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A convenient synthesis of substituted 2,2′:6′,2″-terpyridines

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ABSTRACT

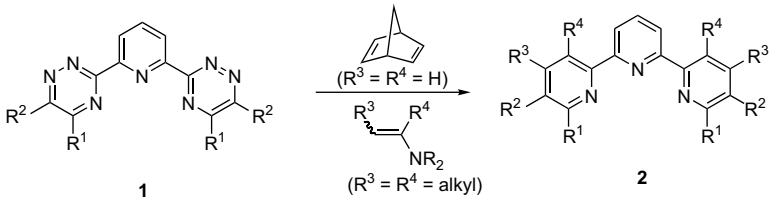
The 2,2′:6′,2″-terpyridines **7a–c** were prepared in good yield by reacting α-acetoxy-α-chloro-β-keto-esters **3a–c** with bis-amidrazone **4** and 2,5-norbornadiene **6** in ethanol at reflux. Compounds **3a** and **3b** gave the 2,2′:6′,2″-terpyridines **9a** and **9b**, respectively, in moderate yield when treated with compound **4** and enamine **8**.

1. Introduction

Synthetic routes to 2,2′:6′,2″-terpyridines have attracted considerable interest because these heterocycles are used extensively in both coordination chemistry and supramolecular chemistry.[1] One approach that has been used to construct the 2,2′:6′,2″-terpyridine system **2** involves the preparation of the 1,2,4-triazine-containing heterocyclic ring system **1** and then subjecting these compounds to an aza Diels–Alder reaction (Scheme 1).[2] Examples of aza dienophiles that have been used include the acetylene equivalent, 2,5-norbornadiene (giving products **2** with R^3 and R^4=H),[2a] tributyl(ethynyl)tin (giving product **2** with R^3=$SnBu_3$ and R^4=H)[2b] and enamines (giving products with R^3 and R^4=alkyl).[2c] This paper describes our work in this area,[3] which builds upon our related aza Diels–Alder approach to pyridine and 2,2′-bipyridine synthesis.[4]

2. Discussion

Our recent work on 2,2′-bipyridines was readily extended to enable the preparation of 2,2′:6′,2″-terpyridines **7a–c** (Scheme 2). There were two possible synthetic strategies to these compounds: the triazines **5** could be prepared, isolated and then subsequently reacted with 2,5-norbornadiene **6** or alternatively a 'one-pot' procedure could be employed in which the triazines **5** were formed in situ in the presence of 2,5-norbornadiene **6**. Preliminary studies showed that 2 equiv of the α-acetoxy-α-chloro-β-keto-esters **3a** and **3b** (which behave as a convenient source of the α,β-diketo ester equivalents, $RCOCOCO_2Et$, when treated with ethanolic methylamine)[3,4f] reacted with the bis-amidrazone **4** yielding the heterocycles **5a** (34%) and **5b** (36%), respectively. In view of the disappointing yields of these two products the 'one-pot' synthetic procedure was investigated. This proved to be successful and the



Scheme 1. Aza Diels–Alder approach to 2,2′:6′,2″-terpyridines **2**.

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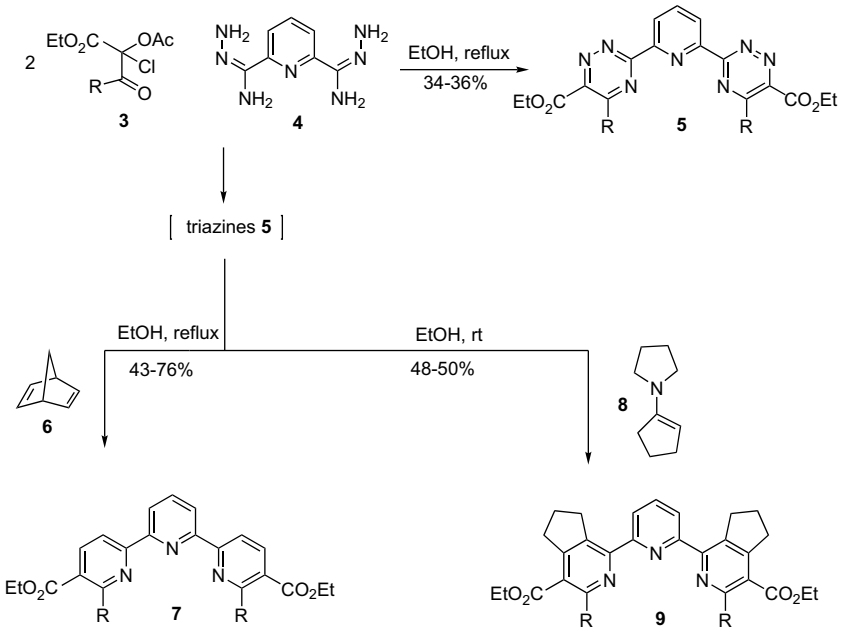


a R = *n*-Pr; **b** R = *i*-Bu; **c** R = Ph

Scheme 2. Synthesis of 2,2′:6′,2″-terpyridines **7** and **9**.

2,2′:6′,2″-terpyridines **7a–c** (43–76%) were obtained when compounds **3a–c** were reacted with the bis-amidrazone **4** in the presence of an excess of 2,5-norbornadiene **6** in ethanol at reflux. In order to introduce additional functionality into the peripheral rings, the 'one-pot' reaction of starting materials **3a** and **4** in the presence of the enamine **8** was attempted. This reaction produced the expected 2,2′:6′,2″-terpyridine derivative **9a** in moderate yield (48%) in ethanol at room temperature. In a similar reaction, the 2,2′:6′,2″-terpyridine **9b** (50%) was formed from compound **3b**.

The α-acetoxy-α-chloro-β-keto-esters **3** required in the reactions described above are readily available in a few steps from their corresponding β-keto-esters as described previously by us.[4f] The bis-amidrazone **4** was prepared from 2,6-dicyanopyridine and hydrazine hydrate.[5] 2,6-Dicyanopyridine is commercially available but expensive. It can, however, be prepared[6] in a few steps in good overall yield from the inexpensive pyridine-2,6-dicarboxylic acid via the diacid dichloride[7] and diamide[8] following the literature procedures. Both starting materials **3** and **4** can be prepared on multi-gram scales.

The synthesis of 2,2′:6′,2″-terpyridine **7** (R=Me) has been described in the literature by other workers.[9] It was prepared in two steps from 2,6-diacetylpyridine. Thus, 2,6-diacetylpyridine and dimethylformamide dimethylacetal gave an enamine [Ar(COCH=CHNMe$_2$)$_2$, Ar=2,6-pyridyl], which was treated with ethyl acetoacetate and ammonium acetate yielding the product **7** (R=Me). This method compliments our procedure for the preparation of general structures **2** (R^1=alkyl, aryl; R^2=ester; R^3=R^4=H). Our methodology does have additional flexibility because the substituents R^3 and R^4 in structure **2** can be other than hydrogen whereas in the synthesis from 2,6-diacetylpyridine the substituents R^3 and R^4 are limited to hydrogen.

3. Conclusion

We have successfully demonstrated that the readily available α-acetoxy-α-chloro-β-keto-esters **3** and bis-amidrazone **4** can be used for the construction of 2,2′:6′,2″-terpyridines of general structure **2** in a 'one-pot' reaction under mild conditions.

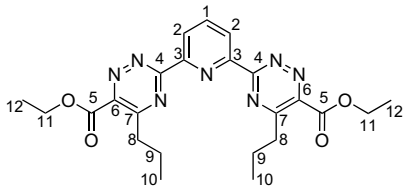
4. Experimental

4.1. General

^{1}H NMR (270 MHz) and ^{13}C NMR (67.5 MHz) spectra were recorded on a Joel JNM EX270 instrument. 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 gel 60 F_{254}. Silica gel for column chromatography was Merck silica gel 60. Details of the synthesis of 2,2′:6′,2″-terpyridines **7a** and **7c**, prepared in 60% and 76% yields, respectively, together will full analytical data for these compounds has been reported in our preliminary communication of this work.[3]

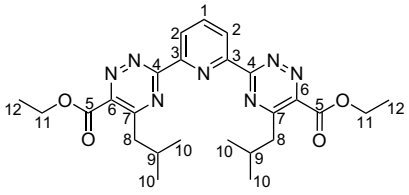
4.1.1. Diethyl 3,3′-(pyridine-2,6-diyl)bis(5-propyl-1,2,4-triazine-6-carboxylate) ***5a***

To a stirred solution of compound **3a** (501 mg, 2.00 mmol, 2.00 equiv) in ethanol (3 mL) was added methylamine (0.49 mL, 33% w/w in ethanol, 3.98 mmol, 3.98 equiv). The mixture was stirred at room temperature for 1 h. Compound **4** (193 mg, 1.00 mmol) was added and the mixture was heated under reflux for 2 h. After cooling to room temperature, the solvent was evaporated and the residue purified by column chromatography (ethyl acetate/petroleum ether (bp 40–60 °C)=3:1; R_f=0.27) yielding compound **5a** (157 mg, 34%) as a brown solid, mp 105–107 °C. IR: ν_{max}/cm^{-1} 2964, 2934, 2874, 1721 (C=O), 1512, 1255, 1081, 1045, 815, 743, 668; ^{1}H NMR ($CDCl_3$): δ 8.85 (d, 2H, 2-H, $J_{2/1}$=7.9 Hz), 8.19 (t, 1H, 1-H, $J_{1/2}$=7.9 Hz), 4.56 (q, 4H, 11-H, $J_{11/12}$=7.2 Hz), 3.23–3.17 (m, 4H, 8-H), 1.98–1.85 (m, 4H, 9-H), 1.48 (t, 6H, 12-H, $J_{12/11}$=7.2 Hz), 1.07 (t, 6H, 10-H, $J_{10/9}$=7.2 Hz) ppm; ^{13}C NMR ($CDCl_3$): δ 164.1, 164.0, 162.4, 153.2, 150.0 (C-3 to C-7), 138.7 (C-1), 127.0 (C-2), 63.0 (C-11), 37.1 (C-8), 22.0 (C-9), 14.3 and 14.2 (C-10, C-12) ppm; HRMS (ESI) for $C_{23}H_{28}N_7O_4$ $[M+H]^+$: calculated: 466.2197, measured: 466.2192.



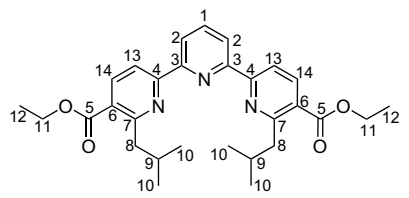
4.1.2. Diethyl 3,3′-(pyridine-2,6-diyl)bis(5-isobutyl-1,2,4-triazine-6-carboxylate) ***5b***

Using a similar procedure to that described above for the preparation of compound **5a**, compound **5b** (156 mg, 36%) was obtained as a yellow solid, mp 99–102 °C, after purification by column chromatography (ethyl acetate/petroleum ether (bp 40–60 °C)=3:1; R_f=0.39). IR: ν_{max}/cm^{-1} 2960, 2871, 1720 (C=O), 1510, 1256, 1085, 1047, 798, 744, 669; ^{1}H NMR ($CDCl_3$): δ 8.84 (d, 2H, 2-H, $J_{2/1}$=7.9 Hz), 8.19 (t, 1H, 1-H, $J_{1/2}$=7.9 Hz), 4.57 (q, 4H, 11-H, $J_{11/12}$=7.2 Hz), 3.13 (d, 4H, 8-H, $J_{8/9}$=7.2 Hz), 2.45–2.30 (m, 2H, 9-H), 1.50 (t, 6H, 12-H, $J_{12/11}$=7.2 Hz), 1.03 (d, 12H, 10-H, $J_{10/9}$=6.7 Hz) ppm; ^{13}C NMR ($CDCl_3$): δ 164.2 (C-5), 163.2 (C-3), 162.4 (C-1), 153.3 (C-2), 150.5 (C-4), 138.7 (C-6), 126.9 (C-7), 63.0 (C-11), 43.2 (C-8), 28.8 (C-9), 22.6 (C-10), 14.3 (C-12) ppm; HRMS (ESI) for $C_{25}H_{32}N_7O_4$ $[M+H]^+$: calculated: 494.2510, measured: 494.2512.



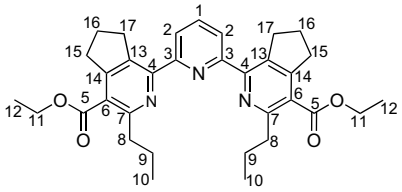
4.1.3. Diethyl 2,2′-(pyridine-2,6-diyl)bis(6-isobutylpyridine-5-carboxylate) ***7b***

To a solution of compound **3b** (461 mg, 1.74 mmol, 1.74 equiv) in ethanol (5 mL) was added methylamine (0.49 mL, 33% w/w in ethanol, 3.98 mmol, 3.98 equiv) and the mixture was left stirring at room temperature for 1 h. Compound **7** (193 mg, 1.00 mmol) and 2,5-norbornadiene **6** (2.15 mL, 19.9 mmol, 19.9 equiv) were added and the mixture was heated under reflux for 20 h. After cooling to room temperature, the solvent was evaporated and the residue purified by column chromatography (ethyl acetate/petroleum ether (bp 40–60 °C)=1:9; R_f=0.35) yielding compound **7b** (182 mg, 372 μmol, 43% based on **3b**), which was obtained as colourless crystals, mp 109–112 °C. IR: ν_{max}/cm^{-1} 2957, 1721 (C=O), 1581, 1552, 1438, 1254, 1099, 1073, 822, 784, 764, 731; ^{1}H NMR ($CDCl_3$): δ 8.58 (d, 2H, 2-H, $J_{2/1}$=7.9 Hz), 8.49+8.31 (2d, 4H, 13-H, 14-H, $J_{13/14}$=$J_{14/13}$=8.3 Hz), 7.91 (t, 1H, 1-H, $J_{1/2}$=7.9 Hz), 4.42 (q, 4H, 11-H, $J_{11/12}$=7.2 Hz), 3.17 (d, 4H, 8-H, $J_{8/9}$=7.2 Hz), 2.36–2.21 (m, 2H, 9-H), 1.44 (t, 6H, 12-H, $J_{12/11}$=7.2 Hz), 1.00 (d, 12H, 10-H, $J_{10/9}$=6.7 Hz) ppm; ^{13}C NMR ($CDCl_3$): δ 167.1 (C-5), 162.1 (C-7), 157.2 (C-4), 154.9 (C-3), 139.4 (C-14), 138.0 (C-1), 125.9 (C-6), 122.3 (C-2), 117.8 (C-13), 61.4 (C-11), 45.3 (C-8), 29.2 (C-9), 22.7 (C-10), 14.4 (C-12) ppm; HRMS (ESI) for $C_{29}H_{36}N_3O_4$ $[M+H]^+$: calculated:490.2700, measured: 490.2699.



4.1.4. Diethyl 1,1′-(pyridine-2,6-diyl)bis(3-propyl-6,7-dihydro-5H-cyclopenta[c]pyridine-4-carboxylate) ***9a***

Method A: A solution of compound **3a** (501 mg, 2.00 mmol, 2.0 equiv) and methylamine (0.49 mL, 33% w/w in ethanol, 3.98 mmol, 3.98 equiv) in ethanol (5 mL) was stirred at room temperature for 1 h. Compound **4** (193 mg, 1.00 mmol) was added and the solution was stirred under reflux for 2 h. 1-Cyclopentenylpyrrolidine **8** (306 μL, 2.10 mmol, 2.10 equiv) was then added and the solution was heated at reflux for another 20 h. After cooling to room temperature the solvent was evaporated and the residue purified by column chromatography (diethyl ether/hexanes=4:1; R_f=0.41) yielding compound **9a** (261 mg, 48%) as a yellow solid, mp 61–63 °C. IR: ν_{max}/cm^{-1} 2962, 2935, 2872, 1717 (C=O), 1557, 1256, 1237, 1122, 1031, 826, 737; ^{1}H NMR ($CDCl_3$): δ 8.18 (d, 2H, 2-H, $J_{2/1}$=7.9 Hz), 7.92 (t, 1H, 1-H, $J_{1/2}$=7.9 Hz), 4.41 (q, 4H, 11-H, $J_{11/12}$=7.2 Hz), 3.29+3.06 (2t, 8H, 15-H, 17-H, $J_{15/16}$=$J_{17/16}$=7.4 Hz), 3.02–2.96 (m, 4H, 8-H), 2.04 (tt, 4H, 16-H, $J_{16/15}$=$J_{16/17}$=7.4 Hz), 1.84 (sextet, 4H, 9-H, $J_{9/8}$=$J_{9/10}$=7.4 Hz), 1.41 (t, 6H, 12-H, $J_{12/11}$=7.2 Hz), 1.03 (t, 6H, 10-H, $J_{10/9}$=7.4 Hz) ppm; ^{13}C NMR ($CDCl_3$): δ 168.4 (C-5), 157.9 and 157.0 (C-4, C-7), 155.8 (C-3), 152.6 (C-14), 137.1 (C-13), 136.9 (C-1), 124.3 (C-6), 123.2 (C-2), 61.2 (C-11), 38.4 (C-8), 33.0 and 32.9 (C-15, C-17), 25.2 (C-16), 23.4 (C-9), 14.4 and 14.3 (C-10, C-12) ppm; HRMS (ESI) for $C_{33}H_{40}N_3O_4$ $[M+H]^+$: calculated: 542.3013, measured: 542.3014.

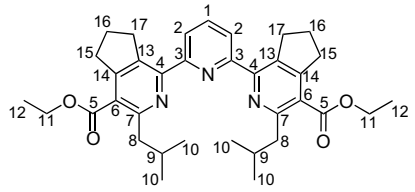


Method B: A solution of compound **3a** (501 mg, 2.00 mmol, 2.0 equiv) and methylamine (0.49 mL, 33% w/w in ethanol, 3.98 mmol, 3.98 equiv) in ethanol (5 mL) was stirred at room temperature for 1 h. Compound **4** (193 mg, 1.00 mmol) and ethanol (5 mL) were added and the solution was stirred under reflux for 1 h. After cooling to room temperature, 1-cyclopentenylpyrrolidine **8** (306 μL, 2.10 mmol, 2.10 equiv) was added and the solution was stirred for 1 h. Glacial acetic acid (1 mL) was then added and the mixture was stirred for another hour and then made basic by the addition of 1 M NaOH (60 mL). The organic layer was separated, the aqueous phase extracted with dichloromethane (2×10 mL) and the combined organic extracts were dried ($MgSO_4$) and evaporated. The residue purified by column chromatography (diethyl ether/hexanes=1:1; R_f=0.58) yielding compound **9a** (219 mg, 40%) identical with an authentic sample.

4.1.5. Diethyl 1,1′-(pyridine-2,6-diyl)bis(3-isobutyl-6,7-dihydro-5H-cyclopenta[c]pyridine-4-carboxylate) ***9b***

A solution of compound **3b** (529 mg, 2.00 mmol, 2.00 equiv) and methylamine (0.49 mL, 33% w/w in ethanol, 3.98 mmol, 3.98 equiv) in ethanol (5 mL) was stirred at room temperature for 1 h. Compound **4** (193 mg, 1.00 mmol) and ethanol (5 mL) were added and the solution was stirred under reflux for 1 h. After cooling to room temperature, 1-cyclopentenylpyrrolidine **8** (306 μL, 2.10 mmol, 2.10 equiv) was added and the solution was stirred for 1 h, glacial acetic acid (1 mL) was added and the mixture was stirred for another hour. The mixture was then made basic by the addition of 1 M NaOH (60 mL), the organic layer was separated and the aqueous phase was extracted with dichloromethane (2×10 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography (diethyl ether/hexanes=4:1; R_f=0.81) yielding compound **9b** (268 mg, 50%) as a yellow wax. IR: ν_{max}/cm^{-1} 2955, 2869, 1718 (C=O), 1557, 1256, 1233, 1119, 1095, 1039, 828, 744; ^{1}H NMR ($CDCl_3$): δ 8.18 (d, 2H, 2-H,

$J_{2/1}$=7.9 Hz), 7.93 (t, 1H, 1-H, $J_{1/2}$=7.9 Hz), 4.42 (q, 4H, 11-H, $J_{11/12}$=7.2 Hz), 3.30+3.06 (2t, 8H, 15-H, 17-H, $J_{15/16}$=$J_{17/16}$=7.4 Hz), 2.89 (d, 4H, 8-H, $J_{8/9}$=7.2 Hz), 2.34–2.18 (m, 2H, 9-H), 2.05 (tt, 4H, 16-H, $J_{16/15}$=$J_{16/17}$=7.4 Hz), 1.42 (t, 6H, 12-H, $J_{12/11}$=7.2 Hz), 0.99 (d, 12H, 10-H, $J_{10/9}$=6.7 Hz) ppm; ^{13}C NMR ($CDCl_3$): δ 168.5 (C-5), 157.1 and 157.0 (C-4, C-7), 155.5 (C-3), 152.5 (C-14), 137.1 (C-13), 136.8 (C-1), 124.8 (C-6), 123.2 (C-2), 61.2 (C-11), 44.7 (C-8), 32.9 (C-15, C-17), 29.3 (C-9), 25.2 (C-16), 22.4 (C-10), 14.4 (C-12) ppm; HRMS (ESI) for $C_{35}H_{44}N_3O_4$ $[M+H]^+$: calculated: 570.3326, measured: 570.3324.



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