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A convenient synthesis of 2,2′-bipyridine derivatives

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Abstract—Picolinates **7** were prepared from the corresponding α-chloro-β-keto-esters **6**. Esters **7** were converted into 2,2′-bipyridine derivatives **10** via triazines **9** using an aza Diels–Alder reaction.

In a series of previous Letters,[1–4] we have described the synthesis of triazines **3** from readily available amidrazones **1** and hydrated α,β-diketo-esters **2** or their equivalents (Scheme 1). These triazines **3** reacted with 2,5-norbornadiene **5** affording pyridine derivatives **4** in an inverse electron-demand aza Diels–Alder reaction. Alternatively, pyridines **4** could be prepared directly from a mixture of amidrazones **1**, α,β-diketo-esters **2** and 2,5-norbornadiene **5** in a convenient 'one-pot' reaction.

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

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

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

Keywords: 2,2′-Bipyridines; 1,2,4-Triazines; Aza Diels–Alder reaction.
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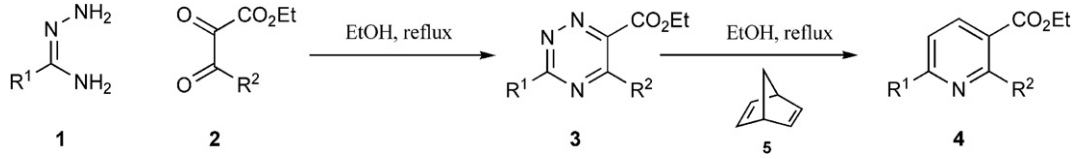
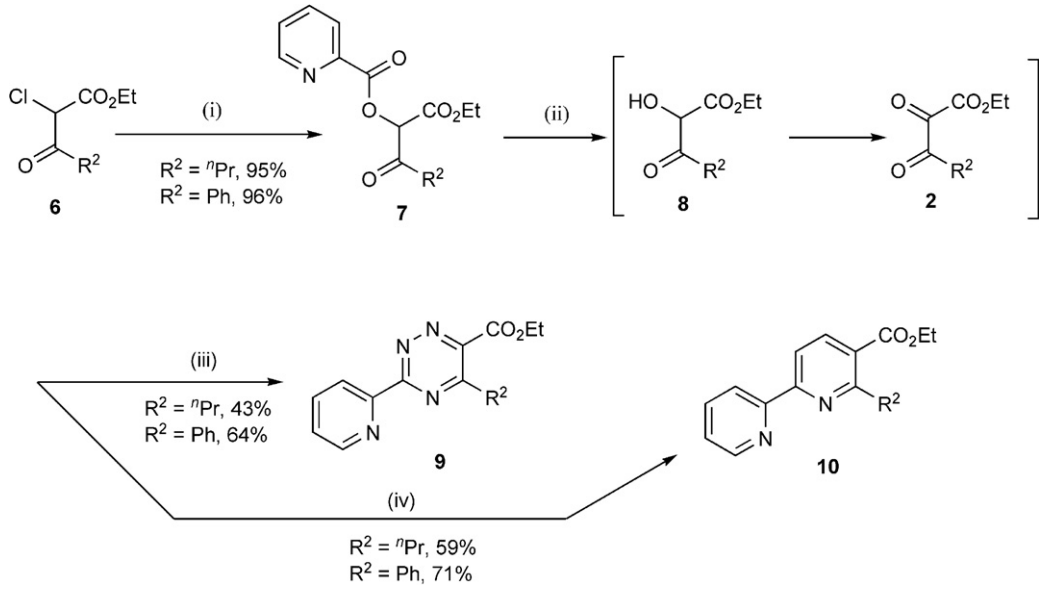


Scheme 1. Synthesis of pyridines **4**.



Scheme 2. Synthesis of bipyridines **10**. Reagents and conditions: (i) picolinic acid, $KHCO_3$, DMF, rt; (ii) $Cu(OAc)_2$, MeOH, CH_2Cl_2 then Na_2EDTA; (iii) amidrazone **1** ($R^1 = 2$-pyridyl), EtOH, reflux; (iv) amidrazone **1** ($R^1 = 2$-pyridyl), **5**, EtOH, reflux.

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

Acknowledgements

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

C*H*OPic), 4.30 (q, 2H, $J = 7.2$ Hz, ester–CH_2–), 1.24 (t, 3H, $J = 7.2$ Hz, ester–CH_3) ppm. ^{13}C NMR: (68 MHz, $CDCl_3$) $\delta = 189.30$ (*C*O), 164.95 (*C*O), 163.58 (*C*O), 150.43 (*C*H), 146.67 (*C*H), 137.21 (*C*H), 134.41 (*C*H), 134.26 (*C*), 129.42 (*C*H), 128.92 (*C*H), 127.60 (*C*H), 125.97 (*C*H), 75.31 (*C*H), 62.77 (*C*H_2), 14.01 (*C*H_3) ppm. HRMS (EI): calcd for $C_{17}H_{15}NO_5$ $(M+H)^+$: 314.1023. Found: 314.1021. *Ethyl 2-picolinoyl-3-oxo-3-hexanoate* **7** ($R^2 = {}^n$Pr): Using a similar procedure to that described above compound **7** ($R^2 = {}^n$Pr) (95%) was obtained as a viscous orange liquid. IR: ν_{max}/cm^{-1} 2968, 1732 (C=O), 1128. ^{1}H NMR: (270 MHz, $CDCl_3$) $\delta = 8.82$ (ddd, 1H, $J = 1.0$, 1.7 and 4.7 Hz, Py–*H*), 8.23 (ddd, 1H, $J = 1.0$, 1.2 and 7.9 Hz, Py–*H*), 7.89 (ddd, 1H, $J = 1.7$, 7.7 and 7.9 Hz, Py–*H*), 7.54 (ddd, 1H, $J = 1.2$, 4.7 and 7.7 Hz, Py–*H*) 5.81 (s, 1H, C*H*OPy), 4.33 (q, 2H, $J = 7.2$ Hz, ester–CH_2–), 2.77 (t, 2 H, $J = 7.2$ Hz, CH_3–CH_2–CH_2–), 1.70 (sextet, 2H, $J = 7.2$ Hz, CH_3–CH_2–CH_2–), 1.33 (t, 3H, $J = 7.2$ Hz, ester–CH_3), 0.96 (t, 3H, $J = 7.2$ Hz, propyl–CH_3) ppm. ^{13}C NMR: (68 MHz, $CDCl_3$) $\delta = 199.55$ (*C*O), 164.48 (*C*O), 163.66 (*C*O), 150.41 (*C*H), 146.73 (*C*), 137.21 (*C*H), 127.60 (*C*H), 125.88 (*C*H), 78.33 (*C*H), 62.72 (*C*H_2), 41.84 (*C*H_2), 16.70 (*C*H_2), 14.13 (*C*H_3), 13.58 (*C*H_3) ppm. HRMS (EI): calcd for $C_{14}H_{17}NO_5$ $(M+H)^+$: 280.1179. Found: 280.1180.

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10. *Typical procedures: Ethyl 6-phenyl-[2,2′]-bipyridine-5-carboxylate* **10** ($R^2 = $ Ph): A mixture of compound **7** ($R^2 = $ Ph) (1.00 g; 3.32 mmol), $Cu(OAc)_2$ (1.32 g; 6.63 mmol; 2.0 equiv) and ethanol (2 mL) in DCM (50 mL) was stirred at room temperature for one day. The reaction was diluted with hexanes (20 mL) and washed with Na_2EDTA (0.1 M aqueous solution) until the aqueous phase remained colourless. The organic phase was dried over $MgSO_4$, filtered and evaporated. The resulting oil was taken up in ethanol (50 mL), compound **1** ($R^1 = $ 2-pyridyl) (361 mg; 2.65 mmol; 0.8 equiv) and 2,5-norbornadiene **5** (2.9 mL; 26.5 mmol; 8.0 equiv) were added and the solution was heated at reflux under a nitrogen atmosphere for 2 days. After cooling to room temperature the mixture was poured onto water and extracted with CH_2Cl_2. The organic layer was washed with water, dried ($MgSO_4$) and evaporated. The crude mixture was purified by column chromatography (silica gel: diethyl ether) giving the product (570 mg; 71%) identical with an authentic sample.[3] *Ethyl 6-propyl-[2,2′]-bipyridine-5-carboxylate* **10** ($R^2 = {}^n$Pr): Using a similar procedure to that described above, compound **10** ($R^2 = {}^n$Pr) (59%) was obtained, identical with an authentic sample.[3]