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A convenient synthesis of pyridine and 2,2′-bipyridine derivatives

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ABSTRACT

α-Chloro-α-acetoxy-β-keto-esters **9** were readily prepared from β-keto-esters **6** in good overall yields. These compounds reacted as α,β-diketo-ester equivalents **2** with amidrazones **1** yielding triazines **3**, generally in good yields. Picolinates **10** provided an alternative source of α,β-diketo-ester equivalents **2** when treated with copper(II) acetate. A 'one-pot' reaction of the α,β-diketo-ester equivalents **2** with amidrazones **1** in the presence of 2,5-norbornadiene **5** in boiling ethanol yielded the pyridines **4** and 2,2′-bipyridines **4** (R^1=2-pyridyl) directly without the need to isolate the corresponding triazines **3**. Triazine **3c** reacted with the aza-dienophiles **13** and **17** affording the products **16** and **18**, respectively, in good yields.

1. Introduction

Pyridine derivatives occupy a central position in modern heterocyclic chemistry particularly in the pharmaceutical and agrochemical fields. Consequently new and efficient methods for the preparation of this important heterocyclic ring system are of contemporary interest.[1] 2,2′-Bipyridine[2] and its derivatives have also been the subject of numerous studies, principally because of their well-developed coordination chemistry.[3] Many applications of 2,2′-bipyridine derivatives have been reported in fields such as supramolecular chemistry,[4] artificial photosynthesis systems,[5] luminescent sensor materials[6] and non-linear optical materials.[7] When the 2,2′-bipyridine framework bears pendent chiral substituents, they have been studied as potential ligands in metal-catalysed asymmetric reactions.[8] 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.[9] 1,2,4-Triazines[10] have been frequently used as 2-azadienes and they have been reacted with a variety of aza-dienophiles, including the acetylene equivalent 2,5-norbornadiene,[2,11] yielding pyridine and 2,2′-bipyridine derivatives.

In a series of previous publications,[12] we have described the synthesis of triazines **3**, pyridines **4** and 2,2′-bipyridines **4** (R^1=2-pyridyl) from readily available amidrazones **1** and hydrated α,β-diketo-esters **2** or their equivalents (Scheme 1) and this work has recently been extended to allow the preparation of 2,2′:6,2″-terpyridines.[12f] The reaction of amidrazones **1** and compounds **2** in ethanol at reflux yielded triazine derivatives **3**, which, in the presence of 2,5-norbornadiene **5**, afforded products **4** via the inverse electron-demand aza Diels–Alder when the group R^1 is electron-deficient (CO_2Et or 2-pyridyl). Thus, compounds **4** are readily accessible in a convenient 'one-pot' reaction from amidrazones **1** (R^1=CO_2Et or 2-pyridyl). The hydrated α,β-diketo-esters **2** were originally prepared from commercially available β-keto-esters by a diazo-transfer reaction giving the corresponding diazo-compounds [$R^2COC(N_2)CO_2Et$] and subsequent treatment of these with *t*-BuOCl.[13] From a manufacturing perspective, the large scale use of these diazo-compounds would not be attractive and their replacement by other α,β-diketo-ester equivalents would be highly desirable. Alternative methods of preparing α,β-diketo-esters **2** similarly have other drawbacks: for example, α,β-diketo-esters are commonly prepared by ozonolysis of phosphorane precursors [$R^2COC(=PPh_3)CO_2Et$],[14] which generates large quantities of triphenylphosphine oxide as an unwanted by-product. In view of these limitations, this paper reports two alternative methods of preparing α,β-diketo-ester equivalents **2** and describes how these reactants can be used for the synthesis of triazine **3** and pyridine **4** derivatives. Some of this work have been published in a preliminary form,[12d,e] and this paper gives a full description of the work and also describes how our earlier studies have been extended.

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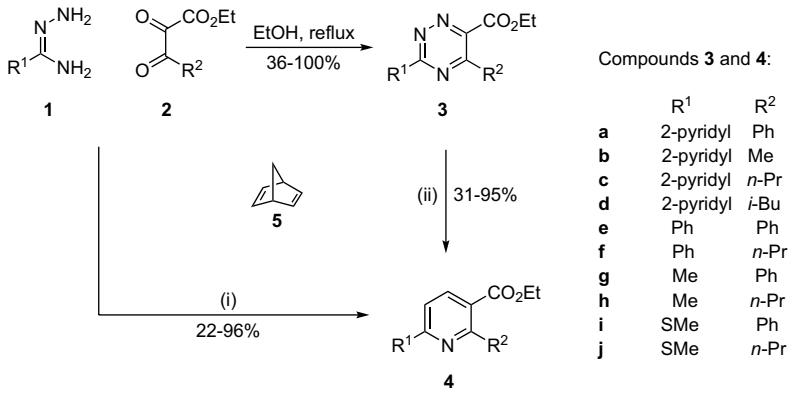


Scheme 1. Synthesis of triazines **3** and pyridines **4**. Reaction conditions: (i) EtOH, reflux, 2,5-norbornadiene **5** (compounds **4a–d**); (ii) xylene reflux or 1,2-dichlorobenzene, 140 °C, 2,5-norbornadiene **5** (compounds **4e–j**).

2. Discussion

We have prepared the α-chloro-α-acetoxy-β-keto-ester derivatives **9a–d** as representative examples of α,β-diketo-ester equivalents (Scheme 2). The readily available β-keto-esters **6a–d** were treated with sulfuryl chloride[15] yielding the α-chloro-β-keto-esters **7a–d**. Treatment of these products with a mixture of acetic acid and triethylamine in dimethylformamide at room temperature yielded the acetates **8a–d** (85–100%). Chlorination of acetates **8a–d** with sulfuryl chloride afforded novel compounds **9a–d** (77–98%) as oils that did not require further purification.

We were also interested in examining the alcohols **11** as potential α,β-diketo-ester **2** precursors (Scheme 3). Hydrolysis of the acetates **8** could give alcohols **11**, which might then be oxidised to the α,β-diketo-esters **2**. In order to avoid this two-step sequence, picolinates **10a–d** were prepared in good yield by reacting the appropriate chloro-derivatives **7** with picolinic acid under basic conditions as shown in Scheme 3. The facile cleavage of picolinates in the presence of copper salts is well known[16] and this property would allow the direct conversion of picolinates **10** into their corresponding α,β-diketo-esters **2**. Thus, in the presence of $Cu(OAc)_2$, picolinates **10** would be expected to give alcohols **11**, which would then be oxidised in situ by $Cu(OAc)_2$[17] into the corresponding α,β-diketo-esters **2**.

In order to assess whether compounds **9** were suitable α,β-diketo-ester equivalents they were reacted in boiling ethanol solution with a range of amidrazones **1**. Amidrazone **1** (R^1=2-pyridyl) was prepared from 2-cyanopyridine and hydrazine hydrate.[18] Amidrazones **1** (R^1=Ph, Me) were prepared in situ by reaction of the corresponding amidine hydrochlorides with hydrazine hydrate and amidrazone **1** (R^1=SMe) was synthesised as its HI salt by methylation of thiosemicarbazide.[19] The resulting 1,2,4-triazine derivatives **3** were isolated with the best yields being obtained when at least 2 equiv of amidrazone **1** was used (Table 1, method A). The work-up for this reaction was straightforward; the solvent

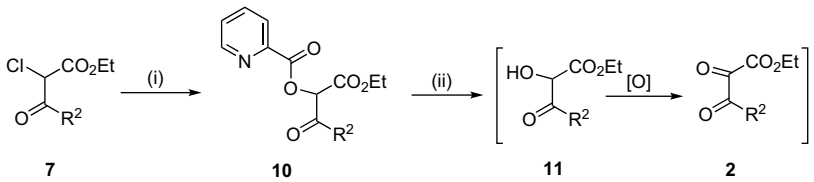
Table 1
Synthesis of triazines **3**

Triazine **3**	R^1	R^2	Method[a] and yield (%)			
			A	B	C	D
a	2-Pyridyl	Ph	97	95	65	63
b	2-Pyridyl	Me	37	—	—	—
c	2-Pyridyl	*n*-Pr	98	79	71	43
d	2-Pyridyl	*i*-Bu	—	—	54	58
e	Ph	Ph	82	80	—	—
f	Ph	*n*-Pr	93	52	65	—
g	Me	Ph	54	—	—	—
h	Me	*n*-Pr	43	51	—	—
i	SMe	Ph	100	90	58	64
j	SMe	*n*-Pr	100	92	58	92

[a] Method A: no pre-treatment of compounds **9**. Method B: pre-treatment of compounds **9** with EtOH/HCl. Method C: pre-treatment of compounds **9** with ethanolic methylamine. Method D: from picolinates **10**.

Compounds **6-9**: **a** R^2 = Ph; **b** R^2 = Me; **c** R^2 = *n*-Pr; **d** R^2 = *i*-Bu

Scheme 2. Synthesis of compounds **9**. Reaction conditions: (i) SO_2Cl_2, CH_2Cl_2, 0 °C to rt; (ii) Et_3N, AcOH, DMF, rt; (iii) SO_2Cl_2, CH_2Cl_2, 0 °C to rt.



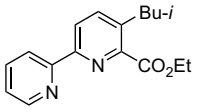
a R^2 = Ph; **b** R^2 = Me; **c** R^2 = *n*-Pr; **d** R^2 = *i*-Bu

Scheme 3. Synthesis of picolinates **10** and their conversion into intermediates **2**. Reaction conditions: (i) picolinic acid, $KHCO_3$, DMF, rt; (ii) $Cu(OAc)_2$ aq, rt.

Table 2
'One-pot' synthesis of 2,2′-bipyridines **4**

Pyridine **4**	R^1	R^2	Method[a] and yield (%)			
			A	B	C	D
a	2-Pyridyl	Ph	50	80	68	71
b	2-Pyridyl	Me	22	—	—	—
c	2-Pyridyl	*n*-Pr	63	96	80	59
d	2-Pyridyl	*i*-Bu	49[b]	—	61[c]	45

[a] Method A: no pre-treatment of compounds **9**. Method B: pre-treatment of compounds **9** with EtOH/HC1. Method C: pre-treatment of compounds **9** with ethanolic methylamine. Method D: from picolinates **10**.
[b] Mixture of **4d**/**12** (2:1).
[c] Mixture of **4d**/**12** (3:1)



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was evaporated and the residue was taken up into dichloromethane, washed with water, and after drying and evaporating the organic layer, triazines **3** were obtained generally in good yield. Low yields were only obtained when either R^1 or R^2 was a methyl group. We reasoned that in the reaction of the amidrazones **1** with the α-chloro-α-acetoxy-β-keto-ester derivative **9a**, 1 equiv of amidrazone **1** might have reacted at the acetate carbonyl group resulting in de-acylation and subsequent collapse of the resulting α-chloro-α-hydroxy-β-keto-esters to the α,β-diketo-esters **2** by loss of hydrogen chloride. If this was the case, then it might be possible to convert compounds **9** into their corresponding α,β-diketo-esters **2** prior to reaction with amidrazones **1**. The α-chloro-α-acetoxy-β-keto-ester derivatives **9** were therefore treated with saturated ethanolic hydrogen chloride solution to induce de-acylation by transesterification and then 1 equiv of an amidrazone **1** was added. Under these conditions the triazines **3** were produced (Table 1, method B), generally in good yield. Alternatively, these α-chloro-α-acetoxy-β-keto-ester derivatives **9** could be pre-treated with ethanolic methylamine prior to addition of 1 equiv of an amidrazone **1** (Table 1, method C) and in this case moderate to good yields of triazines **3** were obtained.

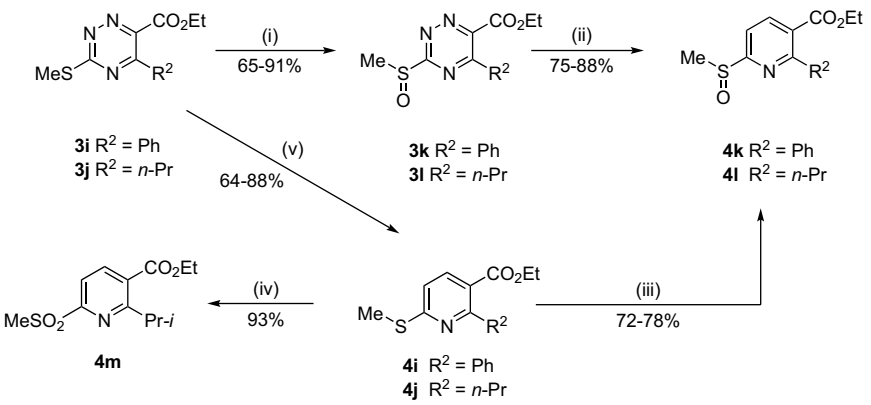
In order to determine the suitability of picolinates **10** as α,β-diketo-esters they were treated with an excess of $Cu(OAc)_2$. After washing with the disodium salt of EDTA, amidrazones **1** (R^1=2-pyridyl or SMe) and ethanol were added and after heating at reflux the appropriate triazines **3** were produced in moderate to good yields (Table 1, method D).

The four methods A–D described above were then assessed in a 'one-pot' synthesis of some selected 2,2′-bipyridine derivatives **4** (Table 2). When 2 equiv of amidrazone **1** (R^1=2-pyridyl) was reacted with the α-chloro-α-acetoxy-β-keto-ester derivatives **9** in the presence of an excess of 2,5-norbornadiene **5** in ethanol at reflux, the 2,2′-bipyridine derivatives **4** were produced generally in moderate yield (method A) except when R^1=Me and a poor yield of 2,2′-bipyridine **4b** was obtained. Prior reaction of selected examples of α-chloro-α-acetoxy-β-keto-ester derivatives **9** with either ethanolic hydrogen chloride (method B) or ethanolic methylamine (method C) gave improved yields of the corresponding 2,2′-bipyridines **4**, whereas the appropriate picolinates **10** produced moderate yields of compounds **4c** and **4d** but a good yield of compound **4a**. It is interesting to note that when R^2=*i*-Bu, an inseparable mixture of regioisomers **4d** and **12** was formed in methods A and C.

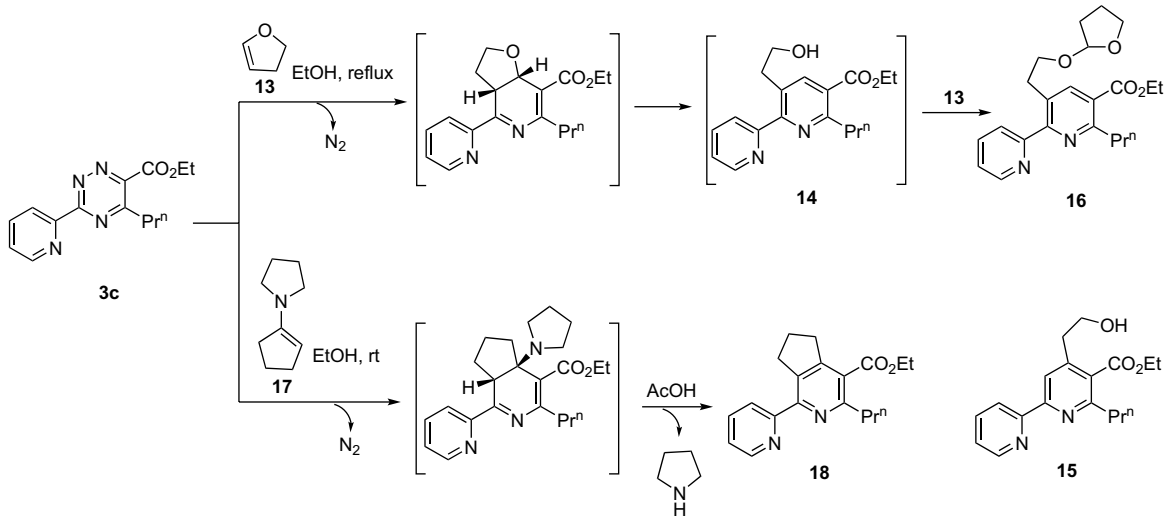
In contrast to triazine **3** (R^1=2-pyridyl), triazines **3** (R^1=Ph, Me, SMe) were not expected to be sufficiently reactive to undergo the inverse electron-demand aza Diels–Alder reaction with 2,5-norbornadiene **5** in boiling ethanol solution at a convenient rate because of the electronic nature of the R^1 groups. Triazines **3e**–**h** were therefore reacted with 2,5-norbornadiene **5** in xylene at reflux yielding the pyridine derivatives **4e**–**h** (31–95%), respectively. The reaction of triazines **3i** and **3j** with 2,5-norbornadiene **5** proceeded in hot (140 °C) 1,2-dichlorobenzene yielding 2,2′-bipyridines **4i** (88%) and **4j** (64%), respectively (Scheme 1). Surprisingly, these two triazines also reacted in neat, boiling 2,5-norbornadiene **5** (bp 89 °C) over 2 days giving products **4i** (64%) and **4j** (66%) together with some unreacted starting material.

Triazines **3i** and **3j** were oxidised by *meta*-chloroperbenzoic acid (MCPA) affording the corresponding sulfoxides **3k** and **3l** (Scheme 4). As anticipated, the electron-deficient sulfoxide group allowed these compounds to react with 2,5-norbornadiene **5** in boiling ethanol giving pyridines **4k** and **4l**. These two pyridine derivatives were also prepared by oxidation of pyridines **4i** and **4j**, respectively, with 1 equiv of $NaBO_3 \cdot 4H_2O$. In order to introduce a group that might eventually be replaced by nucleophiles, sulfone **4m** (93%) was prepared from pyridine derivative **4j** and an excess of $NaBO_3 \cdot 4H_2O$.

Additional functionality can be introduced into the pyridine-ring by using, for example, enamines[20] and enol-ethers[21] as the aza-dienophiles (Scheme 5). Thus, triazine **3c** was reacted in boiling ethanol with an excess of 2,3-dihydrofuran **13** giving the 2,2′-bipyridine derivative **16** (64%) after reaction of the intermediate **14** with additional 2,3-dihydrofuran **13**. The regioselectivity of the cycloaddition process was expected from results previously obtained with this dienophile.[12c] Thus, if the alternative regioisomer **15** had been formed, intramolecular lactonisation



Scheme 4. Synthesis of sulfoxide and sulfone derivatives. Reaction conditions: (i) MCPA; (ii) 2,5-norbornadiene **5**, EtOH, reflux; (iii) $NaBO_3 \cdot 4H_2O$, 1.05–1.10 equiv; (iv) $NaBO_3 \cdot 4H_2O$, 2.5 equiv; (v) 2,5-norbornadiene **5**, 1,2-dichlorobenzene, 140 °C.



Scheme 5. Formation of 2,2′-bipyridines **16** and **18**.

would have been expected to occur. With enamine **17** as the dienophile, the 2,2′-bipyridine derivative **18** (84%) was obtained. This reaction proceeded at room temperature and after the initial cycloaddition process acetic acid was added to the reaction mixture to assist the elimination of pyrrolidine.

3. Conclusion

We have demonstrated that the α-chloro-α-acetoxy-β-keto-ester derivatives **9** and picolinates **10** are readily prepared and that they are effective α,β-diketo-ester equivalents. These compounds are useful intermediates for the synthesis of 1,2,4-triazines **3** and hence 2,2′-bipyridines **4** via an aza Diels–Alder reaction. The transformation of starting materials **9** and **10** into 2,2′-bipyridines **4** can often be carried out in a 'one-pot' reaction without the need to isolate the triazine **3** intermediates.

4. Experimental

4.1. General

^{1}H NMR (270 MHz) and ^{13}C NMR (67.5 MHz) spectra were recorded on a Joel JNM EX270 instrument. Elemental analysis was performed by the Department of Chemistry at the University of Newcastle. High-resolution mass spectra were performed by the EPSRC mass spectrometry service at the University of Wales, Swansea. Melting points are reported uncorrected as determined on a Stuart SMP1 melting point apparatus. Infrared 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. Ethyl 2-chloroacetoacetate **7b** was commercially available.

4.2. Preparation of α-chloro-β-keto-esters 7: general procedure[15]

To a stirred ice-cold solution of the appropriate β-keto-ester **6** in CH_2Cl_2 (10 mL) was added slowly sulfuryl chloride (1.1 equiv). After stirring for 1 h at room temperature the solution was washed with a saturated solution of sodium carbonate, the organic layer was dried ($MgSO_4$) and evaporated giving α-chloro-β-keto-esters **7**, which were used in the subsequent reactions without need for purification.

4.2.1. *Ethyl 2-chloro-3-oxo-3-phenylpropanoate* ***7a***[15]

Compound **7a** was prepared from ethyl benzoylacetate **6a** (1.0 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*), 7.65 (t, 1H, J=7 Hz, Ph–*H*), 7.50 (t, 2H, J=7 Hz, Ph–*H*), 5.67 (s, 1H, –C*H*Cl), 4.28 (q, 2H, J=7 Hz, –OCH_2CH$_3$), 1.23 (t, 3H, J=7 Hz, –OCH$_2$CH_3).

4.2.2. *Ethyl 2-chloro-3-oxohexanoate* ***7c***[15]

Compound **7c** was prepared from ethyl butyrylacetate **6c** (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), 4.23 (q, 2H, J=7 Hz, –OCH_2CH$_3$), 2.65–2.60 (m, 2H, –CH_2–), 1.59 (sextet, 2H, –CH_2–), 1.25 (t, 3H, J=7 Hz, –OCH$_2$CH_3), 0.87 (t, 3H, J=7 Hz, –CH_3).

4.2.3. *Ethyl 2-chloro-5-methyl-3-oxohexanoate* ***7d***

Compound **7d** was prepared from ethyl 5-methyl-3-oxohexanoate **6d**[22] (12.0 g; 69.7 mmol) using the general procedure. Yield (14.6 g, 100%) as a pale yellow liquid (86:14 keto/enol mixture); IR: ν_{max}/cm^{-1} 2962, 1729 (C=O), 1252, 1181, 1022; ^{1}H NMR ($CDCl_3$): δ 12.43 (s, 1H, OH enol form), 4.75 (s, 1H, >C*H*Cl), 4.29 (q, 2H, enol form, J=7.2 Hz, –OCH_2CH$_3$), 4.28 (q, 2H, keto form, J=7.2 Hz, –OCH_2CH$_3$), 2.70 (d, 2H, enol form, J=7.2 Hz, –CH_2Pr-*i*), 2.59 and 2.56 (2d, 2H, keto form, J=7.2 Hz, –CH_2Pr-*i*), 2.19 (nonet, 1H, J=6.7 Hz, 5-H overlapping enol and keto forms, –CH$_2$C*H*Me$_2$), 1.31 (t, 3H, overlapping enol and keto forms, J=7.2 Hz, –OCH$_2$CH_3), 0.99 and 0.96 (2d, 6H, enol form, J=7.2 Hz, –CH$_2$CH*Me*$_2$), 0.94 and 0.93 (2d, 6H, keto form, J=7.2 Hz, –CH$_2$CH*Me*$_2$); ^{13}C NMR ($CDCl_3$) (keto form): δ 198.5 (*C*O), 165.1 (*C*O), 63.2 (*C*H$_2$CH$_3$), 61.3 (*C*H), 47.7 (*C*H$_2$), 24.3 (*C*H), 22.4, 22.3 (*C*H$_3$), 14.0 (*C*H$_3$); HRMS (ESI) for $C_9H_{16}ClO_3$ $[M+H]^+$: m/z calcd: 207.0782; measured: 207.0781.

4.3. Preparation of α-acetoxy-β-keto-esters 8: general procedure[23]

To a stirred ice-cold solution of glacial acetic acid (10 mL, 0.18 mol) in DMF (50 mL) was added slowly NEt_3 (10 mL, 0.10 mol). After warming to room temperature, the appropriate α-chloro-

β-keto-ester **7** (0.02–0.03 mol) was added and the solution was left stirring at room temperature for 20 h. The solution was poured into water, extracted twice with CH_2Cl_2 and the combined organic extracts were dried ($MgSO_4$) and evaporated affording α-acetoxy-β-keto-ester **8**. These compounds were all used in the subsequent reactions without the need for purification.

4.3.1. Ethyl 2-acetoxy-3-oxo-3-phenylpropanoate ***8a***[24a,b]

Compound **8a** was prepared from compound **7a** (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*), 7.64 (t, 1H, J=7 Hz, Ph–*H*), 7.50 (t, 2H, J=7 Hz, Ph–*H*), 6.34 (s, 1H, –C*H*OAc), 4.24 (q, 2H, J=7 Hz, –OC*H*$_2$CH$_3$), 2.22 (s, 3H, –OCOC*H*$_3$), 1.20 (t, 3H, J=7 Hz, –OCH$_2$C*H*$_3$).

4.3.2. Ethyl 2-acetoxy-3-oxobutanoate ***8b***[23,24a,b,25]

Compound **8b** was prepared from compound **7b** (10.0 g, 60.8 mmol) using the general procedure. Yield (9.67 g, 85%) as a yellow liquid; ^{1}H NMR ($CDCl_3$): δ 5.50 (s, 1H, –C*H*OAc), 4.29 (q, 2H, J=7.2 Hz, –OC*H*$_2$CH$_3$), 2.36 (s, 3H, –COC*H*$_3$), 2.24 (s, 3H, –OCOC*H*$_3$), 1.32 (t, 3H, J=7.2 Hz, –OCH$_2$C*H*$_3$).

4.3.3. Ethyl 2-acetoxy-3-oxohexanoate ***8c***[24b,26]

Compound **8c** was prepared from compound **7c** (5.0 g, 27 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), 4.19 (q, 2H, J=7 Hz, –OC*H*$_2$CH$_3$), 2.57 (t, 2H, J=7 Hz, –C*H*$_2$–), 2.14 (s, 3H, –OCOC*H*$_3$), 1.56 (sextet, 2H, J=7 Hz, –C*H*$_2$–), 1.22 (t, 3H, J=7 Hz, –OCH$_2$C*H*$_3$), 0.84 (t, 3H, J=7 Hz, –C*H*$_3$).

4.3.4. Ethyl 2-acetoxy-5-methyl-3-oxohexanoate ***8d***[25]

Compound **8d** was prepared from compound **7d** (5.0 g, 24.2 mmol) using the general procedure. Yield (5.67 g, 100%) as a yellow liquid; ^{1}H NMR ($CDCl_3$): δ 5.46 (s, 1H, >C*H*OAc), 4.27 (q, 2H, J=7.2 Hz, –OC*H*$_2$CH$_3$), 2.53 (d, 2H, J=6.7 Hz, –C*H*$_2$Pr-*i*), 2.22 (s, 3H, –OCOC*H*$_3$), 2.19 (nonet, J=6.7 Hz, 1H, –CH$_2$C*H*Me$_2$), 1.30 (t, 3H, J=7.2 Hz, –OCH$_2$C*H*$_3$), 0.93 and 0.90 (2d, 6H, J=6.7 Hz, –CH$_2$CH*Me*$_2$).

4.4. Preparation of α-acetoxy-α-chloro β-keto-esters 9: general procedure

To a stirred ice-cold solution of the appropriate α-acetoxy-β-keto-ester **8** (2 mmol) in CH_2Cl_2 (5 mL) was added slowly sulfuryl chloride (2.2 mmol unless otherwise stated). After stirring at room temperature for 1 h, the solution was washed with a saturated solution of sodium carbonate, dried ($MgSO_4$) and evaporated yielding crude α-acetoxy-α-chloro-β-keto-ester **9**. These compounds were all used in the subsequent reactions without the need for purification.

4.4.1. Ethyl 2-acetoxy-2-chloro-3-oxo-3-phenylpropanoate ***9a***

Compound **9a** was prepared from compound **8a** (0.5 g, 2 mmol) using the general procedure. Yield (0.44 g, 77%) as a yellow oil. Analytical data (IR, ^{1}H NMR, HRMS) for this compound has been reported previously by us.[12d]

4.4.2. Ethyl 2-acetoxy-2-chloro-3-oxobutanoate ***9b***

Compound **9b** was prepared from compound **8b** (4.0 g, 21.3 mmol) and SO_2Cl_2 (1.88 mL, 23.4 mmol) using the general procedure. Yield (3.83 g; 81 %) as a yellow liquid; IR: ν_{max}/cm^{-1} 2987, 1733 (C=O), 1370, 1252, 1199, 1086, 1042, 1011; ^{1}H NMR ($CDCl_3$): δ 4.33 (q, 2H, J=7.2 Hz, –OC*H*$_2$CH$_3$), 2.50 (s, 3H, –C*H*$_3$), 2.24 (s, 3H, –C*H*$_3$), 1.32 (t, 3H, J=7.2 Hz, –OCH$_2$C*H*$_3$); ^{13}C NMR ($CDCl_3$): δ 194.5 (*C*O), 167.7 (*C*O), 163.3 (*C*O), 90.0 (*C*), 64.0 (*C*H$_2$), 24.8 (*C*CH$_3$), 20.8 (*C*CH$_3$), 13.9 (CH$_2$*C*H$_3$); HRMS (ESI) for $C_8H_{12}ClO_5$ $[M+H]^+$: m/z calcd: 240.0633; measured: 240.0632.

4.4.3. Ethyl 2-acetoxy-2-chloro-3-oxohexanoate ***9c***

Compound **9c** was prepared from compound **8c** (4.0 g, 18 mmol) using the general procedure. Yield (4.62 g, 98%) as a yellow oil. Analytical data (IR, ^{1}H NMR, HRMS) for this compound has been reported previously by us.[12d]

4.4.4. Ethyl 2-acetoxy-2-chloro-5-methyl-3-oxohexanoate ***9d***

Compound **9d** was prepared from compound **8d** (4.97 g, 21.6 mmol) and SO_2Cl_2 (1.91 mL, 23.8 mmol) using the general procedure. Yield (5.45 g, 95%) as a yellow oil; IR: ν_{max}/cm^{-1} 2965, 1735 (C=O), 1247, 1200, 1090, 1021; ^{1}H NMR ($CDCl_3$): δ 4.32 (q, 2H, J=7.2 Hz, –OC*H*$_2$CH$_3$), 2.77–2.70 (m, 2H, –C*H*$_2$Pr-*i*), 2.30–2.15 (m, 1H, –C*H*Me$_2$), 2.24 (s, 3H, –COC*H*$_3$), 1.31 (t, 3H, J=7.2 Hz, –OCH$_2$C*H*$_3$), 1.00–0.94 (m, 6H, –CH*Me*$_2$); ^{13}C NMR ($CDCl_3$): δ 196.2 (*C*O), 167.7 (*C*O), 163.5 (*C*O), 63.9 (*C*H$_2$), 45.5 (*C*H$_2$), 24.1 (*C*H), 22.4 (*C*H$_3$), 22.2 (*C*H$_3$), 20.9 (*C*H$_3$), 13.9 (*C*H$_3$) (the C-2 carbon was not sufficiently intense to be located); HRMS (ESI) for $C_{11}H_{21}ClNO_5$ $[M+NH_4]^+$: m/z calcd: 282.1103; measured: 282.1104.

4.5. Preparation of picolinates 10

The preparation of picolinates **10a** and **10c** and full analytical data for these two compounds have been described in our previous communication.[12e] Picolinates **10b** and **10d** were prepared using a similar procedure. Compound **10b** (77% yield); 93:7 keto/enol mixture; IR: ν_{max}/cm^{-1} 2986, 1727 (C=O), 1290, 1244, 1215, 1126, 1092, 749, 700; ^{1}H NMR ($CDCl_3$): δ 12.35 (s, 1H, OH enol form), 8.82 (ddd, 2H, overlapping keto and enol forms, J=1.0, 1.7 and 4.7 Hz, Py–*H*), 8.23 (ddd 2H, overlapping keto and enol, J=1.0, 1.2 and 7.9 Hz, Py–*H*), 7.90 (ddd, 2H, overlapping keto and enol forms, J=1.7, 7.7 and 7.9 Hz, Py–*H*), 7.55 (ddd, 2H, overlapping keto and enol forms, J=1.2, 4.7 and 7.7 Hz, Py–*H*), 5.81 (s, 1H, 2-H keto form, –C*H*OCO–), 4.34 (q, 2H, keto form, J=7.2 Hz, –OC*H*$_2$CH$_3$), 4.33 (q, 2H, enol form, J=7.2 Hz, –OC*H*$_2$CH$_3$), 2.47 (s, 3H, keto form, –COC*H*$_3$), 2.39 (s, 3H, enol form, –COC*H*$_3$), 1.34 (t, 3H, keto form, J=7.2 Hz, –OCH$_2$C*H*$_3$), 1.33 (t, 3H, enol form, J=7.2 Hz, –OCH$_2$C*H*$_3$); ^{13}C NMR ($CDCl_3$) keto form: δ 197.2 (*C*O), 164.3 (*C*O), 163.6 (*C*O), 150.4 (*C*^{Ar}), 146.6 (*C*^{Ar}), 137.2 (*C*^{Ar}), 127.6 (*C*^{Ar}), 125.9 (*C*^{Ar}), 78.6 (*C*H), 62.8 (*C*H$_2$), 27.5 (*C*H$_3$), 14.1 (*C*H$_3$); HRMS (ESI) for $C_{12}H_{14}NO_5$ $[M+H]^+$: m/z calcd: 252.0866; measured: 252.0866. Compound **10d**: (80% yield); IR: ν_{max}/cm^{-1} 2961, 1725 (C=O), 1308, 1290, 1245, 1192, 1130, 1092, 749, 702; ^{1}H NMR ($CDCl_3$): δ 8.82 (ddd, 1H, J=1.0, 1.7 and 4.7 Hz, Py–*H*), 8.23 (ddd, 1H, J=1.0, 1.2 and 7.9 Hz, Py–*H*), 7.89 (ddd, 1H, J=1.7, 7.7 and 7.9 Hz, Py–*H*), 7.54 (ddd, 1H, J=1.2, 4.7 and 7.7 Hz, Py–*H*), 5.79 (s, 1H, –C*H*OCO–), 4.33 (q, 2H, J=7.2 Hz, –OC*H*$_2$CH$_3$), 2.67 and 2.66 (2d, 2H, J=6.7 Hz, –C*H*$_2$Pr-*i*), 2.26 (nonet, J=6.7 Hz, 1H, –CH$_2$C*H*Me$_2$), 1.33 (t, 3H, J=7.2 Hz, –OCH$_2$C*H*$_3$), 0.98 and 0.96 (2d, 6H, J=6.7 Hz, –CH*Me*$_2$); ^{13}C NMR ($CDCl_3$) keto form: δ 199.0 (*C*O), 164.4 (*C*O), 163.6 (*C*O), 150.4 (*C*^{Ar}), 146.7 (*C*^{Ar}), 137.2 (*C*^{Ar}), 127.6 (*C*^{Ar}), 125.9 (*C*^{Ar}), 78.6 (*C*H), 62.7 (*C*H$_2$), 48.7 (*C*H$_2$), 24.2 (*C*H), 22.5 (*C*H$_3$), 22.4 (*C*H$_3$), 14.1 (*C*H$_3$); HRMS (ESI) for $C_{15}H_{20}NO_5$ $[M+H]^+$: m/z calcd: 294.1336; measured: 294.1332.

4.6. Synthesis of triazines 3

4.6.1. Ethyl 5-phenyl-3-(2-pyridyl)-1,2,4-triazine-6-carboxylate ***3a***

Method A. To a stirred solution of amidrazone **1** (R^1=2-pyridyl) (0.6 g. 4.25 mmol) in ethanol (20 mL) was added compound **9a** (0.5 g, 1.7 mmol) in one portion. The solution was then stirred under reflux for 2 h, allowed to cool to room temperature and poured into water (20 mL). The mixture was extracted several times with CH_2Cl_2 and the combined organic extracts were washed with water, dried ($MgSO_4$) and evaporated giving compound **3a** as an orange oil (0.52 g, 97%); IR: ν_{max}/cm^{-1} 1735 (C=O), 1489, 1281, 1173 and 697; ^{1}H NMR: ($CDCl_3$) δ 8.95 (d, 1H, J=5 Hz, Py–*H*), 8.72 (d, 1H, J=8 Hz, Py–*H*), 7.95 (dt, 1H, J=8 and 2 Hz, Py–*H*), 7.87 (dd, 2H, J=8 and 2 Hz,

Ph–*H*), 7.57–7.53 (m, 4H, Ph–*H* and Py–*H*), 4.42 (q, 2H, *J*=8 Hz, –OC*H*$_2$CH$_3$), 1.30 (t, 3H, *J*=7 Hz, –OCH$_2$C*H*$_3$); ^{13}C NMR: (CDCl$_3$) δ 165.2 (*C*O), 162.5 (*C*), 156.8 (*C*), 152.2 (*C*), 150.7 (*C*H), 150.4 (*C*), 137.3 (*C*H), 134.3 (*C*), 131.8 (*C*H), 129.1 (*C*H), 129.0 (*C*H), 126.1 (*C*H), 124.9 (*C*H), 63.0 (*C*H$_2$), 13.9 (*C*H$_3$); HRMS (EI): *m*/*z* calcd for $C_{17}H_{15}N_4O_2$ [M+H]$^+$: 307.1190, measured: 307.1188.

Method B. A solution of compound **9a** (0.5 g, 1.7 mmol) in saturated ethanolic HCl (5 mL) was stirred at room temperature for 16 h. The solvent was evaporated giving compound **2a** as a yellow oil (0.41 g). A portion of this oil (0.25 g, 0.9 mmol) was added in one portion to a stirred solution of amidrazone **1** (R^1=2-pyridyl) (0.12 g, 0.9 mmol) in ethanol (20 mL). The solution was then stirred under reflux for 2 h, allowed to cool to room temperature and poured into water (20 mL), The mixture was extracted several times with CH_2Cl_2 and the combined organic extracts were washed with water, dried ($MgSO_4$) and evaporated giving compound **3a** as an orange oil (0.26 g, 95%), identical with an authentic sample.

Method C. To a stirred solution of compound **9a** (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 h at room temperature, amidrazone **1** (R^1=2-pyridyl) (0.24 g, 1.7 mmol) was added in one portion. The solution was then stirred under reflux for 2 h, allowed to cool to room temperature and poured into water (20 mL). The mixture was extracted several times with CH_2Cl_2, and the combined organic extracts were washed with water, dried ($MgSO_4$) and evaporated. The crude mixture was purified by column chromatography over silica gel [eluent: ethyl acetate/petroleum ether bp 60–80 °C (6:4)] giving compound **3a** (0.35 g, 64%), identical with an authentic sample.

Method D. A mixture of compound **10a** (1.00 g, 3.32 mmol), Cu(OAc)$_2$ (1.32 g, 6.63 mmol), methanol (20 mL) and CH_2Cl_2 (50 mL) was stirred at room temperature for 1 day. The reaction was diluted with hexane (20 mL) and the organic fraction was washed with Na$_2$EDTA (0.1 M aqueous solution) until the aqueous phase remained colourless. The organic phase was dried ($MgSO_4$) and evaporated. The resulting oil was taken up in ethanol (50 mL) and amidrazone **1** (R^1=2-pyridyl) (361 mg, 2.65 mmol) was added. The solution was stirred under reflux for 1 day, allowed to cool to room temperature, poured into water and extracted with CH_2Cl_2. The combined organic layers were washed with water, dried ($MgSO_4$) and evaporated. The crude mixture was purified by column chromatography over silica gel [ethyl acetate/diethyl ether (1:1)] giving compound **3a** (513 mg, 64%) identical with an authentic sample.

4.6.2. *Ethyl 5-methyl-3-(2-pyridyl)-1,2,4-triazine-6-carboxylate* ***3b***

Using the general procedure (method A), the crude product was purified by column chromatography (ethyl acetate; R_f=0.15) yielding triazine **3b** (786 mg; 36%) as an orange wax, which turned brown on standing; IR: ν_{max}/cm^{-1} 1725 (C=O), 1517, 1250, 1141; ^{1}H NMR: (CDCl$_3$) δ 8.94 (ddd, 1H, *J*=1.0, 1.7 and 4.7 Hz, Py–*H*), 8.77 (ddd, 1H, *J*=1.0, 1.2 and 7.9 Hz, Py–*H*), 7.96 (ddd, 1H, *J*=1.7, 7.7 and 7.9 Hz, Py–*H*), 7.52 (ddd, 1H, *J*=1.2, 4.7 and 7.7 Hz, Py–*H*), 4.58 (q, 2H, *J*=7.2 Hz, –OC*H*$_2$CH$_3$), 2.98 (s, 3H, Ar–C*H*$_3$), 1.51 (t, 3H, *J*=7.2 Hz, –OCH$_2$C*H*$_3$); ^{13}C NMR: (CDCl$_3$) δ 164.0 (*C*O), 162.5 (*C*), 161.2 (*C*), 151.9 (*C*), 150.8 (*C*H), 136.8 (*C*H), 125.8 (*C*H), 125.0 (*C*H), 124.1 (*C*), 62.9 (*C*H$_2$), 23.3 (*C*H$_3$), 14.2 (*C*H$_3$); HRMS (EI): *m*/*z* calcd for $C_{12}H_{13}N_4O_2$ [M+H]$^+$: 245.1033, measured: 245.1030.

4.6.3. *Ethyl 5-propyl-3-(2-pyridyl)-1,2,4-triazine-6-carboxylate* ***3c***

Using the general procedures, triazine **3c** was prepared by methods A–D in the yields given in Table 1. Compound **3c** was produced as an orange solid, mp 68–70 °C; IR: ν_{max}/cm^{-1} 1721 (C=O), 1506, 1247 and 1138; ^{1}H NMR: (CDCl$_3$) δ 8.93 (d, 1H, *J*=5 Hz, Py–*H*), 8.72 (d, 1H, *J*=8 Hz, Py–*H*), 7.94 (dt, 1H, *J*=8 and 2 Hz, Py–*H*), 7.50 (m, 1H, Py–*H*), 4.55 (q, 2H, *J*=8 Hz, –OC*H*$_2$CH$_3$), 3.24–3.17 (m, 2H, propyl–C*H*$_2$–), 1.94–1.80 (m, 2H, propyl–C*H*$_2$–), 1.49 (t, 3H, *J*=7 Hz, propyl–C*H*$_3$), 1.04 (t, 3H, *J*=7 Hz, –OCH$_2$C*H*$_3$); ^{13}C NMR: (CDCl$_3$) δ 164.2 (*C*O), 163.8 (*C*), 162.7 (*C*), 152.2 (*C*), 150.8 (*C*H), 149.9 (*C*), 137.3 (*C*H), 126.1 (*C*H), 125.0 (*C*H), 62.9 (*C*H$_2$), 37.2 (*C*H$_2$), 22.5 (*C*H$_2$), 14.2 (*C*H$_3$), 14.1 (*C*H$_3$); HRMS (EI): *m*/*z* calcd for $C_{14}H_{17}N_4O_2$ [M+H]$^+$: 273.1346, measured: 273.1345. Anal. Calcd for $C_{14}H_{16}N_4O_2$: N 20.57, C 61.75, H 5.92. Found: N 20.38, C 61.39, H 6.05.

4.6.4. *Ethyl 5-isobutyl-3-(2-pyridyl)-1,2,4-triazine-6-carboxylate* ***3d***

Using the general procedures (methods C and D), triazine **3d** was prepared in the yields shown in Table 1. Triazine **3d** was obtained as orange crystals, mp 80–83 °C after column chromatography over silica gel [eluent: ethyl acetate/petroleum ether bp 60–80 °C (2:1)]; IR: ν_{max}/cm^{-1} 2955, 2928, 2868, 1723 (C=O), 1505, 1248, 1137, 1051, 785, 744; ^{1}H NMR (CDCl$_3$): δ 8.94 (ddd, 1H, *J*=1.0, 1.7 and 4.7 Hz, Py–*H*), 8.72 (ddd, 1H, *J*=1.0, 1.2 and 7.9 Hz, Py–*H*), 7.95 (ddd, 1H, *J*=1.7, 7.7 and 7.9 Hz, Py–*H*), 7.51 (ddd, 1H, *J*=1.2, 4.7 and 7.7 Hz, Py–*H*), 4.57 (q, 2H, *J*=7.2 Hz, –OC*H*$_2$CH$_3$), 3.15 (d, 2H, *J*=7.2 Hz, –C*H*$_2$Pr-*i*), 1.50 (t, 3H, *J*=7.2 Hz, –OCH$_2$C*H*$_3$), 2.36–2.21 (m, 1H, –CH$_2$C*H*Me$_2$), 0.99 (d, 6H, *J*=6.7 Hz, –CH*Me*$_2$); ^{13}C NMR (CDCl$_3$): δ 164.3 (*C*O), 163.1 (*C*^{Ar}), 162.5 (*C*^{Ar}), 152.3 (*C*^{Ar}), 150.4 (*C*^{Ar}), 150.8 (*C*^{Ar}), 137.3 (*C*^{Ar}), 126.0 (*C*^{Ar}), 125.0 (*C*^{Ar}), 62.9 (*C*H$_2$), 43.3 (*C*H$_2$), 29.1 (*C*H), 22.5 (*C*H$_3$), 14.3 (*C*H$_3$); HRMS (ESI) for $C_{15}H_{19}N_4O_2$ [M+H]$^+$: *m*/*z* calcd: 287.1503; measured: 287.1504.

4.6.5. *Ethyl 3,5-diphenyl-1,2,4-triazine-6-carboxylate* ***3e***[27]

Method A. To a stirred, ice-cold solution of benzamidine hydrochloride hydrate (0.8 g, 5.1 mmol) in ethanol (10 mL) was added drop-wise 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. Compound **9a** (0.57 g, 2 mmol) and triethylamine (0.52 mL, 3.8 mmol) were slowly added. The solution was stirred under reflux for 20 h, cooled to room temperature and poured into water (10 mL). The mixture was extracted several times with CH_2Cl_2 and the combined organic extracts were washed with water, dried ($MgSO_4$) and evaporated giving compound **3e** as a red oil (0.5 g, 82%); IR: ν_{max}/cm^{-1} 1734 (C=O), 1275, 1151 and 688; ^{1}H NMR: (CDCl$_3$) δ 8.67 (dd, 2H, *J*=8 and 2 Hz, Ph–*H*), 8.12–8.04 (m, 3H, Ph–*H*), 7.87 (dd, 2H, *J*=8 Hz, Ph–*H*), 7.51–7.59 (m, 3H, Ph–*H*), 4.44 (q, 2H, *J*=7 Hz, –OC*H*$_2$CH$_3$), 1.30 (t, 3H, *J*=7 Hz, –OCH$_2$C*H*$_3$); HRMS (EI): *m*/*z* calcd for $C_{18}H_{16}N_3O_2$ [M+H]$^+$: 306.1237, measured: 306.1238.

Method B. To a stirred, ice-cold solution of benzamidine hydrochloride hydrate (0.2 g, 1.27 mmol) in ethanol (5 mL) was added drop-wise 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 compound **2a** (0.2 g, 0.89 mmol) (prepared from compound **9a** and saturated ethanolic HCl as described above in Section 4.6.1, Method B) and triethylamine (0.12 mL, 0.9 mmol) were slowly added. The resulting solution was stirred under reflux for 20 h, cooled to room temperature and poured into water (10 mL). The mixture was extracted several times with CH_2Cl_2 and the combined organic extracts were washed with water, dried ($MgSO_4$) and evaporated yielding compound **3e** (80%), identical with an authentic sample.

4.6.6. *Ethyl 3-phenyl-5-propyl-1,2,4-triazine-6-carboxylate* ***3f***

Using the general procedures (methods A and B), triazine **3f** was prepared in the yields shown in Table 1. Recrystallisation from ethanol gave the pure compound **3f** (0.50 g, 93%) as a yellow solid, mp 58–60 °C; IR: ν_{max}/cm^{-1} 1718 (C=O), 1506, 1259 and 1115; ^{1}H NMR: (CDCl$_3$) δ 8.62 (dd, 2H, *J*=8 and 2 Hz, Ph–*H*), 7.51–7.59 (m, 3H, Ph–*H*), 4.55 (q, 2H, *J*=7 Hz, –OC*H*$_2$CH$_3$), 3.17–3.11 (m, 2H, propyl–C*H*$_2$–), 1.90 (sextet, 2H, *J*=8 Hz, propyl–C*H*$_2$–), 1.49 (t, 3H, *J*=7 Hz, –OCH$_2$C*H*$_3$), 1.07 (t, 3H, *J*=7 Hz, propyl–C*H*$_3$); ^{13}C NMR: (CDCl$_3$)

δ 164.3 (*C*O), 163.3 (*C*), 163.1 (*C*), 148.7 (*C*), 134.3 (*C*), 132.4 (*C*H), 129.0 (2×*C*H), 62.7 (*C*H$_2$), 36.9 (*C*H$_2$), 21.3 (*C*H$_2$), 14.3 (*C*H$_3$), 14.0 (*C*H$_3$); HRMS (EI): *m*/*z* calcd for $C_{15}H_{18}N_3O_2$ [M+H]$^+$: 272.1394, measured: 272.1397. Anal. Calcd for $C_{15}H_{17}N_3O_2$: N 15.49, C 66.40, H 6.32. Found: N 15.81, C 66.43, H 6.22.

4.6.7. Ethyl 3-methyl-5-phenyl-1,2,4-triazine-6-carboxylate **3g**[28]

Method A. To a stirred ice-cold solution of acetamidine hydrochloride hydrate (0.48 g, 5 mmol) in ethanol (10 mL) was added drop-wise hydrazine hydrate (0.25 mL, 5 mmol). After stirring at 0 °C for 15 min, the mixture was allowed to warm to room temperature, stirred for another 15 min, and compound **9a** (0.57 g, 2 mmol) and triethylamine (0.52 mL, 3.8 mmol) were slowly added. The solution was stirred under reflux for 20 h, allowed to cool to room temperature and poured into water (10 mL). The mixture was extracted with CH_2Cl_2 and the combined organic fractions were washed with water, dried ($MgSO_4$) and evaporated giving compound **3g** (0.26 g, 54%) as an orange oil; IR: ν_{max}/cm^{-1} 1736 (C=O), 1506, 1259, 1137 and 693; ^{1}H NMR: ($CDCl_3$) δ 7.76 (dd, 2H, *J*=8 and 2 Hz, Ph–*H*), 7.58–7.51 (m, 3H, Ph–*H*), 4.40 (q, 2H, *J*=7 Hz, –OC*H*$_2$CH$_3$), 2.99 (s, 3H, –C*H*$_3$), 1.27 (t, 3H, *J*=7 Hz, –OCH$_2$C*H*$_3$); ^{13}C NMR: ($CDCl_3$) δ 167.4 (*C*O), 165.3 (*C*), 156.1 (*C*), 149.3 (*C*), 134.4 (*C*), 131.7 (*C*H), 129.0 (*C*H),128.9 (*C*H), 62.9 (*C*H$_2$), 23.9 (*C*H$_3$), 13.9 (*C*H$_3$); HRMS (EI): *m*/*z* calcd for $C_{13}H_{14}N_3O_2$ [M+H]$^+$: 244.1081, measured: 244.1082.

4.6.8. Ethyl 3-methyl-5-propyl-1,2,4-triazine-6-carboxylate **3h**

Using the general procedures (methods A and B), triazine **3h** was prepared in the yields shown in Table 1. Chromatography over silica gel [eluent: petroleum ether bp 60–80 °C/ethyl acetate (6:4)] gave the desired product **3h** as a yellow oil; IR: ν_{max}/cm^{-1} 1728 (C=O), 1515, 1260 and 1094; ^{1}H NMR: ($CDCl_3$) δ 4.52 (q, 2H, *J*=7 Hz, –OC*H*$_2$CH$_3$), 3.04–2.98 (m, 2H, propyl–C*H*$_2$–), 2.90 (s, 3H, –C*H*$_3$), 1.78 (sextet, 2H, *J*=8 Hz, propyl–C*H*$_2$–), 1.46 (t, 3H, *J*=7 Hz, –OCH$_2$C*H*$_3$), 1.02 (t, 3H, *J*=7 Hz, propyl–C*H*$_3$); ^{13}C NMR: ($CDCl_3$) δ 167.7 (*C*O), 164.3 (*C*), 162.7 (*C*), 148.8 (*C*), 62.7 (*C*H$_2$), 36.8 (*C*H$_2$), 23.9 (*C*H$_2$), 22.7 (*C*H$_3$), 14.2 (*C*H$_3$), 14.0 (*C*H$_3$); HRMS (EI): *m*/*z* calcd for $C_{10}H_{16}N_3O_2$ [M+H]$^+$: 210.1237, measured: 210.1236.

4.6.9. Ethyl 3-methylthio-5-phenyl-1,2,4-triazine-3-carboxylate **3i**

Method A. To a stirred solution of compound **9a** (0.5 g, 1.75 mmol) and sodium bicarbonate (0.41 g, 4.9 mmol) in EtOH (20 mL) was added amidrazone **1** (R^1=SMe·HCl) (4.4 mmol, 1.02 g). The solution was then stirred under reflux for 2 h, allowed to cool to room temperature, poured into water (20 mL) and extracted with CH_2Cl_2. The combined organic extracts were washed with water, dried ($MgSO_4$) and evaporated yielding compound **3i** (0.37 g, 80%) as a red solid, mp 62–64 °C; IR: ν_{max}/cm^{-1} 1727 (C=O), 1483, 1224 and 1210; ^{1}H NMR: ($CDCl_3$) δ 7.74 (d, 2H, *J*=8 Hz, Ph–*H*), 7.50–7.53 (m, 3H, Ph–*H*), 4.40 (q, 2H, *J*=7 Hz, –OC*H*$_2$CH$_3$), 2.75 (s, 3H, –SC*H*$_3$), 1.27 (t, 3H, *J*=7 Hz, –OCH$_2$C*H*$_3$); ^{13}C NMR: ($CDCl_3$) δ 174.4 (*C*O), 165.1 (*C*), 155.8 (*C*), 146.9 (*C*), 134.2 (*C*), 131.8 (*C*H), 129.0 (*C*H), 128.9 (*C*H), 62.7 (*C*H$_2$), 14.0 (*C*H$_3$), 13.9 (*C*H$_3$); HRMS (EI): *m*/*z* calcd for $C_{13}H_{14}N_3O_2S$ [M+H]$^+$: 276.0801, measured: 276.0800.

Method B. To a solution of amidrazone **1** (R^1=SMe·HCl) (0.2 g, 0.9 mmol) and sodium bicarbonate (0.09 g, 1.17 mmol) in ethanol (15 mL) was added in one portion compound **2a** (0.25 g, 1.1 mmol) (prepared from compound **9a** and saturated ethanolic HCl as described in Section 4.6.1, method B). The solution was then stirred under reflux for 2 h, allowed to cool to room temperature, poured into water (20 mL) and extracted with CH_2Cl_2. The combined organic extracts were washed with water, dried ($MgSO_4$) and evaporated giving compound **3i** (0.22 g, 90%), identical with an authentic sample.

Method C. To a stirred solution of compound **9a** (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 h at room temperature, amidrazone **1** (R^1=SMe·HCl) (0.41 g, 1.7 mmol) and sodium bicarbonate (0.18 g, 2 mmol) were added in one portion. The solution was then stirred under reflux for 2 h, allowed to cool to room temperature, poured into water (20 mL) and extracted with CH_2Cl_2. The combined organic extracts were washed with water, dried ($MgSO_4$) and evaporated affording compound **3i** (0.28 g, 58%), identical with an authentic sample.

4.6.10. Ethyl 3-methylthio-5-propyl-1,2,4-triazine-6-carboxylate **3j**

Using similar procedures to those described above for the preparation of compound **3i**, compound **3j** was prepared by methods A–C in the yields reported in Table 1. Compound **3j** was obtained as an orange oil; IR: ν_{max}/cm^{-1} 1723 (C=O), 1496, 1210 and 1182; ^{1}H NMR: ($CDCl_3$) δ 4.50 (q, 2H, *J*=7 Hz, –OC*H*$_2$CH$_3$), 3.06–2.98 (m, 2H, propyl–C*H*$_2$–), 2.70 (s, 3H, –SC*H*$_3$), 1.79 (sextet, 2H, *J*=7 Hz, propyl–C*H*$_2$–), 1.46 (t, 3H, *J*=7 Hz, propyl–C*H*$_3$), 1.02 (t, 3H, *J*=7 Hz, –OCH$_2$C*H*$_3$); ^{13}C NMR: ($CDCl_3$) δ 174.8 (*C*O), 164.1 (*C*), 162.7 (*C*), 146.2 (*C*), 62.5 (*C*H$_2$), 36.8 (*C*H$_2$), 21.3 (*C*H$_2$), 14.2 (*C*H$_3$), 14.0 (*C*H$_3$), 13.9 (*C*H$_3$); HRMS (EI): *m*/*z* calcd for $C_{10}H_{16}N_3O_2S$ [M+H]$^+$: 242.0958, measured: 242.0959.

4.7. Synthesis of pyridines 4a–d

The methods A–D that were described for the preparation of the triazines **3** in Section 4.6 above were followed except that 2,5-norbornadiene **5** (5–10 equiv) was added to the reaction mixture and the mixture was heated at reflux overnight. The yields of products are given in Table 2.

4.7.1. Ethyl 6-phenyl[2,2′]bipyridyl-5-carboxylate **4a**

Chromatography over silica gel [eluent: ethyl acetate/petroleum ether bp 60–80 °C (6:4)] gave compound **4a** as an orange oil, identical with an authentic sample.[12c]

4.7.2. Ethyl 6-methyl[2,2′]bipyridyl-5-carboxylate **4b**

Column chromatography over silica gel (diethyl ether/hexanes=4:1; R_f=0.41) yielded compound **4b** as white needles, mp 77–79 °C; lit.[29]: 80 °C (from ethanol); ^{1}H NMR ($CDCl_3$): δ 8.71 (ddd, 1H, *J*=1.0, 1.7 and 4.7 Hz, Py–*H*), 8.51 (ddd, 1H, *J*=1.0, 1.2 and 7.9 Hz, Py–*H*), 8.34 (d, 1H, *J*=8.2 Hz, Py–3*H* or Py–4*H*), 8.29 (d, 1H, *J*=8.2 Hz, Py–3*H* or Py–4*H*), 7.84 (ddd, 1H, *J*=1.7, 7.7 and 7.9 Hz, Py–*H*), 7.35 (ddd, 1H, *J*=1.2, 4.7 and 7.7 Hz, Py–*H*), 4.41 (q, 2H, *J*=7.2 Hz, –OC*H*$_2$CH$_3$), 2.93 (s, 3H, –C*H*$_3$), 1.43 (t, 3H, *J*=7.2 Hz, –OCH$_2$C*H*$_3$).

4.7.3. Ethyl 6-propyl[2,2′]bipyridyl-5-carboxylate **4c**

Chromatography over silica gel [eluent: ethyl acetate/petroleum ether bp 60–80 °C (6:4)] gave the desired product **4c** as an orange oil, identical with an authentic sample.[12c]

4.7.4. Ethyl 6-isobutyl[2,2′]bipyridyl-5-carboxylate **4d** and ethyl 5-isobutyl[2,2′]bipyridyl-6-carboxylate **12**

Compound **4d** was obtained as a brown oil after chromatography over silica gel [eluent: diethyl ether/hexane (1:2)]. In methods A and C an inseparable mixture of **4d** and **12** was produced in the ratios given in Table 2. Compound **4d**: IR: ν_{max}/cm^{-1} 3057, 2957, 2930, 2870, 1719 (C=O), 1583, 1555, 1254, 1093, 1052, 770, 744; ^{1}H NMR ($CDCl_3$): δ 8.70 (ddd, 1H, *J*=1.0, 1.7 and 4.7 Hz, Py–*H*), 8.52 (ddd, 1H, *J*=1.0, 1.2 and 7.9 Hz, Py–*H*), 8.30 (d, 1H, *J*=8.2 Hz, Py–3*H* or Py–4*H*), 8.27 (d, 1H, *J*=8.2 Hz, Py–3*H* or Py–4*H*), 7.84 (ddd, 1H, *J*=1.7, 7.7 and 7.9 Hz, Py–*H*), 7.34 (ddd, 1H, *J*=1.2, 4.7 and 7.7 Hz, Py–*H*), 4.40 (q, 2H, *J*=7.2 Hz, –OC*H*$_2$CH$_3$), 3.16 (d, 2H, *J*=6.7 Hz, –C*H*$_2$Pr-*i*), 2.26 (nonet, *J*=6.7 Hz, 1H, –CH$_2$C*H*Me$_2$), 1.43 (t, 3H, *J*=7.2 Hz, –OCH$_2$C*H*$_3$), 0.99 (d, 6H, *J*=6.7 Hz, –CH*Me*$_2$); ^{13}C NMR ($CDCl_3$): δ 167.1 (*C*O), 162.1 (*C*^{Ar}), 157.3 (*C*^{Ar}), 155.7 (*C*^{Ar}), 149.3 (*C*^{Ar}), 139.4 (*C*^{Ar}), 137.1 (*C*^{Ar}), 125.8 (*C*^{Ar}), 124.3 (*C*^{Ar}), 121.9 (*C*^{Ar}), 117.7 (*C*^{Ar}), 61.3

(CH_2CH_3), 45.3 (CH_2Pr-*i*), 29.1 ($CHMe_2$), 22.7 (CH_3), 14.3 (CH_2CH_3); HRMS (ESI): *m*/*z* calcd for $C_{17}H_{21}N_2O_2$ $[M+H]^+$: 285.1598, measured: 285.1598. Compound **12**: ^{1}H NMR ($CDCl_3$): δ 8.70 (ddd, 1H, *J*=1.0, 1.7 and 4.7 Hz, Py–*H*), 8.58 (ddd, 1H, *J*=1.0, 1.2 and 7.9 Hz, Py–*H*), 8.42 (d, 1H, *J*=8.2 Hz, Py–3*H* or Py–4*H*), 8.33 (d, 1H, *J*=8.2 Hz, Py–3*H* or Py–4*H*), 7.85 (ddd, 1H, *J*=1.7, 7.7 and 7.9 Hz, Py–*H*), 7.36 (ddd, 1H, *J*=1.2, 4.7 and 7.7 Hz, Py–*H*), 4.43 (q, 2H, *J*=7.2 Hz, –OCH_2CH_3), 2.54 (d, 2H, *J*=6.9 Hz, –CH_2Pr-*i*), 2.30–2.15 (m, 1H, –CH_2CHMe_2), 1.31 (t, 3H, *J*=7.2 Hz, –OCH_2CH_3), 0.89 (d, 6H, *J*=6.7 Hz, –$CHMe_2$).

4.8. Synthesis of pyridines 4e–m and 14 and 18

4.8.1. Ethyl 2,6-diphenylpyridine-3-carboxylate **4e**[30]

A solution of compound **3e** (0.43 g, 1.4 mmol) and 2,5-norbornadiene **5** (1.5 mL, 14 mmol) in xylene (15 mL) was heated at reflux overnight. The solvent was evaporated and the residue was purified by column chromatography over silica gel [eluent: ethyl acetate/petroleum ether bp 60–80 °C (2:8)] giving compound **4e** (0.19 g, 44%) as a brown oil; IR: ν_{max}/cm^{-1} 1714 (C=O), 1573, 1289, 1140, 758, 691; ^{1}H NMR: ($CDCl_3$) δ 8.18 (d, 1H, *J*=8 Hz, Py–*H*), 8.12 (dd, 2H, *J*=8 and 2 Hz, Ph–*H*), 7.78 (d, 1H, *J*=8 Hz, Py–*H*), 7.65 (dd, 2H, *J*=8 and 2 Hz, Ph–*H*), 7.48–7.42 (m, 6H, Ph–*H*), 4.18 (q, 2H, *J*=7 Hz, –OCH_2CH_3), 1.07 (t, 3H, *J*=7 Hz, –OCH_2CH_3); HRMS (EI): *m*/*z* calcd for $C_{20}H_{18}NO_2$ $[M+H]^+$: 303.1254, measured: 303.1258.

4.8.2. Ethyl 6-phenyl-2-propylpyridine-3-carboxylate **4f**

Compound **4f** was synthesised from triazine **3f** (0.1 g, 0.37 mmol) in xylene following the procedure described above for the preparation of compound **4e** from compound **3e**. Chromatography over silica gel [eluent: ethyl acetate/petroleum ether bp 60–80 °C (2:8)] gave the desired product **4f** (0.05 g, 31%) as a yellow oil. IR ν_{max}/cm^{-1} 1719 (C=O), 1582, 1261, 1088; ^{1}H NMR: ($CDCl_3$) δ 8.22 (d, 1H, *J*=8 Hz, Py–*H*), 8.05 (dd, 2H, *J*=8 and 2 Hz, Ph–*H*), 7.61 (d, 1H, *J*=8 Hz, Py–*H*), 7.46 (t, 2H, *J*=7 Hz, Ph–*H*), 7.15 (t, 1H, *J*=7 Hz, Ph–*H*), 4.39 (q, 2H, *J*=7 Hz, –OCH_2CH_3), 3.25–3.18 (m, 2H, propyl–CH_2–), 1.88–1.80 (m, 2H, propyl–CH_2–), 1.42 (t, 3H, *J*=7 Hz, –OCH_2CH_3), 1.04 (t, 3H, *J*=7 Hz, propyl–CH_3); ^{13}C NMR: ($CDCl_3$) δ 166.9 (*C*O), 163.4 (*C*), 158.9 (*C*), 139.4 (*C*H), 138.7 (*C*), 129.6 (*C*H), 128.9 (*C*H), 127.4 (*C*H), 123.8 (*C*), 117.2 (*C*H), 61.3 (CH_2), 39.2 (CH_2), 23.1 (CH_2), 14.4 (CH_3), 14.3 (CH_3); HRMS (EI): *m*/*z* calcd for $C_{17}H_{20}NO_2$ $[M+H]^+$: 270.1489, measured: 270.1490.

4.8.3. Ethyl 2-methyl-6-phenylpyridine-3-carboxylate **4g**[1e]

Compound **4g** was synthesised from compound **3g** (0.18 g, 0.74 mmol) following the procedure described above for the preparation of compound **4e**. Chromatography over silica gel [eluent: ethyl acetate/petroleum ether bp 60–80 °C (2:8)] gave the desired product **4g** (0.17 g, 95%) as a brown oil; IR: ν_{max}/cm^{-1} 1715 (C=O), 1278, 1136, 765, 696; ^{1}H NMR: ($CDCl_3$) δ 8.02 (d, 1H, *J*=8 Hz, Py–*H*), 7.50 (dd, 2H, *J*=8 and 2 Hz, Ph–*H*), 7.45–7.38 (m, 3H, Ph–*H*), 7.19 (d, 1H, *J*=8 Hz, Py–*H*), 4.12 (q, 2H, *J*=7 Hz, –OCH_2CH_3), 2.65 (s, 3H, –CH_3), 1.02 (t, 3H, *J*=7 Hz, –OCH_2CH_3); HRMS (EI): *m*/*z* calcd for $C_{15}H_{16}NO_2$ $[M+H]^+$: 242.1176, measured: 242.1173.

4.8.4. Ethyl 6-methyl-2-propylpyridine-3-carboxylate **4h**

Compound **4h** was synthesised from compound **3h** (0.15 g, 0.72 mmol) following the procedure described above for the preparation of compound **4e**. Chromatography over silica gel [eluent: ethyl acetate/petroleum ether bp 60–80 °C (2:8)] gave the desired product **4h** (0.1 g, 67%) as a brown oil; IR: ν_{max}/cm^{-1} 1721 (C=O), 1250, 1095; ^{1}H NMR: ($CDCl_3$) δ 8.06 (d, 1H, *J*=8 Hz, Py–*H*), 7.04 (d, 1H, *J*=8 Hz, Py–*H*), 4.36 (q, 2H, *J*=7 Hz, –OCH_2CH_3–), 3.10–3.00 (m, 2H, propyl–CH_2–), 2.60 (s, 3H, –CH_3), 1.72–1.63 (m, 2H, propyl–CH_2–), 1.39 (t, 3H, *J*=7 Hz, –OCH_2CH_3), 1.01 (t, 3H, *J*=7 Hz, propyl–CH_3); HRMS (EI): *m*/*z* calcd for $C_{12}H_{18}NO_2$ $(M+H)^+$: 208.1332, measured: 208.1334.

4.8.5. Ethyl 6-methylthio-2-phenylpyridine-3-carboxylate **4i**

Method A. A stirred solution of triazine **3i** (2.00 g, 7.26 mmol) and 2,5-norbornadiene **5** (27.4 mL, 254 mmol, 35.0 equiv) in 1,2-dichlorobenzene (100 mL) was heated to 140 °C under a nitrogen atmosphere for 1 day. After cooling to room temperature, the solvent was evaporated and the residue purified by column chromatography over silica gel [eluent: ethyl acetate/hexanes (1:4); R_f=0.32] giving compound **4i** (1.75 g, 88%) as an orange liquid; IR: ν_{max}/cm^{-1} 2982, 2928, 1710 (C=O), 1567, 1427, 1385, 1281, 1265, 1152, 1130, 1046, 764, 697; ^{1}H NMR ($CDCl_3$): δ 7.92 (d, 1H, *J*=8.2 Hz, Py–4*H*), 7.58–7.40 (m, 5H, Ph–*H*), 7.18 (d, 1H, *J*=8.2 Hz, Py–5*H*), 4.13 (q, 2H, *J*=7.2 Hz, –OCH_2CH_3), 2.61 (s, 3H, –SCH_3), 1.05 (t, 3H, *J*=7.2 Hz, –OCH_2CH_3); ^{13}C NMR ($CDCl_3$): δ 168.2 (*C*O), 162.6 (C^{Ar}), 158.9 (C^{Ar}), 140.3 (C^{Ar}), 137.7 (C^{Ar}), 128.9 (C^{Ar}), 128.7 (C^{Ar}), 128.0 (C^{Ar}), 122.3 (C^{Ar}), 119.2 (C^{Ar}), 61.3 (CH_2CH_3), 13.8 (CH_3), 13.3 (CH_3); HRMS (ESI) for $C_{15}H_{16}NO_2S$ $[M+H]^+$: *m*/*z* calcd: 274.0896; measured: 274.0894.

Method B. In neat 2,5-norbornadiene **5** (50 equiv) at reflux for 2 days compound **4i** (64%), identical with an authentic sample, was obtained together with recovered triazine **3i** (8%).

4.8.6. Ethyl 6-methylthio-2-propylpyridine-3-carboxylate **4j**

Method A. A stirred solution of triazine **3j** (100 mg, 414 μmol) and 2,5-norbornadiene **5** (0.45 mL, 4.17 mmol, 10.1 equiv) in 1,2-dichlorobenzene (5 mL) was heated to 140 °C under a nitrogen atmosphere for 1 day. After cooling to room temperature, the solvent was evaporated and the residue purified by column chromatography [eluent: ethyl acetate/hexanes (1:4); R_f=0.55] yielding compound **4j** (63 mg, 64%) as a yellow liquid; IR: ν_{max}/cm^{-1} 2962, 2931, 2872, 1718 (C=O), 1575, 1441, 1375, 1260, 1144, 1094; ^{1}H NMR ($CDCl_3$): δ 7.97 (d, 1H, *J*=8.2 Hz, Py–4*H*), 7.04 (d, 1H, *J*=8.2 Hz, Py–3*H*), 4.34 (q, 2H, *J*=7.2 Hz, –OCH_2CH_3), 3.15–3.09 (m, 2H, propyl–CH_2–), 2.59 (s, 3H, –SCH_3), 1.84–1.70 (m, 2H, propyl–CH_2–), 1.39 (t, 3H, *J*=7.2 Hz, –OCH_2CH_3), 1.00 (t, 3H, *J*=7.2 Hz, propyl–CH_3); ^{13}C NMR ($CDCl_3$): δ 166.8 (*C*O), 163.6 (C^{Ar}), 163.0 (C^{Ar}), 138.1 (C^{Ar}), 120.6 (C^{Ar}), 118.1 (C^{Ar}), 61.0 (CH_2CH_3), 39.0 (CH_2), 22.8 (CH_2), 14.4 (CH_3), 14.3 (CH_3), 13.2 (CH_3); HRMS (ESI) for $C_{12}H_{18}NO_2S$ $[M+H]^+$: *m*/*z* calcd: 240.1053; measured: 240.1052.

Method B. In neat 2,5-norbornadiene **5** (45 equiv) at reflux for 2 days compound **4j** (66%), identical with an authentic sample, was obtained together with recovered triazine **3j** (8%).

4.8.7. Ethyl 6-methanesulfoxy-2-phenylpyridine-3-carboxylate **4k**

Method A. To a stirred, ice-cold solution of triazine **3i** (0.26 g, 0.9 mmol) in CH_2Cl_2 (15 mL) was added 80% 3-chloroperbenzoic acid (0.21 g, 1.2 mmol) and the mixture was stirred 1 h at 0 °C and then 1 h at room temperature. The reaction mixture was poured into water (10 mL), the organic layer was separated and washed with a saturated solution of $NaHCO_3$ (2×15 mL), dried ($MgSO_4$) and evaporated under giving compound **3k** as a red oil (0.25 g, 91%), which was used without further purification; ^{1}H NMR: ($CDCl_3$) δ 7.88 (d, 2H, *J*=7 Hz, Ph–*H*), 7.63–7.51 (m, 3H, Ph–*H*), 4.45 (q, 2H, *J*=7 Hz, –OCH_2CH_3), 3.15 (s, 3H, –SOCH_3) and 1.27 (t, 3H, *J*=7 Hz, –OCH_2CH_3). A solution of compound **3k** (0.17 g, 0.6 mmol) and 2,5-norbornadiene **5** (0.65 mL, 6 mmol) in ethanol (15 mL) was stirred under reflux and an atmosphere of nitrogen for 12 h and then allowed to cool to room temperature. The solvent was evaporated and water (10 mL) was added to the residue. The mixture was extracted with CH_2Cl_2 and the combined organic extracts were dried ($MgSO_4$) and evaporated giving compound **4k** (0.13 g, 75%) as an orange oil after chromatography over silica gel [eluent: CH_2Cl_2/methanol (9:1)]; IR: ν_{max}/cm^{-1} 1718 (C=O), 1281, 1085, 1047, 698; ^{1}H NMR: ($CDCl_3$) δ 8.33 (d, 1H, *J*=8 Hz, Py–*H*), 8.09 (d, 1H, *J*=8 Hz,

Py–*H*), 7.57–7.44 (m, 5H, Ph–*H*), 4.20 (q, 2H, *J*=7 Hz, –OC*H*$_2$CH$_3$), 2.93 (s, 3H, –SOC*H*$_3$), 1.08 (t, 3H, *J*=7 Hz, –OCH$_2$C*H*$_3$); ^{13}C NMR (CDCl$_3$): δ 168.06 (*C*O), 167.45 (*C*^{Ar}), 158.73 (*C*^{Ar}), 139.92 (*C*^{Ar}), 138.80 (*C*^{Ar}), 129.42 (*C*^{Ar}), 128.74 (*C*^{Ar}), 128.34 (*C*^{Ar}), 117.26 (*C*^{Ar}), 62.02 (*C*H$_2$), 41.33 (*C*H$_3$), 13.73 (*C*H$_3$) (one aryl signal was not sufficiently intense to be located); HRMS (EI): *m*/*z* calcd for $C_{15}H_{16}N_3O_3S$ [M+H]$^+$: 290.0845, measured: 290.0846.

Method B. A suspension of $NaBO_3 \cdot 4H_2O$ (59 mg; 383 μmol; 1.05 equiv) in glacial acetic acid (2.5 mL) was heated to 50–60 °C and compound **4i** (100 mg; 366 μmol) was added. The mixture was stirred for 4 h, allowed to cool to room temperature and filtered. The filtrate was evaporated yielding compound **4k** (83 mg, 78%) identical with an authentic sample.

4.8.8. Ethyl 6-methanesulfoxy-2-propylpyridine-3-carboxylate *4l*

Method A. Compound **3l** (65%) was obtained as a red oil by oxidation of compound **3j** following the procedure described above for the preparation of compound **3k** from compound **3i** and was used without further purification; ^{1}H NMR: (CDCl$_3$) δ 4.54 (q, 2H, *J*=7 Hz, –OC*H*$_2$CH$_3$), 3.18–3.11 (m, 2H, –C*H*$_2$–), 3.08 (s, 3H, –SOC*H*$_3$), 1.83 (sextet, 2H, *J*=8 Hz, propyl–C*H*$_2$–), 1.46 (t, 3H, *J*=7 Hz, –OCH$_2$C*H*$_3$), 1.02 (t, 3H, *J*=7 Hz, propyl–C*H*$_3$). A solution of compound **3l** (0.63 g, 2.4 mmol) and 2,5-norbornadiene **5** (2.65 mL, 24 mmol) in ethanol (15 mL) was stirred at reflux under an atmosphere of nitrogen for 12 h and then allowed to cool to room temperature. The reaction mixture was worked-up as described above for the synthesis of compound **4k** giving compound **4l** (0.55 g, 88%) as an orange oil; IR: ν_{max}/cm^{-1} 1721 (C=O), 1262, 1095, 1065; ^{1}H NMR: (CDCl$_3$) δ 8.38 (d, 1H, *J*=8 Hz, Py–*H*), 7.93 (d, 1H, *J*=8 Hz, Py–*H*), 4.41 (q, 2H, *J*=7 Hz, –OC*H*$_2$CH$_3$), 3.15–3.07 (m, 2H, propyl–C*H*$_2$–), 2.87 (s, 3H, –SOC*H*$_3$), 1.74 (sextet, 2H, *J*=8 Hz, propyl–C*H*$_2$–), 1.42 (t, 3H, *J*=7 Hz, –OCH$_2$C*H*$_3$), 0.99 (t, 3H, *J*=7 Hz, propyl–C*H*$_3$); ^{13}C NMR (CDCl$_3$): δ 168.2 (*C*O), 166.0 (*C*^{Ar}), 163.7 (*C*^{Ar}), 140.4 (*C*^{Ar}), 126.7 (*C*^{Ar}), 116.3 (*C*^{Ar}), 61.8 (*C*H$_2$), 41.2 (*C*H$_3$), 38.5 (*C*H$_2$), 22.9 (*C*H$_2$), 14.3 (*C*H$_3$), 14.1 (*C*H$_3$); HRMS (EI): *m*/*z* calcd for $C_{12}H_{18}NO_3S$ [M+H]$^+$: 256.1002, measured: 256.1001.

Method B. Following a similar procedure to that described above in Section 4.8.7, method B for the synthesis of compound **4k**, compound **4l** (72%) was obtained, identical with an authentic sample.

4.8.9. Ethyl 6-methylsulfonyl-2-propylpyridine-3-carboxylate *4m*

A suspension of $NaBO_3 \cdot 4H_2O$ (1.61 g, 10.5 mmol, 2.50 equiv) in glacial acetic acid (50 mL) was heated to 50–60 °C and pyridine **4j** (1.00 g; 4.18 mmol) was added. The mixture was stirred for 2 h, allowed to cool to room temperature and filtered. A saturated, aqueous solution of $NaHCO_3$ (200 mL) was added to the filtrate and the mixture was extracted with dichloromethane (200 mL). The organic phase was separated and washed sequentially with a saturated aqueous solution of $NaHCO_3$ and water (200 mL each), dried ($MgSO_4$) and evaporated yielding compound **4m** (1.06 g, 93%) as a yellow oil; IR: ν_{max}/cm^{-1} 2964, 2935, 2875, 1724 (C=O), 1309, 1265, 1128, 1095, 758; ^{1}H NMR (CDCl$_3$): δ 8.37 (d, 1H, *J*=8.2 Hz, Py–4*H*), 7.96 (d, 1H, *J*=8.2 Hz, Py–5*H*), 4.43 (q, 2H, *J*=7.2 Hz, –OC*H*$_2$CH$_3$), 3.27 (s, 3H, –SOC*H*$_3$), 3.22–3.16 (m, 2H, propyl–C*H*$_2$–), 1.83–1.76 (m, 2H, propyl–C*H*$_2$–), 1.43 (t, 3H, *J*=7.2 Hz, –OCH$_2$C*H*$_3$), 1.01 (t, 3H, *J*=7.4 Hz, propyl–C*H*$_3$); ^{13}C NMR (CDCl$_3$): δ 165.5 (*C*O), 164.2 (*C*^{Ar}), 159.1 (*C*^{Ar}), 140.6 (*C*^{Ar}), 129.4 (*C*^{Ar}), 117.7 (*C*^{Ar}), 62.2 (*C*H$_2$CH$_3$), 39.6 (*C*H$_3$), 38.5 (*C*H$_2$), 22.7 (*C*H$_2$), 14.3 (*C*H$_3$), 14.1 (*C*H$_3$); HRMS (ESI) for $C_{12}H_{18}NO_4S$ [M+H]$^+$: *m*/*z* calcd: 272.0951; measured: 272.0951.

4.8.10. Ethyl 6-propyl-3-(2-(tetrahydrofuran-2-yloxy)ethyl)-[2,2′]bipyridine-5-carboxylate *16*

Under a nitrogen atmosphere, a solution of triazine **3c** (256 mg, 940 μmol) in 2,3-dihydrofuran **13** (2.11 g, 30.1 mmol, 32.0 equiv) and ethanol (20 mL) was stirred under reflux for 20 h. After evaporation of the solvent, the residue was purified by column chromatography over silica gel [eluent: diethyl ether/hexanes (9:1); R_f=0.33] yielding compound **16** (233 mg, 64%) as a brown oil; IR: ν_{max}/cm^{-1} 2960, 2873, 1718 (C=O), 1252, 1184, 1091, 1034; ^{1}H NMR (CDCl$_3$): δ 8.66 (ddd, 1H, *J*=1.0, 1.7 and 4.7 Hz, Py–*H*), 8.17 (s, 1H, Py–4*H*), 7.88 (ddd, 1H, *J*=1.0, 1.5 and 7.9 Hz, Py–*H*), 7.82 (ddd, 1H, *J*=1.7, 7.7 and 7.9 Hz, Py–*H*), 7.31 (ddd, 1H, *J*=1.5, 4.7 and 7.7 Hz, Py–*H*), 5.10–5.03 (m, 1H, >C*H*–), 4.40 (q, 2H, *J*=7.2 Hz, –OC*H*$_2$CH$_3$), 3.85 and 3.65 (dt, 2H, *J*=6.7 and 9.0 Hz, –C*H*$_2$CH$_2$–), 3.82–3.74 (m, 2H, –OC*H*$_2$–), 3.19 (t, 2H, *J*=6.7 Hz, –C*H*$_2$CH$_2$–), 3.18–3.13 (m, 2H, propyl–C*H*$_2$–), 2.04–1.70 (m, 6H, aliphatic–*H*), 1.43 (t, 3H, *J*=7.2 Hz, –OCH$_2$C*H*$_3$), 1.01 (t, 3H, *J*=7.4 Hz, propyl–C*H*$_3$); ^{13}C NMR (CDCl$_3$): δ 167.0 (*C*O), 160.4 (*C*^{Ar}), 158.4 (*C*^{Ar}), 157.8 (*C*^{Ar}), 148.5 (*C*^{Ar}), 141.7 (*C*^{Ar}), 136.8 (*C*^{Ar}), 130.7 (*C*^{Ar}), 124.7 (*C*^{Ar}), 123.1 (*C*^{Ar}), 103.7 (*C*H), 67.1 (*C*H$_2$), 66.9 (*C*H$_2$), 61.3 (*C*H$_2$CH$_3$), 38.7 (*C*H$_2$), 32.4 (*C*H$_2$), 32.4 (*C*H$_2$), 23.4 (*C*H$_2$), 14.4 (*C*H$_3$), 14.3 (*C*H$_3$) (one aromatic and one aliphatic carbon could not be located); HRMS (ESI) for $C_{22}H_{29}N_2O_4$ [M+H]$^+$: *m*/*z* calcd: 385.2122; measured: 385.2118.

4.8.11. Ethyl 3-propyl-1-(pyridin-2-yl)-6,7-dihydro-5H-cyclopenta[c]pyridine-4-carboxylate *18*

A solution of triazine **3c** (128 mg, 470 μmol) and 1-cyclopentenylpyrrolidine (76 μL, 521 μmol, 1.11 equiv) in ethanol (5 mL) was stirred at room temperature for 1 h. Glacial acetic acid (0.5 mL) was added and the mixture was stirred for another hour. NaOH (1 M, 15 mL) was then added to the mixture and the organic layer was separated and the aqueous layer was extracted with dichloromethane (2×5 mL). The combined organic extracts were dried ($MgSO_4$) and the solvent evaporated yielding compound **18** (122 mg, 84%) as a brown oil; IR: ν_{max}/cm^{-1} 2961,2873, 1717 (C=O), 1568, 1555, 1255, 1231, 1116, 1093, 1024, 743; ^{1}H NMR (CDCl$_3$): δ 8.68 (ddd, 1H, *J*=1.0, 1.7 and 4.7 Hz, Py–*H*), 8.25 (ddd, 1H, *J*=1.0, 1.2 and 7.9 Hz, Py–*H*), 7.80 (ddd, 1H, *J*=1.7, 7.7 and 7.9 Hz, Py–*H*), 7.27 (ddd, 1H, *J*=1.2, 4.7 and 7.7 Hz, Py–*H*), 4.42 (q, 2H, *J*=7.2 Hz, –OC*H*$_2$CH$_3$), 3.38 (t, 2H, *J*=7.7 Hz, –C*H*$_2$CH$_2$CH$_2$–), 3.06 (t, 2H, *J*=7.7 Hz, –C*H*$_2$CH$_2$CH$_2$–), 3.01–2.95 (m, 2H, propyl–C*H*$_2$–), 2.09 (dt, 2H, 18H, *J*=7.7 and 7.7 Hz), 1.82 (m, 2H, propyl–C*H*$_2$–), 1.42 (t, 3H, *J*=7.2 Hz, –OCH$_2$C*H*$_3$), 1.01 (t, 3H, *J*=7.4 Hz, propyl–C*H*$_3$); ^{13}C NMR (CDCl$_3$): δ 168.5 (*C*O), 158.2 (*C*^{Ar}), 157.9 (*C*^{Ar}), 155.9 (*C*^{Ar}), 152.0 (*C*^{Ar}), 148.6 (*C*^{Ar}), 137.0 (*C*^{Ar}), 136.5 (*C*^{Ar}), 124.3 (*C*^{Ar}), 123.5 (*C*^{Ar}), 123.0 (*C*^{Ar}), 61.2 (*C*H$_2$CH$_3$), 38.4 (*C*H$_2$), 33.0 (*C*H$_2$), 32.9 (*C*H$_2$), 25.1 (*C*H$_2$), 23.4 (*C*H$_2$), 14.4 (*C*H$_3$), 14.3 (*C*H$_3$); HRMS (ESI) for $C_{19}H_{23}N_2O_2$ [M+H]$^+$: *m*/*z* calcd: 311.1754; measured: 311.1750.

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