

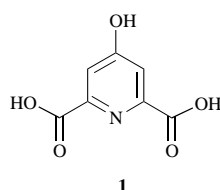
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4-Substituted-2,6-diacetylpyridines **2–4** have been synthesised; by using the Kröhnke-methodology, chalcone and methylacetylpyridinium salts have been reacted to yield 4'-ethoxy-2,2':6',2''-terpyridines **5–7**. These novel 2,2':6',2''-terpyridines are functionalised at C(4') and possess substituents at C(4), C(5) and C(6) of both terminal pyridines, respectively. The ethyl ether protecting group has been cleaved to obtain 4'-hydroxy-2,2':6',2''-terpyridine **8**.

Oligopyridines have received considerable attention in supramolecular chemistry<sup>1</sup> and have been incorporated into helicates,<sup>2</sup> catenanes,<sup>3</sup> dendrimers<sup>4</sup> and knots<sup>5</sup> among others. An interesting field in supramolecular chemistry relates to the photochemical properties of homo- and hetero-metallic complexes using oligopyridine metal-binding domains.<sup>6,7</sup>

The 2,2':6',2''-terpyridine metal-binding is commonly incorporated into multinucleating systems using 4'-chloro- or 4'-hydroxy-functionalised derivatives.<sup>8</sup> To date the synthetic approaches to these key intermediates have not permitted additional functionalisation on the terminal rings. We now report the synthesis of 4'-hydroxy derivatives bearing functionality at the 4,4'', 5,5''- or 6,6''-positions.



Chelidamic acid **1** has not, to the best of our knowledge, been used as a starting material for the synthesis of oligopyridines. The presence of functionality in a position destined to become C(4') of a 2,2':6',2''-terpyridine makes it an attractive starting point.

Chelidamic acid **1** was esterified to diethyl 4-chloropyridine-2,6-dicarboxylate which was then reacted with sodium ethoxide to obtain diethyl 4-ethoxypyridine-2,6-dicarboxylate.<sup>†,9</sup> This ester was hydrolysed and converted to 4-ethoxypyridine-2,6-dicarbonyl dichloride on reaction with thionyl chloride. The reaction of 4-ethoxypyridine-2,6-dicarbonyl dichloride with 2,2-dimethyl-1,3-dioxane-4,6-dione (Meldrum's acid)<sup>10</sup> followed by hydrolysis with aqueous acetic acid<sup>11</sup> gave 4-ethoxy-

2,6-diacetylpyridine **2** as yellowish crystals in 30% overall yield from 4-ethoxypyridine-2,6-dicarboxylic acid.<sup>‡</sup>

Alternatively diethyl 4-chloropyridine-2,6-dicarboxylate was hydrolysed to 4-chloropyridine-2,6-dicarboxylic acid which readily reacted with thionyl chloride to give 4-chloropyridine-2,6-dicarbonyl dichloride.<sup>12</sup> The reaction of 4-chloropyridine-2,6-dicarbonyl dichloride with Meldrum's acid gave, after evaporation of solvent, brown crystals which were hydrolysed with aqueous acetic acid to give 4-chloro-2,6-diacetylpyridine **3** as yellow crystals in 32% overall yield from 4-chloropyridine-2,6-dicarboxylic acid.<sup>§</sup>

Chelidamic acid **1** was esterified to diethyl 4-hydroxypyridine-2,6-dicarboxylate then reacted with benzyl bromide in the presence of crown ether to give diethyl 4-benzyloxy-pyridine-2,6-dicarboxylate.<sup>13</sup> This ester was hydrolysed, reacted with thionyl chloride and after treatment with Meldrum's acid and aqueous hydrolysis gave 4-benzyloxy-2,6-diacetylpyridine **4**¶ as colorless crystals in 35% overall yield from 4-benzyloxy-pyridine-2,6-dicarboxylic acid.

All data for the fully characterised protected 4-hydroxy-2,6-diacetylpyridines **2–4** are in agreement with the expected properties of these compounds in comparison with the known 2,6-diacetylpyridine.

Among the existing methods for the synthesis of pyridines and oligopyridines the Kröhnke-methodology is the most commonly used.<sup>14</sup> The synthesis consists of the reaction of a chalcone and a methylacetylpyridinium [*N*-(2-oxoalkyl)pyridinium] salt. The same methodology was applied to 4-ethoxy-2,6-diacetylpyridine **2**. Thus we were able to synthesise terpyridines with substituents at C(4), C(5) and C(6) of both terminal pyridines while the 4'-position of terpyridine is functionalised as a protected hydroxy group.

Compound **2** was reacted with *p*-tolualdehyde in ethanol at 0 °C to obtain the chalcone which readily gave 4'-ethoxy-6,6''-dimethyl-4,4''-di(*p*-tolyl)-2,2':6',2''-terpyridine **5**|| in the reaction

‡ Compound **2**: yellow crystals; mp 103–4 °C (hexane);  $\nu_{\max}$ (KBr)/cm<sup>-1</sup> 1704;  $\delta_{\text{H}}$ (CDCl<sub>3</sub>; *J*/Hz) 7.60 (s, 2H), 4.13 (q, *J* 7.3, 2H), 2.70 (s, 6H), 1.41 (t, *J* 7.33, 3H);  $\delta_{\text{C}}$ (CDCl<sub>3</sub>) 199.34 (H<sub>3</sub>C=O), 166.70 [C(4)], 154.39 [C(2,6)], 110.72 [C(3,5)], 64.37 (H<sub>3</sub>CCH<sub>2</sub>O), 25.56 (H<sub>3</sub>CC=O), 14.24 (H<sub>3</sub>CCH<sub>2</sub>O).

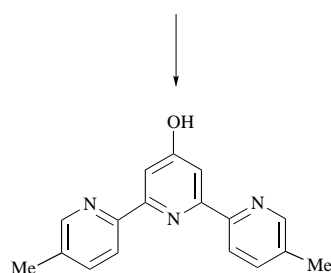
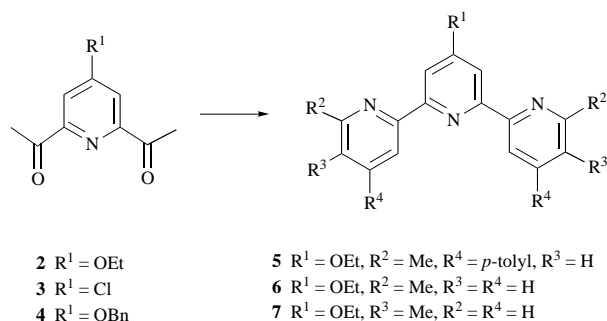
§ Compound **3**: yellow crystals; mp 64 °C (hexane);  $\nu_{\max}$ (KBr)/cm<sup>-1</sup> 1704;  $\delta_{\text{H}}$ (CDCl<sub>3</sub>) 8.17 (s, 2H), 2.77 (s, 6H);  $\delta_{\text{C}}$ (CDCl<sub>3</sub>) 197.95 (H<sub>3</sub>C=O), 153.73 [C(2,6)], 146.75 [C(4)], 124.78 [C(3,5)], 25.50 (H<sub>3</sub>CC=O).

¶ Compound **4**: colorless crystals; mp 74 °C (hexane);  $\nu_{\max}$ (KBr)/cm<sup>-1</sup> 1699;  $\delta_{\text{H}}$ (CDCl<sub>3</sub>) 7.78 (s, 2H), 7.41–7.37 (m, 5H), 5.21 (s, 2H), 2.77 (s, 6H);  $\delta_{\text{C}}$ (CDCl<sub>3</sub>) 199.26, 166.49, 154.53, 134.91, 128.72, 128.50, 127.51, 111.11, 70.41, 25.62.

|| Compound **5**: colorless crystals; mp 116–117 °C (ethanol);  $\delta_{\text{H}}$ (CDCl<sub>3</sub>; *J*/Hz) 8.63 (m, 2H), 8.04 (s, 2H), 7.68 (d, *J* 7.80, 2H), 7.40 (m, 2H), 7.31 (d, *J* 7.80, 2H), 4.34 (q, *J* 7.3, 2H), 2.70 (s, 6H), 2.44 (s, 6H), 1.51 (t, *J* 7.3, 3H).

† The Claisen condensation of 4-ethoxy and 4-benzyloxy<sup>9</sup> diethyl pyridine-2,6-dicarboxylates with sodium ethoxide and ethyl acetate to give a  $\beta$ -keto ester failed, although the reaction of diethyl pyridine-2,6-dicarboxylate to obtain 2,6-diacetylpyridine has already been reported.<sup>16</sup>

with *N*-(methylacetyl)pyridinium chloride [*N*-(2-oxopropyl)pyridinium chloride] in 60% yield. A bis-Mannich-base was obtained in the reaction of **2** with paraformaldehyde and dimethylamine in DMF which readily reacted with *N*-(methylacetyl)pyridinium chloride to give 4'-ethoxy-6,6''-dimethyl-2,2':6',2''-terpyridine **6**†† in 56% yield.



Scheme 1

2,6-Bis(1-oxo-2-pyridinoethyl)-4-ethoxypyridine diiodide was obtained by the reaction of **2** with iodine in pyridine; this reacted with methacrolein (2-methylpropenal) to give a terpyridine substituted at C(5) of both terminal pyridines, namely 4'-ethoxy-5,5''-dimethyl-2,2':6',2''-terpyridine **7**‡‡ in 45% yield. The ethyl ether protecting group was cleaved in pyridine and hydrochloric acid at elevated temperature<sup>15</sup> and 5,5''-dimethyl-4'-hydroxy-2,2':6',2''-terpyridine **8** was obtained in 50% yield.§§

†† Compound **6**: colorless crystals; mp 169–170 °C (ethanol);  $\delta_{\text{H}}$ (CDCl<sub>3</sub>; *J*/Hz) 8.39 (d, *J*7.80, 2H), 8.01 (s, 2H), 7.72 (t, *J*7.80, 2H), 7.18 (d, *J*7.80, 2H), 4.31 (q, *J*7.3, 2H), 2.64 (s, 6H), 1.49 (t, *J*7.3, 3H).  
‡‡ Compound **7**: yellow needles; mp 140–141 °C (ethanol);  $\delta_{\text{H}}$ (CDCl<sub>3</sub>; *J*/Hz) 8.50 (s, 2H), 8.48 (d, *J*7.3, 2H), 7.93 (s, 2H), 7.63 (d, *J*7.3, 2H), 4.28 (q, *J*7.3, 2H), 2.40 (s, 6H), 1.47 (t, *J*7.3, 3H);  $\delta_{\text{C}}$ (CDCl<sub>3</sub>) 167.21, 156.26, 152.84, 148.83, 137.88, 133.74, 121.12, 107.12, 64.02, 18.32, 14.53.

§§ Compound **8**: colorless crystals; mp 168–169 °C (hexane);  $\delta_{\text{H}}$ (CDCl<sub>3</sub>) 8.59 (s, 2H), 7.81 (d, *J*8.30, 2H), 7.67 (dd, *J*8.30, *J*1.95, 2H), 7.02 (s, 2H), 2.43 (s, 6H);  $\delta_{\text{C}}$ (CDCl<sub>3</sub>) 149.66, 146.18, 144.59, 137.78, 135.01, 119.71, 112.65, 18.31.

The data for the new terpyridines **5–8** are in agreement with the expected properties of the known 4'-hydroxy-2,2':6',2''-terpyridine.<sup>8</sup> In the <sup>1</sup>H NMR spectrum of **8** the protons at C(6,6'') and C(3',5') were each observed as singlets at 8.59 and 7.02 ppm, respectively, while protons at C(3,3') were observed as a doublet at 7.81 ppm and protons at C(4,4') as a doublet of doublets at 7.67 ppm, respectively. The methyl groups were observed as a singlet at 2.43 ppm. Compound **8** has been fully characterised. While terpyridines **7** and **8** react readily at ambient temperature to give purple Fe<sup>II</sup>-complexes, the Fe<sup>II</sup>-complexes of **5** and **6** are formed only at elevated temperatures, because of the substituents at the 6,6''-positions.

In conclusion, we have established a methodology for preparing **8** which has the potential for undergoing regioselective reactions both at C(5), C(5'') and, more importantly, at C(4') which possesses a hydroxy group.

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