenta-1,3-diene (Scheme 12), and was found to act as an efficient acetylene equivalent. As well as being an electron-rich compound, it has the added advantage of being a strained ring system which can easily eliminate cyclopenta-1,3-diene. This provides an essential driving force, which allows its participation in the aza Diels-Alder reaction with 1,2,4-triazines.



41

Scheme 12 Formation of 2,5-norbonadiene

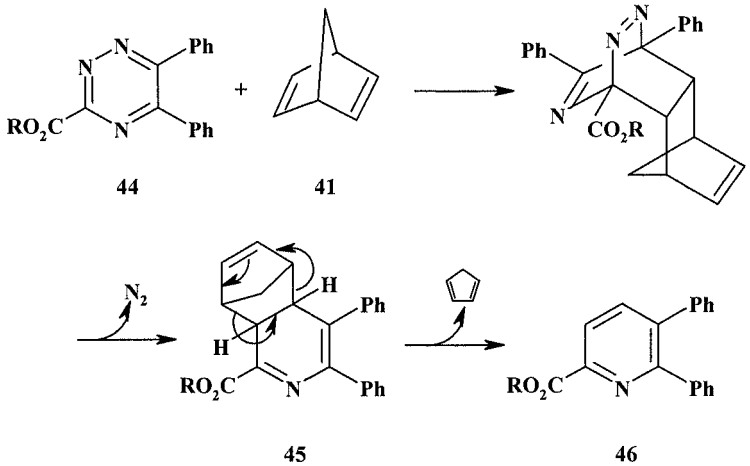
Thus, the cycloaddition reaction of 2,5-norbornadiene **41** with a 1,2,4-triazine was first described in 1969 by Sauer and colleagues[26] (Scheme 13). The triazines **42a-e** (**a**, R=CO_2Me; **b**, R=Ph; **c**, R=*p*-nitrophenyl; **d**, R=Me; **e**, R=H) were heated in the presence of excess 2,5-norbornadiene **41** and the corresponding pyridines **43a-e** were isolated in yields ranging from 70-94 %.



42a-e **41** **43a-e**

Scheme 13 Reaction conditions: benzene, reflux, 4 days

The pathway of the above reaction was later confirmed by Elix and colleagues[27] to be that shown in Scheme 14, whereby the pyridines **46** are obtained from 1,2,4-triazines **44** (R=Et, Me) *via* the dihydropyridines **45**.

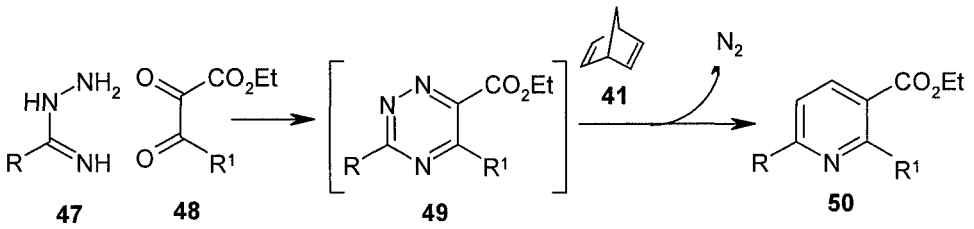


44 **41**

45 **46**

Scheme 14 The general reaction pathway of 1,2,4-triazine **44** with 2,5-norbornadiene **41**

The use of 2,5-norbornadiene **41** as a dienophile in the inverse electron demand Diels-Alder reaction of 1,2,4-triazines has been widely studied. Pyridine derivatives **50a-d** were obtained in one pot by reaction of amidrazone **47**, tricarbonyl **48** and an excess of 2,5-norbonadiene **41** in ethanol at reflux for 20 hours, without the isolation of triazine **49** (Scheme 15). The corresponding 2,2'-bipyridyls **50a-b** and pyridines derivatives **50c-d** were obtained in 59-87% yield.[28,29] Table 4 shows a summary of the results.



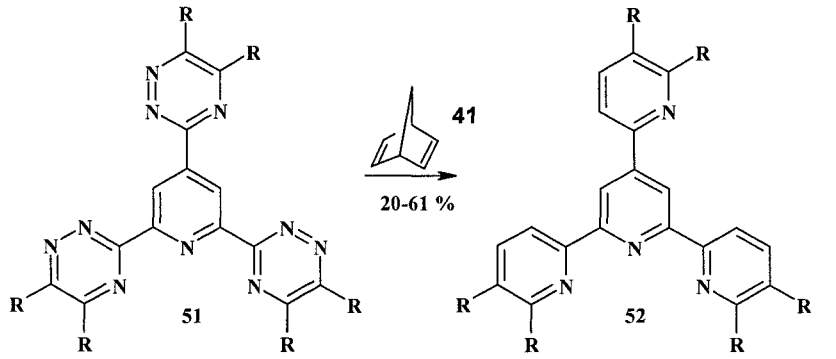
Scheme 15 Reaction conditions: ethanol, reflux, 20 h.

Pyridine 50	R	R^1	Yield (%)
a	2-pyridyl	Ph	87
b	2-pyridyl	*n*-Pr	81
c	CO_2Et	Ph	59
d	CO_2Et	*n*-Pr	78

Table 4 Results obtained for the one-pot procedure to pyridines **50**

Sauer and colleagues have particularly exploited the use of 2,5-norbornadiene **41** in the 'LEGO' type synthesis of various thienyl substituted oligopyridines[30], 2,6-oligopyridines[31], branched oligopyridines[32], superbranched oligopyridines [33] and 6-oligopyridyl-1,5,12-triazaphenylenes[34] from their corresponding 1,2,4-triazines in moderate to excellent yields.

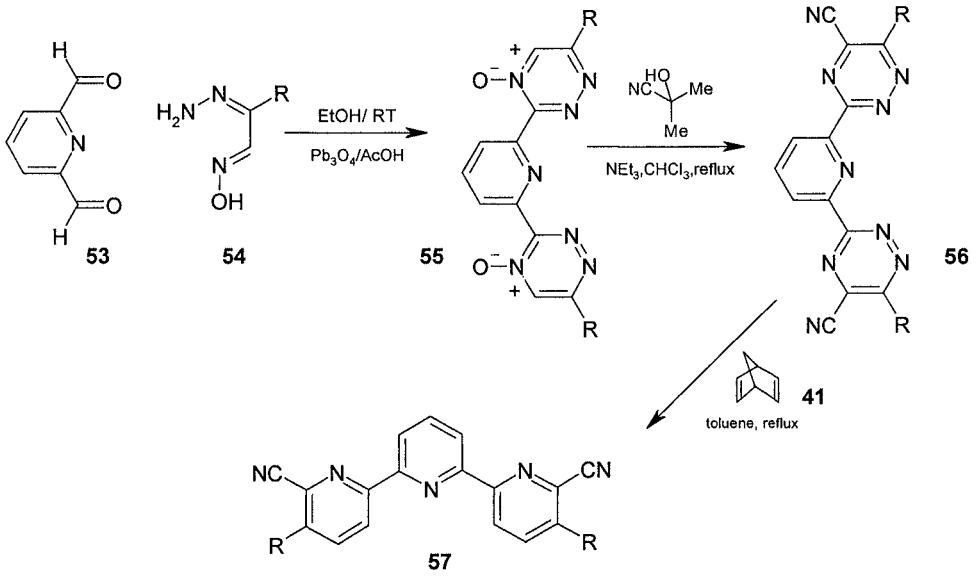
Scheme 16 below shows an example from Sauer's LEGO chemistry where the 1,2,4-triazines **51** reacted with excess of 2,5-norbornadiene **41** to yield the superbranched pyridines **52**.[33]



R=	2-thienyl	**30%**
	2-pyridyl	**49%**
	[2,2']bipyridinyl	**61%**

Scheme 16 Reaction conditions: xylene, 140°C, 1-6 days

Recently, Kozhevnikov and colleagues have exploited the use of the electron-rich compound, 2,5-norbonadiene, in the synthesis of 2,2'-bipyridines and 2,2':6',2"-terpyridines from their corresponding functionalised 1,2,4-triazine-4-oxides[35,36]. 1,2,4-Triazine-4-oxides **55**, obtained from the reaction of hydrazones **54** and pyridine aldehydes **53**, are very electrophilic heterocycles so a cyano group can be easily introduced by nucleophilic substitution. The resulting compounds **56** undergo aza Diels-Alder reaction with 2,5-norbornadiene **41** giving the substituted terpyridines **57** in 70-89% yields (Scheme 17). The cyano group can be readily substituted by water, various aliphatic alcohols, amines or carbanions to give a wide variety of pyridine derivatives.

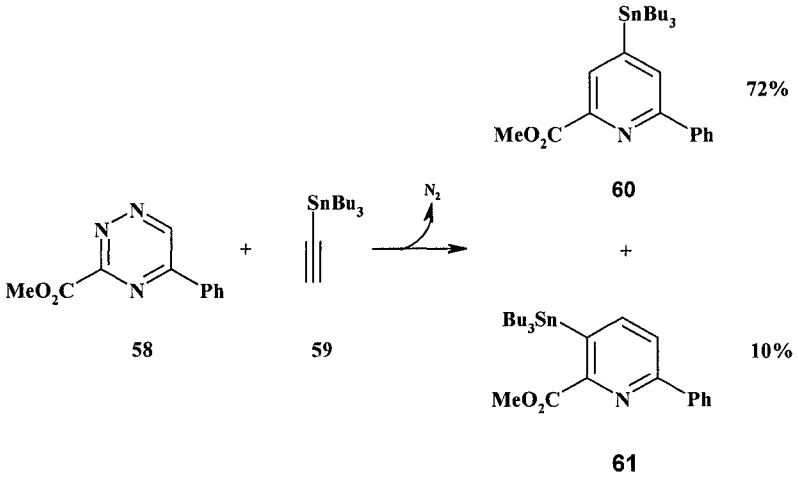


Scheme 17 Synthesis of substituted terpyridines

1.2.1.1.3.2. Ethynyltributyltin

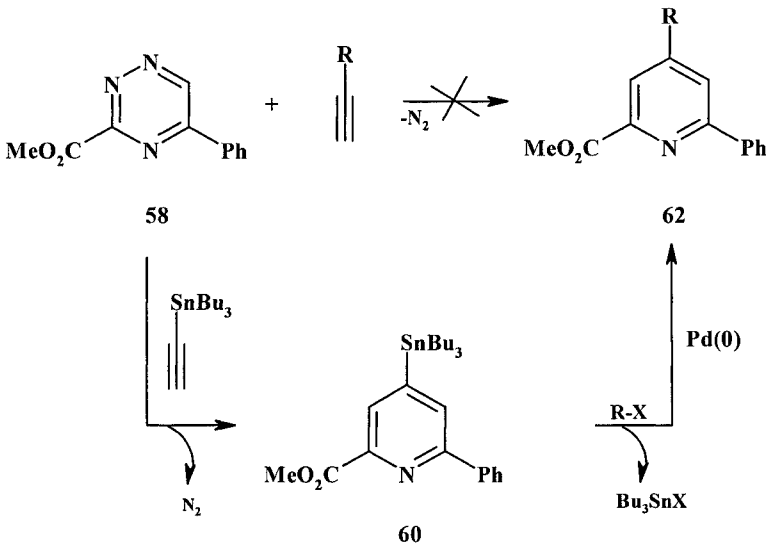
Various reports concerned with the use of organotin compounds in organic synthesis have been described. The trialkylstannyl group undergoes numerous transformations under mild conditions including participating as electron-rich dienophiles in the inverse electron demand aza Diels-Alder reactions with 1,2,4,5-tetrazines[37]. Sauer and colleagues extended the scope of the cycloaddition route towards the synthesis of stannylated pyridines using 1,2,4-triazines.[38]

Therefore, 1,2,4-triazine **58** and ethynyltributyltin **59** were heated at 180 °C in 1,2-dichlorobenzene as solvent for 16 hours and it was found that the regio-isomer **60** was formed predominantly along with **61** as the minor isomer (Scheme 18). The regioselectivity was controlled by steric repulsive forces between the ester functionality of the triazine and the bulky tributyltin substituent of the alkyne. Both isomers could be separated by flash column chromatography.[38]



Scheme 18 Reagents and conditions: 1,2-dichlorobenzene, 180°C, 16 h

The tributyltin substituent of pyridine **60** can be replaced by Pd-catalyzed acylation and arylation and by halogenation to yield functionalised pyridines, which are not available by direct cycloaddition of the corresponding alkynes (Scheme 19). This two-step procedure overcame the most important restriction on the aza Diels-Alder reaction, where the combination of electron deficient dienes and electron deficient dienophiles is not possible and should therefore be of general synthetic importance. Some of the results obtained by Sauer[38] are summarized in Table 5.



Scheme 19 Reaction conditions: see Table 5

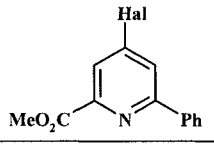
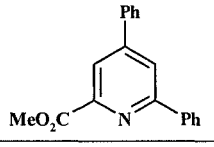
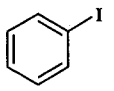
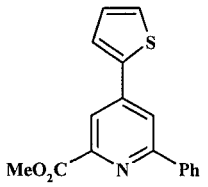
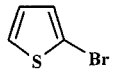
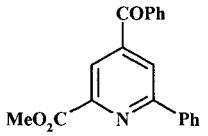
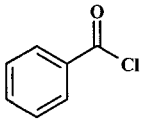
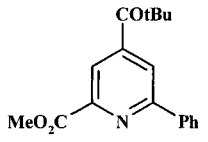
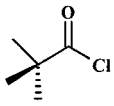
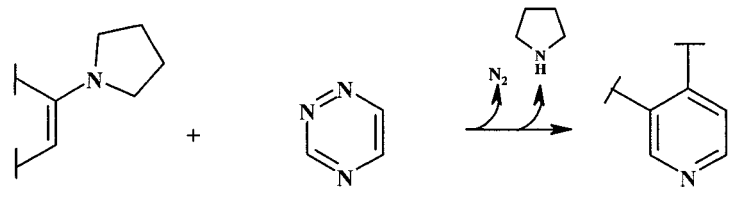
Product 62	R-X	Reaction conditions	Yield (%)
	HCl, Cl_2, Br_2	THF, rt, 20 h	62, 67, 70
		Toluene, 110°C, 2 h, 1.5 % mol $Pd(PPh_3)_4$	63
		Toluene, 110°C, 7 h, 1.5 % mol $Pd(PPh_3)_4$	69
		$CHCl_3$, 65°C, 18 h, 1.5 % mol $BnPdCl(PPh_3)_2$	86
		$CHCl_3$, 65°C, 18 h, 1.7 % mol $BnPdCl(PPh_3)_2$	72

Table 5 Results obtained for the synthesis of pyridines **62**

1.2.1.1.4. Enamines

Boger and colleagues investigated methods for the construction of novel substituted pyridines **65a-g**[39] *via* the inverse electron demand aza Diels-Alder reaction of 1,2,4-triazines **64** with pyrrolidine and morpholino enamines **63a-g** (Scheme 20).



63a-g **64** **65a-g**

Scheme 20 Reaction conditions: DCM, 45 °C, 16-35 h

The pyrrolidine enamines of aliphatic ketones **63a**, cyclopentanones **63d**, and cycloheptanones **63g** proved to be reactive electron-rich dienophiles and generally resulted in clean, rapid and efficient preparation of the annulated pyridines **65b,d-g** with no trace of isomeric pyridines in yields ranging from 64-78 %, whereas cyclohexanone derivatives **63b,c,f** result in lower overall yields. Morpholino enamines **63e** were shown not to be as reactive as pyrrolidine enamines. Table 6 shows a summary of results.

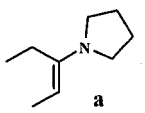
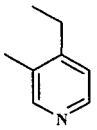
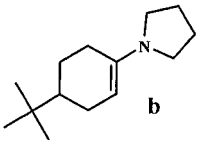
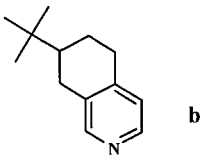
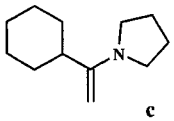
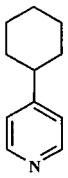
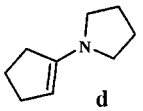
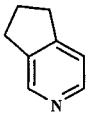
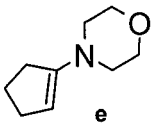
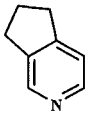
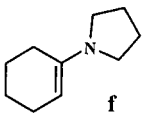
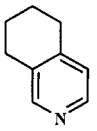
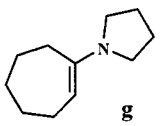
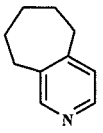
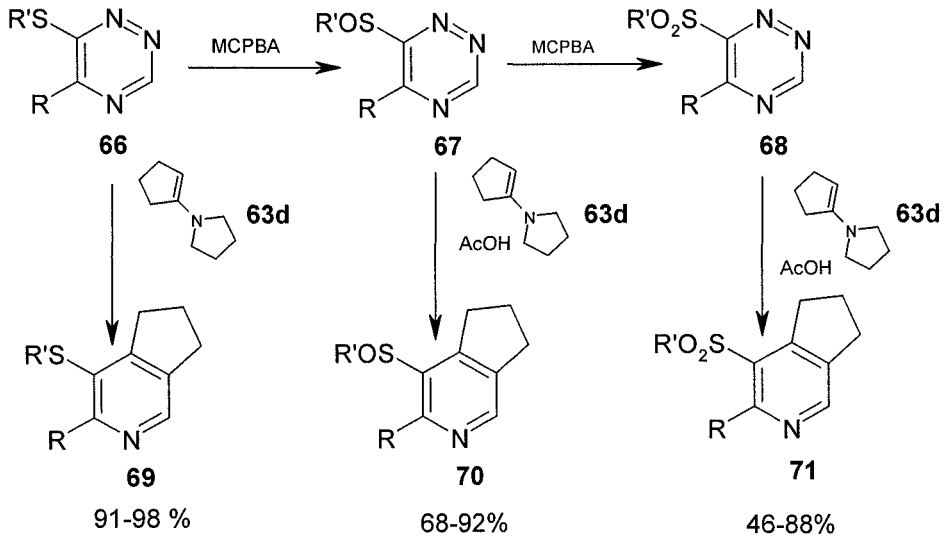
Enamine 63	**Product 65**	**Yield (%)**
 **a**	 **a**	68
 **b**	 **b**	35
 **c**	 **c**	64
 **d**	 **d**	74
 **e**	 **d**	<30
 **f**	 **f**	40
 **g**	 **g**	78

Table 6 Results obtained for the synthesis of pyridines **65**

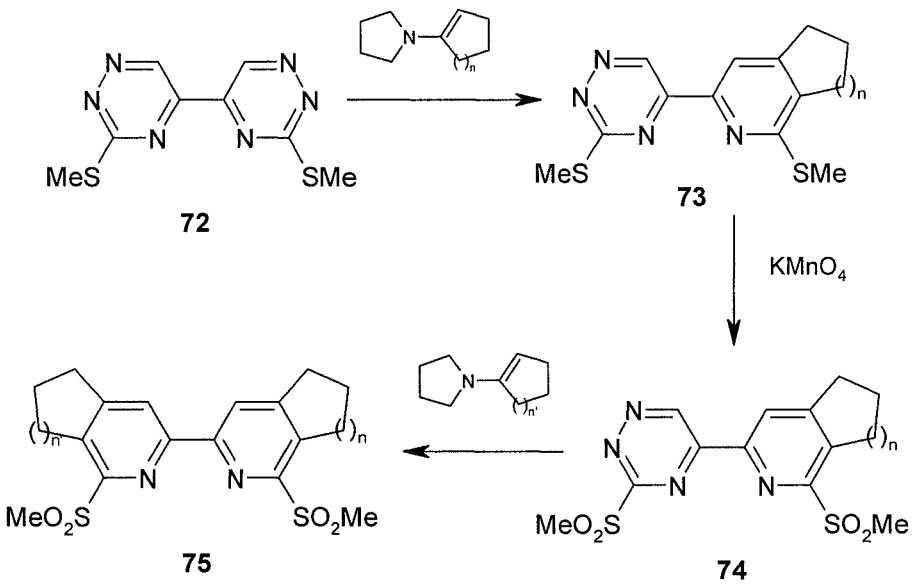
Taylor and colleagues[40] explored the synthesis of substituted pyridines **69** from alkylthio-1,2,4-triazines **66** and enamine **63d**, derived from cyclopentanone.

The triazine **66** could be oxidised with 1 or 2 equivalent of *m*-chloroperbenzoic acid to the corresponding sulphoxide **67** and sulphone **68** respectively. Both **67** and **68** proved to be extremely sensitive toward nucleophiles, but "acidic enamine" conditions in which the nucleophilicity of the enamine **63d** is attenuated by addition of acetic acid to the reaction mixture, leads to the substituted pyridines **70** and **71** (Scheme 21).



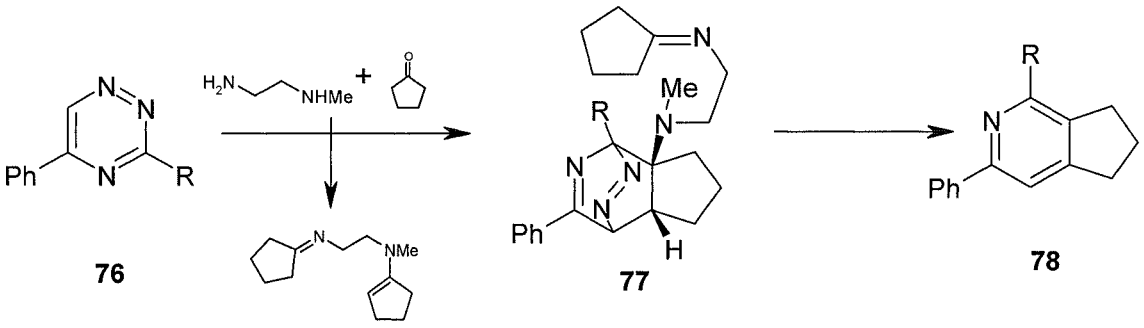
Scheme 21 Reaction of 1,2,4-triazines with enamines

Rykowski and colleagues investigated the use of pyrrolidine enamines in the formation of symmetrical and unsymmetrical bipyridyls. 5,5'-Bi-1,2,4-triazines **72** reacted in boiling dioxane with cyclic enamines to give 5-(heteroaryl)-1,2,4-triazines **73**. These compounds can be oxidised with $KMnO_4$ to the methylsulphonyl derivative **74**, which easily undergo the aza Diels-Alder reactions with different enamines to give unsymmetrical, annulated 2,2'-bipyridines **75** (Scheme 22).[41]



Scheme 22 Formation of unsymmetrical bipyridyls

Taylor and colleagues developed a tethered enamine-imine methodology for the direct conversion of 1,2,4-triazines into highly substituted pyridines *via* the inverse electron demand Diels-Alder reaction, which avoids the need for an aromatisation step. As shown in Scheme 23 the use of a tethered enamine-imine provides an intermediate **77** that exists as a zwitterion, which undergoes elimination *in situ*, leading directly to the pyridine **78**.[42,43]



Scheme 23 Reaction conditions: toluene, reflux

The results summarized in Table 6 show that cyclic ketones comprising small to medium-sized rings (cyclopentanone to cyclooctanone) reacted with triazine **76** to give pyridines **78**

in good to quantitative yields. Much larger rings (cyclododecanone), gave none of the desired pyridines, presumably due to steric factors.

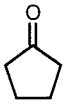
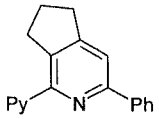
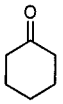
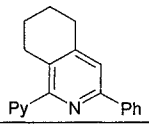
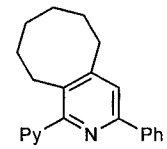
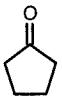
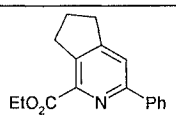
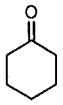
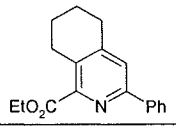
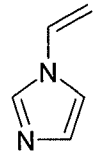
Triazine 76	R	Ketone	Product 78	Yield (%)
a	2-pyridyl			74
				79
				100
b	CO_2Et			33
				61

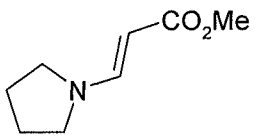
Table 6 Results obtained for the formation of pyridines **78**

1-Vinylimidazole **79** has also been used as a dienophile in the inverse electron demand Diels-Alder reaction giving the single cycloaddition product, which is a useful intermediate in the synthesis of unsymmetrical, bisfunctionalized 2,2'-bipyridines.[44]

Enaminones **80** can also be employed as dienophiles in inverse electron demand Diels-Alder reactions with reactive 1,2,4-triazines[40]. Since they are less electron-rich than an enamine, it reacted best with the most electron-poor dienes. This reaction gave a mixture of cycloaddition and nucleophilic substitution products.



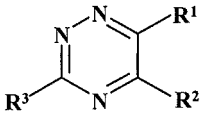
79



80

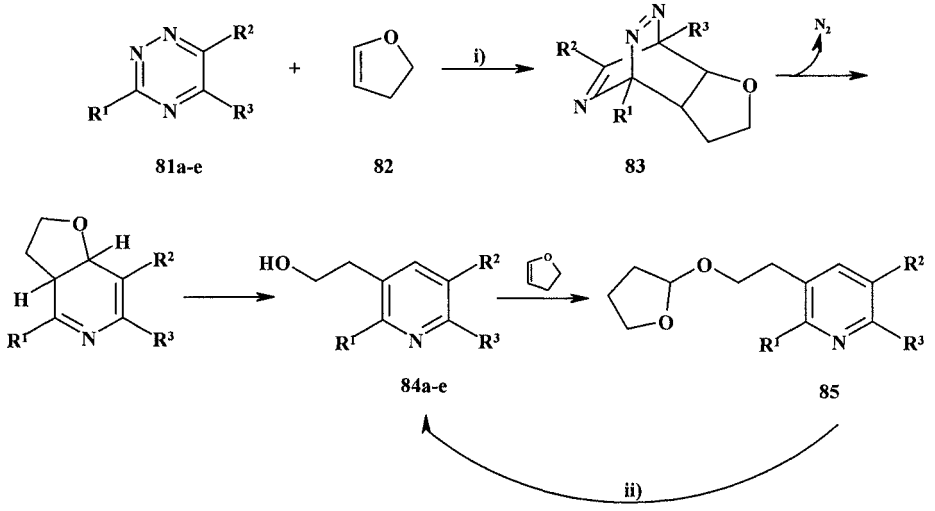
1.2.1.1.5. Cyclic vinyl ethers

Gilchrist and colleagues[45] have explored the aza Diels-Alder reaction of a range of 1,2,4-triazines **81a-e** with cyclic vinyl ethers as a new route to pyridines with functionalised side chains.



81a $R^1 = R^2 = CO_2Et$, $R^3 = NH_2$
81b $R^1 = R^2 = Ph$, $R^3 = CO_2Et$
81c $R^1 = R^2 = CO_2Et$, $R^3 = NHCOMe$
81d $R^1 = R^2 = CO_2Et$, $R^3 = Me$
81e $R^1 = R^2 = R^3 = CO_2Et$

With 2,3-dihydrofuran **82**, 1,2,4-triazines **81b-e** reacted regioselectively to form a cycloadduct **83** which after eliminating nitrogen and opening of the saturated ring yielded the corresponding pyridines **84b-e** (Scheme 24). These however, reacted with further 2,3-dihydrofuran **82** present in excess to give the acetals **85**. The unprotected pyridines **84b-e** were easily obtained by deprotection promoted by either aqueous perchloric or hydrochloric acid. Table 7 shows a summary of these results.



Scheme 24 Reaction conditions: (i) chloroform, reflux; (ii) aq $HClO_4$ or HCl

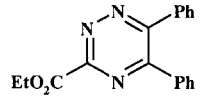
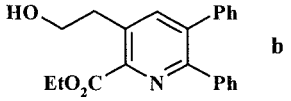
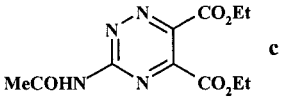
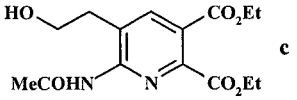
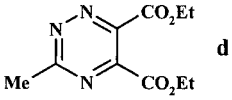
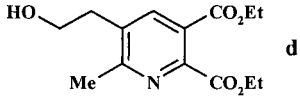
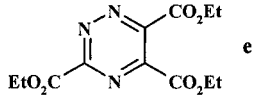
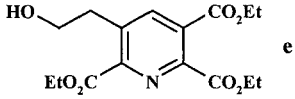
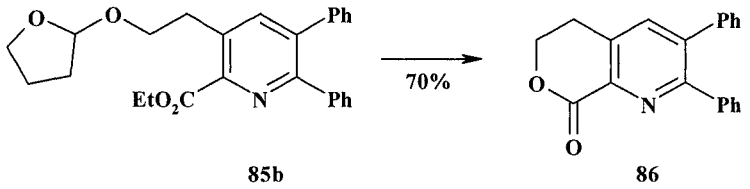
Triazine 81	Unprotected Pyridine 84
 b	 b
 c	 c
 d	 d
 e	 e

Table 7

The reactivity observed was significantly affected by the nature of the 1,2,4-triazine substituents. 1,2,4-Triazines **81d** (activated by two ethoxycarbonyl substituents) and **81e** (activated by three ethoxycarbonyl substituents) proved to be the most reactive giving their corresponding substituted pyridines **85d-e** both in 80 % yield. 1,2,4-Triazine **81b** (with one ethoxycarbonyl substituents) and **81c** (with two ethoxycarbonyl and an electron-donating acetamido substituents) were less reactive giving pyridines **85** in 55 % and 67 % yields respectively. Compound **81a** was not reactive enough to participate in these reactions.

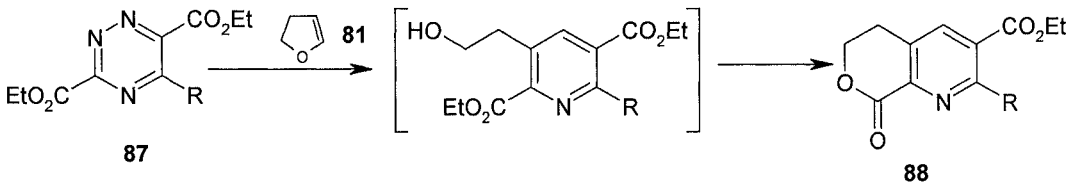
In one case the deprotection procedure led to a different result. On treating the protected pyridine **85b** dissolved in chloroform and in the presence of water with an excess of perchloric acid an intramolecular cyclisation occurred forming the lactone **86** in good yield (70 %) (Scheme 25).



85b 86

Scheme 25 Reaction conditions: aq. $HClO_4$

Triazines **87** have been shown to react with 2,3-dihydrofuran **81** in ethanol at reflux in a 'one-pot' reaction yielding the lactones **88**, in moderate yields (both 44%) as shown in Scheme 26.[29]



87 88

R= Me
n-Pr
Ph

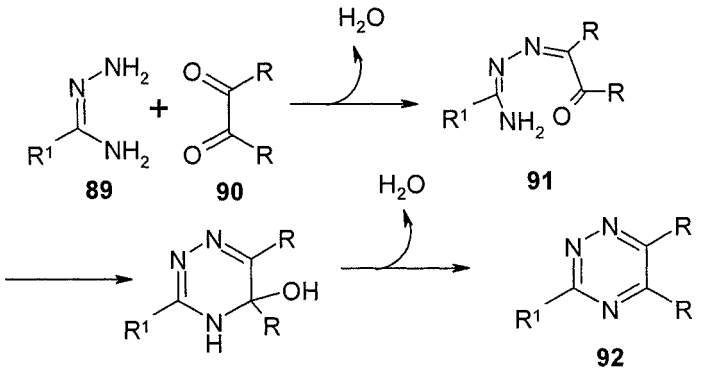
Scheme 26 Reaction conditions: ethanol, reflux

1.3. 1,2,4-Triazines

1.3.1. Formation of 1,2,4-triazines

1.3.1.1. From dicarbonyls

Probably the best method for the synthesis of alkyl, aryl or heteroaryl substituted 1,2,4-triazines is by reaction of amidrazones **89** with 1,2-dicarbonyl compounds **90** (Scheme 27). Since the first step of this reaction, the condensation the hydrazine nitrogen with one carbonyl group (to give the intermediate **91**), is fast, while condensation of the amine group with the other carbonyl group (to give the 1,2,4-triazine **92**) is often slow, the intermediate **91** has been isolated in a few cases.



Scheme 27 Preparation of 1,2,4-triazines using amidrazones

A wide range of examples can be found in the literature for the formation of 1,2,4-triazines from amidrazone and symmetrical dicarbonyls. Table 8 below shows a few selected examples. The yields are generally good to excellent.

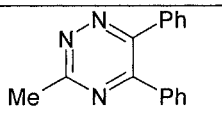
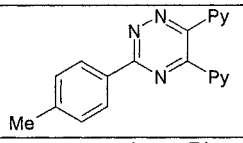
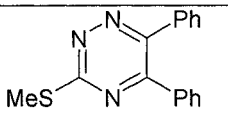
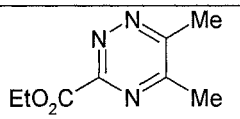
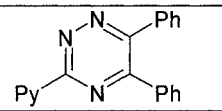
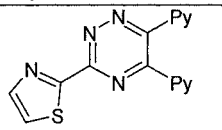
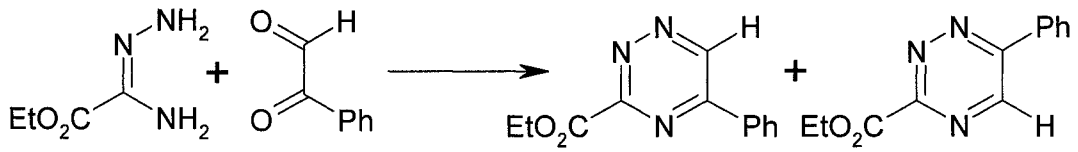
R^1	R	Reaction conditions	Product 92	Yield (%)	Ref
Me	Ph	Ethanol, reflux		96	46
p-CH_3-C_6H_4	2-Pyridyl	Ethanol, reflux		95	46
SMe	Ph	Ethanol, reflux		88	47
CO_2Et	Me	i) Ethanol, RT, 16 h ii) reflux, 1 h		69	48
2-Pyridyl	Ph	Ethanol, RT, 16 h		57	49
2-Thiazolyl	2-Pyridyl	DMF, RT		73	49

Table 8 Formation of 1,2,4-triazines **91** from symmetrical dicarbonyls

The reaction of amidrazone **93** with unsymmetrical dicarbonyl **94** gives a mixture of isomers **95** and **96** (34:1) as shown in Scheme 28[48]. The formation of the major isomer results from the attack of the more reactive hydrazine nitrogen at the least sterically crowded aldehyde carbonyl group of the dicarbonyl.

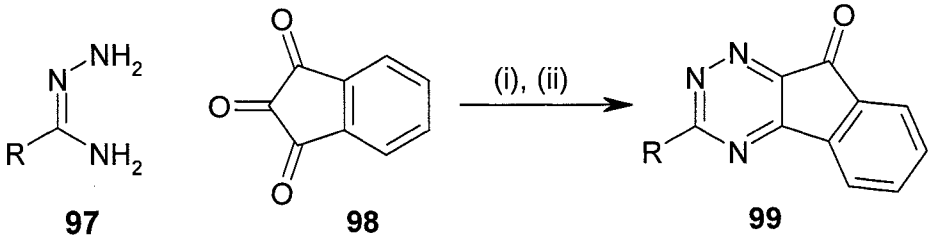


93 **94** **95** **96**

Scheme 28 Reaction conditions: ethanol, reflux

1.3.1.2. From tricarbonyls

Symmetrical tricarbonyl compounds, such as ninhydrin **98**, have been shown to react regioselectively with amidrazones **97** at the central carbonyl group, yielding the corresponding 1,2,4-triazines **99**. Case and colleagues[50] exploited this method to synthesise a number of 3-substituted-1,2,4-triazafluoren-9-ones **99** in yields ranging from 35-74% (Scheme 29).

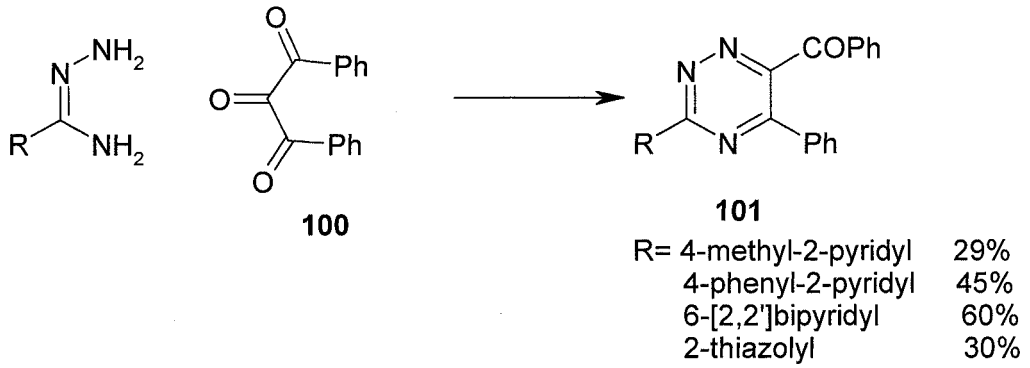


97 **98** **99**

R= 4-methyl-2-pyridyl	41%
4-phenyl-2-pyridyl	45%
6-[2,2']bipyridyl	35%
2-thiazolyl	74%

Scheme 29 Reaction conditions: (i) ethanol, RT, 3h; (ii) precipitate heated at 180°C, 1 h

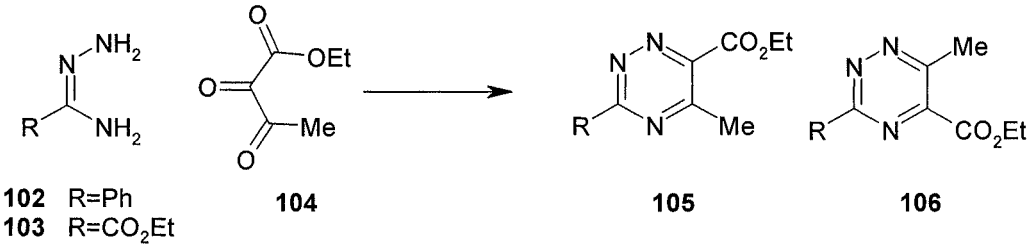
Tricarbonyl compound **100** has also been shown to react regioselectively[50] with a wide range of amidrazones to yield the 3-substituted-5-phenyl-6-benzoyl-1,2,4-triazines **101** in yields ranging from 29-60% as shown in Scheme 30.



Scheme 30 Reaction conditions: ethanol, reflux, 2.5 h

Interestingly, with the exception of a few isolated examples, the reactions of amidrazones with unsymmetrical tricarbonyl compounds have not been studied in detail.

When the amidrazone **102** was reacted with tricarbonyl **104** a mixture of triazines **105** (R=Ph) and **106** (R=Ph) (resulting from attack of the hydrazine moiety of the amidrazone at each of the keto-carbonyl compound **104**) were obtained in unspecified yields[51] (Scheme 31). Synder and co-workers[48] studied the reaction of the same tricarbonyl with amidrazone **103** and obtained a 10.5:1 mixture of triazines **105** (R=CO_2Et) and **106** (R=CO_2Et).



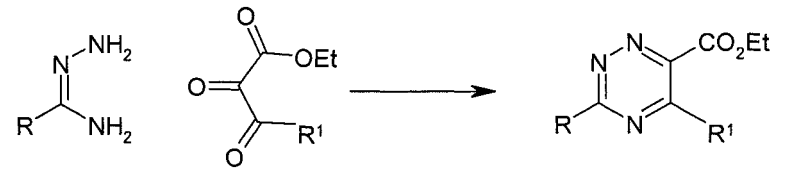
102 R=Ph
103 R=CO_2Et

104 **105** **106**

Scheme 31 Reaction conditions: ethanol, reflux

However, amidrazone **102** reacted regioselectively with unsymmetrical tricarbonyl **108a** (R^1=Ph) to give 3,5-diphenyl[1,2,4]triazine-6-carboxylate **109a** in 77% yield with no trace of any regioisomer [52] (Scheme 32). It appeared that the more reactive hydrazine nitrogen of the amidrazone reacted only at the central ketone carbonyl followed by cyclisation and dehydration, thus producing only one regioisomer. Tricarbonyl **108a** (R^1=Ph) also reacted with amidrazone **103** and **107** to give a single triazine **110a** and **111a** in 82 % and 94% yield respectively[29].

The size of the substituent in the tricarbonyl seemed to have an effect in the regioselectivity of the formation of 1,2,4-triazines. It was anticipated that tricarbonyl compounds with sterically crowded R^1 substituents might react regioselectively with amidrazones **103** and **104** yielding the corresponding 1,2,4-triazines **110** and **111** without formation of regioisomers. Therefore, Stanforth and co-workers decided to study the effect of larger substituents in the tricarbonyl **108** (**a** R^1= Ph; **b** R^1= *n*-Pr; **c** R^1=*i*-Pr) and showed that in these cases only one isomer **110a-c** and **111a-c** was formed in excellent yields (>90%). Table 9 shows a summary of the results.



102 R=Ph
103 R=CO_2Et
107 R=2-Pyridyl

108a-c

109a R=Ph
110a-c R=CO_2Et
111a-c R=2-Pyridyl

Scheme 32 Reaction conditions: ethanol, reflux

Triazine	R	R^1	Yield (%)	Ref.
109a	Ph	Ph	77	52
110a	CO_2Et	Ph	82	29
110b	CO_2Et	*n*-Pr	>90%	29
110c	CO_2Et	*i*-Pr	>90%	29
111a	2-Pyridyl	Ph	94%	28
111b	2-Pyridyl	*n*-Pr	97%	28
111c	2-Pyridyl	*i*-Pr	90%	28

Table 9 Results obtained for the formation of 1,2,4-triazines

1.4. 1,2,3-Tricarbonyls

Vicinal tricarbonyls have been known in organic chemistry for almost a century. The highly electrophilic nature of the carbonyl groups, particularly the central carbonyl, favours intramolecular or intermolecular nucleophilic reactions. Thus, tricarbonyls are very reactive compounds.

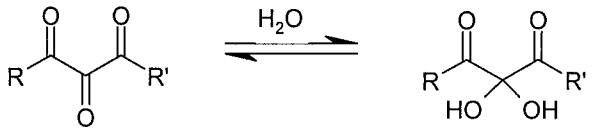
However, despite the relatively straightforward availability of these compounds and high reactivity, they received little attention as reagents in organic synthesis until late in the 20th century. Since then, this functionality has played a key role in the preparation of a number of natural products as well as being a versatile electrophilic intermediate for the synthetic chemist, particularly in the preparation of heterocyclic systems. The discovery that related tricarbonyl subunits are contained in the immunosuppressant FK-506[53], rapamycin[54] and other biologically important compounds (such as potent serine protease inhibitors)[55] has drawn special attention to the study of these compounds.

They have also received remarkable interest by virtue of their wide applications for analytical purposes. Thus, they are used for the quantitative analysis of amino acids (Strecker degradation) as well as for the detection of peptides, proteins, primary amines and ammonia, particularly, in biological fluids.

1.4.1. Formation of 1,2,3-tricarbonyls

Numerous methods have been reviewed in the literature to the date for the synthesis of vicinal tricarbonyls.[56-58] However, these methods have limitations with respect of the efficiency of the reaction sequences and the functionalities which can tolerate the strong oxidizing conditions. The development of new methods for preparing vicinal tricarbonyls is therefore, highly desirable.

Since many procedures for the synthesis of tricarbonyls **112** involve aqueous medium, these compounds are usually isolated as their hydrates **113,** although they can be converted to the free tricarbonyl **112** by processes such as distillation, sublimation and heating over phosphorus pentoxide at reduced pressure *etc.* However, in this thesis, tricarbonyl compounds have been represented as shown in formulae **112** for simplicity.

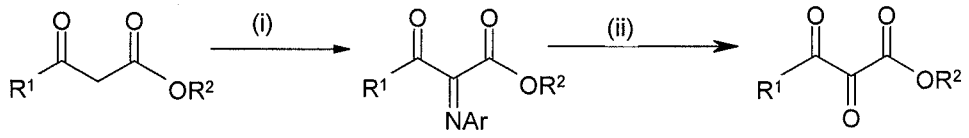


112 **113**

Scheme 33

1.4.1.1. From 1,3-dicarbonyl compounds

The readily availability and the enhanced reactivity of their α-position have made β-dicarbonyls starting materials of choice for the synthesis of tricarbonyls. Sachs reported the first method for preparing a vicinal tricarbonyl from a dicarbonyl compound in 1901. The synthesis consisted of a base catalysed condensation of the β-dicarbonyl **114** with *p*-dimethylaminonitrosobenzene (which is very toxic) giving an imine intermediate **115** that was hydrolyzed by strong acid to form the central carbonyl (Scheme 33). This method has afforded good yields of tricarbonyls in cases where oxidation procedures could not be employed, including indole derivatives **116a** [59], vinylpyrroles **116b** [60] and the *p*-dimethylaminophenyl derivative **116c** [61], as shown in Table 10.



114 **115** **116**

Scheme 34 Reaction conditions: (i) *p*-dimethylaminonitrosobenzene, KOH, EtOH, RT. (ii) 6N HCl, DCM, 0°C

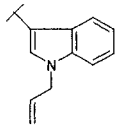
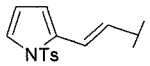
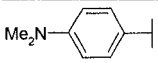
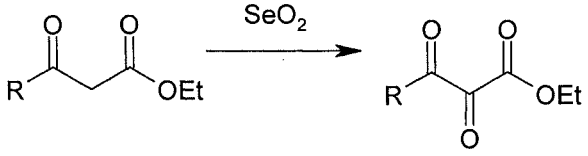
Entry	R^1	R^2	Yield (%)
116a		^{t}Bu	51
116b		Et	70
116c		^{t}Bu	48

Table 10 Results obtained for the formation of **116**

1.4.1.1.1. Direct oxidation of β-dicarbonyls

Selenium dioxide has been used as a reagent with β-dicarbonyls **117** in a few cases for the preparation of tricarbonyls [62] (Scheme 35). Yields ranged from 65-88% (Table 11). However, this reagent frequently affords quite complex reaction mixtures and products contaminated with toxic selenium impurities that are difficult to remove, and is restricted to aryl substituents.



117 **118**

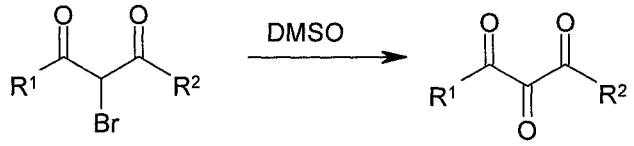
Scheme 35 Reaction conditions: SeO_2, dioxane, reflux, 18h.

Tricarbonyl	R	Yield (%)
118a	Ph	66
118b	*p*-$NO_2C_6H_4$	88
118c	*p*-$CH_3C_6H_4$	69
118d	*p*-$CH_3OC_6H_4$	65

Table 11 Results obtained for the direct oxidation to **118a-d**

1.4.1.1.2. From bromodicarbonyls

The conversion of β-dicarbonyl compounds to monobromo derivatives **119** followed by replacement of the activated bromine atom by a carbonyl oxygen with dimethyl sulfoxide (DMSO) has been investigated by Wolfe *et al.*[63] and Dahn and co-workers [62] (Scheme 36). This method provides high yields of the tricarbonyls **120**, some of which are shown in Table 12. However, the starting halo ketones are quite sensitive substances and must be used shortly after their preparation to ensure high overall yields. This chemistry is restricted to aryl substituents.



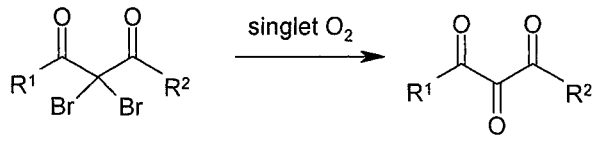
119 **120**

Scheme 36 Reaction conditions: 18h, 80 °C

Tricarbonyl 120	R^1	R^2	Yield (%)
a	Ph	Ph	85
b	*p*-Cl-Ph	*p*-Cl-Ph	91
c	*p*-CH_3O-Ph	*p*-CH_3O-Ph	90
d	*p*-CH_3O-Ph	Ph	86

Table 12 Results obtained for the formation of tricarbonyls **120**

Wamhoff *et al*[64] reported the reaction of dihalodiones **121** (dibromides or dichlorides) with singlet oxygen (generated by methylene blue sensitized photolysis) to yield the tricarbonyls **120** in excellent yields (Scheme 37). Table 13 shows a summary of results.



121 **120**

Scheme 37

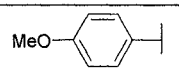
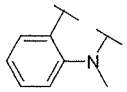
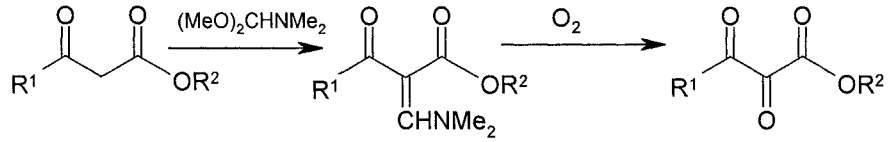
Tricarbonyl 120	R^1	R^2	Yield (%)
a	Ph	Ph	90
d	Ph		85
e			90

Table 13 Results obtained for the oxidation of dibromides **121**

1.4.1.1.3. From 2-enamino-3-ketoesters

The β-dicarbonyl **114** reacted under very mild conditions, dimethylformamide dimethylacetal at room temperature, to form dimethylaminomethylene derivatives **122**[65] (Scheme 38). The cleavage of the enamine to form the tricarbonyl **116** could be accomplished either by photooxidation or ozonolysis, but the yields were generally better using the singlet oxygen photooxidation (Table 14).



114 **122** **116**

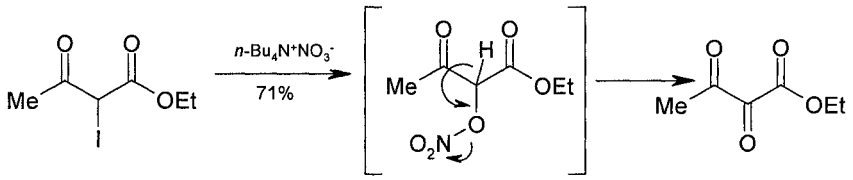
Scheme 38

Tricarbonyl 116	R^1	R^2	Yield (%) photooxidation
d	Me	^{t}Bu	79
e	Me	CH_2Ph	83
f	OEt	Et	84
g		Et	83

Table 14

1.4.1.1.4. From nitrate esters

Tricarbonyl compounds were prepared in a few cases by reacting some electrophiles, bearing a C=O vicinal to the leaving group (α-halo-β-dicarbonyl), with an anion exchanger, in the nitrate form, or with the ammonium salt n-$Bu_4N^+NO_3^-$ [66]. In some cases the reaction of electrophiles resulted in the direct formation of tricarbonyls, owing to spontaneous decomposition of the intermediate nitrate esters as illustrated in Scheme 39.

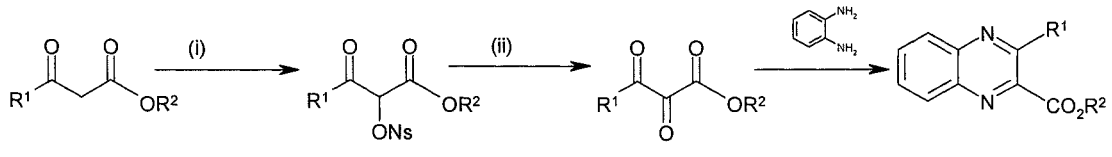


123 124

Scheme 39 Reaction conditions: benzene, RT.

1.4.1.1.5. From *p*-Nitrobenzenesulfonates

Hoffman and co-workers[67] investigated the conversion of 2-(nosyloxy)-3-keto esters to tricarbonyls (Scheme 40). The β-dicarbonyls **114** reacted under mild conditions with *p*-nitrobenzenesulfonyl peroxide to give the 2-(nosyloxy)-3-keto esters **125**. These compounds, bearing a functional group with excellent leaving ability, were converted to their corresponding tricarbonyl compounds **116** in high yields, by treatment with triethylamine in benzene at room temperature. The isolation of the tricarbonyls was unsuccessful but they were reacted *in situ* with *o*-phenylenediamine to form quinoxalines **126** in excellent yields, indicating that the tricarbonyls had been formed very efficiently. Table 15 shows a summary of results.



114 125 116 126

Scheme 40 Reaction conditions: (i) (p-$NO_2C_6H_4SO_2O)_2$, DCM, 0 °C.
(ii) NEt_3, benzene, 25 °C, 1h.

R^1	R^2	Yield of 126 (%)
Me	Et	74
Me	Me	94
$CH(CH_3)_2$	Et	84
Ph	Et	92

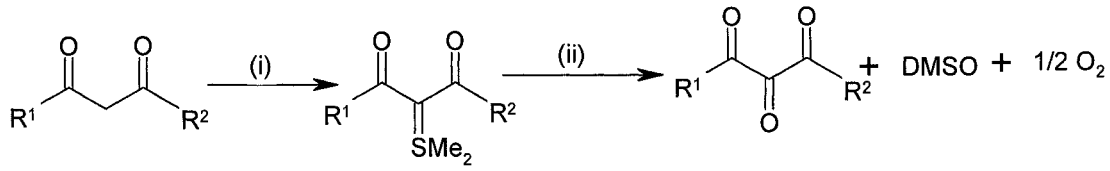
Table 15 Results obtained for the synthesis of **126**

1.4.1.1.6. Oxidative cleavage of ylides

Schank and co-workers developed several procedures for the preparation of tricarbonyls in good yields by ozonolysis of sulfonium, pyridinium, iodonium and phosphonium ylides.

1.4.1.1.6.1. Sulfonium ylides

Dimethylsulfonium ylides **128** were obtained by reaction of β-dicarbonyl compounds **127** with acetic anhydride and DMSO. Further ozonolysis of **128** in methylene chloride at low temperature produced DMSO and the corresponding tricarbonyl compound **120** in good yields[68,69] (Scheme 41). Table 16 shows some selected results.



127 **128** **120**

Scheme 41 Reaction conditions: (i) DMSO, Ac_2O; (ii) O_3, DCM, -70 °C.

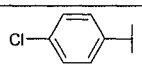
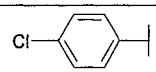
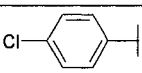
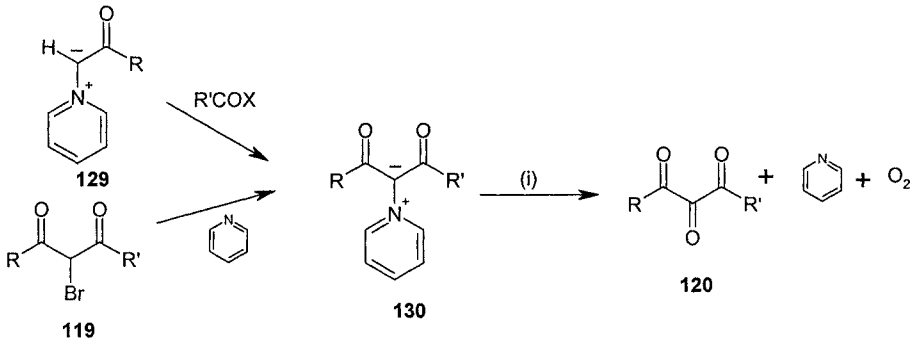
R^1	R^2	Yield of 120(%)
Ph	Ph	88
Ph		93
		91

Table 16 Results obtained for the oxidation of sulfonium ylides **128**

1.4.1.1.6.2. Pyridinium ylides

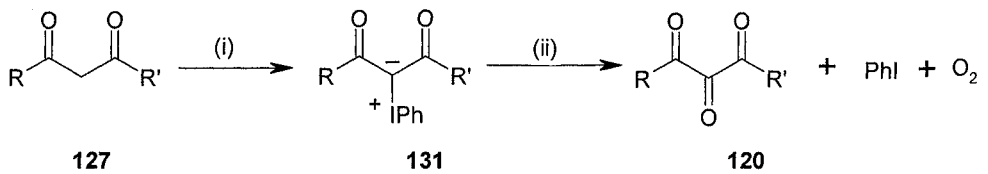
Pyridinium ylides **130** were prepared either by reaction of pyridine with α-bromo-β-diketones **119** or by reaction of preformed ylides **129** with acid chlorides. Further ozonolysis afforded tricarbonyls **120** directly[70] (Scheme 42).



Scheme 42 Reaction conditions: (i) O_3, DCM, -70 °C

1.4.1.1.6.3. Iodonium ylides

Iodonium ylides **131** were obtained by reaction of β-dicarbonyl compounds **127** with phenyl iodosoacetate[71]. Compounds **131** were then oxidized by ozone to give the tricarbonyls **120** and iodobenzene as a by-product (Scheme 43). Yields ranged from 65-92%. However, this method failed for the last two entries in Table 17 in which a functionality that can be attacked by ozone is present and therefore, peroxidic products were found. Some results are summarized in Table 17.



Scheme 43 Reaction conditions: (i) $PhI(OAc)_2$, EtOH, Na_2CO_3; (ii) O_3, DCM, -40 °C

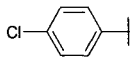
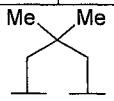
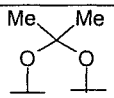
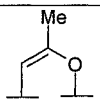
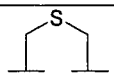
R	R'	Yield (%)
Me	Me	71
Ph	Ph	70
Ph		73
		82
		88
		-
		-

Table 17

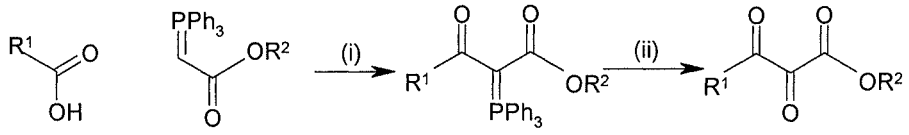
1.4.1.1.6.4. Phosphonium ylides

Bestmann and Kloeters[72] first showed that a triketone was obtained by ozonolysis of a phosphorous ylide in their preparation of ninhydrin. This method has been used extensively by Wasserman and co-workers for the preparation of many diketoesters.

Wasserman and co-workers [73] developed a method to generate precursors of the tricarbonyl system by a mild, generally applicable coupling reaction starting with carboxylic acids. The carboxylic acid **132** or its acid chloride undergoes reaction with the phosphorane **133** to form the ylide **134** in yields ranging from 76-97 %, as shown in Scheme 44.

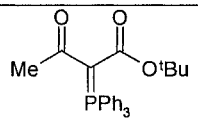
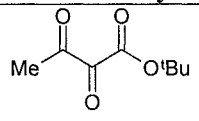
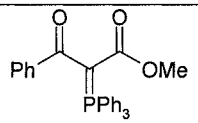
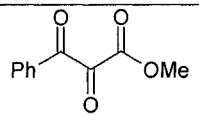
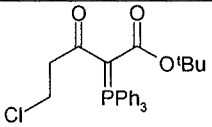
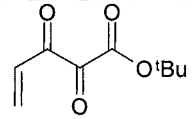
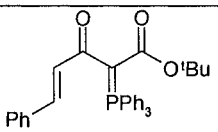
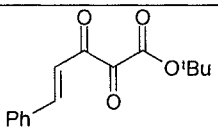
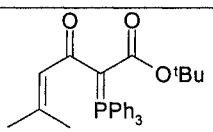
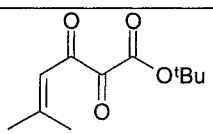
This ylide can be readily converted to the tricarbonyl **120** by oxidative cleavage of the carbon=phosphorus double bond by singlet oxygen, ozone and "Oxone"[74] (commercial name for potassium peroxymonosulphate). The "Oxone" reaction was slower than ozonolysis but more selective in complex cases. Seeking to obtain selectivity in the oxidative generation of the tricarbonyl, dimethyldioxirane (DMD, prepared by reaction of "Oxone" with acetone) has been recently investigated as an oxidant, providing a better and milder reaction. A list of α,β-diketoesters prepared in this way is presented in Table 18.

In reactions where oxidation selectivity was required, such as conjugated olefins (entries 3-5) where the carbonyl conjugated olefin could also be oxidized, DMD was added at -78 °C, resulting in a selective oxidation. This examples show that DMD can oxidize the carbon-phosphorus double bond in the presence of unsaturation and that the conversions to the tricarbonyls are therefore improved relative to known methods. Tricarbonyls with substituents containing heteroatoms and heteroaromatics are of special interest in the synthesis of biologically interesting agents, and have also been successfully synthesized using DMD as the oxidant.



132 **133** **134** **120**

Scheme 44 Reaction conditions:
(i) EDCl, DCM, RT, 16 h
(ii) DMD, DCM, RT, 1h

Entry	Ylide	Tricarbonyl	Yield (%)
1			100
2			100
3			82
4			85
5			100

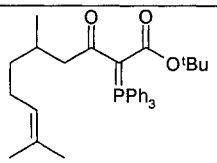
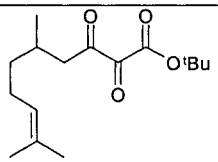
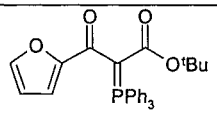
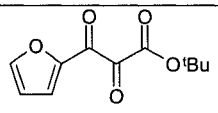
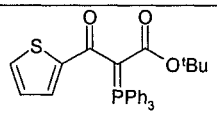
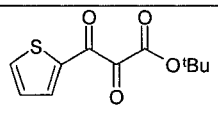
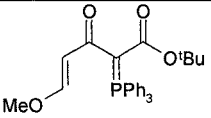
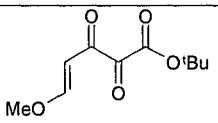
6			83
7			97
8			97
9			70

Table 18 Results obtained for the oxidation of phosphonium ylides **134**

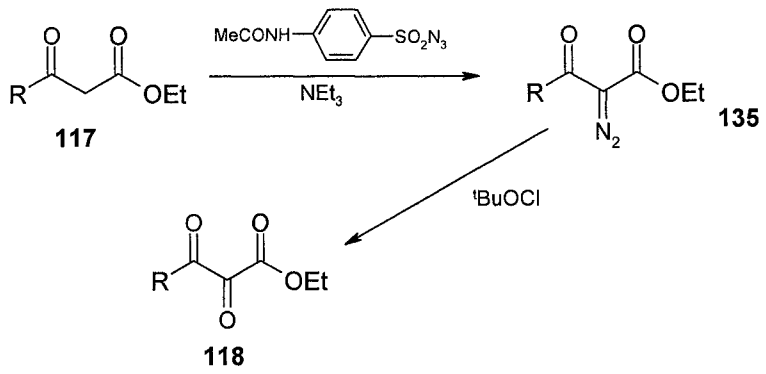
This procedure could also be applied for the synthesis of bis-vicinal tricarbonyls from readily available diacids[75]. Interestingly, these compounds have been shown to be effective interstrand DNA cross-linking agents. A group of di- and tri-peptides terminating in vicinal tricarbonyls were also synthesized and have proven to be potent serine protease inhibitors. These results prove the high biological activity of this powerful electrophilic unit.

However, despite the efficiency and high selectivity of DMD as an oxidant for a variety of substrates, like other oxidizing agents previously studied, it was not selective in oxidizing phosphorus ylides in the presence of nitrogen heterocycles including pyrroles, indoles, and pyridines. In addition to that, this method of preparing α,β-diketoester equivalents would generate large quantities of triphenylphosphine oxide as a by-product which would not be desirable when manufacturing large quantities of compounds.

1.4.1.1.7. Diazo-dicarbonyl compounds

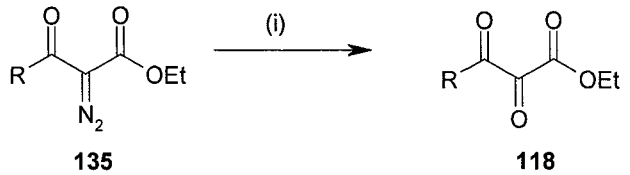
Tricarbonyls could be obtained from the β-dicarbonyls *via* the diazo compound in good yields. The "diazo-transfer" reaction reviewed by Regitz[76,77] provides an efficient method for the synthesis of α-diazo-β-dicarbonyls **135**. These compounds react with a variety of substrates to give mono-substituted β-dicarbonyls, some of which can be converted to tricarbonyl compounds.

The α-diazo-β-dicarbonyls **135** have been shown to react with *t*-butyl hypochlorite[78] to provide diaryl and alkylaryl tricarbonyl derivatives **118** in nearly quantitative yields.



Scheme 45

The reaction of the α-diazo-β-dicarbonyls **135** with dimethyldioxirane (DMD) (Scheme 46), reported by Saba and co-workers showed to also give high yields of tricarbonyls **118** (100% yield for R= Me and 94 % yield for R= Ph).



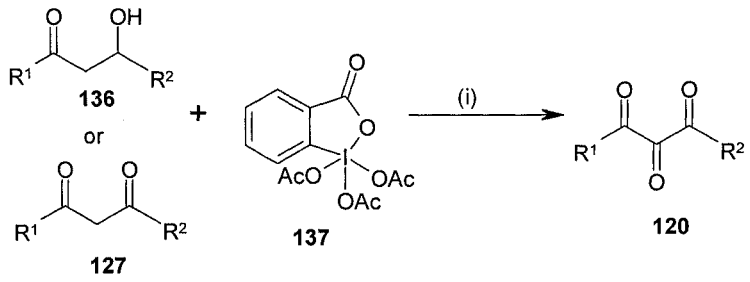
Scheme 46 Reaction conditions: (i) DMD, acetone, RT, 25 h

Using this methodology, Wang *et al.*[79] have recently developed a one-pot approach for the synthesis of aryl-dicarbonyls through diazo transfer, followed by oxidation with DMD generated *in situ* from acetone and commercially available "Oxone".

1.4.1.1.8. Dess Martin reagent

Golec *et al.* [80] showed that tricarbonyls **120** were formed in one step by treatment of β-dicarbonyls **127** with Dess-Martin periodinane reagent **137**. Similarly β-hydroxycarbonyl **136** were oxidized to their corresponding tricarbonyls in relatively good yields. Apparently, hydroxyketones are oxidized to diketones which then are converted to tricarbonyls **120** as shown in Scheme 47. Table 20 shows a summary of results.

Interestingly unlike known oxidizing agents, this method is selective in the presence of nitrogen heterocycles. However, the high cost of this reagent and the formation of potentially explosive intermediates do not make this route viable for a large scale work.



Scheme 47 Reaction conditions: DCM, RT, pyridine

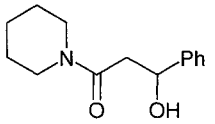
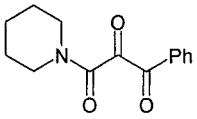
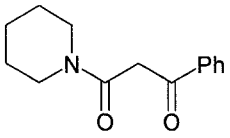
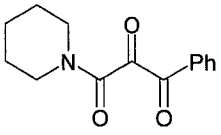
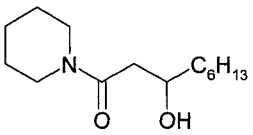
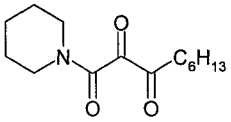
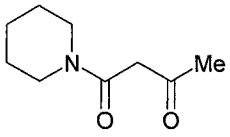
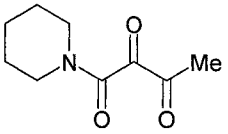
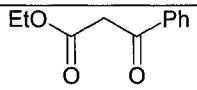
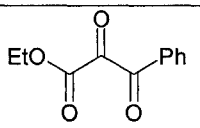
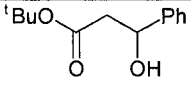
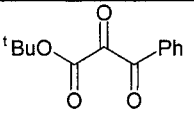
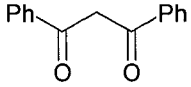
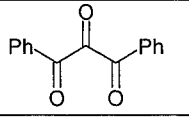
Substrate	Product	Yield (%)
		74
		75
		52
		56
		80
		73
		57

Table 20 Results obtained for the synthesis of **120** with Dess Martin reagent

DISCUSSION

2. Discussion

2.1. Research proposal

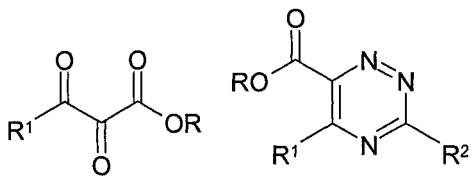
As previously discussed, pyridine derivatives are very important building blocks for pharmaceuticals and fine chemicals. Opportunities exist to develop new routes to functionalised pyridine derivatives that avoid some of the shortfalls encountered in the known methods. The use of unsymmetrical tricarbonyls as building blocks for the formation of pyridine derivatives gives the possibility of introducing a wide variety of functionality around the pyridine ring. However, this route has not been widely studied, probably due to the desirability of better methods of preparing 1,2,3-tricarbonyls.

We have therefore been interested in investigating new methods to unsymmetrical 1,2,3-tricarbonyls and their further reaction with amidrazones to form novel functionalized 1,2,4-triazines. In addition, we wanted to exploit the intermolecular aza Diels-Alder cycloaddition reaction of these 1,2,4-triazines to prepare novel pyridine derivatives

2.2. Research programme

Our initial project plan was to investigate the synthesis of unsymmetrical tricarbonyls **116** from readily available β-dicarbonyls and their further condensation reaction with amidrazones giving tri-substituted 1,2,4-triazines **138**.

Then, we would subject these 1,2,4-triazines **138** to aza Diels-Alder cycloaddition reactions to yield their corresponding pyridines. We chose to investigate the reactions of 1,2,4-triazines with 2,5-norbornadiene **41**. Although related reactions have been investigated in the literature (see Introduction, Section 1.2.1.1.3.1), opportunities exist to extend the scope of the aza Diels-Alder reaction of 2,5-norbornadiene **41** with novel 1,2,4-triazines thus producing pyridine derivatives with novel substitution patterns.



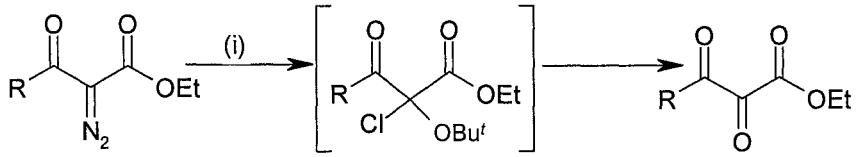
116 **138** **41**

2.3. Tricarbonyl compounds and derivatives

2.3.1. Preparation of tricarbonyl compounds

2.3.1.1. From α-diazo-β-dicarbonyl compounds

As previously discussed, 1,2,3-tricarbonyls **118** can be obtained by reaction of α-diazo-β-dicarbonyls **135** with *t*-butylhypochlorite in nearly quantitative yields (See Introduction Section 1.4.1.1.7.). The reaction in acetonitrile[78] has been shown to proceed directly to the tricarbonyls **118**, possibly through the intermediate **139** as shown in Scheme 48. The synthesis of the α-diazo-β-dicarbonyls **135** is achieved using the "diazo-transfer" reaction reviewed by Regitz[77].



135 **139** **118**

Scheme 48 Reagents and reaction conditions: (i) *t*-BuOCl, $MeCN/H_2O$, 0°C, 20 min

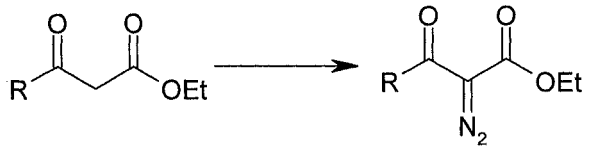
We have used this convenient methodology to prepare the tricarbonyl compounds **118a-b** from their corresponding α-diazo-β-dicarbonyl compounds **135a-b**[78]. The yields obtained in this reaction were very good and the resulting tricarbonyl compounds were used in the subsequent condensation reactions without need for further purification. Table 21 shows a summary of the results.

Tricarbonyl 118	R	Crude yield (%)
a	Ph	88
b	*n*-Pr	90

Table 21

Preparation of α-diazo-β-dicarbonyl compounds

The α-diazo-β-dicarbonyls **135a-b** were prepared in excellent yields (Table 21) from the corresponding commercially available β-dicarbonyl compounds **117a-b** using the diazo-transfer reaction. 4-Acetamidobenzenesulphonyl azide[81] in dichloromethane was employed as the diazo transfer reagent and potassium fluoride was used as a base (Scheme 49). The resulting α-diazo-β-dicarbonyl compounds **135a-b** were used in subsequent oxidation reactions with *t*-butyl hypochlorite[82] without need for further purification. However, α-diazo-β-dicarbonyl compounds **135a-b** are potentially explosive so a new method to tricarbonyls is highly desirable.



117 **135**

Scheme 49 Reagents and reaction conditions: TsN_3/KF, DCM, RT, 24 h

α-Diazo-β-dicarbonyl 135	R	Crude yield (%)
a	Ph	85
b	*n*-Pr	82

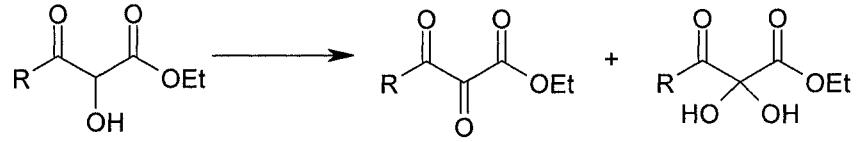
Table 22 The β-dicarbonyl compounds **117a-b** are all commercially available.

2.3.1.1.2. From alcohols

Looking for new methods to obtain tricarbonyl compounds **118**, the oxidations of alcohols was investigated. Lluch and colleagues[83] reported the oxidation of alcohol **140** using $Cu(OAc)_2$ as an oxidant to give the corresponding tricarbonyl as a (4:1) keto-hydrate mixture of **118** and **141** in 67% yield.

The selective oxidation of primary alcohols leaving secondary alcohols intact[84] has been exploited using NaOCl in acetonitrile in the presence of TEMPO **142** as a catalyst. This might provide an alternative method for the oxidation of alcohol **140**.

Therefore, we decided to investigate and compare the TEMPO and $Cu(OAc)_2$ methods of oxidation of alcohols **140** giving tricarbonyls **118**. Table 23 shows a summary of the results. The ^{1}H-NMR spectral data was identical to that reported in the literature[83] and the ratio of keto forms to hydrates varied with every experiment.



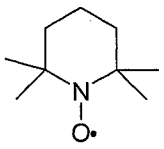
140 **118** **141**

Scheme 50 Reagents and reaction conditions: see Table 23

Tricarbonyl 118	R	Yield (%)	
		Method A	Method B
a	Ph	70	86
b	*n*-Pr	60	77
c	*t*-Bu *	59	75

Table 23 Comparison of results for oxidation of **140a-c** to **118a-c**.
(*) The methyl ester was used in this case

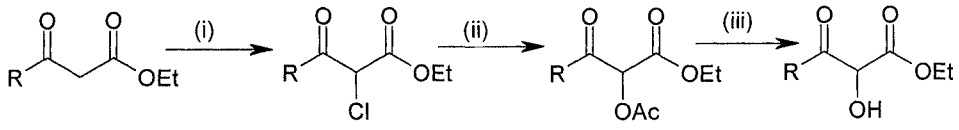
Method A: $Cu(OAc)_2$,H_2O, RT, 0.5h
Method B: NaOCl, TEMPO, KBr, ^{t}BuNH$_4$Cl,
$NaHCO_3$, H_2O, DCM, RT, 0.5 h



TEMPO
142

Preparation of alcohols

The alcohol compounds **140** were prepared from the corresponding β-dicarbonyl compounds **117** in a three step sequence as shown in Scheme 51.



117 **143** **144** **140**

Scheme 51 Reagents and reaction conditions:
(i) SO_2Cl_2, DCM, RT, 1h
(ii) AcOH, DMF, NEt_3, RT, 20 h
(iii) ethanolic HCl, RT, 20 h

The commercially available β-dicarbonyls **117a-c** reacted with 1.1 molar equivalents of sulfuryl chloride[85,86] to give the corresponding α-chloro-β-dicarbonyls **143a-c** in excellent yields with no trace of dichloro compound (Table 24). The ^{1}H-NMR spectral data of compound **143a** is consistent with that found in the literature[87] (Table 25). There is no ^{1}H-NMR spectral data reported for compounds **143b-c**, however they all show a singlet at ~ 5 ppm, resulting from the proton adjacent to the chlorine atom, which confirmed the structure of compounds **143b-c.**

α-Chloro-β-dicarbonyls 143	R	Yield (%)
a	Ph	88
b	*n*-Pr	90
c	*t*-Bu*	85

Table 24 Yields obtained for α-chloro-β-dicarbonyls **143a-c**
(*) The methyl ester was used in this case

Chemical shift (δ) (ppm)	Number of protons and multiplicity	Coupling constant J (Hz)	Assignment
8.02	2H, d	7	Ph-*H*
7.65	1H, t	7	Ph-*H*
7.50	2H, t	8	Ph-*H*
5.67	1H, s	-	-C*H*Cl
4.28	2H, q	7	ester-CH_2-
1.23	3H, t	7	ester-CH_3

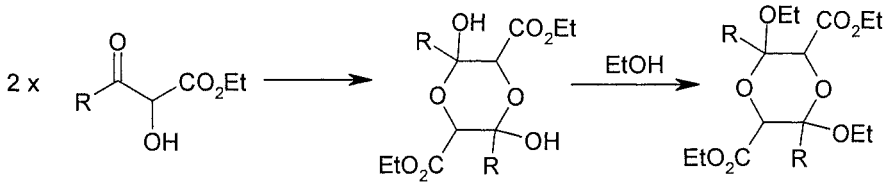
Table 25 The ^{1}H-NMR spectral data of α-chloro-β-dicarbonyl **143a**

The α-acetoxy-β-dicarbonyls **144a-c** were synthesised in excellent yields by treatment of α-chloro-β-dicarbonyls **143a-c** with acetic acid and triethylamine[88-90]. Table 26 shows a summary of the results.

α-Acetoxy-β-dicarbonyls 144	R	Yield (%)
a	Ph	95
b	*n*-Pr	90
c	*t*-Bu*	90

Table 26 Yields obtained for α-acetoxy-β-dicarbonyls **144a-c**
(*) The methyl ester was used in this case

The α-acetoxy-β-dicarbonyls **144a-c** were converted to alcohols **140a-c** in good yields (63-80 %) by treatment with saturated ethanolic HCl (for the synthesis of **140c** methanolic HCl was used instead). This method of removal of acetate groups in structurally related compounds has been reported by Boehme and Schenider[91], who also reported that solvolysis of acetates in ethanol can also give 'dimeric' type products as shown in Scheme 52. However, the ^{1}H-NMR spectral data of α-hydroxy-β-dicarbonyls **140a-c** show quartets ~ 4-4.5 ppm, typical of ethyl esters, whereas quartets at ~3.4 ppm would be expected for ethyl ethers. We are therefore confident that the required alcohols have been produced.



Scheme 52 Formation of 'dimeric' type products

The ^{1}H-NMR spectral data of the α-hydroxy-β-dicarbonyls **140a-c** were complex, reflecting keto-enol tautomerism[83]. The alcohol compounds **140** were all used in further oxidation reactions without need for purification. Table 27 shows a summary of the results obtained.

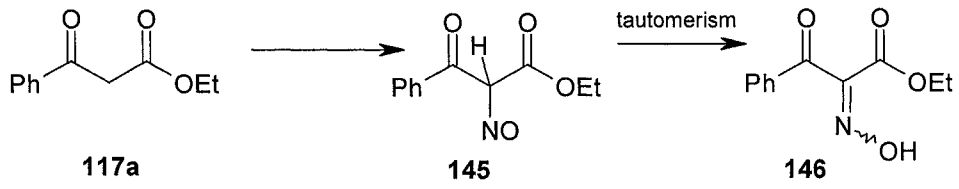
α-Hydroxy-β-dicarbonyls 140	R	Yield (%)
a	Ph	70
b	*n*-Pr	80
c	*t*-Bu*	63

Table 27 Yields obtained for α-hydroxy-β-dicarbonyls **140a-c**
(*) The methyl ester was used in this case

2.3.1.3. From oximes

There are a number of methods for converting oximes into carbonyl compounds[92], some of which are suitable for generating dicarbonyl compounds. Although we are not aware of any of the methods reviewed being used for generating tricarbonyls, the ease of preparation of the oximes from readily available β-keto esters and the wide variety of methods available for generating carbonyl groups from oximes makes this potential two-step synthesis of tricarbonyls worthy of investigation.

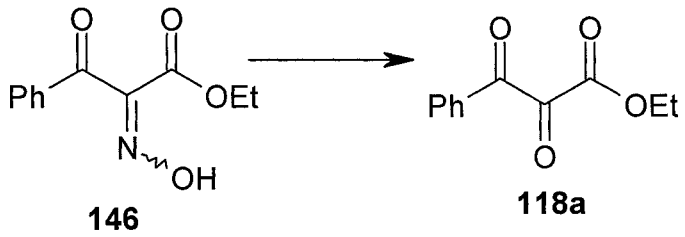
β-Ketoesters react readily with sodium nitrite in acid solution to give oximes *via* nitroso intermediate **145** as shown in Scheme 53. Using this methodology compound **146** was synthesised in 85 % yield from commercially available ethyl benzoylacetate **117a**. The melting point and ^{1}H-NMR of this compound was consistent with that found in the literature [93].



Scheme 53 Reagents and reaction conditions: $NaNO_2$, AcOH, RT, 0.5 h

Several methods for generating a carbonyl group from oximes have been investigated. The oxime **146** was treated with sodium nitrite in acetic acid; bleach; NBS; $KMnO_4$; aqueous hydrogen peroxide and HCl; a large excess of acetone in the presence of amberlyst 15 (as an acid catalyst). Unfortunately, the oxime was recovered essentially unchanged in all of these cases.

Reaction of oxime **146** with ^{t}BuOCl gave the tricarbonyl **118a** in very low yield (24%) as shown in Scheme 54. The difficulties in regenerating tricarbonyls from oximes might be due to the delocalisation of the lone pair of electrons on the oxime oxygen atom over the two carbonyl groups, making oximes of tricarbonyls significantly more resistant to oxidation than mono-oximes derived from ketones.



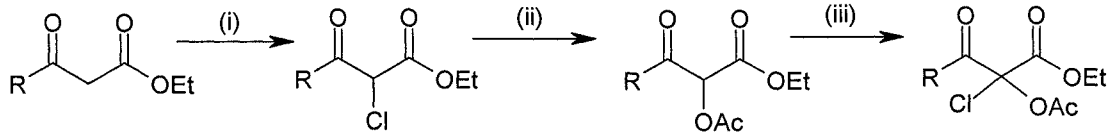
Scheme 54 Reagent and reaction conditions: ^{t}BuOCl, MeCN, H_2O, RT, 0.5 h

2.3.2 Preparation of tricarbonyl equivalents

2.3.2.1. Preparation of α-acetoxy-α-chloro-β-dicarbonyls

The formation of tricarbonyl equivalents was studied to investigate the further reaction of these compounds with amidrazones to form 1,2,4-triazines. α-Acetoxy-α-chloro-β-dicarbonyls **147a-e** were synthesised in a three step reaction as shown in Scheme 55. The α-acetoxy-β-dicarbonyls **144a-c** were prepared as previously discussed. Similarly, β-dicarbonyl **117d** can be easily chlorinated with sulfuryl chloride and **143e** is commercially available (Table 28 shows a summary of results). The α-chloro-β-dicarbonyls **143d-e** are converted in excellent yields to their corresponding acetates **144d-e** by reaction with acetic acid and triethylamine in DMF (Table 29).

The α-acetoxy-β-dicarbonyls **144a-e** underwent a further chlorination with sulfuryl chloride yielding the α-acetoxy-α-chloro-β-dicarbonyls **147a-e** (Table 30). The structure of compounds **147a-e** was confirmed using ^{1}H-NMR spectroscopy (Tables 31-35), where the singlet attributed to the –CH proton in compounds **144a-e** at ~5 ppm disappears, and high-resolution mass spectrometry (Table 36). Unfortunately, the chlorination of compound **144c** to give **147c** could not be reproduced.



117 **143** **144** **147**

Scheme 55 Reagents and reaction conditions:
(i) SO_2Cl_2, DCM, RT, 1h
(ii) AcOH, DMF, NEt_3, RT, 20 h
(iii) SO_2Cl_2, DCM, RT, 1h

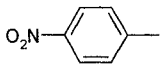
α-Chloro-β-dicarbonyls 143	R	Yield (%)
a	Ph	88
b	*n*-Pr	90
c	*t*-Bu*	85
d		85

Table 28 Yields obtained for α-chloro-β-dicarbonyls **143a-d**
(*) The methyl ester was used in this case

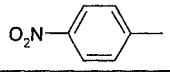
α-Acetoxy-β-dicarbonyls 144	R	Yield (%)
a	Ph	95
b	*n*-Pr	90
c	*t*-Bu*	90
d		88
e	Me	84

Table 29 Yields obtained for α-acetoxy-β-dicarbonyls **144a-e**
(*) The methyl ester was used in this case

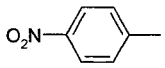
α-Acetoxy-α-chloro-β-dicarbonyls **147**	R	Yield (%)
a	Ph	77
b	*n*-Pr	98
c	*t*-Bu*	87
d		52
e	Me	97

Table 30 Yields obtained for α-acetoxy-α-chloro-β-dicarbonyls **147a-e**
(*) The methyl ester was used in this case. This reaction could not be reproduced.

Chemical shift (δ) (ppm)	Number of protons and multiplicity	Coupling constant J (Hz)	Assignment
8.13	2H, d	7	Ph-*H*
7.64	1H, t	7	Ph-*H*
7.50	2H, t	8	Ph-*H*
4.31	2H, q	7	ester-C*H*$_2$-
2.23	3H, s	-	acetate-C*H*$_3$
1.29	3H, t	7	ester-C*H*$_3$

Table 31 The ^{1}H-NMR spectral data of α-acetoxy-α-chloro-β-dicarbonyl **147a**

Chemical shift (δ) (ppm)	Number of protons and multiplicity	Coupling constant J (Hz)	Assignment
4.32	2H, q	7	ester-C*H*$_2$-
2.85	2H, q	7	-C*H*$_2$-
2.24	3H, s	-	acetate-C*H*$_3$
1.69	2H, sextet	7	-C*H*$_2$-
1.32	3H, t	7	ester-C*H*$_3$
0.96	3H, t	7	-C*H*$_3$

Table 32 The ^{1}H-NMR spectral data of α-acetoxy-α-chloro-β-dicarbonyl **147b**

Chemical shift (δ) (ppm)	Number of protons and multiplicity	Coupling constant J (Hz)	Assignment
3.79	3H, s	-	ester-C*H*$_3$
2.19	3H, s	-	acetate-C*H*$_3$
1.24	9H, s	-	-C(C*H*$_3$)$_3$

Table 33 The ^{1}H-NMR spectral data of α-acetoxy-α-chloro-β-dicarbonyl **147c**

Chemical shift (δ) (ppm)	Number of protons and multiplicity	Coupling constant J (Hz)	Assignment
8.33	2H, d	9	Ph-*H*
8.26	2H, d	9	Ph-*H*
4.36	2H, q	7	ester-C*H*$_2$-
2.23	3H, s	-	acetate-C*H*$_3$
1.33	3H, t	7	ester-C*H*$_3$

Table 34 The ^{1}H-NMR spectral data of α-acetoxy-α-chloro-β-dicarbonyl **147d**

Chemical shift (δ) (ppm)	Number of protons and multiplicity	Coupling constant J (Hz)	Assignment
4.32	2H, q	7	ester-C*H*$_2$-
2.50	3H, s	-	-C*H*$_3$
2.24	3H, s	-	acetate-C*H*$_3$
1.33	3H, t	7	ester-C*H*$_3$

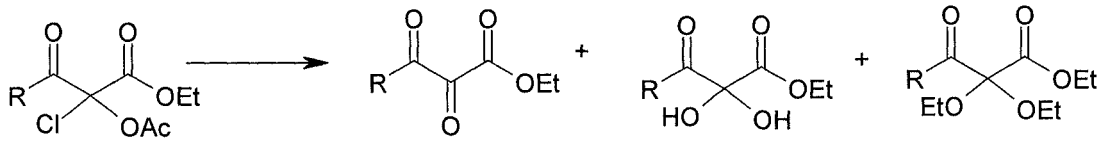
Table 35 The ^{1}H-NMR spectral data of α-acetoxy-α-chloro-β-dicarbonyl **147e**

α-Acetoxy-α-chloro-β-dicarbonyl 147	Calculated mass $(M+H)^+$	Measured mass $(M+H)^+$
a	285.0524	285.0526
b	268.0946	268.0948
d	240.0633	240.0632

Table 36 High-resolution mass spectral data of α-acetoxy-α-chloro-β-dicarbonyl **147**

2.3.2.2. Decomposition of α-acetoxy-α-chloro-β-dicarbonyls

The decomposition of α-acetoxy-α-chloro-β-dicarbonyl compounds **147** might lead to the formation of tricarbonyls **118**. Thus, α-acetoxy-α-chloro-β-dicarbonyl compounds **147a-b** were treated with saturated ethanolic HCl giving in excellent yields (Table 37) a mixture of tricarbonyl **118** or its hydrate **141** and the ketal of the tricarbonyl **148**. The ketal of tricarbonyl is obtained as the minor product, and the ratio varies with every experiment. There is no ^{1}H-NMR spectral data reported for compounds **148a-b**; however they show evidence of a quadruplet at ~ 3.45 ppm which is consistant with that found in the literature[94] for the -C*H*$_2$- in the ketal of benzyl. These compounds were used directly in the preparation of 1,2,4-triazines without any further characterisation.



147 **118** **141** **148**

Scheme 56 Reagent and reaction conditions: saturated ethanolic HCl, RT, 16 h

From α-acetoxy-α-chloro-β-dicarbonyl 147	R	Yield (%)	Ratio (118+141) : 148
a	Ph	84	4 : 1
b	*n*-Pr	82	3 : 1

Table 37 Yields of decomposition of α-acetoxy-α-chloro-β-dicarbonyl **147a-b** with saturated ethanolic HCl.

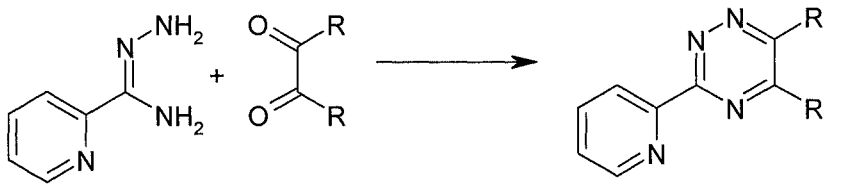
2.4. 1,2,4-Triazines

2.4.1. Preparation of 1,2,4-triazines

2.4.1.1. From dicarbonyls

As previously reviewed in the introduction there are many examples of the reaction of amidrazones with symmetrical 1,2-dicarbonyl compounds in the literature.

In order to get an insight in the formation of 1,2,4-triazines and using the methodology described in the literature[95], 5,6-diphenyl-3-pyridin-2-yl-1,2,4-triazine **152**, 5,6-dimethyl-3-pyridin-2-yl-1,2,4-triazine **153** and novel 5,6-diethyl-3-pyridin-2-yl-1,2,4-triazine **154** were synthesised in 74 %, 91 % and 96 % respectively by the condensation reaction of pyridine 2-carboximidohydrazide **107** with the corresponding commercially available 1,2 dicarbonyl compounds **149**, **150** and **151**.



107

149 R= Ph
150 R= Me
151 R= Et

152 R= Ph
153 R= Me
154 R= Et

Scheme 57 Reaction conditions: ethanol, reflux, 24 h.

There are no ^{1}H-NMR spectral data reported for compounds **152**, **153** and **154**. However, the melting points of compound **152** and **153** (189-190 °C and 92-93 °C respectively) are identical to those reported in the literature[95]. Tables 38, 39 and 40 show the ^{1}H-NMR spectral data of compounds **152**, **153** and **154** respectively.

Chemical shift (δ) (ppm)	Number of protons and multiplicity	Coupling constant J (Hz)	Assignment
8.93	1H, d	5	Py-*H*
8.71	1H, d	8	Py-*H*
7.95	1H, t	8	Py-*H*
7.70-7.62	5H, m	-	Ph-*H*
7.49-7.33	6H, m	-	Ph-*H*, Py-*H*

Table 38 ^{1}H-NMR spectral data of compound **152**

Chemical shift (δ) (ppm)	Number of protons and multiplicity	Coupling constant J (Hz)	Assignment
8.99	1H, d	5	Py-*H*
8.65	1H, d	8	Py-*H*
7.90	1H, t	8	Py-*H*
7.45	1H, m	-	Py-*H*
2.80	3H, s	-	-C*H*$_3$
2.70	3H, s	-	-C*H*$_3$

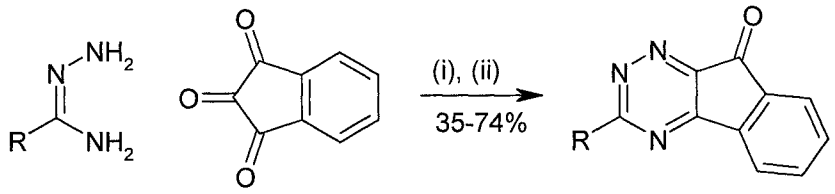
Table 39 ^{1}H-NMR spectral data of compound **153**

Chemical shift (δ) (ppm)	Number of protons and multiplicity	Coupling constant J (Hz)	Assignment
8.89	1H, d	5	Py-*H*
8.63	1H, d	8	Py-*H*
7.90	1H, t	8	Py-*H*
7.45	1H, m	-	Py-*H*
3.10	2H, q	8	-C*H*$_2$-
3.00	2H, q	8	-C*H*$_2$-
1.45	3H, t	7	-C*H*$_3$
1.40	3H, t	7	-C*H*$_3$

Table 40 ^{1}H-NMR spectral data of compound **154**

2.4.1.2. From tricarbonyls

The reaction of amidrazones with symmetrical tricarbonyl compounds such as ninhydrin **98** have been shown to react regioselectively at the central carbonyl group yielding the corresponding 1,2,4-triazines. Case and colleagues[50] exploited this method to synthesize a number of 3-substituted-1,2,4-triazafluoren-9-ones **99** (R= 4-methyl-2-pyridyl, 4-phenyl-2-pyridyl, 6-[2,2']bipyridyl and 2-thiazolyl) in 41%, 45%, 35% and 74% yields respectively.

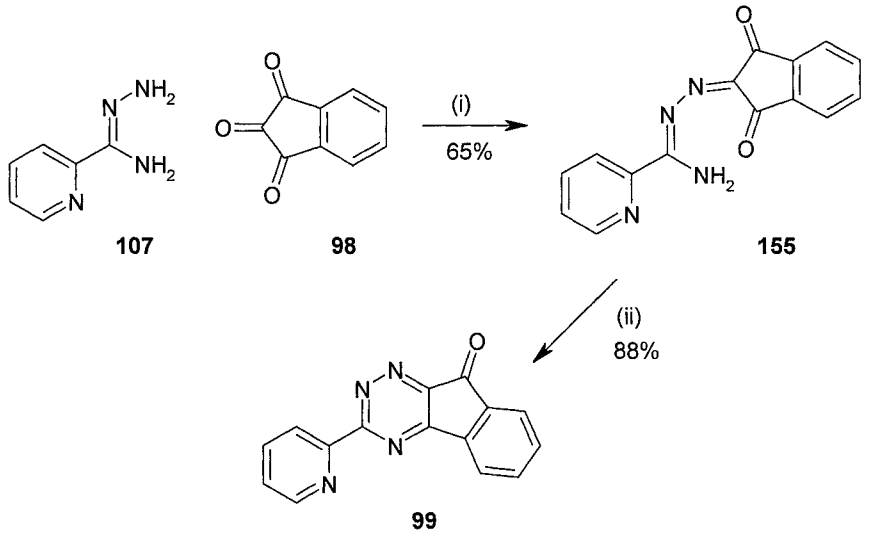


107 **98** **99**

Scheme 58 Reaction conditions: (i) ethanol, 0°C, 48 h; (ii) reflux, 2.5 h

2.4.1.2.1. With pyridine-2-carboximidohydrazide

Ried and coworkers[96] described the synthesis of the 1,2,4-triazine **99**. Pyridine-2-carboximidohydrazide **107** reacted with ninhydrin **98** to give the intermediate **155**, which was isolated in 65% yield. Further cyclization of compound **155** yielded the 1,2,4-triazine **99** in 88% yield, as shown in Scheme 59.

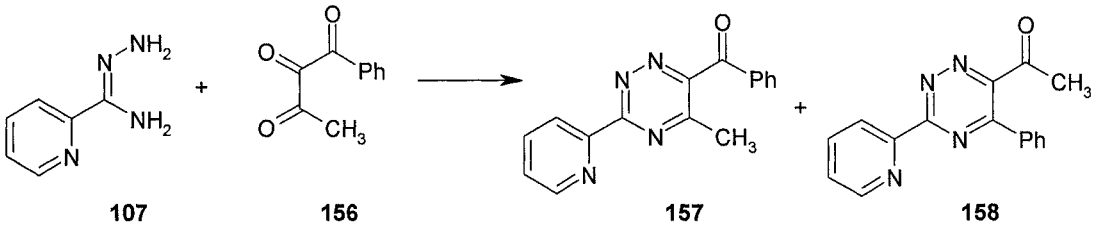


107 **98** **155**

99

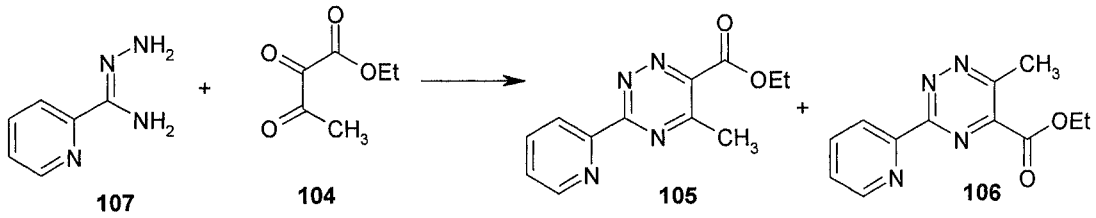
Scheme 59 Reaction conditions: (i) ethanol, RT, 3h; (ii) precipitate heated at 180 °C

When pyridine-2-carboximidohydrazide **107** was reacted by previous workers with the unsymmetrical tricarbonyl 1-phenyl-1,2,3-trione **156** a 50:50 mixture of regioisomers **157** and **158** was obtained in 100 % yield by ^{1}H-NMR spectroscopy[97] (Scheme 60). This mixture resulted from attack of the more reactive hydrazine nitrogen at the central carbonyl followed by attack at either of the remaining carbonyls.



Scheme 60 Reaction conditions: ethanol, reflux, 20 h

The reaction of pyridine-2-carboximidohydrazide **107** with 2,3-dioxo-butyric acid diethyl ester **104** has also been shown by previous workers to give a mixture of regioisomers **105** and **106** (Scheme 61) with varying ratios depending on the reaction conditions as shown in Table 41.[97]

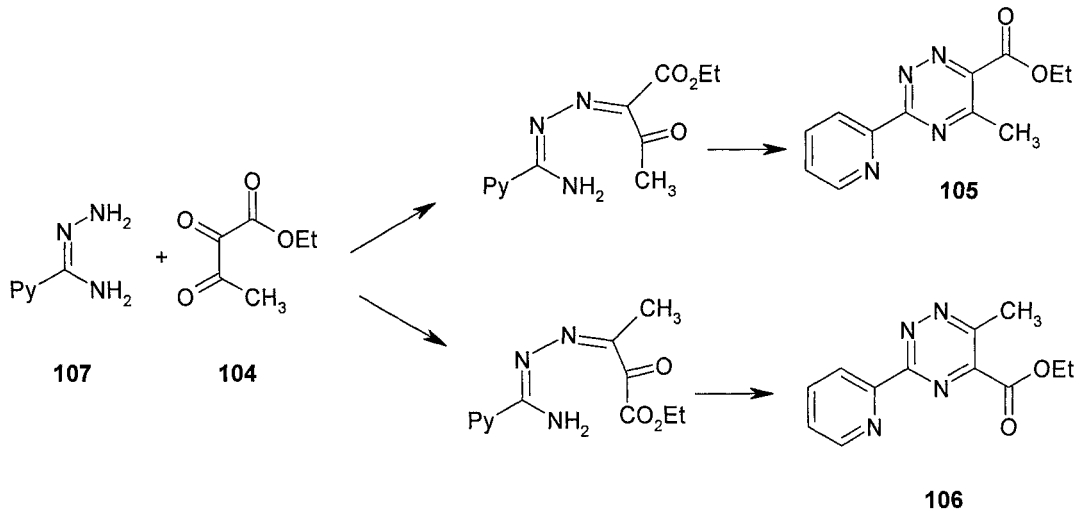


Scheme 61 Reaction conditions: see Table 40

Ratio 105 : 106		Crude yield (%)
72	28	92 (i)
86	14	95 (ii)

Table 41 Reaction conditions: (i) ethanol, RT, 24 h, reflux 3h; (ii) ethanol, reflux, 24 h

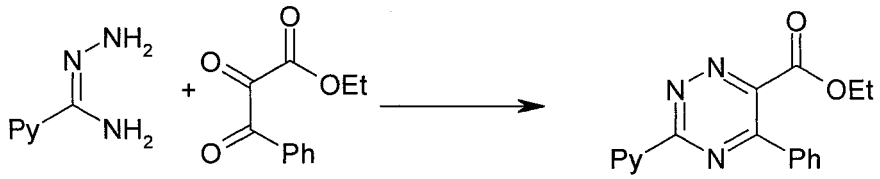
Scheme 62 below shows a possible explanation for the formation of regioisomers observed in the reaction of amidrazone **107** with 2,3-dioxo-butyric acid diethyl ester **104**. The more reactive hydrazine nitrogen of the amidrazone can attack either of the two ketones carbonyl groups of the tricarbonyl producing the corresponding intermediates which can the undergo cyclisation and dehydration giving each of the two possible regioisomers.



Scheme 62

However, when amidrazone **107** was reacted with 2,3-dioxo-3-phenylpropionic acid ethyl ester **118a**, obtained from the 2-diazo-3-phenylpropionic acid ethyl ester **135a** , only 1,2,4-triazine **111a** was formed in 94 % yield with no trace of any regioisomer by ^{1}H-NMR spectroscopy (Scheme 63). When the 2,3-dioxo-3-phenylpropionic acid ethyl ester **118a** employed was prepared by the oxidation of 2-hydroxy-3-oxo-3-phenyl-propionic acid ethyl ester **140a** with copper(II) acetate, the 1,2,4-triazine **111a** was obtained in 52% yield.

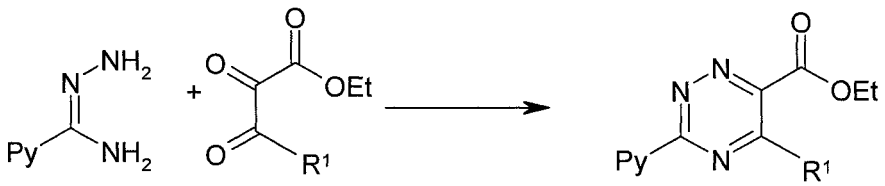
The ^{1}H-NMR spectral data of compound **111a** is consistent with that found in the literature[22,97]. In this particular reaction, it appeared that the more reactive hydrazine nitrogen of the amidrazone reacted only at the central ketone carbonyl followed by cyclisation and dehydration, thus producing only one regioisomer.



107 **118a** **111a**

Scheme 63 Reaction conditions: ethanol, reflux, 2 h

The regioselectivity of this reaction has been previously investigated[97], and as expected, tricarbonyl compounds **118** with sterically crowded substituents react regioselectively with amidrazone **107** yielding the corresponding 1,2,4-triazine **111** without formation of regioisomers.



107 **118** **111**

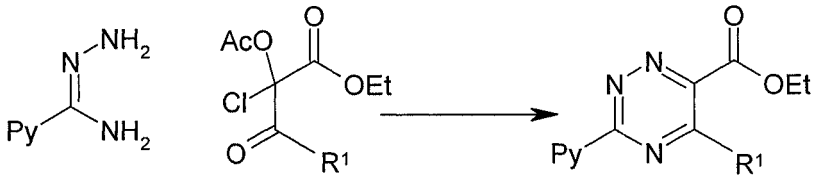
Scheme 64 Reaction conditions: ethanol, reflux, 2 h

Thus, in our work, the tricarbonyl **118b** (R^1= *n*-Pr), obtained from the ethyl 2-diazo-3-oxo-3-hexanoate **135b**, was reacted with pyridyl-2-carboximidohydrazide **107** under standard reaction conditions. ^{1}H-NMR spectroscopy showed the presence of only one product and the corresponding 1,2,4-triazine **111b** was isolated in 97% yield with no trace of regioisomers. When the tricarbonyl **118b** (R^1= *n*-Pr) was prepared by the oxidation of ethyl 2-hydroxy-3-propyl-3-oxohexanoate **140b** with copper(II) acetate or TEMPO, the 1,2,4-triazine **111b** was obtained in 80% and 60% respectively. The structures of compounds **111a-b** were also confirmed by high resolution mass spectroscopy as shown in Table 42.

Triazine 111	R^1	Calculated mass $(M+H)^+$	Measured mass $(M+H)^+$
a	Ph	307.1190	307.1188
b	*n*-Pr	273.1346	273.1345

Table 42 High-resolution spectral data of triazines **111a-b**

Using this methodology, the reaction of tricarbonyl equivalents, α-acetoxy-α-chloro-β-dicarbonyls **147a,b,d,e** with amidrazone **107** was investigated (Scheme 65). Table 43 shows a summary of results. The novel 1,2,4-triazine **111d** was obtained using this methodology and its structure confirmed by high resolution mass spectrometry (calculated mass of molecular ion, $(M+H)^+$ 352.1040; measured mass of molecular ion, 352.1043). Table 44 shows the spectral data for this compound. The regioselectivity of the reaction of formation of triazine **111e** was improved using this methodology. Mainly one isomer of triazine **111e** was observed by ^{1}H-NMR spectroscopy, with small traces of the regioisomer. The major isomer could be isolated by column chromatography. Table 45 shows the spectral data obtained for the major isomer. The ^{1}H-NMR spectral data of compounds **111a-b** was identical to that of the 1,2,4-triazines synthesised from the tricarbonyls **118**.



107 **147** **111**

Scheme 65 Reaction conditions: ethanol, reflux, 2 h

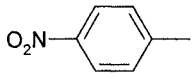
α-Acetoxy-α-chloro-β-dicarbonyls 147	R^1	Triazine 111	Crude yield (%)
a	Ph	**a**	97
b	*n*-Pr	**b**	98
d		**d**	32
e	Me	**e**	79

Table 43 Yields obtained for α-acetoxy-α-chloro-β-dicarbonyls **147**

Chemical shift (δ) (ppm)	Number of protons and multiplicity	Coupling constant J (Hz)	Assignment
8.92	1H, d	5	Py-*H*
8.77	1H, d	5	Py-*H*
8.41	2H, d	9	Ph-*H*
8.02	2H, d	9	Ph-*H*
7.99	1H, m	-	Py-*H*
7.52	1H, m	-	Py-*H*
4.47	2H, q	7	ester-C*H*$_2$-
1.35	3H, t	7	ester-C*H*$_3$

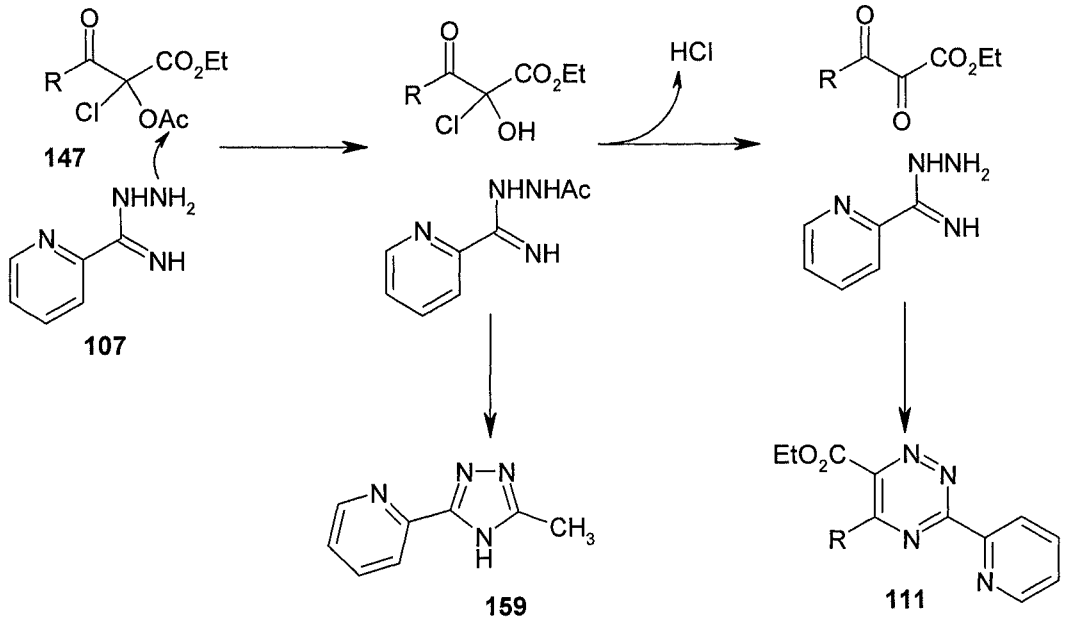
Table 44 ^{1}H-NMR spectral data for compound **111d**

Chemical shift (δ) (ppm)	Number of protons and multiplicity	Coupling constant J (Hz)	Assignment
8.94	1H, d	5	Py-*H*
8.77	1H, d	5	Py-*H*
7.96	1H, t	-	Py-*H*
7.52	1H, m	-	Py-*H*
4.57	2H, q	7	ester-C*H*$_2$-
2.97	3H, s	-	-C*H*$_3$
1.50	3H, t	7	ester-C*H*$_3$

Table 45 ^{1}H-NMR spectral data for compound **111e**

Interestingly, 2.5 molar equivalents of amidrazone **107** were required in this reaction to yield the corresponding triazines in good yields. A possible explanation for this is that the amidrazone is required to initiate decomposition of the α-acetoxy-α-chloro-β-dicarbonyls **147** as shown in Scheme 66. Thus, 2.5 equivalents of the amidrazone **107** were necessary in order to obtain good yields of triazines **111** after an aqueous wash. The crude product was very 'clean' by ^{1}H-NMR spectroscopy and chromatography was not required.

The additional equivalent of the amidrazone **107** is possibly transformed into the triazole **159**. This triazole can be made by acylation of pyridyl-2-carboximidohydrazide **107** but is only isolated in relatively low yield when extracted from an aqueous solution, probably due to its relative high solubility in water. In our reaction the aqueous wash might be enough to remove this by-product.

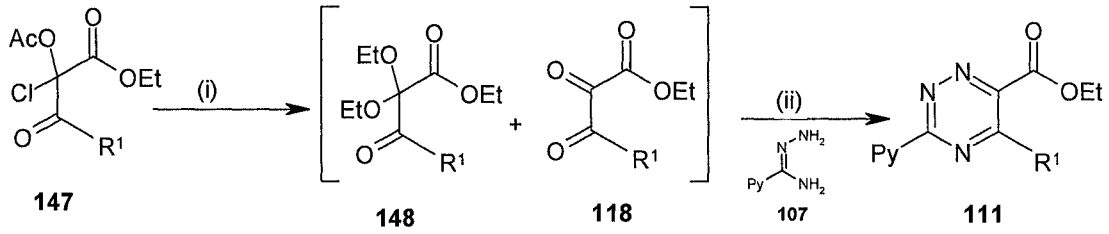


Scheme 66

We attempted to make an authentic sample of the triazole **159** from pyridyl-2-carboximidohydrazide **107** and acetic anhydride using a literature method[95]. We could then confirm this comound as a by-product formed in the de-acylation step in the reaction of **107** and α-acetoxy-α-chloro-β-dicarbonyls **147**. However, synthesis of **159** was unsuccessful; the reaction mixture obtained was very complex by ^{1}H-NMR spectroscopy.

In view of the development described above, the decomposition of the α-acetoxy-α-chloro-β-dicarbonyls **147** *prior* to reaction with the amidrazone **107** was investigated. If this could be achieved, only one equivalent of amidrazone would be required for the formation of the triazines **111**.

Thus, the α-acetoxy-α-chloro-β-dicarbonyls **147a-b** were treated with saturated ethanolic HCl yielding a mixture of ketals **148a-b** and tricarbonyls **118a-b** as previously discussed (see Section 2.3.2). The crude product was then reacted with one equivalent of amidrazone **107** to yield the corresponding 1,2,4-triazines **111a-b** in good yields. The ^{1}H-NMR spectral data was identical to that of the 1,2,4-triazines synthesised from the tricarbonyls **118a-b**.



Scheme 61 Reagents and reaction conditions:
(i) saturated ethanolic HCl, RT, 16 h
(ii) ethanol, reflux, 2 h

Similarly, decomposition of the α-acetoxy-α-chloro-β-dicarbonyls **147** was achieved by treatment with 33% wt methylamine in ethanol *prior* to addition of one equivalent of the amidrazone **107** to yield the triazines **111** in good yields. This reaction was achieved in 'one-pot' and the isolation of the intermediate was not required. Decomposition was achieved for **147a-b** and their corresponding 1,2,4-triazines **111a-b** were obtained in 65% and 61% yields respectively. However, decomposition of the α-acetoxy-α-chloro-β-dicarbonyls **147d-e** was not successful. Thus, the formation of the corresponding triazines **111d-e** was not clean and a mixture of products was obtained by ^{1}H-NMR spectroscopy. Table 46 shows a summary of results.

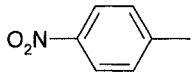
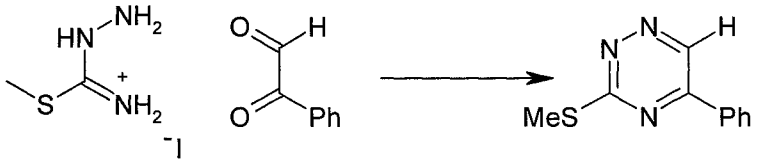
α-Acetoxy-α-chloro-β-dicarbonyls 147	R^1	Triazine 111	Yield (%)	
			Method A	Method B
a	Ph	**a**	95	65
b	*n*-Pr	**b**	79	61
d		**d**	-	-
e	Me	**e**	-	-

Table 46 Comparison of yields of formation of 1,2,4-triazines after decomposition of α-acetoxy-α-chloro-β-dicarbonyls **147** using two different methods.

Method A: decomposition of α-acetoxy-α-chloro-β-dicarbonyls **147**with saturated ethanolic HCl
Method B: decomposition of α-acetoxy-α-chloro-β-dicarbonyls **147** with 33% wt methylamine in ethanol

2.4.1.2.2. With *S*-methylthiosemicarbazide hydrogen iodide

The use of *S*-methylthiosemicarbazide hydrogen iodide **160** as an amidrazone in the formation of 1,2,4-triazines has been investigated. Using the reaction conditions described by Paudler and Chen[47], the commercially available phenylglyoxal hydrate **94** was reacted with *S*-methylthiosemicarbazide hydrogen iodide **160** to give 1,2,4-triazine **161** in 86% yield (Scheme 62). There is no ^{1}H-NMR spectral data reported for compound **161**; however, the melting point of **161** (99-100 °C) is identical to the melting point described in the literature[47]. Table 47 shows the ^{1}H-NMR spectral data of compound **161**.



160 **94** **161**

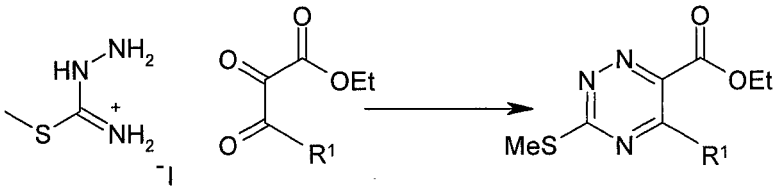
Scheme 62 Reaction conditions: hot water, 1.2 eq. of $NaHCO_3$

Chemical shift (δ) (ppm)	Number of protons and multiplicity	Coupling constant J (Hz)	Assignment
9.38	1H, s	-	-C*H*
8.16	2H, dd	7	Ph-*H*
7.61-7.52	3H, m	-	Ph-*H*
2.73	3H, s	-	-C*H*$_3$

Table 47 ^{1}H-NMR spectral data of compound **161**

In addition, there are several examples in the literature where the methylthio substituent is readily displaced by nucleophiles, including carbon nucleophiles[98-100]. Therefore, we decided to investigate the reaction of *S*-methylthiosemicarbazide hydrogen iodide **160** with unsymmetrical tricarbonyls **118** and tricarbonyl derivatives, α-acetoxy-α-chloro-β-dicarbonyls **147**. This might provide an alternative and possibly better approach to introducing carbon functionality at the 1,2,4-triazine 3-position.

S-Methylthiosemicarbazide hydrogen iodide **160** reacted with tricarbonyls **118a-b**, obtained by oxidation of the alcohols **140a-b** with copper(II) acetate, to give the corresponding 1,2,4-triazines **162a-b** in 58% and 61% yields respectively (Scheme 63). When the tricarbonyls **118a-b** were obtained from the diazo compounds **135a-b**, 1,2,4-triazines **162a-b** were obtained in 57 % and 30% yields respectively. The structure of triazines **162a-b** was confirmed using ^{1}H-NMR spectroscopy and high-resolution mass spectrometry (Tables 48-50).



160 **118** **162**

Scheme 63 Reaction conditions: 1.2 eq. $NaHCO_3$, ethanol, reflux, 2 h

Chemical shift (δ) (ppm)	Number of protons and multiplicity	Coupling constant J (Hz)	Assignment
7.74	2H, d	8	Ph-*H*
7.50- 7.53	3H, m	-	Ph-*H*
4.40	2H, q	7	ester-C*H*$_2$-
2.75	3H, s	-	-SC*H*$_3$
1.27	3H, t	7	ester-C*H*$_3$

Table 48 The ^{1}H-NMR spectral data of triazine **162a**

Chemical shift (δ) (ppm)	Number of protons and multiplicity	Coupling constant J (Hz)	Assignment
4.50	2H, q	7	ester-C*H*$_2$-
3.02	2H, m	-	propyl- C*H*$_2$-
2.70	3H, s	-	-SC*H*$_3$
1.79	2H, sextet	-	propyl-C*H*$_2$-
1.46	3H, t	7	propyl-C*H*$_3$
1.02	3H, t	7	ester-C*H*$_3$

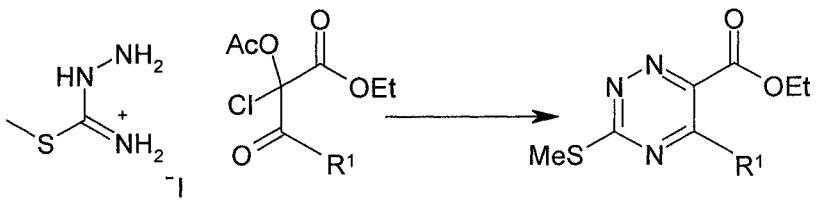
Table 49 The ^{1}H-NMR spectral data of triazine **162b**

Triazine 162	Calculated mass $(M+H)^+$	Measured mass $(M+H)^+$
a	276.0801	276.0800
b	242.0958	242.0959

Table 50 High-resolution mass spectral data of triazines **162a-b**

Using this methodology, triazines **162a,b,d,e** were also synthesised in good yields from α-acetoxy-α-chloro-β-dicarbonyls **147a,b,d,e** and 2.5 molar equivalent of *S*-methylthiosemicarbazide hydrogen iodide **160** (Scheme 64). The ^{1}H-NMR spectral data of triazines **162a-b** was consistent with that obtained for **162a-b** from **118a-b**.

The reaction of ethyl 2-acetoxy-2-chloro-3-oxo-3-(4-nitrophenyl)propanoate **147d** and ethyl 2-acetoxy-2-chloro-3-oxo-butanoate **147e** with *S*-methylthiosemicarbazide hydrogen iodide gave in 69% and 42% yields the corresponding triazines **162d** and **162e** with no trace of regioisomers by ^{1}H-NMR spectroscopy.



160 **147** **162**

Scheme 64 Reaction conditions: ethanol, 1.2 eq. $NaHCO_3$, reflux, 2h

Decomposition of α-acetoxy-α-chloro-β-dicarbonyls **147a-b** was also attempted *prior to* reaction with *S*-methylthiosemicarbazide hydrogen iodide **160**. Table 51 shows a summary of the results.

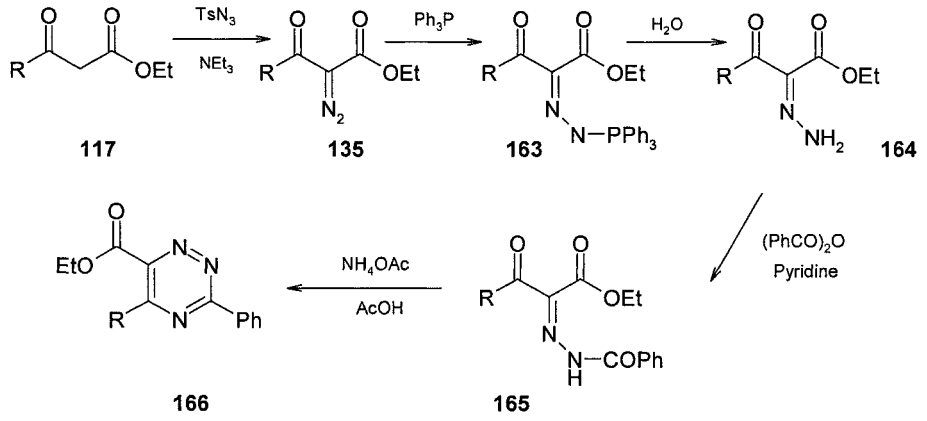
Triazine 162	R^1	Yield (%)		
		Method A	Method B	Method C
a	Ph	80	90	58
b	*n*-Pr	83	92	58
d		69	-	-
e	Me	42	-	-

Table 51 Comparison of yields of formation of 1,2,4-triazines **162a-e**

Method A: from α-acetoxy-α-chloro-β-dicarbonyls **147** and 2.5 eq of amidrazone
Method B: decomposition of α-acetoxy-α-chloro-β-dicarbonyls **147** with ethanolic HCl *prior to* reaction with 1 eq of amidrazone
Method C: decomposition of α-acetoxy-α-chloro-β-dicarbonyls **147** with methylamine in ethanol 33% wt *prior* reaction with 1 eq of amidrazone

2.4.1.2.3. With benzamidrazone

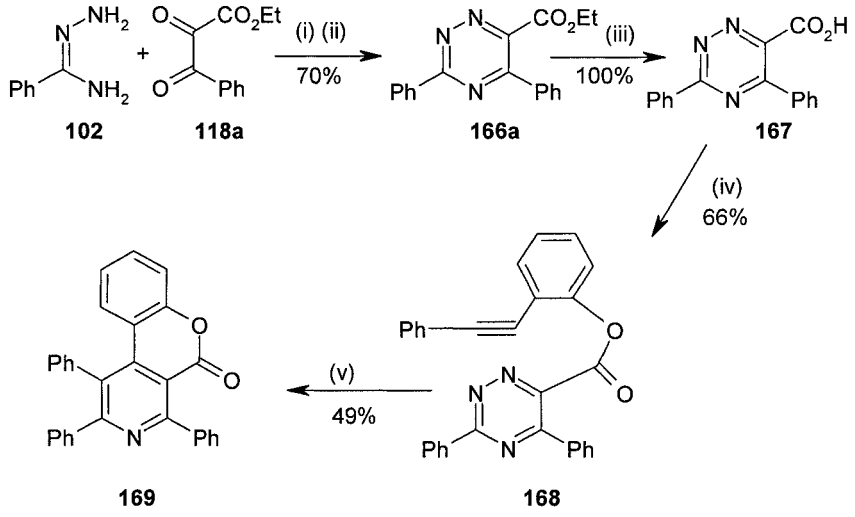
The reaction of benzamidrazone **102** with 2,3-dioxo-butyric acid diethyl ester **104** yielded mixtures of regioisomers **105** and **106** in unknown ratios by standard methods (see Introduction page 29). Seeking some improvement in the regioselectivity of this reaction, Neunhoeffer[51] developed a method to 1,2,4-triazines **166**. Commercially available β-dicarbonyls **117** were treated with *p*-toluenesulfonyl azide and triethylamine to give the α-diazo compound **135**, which formed phosphazines **163** when reacted with triphenylphosphine. The phosphazines **163** were hydrolyzed in aqueous ethanol to give the hydrazones **164**, as described by Bestmann and co-workers[101]. The hydrazones **164** were acylated in the presence of pyridine and the acylhydrazones **165** obtained heated with ammonium acetate in acetic acid to give triazines **166** with no trace of regioisomers.



Scheme 65

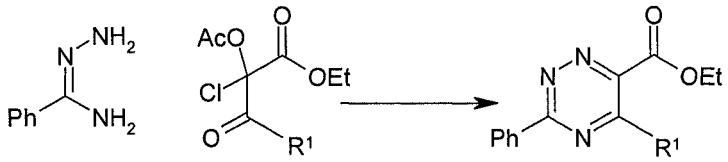
In 1990, Yamanaka and colleagues [52] reported a regioselective reaction between benzamidrazome **102** and 2,3-dioxo-3-phenylpropionic acid **118a** to yield triazine **166a** in 70% yield with no trace of any regioisomer by ^{1}H-NMR spectroscopy (Scheme 66).

The phenyl ester **167** was then prepared from the 1,2,4-triazine **166** and subjected to an intramolecular aza Diels-Alder reaction to yield the tricyclic lactone **168** in 49% yield. This reaction confirmed the regiochemistry of the 1,2,4-triazine **166a** as the cycloaddition could not have occurred if the regioisomer of **166a** was employed in this reaction.



Scheme 66 Reagents and reaction conditions:(i) ethanol, 0°C, 48 h; (ii) reflux, 2.5 h (iii) ethanol, KOH, RT, 12 h; (iv) THF, triethylamine, ethylchloroformate, 2-phenylnylphenol, 3 h, RT.

Thus, benzamidrazone **102** (2.5 molar equivalent made *in situ* from benzamidine hydrochloride hydrate and hydrazine hydrate) was reacted with α-acetoxy-α-chloro-β-dicarbonyls **147a-e** to yield the corresponding 1,2,4-triazines **166a,b-e** in good yields (Table 52), with no trace of regioisomers (Scheme 67). The ^{1}H-NMR spectral data of triazines **166a,e** was identical to that reported in the literature[51,52]. Table 53 shows the ^{1}H-NMR spectral data of triazine **166b**. The structure of triazines **166a,b,e** was also confirmed by high-resolution mass spectroscopy (Table 54).



102 **147** **166**

Scheme 67 Reaction conditions: ethanol, triethylamine, reflux, 20 h

Decomposition of the α-acetoxy-α-chloro-β-dicarbonyls **147a,b** was achieved with saturated ethanolic HCl, and further reaction of the crude mixture with one equivalent of benzamidrazone **102** (prepared *in situ*) yielded 1,2,4-triazines **166a,b** in 80% and 52% yields respectively (Table 52). The ^{1}H-NMR spectral data of the triazines obtained was identical to that of the 1,2,4-triazines synthesised from the α-acetoxy-α-chloro-β-dicarbonyls **147a,b.**

Triazine 166	**R^1**	**Yield (%)**	
		Method A	**Method B**
a	Ph	82	80
b	*n*-Pr	93	52
e	Me	46	-

Table 52 Comparison of yields of formation of 1,2,4-triazines **166**

Method A: from α-acetoxy-α-chloro-β-dicarbonyls **147** and 2.5 eq of amidrazone
Method B: decomposition of α-acetoxy-α-chloro-β-dicarbonyls **147** with ethanolic HCl *prior* reaction with 1 eq of amidrazone

Chemical shift (δ) (ppm)	Number of protons and multiplicity	Coupling constant J (Hz)	Assignment
8.62	2H, dd	8 and 2	Ph-*H*
7.51-7.59	3H, m	-	Ph-*H*
4.55	2H, q	7	ester-C*H*$_2$-
3.15	2H, m	-	propyl-C*H*$_2$-
1.90	2H, sextet	8	propyl-C*H*$_2$-
1.49	3H, t	7	ester-C*H*$_3$
1.07	3H, t	7	propyl-C*H*$_3$

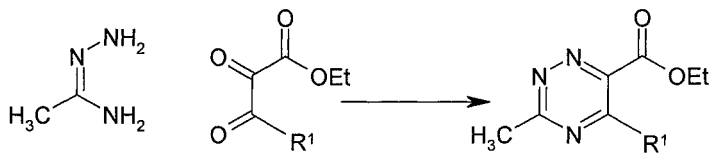
Table 53 ^{1}H-NMR spectral data for triazine **166b**

Triazine 166	Calculated mass $(M+H)^+$	Measured mass $(M+H)^+$
a	306.1237	306.1238
b	272.1394	272.1397
e	244.1081	244.1083

Table 54 High-resolution mass spectral data of triazines **166**

2.4.1.2.4. With acetamidrazone

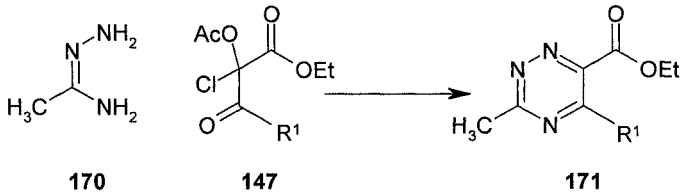
Following the methodology described above, acetamidrazone **170** was synthesized *in situ* by reaction of acetamidine hydrochloride and hydrazine hydrate (Scheme 68). The addition of one equivalent of tricarbonyl **118a-b**, obtained by oxidation of the alcohols **140a-b** with copper(II) acetate, yielded the corresponding 1,2,4-triazines **171a-b** in 44% and 19% respectively. The ^{1}H-NMR spectral data of **171a** was identical to that found in the literature[51]. Table 56 shows the ^{1}H-NMR spectral data for triazine **171b** and its structure was confirmed by high-resolution mass spectroscopy (Table 57).



170 **118** **171**

Scheme 68 Reaction conditions: ethanol, triethylamine, reflux, 20 h

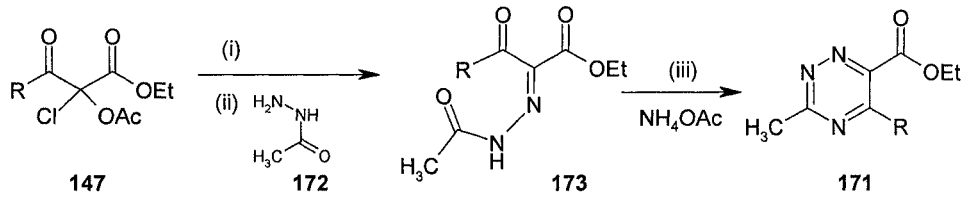
These yields were slightly improved when α-acetoxy-α-chloro-β-dicarbonyls **147a,b-e** were reacted with 2.5 molar equivalents of **170** (Scheme 69). The ^{1}H-NMR spectral data of triazines **171a,e** was identical to that found in the literature[51]. In this case, triazine **171e** was obtained regioselectively from **147e** according to ^{1}H-NMR spectroscopy, unlike the method reported[51] where mixtures of regioisomers were obtained in the formation of **171e** from the tricarbonyl **104**.



170 **147** **171**

Scheme 69 Reaction conditions: ethanol, triethylamine, reflux, 20 h

Looking to improve the yields in the formation of 1,2,4-triazines **171a-b**, the method described by Neunhoeffer[51] was followed. Decomposition of α-acetoxy-α-chloro-β-dicarbonyls **147a,b** was achieved by treatment with saturated ethanolic HCl; further reaction with acetic hydrazide **172** gave intermediate **173**, which was cyclised with ammonium acetate to the corresponding 1,2,4-triazine **171a-b** (Scheme 70). The ^{1}H-NMR spectral data was identical to that of the 1,2,4-triazines synthesised from the α-acetoxy-α-chloro-β-dicarbonyls **147a,b.** Table 55 shows a comparison of the results obtained following the different methods.



147 **172** **173** **171**

Scheme 70 Reagents and reaction conditions: (i) saturated ethanolic HCl, RT, 16 h; (ii) ethanol, RT, 5 h; (iii) glacial acetic acid, reflux, 12 h.

Triazine 171	R	Yield (%)		
		Method A	Method B	Method C
a	Ph	44	54	78
b	*n*-Pr	19	43	51
e	Me	Mixture	15	-

Table 55 Comparison of yields of formation of 1,2,4-triazines **171**

Method A: from tricarbonyls **118** and one equivalent of acetimidrazone **170**
Method B: from α-acetoxy-α-chloro-β-dicarbonyls **147** and 2.5 eq of acetimidrazone **170**
Method C: decomposition of α-acetoxy-α-chloro-β-dicarbonyls **147** with saturated ethanolic HCl *prior* reaction with acetic hydrazide **172** and ammonium acetate

Chemical shift (δ) (ppm)	Number of protons and multiplicity	Coupling constant J (Hz)	Assignment
4.52	2H, q	7	ester-C*H*$_2$-
3.01	2H, m	-	propyl-C*H*$_2$-
2.90	3H, s	-	-C*H*$_3$
1.78	2H, sextet	8	propyl-C*H*$_2$-
1.46	3H, t	7	ester-C*H*$_3$
1.02	3H, t	7	propyl-C*H*$_3$

Table 56 ^{1}H-NMR spectral data for triazine **171b**

Triazine 171	Calculated mass $(M+H)^+$	Measured mass $(M+H)^+$
a	244.1081	244.1082
b	210.1237	210.1236

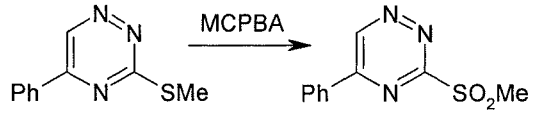
Table 57 High-resolution mass spectral data of triazines **171a-b**

2.4.2. Reactivity of 1,2,4-triazines

2.4.2.1. Oxidation of 1,2,4-triazines

The oxidation of 3-methylthio-1,2,4-triazines to sulphones has been carried out using two equivalents of *m*-chloroperbenzoic acid (MCPBA)[102]. The resulting sulphones must be handled with care, since they readily undergo displacement of methyl sulphinate by nucleophiles as weak as cyanide or water. The sulphone group provides an electron-deficient substituent which would assist the aza Diels-Alder reactions. Taylor and colleagues[103-108] have reported a significant number of intramolecular aza Diels-Alder reactions of these compounds; however, there are few intermolecular examples of this reaction, leaving considerable scope for investigation of these reactions.

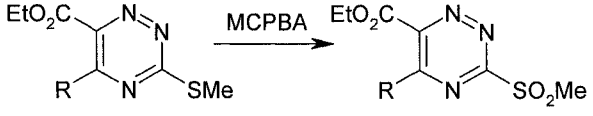
Using a literature method [105] 3-methylsulfonyl-1,2,4-triazine **174** was prepared from 3-methylthio-1,2,4-triazine **161** in 66% yield (Scheme 71). The ^{1}H-NMR spectral data and melting point was consistent with that found in the literature[105].



161 **174**

Scheme 71 Reaction conditions: DCM, RT, 4 h

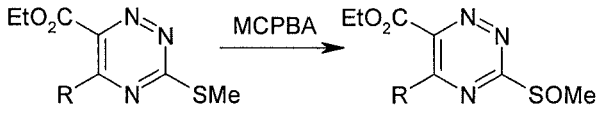
Similarly, triazines **162a-b** (**a** R=Ph, **b** R=*n*-Pr) were oxidised to their corresponding sulphones **175a-b** in 80% and 60 % respectively (Scheme 72). There is no data reported for these compounds; however, by comparing the ^{1}H-NMR data of the product with that of the starting material, the peak corresponding to the protons in the methylthio group has shifted from ~2.70 ppm in the starting material to ~3.30 ppm in the products, implying that oxidation was successful.



162 **175**

Scheme 72 Reaction conditions: DCM, RT, 4 h

We then decided to investigate the synthesis of more stable triazines, which do not undergo readily displacement by nucleophiles, but still provide electron-deficient substituent to assist in the aza Diels-Alder reaction. Treatment of 3-methylthio-1,2,4-triazines **162** with one equivalent of *m*-chloroperbenzoic acid gave the corresponding sulphoxides **176**, in good yields (Scheme73) as shown in Table 58. There is no data reported in the literature for compounds **176**, however, they all show a peak at ~3 ppm by ^{1}H-NMR spectroscopy, which corresponds to the protons in the methylsulphoxy group.



162 **176**

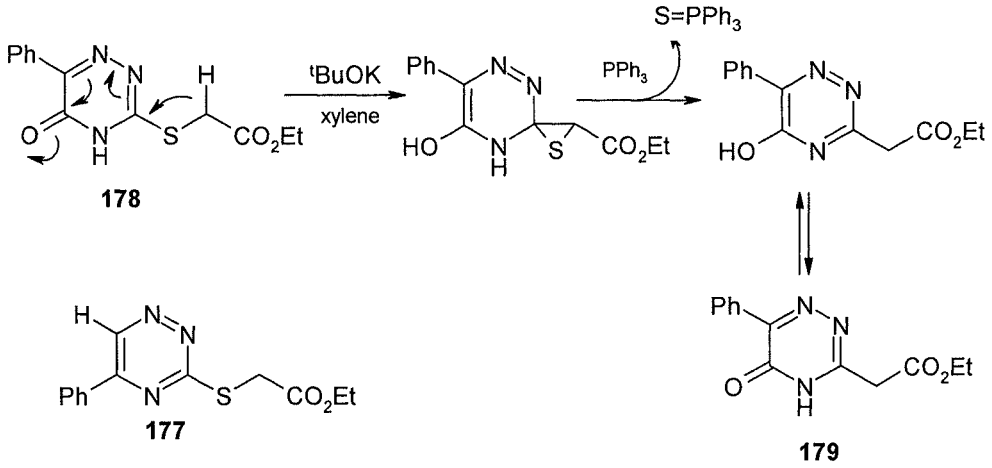
Scheme 73 Reaction conditions: DCM, RT, 2 h

Triazine 176	R	Yield (%)
a	Ph	91
b	*n*-Pr	65
e	Me	29

Table 58 Yields obtained for triazines **176a-e**

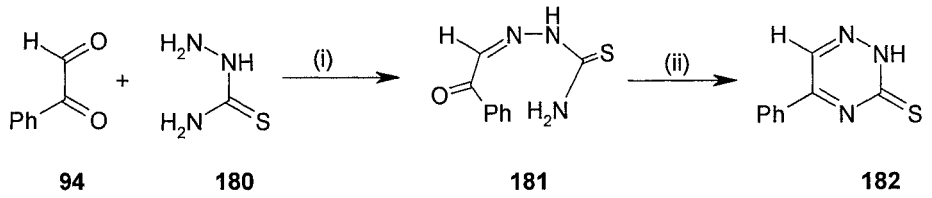
2.4.2.2. Eschenmoser reaction

Following the investigation of sulphur containing 1,2,4-triazines and in attempt to introduce different functionality in the 1,2,4-triazine, the Eschenmoser reaction has been investigated. This sulphur extrusion reaction has been observed in structurally related 2-pyrimidones[109]. Thus, the Eschenmoser reaction is expected to be relatively facile for 1,2,4-triazine **177** and even easier for **178** because the electron density can flow towards the carbonyl group giving the 1,2,4-triazine **179** as shown in Scheme 74. Additionally, the carbonyl group could be converted into a chloro substituent at a later stage.



Scheme 74

Therefore, triazines **177** and **178** were prepared and the Eschenmoser reaction investigated. Using the methodology described in the literature [110] triazine 5-phenyl -2,3-dihydro-1,2,4-triazine-3-thione **182** was prepared in 76% yield by condensation of phenylglyoxal **94** with thiosemicarbazide **180** and further cyclisation of the thiosemicarbazone intermediate **181** (Scheme 75). There is no ^{1}H-NMR spectral data reported in the literature for compound **182** however the melting point of **182** (192-194 °C) corresponds to that described in the literature[110]. Table 59 shows the ^{1}H-NMR spectral data of compound **182**.

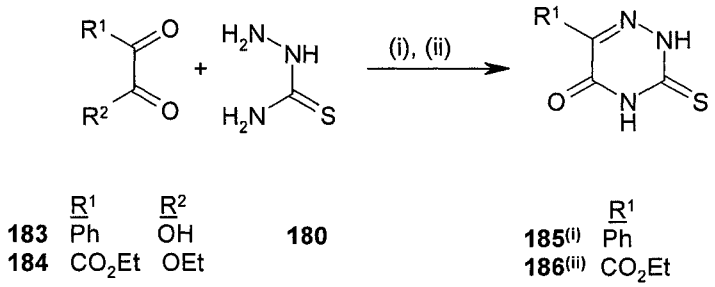


Scheme 75 Reagents and reaction conditions:
(i) warm H_2O; (ii) 10% aq K_2CO_3, reflux, 10 min.

Chemical shift (δ) (ppm)	Number of protons and multiplicity	Coupling constant J (Hz)	Assignment
8.52	1H, s	-	-C*H*
8.18	2H, d	8	Ph-*H*
7.71-7.54	3H, m	-	Ph-*H*
1.57	broad singlet	-	-N*H*

Table 59 ^{1}H-NMR spectral data of compound **182**

Similarly phenylglyoxylic acid **183** and diethyl oxomalonate **184** condensed with thiosemicarbazide **180** to give the corresponding 1,2,4-triazines **185** [111] and **186** [112] in 78% and 61% yield respectively as shown in Scheme 76.



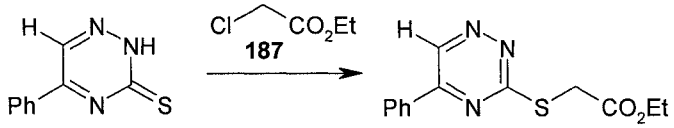
	R1	R2
183	Ph	OH
184	CO_2Et	OEt

180

	R1
185(i)	Ph
186(ii)	CO_2Et

Scheme 76 Reaction conditions: (i) water, 70 °C (ii) ethanol, reflux

Alkylation of triazine **182** with ethyl chloroacetate **187** gave the novel and desired *S*-alkylated product **177** in 62% yield (Scheme 77). Table 60 shows the ^{1}H-NMR spectral data of compound **177**.



182 **177**

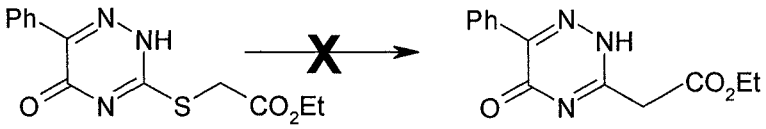
Scheme 77 Reaction conditions: DMF, K_2CO_3, room temperature

Chemical shift (δ) (ppm)	Number of protons and multiplicity	Coupling constant J (Hz)	Assignment
9.41	1H, s	-	-C*H*
8.16	2H, dd	7	Ph-*H*
7.62-7.53	3H, m	-	Ph-*H*
4.23	2H, q	7	ester-CH_2
4.08	2H, s	7	-CH_2-
1.28	3H, t	7	ester-CH_3

Table 60 ^{1}H-NMR spectral data for compound **177**

When more reactive bromo-compounds were used as alkylating agents (phenacyl bromide and diethyl bromomalonate) the reaction with triazine **182** was not clean, probably in these cases, some *N*-alkylation as well as *S,N*-dialkylation may have occurred. The mono-alkylation of compound **185** has been achieved using ethanolic potassium hydroxide. The structure of compound **178** was confirmed by ^{1}H-NMR spectroscopy.

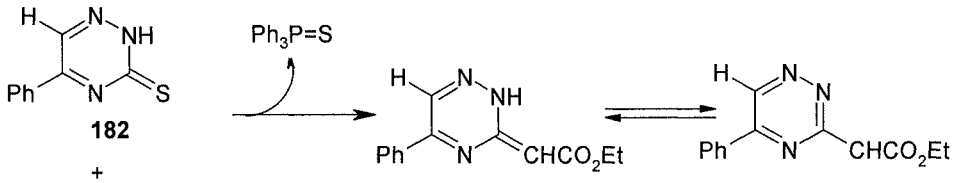
The Eschenmoser reaction of compound **178** was attempted in refluxing xylene using potassium *tert* butoxide as a base as a route to compound **179** (Scheme 78). Unfortunately, the crude reaction mixture only showed starting material **178** to be present by ^{1}H-NMR spectroscopy. The thermal Eschenmoser reaction of compound **177** also failed and starting material was mainly recovered.



178 **179**

Scheme 78 Reaction conditions: xylene, ^{t}BuO$^-$$^+$K, reflux

Looking into sulphur extrusion reactions, the thio-Wittig reaction was attempted. As most successful thio-Wittig reactions have been reported on thioimides and triazines **182** and **185** possess a thioimide fragment we decided to try this reaction. However, when triazine **182** was reacted with phosphorane as a potential route to compound **188** (Scheme 79), only a complex mixture was obtained by ^{1}H-NMR spectroscopy.



182

+

$Ph_3P{=}CHCO_2Et$

188

189

Scheme 79 Reaction conditions: xylene, reflux

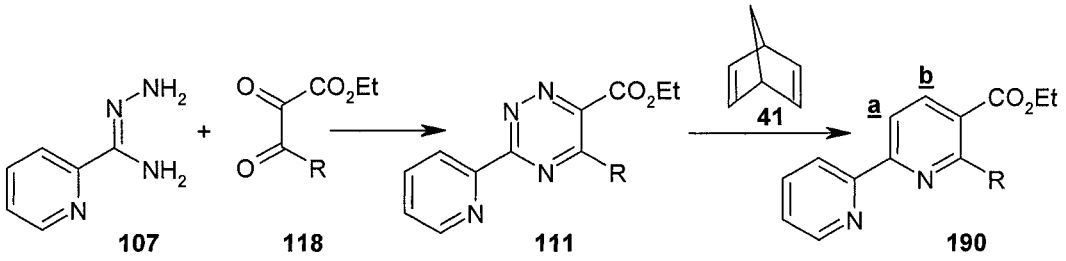
2.5. Pyridines

2.5.1. Aza Diels-Alder reaction of 1,2,4-triazines

The aza Diels-Alder reaction of 1,2,4-triazines with 2,5-norbornadiene **41** to form pyridines has been widely studied.

Stanforth and co-workers[28] reported the synthesis of bipyridyls **190** using a one-pot procedure in ethanol from the corresponding 1,2,4-triazines **111** (generated *in situ* from the corresponding tricarbonyls **118** and not isolated), as shown in Scheme 80.

Using this methodology and, to gain an insight into the chemistry, bipyridyls **190a-c** were synthesised in overall good yields from tricarbonyls **118a-c** (prepared from the diazo-compounds **135a-b** and the oxidation of the alcohol **140c** with $Cu(OAc)_2$ respectively) in a one-pot procedure (Scheme 80). Table 61 summarises some of the results. When tricarbonyl **118b** was prepared by oxidation of the alcohol **140b** with $Cu(OAc)_2$ or TEMPO, the bipyridyl **190b** was obtained in 30% and 58% yields respectively. By comparing the ^{1}H-NMR spectral data of the bipyridyl **190** formed with that of the triazine **111** (isolated in section 2.4.1.1), there were addition signals present (the protons **a** and **b** in formulae **190**) resulting from the cycloaddition of 2,5-norbornadiene **41**. The ^{1}H-NMR spectral data of compounds **190a-c** is consistent with the data found in the literature[97]. Table 61 and 62 shows a summary of results and some partial ^{1}H-NMR spectral data of pyridines **190**.



Scheme 80 Reaction conditions: ethanol, reflux, 20 h

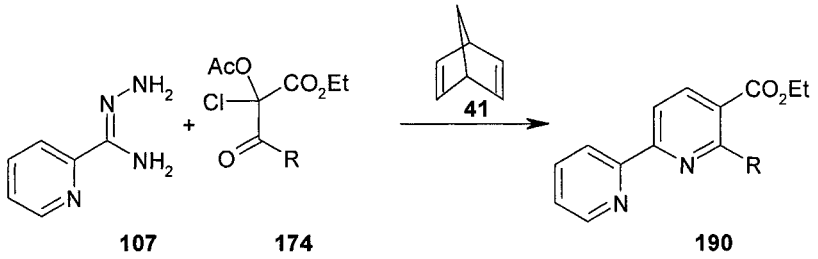
Bipyridyl 190	R	Yield (%)
a	Ph	87
b	*n*-Pr	81
c*	^{t}Bu	11

Table 61 Formation of bipyridyls **190a-c** from tricarbonyls **118a-c** (prepared from **135a-b** and oxidation with $Cu(OAc)_2$ of alcohol **140c**) in a one-pot procedure
(*) The methyl ester was used in this case.

Bipyridyl 190	R	Multiplicity	Coupling constant J (Hz)	Chemical shift δ (ppm)	
				a	**b**
a	Ph	d	8	8.45	8.23
b	*n*-Pr	s	-	8.28	
c	^{t}Bu	d	8	8.52	8.26

Table 62 The ^{1}H-NMR spectral data of bipyridyls **190a-c**

Thus, bipyridyl derivatives **190a,b,d,e** were prepared in a one-pot procedure from α-acetoxy-α-chloro-β-dicarbonyls **174a,b,d,e**, 2.5 molar equivalent of pyridyl-2-carboximidohydrazide **107** and 2,5-norbornadiene **41** (Scheme 81). The ^{1}H-NMR spectral data of compounds **190a-b** was identical to that obtained from the tricarbonyls **118a-b**. Bipyridyls **190d-e** were purified by recrystallisation and column chromatography respectively to obtain the pure product. Table 64 shows selected ^{1}H-NMR spectral data of pyridines **190d-e**. The structures of compounds **190d-e** were also confirmed by high-resolution mass spectrometry as shown in Table 64.



Scheme 81 Reaction conditions: ethanol, reflux, 20 h

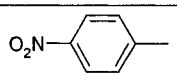
Bipyridyl 190	R	Yield (%)
a	Ph	50
b	*n*-Pr	63
d		14
e	Me	18

Table 63 Yields obtained for bipyridyls **190a,b,d,e** from α-acetoxy-α-chloro-β-dicarbonyls **147a,b,d,e**

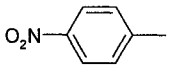
Bipyridyl 190	R	Calculated mass $(M+H)^+$	Measured mass $(M+H)^+$	Multiplicity	Coupling constant J (Hz)	Chemical shift δ (ppm)	
						a	**b**
d		350.1135	350.1135	d	8	8.56	8.36
e	Me	243.1128	243.1128	s	-	8.31	

Table 64 The high-resolution mass and ^{1}H-NMR spectral data of bipyridyls **190d-e**

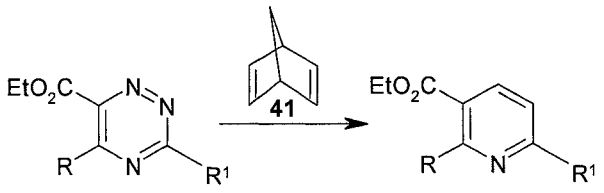
The decomposition of the α-acetoxy-α-chloro-β-dicarbonyls **174a-b** *prior to* reaction in a one-pot procedure to bipyridyls **190a-b** was also investigated. This was achieved using saturated ethanolic HCl or 33% wt methylamine in ethanol and Table 65 compares the yields obtained using both different decomposition methods.

Bipyridyl 190	R	Yield (%)	
		Method A	**Method B**
a	Ph	80	96
b	*n*-Pr	68	80

Table 65 Yields obtained for bipyridyls **190a-b** from decomposition of α-acetoxy-α-chloro-β-dicarbonyls **147a-b**

Method A: decomposition with saturated ethanolic HCl
Method B: decomposition with 33%wt methylamine in ethanol

The synthesis of pyridine derivatives **191** and **192** from benzamidrazone **102** and acetamidrazone **170** using the one-pot procedure in ethanol was then investigated. However, the main product obtained was 1,2,4-triazines **166** and **171** respectively, with small traces of the pyridine by ^{1}H-NMR spectroscopy. As previously discussed, electron-withdrawing groups in the 1,2,4-triazine will assist the aza Diels-Alder reaction to form pyridine derivatives. For 1,2,4-triazines **166** and **171**, bearing two electron-donating groups, a higher boiling point solvent (xylene) was required to take the reaction to pyridines **191** and **192** to completion. Table 66 and 67 show a summary of results and some partial ^{1}H-NMR spectral data for pyridines **191** and **192**.



166 R^1=Ph
171 R^1=Me

191 R^1=Ph
192 R^1=Me

Scheme 82 Reaction conditions: xylene, reflux, 12 h

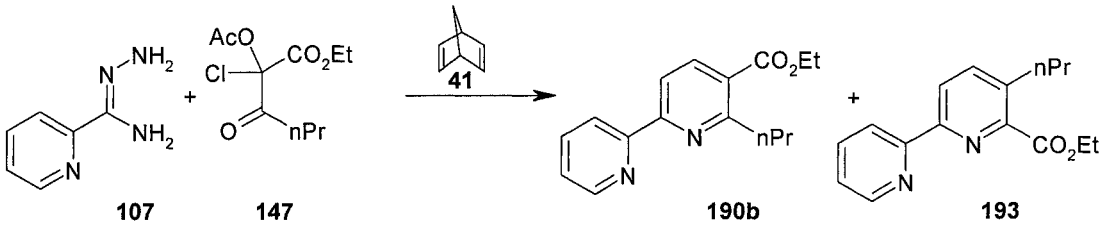
Pyridine	R^1	R	Yield (%)
191a	Ph	Ph	44
191b		*n*-Pr	31
192a	Me	Ph	95
192b		*n*-Pr	67

Table 66 Formation of pyridines **191a-b** and **192a-b**.

Pyridine	R^1	R	Multiplicity	Coupling constant J (Hz)	Chemical shift δ (ppm)	
					a	b
191a	Ph	Ph	d	8	8.18	7.78
191b		*n*-Pr	d	8	8.22	7.61
192a	Me	Ph	d	8	8.02	7.19
192b		*n*-Pr	d	8	8.06	7.04

Table 67 The ^{1}H-NMR spectral data of pyridines **191a-b** and **192a-b**.

Therefore, the use of different solvents in the one-pot procedure to pyridines was studied for a known reaction. When the one-pot procedure to bipyridyl **190** was carried out in toluene, mixtures of regioisomers **190b** and **193** were obtained (Scheme 83). Separation by column chromatography was not successful. The effect of the solvent in the formation of 1,2,4-triazines is therefore evident. While toluene gives a mixture of regioisomers, when the reaction was carried out in ethanol only one isomer was observed by ^{1}H-NMR spectroscopy. Therefore, it is expected that pyridines **191** and **192** could not be synthesised using the one-pot procedure, isolation of the 1,2,4-triazine is necessary and solvent changed for the aza Diels-Alder reaction to go to completion.



107 **147** **190b** **193**

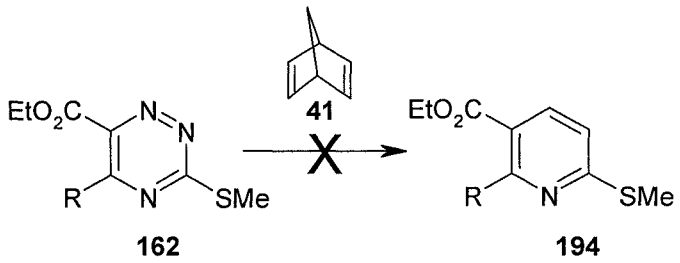
Scheme 83 Reaction conditions: see Table 67

Reaction conditions	Ratio 190b:193		Yield (%)
Ethanol, reflux, 20 h	100	0	63
Toluene, reflux, 20 h	80	20	80

Table 68

3-Methylthio-1,2,4-triazines **162a-b** and 2,5-norbornadiene **41** were heated at reflux in ethanol but unfortunately ^{1}H-NMR spectroscopy did not show any evidence of a cycloaddition reaction occurring and the starting material **162a-b** was recovered (Scheme 84). This was expected because 3-methylthio is a very electron-rich substituent that would not assist the aza Diels-Alder reaction to pyridines.

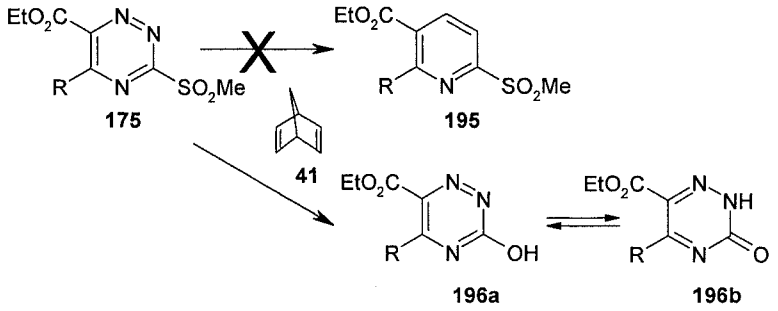
When this reaction was carried out in toluene, some traces of product were present by ^{1}H-NMR spectroscopy, but mainly starting material was recovered. In xylene the reaction also seemed to be very slow and a (1:1) mixture of **194** and starting material **162** was observed by ^{1}H-NMR spectroscopy. Due to the problems encountered to take these reactions to completion, we decided to investigate the aza Diels-Alder reaction of more reactive 1,2,4-triazines.



162 **194**

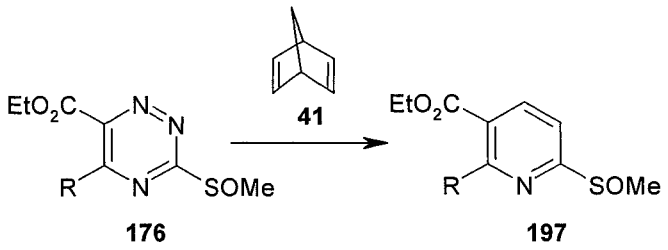
Scheme 84 Reaction conditions: ethanol, reflux, 12 h

3-Methanesulphonyl-1,2,4-triazines **175** have two electron withdrawing groups so they are expected to easily undergo aza Diels-Alder reactions with electron-rich dienophiles to give the corresponding pyridines. However, when **175a** (R=Ph) was reacted with 2,5-norbornadiene **41** in boiling ethyl acetate the ^{1}H-NMR spectral data of the crude mixture did not look promising. The methyl signal had disappeared, suggesting that the methanesulphonyl group was not present in the product. In 1,2,4-triazine systems, sulphone groups at the 3-position can be replaced by nucleophiles and the presence of an ester '*para*' to this group might enhance its lability. We did not use vigorously anhydrous conditions and apparently substitution might have taken place by traces of water (Scheme 85). The product was strongly implied to be **196a** (or its tautomer **196b**) by mass spectrometry E.I.M.S., m/z (relative abundance): 246 (100) $[M+H]^+$.



Scheme 85

We then decided to investigate the 1,2,4-triazines bearing a methanesulphoxy group, which is electron-withdrawing enough to assist the aza Diels-Alder reaction but not as susceptible to nucleophilic attack. Therefore, 3-methanesulphoxy-1,2,4-triazines **176a-e** were reacted with 2,5-norbornadiene **41** in boiling ethanol to give the corresponding pyridines **197** in good overall yields (Scheme 86). Tables 69 and 70 show a summary of results and some partial ^{1}H-NMR spectral data for pyridines **197**.



Scheme 86 Reaction conditions: ethanol, reflux, 12 h

Pyridine 197	R	Yield (%)
a	Ph	75
b	*n*-Pr	88
e	Me	41

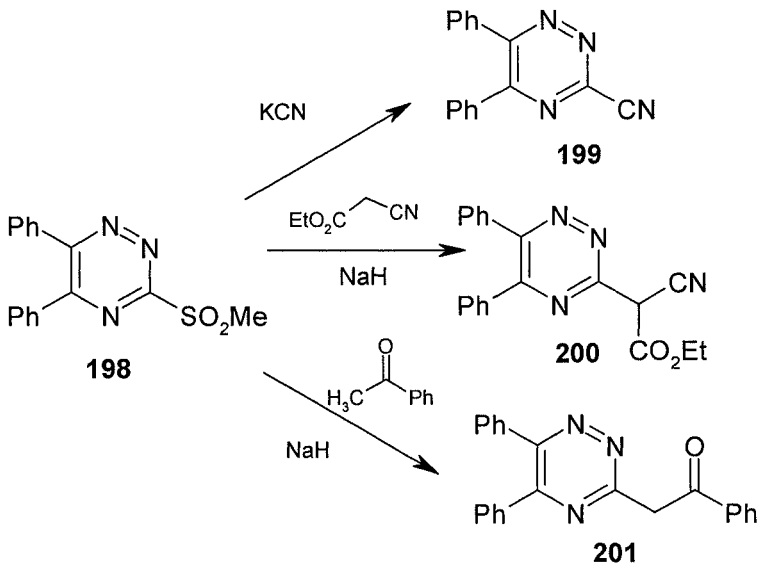
Table 69 Results obtained for the formation of pyridines **197**

Pyridine 197	R	Multiplicity	Coupling constant J (Hz)	Chemical shift δ (ppm)	
				a	**b**
a	Ph	d	8	8.33	8.09
b	*n*-Pr	d	8	8.38	7.93
e	Me	d	8	8.44	7.94

Table 70 The ^{1}H-NMR spectral data of pyridines **197**

2.5.2. Substitution reactions on pyridine

The substitution of the 3-methanesulphonyl group of 1,2,4-triazines has been previously studied (Scheme 87). The 3-methanesulphonyl-1,2,4-triazine **198** has been shown to readily react not only with active methylene compounds, but also with methyl or methylene ketones under basic conditions, to give the substituted 1,2,4-triazine with new functionality in the C-3[102].



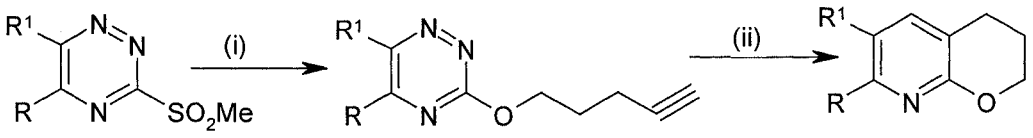
Scheme 87

Substituted triazine	Reaction conditions	Yield (%)
199	DMF, room temperature, 45 min.	58
200	dry THF, reflux, 3 h.	58
201	dry THF, reflux, 3 h.	17

Table 71

Taylor and colleagues explored high reactivity of 1,2,4-triazines **202** towards nucleophiles to obtain a dienophilic side-chain tethered to C-3, that would undergo intramolecular Diels-Alder reactions to give fused pyridines such as, [2,3-*b*]pyridines[113], furo [2,3-*b*]pyridines[105], dihydropyrrolo [2,3-*b*]pyridines[114], 2,3-cyclopentenopyridines[108] and 5,6,7,8-tetrahydroquinolines[108]. The nature of the ring fused to the pyridine ring is determined by the structure of the dienophilic side-chain tethered to the 3-position of the 1,2,4-triazine.

Scheme 88 below shows an example of these chemistry, where the 3-methylsulphonyl-1,2,4-triazines **202** undergoes nucleophilic substitution, and further intramolecular Diels-Alder reaction of compound **203** yields the 2,3-dihydropyrano[2,3-*b*]pyridines **204** in good yields (42-79%)[105].

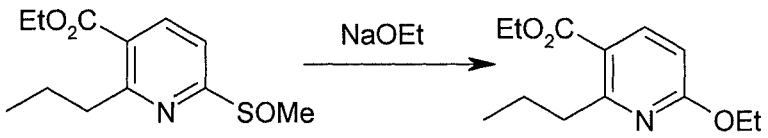


202 **203** **204**

Scheme 88 Reagents and reaction conditions: (i) sodium 4-pentynyl-1-oxide, dry THF, 0 °C, 30 h (ii) reflux

Therefore, we decided to investigate the substitution reaction of pyridines **197** bearing a methanesulphoxy group in the C-3. These reactions have not been explored in the literature and opportunities exist to investigate and extend the scope of this reaction introducing new functionality to the pyridine ring.

It is anticipated that this work will be done by future workers. However, a preliminary investigation was carried out. Thus, ethyl 5-carboxylate-2-methanesulphoxy-6-propylpyridine **197b** was treated with NaOEt and the mixture was stirred under reflux for 1 hour to give the substituted ethyl 5-carboxylate-2-ethoxy-6-propylpyridine **205** in 53% yield.



197b **205**

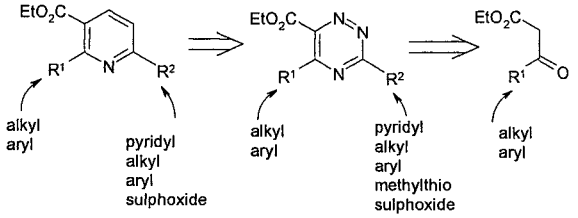
Scheme 89 Reaction conditions: reflux, 1 h.

2.6. Conclusion

Three 1,2,3-tricarbonyls **118a-c** were obtained by oxidation of the corresponding alcohol compounds **140a-c** in good yields following two different oxidation methods. The alcohol compounds were obtained in excellent yields from readily available β-ketoesters in a three step sequence. These provided a new route to tricarbonyls that avoided the shortfalls encountered in the known methods. Four novel tricarbonyl derivatives, α-chloro-α-acetoxy-β-dicarbonyls **147**, were prepared in excellent yields and they were shown to react as tricarbonyl equivalents in the formation of 1,2,4-triazines with 2.5 equivalents of amidrazone. The α-chloro-α-acetoxy-β-dicarbonyls **147** could be decomposed *prior to* reaction with 1 equivalent of amidrazone yielding the corresponding 1,2,4-triazines in good yields.

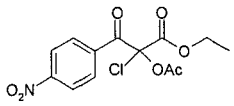
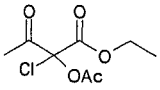
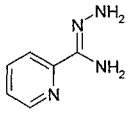
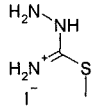
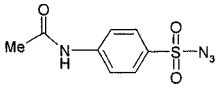
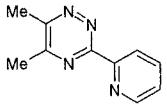
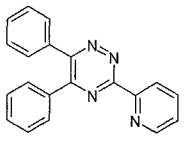
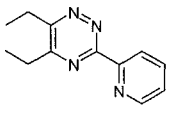
A wide variety of amidrazones were reacted with different tricarbonyls and tricarbonyl derivatives to yield a series of novel 1,2,4-triazine derivatives in good yields. These 1,2,4-triazines reacted successfully with 2,5-norbornadiene **41** following an aza Diels-Alder cycloaddition reactions to yield their corresponding novel 2,3,6-trisubstituted pyridines in moderate to excellent yields. Those pyridines bearing electron withdrawing groups as substituents could be obtained in a 'one-pot' reaction in ethanol, from their corresponding tricarbonyls or tricarbonyl derivatives. Those 1,2,4-triazines bearing electron donating groups could not be converted to their corresponding pyridines in a 'one-pot' procedure. Therefore, a change in the reaction conditions or, when possible, the conversion of the electron donating group into a more electron withdrawing substituent by oxidation (e.g. sulphoxide substituent) was required to yield the corresponding pyridines.

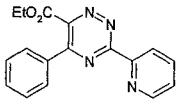
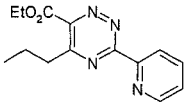
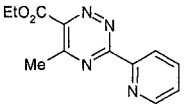
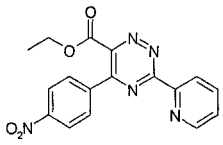
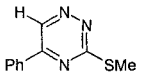
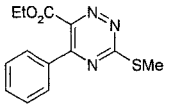
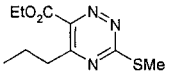
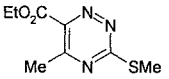
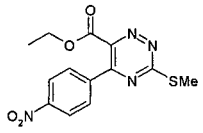
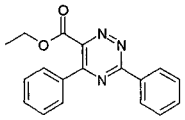
Pyridines bearing a sulphoxide substituent have been demonstrated to undergo nucleophilic substitutions, giving great scope to investigate these reactions and introduce different functionality in the C-6 of the pyridines.

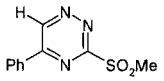
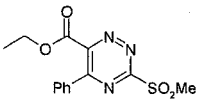
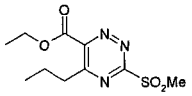
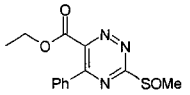
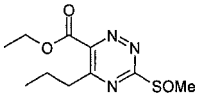
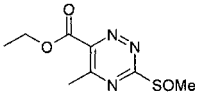


EXPERIMENTAL

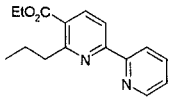
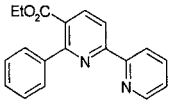
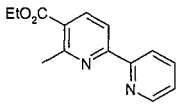
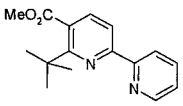
3.1. List of compounds

	Compound	Page
	Ethyl 2-Acetoxy-2-chloro-3-oxo-3-(4-nitro phenyl)propanoate **147d**	114
	Ethyl 2-Acetoxy-2-chloro-3-oxo-3-butanoate **147e**	115
Other reactants		
	Pyridine-2-carboximidohydrazide **107**	115
	*t*-Butylhypochlorite	115
	*S*-Methylthiosemicarbazide hydrogen iodide **160**	116
	4-Acetamidobenzenesulphonyl azide	116
1,2,4-Triazines		
	5,6-Dimethyl-3-pyridin-2-yl-1,2,4-triazine **153**	117
	5,6-Diphenyl-3-pyridin-2-yl-1,2,4-triazine **152**	117
	5,6-Diethyl-3-pyridin-2-yl-1,2,4-triazine **154**	118

	Compound	Page
	Ethyl 6-Carboxylate-5-phenyl-3-pyridin-2-yl-1,2,4-triazine **111a**	118
	Ethyl 6-Carboxylate-5-propyl-3-pyridin-2-yl-1,2,4-triazine **111b**	120
	Ethyl 6-Carboxylate-5-methyl-3-pyridin-2-yl-1,2,4-triazine **111e**	122
	Ethyl 6-Carboxylate-5-(4-nitrophenyl)-3-pyridin-2-yl-1,2,4-triazine **111d**	123
	3-Methylsulfanyl-5-phenyl-1,2,4-triazine **161**	124
	Ethyl 6-Carboxylate-3-methylthio-5-phenyl-1,2,4-triazine **162a**	124
	Ethyl 6-Carboxylate-3-methylthio-5-propyl-1,2,4-triazine **162b**	126
	Ethyl 6-Carboxylate-3-methyl -5-methylthio-1,2,4-triazine **162e**	127
	Ethyl 6-Carboxylate-3-methylthio-5-(4-nitro)phenyl-1,2,4-triazine **162d**	128
	Ethyl 6-Carboxylate-3,5-diphenyl-1,2,4-triazine **166a**	128

	Compound	Page
	6-Methanesulphonyl-5-phenyl-1,2,4-triazine **174**	136
	Ethyl 6-Carboxylate-3-methanesulphonyl-5-phenyl-1,2,4-triazine **175a**	137
	Ethyl 6-Carboxylate-3-methanesulphonyl-5-propyl-1,2,4-triazine **175b**	137
	Ethyl 6-Carboxylate-3-methanesulphoxy-5-phenyl-1,2,4-triazine **176a**	138
	Ethyl 6-Carboxylate-3-methanesulphoxy-5-propyl-1,2,4-triazine **176b**	138
	Ethyl 6-Carboxylate-5-methyl-3-methanesulphoxy-1,2,4-triazine **176e**	138

Pyridines

	Ethyl 5-Carboxylate-6-propyl-[2,2']bipyridyl **190b**	139
	Ethyl 5-Carboxylate-6-phenyl-[2,2']bipyridyl **190a**	140
	Ethyl 5-Carboxylate-6-methyl-[2,2']bipyridyl **190e**	142
	Methyl 5-Carboxylate-6-*tert*butyl-[2,2']bipyridyl **190c**	142

3.2. Experimental Directions

^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Joel JNM EX270 instrument (270 MHz). All chemical shifts are quoted in ppm relative to tetramethylsilane (TMS) as an internal standard in either deuterio-trichloromethane or deuterio-dimethylsulphoxide. All chemical shifts are reported as follows: δ value in ppm (multiplicity, number of protons, coupling constant in Hz, and assignments). The multiplicity of signals is expressed as follows: s, singlet; d, doublet; dd, double doublet; ddd, double doublet of doublets; t, triplet; dt, double triplet and m, multiplet.

GC/MS were recorded using a Hewlett Packard 5890 series II instrument in conjunction with a Hewlet Packard 5971A mass detector.

Elemental analysis was performed by the Department of Chemistry at the University of Newcastle. High-resolution mass spectra were performed by the EPSRC's mass spectrometry service at the University of Wales, Swansea. Melting points are reported uncorrected as determined on a Stuart SMP1 melting point apparatus. Infra-red spectra were obtained using a diamond anvil on a Perkin Elmer 1000 spectrophotometer.

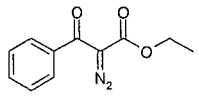
Thin layer chromatography was performed on Merck plastic foil plates pre-coated with silica get $60F_{254}$. Silica gel for column chromatography was Merck silica gel 60.

3.3. Experimental

3.3..1. Tricarbonyl intermediates

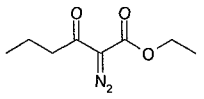
Preparation of α-diazo-β-dicarbonyls

To a stirred solution of the appropriate dicarbonyl compound **117a-b** and KF in DCM (50 mL) was added 4-acetamidobenzenesulphonyl azide. The solution was protected from the light, stirred for 16 hours and then filtered through a layer of silica gel (2-3 cm). The filtrate was washed with 5 % KOH solution, water (3 x 10 mL), dried over $MgSO_4$ and evaporated under reduced pressure to give the crude α-diazo-β-dicarbonyl compound. The α-diazo-β-dicarbonyl compounds **135a-b** were all used in the subsequent reactions with *t*-butylhypochlorite without need for purification.



Ethyl 2-Diazo-3-oxo-3-phenylpropanoate 135a

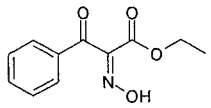
Compound **135a** was prepared from ethyl benzoylacetate **117a** (3.84 g, 20 mmol), KF (2.56 g, 44 mmol) and 4-acetamidobenzenesulphonyl azide (4.32 g, 18 mmol) following the general procedure described above. Yield (3.4 g, 80%) as a yellow oil. ^{1}H-NMR: ($CDCl_3$) δ 7.61 (d, 2H, J= 8 Hz, Ph-*H*), δ 7.46 (m, 3H, Ph-*H*), δ 4.23 (q, 2H, J= 7 Hz, -C*H*$_2$-) and δ 1.25 (t, 3H, J=7 Hz, Ph-*H*) ppm. The ^{1}H-NMR spectral data above is consistent with that found in the literature[115].



Ethyl 2-Diazo-3-oxo-3-hexanoate 135b

Compound **135b** was prepared from ethyl butyrylacetate **117b** (2.0 g, 13 mmol), KF (1.67 g, 28 mmol) and 4-acetamidobenzenesulphonyl azide (2.81 g, 12 mmol) following the general procedure described above. Yield (1.73 g, 74%) as a yellow oil. ^{1}H-NMR: ($CDCl_3$) δ 4.19 (q, 2H, J= 7 Hz, ester-C*H*$_2$-), δ 2.52 (t, 2H, J= 7 Hz, propyl-C*H*$_2$-), δ 1.60 (sextet, J= 7 Hz, 2H, propyl-C*H*$_2$-), δ 1.32 (t, 3H, J= 7 Hz, propyl-C*H*$_3$) and δ 0.91 (t, 3H, J=7 Hz, ester-C*H*$_3$) ppm.

Preparation of oximes



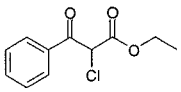
Ethyl-2-hydroxyimino-3-oxo-3-phenylpropanoate 146

A solution of ethyl benzoylacetate **117a** (1.92 g, 10mmol) in glacial acetic acid (5 mL) was cooled to 0 °C and a solution of sodium nitrite (0.83 g, 12mmol) in water (3 mL) added dropwise, maintaining the temperature below 10 °C. After stirring 30 min. at RT, the solution was poured into water (5 mL) and stirred for 15 min. The precipitate was filtered, washed with brine and water and dried to give compound **146**.Yield (1.85 g, 85%) as a white solid, m.p. 122-124 °C (lit. m.p. 121-122 °C)[93]. ^{1}H-NMR: ($CDCl_3$) δ 7.90 (d, 2H, J=7 Hz, Ph-*H*), δ 7.66 (t, 1H, J=7 Hz, Ph-*H*), δ 7.53 (t, 2H, J= 8 Hz, Ph-*H*), δ 4.32 (q, 3H, J= 7 Hz, ester-C*H*$_3$) and δ 1.27 (t, 3H, J=7 Hz, ester-C*H*$_3$) ppm. The melting point and ^{1}H-NMR spectral data are consistent with that found in the literature[93].

Preparation of α-chloro-β-dicarbonyl compounds

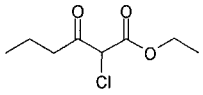
General procedure

To a stirred ice cold solution of the appropriate β-dicarbonyl compound **117a-d** in DCM (10 mL) was added slowly sulfuryl chloride (1.1 mol equivalent). After stirring for 1 hour at RT the solution was washed with a saturated solution of sodium carbonate, dried over $MgSO_4$ and evaporated under reduced pressure to give the crude α-chloro-β-dicarbonyl compound **143a-d**. These compounds were all used in the subsequent reactions without need for purification.



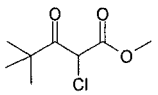
Ethyl 2-Chloro-3-oxo-3-phenylpropanoate 143a

Compound **143a** was prepared from ethyl benzoylacetate **117a** (1 g, 5.2 mmol) using the general procedure. Yield (1.03 g, 88 %) as a yellow oil. ^{1}H-NMR: ($CDCl_3$) δ 8.02 (d, 2H, J=7 Hz, Ph-*H*), δ 7.65 (t, 1H, J=7 Hz, Ph-*H*), δ 7.50 (t, 2H, J=8 Hz, Ph-*H*), δ 5.67 (s, 1H, -C*H*Cl) δ 4.28 (q, 2H, J=7 Hz, ester-CH_2-) and δ 1.23 (t, 3H, J=7 Hz, ester-CH_3) ppm. The ^{1}H-NMR spectral data above is consistent with that found in the literature.[86]



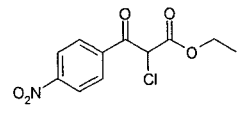
Ethyl 2-Chloro-3-oxo-3-hexanoate 143b

Compound **143b** was prepared from ethyl butyrylacetate **117b** (20 g, 0.12 mol) using the general procedure. Yield (21.95 g, 90 %) as a yellow liquid. ^{1}H-NMR: ($CDCl_3$) δ 4.74 (s, 1H, -C*H*Cl) δ 4.23 (q, 2H, J=7 Hz, ester-CH_2-), δ 2.63 (dt, 2H, J=7 and 3 Hz, -CH_2-), δ 1.59 (sextet, 2H, J= 7 Hz, -CH_2-), δ 1.25 (t, 3H, J=7 Hz ester-CH_3) and δ 0.87 (t, 3H, J=7 Hz, -CH_3) ppm. This compound was used without any further characterisation.
This reaction was scaled up to 100 g successfully.



Methyl 2-Chloro-4,4-dimethyl-3-oxo-3-pentanoate 143c

Compound **143c** was prepared from methyl pivaloylacetate **117c** (5.0 g, 0.03 mol) using the general procedure. Yield (5.13 g, 85%) as a yellow liquid. ^{1}H-NMR: ($CDCl_3$) δ 5.28 (s, 1H, -C*H*Cl), δ 3.80 (s, 3H, ester-CH_3) and δ 1.25 (s, 9H, -C(CH_3)$_3$) ppm. This compound was used without any further characterisation.



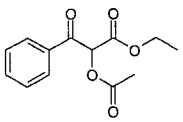
Ethyl 2-Chloro-3-oxo-3-(4-nitrophenyl)propanoate 143d

Compound **143d** was prepared from ethyl 4-nitrobenzoylacetate **117d** (1.0 g, 4.2 mmol) using the general procedure. Yield (0.84 g, 73%) as a yellow solid, m.p. 88-90 °C. The ^{1}H-NMR spectral data suggested a mixture of keto-enol tautomers. The major product found is the enol tautomer with small traces of the keto form. ^{1}H-NMR (major isomer): ($CDCl_3$) δ 12.86 (s, 1H,-C*H*OH), δ 8.36 (d, J=9 Hz, Ph-*H*), δ 8.30 (d, J=9 Hz, Ph-*H*), δ δ 8.18 (d, J=9 Hz, Ph-*H*), δ 7.94 (d, J=9 Hz, Ph-*H*), δ 5.58 (s, 1H, -C*H*Cl), δ 4.32 (q, 2H, J=7 Hz, ester-CH_2-), and δ 1.27 (t, 3H, J=7 Hz, ester-CH_3) ppm. There is no data reported in the literature for this compound.

Preparation of α-acetoxy-β-dicarbonyl compounds

General procedure

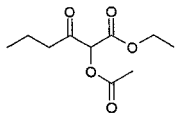
To a stirred ice cold solution of glacial acetic acid (10mL, 0.18 mol) in DMF (50mL) was added slowly NEt_3 (10 mL, 0.10 mol). After warming to RT, the appropriate α-chloro-β-dicarbonyl compound **143a-e** was added and the solution was left stirring at RT for 20 hours. The solution was poured onto water (50 mL), extracted with DCM (2 x 15 mL), dried over $MgSO_4$ and evaporated under reduced pressure to give the crude α-acetoxy-β-dicarbonyl **144a-e**. These compounds were all used in the subsequent reactions without need for purification.



Ethyl 2-Acetoxy-3-oxo-3-phenylpropanoate 144a

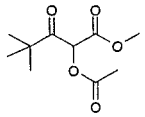
Compound **144a** was prepared from ethyl 2-chloro-3-oxo-3-phenylpropanoate **143a** (5.0 g, 0.02 mol) using the general procedure. Yield (5.24 g, 95 %) as a yellow liquid. ^{1}H-NMR: ($CDCl_3$) δ 8.00 (d, 2H, J=7 Hz, Ph-*H*), δ 7.64 (t, 1H, J=7 Hz, Ph-*H*), δ 7.50 (t, 2H, J=8 Hz,

Ph-*H*), δ 6.34 (s, 1H, -C*H*OAc) δ 4.24 (q, 2H, J=7 Hz, ester-CH_2-), δ 2.22 (s, 3H, acetate-CH_3) and δ 1.20 (t, 3H, J=7 Hz, ester-CH_3) ppm.



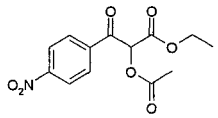
Ethyl 2-Acetoxy-3-oxo-3-hexanoate 144b

Compound **144b** was prepared from ethyl 2-chloro-3-oxo-3-hexanoate **143b** (5.0 g, 26 mmol) using the general procedure. Yield (5.0 g, 90 %) as a yellow liquid. ^{1}H-NMR: ($CDCl_3$) δ 5.50 (s, 1H, -C*H*OAc) δ 4.19 (q, 2H, J=7 Hz, ester-CH_2-), δ 2.57 (t, 2H, J=7 Hz, -CH_2-), δ 2.14 (s, 3H, acetate-CH_3), δ 1.56 (sextet, 2H, J=7 Hz, -CH_2-), δ 1.22 (t, 3H, J=7 Hz ester-CH_3) and δ 0.84 (t, 3H, J=7 Hz, -CH_3) ppm.



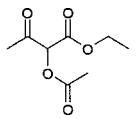
Methyl 2-Acetoxy-4,4-dimethyl-3-oxo-3-pentanoate 144c

Compound **144c** was prepared from methyl 2-chloro-4,4-dimethyl-3-oxo-3-pentanoate **143c** (1.15 g, 5.9 mmol) using the general procedure. Yield (1.05 g, 86%) as a yellow liquid.^{1}H-NMR: ($CDCl_3$). δ 5.86 (s, 1H, -C*H*OAc), δ 3.72 (s, 3H, ester-CH_3), δ 2.14 (s, 3H, acetate-CH_3) and δ 1.16 (s, 9H, -C(CH_3)$_3$) ppm.



Ethyl 2-Acetoxy-3-oxo-3-(4-nitrophenyl)propanoate 144d

Compound **144d** was prepared from ethyl 2-chloro-3-oxo-3-(4-nitrophenyl)propanoate **143d** (5 g, 18 mmol) using the general procedure. Yield (5.04 g, 88%) as a red oil. The ^{1}H-NMR spectral data suggested a mixture of keto-enol tautomers. ^{1}H-NMR (major tautomer): ($CDCl_3$) δ 8.36 (d, 2H, J=9 Hz, Ph-*H*), δ 8.18 (d, 2H, J= 9 Hz, Ph-*H*), δ 6.30 (s, 1H, -C*H*OAc), δ 4.27 (q, 2H, J= 7 Hz, ester-CH_2-), δ 2.25 (s, 3H, acetate-CH_3) and δ 1.23 (t, 3H, J= 7 Hz, ester-CH_3) ppm.



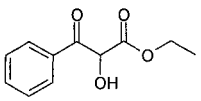
Ethyl 2-Acetoxy-3-oxo-3-butanoate 144e

Compound **144e** was prepared from ethyl 2-chloroacetoacetate **143e** (3.0 g, 18 mmol) using the general procedure. Yield (2.86 g, 84 %) as an orange oil. ^{1}H-NMR: ($CDCl_3$) δ 5.50 (s, 1H, -C*H*OAc), δ 4.28 (q, 2H, J= 7 Hz, ester-CH_2-), δ 2.35 (s, 3H, -CH_3), δ 2.24 (s, 3H, acetate-CH_3) and δ 1.32 (t, 3H, J= 7 Hz, ester-CH_3). The ^{1}H-NMR spectral data above is consistent with that found in the literature[116].

Preparation of alcohols

General procedure

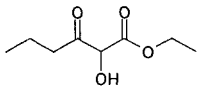
The appropriate α-acetoxy-β-dicarbonyl **144a-c** (4 mmol) was stirred in saturated ethanolic HCl (5 mL) at room temperature for 12 hours. The solution was poured onto water (10 mL) and extracted with ether, washed with a saturated solution of sodium bicarbonate, dried over Mg_2SO_4 and evaporated under reduced pressure to give the corresponding alcohol **140a-c**. These compounds were all used in the subsequent reactions without need for purification.



Ethyl 2-Hydroxy-3-oxo-3-phenylpropanoate 140a

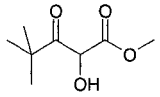
Compound **140a** was prepared from ethyl 2-acetoxy-3-oxo-3-phenylpropanoate **144a** (1.0 g, 4 mmol) using the general procedure. Yield (0.58 g, 70%) as a yellow oil. ^{1}H-NMR data suggested a keto:enol mixture. ^{1}H-NMR: ($CDCl_3$) δ 8.09 (d, 2H, Ph-*H*), δ 8.07 (d, 2H, Ph-*H*), δ 7.65 (m, 1H, Ph-*H*), δ 7.52 (m, 2H, Ph-*H*), δ 5.59 (s, 1H, *H*-2), δ 4.38 (q, 2H, J= 7Hz, ester-CH_2-keto form), δ 4.18 (q, 2H, J= 7Hz, ester-CH_2-enol form), δ 1.40 (t, 3H, J= 7Hz,

ester-CH_3 keto form) and δ 1.16 (t, 3H, J= 7Hz, ester-CH_3 enol form) ppm. The ^{1}H-NMR spectral data above is consistent with that found in the literature.[83]



Ethyl 2-Hydroxy-3-oxo-3-hexanoate 140b

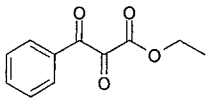
Compound **140b** was prepared from ethyl 2-acetoxy-3-oxo-3-hexanoate **144b** (1.0 g, 4.6 mmol) using the general procedure. Yield (0.55 g, 80%) as a yellow oil. ^{1}H-NMR: ($CDCl_3$) δ 4.77 (s, 1H, *H*-2), δ 4.29 (q, 2H, J= 7 Hz, ester-CH_2-), δ 2.68 (m, 2H, -CH_2-), δ 1.67 (sextet, 2H, J=7 Hz, -CH_2-), δ 1.32 (t, 3H, J=7 Hz, ester-CH_3) and δ 0.93 (t, 3H, J= 7Hz, -CH_3) ppm.



Methyl-4,4-dimethyl-2-hydroxy-3-oxo-3-pentanoate 140c

Compound **140c** was prepared from methyl-2-acetoxy-4,4-dimethyl-3-oxo-3-pentanoate **144c** (1.0 g, 4.6 mmol) and saturated methanolic HCl following the general procedure. Yield (0.44 g, 63%) as a yellow oil. ^{1}H-NMR: ($CDCl_3$) δ 4.40 (s, 1H, *H*-2), δ 3.79 (s, 3H, -CH_3) and δ 1.23 (s, 9H, -C(CH_3)$_3$) ppm.

3.3.2. Preparation of tricarbonyls and tricarbonyl equivalents



Ethyl 2,3-Dioxo-3-phenylpropanoate 118a

A) Oxidation of alcohol with copper (II) acetate

A solution of copper(II) acetate (1.9 g, 9.6 mmol) in water (5 mL) was added dropwise to a suspension of ethyl 2-hydroxy-3-oxo-3-phenylpropanoate **140a** (0.5 g, 2.4 mmol) in water (3 mL) and the mixture was stirred at RT for 0.5 hour. The solution changed colour from blue to green showing that oxidation had occurred. The crude reaction mixture was decanted and extracted with DCM (2 x 10 mL), washed well with H_2O containing a few drops of pyridine until all the copper was removed. The mixture was dried over $MgSO_4$ and solvent evaporated under reduced pressure to leave a yellow oil (0.34 g, 70 %). ^{1}H-NMR: ($CDCl_3$) δ 7.61 (d, 2H, J=8 Hz, Ph-*H*), δ 7.55-7.39 (m, 3H, Ph-*H*), δ 4.23 (q, 2H, J=7 Hz, ester-C*H*$_2$-) and δ 1.25 (t, 3H, J=7 Hz ester-C*H*$_3$) ppm. The ^{1}H-NMR spectral data is consistent with that found in the literature [83].

B) Oxidation of alcohol with NaOCl/TEMPO[84]

A solution of ethyl 2-hydroxy-3-oxo-3-phenylpropanoate **140a** (1.2 g, 5.7 mmol) in DCM (15 mL), TEMPO (a few mg), a saturated aqueous solution of $NaHCO_3$ (10 mL), KBr (60 mg) and ^{t}BuNH$_4$Cl (80 mg) was stirred at 0 °C. A solution of 1.6 M NaOCl (5 mL), saturated aqueous solution of $NaHCO_3$ (6 mL) and brine (12 mL) was added dropwise over 0.5 hour and solution stirred at 0 °C for 1 hour and then at RT for 0.5 hour. The mixture was extracted with DCM, washed with a saturated solution of sodium bicarbonate and brine, dried over Mg SO_4 and solvent evaporated under reduced pressure to give a yellow oil. Yield (1.06 g, 86%). The ^{1}H-NMR spectral data is consistent with that of compound **118a** obtained by oxidation of the alcohol **140a** with copper(II) acetate.

C) From decomposition of α-acetoxy-α-chloro-β-dicarbonyls

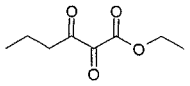
A solution of ethyl 2-acetoxy-2-chloro-3-oxo-3-phenylpropanoate **147a** (0.5g, 1.7 mmol) was stirred in saturated ethanolic HCl (5 mL) at RT for 16 hours. The solvent was evaporated under reduced pressure to give as a yellow oil (0.41 g, 84%) a mixture of tricarbonyl **118a** with small traces of ketal of the tricarbonyl (see Discussion Section 2.3.2.2.). The ^{1}H-NMR spectral data is consistent with that of compound **118a** obtained by oxidation of the alcohol **140a** with copper(II) acetate.

D) From diazo-compounds

To a stirred ice cold solution of ethyl 2-diazo-3-oxo-3-phenylpropanoate **135a** (1.0 g, 4.6 mmol) in acetonitrile (11mL) and water (1.0 mL) was added slowly *t*-butylhypochlorite (1.2 mole equivalents). After 0.5 hour the solution was poured onto water (50 mL), extracted with DCM (2 x 10 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude tricarbonyl compound **118a** as a yellow oil (0.76 g, 81%). The ^{1} H-NMR spectral data is consistent with that found in the literature[66].

E) From oximes

To a stirred ice cold solution of ethyl 2-hydroxyimino-3-oxo-3-phenylpropanoate **146** (0.9 mmol) in acetonitrile (5 mL) and water (1 mL) was added slowly *t*-butylhypochlorite (2.5 mol equivalent). After stirring 0.5 hour at RT the solution was poured onto water, extracted with DCM, washed, dried over $MgSO_4$ and the solvent evaporated under reduced pressure to give a yellow oil (0.18 g). The ^{1}H-NMR spectral data showed evidence of a mixture of product and starting material [1:4].



Ethyl 2,3-Dioxo-3-hexanoate 118b

A) Oxidation of alcohol with copper(II) acetate

Compound **118b** was prepared from ethyl 2-hydroxy-3-oxo-3-hexanoate **140b** (0.5 g, 2.9 mmol) following the procedure described above for the preparation of compound **118a** by oxidation with copper (II) acetate. Yield (0.29 g, 60%) as a yellow oil. ^{1}H-NMR: ($CDCl_3$) δ 4.31 (q, 2H, J=7 Hz, ester-C*H*$_2$), δ 2.57 (t, 2H, J=7 Hz, propyl-C*H*$_2$-), δ 1.67 (sextet, 2H, J=7 Hz, propyl-C*H*$_2$-) and δ 1.30 (t, 3H, J=7 Hz, ester-C*H*$_3$) and δ 0.93 (t, 3H, J=7 Hz, propyl-C*H*$_3$)ppm.

B) Oxidation of alcohol with NaOCl/TEMPO

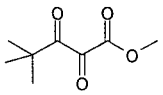
Compound **118b** was prepared from ethyl 2-hydroxy-3-oxo-3-hexanoate **140b** (1.0 g, 5.7 mmol) following the procedure described above for the preparation of compound **118a** by oxidation with NaOCl/TEMPO. Yield (0.79 g, 77%) as a yellow oil. The ^{1}H-NMR spectral data is consistent with that of compound **118b** obtained by oxidation of the alcohol **140b** with copper (II) acetate.

C) From decomposition of α-acetoxy-α-chloro-β-dicarbonyls

Compound **118b** was prepared from ethyl 2-acetoxy-2-chloro-3-oxo-3-hexanoate **147b** (0.5 g, 2 mmol) and saturated ethanolic HCl (5 mL) following the procedure described above for the preparation of compound **118a** from **147a**. Yield (0.40 g, 82%) as a yellow oil. The ^{1}H-NMR spectral data is consistent with that of compound **118b** obtained by oxidation of the alcohol **140b** with copper(II) acetate and shows evidence of the ketal of the tricarbonyl.

D) From diazo-compound

Compound **118b** was prepared from ethyl 2-diazo-3-oxo-3-hexanoate **135b** (1.0 g, 5.7 mmol) following the procedure described above for the preparation of compound **118a** from **135a**. Yield (0.91 g, 97%) as a yellow oil. The ^{1}H-NMR spectral data is consistent with that of compound **118b** obtained by oxidation of the alcohol **140b** with copper(II) acetate.



Methyl 4,4-Dimethyl-2,3-dioxo-pentanoate 118c

A) Oxidation of alcohol with copper(II) acetate

Compound **118c** was prepared from methyl 4,4-dimethyl-2-hydroxy-3-oxo-3-pentanoate **140c** (0.5 g, 2.88 mmol) following the procedure described above for the preparation of compound **118a** by oxidation with copper (II) acetate. Yield (0.29 g, 59%) as a yellow oil. ^{1}H-NMR: ($CDCl_3$) δ 3.48 (s, 3H, -CH_3) and δ 1.23 (s, 9H, -C(CH_3)$_3$) ppm.

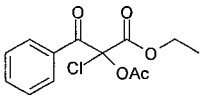
B) Oxidation of alcohol with NaOCl/TEMPO

Compound **118c** was prepared from methyl-4,4-dimethyl-2-hydroxy-3-oxo-3-pentanoate **140c** (0.5 g, 2.8 mmol) following the procedure described above for the preparation of compound **118a** by oxidation with NaOCl/TEMPO. Yield (0.37 g, 75%) as a yellow oil. The ^{1}H-NMR spectral data is consistent with that of compound **118c** obtained by oxidation of the alcohol **140c** with copper (II) acetate.

Preparation of α-acetoxy-α–chloro dicarbonyl compounds

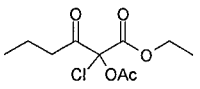
General procedure

To a stirred ice cold solution of the appropriate α-acetoxy-β-dicarbonyl compound **144a-e** (2 mmol) in DCM (5 mL) was added slowly sulfuryl chloride (1.1 molar equivalents). After stirring 1 hour at RT the solution was washed with a saturated solution of sodium carbonate, dried over $MgSO_4$ and evaporated under reduced pressure to give the crude α-acetoxy-α-chloro-β-dicarbonyl compound **147a-e**. These compounds were all used in the subsequent reactions without need for purification.



Ethyl 2-Acetoxy-2-chloro-3-oxo-3-phenylpropanoate 147a

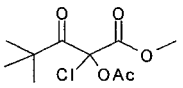
Compound **147a** was prepared from ethyl 2-acetoxy-3-oxo-3-phenylpropanoate **144a** (0.5 g, 2 mmol) using the general procedure. Yield (0.44 g, 77%) as a yellow oil. ^{1}H-NMR: ($CDCl_3$) δ 8.13 (d, 2H, J=7 Hz, Ph-*H*), δ 7.64 (t, 1H, J=7 Hz, Ph-*H*), δ 7.50 (t, 2H, J=8 Hz, Ph-*H*), δ 4.31 (q, 2H, J=7 Hz, ester-CH_2-), δ 2.23 (s, 3H, acetate-CH_3) and δ 1.29 (t, 3H, J=7 Hz, ester-CH_3) ppm. ^{13}C-NMR: ($CDCl_3$) δ 185.6 (*C*O), δ 167.4 (*C*O), δ 163.6 (*C*O), δ 134.2 (*C*H), δ 131.8 (*C*), δ 130.2 (*C*H), δ 128.7 (*C*H), δ 91.5 (*C*), δ 64.1 (*C*H_2), δ 21.1 (*C*H_3), δ 13.8 (*C*H_3) ppm. High-resolution M.S.E.I. for $C_{13}H_{13}ClO_5$. Calculated mass of molecular ion: 285.0524 $(M+H)^+$; Measured mass: 285.0526 $(M+H)^+$. ν_{max}/ cm^{-1} 1767 (C=O), 1750 (C=O), 1691 (C=O), 1246 (C-O), 1196 (C-O), 1079 (C-O), 900 (C-O) and 690 (CH).



Ethyl 2-Acetoxy-2-chloro-3-oxo-3-hexanoate 147b

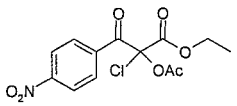
Compound **147b** was prepared from ethyl 2-acetoxy-3-oxo-3-hexanoate **144b** (4.0 g, 18 mmol) using the general procedure. Yield (4.62 g, 98%) as a yellow oil.^{1}H-NMR: ($CDCl_3$) δ 4.32 (q, 2H, J=7 Hz, ester-CH_2-), δ 2.85 (q, 2H, J=7Hz, -CH_2-), δ 2.24 (s, 3H, acetate-

C*H*$_3$), δ 1.69 (sextet, 2H, J=7 Hz, -C*H*$_2$-), δ 1.32 (t, 3H, J=7 Hz, ester-C*H*$_3$) and δ 0.96 (t, 3H, J=7 Hz, -C*H*$_3$) ppm. ^{13}C-NMR: ($CDCl_3$) δ 196.9 (*C*O), δ 167.7 (*C*O), δ 163.4 (*C*O), δ 90.0 (*C*), δ 63.8 (*C*H$_2$), δ 38.7 (*C*H$_2$), δ 20.7 (*C*H$_3$), δ 16.9 (*C*H$_2$), δ 13.8 (*C*H$_3$) and δ 13.4 (*C*H$_3$) ppm. High-resolution M.S.E.I. for $C_{10}H_{15}ClO_5$. Calculated mass of molecular ion: 268.0946 $(M+H)^+$; Measured mass: 268.0948 $(M+H)^+$. ν_{max} / cm^{-1} 1749 (C=O), 1733 (C=O), 1248 (CO), 1199 (CO), 1082 (CO), 1018 (CO).



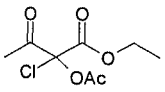
Methyl 2-Acetoxy-2-chloro-4,4-dimethyl-3-oxo-3-pentanoate 147c

Compound **147c** was prepared from methyl 2-acetoxy-4,4-dimethyl-3-oxo-3-pentanoate **144c** (0.81 g, 3.7 mmol) using the general procedure. Yield (0.82 g, 87%) as a yellow oil.^{1}H-NMR: ($CDCl_3$) δ 3.79 (s, 3H, ester-C*H*$_3$) δ 2.19 (s, 3H, acetate-C*H*$_3$) and δ 1.24 (s, 9H, -C(C*H*$_3$)$_3$) ppm.



Ethyl 2-Acetoxy-2-chloro-3-oxo-3-(4-nitrophenyl)propanoate 147d

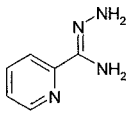
Compound **147d** was prepared from ethyl 2-acetoxy-3-oxo-3-(4-nitrophenyl)propanoate **144d** (4.21 g, 14 mmol) using the general procedure. Yield (2.42 g, 52%) as a yellow oil.^{1}H-NMR: ($CDCl_3$) δ 8.33 (d, 2H, J=9 Hz, Ph-*H*), δ 8.26 (d, 2H, J=9 Hz, Ph-*H*), δ 4.36 (q, 2H, J=7 Hz, ester-C*H*$_2$-), δ 2.23 (s, 3H, acetate-C*H*$_3$) and δ 1.33 (t, 3H, J=7 Hz, ester-C*H*$_3$) ppm. ^{13}C-NMR: ($CDCl_3$) δ 184.9 (*C*O), δ 167.3 (*C*O), δ 163.0 (*C*O), δ 150.6 (*C*), δ 136.9 (*C*), δ 131.2 (*C*H), δ 123.9 (*C*), δ 123.7 (*C*H), δ 64.5 (*C*H$_2$), δ 20.9 (*C*H$_3$) and δ 13.9 (*C*H$_3$) ppm. ν_{max} / cm^{-1} 1754 (C=O), 1705 (C=O), 1520 (NO_2), 1347 (NO_2), 1228 (C-O), 1100 (C-O) and 1009 (C-O).



Ethyl 2-Acetoxy-2-chloro-3-oxo-3-butanoate 147e

Compound **147e** was prepared from ethyl 2-acetoxy-3-oxo-3-butanoate **144e** (2.74 g, 15 mmol) using the general procedure. Yield (3.25 g, 97%) as a yellow oil.^{1}H-NMR: ($CDCl_3$) δ 4.32 (q, 2H, J=7 Hz, ester-C*H*$_2$-), δ 2.50 (s, 3H, -C*H*$_3$), δ 2.24 (s, 3H, acetate-C*H*$_3$) and δ 1.32 (t, 3H, J=7 Hz, ester-C*H*$_3$) ppm. High-resolution M.S.E.I. for $C_8H_{11}ClO_5$. Calculated mass of molecular ion: 240.0633 $(M+H)^+$; Measured mass: 240.0632 $(M+H)^+$.

3.2.3. Other reactants



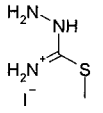
Pyridine-2-carboximidohydrazide 107

To a stirred solution of pyridine-2-carbonitrile (5.2 g, 0.05 mol) in ethanol (9 mL) was added hydrazine monohydrate (15 mL). After 2 hours at room temperature the resulting precipitate was filtered at the pump and washed with cold ethanol to give compound **107** (3.5 g, 58 %) as a white crystalline solid, wich turned yellow over time, m.p. 96-98 °C (lit. 95- 96 °C)[49]. ^{1}H-NMR: ($CDCl_3$) δ 8.51 (dd, 1H, J=5 and 1 Hz, Py-*H*), δ 8.03 (d, 1H, J=8 Hz, Py-*H*), δ 7.67 (dt, 1H, J=8 and 2 Hz, Py-*H*), δ 7.27 (m, 1H, Py-*H*), δ 5.2 (broad singlet, - N*H*$_2$) and δ 4.57 (broad singlet, - N*H*$_2$) ppm.

***t*-Butylhypochlorite[82]**

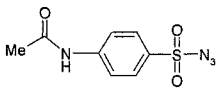
To a stirred ice cold solution of sodium hypochlorite (250 mL, 12% available chlorine) was slowly added a solution of *t*-butyl alcohol (19.5 mL, 0.195 mol) and glacial acetic acid (12.3 mL, 0.21 mol). (Hazard: lights were turned off and RB flask covered with foil). The solution was rapidly stirred for 5 min., the lower aqueous layer discarded and the yellow

liquid washed with 2M Na_2CO_3 (3 x 10 mL) and dried over $MgSO_4$ to leave the desired product as a yellow liquid (9.79 g, 46%). The product was employed as an oxidising reagent without need for purification.



_S_-Methylthiosemicarbazide hydrogen iodide 160

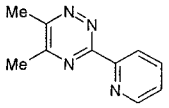
To a solution of thiosemicarbazide (1.0 g, 0.01 moles) in absolute ethanol (10 mL) was added MeI (1 equivalent, 0.7 mL) and the solution stirred under reflux and a nitrogen atmosphere for 1 hour. The solvent was evaporated to half volume and the precipitate filtered giving a white solid, m.p. 138-139 °C (lit. m.p. 140 °C)[117]. Yield (1.35g, 53%). There is no ^{1}H-NMR spectral data reported for compound **160** in the literature.



4-Acetamidobenzenesulphonyl azide

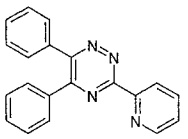
A solution of sodium azide (6.75 g, 0.1 mol) in water (20 mL) was prepared and diluted with ethanol (50 mL). To this solution was then added with stirring, a warm solution of 4-acetamidobenzene sulphonyl chloride (25.7 g, 0.11 mol) in ethanol (100 mL). Stirring was continued for 2.5 hours and most of the solvent was removed under reduced pressure (Hazard: the water temperature was kept below 40 °C). Water was added and the resulting precipitate filtered. Yield (20.67 g, 83%) as a white creamy solid. The product was employed as a diazo-transfer reagent without need for purification.

3.2.4. Formation of 1,2,4-triazines



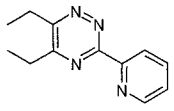
5,6-Dimethyl-3-pyridin-2-yl-1,2,4-triazine 153

To a stirred solution of pyridine-2-carboximidohydrazide **107** (1.0 g, 7.35 mmol) in ethanol (20 mL) was added butane-2,3-dione (0.63 g, 7.35 mmol) in one portion. The mixture was then stirred under reflux for 24 hours, allowed to cool to room temperature and the resulting precipitate was filtered at the pump to give compound **153** (1.25 g, 91%) as a yellow solid, m.p. 91-93 °C (lit. m.p. 92-93 °C)[95].^{1}H-NMR: ($CDCl_3$) δ 8.99 (d, 1H, J=5 Hz, Py-*H*), δ 8.65 (d, 1H, J=8 Hz, Py-*H*), δ 7.90 (t, 1H, J=8 Hz, Py-*H*), δ 7.45 (m, 1H, Py-*H*), δ 2.80 (s, 3H, -CH_3) and δ 2.70 (s, 3H, -CH_3) ppm



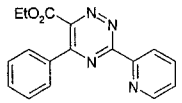
5,6-Diphenyl-3-pyridin-2-yl-1,2,4-triazine 152

Compound **152** was synthesised using 1,2-diphenylpropenone (250 g, 1.19 mol) and pyridine-2-carboximidohydrazide **107** (0.16 g, 1.19 mmol) following the procedure described above for the preparation of compound **153**. Yield (272.4 g, 74 %) as a yellow solid, m.p. 190-192 °C (lit. m.p. 189-190 °C)[95]. ^{1}H-NMR: ($CDCl_3$) δ 8.93 (d, 1H, J=5 Hz, Py-*H*), δ 8.71 (d, 1H, J=8 Hz, Py-*H*), δ 7.95 (t, 1H, J=8 Hz, Py-*H*), δ 7.70-7.62 (m, 5H, Ph-*H*) and δ 7.49-7.33 (overlapping multiplets, 6H, Ph-*H*, Py-*H*) ppm.



5,6-Diethyl-3-pyridin-2-yl-1,2,4-triazine 154

Compound **154** was synthesised using 3,4-hexanedione (1.39 g, 0.01 mol) and pyridine-2-carboximidohydrazide **107** (1.36 g, 0.01 mol) following the procedure described above for the preparation of compound **153**. Yield (2.5 g, 96 %) as a bright yellow solid, m.p. 62-64 °C. ^{1}H-NMR: ($CDCl_3$) δ 8.89 (d, 1H, J=5 Hz, Py-*H*), δ 8.63 (d, 1H, J=8 Hz, Py-*H*), δ 7.90 (t, 1H, J=8 Hz, Py-*H*), δ 7.45 (m, 1H, Py-*H*), δ 3.10 (q, 2H, J=8 Hz, -C*H*$_2$ -), δ 3.00 (q, 2H, J=8 Hz, -C*H*$_2$ -), δ 1.45 (t, 3H, J=7 Hz, -C*H*$_3$) and δ 1.40 (t, 3H, J=7 Hz, -C*H*$_3$) ppm.



Ethyl 6-Carboxylate-5-phenyl-3-pyridin-2-yl-1,2,4-triazine 111a

To a stirred solution of pyridine-2-carboximidohydrazide **107** (0.2g, 1.47 mmol) in ethanol (20 mL) was added in one portion ethyl 2,3-dioxo-3-phenylpropanoate **118a** (0.3 g, 1.47 mmol), prepared from ethyl 2-diazo-3-oxo-3-phenylpropanoate **135a**. The solution was stirred under reflux for 2 hours, allowed to cool to room temperature, filtered and the solvent evaporated under reduced pressure to leave an orange oil (0.42 g, 94%). This was shown to be ethyl 6-carboxylate-5-phenyl-3-pyridin-2-yl-1,2,4-triazine **111a** by ^{1}H-NMR spectroscopy. ^{1}H-NMR: ($CDCl_3$) δ 8.95 (d, 1H, J=5 Hz, Py-*H*), δ 8.72 (d, 1H, J=8 Hz, Py-*H*), δ 7.95 (dt, 1H, J=8 and 2 Hz, Py-*H*), δ 7.87 (dd, 2H, J= 8 and 2 Hz, Ph-*H*), 7.57-7.53 (m, 4H, Ph-*H* and Py-*H*), δ 4.42 (q, 2H, J=8 Hz, ester-C*H*$_2$-) and δ 1.30 (t, 3H, J=7 Hz, ester-C*H*$_3$) ppm. ^{13}C-NMR: ($CDCl_3$) δ 165.2 (*C*O), δ 162.5 (*C*), δ 156.8 (*C*), δ 152.2 (*C*), δ 150.7 (*C*H), δ 150.4 (*C*), δ 137.3 (*C*H), δ 134.3 (*C*), δ 131.8 (*C*H), δ 129.1 (2 x *C*H), δ 129.0 (2 x *C*H), δ 126.1 (*C*H), δ 124.9 (*C*H), δ 63.0 (*C*H$_2$) and δ 13.9 (*C*H$_3$) ppm. High-resolution M.S.E.I. For $C_{17}H_{14}N_4O_2$. Calculated mass of molecular ion 307.1190 $(M+H)^+$. Measured mass: 307.1188 $(M+H)^+$. ν_{max} / cm^{-1} 1735 (C=O), 1489 (C=N), 1281 (CO), 1173

(CO) and 697 (CH). Anal. for $C_{17}H_{14}N_4O_2$: calc, N 18.29, C 66.66, H 4.61; found N 18.35, C 65.84, H 4.73.

The ^{1}H-NMR spectral data above is consistent with that previously described in the literature[97]. When ethyl 2,3-dioxo-3-phenylpropanoate **118a** used in this reaction was prepared from oxidation of ethyl 2-hydroxy-3-oxo-3-phenylpropanoate **140a** with copper (II) acetate, compound **111a** was obtained in 52% yield.

Synthesis of compound 111a from chloroacetate 147a.

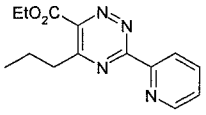
To a stirred solution of pyridine-2-carboximidohydrazide **107** (0.6 g. 4.25 mmol) in ethanol (20 mL) was added ethyl 2-acetoxy-2-chloro-3-oxo-3-phenylpropanoate **147a** (0.5 g, 1.7 mmol) in one portion. The solution was then stirred under reflux for 2 hours, allowed to cool to room temperature, poured onto water (20 mL), extracted with DCM, washed with water, dried over $MgSO_4$ and the solvent evaporated under reduced pressure to leave an orange oil (0.52 g, 97%). The ^{1}H-NMR spectral data of this compound was identical to that of compound **111a** synthesised from the tricarbonyl **118a**.

Synthesis of compound 111a from chloroacetate 147a and saturated ethanolic HCl

To a stirred solution of pyridine-2-carboximidohydrazide **107** (0.12 g, 0.9 mmol) in ethanol (15 mL) was added ethyl 2,3-dioxo-3-phenylpropanoate **118a** (0.25 g, 0.9 mmol), prepared from ethyl 2-acetoxy-2-chloro-3-oxo-3-phenylpropanoate **147a** and saturated ethanolic HCl, in one portion. The solution was the stirred under reflux for 2 hours, allowed to cool to room temperature, poured onto water (20 mL), extracted with DCM, washed with water, dried over $MgSO_4$ and the solvent evaporated under reduced pressure to leave an orange oil (0.26 g, 95 %). The ^{1}H-NMR spectral data of this compound was identical to that of compound **111a** synthesised from the tricarbonyl **118a**.

Synthesis of compound 111a from chloroacetate 147a and methylamine.

To a stirred solution of ethyl 2-acetoxy-2-chloro-3-oxo-3-phenylpropanoate **147a** (0.5 g, 1.7 mmol) in ethanol (3 mL) was added a solution of 33% wt methylamine in ethanol (0.43 mL, 3.5 mmol). After stirring for 1 hour at room temperature pyridine-2-carboximidohydrazide **107** (0.24 g, 1.7 mmol) was added in one portion. The solution was then stirred under reflux for 2 hours, allowed to cool to room temperature, poured onto water (20 mL), extracted with DCM, washed with water, dried over $MgSO_4$ and the solvent evaporated under reduced pressure. The crude mixture was purified by column chromatography [eluent: ethyl acetate/petroleum ether b.p. 60-80 °C (6:4)] giving an orange oil (0.35g, 65%). The ^{1}H-NMR spectral data of this compound was identical to that of compound **111a** synthesised from the tricarbonyl **118a**.



Ethyl 6-Carboxylate-5-propyl-3-pyridin-2-yl-1,2,4-triazine 111b

Compound **111b** was synthesised using ethyl 2,3-dioxo-hexanoate **118b** (0.25 g, 1.48 mmol) following the procedure described above for the preparation of compound **111a** from **118a**. Yield (0.39 g, 97%) as an orange solid, m.p. 68-70 °C (lit. 67-70 °C)[97].^{1}H-NMR: ($CDCl_3$) δ 8.93 (d, 1H, J=5 Hz, Py-*H*), δ 8.72 (d, 1H, J=8 Hz, Py-*H*), δ 7.94 (dt, 1H, J=8 and 2 Hz, Py-*H*), δ 7.50 (m, 1H, Py-*H*), δ 4.55 (q, 2H, J=8 Hz, ester-C*H*$_2$-), δ 3.19 (m, 2H, propyl- C*H*$_2$-), δ 1.85 (m, 2H, propyl-C*H*$_2$-), δ 1.49 (t, 3H, J=7Hz, propyl-C*H*$_3$) and δ 1.04 (t, 3H, J=7 Hz, ester-C*H*$_3$) ppm. ^{13}C-NMR: ($CDCl_3$) δ 164.2 (*C*O), δ 163.8 (*C*), δ 162.7 (*C*), δ 152.2 (*C*), δ 150.8 (*C*H), δ 149.9 (*C*), δ 137.3 (*C*H), δ 126.1 (*C*H), δ 125.0 (*C*H), δ 62.9 (*C*H$_2$), δ 37.2 (*C*H$_2$), δ 22.5 (*C*H$_2$), δ 14.2 (*C*H$_3$) and δ 14.1 (*C*H$_3$) ppm. High-resolution M.S.E.I. For $C_{14}H_{16}N_4O_2$. Calculated mass of molecular ion 273.1346 $(M+H)^+$. Measured mass: 273.1345 $(M+H)^+$. ν_{max} / cm^{-1} 1721 (C=O), 1506 (C=N), 1247 (CO) and 1138 (CO). Anal. for $C_{14}H_{16}N_4O_2$: calc, N 20.57, C 61.75, H 5.92; found N 20.38, C 61.39, N 6.05. The ^{1}H-NMR spectral data above is consistent with that reported in the literature[97].

Synthesis of compound 111b from chloroacetate 147b.

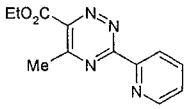
Compound **111b** was synthesised using ethyl 2-acetoxy-2-chloro-3-oxo-hexanoate **147b** (0.5 g, 2 mmol) following the procedure described above for the preparation of compound **111a** from **147a**. Yield (0.53 g, 98%) as an orange solid. The melting point and ^{1}H-NMR spectral data of this compound was identical to that of compound **111b** synthesised from the tricarbonyl **118b**.

Synthesis of compound 111b from chloroacetate 147b and saturated ethanolic HCl

Compound **111b** was synthesised using ethyl 2,3-dioxo-3-hexanoate **118b** (0.3 g, 1.2 mmol), prepared from ethyl 2-acetoxy-2-chloro-3-oxo-3-hexanoate **147b** and saturated ethanolic HCl, following the procedure described above for the preparation of compound **111a** from **118a**. Yield (0.26g, 79%) as an orange solid. The melting point and ^{1}H-NMR spectral data of this compound was identical to that of compound **111b** synthesised from the tricarbonyl **118b**.

Synthesis of compound 111b from chloroacetate 147b and methylamine.

Compound **111b** was synthesised using ethyl 2-acetoxy-2-chloro-3-oxo-3-hexanoate **147b** (0.5 g, 2 mmol) following the procedure described above for the preparation of compound **111a** from **147a** and methylamine. The crude mixture was purified by column chromatography [eluent: ethyl acetate/petroleum ether b.p. 60-80 °C (6:4)] giving an orange oil (0.33g, 61%). The melting point and ^{1}H-NMR spectral data of this compound was identical to that of compound **111b** synthesised from the tricarbonyl **118b**.

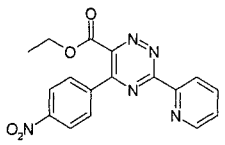


Ethyl 6-Carboxylate-5-methyl-3-pyridin-2-yl-1,2,4-triazine 111e

Compound **111e** was synthesised using ethyl 2-acetoxy-2-chloro-3-oxo-butanoate **147e** (0.3 g, 1.35 mmol) following the procedure described above for the preparation of compound **111a** from **147a**. The ^{1}H-NMR spectroscopic data showed this to be mainly ethyl 6-carboxylate-5-methyl-3-pyridin-2-yl-1,2,4-triazine **111e** with small traces of ethyl 5-carboxylate-6-methyl-3-pyridin-2-yl-1,2,4-triazine. This mixture was purified by column chromatography [eluent: ethyl acetate/petroleum ether b.p. 60-80 °C (8:2)] and the major isomer **111e** obtained. Yield (0.26g, 79%) as an orange wax.^{1}H-NMR: ($CDCl_3$) δ 8.94 (d, 1H, J=5 Hz, Py-*H*), δ 8.77 (d, 1H, J=5 Hz, Py-*H*), δ 7.96 (t,1H, Py-*H*), δ 7.52 (m, 1H, Py-*H*), δ 4.57 (q, 2H, J=7 Hz, ester-C*H*$_2$-), δ 2.97 (s, 3H, -C*H*$_3$) and δ 1.50 (t, 3H, J=7 Hz, ester-C*H*$_3$) ppm. ^{13}C-NMR: ($CDCl_3$) δ 164.0 (*C*O), δ 162.5 (*C*), δ 161.2 (*C*), δ 151.9 (*C*), δ 150.8 (*C*H), δ 136.8 (*C*H), δ 125.8 (*C*H), δ 125.0 (*C*H), δ 124.1 (*C*), δ 62.9 (*C*H$_2$), δ 23.3 (*C*H$_3$) and δ 14.2 (*C*H$_3$) ppm. High-resolution M.S.E.I. For $C_{12}H_{12}N_4O_2$. Calculated mass of molecular ion 245.1033 $(M+H)^+$. Measured mass: 245.1030 $(M+H)^+$. ν_{max} / cm^{-1} 1725 (C=O), 1517 (C=N), 1250 (CO) and 1141 (CO).

Attempted synthesis of 111e from chloroacetate 147e and methylamine.

The synthesis of compound **111e** was attempted using ethyl 2-acetoxy-2-chloro-3-oxo-butanoate **147e** (0.3 g, 1.35 mmol) following the procedure described above for the preparation of compound **111a** from **147a** and methylamine. The product suggested a mixture of compounds by ^{1}H-NMR spectroscopy.

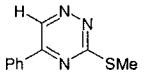


Ethyl 6-Carboxylate-5-(4-nitrophenyl)-3-pyridin-2-yl-1,2,4-triazine 111d

Compound **111d** was synthesised using ethyl 2-acetoxy-2-chloro-3-oxo-3-(4-nitrophenyl)propanoate **147d** (0.3 g, 0.9 mmol) following the procedure described above for the preparation of compound **111a** from **147a**. Recrystallisation from ethanol and water gave the desired product as a yellow solid (0.1 g, 32%), m.p. 206-208 °C. ^{1}H-NMR: ($CDCl_3$) δ 8.92 (d, 1H, J=5 Hz, Py-*H*), δ 8.77 (d, 1H, J=5 Hz, Py-*H*), δ 8.41 (d, 2H, J=9 Hz, Ph-*H*), δ 8.02 (d, 2H, J=9 Hz, Ph-*H*), δ 7.99 (m, 1H, Py-*H*), δ 7.52 (m, 1H, Py-*H*), δ 4.47 (q, 2H, J=7 Hz, ester-C*H*$_2$-), δ 1.35 (t, 3H, J= 7 Hz, ester-C*H*$_3$) ppm. ^{13}C-NMR: ($CDCl_3$) δ 164.2 (*C*O), δ 155.6 (*C*), δ 151.6 (*C*H), δ 150.9 (*C*H), δ 149.7 (*C*), δ 149.6 (*C*), δ 140.5 (*C*H), δ 137.5 (*C*H), δ 130.4 (*C*H), δ 126.5 (*C*), δ 125.2 (*C*), δ 124.0 (*C*H), δ 63.5 (*C*H$_2$) and δ 14.0 (*C*H$_3$) ppm. High-resolution M.S.E.I. For $C_{17}H_{13}N_5O_4$. Calculated mass of molecular ion 352.1040 $(M+H)^+$. Measured mass: 352.1043 $(M+H)^+$. ν_{max} / cm^{-1} 1719 (C=O), 1520 (NO_2), 1346 (NO_2), 1300 (CO) and 1175 (CO).

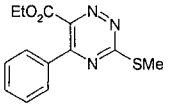
Attempted synthesis of 111d from chloroacetate 147d and methylamine.

The synthesis of compound **111d** was attempted using ethyl 2-acetoxy-2-chloro-3-oxo-3-(4-nitrophenyl)propanoate **147d** (0.3 g, 0.9 mmol) following the procedure described above for the preparation of compound **111a** from **147a** and methylamine. ^{1}H-NMR spectroscopy does not show evidence of the desired product.



3-Methylsulfanyl-5-phenyl-1,2,4-triazine 161

To a solution of phenylglyoxal hydrate (0.50 g, 3.33 mmol) in hot water (20 mL) was added a solution of *S*-methylthiosemicarbazide hydrogen iodide **160** (0.77 g, 1 equivalent) and sodium bicarbonate (0.36g, 1.3 equivalents) in hot water (30 mL). After cooling the mixture to room temperature the resulting precipitate was filtered at the pump and washed with water giving compound **161** (0.58g, 86%) as a yellow solid, m.p. 98-100°C (lit.99-100°C)[47]. ^{1}H-NMR: ($CDCl_3$) δ 9.38 (s, 1H, -C*H*), δ 8.16 (dd, 2H, J=7 Hz, Ph-*H*), δ 7.61-7.52 (m, 3H, Ph-*H*) and δ 2.73 (s, 3H, -CH_3) ppm.



Ethyl 6-Carboxylate-3-methylthio-5-phenyl-1,2,4-triazine 162a

General procedure

To a stirred solution of ethyl 2,3-dioxo-3-phenylpropanoate **118a** (0.13g, 0.63 mmol), obtained by oxidation of ethyl 2-hydroxy-3-oxo-3-phenylpropanoate **140a** with copper(II) acetate, and sodium bicarbonate (0.07 g, 0.82 mmol) in EtOH (5 mL) was added *S*-methylthiosemicarbazide hydrogen iodide **160** (0.15 g, 0.63 mmol). After stirring 1 hour under reflux, the mixture was allowed to cool to room temperature and the solvent evaporated under reduced pressure to give an orange oil. Chromatography over silica gel (eluent: DCM) gave the pure compound (0.1 g, 58%) as a red solid, m.p. 62-64 °C. ^{1}H-NMR: ($CDCl_3$) δ 7.74 (d, 2H, J=8 Hz, Ph-*H*), δ 7.50- 7.53 (m, 3H, Ph-*H*), δ 4.40 (q, 2H, J=7 Hz, ester-CH_2-), δ 2.75 (s, 3H, -SCH_3) and δ 1.27 (t, 3H, J=7 Hz, ester-CH_3) ppm. ^{13}C-NMR: ($CDCl_3$) δ 174.4 (*C*), δ 165.1 (*C*O), δ 155.8 (*C*), δ 146.9 (*C*), δ 134.2 (*C*), δ 131.8 (*C*H), δ 129.0 (*C*H), δ 128.9 (*C*H), δ 62.7 (*C*H_2), δ 14.0 (*C*H_3) and δ 13.9 (*C*H_3) ppm. High-resolution M.S.E.I. For $C_{13}H_{13}N_3O_2S$. Calculated mass of molecular ion 276.0801 $(M+H)^+$. Measured mass: 276.0800 $(M+H)^+$. ν_{max} / cm^{-1} 1727 (C=O), 1483 (C=N), 1224 (CO) and 1210 (CO).

Synthesis of compound 162a from chloroacetate 147a

To a stirred solution of ethyl 2-acetoxy-2-chloro-3-oxo-3-phenylpropanoate **147a** (0.5 g, 1.75 mmol) and sodium bicarbonate (0.41 g, 4.9 mmol) in EtOH (20 mL) was added *S*-methylthiosemicarbazide hydrogen iodide **160** (4.4 mmol, 1.02 g.). The solution was the stirred under reflux for 2 hours, allowed to cool to room temperature, poured onto water (20 mL), extracted with DCM, washed with water, dried over $MgSO_4$ and the solvent evaporated under reduced pressure to leave a red solid (0.37 g, 80%). The ^{1}H-NMR spectral data of this compound was identical to that of compound **162a** synthesised from the tricarbonyl **118a**.

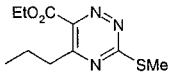
Synthesis of compound 162a from chloroacetate 147a and saturated ethanolic HCl

To a solution of *S*-methylthiosemicarbazide hydrogen iodide **160** (0.2 g, 0.9 mmol) and sodium bicarbonate (0.09 g, 1.17 mmol) in ethanol (15 mL) was added in one portion ethyl 2,3-dioxo-3-phenylpropanoate **118a** (0.25 g, 0.9 mmol), prepared from ethyl 2-acetoxy-2-chloro-3-oxo-3-phenylpropanoate **147a** and saturated ethanolic HCl. The solution was then stirred under reflux for 2 hours, allowed to cool to room temperature, poured onto water (20 mL), extracted with DCM, washed with water, dried over $MgSO_4$ and the solvent evaporated under reduced pressure to leave a red solid (0.22g, 90%). The ^{1}H-NMR spectral data of this compound was identical to that of compound **162a** synthesised from the tricarbonyl **118a**, prepared by oxidation of the alcohol **140a** with copper(II) acetate.

Synthesis of compound 162a from chloroacetate 147a and methylamine

To a stirred solution of ethyl 2-acetoxy-2-chloro-3-oxo-3-phenylpropanoate **147a** (0.5 g, 1.7 mmol) in ethanol (3 mL) was added a solution of 33% wt methylamine in ethanol (0.43 mL, 3.5 mmol). After stirring for 1 hour at room temperature, *S*-methylthiosemicarbazide hydrogen iodide **160** (0.41 g, 1.7 mmol) and sodium bicarbonate (0.18 g, 2 mmol) was added in one portion. The solution was then stirred under reflux for 2 hours, allowed to cool

to room temperature, poured onto water (20 mL), extracted with DCM, washed with water, dried over $MgSO_4$ and the solvent evaporated under reduced pressure to leave a red solid (0.28 g, 58 %). The ^{1}H-NMR spectral data of this compound was identical to that of compound **162a** synthesised from the tricarbonyl **118a**.



Ethyl 6-Carboxylate-3-methylthio-5-propyl-1,2,4-triazine 162b

Compound **162b** was synthesised using ethyl 2,3-dioxo-3-hexanoate **118b** (0.2 g, 1.16 mmol), obtained by oxidation of ethyl 2-hydroxy-3-oxo-3-hexanoate **140b** with copper(II) acetate, following the procedure described above for the preparation of compound **162a** from **118a.**Yield (0.17 g, 61%) as an orange oil. ^{1}H-NMR: ($CDCl_3$) δ 4.50 (q, 2H, J=7 Hz, ester-C*H*$_2$-), δ 3.02 (m, 2H, propyl- C*H*$_2$-), δ 2.70 (s, 3H, -SC*H*$_3$), δ 1.79 (sextet, 2H, propyl-C*H*$_2$-), δ 1.46 (t, 3H, J= 7Hz, propyl-C*H*$_3$) and δ 1.02 (t, 3H, J=7 Hz, ester-C*H*$_3$) ppm. ^{13}C-NMR: ($CDCl_3$) δ 174.8 (*C*), δ 164.1 (*C*O), δ 162.7 (*C*), δ 146.2 (*C*), δ 62.5 (*C*H$_2$), δ 36.8 (*C*H$_2$), δ 21.3 (*C*H$_2$), δ 14.2 (*C*H$_3$), δ 14.0 (*C*H$_3$) and δ 13.9 (*C*H$_3$) ppm. High-resolution M.S.E.I. For $C_{10}H_{15}N_3O_2S$. Calculated mass of molecular ion 242.0958 $(M+H)^+$. Measured mass: 242.0959 $(M+H)^+$. ν_{max} / cm^{-1} 1723 (C=O), 1496 (C=N), 1210 (CO) and 1182 (CO)

Synthesis of compound 162b from chloroacetate 147b.

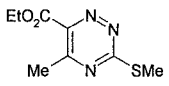
Compound **162b** was synthesised using ethyl 2-acetoxy-2-chloro-3-oxo-3-hexanoate **147b** (0.5 g, 20 mmol) following the procedure described above for the preparation of compound **162a** from **147a.** Yield (0.4g, 83%) as an orange oil. The ^{1}H-NMR spectral data of this compound was identical to that of compound **162b** synthesised from the tricarbonyl **118b**.

Synthesis of compound 162b from chloroacetate 147b and saturated ethanolic HCl

Compound **162b** was synthesised using ethyl 2,3-dioxo-3-hexanoate **118b** (0.3 g, 1.2 mmol), prepared from ethyl 2-acetoxy-2-chloro-3-oxo-3-hexanoate **147b** and saturated ethanolic HCl, following the procedure described above for the preparation of compound **162a** from **118a**. Yield (0.27g, 92%) as an orange oil. The ^{1}H-NMR spectral data of this compound was identical to that of compound **162b** synthesised from the tricarbonyl **118b**, prepared by oxidation of the alcohol **140b** with copper(II) acetate.

Synthesis of compound 162b from chloroacetate 147b and methylamine

Compound **162b** was synthesised using ethyl 2-acetoxy-2-chloro-3-oxo-3-hexanoate **147b** (0.5 g, 2 mmol) following the procedure described above for the preparation of compound **162a** from **147a** and methylamine. Yield (0.28 g, 58%) as an orange oil. The ^{1}H-NMR spectral data of this compound was identical to that of compound **162b** synthesised from the tricarbonyl **118b**.

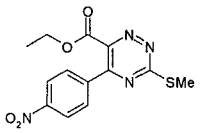


Ethyl 6-Carboxylate-3-methyl -5-methylthio-1,2,4-triazine 162e

Compound **162e** was synthesised using ethyl 2-acetoxy-2-chloro-3-oxo-butanoate **147e** (1.5 g, 6.7 mmol) following the procedure described above for the preparation of compound **162a** from **147a**. Yield (0.6 g, 42%) as an orange oil. ^{1}H-NMR: ($CDCl_3$) δ 4.48 (q, 2H, J=7 Hz, ester-C*H*$_2$-), δ 2.75 (s, 3H, -C*H*$_3$), δ 2.70 (s, 3H, -SC*H*$_3$) and δ 1.44 (t, 3H, J=7 Hz, ester-C*H*$_3$) ppm. ^{13}C-NMR:($CDCl_3$) δ 174.9 (*C*), δ 164.1 (*C*O), δ 159.9 (*C*), δ 146.1 (*C*), δ 62.6 (*C*H$_2$), δ 23.1 (*C*H$_3$), δ 14.2 (*C*H$_3$) and δ 14.0 (*C*H$_3$) ppm. ν_{max} / cm^{-1} 1722 (C=O), 1219 (CO) and 1186 (CO).

Attempted synthesis of 162e from chloroacetate 147e and methylamine.

The synthesis of compound **162e** was attempted using ethyl 2-acetoxy-2-chloro-3-oxo-butanoate **147e** (0.3 g, 1.35 mmol) following the procedure described above for the preparation of compound **162a** from **147a** and methylamine. The product suggested a mixture of compounds by ^{1}H-NMR spectroscopy.

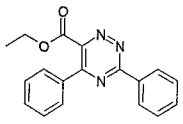


Ethyl 6-Carboxylate-3-methylthio-5-(4-nitrophenyl)-1,2,4-triazine 162d

Compound **162d** was synthesised using ethyl 2-acetoxy-2-chloro-3-oxo-3-(4-nitrophenyl)propanoate **147d** (0.3 g, 0.9 mmol) following the procedure described above for the preparation of compound **162a** from **147a**. Yield (0.21g, 69 %) as an orange solid, m.p. 88-90 °C. ^{1}H-NMR: ($CDCl_3$) δ 8.36 (d, 2H, J=9 Hz, Ph-*H*), δ 7.87 (d, 2H, J=9 Hz, Ph-*H*), δ 4.42 (q, 2H, J=7 Hz, ester-C*H*$_2$-), δ 2.77 (s, 3H, -SC*H*$_3$), δ 1.33 (t, 3H, J=7 Hz, ester-C*H*$_3$).

Attempted synthesis of 162d from chloroacetate 147d and methylamine.

Compound **162d** was attempted to be synthesised using ethyl 2-acetoxy-2-chloro-3-oxo-3-(4-nitrophenyl)propanoate **147d** (0.3 g, 0.9 mmol) following the procedure described above for the preparation of compound **162a** from **147a** and 33% wt methylamine in ethanol. The product obtained was not consistent with **162d** by ^{1}H-NMR spectroscopy.



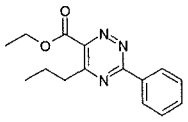
Ethyl 6-Carboxylate-3,5-diphenyl-1,2,4-triazine 166a

To a stirred ice cold solution of benzamidine hydrochloride hydrate (0.8 g, 5.1 mmol) in ethanol (10 mL) was added dropwise hydrazine hydrate (0.25 mL, 5.1 mmol). After stirring at 0 °C for 15 min., the mixture was warmed to room temperature and stirred for another 15

min. and ethyl 2-acetoxy-2-chloro-3-oxo-3-phenylpropanoate **147a** (0.57g, 2 mmol) and triethylamine (1 equivalent, 0.52mL) were slowly added. Solution was stirred under reflux for 20 hours, cooled to room temperature and poured onto water (10 mL). The organic compounds were extracted with DCM, washed with water, dried over $MgSO_4$ and solvent evaporated under reduced pressure to give a bright red oil (0.5 g, 82%). ^{1}H-NMR: ($CDCl_3$) δ 8.67 (dd, 2H, J=8 and 2 Hz, Ph-*H*), δ 8.08 (m, 3H, Ph-*H*), δ 7.87 (dd, 2H, J=8 Hz, Ph-*H*) ,δ 7.51-7.59 (m, 3H, Ph-*H*), δ 4.44 (q, 2H, J=7 Hz, ester-C*H*$_2$-) and δ 1.30 (t, 3H, J=7 Hz, ester-C*H*$_3$) ppm. ^{13}C-NMR: ($CDCl_3$) δ 165.4 (*C*), δ 163.2 (*C*O), δ 156.2 (*C*), δ 149.1 (*C*), δ 134.6 (*C*), δ 134.2 (*C*), δ 132.5 (*C*H), δ 131.8 (*C*H), δ 128.9 (3 x *C*H), δ 126.9 (*C*H), δ 62.9 (*C*H$_2$) and δ 14.0 (*C*H$_3$) ppm. High-resolution M.S.E.I. For $C_{18}H_{15}N_3O_2$. Calculated mass of molecular ion 306.1237 $(M+H)^+$. Measured mass: 306.1238 $(M+H)^+$. ν_{max} / cm^{-1} 1734 (C=O), 1275 (CO), 1151 (CO) and 688 (CH). The ^{1}H-NMR spectral data obtained is identical to that found in the literature[52].

Synthesis of compound 166a from chloroacetate 147a and saturated ethanolic HCl

To a stirred ice cold solution of benzamidine hydrochloride hydrate (0.2 g, 1.27 mmol) in ethanol (5 mL) was added dropwise hydrazine hydrate (0.06 mL, 1.27 mmol). After stirring at 0 °C for 15 min., the mixture was warmed to room temperature and stirred for another 15 min, and ethyl 2,3-dioxo-3-phenylpropanoate **118a** (0.2g, 1.3 mmol), prepared from ethyl 2-acetoxy-2-chloro-3-oxo-3-phenylpropanoate **147a** and saturated ethanolic HCl, and triethylamine (1 equivalent, 0.12mL) were slowly added. Solution was stirred under reflux for 20 hours, cooled to room temperature and poured onto water (10 mL). The organic compounds were extracted with DCM, washed with water, dried over $MgSO_4$ and solvent evaporated under reduced pressure to give a bright red oil (0.17 g, 80%). The ^{1}H-NMR spectral data of this compound was identical to that of compound **166a** synthesised from compound **147a**.



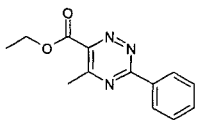
Ethyl 6-Carboxylate-3-phenyl-5-propyl-1,2,4-triazine 166b

Compound **166b** was synthesised using ethyl 2-acetoxy-2-chloro-3-oxo-3-hexanoate **147b** (0.5 g, 2 mmol) following the procedure described above for the preparation of compound **166a** from **147a.** Recrystallisation from ethanol gave the pure compound. Yield (0.50g, 93%) as a yellow solid, m.p. 58-60 °C. ^{1}H-NMR: ($CDCl_3$) δ 8.62 (dd, 2H, J=8 and 2 Hz, Ph-*H*),δ 7.51-7.59 (m, 3H, Ph-*H*), δ 4.55 (q, 2H, J=7 Hz, ester-CH_2-), δ 3.15 (m, 2H, propyl-CH_2-), δ 1.90 (sextet, 2H, J=8 Hz, propyl-CH_2-), δ 1.49 (t, 3H, J=7 Hz, ester-CH_3) and δ 1.07 (t, 3H, J=7 Hz, propyl-CH_3) ppm. ^{13}C-NMR: ($CDCl_3$) δ 164.3 (*C*O), δ 163.3 (*C*), δ 163.1 (*C*), δ 148.7 (*C*), δ 134.3 (*C*), δ 132.4 (*C*H), δ 129.0 (2 x *C*H), δ 62.7 (*C*H_2), δ 36.9 (*C*H_2), δ 21.3 (*C*H_2), δ 14.3 (*C*H_3) and δ 14.0 (*C*H_3) ppm. High-resolution M.S.E.I. For $C_{15}H_{17}N_3O_2$. Calculated mass of molecular ion 272.1394 $(M+H)^+$. Measured mass: 272.1397 $(M+H)^+$. ν_{max} / cm^{-1} 1718 (C=O), 1506 (C=N), 1259 (CO) and 1115 (CO). Anal. for $C_{15}H_{17}N_3O_2$: calc. N 15.49, C 66.40, H 6.32; found N 15.81, C 66.43, H 6.22.

There is no spectral data recorded for this compound in the literature.

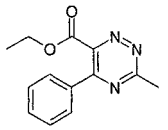
Synthesis of compound 166b from chloroacetate 147b and saturated ethanolic HCl

Compound **166b** was synthesised using ethyl 2,3-dioxo-3-hexanoate **118b** (0.3 g, 1.2 mmol), prepared from ethyl 2-acetoxy-2-chloro-3-oxo-3-hexanoate **147b** and saturated ethanolic HCl, following the procedure described above for the preparation of compound **166a** from **118a**. Yield (0.17g, 52%) as an orange oil. The ^{1}H-NMR spectral data of this compound was identical to that of compound **166b** synthesised from compound **147b**.



Ethyl 6-Carboxylate-5-methyl-3-phenyl-1,2,4-triazine 166e

Compound **166e** was synthesised using ethyl 2-acetoxy-2-chloro-3-oxo-3-butanoate **147e** (0.5 g, 2.25 mmol) following the procedure described above for the preparation of compound **166a** from **147a.** Yield (0.25 g, 46%). ^{1}H-NMR spectroscopy suggested this to be mainly ethyl 6-carboxylate-5-methyl-3-phenyl-1,2,4-triazine **166e** and small traces of the regioisomer. ^{1}H-NMR: ($CDCl_3$) δ 8.61 (dd, 2H, J=8 and 2 Hz, Ph-*H*), δ 7.54-7.58 (m, 3H, Ph-*H*), δ 4.54 (q, 2H, J=7 Hz, ester-C*H*$_2$-), δ 2.89 (s, 3H, -C*H*$_3$) and δ 1.49 (t, 3H, J=7 Hz, ester-C*H*$_3$) ppm. High-resolution M.S.E.I. For $C_{13}H_{13}N_3O_2$. Calculated mass of molecular ion 244.1081 $(M+H)^+$. Measured mass: 244.1083 $(M+H)^+$. ν_{max} / cm^{-1}1733 (C=O), 1518 (C=N), 1262 (CO) and 1121 (CO).



Ethyl 6-Carboxylate-3-methyl-5-phenyl-1,2,4-triazine 171a

To a stirred ice cold solution of acetamidine hydrochloride hydrate (0.5 g, 5.2 mmol) in ethanol (10 mL) was added dropwise hydrazine hydrate (0.26 mL, 5.2 mmol). After stirring at 0 °C for 15 min, the mixture was warmed to room temperature and stirred for another 15 min, and ethyl 2,3- dioxo-3-phenylpropanoate **118a** (0.9 g, 0.8 mmol), obtained by oxidation of the alcohol **140a** and copper(II) acetate, and triethylamine (1 equivalent, 0.7 mL) were slowly added. Solution was stirred under reflux for 20 hours, cooled to room temperature and poured onto water (10 mL). The organic compounds were extracted with DCM, washed with water, dried over $MgSO_4$ and solvent evaporated under reduced pressure to leave an orange oil. Yield (0.47g, 44%). ^{1}H-NMR: ($CDCl_3$) δ 7.76 (dd, 2H, J=8 Hz and 2 Hz, Ph-*H*), δ 7.58- 7.51 (m, 3H, Ph-*H*), δ 4.40 (q, 2H, J=7 Hz, ester-C*H*$_2$-), δ 2.99 (s, 3H, -C*H*$_3$) and δ 1.27 (t, 3H, J=7 Hz, ester-C*H*$_3$) ppm. ^{13}C-NMR: ($CDCl_3$) δ 167.4 (*C*), δ 165.3 (CO), δ 156.0 (*C*), δ 149.3 (*C*), δ 134.4 (*C*), δ 131.7 (CH), δ 129.0 (CH), δ 128.8

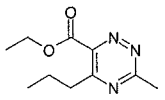
(CH), δ 62.8 (CH_2), δ 23.9 (CH_3) and δ 13.8 (CH_3) ppm. High-resolution M.S.E.I. For $C_{13}H_{13}N_3O_2$. Calculated mass of molecular ion 244.1081 $(M+H)^+$. Measured mass: 244.1082 $(M+H)^+$. ν_{max} / cm^{-1} 1736 (C=O), 1506 (C=N), 1259 (CO), 1137 (CO) and 693 (CH).

Synthesis of compound 171a from the chloroacetate 147a

To a stirred ice cold solution of acetamidine hydrochloride hydrate (0.48 g, 5 mmol) in ethanol (10 mL) was added dropwise hydrazine hydrate (0.25 mL, 5 mmol). After stirring at 0 °C for 15 min., the mixture was warmed to room temperature and stirred for another 15 min, and ethyl 2-acetoxy-2-chloro-3-oxo-3-phenylpropanoate **147a** (0.57 g, 2 mmol) and triethylamine (1 equivalent, 0.52mL) were slowly added. Solution was stirred under reflux for 20 hours, cooled to room temperature and poured onto water (10 mL). The organic compounds were extracted with DCM, washed with water, dried over $MgSO_4$ and solvent evaporated under reduced pressure to leave an orange oil. Yield (0.26 g, 54%). The ^{1}H-NMR spectral data of this compound was identical to that of compound **171a** synthesised from the tricarbonyl **118a**.

Synthesis of compound 171a from chloroacetate 147a and saturated ethanolic HCl

To a stirred solution of acetic hydrazide (0.13 g, 1.8 mmol) in EtOH (5 mL) was added ethyl 2,3-dioxo-3-phenylpropanoate **118a** (0.5 g, 1.8 mmol), prepared from ethyl 2-acetoxy-2-chloro-3-oxo-3-phenylpropanoate **147a** and saturated ethanolic HCl, and the mixture stirred at room temperature for 5 h. The solvent was evaporated under reduced pressure and NH_4OAc (0.28 g, 3.6 mmol) and glacial acetic acid (10 mL) added to the crude mixture. The solution was stirred under reflux for 12 hours, cooled to room temperature, poured onto water (10 mL) and neutralized with K_2CO_3. The organic compounds were extracted with DCM, washed with a saturated solution of K_2CO_3, dried over $MgSO_4$ and solvent evaporated under reduced pressure to give a bright red oil (0.29 g, 78%). The ^{1}H-NMR spectral data of this compound was identical to that of compound **171a** synthesised from compound **118a**.



Ethyl 6-Carboxylate-3-methyl-5-propyl-1,2,4-triazine 171b

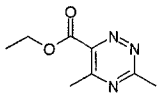
Compound **171b** was synthesised using ethyl 2,3-dioxo-hexanoate **118b** (0.73g, 4.2 mmol), obtained by oxidation of the alcohol **140b** and copper(II) acetate, following the procedure described above for the preparation of compound **171a** from **118a**.Yield (0.17g, 19 %) as a yellow oil. ^{1}H-NMR: ($CDCl_3$) δ 4.52 (q, 2H, J=7 Hz, ester-C*H*$_2$-), δ 3.01 (m, 2H, propyl-C*H*$_2$-), δ 2.90 (s, 3H, -C*H*$_3$), δ 1.78 (sextet, 2H, J=8 Hz, propyl-C*H*$_2$-), δ 1.46 (t, 3H, J=7 Hz, ester-C*H*$_3$) and δ 1.02 (t, 3H, J=7 Hz, propyl-C*H*$_3$) ppm. ^{13}C-NMR: ($CDCl_3$) δ 167.7 (*C*), δ 164.3 (*C*O), δ 162.7 (*C*), δ 148.8 (*C*), δ 62.7 (*C*H$_2$), δ 36.8 (*C*H$_2$), δ 23.9 (*C*H$_2$), δ 22.7 (*C*H$_3$), δ 14.2 (*C*H$_3$) and δ 14.0 (*C*H$_3$) ppm. High-resolution M.S.E.I. For $C_{10}H_{15}N_3O_2$. Calculated mass of molecular ion 210.1237 $(M+H)^+$. Measured mass: 210.1236 $(M+H)^+$. ν_{max} / cm^{-1} 1728 (C=O), 1515 (C=N), 1260 (CO) and 1094 (CO).

Synthesis of compound 171b from the chloroacetate 147b

Compound **171b** was synthesised using ethyl 2-acetoxy-2-chloro-3-oxo-3-hexanoate **147b** (0.5 g, 2 mmol) following the procedure described above for the preparation of compound **171a** from **147a**. Chromatography over silica gel [eluent: petroleum ether b.p. 60-80°C/ ethyl acetate (6:4)] gave the desired product **171b** as a yellow oil (0.18g, 43%). The ^{1}H-NMR spectral data of this compound was identical to that of compound **171b** synthesised from compound **118b**.

Synthesis of compound 171b from chloroacetate 147b and saturated ethanolic HCl

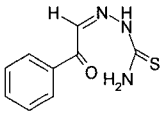
Compound **171b** was synthesised using ethyl 2,3-dioxo-3-hexanoate **118b** (0.3 g, 1.2 mmol), prepared from ethyl 2-acetoxy-2-chloro-3-oxo-3-hexanoate **147b** and saturated ethanolic HCl, following the procedure described above for the preparation of compound **171a** from **118a**. Yield (0.13g, 51%) as a yellow oil. The ^{1}H-NMR spectral data of this compound was identical to that of compound **171b** synthesised from compound **118b**.



Ethyl 6-Carboxylate-3,5-dimethyl-1,2,4-triazine 171e

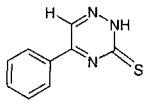
Compound **171e** was synthesised using ethyl 2-acetoxy-2-chloro-3-oxo-3-butanoate **147e** (0.5 g, 2.25 mmol) following the procedure described above for the preparation of compound **171a** from **147a**. Yield (0.06 g, 15 %) as an orange oil. ^{1}H-NMR: ($CDCl_3$) δ 4.53 (q, 2H, J=7 Hz, ester-C*H*$_2$-), δ 2.90 (s, 3H, -C*H*$_3$), δ 2.78 (s, 3H, -C*H*$_3$), δ 1.47 (t, 3H, J=7 Hz, ester-C*H*$_3$) ppm. ν_{max} / cm^{-1} 1727 (C=O), 1519 (C=N), 1260 (CO) and 1111 (CO).

Eschenmoser reaction



Phenylglyoxal-monothiosemicarbazone 181

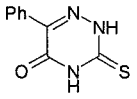
To a solution of phenylglyoxal hydrate (1.52 g, 10 mmol) in hot water (25 mL) was added a solution of thiosemicarbazide (0.91 g, 10 mmol) in hot water (50 mL) acidified with glacial acetic acid. After cooling the mixture to room temperature the resulting precipitate was filtered at the pump and washed with water to give compound **181** (0.86g, 42%) as a yellow solid, m.p. 158-160 °C (lit 170 °C)[110]. There is no ^{1}H-NMR spectral data reported for compound **112** in the literature.^{1}H-NMR: ($CDCl_3$) δ 8.52 (s, 1H, -C*H*), δ 8.18 (d, 2H, J=8 Hz, Ph-*H*), δ 7.71-7.54 (m, 3H, Ph-*H*) and δ 1.57 (broad singlet, -N*H*) ppm.



5-Phenyl-2,3-dihydro-1,2,4-triazine-3-thione 182

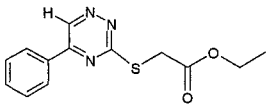
A solution of compound **181** (0.85 g, 4.1 mmol) in 10% aqueous solution of K_2CO_3 (15 mL) was stirred under reflux for 10 min. After cooling to room temperature the reaction

mixture was acidified with diluted HCl and the resulting precipitate filtered at the pump. Recrystallization from EtHO and H_20 (1:1) gave the desired product **182**. Yield (0.6 g, 76%) as red needles, m.p. 192-194 °C (lit. 197-198°C)[110]. There is no ^{1}H-NMR spectral data reported for compound **182** in the literature.^{1}H-NMR: ($CDCl_3$) δ 8.52 (s, 1H, -C*H*), δ 8.18 (d, 2H, J=8 Hz, Ph-*H*), δ 7.68 (t, 1H, Ph-*H*), δ 7.57 (t, 2H, Ph-*H*) and δ 1.57 (broad singlet, -NH) ppm.



6-Phenyl-3-thioxo-3,4-dihydro-*2H*-1,2,4-triazin-5-one 185

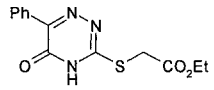
To a solution of benzoylformic acid (0.50 g, 3.33 mmol) in hot water (10 mL) was added a solution of thiosemicarbazide (0.30 g, 1 equivalent) in hot water (20 mL) acidified with glacial acetic acid. After cooling the mixture to room temperature the resulting precipitate was filtered at the pump and washed with water. NaOH 2M (15 mL) was added to the precipitate and the solution stirred under reflux for 1 hour. After cooling to room temperature the reaction mixture was acidified with diluted HCl and the resulting precipitate filtered at the pump giving compound **185** (0.15g, 22%) as a yellow solid, m.p. 274-276 °C (lit.278 °C)[118]. ^{1}H-NMR: ($CDCl_3$) δ 7.89 (d, 2H, J=8 Hz, Ph-*H*), δ 7.43-7.46 (m, 3H, Ph-*H*) ppm and the NH peaks were so broad they could not be detected.



Ethyl-3-methylthioacetate-5-phenyl-1,2,4-triazine 177

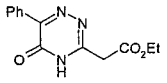
To a solution of 5-phenyl-2,3-dihydro-1,2,4-triazine-3-thione **182** (0.2 g, 1.06 mmol) in DMF (5 mL) was added K_2CO_3 (1.3 molar equivalents) and ethyl chloroacetate (1 equivalent, 0.09 mL). The solution was stirred at room temperature for 1.5 hour. The reaction mixture was poured into water and the resulting precipitate filtered at the pump giving compound **177** (0.18g, 62%) as a yellow solid, m.p. 104-106 °C. There is no spectroscopic data reported for this compound in the literature. ^{1}H-NMR: ($CDCl_3$) δ 9.41

(s, 1H, -C*H*), δ 8.16 (dd, 2H, J=7 Hz, Ph-*H*), δ 7.62-7.53 (m, 3H, Ph-*H*), δ 4.23 (q, 2H, J=7 Hz, ester-CH_2-), δ 4.08 (s, 2H, -CH_2-) and δ 1.28 (t, 3H, J=7 Hz, ester-CH_3) ppm.



Ethyl-4-hydro-3-methylthioacetate-6-phenyl-1,2,4-triazin-5-one 178

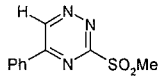
Compound **178** was prepared from 6-phenyl-3-thioxo-3,4-dihydro-*2H*-1,2,4-triazin-5-one **185** (0.1 g, 0.5 mmol) following the procedure described above for the preparation of compound **177**. Yield (0.04 g, 32%) as a white solid, m.p. 104-106 °C. ^{1}H-NMR: ($CDCl_3$) δ 8.12 (d, 2H, J=7 Hz, Ph-*H*), δ 7.42 (m, 3H, Ph-*H*), δ 4.28 (q, 2H, J=7 Hz, ester-CH_2-), δ 4.14 (s, 2H, -CH_2-) and δ 1.31 (t, 3H, J=7 Hz, ester-CH_3) ppm. In view of subsequent failure of the following reaction, full characterisation was not carried out.



Attempted Eschenmoser reaction to form 179

To a solution of **178** (0.5 g, 1.8 mmol) in dry xylene (10 mL) was added potassium tert-butoxide (0.04g, 0.36 mmol)) and triphenylphosphine (1.9g, 7.2 mmol). The solution was stirred under reflux and a nitrogen atmosphere for 28 hour. The reaction mixture was poured into water and the resulting precipitate filtered at the pump (0.4 g) as a yellow solid, m.p. 104-106 °C. The ^{1}H-NMR spectral data and melting point of the product showed this to be starting material **178**, suggesting that no reaction took place.

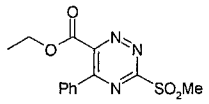
Oxidation of 1,2,4-triazines



6-Methanesulfonyl-5-phenyl-1,2,4-triazine 174

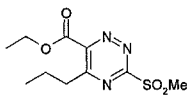
To a stirred ice cold solution of 3-methylsulfanyl-5-phenyl-1,2,4-triazine **161** (0.3 g, 1.5 mmol) in DCM (5 mL) was added a solution of MCPBA (2.2 equivalents, 1.12 g) in DCM (10 mL) and the mixture was stirred at RT for 4 hours. The resulting precipitate was filtered

at the pump giving compound **174** (0.23 g, 66%) as an orange solid, m.p. 147 °C (lit.146-148 °C)[105]. ^{1}H-NMR: ($CDCl_3$) δ 9.86 (s, 1H, -C*H*), δ 8.29 (dd, 2H, J=7 Hz, Ph-*H*), δ 7.65-7.62 (m, 3H, Ph-*H*) and δ 3.56 (s, 3H, -SO_2CH_3) ppm. The ^{1}H-NMR spectral data and melting point are consistant with that found in the literature[105].



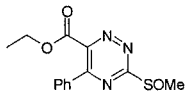
Ethyl 6-Carboxylate-3-methanesulfonyl-5-phenyl-1,2,4-triazine 175a

Compound **175a** was prepared from ethyl 6-carboxylate-3-methylthio-5-phenyl-1,2,4-triazine **162a** (0.3g, 1 mmol) following the procedure described above for the preparation of compound **174**. Yield (0.27g, 80%) as a yellow solid. ^{1}H-NMR: ($CDCl_3$) δ 7.74 (d, 2H, J=7 Hz, Ph-*H*), δ 7.50- 7.53 (m, 3H, Ph-*H*), δ 4.40 (q, 2H, J=7 Hz, ester-CH_2-), δ 3.35 (s, 3H, -SO_2CH_3) and δ 1.27 (t, 3H, J=7 Hz, ester-CH_3) ppm. In view of subsequent failure of the following reaction, full characterisation was not carried out.



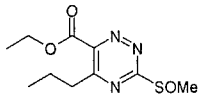
Ethyl 6-Carboxylate-3-methanesulfonyl-5-propyl-1,2,4-triazine 175b

Compound **175b** was prepared from ethyl 6-carboxylate-3-methylthio-5-propyl-1,2,4-triazine **162b** (0.2g, 0.83 mmol) following the procedure described for the preparation of compound **174**. Yield (0.13 g, 60%) as a yellow solid. ^{1}H-NMR: ($CDCl_3$) δ 4.45 (q, 2H, J=7 Hz, ester-CH_2-), δ 3.30 (s, 3H, -SO_2CH_3), δ 3.11 (m, 2H, propyl-CH_2-), δ 1.68 (sextet, 2H, propyl-CH_2-), δ 1.44 (t, 3H, J=7 Hz, ester-CH_3) and δ 0.96 (t, 3H, J=7 Hz, propyl-CH_3) ppm. In view of subsequent failure of the following reaction, full characterisation was not carried out.



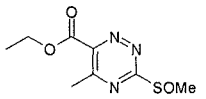
Ethyl 6-Carboxylate-3-methanesulfoxy-5-phenyl-1,2,4-triazine 176a

To a stirred ice cold solution of ethyl 6-carboxylate-3-methylthio-5-phenyl-1,2,4-triazine **162a** (0.26g, 0.9 mmol) in DCM (15 mL) was added a solution of MCPBA (1.1 molar equivalents, 1.12 g) and the mixture was stirred 1 hour at 0°C and 1 hour at RT. The reaction mixture was poured onto water (10 mL), washed with a saturated solution of $NaHCO_3$, (2 x 15 mL), dried over $MgSO_4$ and the solvent evaporated under reduced pressure to leave the desired product **176a** as a red oil. (0.25g, 91%). ^{1}H-NMR: ($CDCl_3$) δ 7.88 (d, 2H, J=7 Hz, Ph-*H*), δ 7.63-7.51 (m, 3H, Ph-*H*), δ 4.45 (q, 2H, J=7 Hz, ester-CH_2-), δ 3.15 (s, 3H, -SOCH_3) and δ 1.27 (t, 3H, J=7 Hz, ester-CH_3) ppm.



Ethyl 6-Carboxylate-3-methanesulfoxy-5-propyl-1,2,4-triazine 176b

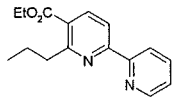
Compound **176b** was prepared from ethyl 6-carboxylate-3-methylthio-5-propyl-1,2,4-triazine **162b** (2.6 g, 0.01 mol) following the procedure described above for the preparation of compound **176a** from **162a**. Yield (1.75 g, 65%) as a red oil. ^{1}H-NMR: ($CDCl_3$) δ 4.54 (q, 2H, J=7 Hz, ester-CH_2-), δ 3.14 (m, 2H, -CH_2-), δ 3.08 (s, 3H, -SOCH_3), δ 1.83 (sextet, 2H, J=8 Hz, propyl-CH_2-), δ 1.46 (t, 3H, J=7 Hz, ester-CH_3) and δ 1.02 (t, 3H, J=7 Hz, propyl-CH_3) ppm.



Ethyl 6-Carboxylate-5-methyl-3-methanesulfoxy-1,2,4-triazine 176e

Compound **176e** was prepared from ethyl 6-carboxylate-5-methyl-3-methylthio-1,2,4-triazine **162e** (0.55g, 2.58 mmol) following the procedure described above for the preparation of compound **176a** from **162a**. Yield (0.17 g, 29%) as a red oil. ^{1}H-NMR: ($CDCl_3$) δ 4.57 (q, 2H, J=7 Hz, ester-CH_2-), δ 3.11 (s, 3H, -SOCH_3), δ 2.96 (s, 3H, -CH_3) and δ 1.49 (t, 3H, J=7 Hz, ester-CH_3) ppm.

3.3.5. Pyridines



Ethyl 5-Carboxylate-6-propyl-[2,2']bipyridyl 190b

To a solution of pyridine-2-carboximidohydrazide **107** (0.24 g, 1.8 mmol) in ethanol (15 mL) was added ethyl 2,3-dioxo-hexanoate **118b** (0.3 g, 1.8 mmol), prepared from the diazo-compound **135b**, and 2,5-norbornadiene **41** (1.94 mL, 18 mmol). This solution was heated under reflux and an atmosphere of nitrogen for 20 hours, allowed to cool to room temperature, and evaporated under reduced pressure to leave the crude product as an orange oil. Chromatography over silica gel [eluent: ethyl acetate/ petroleum ether b.p. 60-80 °C (6:4)] gave the desired product **190b** as an orange oil (0.4 g, 81%). ^{1}H-NMR: ($CDCl_3$) δ 8.70 (dd, 1H, J=5 and 2 Hz, Py-*H*), δ 8.52 (d, 1H, J=8 Hz, Py-*H*), δ 8.28 (s, 2H, Py-*H*), δ 7.84 (dt, 1H, J=8 and 2Hz, Py-*H*), δ 7.33 (m, 1H, Py-*H*), δ 4.40 (q, 2H, J=7 Hz, ester-CH_2-), δ 3.22 (m, 2H, -CH_2-), δ 1.83 (sextet, 2H, -CH_2-), δ 1.49 (t, 3H, J=7 Hz, ester-CH_3) and δ 1.04 (t, 3H, J=7 Hz, -CH_3) ppm. The ^{1}H-NMR spectral data above is consistent with that found in the literature[28].

Synthesis of 190b with chloroacetate 147b

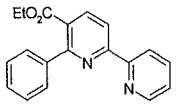
To a solution of pyridine-2-carboximidohydrazide **107** (0.68 g, 5 mmol) in ethanol (15 mL) was added ethyl 2-acetoxy-2-chloro-3-oxo-3-hexanoate **147b** (0.5 g, 2mmol) and 2,5-norbornadiene (2.2 mL, 20 mmol). This solution was heated at reflux under an atmosphere of nitrogen for 20 hours, allowed to cool to room temperature, and evaporated under reduced pressure to leave the crude product as an orange oil. Chromatography over silica gel [eluent: ethyl acetate/ petroleum ether b.p. 60-80 °C (6:4)] gave the desired product **190b** as an orange oil (0.34 g, 63%). The ^{1}H-NMR spectral data is consistant with that of compound **190b** synthesised from compound **118b**.

Synthesis of 190b from chloroacetate 147b and saturated ethanolic HCl

To a solution of pyridine-2-carboximidohydrazide **107** (0.28 g, 2 mmol) in ethanol (15 mL) was added ethyl 2,3-dioxo-3-hexanoate **118b** (0.5 g, 2mmol), prepared from ethyl 2-acetoxy-2-chloro-3-oxo-3-hexanoate **147b** and saturated ethanolic HCl, and 2,5-norbornadiene **41** (2.2 mL, 20 mmol). This solution was heated at reflux under an atmosphere of nitrogen for 20 hours, allowed to cool to room temperature, and the solvent evaporated. The crude product was poured onto water (10 mL), extracted with DCM (2 x 15 mL), dried over $MgSO_4$ and evaporated under reduced pressure to give compound **190b** as an orange oil (0.52g, 96%). The ^{1}H-NMR spectral data is consistant with that of compound **190b** synthesised from compound **118b**.

Synthesis of 190b from chloroacetate 147b and methylamine

To a stirred solution of ethyl 2-acetoxy-2-chloro-3-oxo-3-hexanoate **147b** (0.5 g, 2 mmol) in ethanol (3 mL) was added a solution of 33% wt methylamine in ethanol (0.49 mL, 4 mmol). After stirring 1 hour at room temperature pyridine-2-carboximidohydrazide **107** (0.27 g, 2 mmol) and 2,5-norbornadiene **41** (2.15 mL, 20 mmol) was added in one portion. The solution was then stirred under reflux for 2 hours, allowed to cool to room temperature, poured onto water (20 mL), extracted with DCM, washed with water, dried over $MgSO_4$ and the solvent evaporated under reduced pressure to leave a brown oil (0.43 g, 80 %). The ^{1}H-NMR spectral data of this compound was identical to that of compound **190b** synthesised from compound **118b**.



Ethyl 5-Carboxylate-6-phenyl-[2,2']bipyridyl 190a

Compound **190a** was synthesized from ethyl 2,3-dioxo-3-oxo-3-phenylpropanoate **118a** (0.5 g, 2.4 mmol), prepared from the diazo-compound **135a,** following the procedure described above for the preparation of compound **190b** from **118b.** Chromatography over silica gel [eluent: ethyl acetate/ petroleum ether b.p. 60-80 °C (6:4)] gave compound **190a** as an orange oil. Yield (0.64 g, 87%). ^{1}H-NMR: ($CDCl_3$) δ 8.70 (dd, 1H, J=5 and 2 Hz, Py-*H*), δ 8.57 (dd, 1H, J=7 and 2 Hz, Py-*H*), δ 8.45 (d, 1H, J=8 Hz, Py-*H*), δ 8.23 (d, 1H, J=8 Hz, Py-*H*), δ 7.80 (dt, 1H, J=8 Hz, Py-*H*), δ 7.67-7.63 (m, 1H, Ph-*H*), δ 7.49-7.43 (m, 4H, Ph-*H*), δ 7.33 (m, 1H, Py-*H*), δ 4.40 (q, 2H, J=7 Hz, ester-CH_2-) and δ 1.09 (t, 3H (s, 3H, J=7 Hz, ester-CH_3) ppm. The ^{1}H-NMR spectral data above is consistent with that found in the literature[28].

Synthesis of 190a from chloroacetate 147a

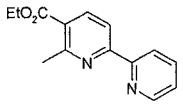
Compound **190a** was synthesised from ethyl 2-acetoxy-2-chloro-3-oxo-3-phenylpropanoate **147a** (0.5 g, 1.75 mmol) following the procedure described above for the preparation of compound **190b** from **147b**. Chromatography over silica gel [eluent: ethyl acetate/ petroleum ether b.p. 60-80 °C (6:4)] gave compound **190a** as an orange oil (0.27 g, 50%). The ^{1}H-NMR spectral data of this compound is consistant with that of compound **190a** synthesised from compound **118a**.

Synthesis of 190a from chloroacetate 147a and saturated ethanolic HCl

Compound **190a** was synthesised from ethyl 2,3-dioxo-3-phenylpropanoate **118a**, prepared from ethyl 2-acetoxy-2-chloro-3-oxo-phenylpropanoate **147a** and saturated ethanolic HCl, following the procedure described above for the preparation of compound **190b** from **148b**. Yield (0.48 g, 80%) as an orange oil. The ^{1}H-NMR spectral data of this compound is consistant with that of compound **190a** synthesised from compound **118a**.

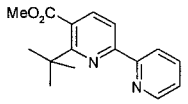
Synthesis of 190a from chloroacetate 147a and methylamine

Compound **190a** was synthesised from ethyl 2-acetoxy-2-chloro-3-oxo-3-phenylpropanoate **147a** (0.5 g, 1.75 mmol) following the procedure described above for the preparation of compound **190b** from **147b** and methylamine. Yield (0.36 g, 68 %) as an orange oil. The ^{1}H-NMR spectral data of this compound is consistant with that of compound **190a** synthesised from compound **118a**.



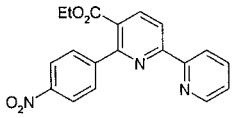
Ethyl 5-Carboxylate-6-methyl-[2,2']bipyridyl 190e

Compound **190e** was synthesised from ethyl 2-acetoxy-2-chloro-3-oxo-3-butanoate **147e** (0.5 g, 2.26 mmol) following the procedure described above for the preparation of **190a** from **147a.** The product suggests a complex mixture of compounds by ^{1}H-NMR spectroscopy. Purification by column chromatography [eluent: ethyl acetate/ Petroleum ether b.p. 60-80 °C (4:6)] gave the pure compound **190e** as a yellow oil. Yield (0.09g, 18%). ^{1}H-NMR: ($CDCl_3$) δ 8.70 (dd, 1H, J=5 and 2 Hz, Py-*H*), δ 8.50 (d, 1H, J=8 Hz, Py-*H*), δ 8.31 (d, 2H, Py-*H*), δ 7.84 (dt, 1H, J=8 and 2 Hz, Py-*H*), δ 7.34 (m, 1H, Py-*H*), δ 4.40 (q, 2H, J=7 Hz, ester-C*H*$_2$-), δ 2.92 (s, 3H, -C*H*$_3$) and δ 1.43 (t, 3H, J=7 Hz, ester-C*H*$_3$) ppm. ^{13}C-NMR: ($CDCl_3$) δ 166.7 (*C*O), δ 159.6 (*C*), δ 157.7 (*C*), δ 155.4 (*C*), δ 149.4 (*C*H), δ 139.5 (*C*H), δ 137.1 (*C*H), δ 125.2 (*C*), δ 124.3 (*C*H), δ 121.9 (*C*H), δ 118.1 (*C*H), δ 61.3 (*C*H$_2$), δ 25.3 (*C*H$_3$) and δ 14.4 (*C*H$_3$) ppm. High-resolution M.S.E.I. For $C_{14}H_{14}N_2O_2$. Calculated mass of molecular ion 243.1128 $(M+H)^+$. Measured mass: 243.1128 $(M+H)^+$. ν_{max} / cm^{-1} 1719 (C=O), 1252 (CO), 1099 (CO) and 765 (CH).



Methyl 5-Carboxylate-6-*tert*butyl-[2,2']bipyridyl 190c

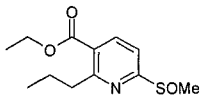
Compound **190c** was synthesised from methyl 4,4-dimethyl-2,3-dioxo-pentanoate **118c** (0.29 g, 1.6 mmol), prepared by oxidation of the alcohol **140c** with copper(II) acetate, in methanol following the procedure described above for the preparation of compound **190a** from **118a**. Chromatography over silica gel [eluent: DCM/methanol (95:5)] gave the desired product **190c** as a yellow oil. Yield (0.05 g, 11 %). ^{1}H-NMR: ($CDCl_3$) δ 8.67 (dd, 1H, J=5 and 2 Hz, py-H), δ 8.52 (d, 1H, J=8 Hz, py-H), δ 8.26 (d, 1H, J=8 Hz, py-H), δ 7.82 (dt, 1H, J=8 and 2Hz, py-H), δ 7.78 (d, 1H, J=8 Hz, py-H), δ 7.32 (m, 1H, py-H), δ 3.93 (s, 3H, ester-CH_3) and δ 1.49 (s, 9H, -$C(CH_3)_3$) ppm. In view of the low yield, full characterisation was not carried out.



Ethyl 5-Carboxylate-6-(4-nitro)phenyl-[2,2']bipyridyl 190d

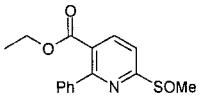
Compound **190d** was synthesised from ethyl 2-acetoxy-2-chloro-3-oxo-3-(4-nitrophenyl)propanoate **147d** (0.27 g, 0.82 mmol) following the procedure described above for the preparation of compound **190a** from **147a**. Recrystallisation from ethanol and water gave the desired product as a yellow solid, m.p. 142-144 °C. Yield (0.04 g, 14%). ^{1}H-NMR: ($CDCl_3$) δ 8.71 (dd, 1 H, J=5 and 2 Hz, Py-*H*), δ 8.56 (d, 1H, J=8 Hz, Py-*H*), δ 8.50 (m, 1H, Py- *H*), δ 8.36 (d, 1H, J=8 Hz, Py-*H*), δ 8.364 (d, 1H, J=9 Hz, Ph-*H*), δ 7.82 (m, 1H, Py-*H*), δ 7.78 (d, 2H, J=9 Hz, Ph-*H*), δ 7.39 (m, 1H, Py-*H*), δ 4.24 (q, 2H, J=7 Hz, ester-CH_2-) and δ 1.17 (t, 3H, J=7 Hz, ester-CH_3) ppm. ^{13}C-NMR: ($CDCl_3$) δ 166.9 (*C*O), δ 157.8 (*C*), δ 156.6 (*C*), δ 154.7 (*C*), δ 149.5 (*C*H), δ 147.0 (*C*), δ 139.7 (*C*H), δ 137.2 (*C*H), δ 129.9 (*C*H), δ 126.6 (*C*), δ 124.8 (*C*H), δ 123.3 (*C*H), δ 121.9 (*C*H), δ 119.9 (*C*H), δ 61.8 (CH_2) and δ 13.9 (CH_3) ppm. High-resolution M.S.E.I. For $C_{19}H_{15}N_3O_4$. Calculated mass of molecular ion 350.1135 $(M+H)^+$. Measured mass: 350.1135 $(M+H)^+$. ν_{max} / cm^{-1} 1716

(C=O), 1513 (NO_2), 1347 (NO_2), 1261 (CO), 1143 (CO) and 779 (CH). Anal. for $C_{19}H_{15}N_3O_4$: calc, N 12.03, C 65.32, H 4.33; found N 12.16, C 64.98, H 4.45.



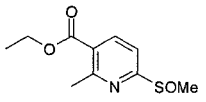
Ethyl 6-Carboxylate-2-methanesulfoxy-6-propylpyridine 197b

A solution of ethyl 6-carboxylate-3-methanesulfoxy-5-propyl-1,2,4-triazine **176b** (0.63 g, 2.4 mmol) and 2,5-norbornadiene **41** (2.65 mL, 24 mmol, 10 mole equivalents) in ethanol (15 mL) was stirred under reflux and an atmosphere of nitrogen for 12 hours and then allowed to cool to room temperature. The solvent was evaporated and the crude product poured onto water (10 mL), extracted with DCM (2x15 mL), dried over $MgSO_4$ and evaporated under reduced pressure to give compound **197b** as an orange oil (0.55g, 88%). ^{1}H-NMR: ($CDCl_3$) δ 8.38 (d, 1H, J=8 Hz, Py-*H*), δ 7.93 (d, 1H, J=8 Hz, Py-*H*), δ 4.41 (q, 2H, J=7 Hz, ester-C*H*$_2$-), δ 3.15 (m, 2H, propyl-C*H*$_2$-), δ 2.87 (s, 3H, -SOC*H*$_3$), δ 1.74 (sextet, 2H, J=8 Hz, propyl-C*H*$_2$-), δ 1.42 (t, 3H, J=7 Hz, ester-C*H*$_3$) and δ 0.99 (t, 3H, J=7 Hz, propyl-C*H*$_3$) ppm. High-resolution M.S.E.I. For $C_{12}H_{17}NO_3S$. Calculated mass of molecular ion 256.1002 $(M+H)^+$. Measured mass: 256.1001 $(M+H)^+$. ν_{max} / cm^{-1} 1721 (C=O), 1262 (CO), 1095 (CO) and 1065 (SO).



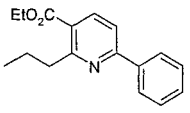
Ethyl 5-Carboxylate-2-methanesulfoxy-6-phenylpyridine 197a

Compound **197a** was synthesised from ethyl 6-carboxylate-3-methanesulfoxy-5-phenyl-1,2,4-triazine **176a** (0.17 g, 0.6 mmol) following the procedure described above for the preparation of compound **197b** from **176a**. Chromatography over silica gel [eluent: DCM/ methanol (9:1)] gave compound **197a** as an orange oil (0.13 g, 75 %). ^{1}H-NMR: ($CDCl_3$) δ 8.33 (d, 1H, J=8 Hz, Py-*H*), δ 8.09 (d, 1H, J=8 Hz, Py-*H*), δ 7.53 (m, 1H, Ph-H), δ 7.46 (m, 4H, Ph-*H*), δ 4.20 (q, 2H, J=7 Hz, ester-C*H*$_2$-), δ 2.93 (s, 3H, -SOC*H*$_3$) and δ 1.08 (t, 3H, J=7 Hz, ester-C*H*$_3$) ppm. ν_{max} / cm^{-1} 1718 (C=O), 1281 (CO), 1085 (CO), 1047 (SO) and 698 (CH).



Ethyl 5-Carboxylate-2-methanesulfoxy-6-methylpyridine 197e

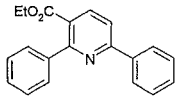
Compound **197e** was synthesised using ethyl 6-carboxylate-3-methanesulfoxy-5-methyl-1,2,4-triazine **176e** (0.2 g, 0.9 mmol) following the procedure described above for the preparation of compound **197b** from **176b.** Yield (0.08 g, 41%) as an orange oil. ^{1}H-NMR: ($CDCl_3$) δ 8.44 (d, 1H, J=8 Hz, Py-*H*), δ 7.94 (d, 1H, J=8 Hz, Py-*H*), δ 4.41 (q, 2H, J=7 Hz, ester-C*H*$_2$-), δ 2.87 (s, 3H, -C*H*$_3$), δ 2.85 (s, 3H, -C*H*$_3$) and δ 1.42 (t, 3H, J=7 Hz, ester-C*H*$_3$) ppm. ^{13}C-NMR: ($CDCl_3$) δ 168.3 (*C*), δ 165.8 (*C*O), δ 160.3 (*C*), δ 140.3 (*C*H), δ 126.6 (*C*), δ 116.5 (*C*H), δ 61.8 (*C*H$_2$), δ 41.3 (*C*H$_3$), δ 24.8 (*C*H$_3$) and δ 14.3 (*C*H$_3$) ppm. High-resolution M.S.E.I. For $C_{12}H_{17}NO_3S$. Calculated mass of molecular ion 228.0689 $(M+H)^+$. Measured mass: 228.0690 $(M+H)^+$. ν_{max} / cm^{-1} 1719 (C=O), 1268 (CO) and 1064 (SO).



Ethyl 5-Carboxylate-2-phenyl-6-propylpyridine 191b

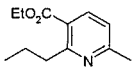
Compound **191b** was synthesised using ethyl 6-carboxylate-3-phenyl-5-propyl-1,2,4-triazine **166b** (0.1 g, 0.37 mmol) in xylene following the procedure described above for the preparation of compound **197b** from **176b.** Chromatography over silica gel [eluent: ethyl acetate/petroleum ether b.p. 60-80 °C (2:8)] gave the desired product **191b** as a yellow oil. Yield (0.05 g, 31%). ^{1}H-NMR: ($CDCl_3$) δ 8.22 (d, 1H, J=8 Hz, Py-*H*), δ 8.05 (dd, 2H, J=8 and 2 Hz, Ph-*H*), δ 7.61 (d, 1H, J=8 Hz, Py-*H*), δ 7.46 (t, 2H, J=7 Hz, Ph-*H*), δ 7.15 (t, 1H, J=7 Hz, Ph-*H*), δ 4.39 (q, 2H, J=7 Hz, ester-C*H*$_2$-), δ 3.21 (m, 2H, propyl-C*H*$_2$-), δ 1.84 (sextet, 2H, propyl-C*H*$_2$-), δ 1.42 (t, 3H, J=7 Hz, ester-C*H*$_3$) and δ 1.04 (t, 3H, J=7 Hz, propyl-C*H*$_3$) ppm. ^{13}C-NMR: ($CDCl_3$) δ 166.9 (*C*O), δ 163.4 (*C*), δ 158.9 (*C*), δ 139.4 (*C*H), δ 138.7 (*C*), δ 129.6 (*C*H), δ 128.9 (2 x *C*H), δ 127.4 (2 x *C*H), δ 123.8 (*C*), δ 117.2 (*C*H), δ 61.3 (*C*H$_2$), δ 39.2 (*C*H$_2$), δ 23.1 (*C*H$_2$), δ 14.4 (*C*H$_3$) and δ 14.3 (*C*H$_3$) ppm. ν_{max} /

cm^{-1} 1719 (C=O), 1582 (C=N), 1261 (CO) and 1088 (CO). E.I.M.S., m/z (relative abundance): 270 (95) $[M+H]^+$ and 242 (100) $[M-27]^+$.



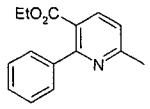
Ethyl 5-Carboxylate-2,6-diphenylpyridine 191a

Compound **191a** was synthesised using ethyl 6-carboxylate-3,5-diphenyl-1,2,4-triazine **166a** (0.43 g, 1.4 mmol) in xylene following the procedure described above for the preparation of compound **197b** from **176b.** Yield (0.19g, 44%) as a brown oil. ^{1}H-NMR: ($CDCl_3$) δ 8.18 (d, 1H, J=8 Hz, Py-*H*), δ 8.12 (dd, 2H, J=8 and 2 Hz, Ph-*H*), δ 7.78 (d, 1H, J=8 Hz, Py-*H*), δ 7.65 (dd, 2H, J=8 and 2 Hz, Ph-*H*), δ 7.46 (m, 6H, Ph-*H*), δ 4.18 (q, 2H, J=7 Hz, ester-CH_2-) and δ 1.07 (t, 3H, J=7 Hz, ester-CH_3) ppm. High-resolution M.S.E.I. For $C_{20}H_{17}NO_2$. Calculated mass of molecular ion 303.1254 $(M+H)^+$. Measured mass: 303.1258 $(M+H)^+$. ν_{max} / cm^{-1} 1714 (C=O), 1573 (C=N), 1289 (CO), 1140 (CO), 758 (CH) and 691 (CH).



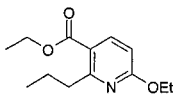
Ethyl 5-Carboxylate-2-methyl-6-propylpyridine 192b

Compound **192b** was synthesised using ethyl 6-carboxylate-3-methyl-5-propyl-1,2,4-triazine **171b** (0.15 g, 0.72 mmol) in xylene following the procedure described above for the preparation of compound **197b** from **176b.** Yield (0.1 g, 67%) as a brown oil. ^{1}H-NMR: ($CDCl_3$) δ 8.06 (d, 1H, J=8 Hz, Py-*H*), δ 7.04 (d, 1H, J=8 Hz, Py-*H*), δ 4.36 (q, 2H, J=7 Hz, ester-CH_2-), δ 3.09 (m, 2H, ester-CH_2-), δ 2.6 (s, 3H, -CH_3), δ 1.69 (sextet, 2H, propyl-CH_2-), δ 1.39 (t, 3H, J=7 Hz, ester-CH_3) and δ 1.01 (t, 3H, J=7 Hz, propyl-CH_3) ppm. High-resolution M.S.E.I. For $C_{12}H_{17}NO_2$. Calculated mass of molecular ion 208.1332 $(M+H)^+$. Measured mass: 208.1334 $(M+H)^+$ ν_{max} / cm^{-1} 1721 (C=O), 1250 (CO) and 1095 (CO).



Ethyl 5-Carboxylate-2-methyl-6-phenylpyridine 192a

Compound **192a** was synthesised using ethyl 6-carboxylate-3-methyl-5-phenyl-1,2,4-triazine **171a** (0.18 g, 0.74 mmol) in xylene following the procedure described above for the preparation of compound **197b** from **176b.** Yield (0.17 g, 95%) as a brown oil. ^{1}H-NMR: ($CDCl_3$) δ 8.02 (d, 1H, J=8 Hz, Py-*H*), δ 7.50 (dd, 2H, J=8 and 2 Hz, Ph-*H*), δ 7.41 (m, 3H, Ph-*H*), δ 7.19 (d, 1H, J=8 Hz, Py-*H*), δ 4.12 (q, 2H, J=7 Hz, ester-C*H*$_2$-), δ 2.65 (s, 3H, -C*H*$_3$) and δ 1.02 (t, 3H, J=7 Hz, ester-C*H*$_3$) ppm. ν_{max} / cm^{-1} 1715 (C=O), 1278 (CO), 1136 (CO), 765 (CH) and 696 (CH). High-resolution M.S.E.I. For $C_{15}H_{15}NO_2$. Calculated mass of molecular ion 242.1176 $(M+H)^+$. Measured mass: 242.1173 $(M+H)^+$.



Ethyl 5-Carboxylate-2-ethoxy-6-propylpyridine 205

A solution of ethyl 5-carboxylate-2-methanesulfoxy-6-propylpyridine **197b** (0.23 g, 0.9 mmol) in NaOEt (3 mL) was stirred under reflux for 1 hour and then allowed to cool to room temperature. The solvent was evaporated and the crude product poured onto water (10 mL), extracted with DCM (2x15 mL), washed with a saturated solution of $NaHCO_3$, dried over $MgSO_4$ and evaporated under reduced pressure to give compound **205** as an orange oil (0.11g, 53%). ^{1}H-NMR: ($CDCl_3$) δ 8.09 (d, 1H, J=8 Hz, Py-*H*), δ 6.54 (d, 1H, J=8 Hz, Py-*H*), δ 4.41 (q, 2H, J=7 Hz, ester-C*H*$_2$-), δ 4.33 (t, 2H, J=7 Hz, ester-C*H*$_2$-), δ 3.06 (m, 2H, propyl-C*H*$_2$-), δ 1.74 (sextet, 2H, J=8 Hz, propyl-C*H*$_2$-), δ 1.38 (t, 3H, J=7 Hz, ester-C*H*$_3$) and δ 0.99 (t, 3H, J=7 Hz, propyl-C*H*$_3$) ppm. ν_{max} / cm^{-1} 1716 (C=O), 1590 (C=N), 1245 (CO), 1093 (CO) and 1035 (CO).

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The preparation of 1,2,4-triazines from α,β-diketo-ester equivalents and their application in pyridine synthesis

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Abstract—The α-Chloro-α-acetoxy-β-keto-esters were prepared from β-keto-esters in good overall yields. These compounds reacted as α,β-diketo-ester equivalents with amidrazones yielding triazines, generally in good yields, or with an amidrazone and 2,5-norbornadiene in a one-pot aza Diels–Alder reaction to give the corresponding pyridines.
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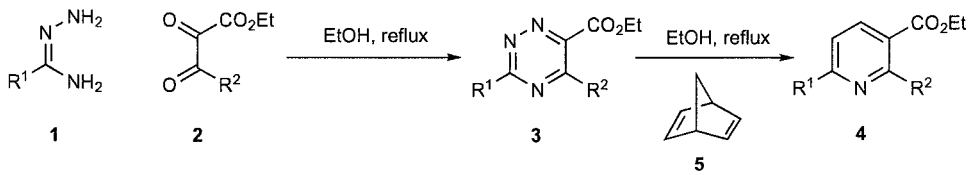
Pyridine derivatives occupy a central position in modern heterocyclic chemistry and consequently new and efficient methods for the preparation of this important heterocyclic ring system are of contemporary interest.[1] The aza Diels–Alder reaction has become an important and versatile method for the preparation of pyridine derivatives and several recent reviews have discussed the scope and application of this useful reaction.[2] 1,2,4-Triazines[3] have been used as 2-azadiene equivalents on many occasions and these heterocycles have been reacted with suitable acetylene equivalents, including 2,5-norbornadiene,[4] yielding pyridine derivatives. We have recently described the 'one-pot' reaction of amidrazones **1** ($R^1 = CO_2Et$ or 2-pyridyl) with the α,β-diketo-ester derivatives **2** (R^2 = Ph, *n*-Pr or *i*-Pr) in the presence of 2,5-norbornadiene **5** in ethanol at reflux yielding the appropriate pyridine derivatives **4** in good overall yield without isolation of the 1,2,4-triazine intermediates **3** (Scheme 1).[5]

The α,β-diketo-esters **2** were prepared from commercially available β-keto-esters ($R^2COCH_2CO_2Et$) by a diazo-transfer reaction giving the corresponding diazo-compounds [$R^2COC(N_2)CO_2Et$] and subsequent treatment of these with ^{t}BuOCl.[6] Although these α,β-di-keto-esters **2** are hydrated at the α-carbonyl group, they have been depicted in their keto form for simplicity. 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. α,β-Diketo-esters are also commonly prepared by ozonolysis of phosphorane precursors [$R^2COC(=PPh_3)CO_2Et$] and this subject has recently been reviewed by Wassermann and Parr.[7] This



1 **2** **3** **5** **4**

Scheme 1.

Keywords: 1,2,4-Triazines; α,β-Diketo-esters; Aza Diels–Alder reaction.
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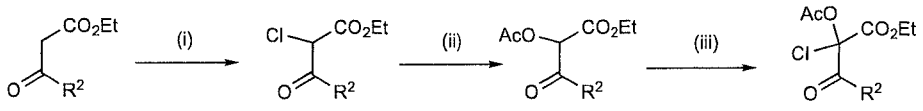

6a R^2 = Ph
6b R^2 = *n*-Pr

7a R^2 = Ph
7b R^2 = *n*-Pr

8a R^2 = Ph
8b R^2 = *n*-Pr

9a R^2 = Ph
9b R^2 = *n*-Pr

Scheme 2. Reagents and conditions: (i) SO_2Cl_2, CH_2Cl_2, rt; (ii) Et_3N, AcOH, DMF, rt; (iii) SO_2Cl_2, CH_2Cl_2, rt.

method of preparing α,β-diketo-esters would generate large quantities of triphenylphosphine oxide as a by-product which would not be desirable on a manufacturing scale.

As a continuation of our previous studies,[5] we have been interested in preparing triazines **3** as substrates for aza Diels–Alder reactions. In view of the limitations described above, we have prepared the α-chloro-α-acetoxy-β-keto-ester derivatives **9a** and **b** as representative examples of α,β-diketo-ester equivalents (Scheme 2). Thus, the α-chloro-β-keto-esters **7a** and **b** were prepared by chlorination of the β-keto-esters **6a** and **b** with sulfuryl chloride[8] and then treatment of products **7a** and **b** with a mixture of acetic acid and triethylamine in dimethylformamide at room temperature yielded the acetates **8a** (95%) and **8b** (90%), reported previously[9,10] by treatment of **6a** and **b**, respectively, with lead tetraacetate. Chlorination of these acetates **8a** and **b** using sulfuryl chloride gave the novel compounds **9a** (77%) and **9b** (98%) as oils that did not require further purification.[11]

Compounds **9a** and **b** were reacted in boiling ethanol solution with a range of amidrazones **1** giving the corresponding 1,2,4-triazine derivatives **3** (Table 1).[12] The best yields were obtained with 2 equiv of the amidrazone. The work-up for this reaction was straightforward; the solvent was evaporated and the residue was taken up into dichloromethane, washed with water and, after drying and evaporating the organic layer, almost pure tri- azines were produced as indicated by ^{1}H NMR spectroscopy.

Additionally, when compounds **9a** and **b** were reacted with 2 equiv of the amidrazone **1** (R^1 = 2-pyridyl) and an excess of 2,5-norbornadiene **5** in ethanol at reflux the corresponding bipyridyls **4** were formed in moderate yield (50% and 63%, respectively), being identical with the compounds described previously.[5c]

Table 1. Preparation of triazines **3**

Triazine **3**		Yield (%)
R^1	R^2	
2-Pyridyl	Ph	98
2-Pyridyl	*n*-Pr	97
Ph	Ph	82
Ph	*n*-Pr	65
SMe	Ph	77
SMe	*n*-Pr	83
Me	Ph	54
Me	*n*-Pr	53

In conclusion, we have prepared the α,β-diketo-ester equivalents **9a** and **b** and shown that these compounds react with amidrazones giving 1,2,4-triazines **3** in good yields.

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11. Compound **9a**: ^{1}H NMR (270 MHz, $CDCl_3$): δ 8.13 (d, 2H, $J = 7$ Hz, Ph*H*), 7.64 (t, 1H, $J = 7$ Hz, Ph*H*), 7.50 (m, 2H, Ph*H*), 4.31 (q, 2H, $J = 7$ Hz, $-CO_2CH_2CH_3$), 2.23 (s, 3H, $OCOCH_3$) and 1.29 (t, 3H, $J = 7$ Hz, $-CO_2CH_2CH_3$). HRMS (EI^+) for $C_{13}H_{13}ClO_5$: calculated mass of molecular ion: 285.0524 (M+H); measured mass: 285.0526. Compound **9b**: ^{1}H NMR (270 MHz, $CDCl_3$): δ 4.32 (q, 2H, $J = 7$ Hz, $-COCH_2CH_3$), 2.85 (q, 2H, $J = 7$ Hz, $-COCH_2-$), 2.24 (s, 3H, $-OCOCH_3$), 1.69 (sextet, 2H, $J = 7$ Hz, $-CH_2-$), 1.32 (t, 3H, $J = 7$ Hz, $-CO_2CH_2CH_3$) and 0.96 (t, 3H, $J = 7$ Hz, $-CH_3$). HRMS (EI^+) for $C_{10}H_{15}ClO_5$: calculated mass of molecular ion: 268.0946 ($M+NH_4$); measured mass: 268.0948.
12. All triazine derivatives gave satisfactory ^{1}H NMR spectra and high resolution mass spectra.