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A Convergent Approach to a Solubilised Septipyridine

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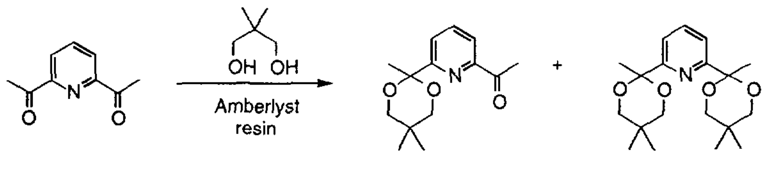
Abstract: The synthesis of a new solubilised 2,2':6',2":6",2"':6"'.2"":6"",2""':6""",2""""-septipyridine derivative is described. © 1997, Elsevier Science Ltd. All rights reserved.

INTRODUCTION

Oligopyridines and ligands containing oligopyridine metal-binding domains have proved to be versatile components in metallosupramolecular chemistry.[1] Although the chemistry of the lower members of series is well-established, synthetic approaches to the higher oligomers with seven or more pyridine rings are relatively scarce. Three principal routes have been adopted: Pott's syntheses [2], Krohnke syntheses [3] and dimerisation reactions.[4] The latter approach is best suited to the preparation of oligopyridines bearing even numbers of pyridine rings, although cross-coupling reactions and boronic acid methodology offer hopes for the future. In this paper, we describe a synthesis of a solubilised 2,2':6',2":6",2"':6"'.2"":6"",2""':6""",2""""-septipyridine using Krohnke methodology. We also note that this same compound may be obtained as an unexpected product from Krohnke reactions designed to yield novi or decipyridnes.

RESULTS AND DISCUSSION

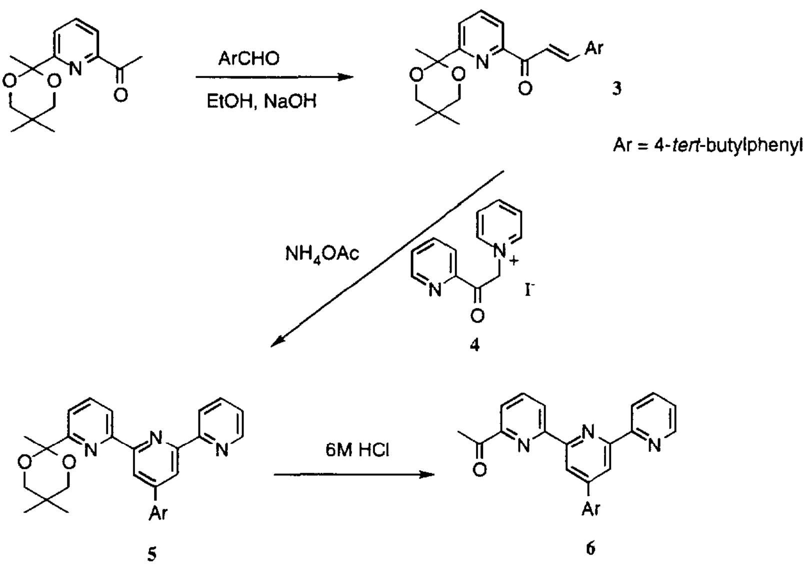


1 2

Scheme 1

Strategy. Our synthetic approach relied upon a 6-acetyl-2,2':6',2"-terpyridine as a synthon containing three pyridine rings. Such compounds are not readily accessible by conventional lithiation methodology [2,5] and we decided to devise a synthetic route leading to a protected derivative of such a compound. Furthermore, we wished the approach to yield a solubilised species bearing *tert*-butylphenyl substituents [6] The key intermediate in our synthetic approach was a monoprotected 2,6-diacetylpyridine bearing a functionality which could be converted to an acetyl group later in the synthesis. Our starting point was commercially available 2,6-diacetylpyridine.

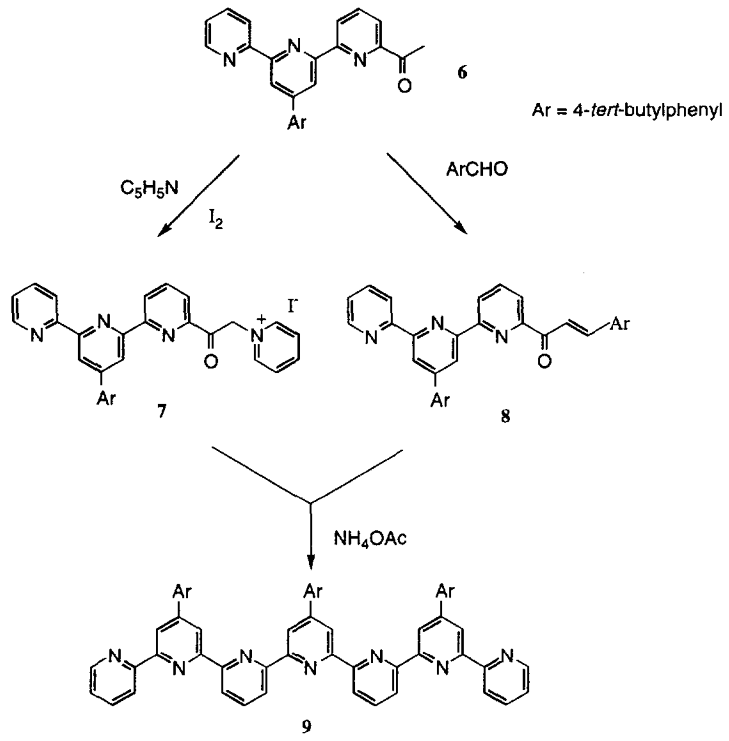
Synthesis. The reaction of 2,6-diacetylpyridine with 1.2 molar equivalents of 2,2-dimethylpropane-1,3-diol in dichloromethane in the presence of Amberlyst resin afforded a mixture of mono- (**1**) and bisketals (**2**) (Scheme 1) together with some unreacted starting material. After removal of the resin and solvent, the bisketal **2** could be easily removed as a white solid by the addition of cold ethanol. The desired monoketal (**1**) was purified by column chromatography of the ethanolic solution and was obtained as a yellow oil in 38% yield. Although it was not possible to form **1** selectively in this reaction under a variety of conditions the overall pass yield was respectable because unreacted 2,6-diacetylpyridine could be recovered and **2** could be quantitatively hydrolysed back to the bisketone with 6M hydrochloric acid.



Scheme 2.

The chalcone (**3**) was prepared in 75% yield from the reaction of 4-*tert*-butylbenzaldehyde with the monoketal (**1**) under basic conditions. This was then reacted with the Kröhnke reagent *N*-[2-(2-pyridyl)-2-oxoethyl]-pyridinium iodide [3] (**4**) to give the 2,2':6',2"-terpyridine derivative (**5**). Cleavage of the protecting group was achieved by hydrolysis with hydrochloric acid to give the desired substituted 6-acetyl-2,2':6',2"-terpyridine (**6**) in 92% yield (Scheme 2). The ^{1}H NMR spectrum of a $CDCl_3$ solution of **6** showed only two aliphatic resonances corresponding to the *tert*-butyl and methyl groups at δ1.41 and 2.89, respectively. The eleven aromatic proton environments were unambiguously assigned with the aid of a double quantum filtered COSY experiment.

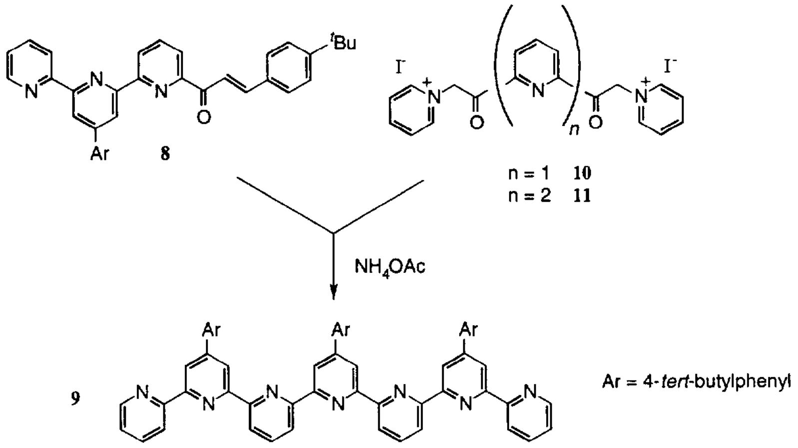
The 6-acetyl-2,2':6',2"-terpyridine derivative (**6**) can now serve as the starting material for the two precursers to the 2,2':6',2":6",2"':6"'.2"":6"",2""':6""',2""""-septipyridine derivative. The reaction of **6** with iodine in pyridine afforded the pyridinium salt (**7**) (Scheme 3) which could be readily identified by the characteristic carbonyl stretching frequency at 1718 cm^{-1} in its IR spectrum, as compared to 1697 cm^{-1} for the free ketone (**6**). The condensation of **6** with one equivalent of 4-*tert*-butylbenzaldehyde under basic conditions afforded the new chalcone (**8**) as an off-white solid. This compound is characterised by a carbonyl group stretching mode at a lower frequency (1672 cm^{-1}) than **6**. The ^{1}H NMR spectrum of **8** was fully consistent with the product being the chalcone and exhibited two *tert*-butyl resonances at δ1.38 and 1.44 and two sets of 1,4-substituted phenyl resonances.



Scheme 3

The reaction of **7** with **8** in the presence of ammonium acetate afforded an off-white solid which was characterised as the 2,2':6',2'':6'',2''':6'''.2'''':6'''',2''''':6''''',2''''''-septipyridine derivative (**9**) in 68% yield. Time of Flight mass spectrometry showed a signal at *m/z* 937 corresponding to the parent molecular ion. The ^{1}H NMR spectrum exhibited two resonances corresponding to two *tert*-butyl environments at δ 1.43 and 1.45 in a 2:1 ratio. The aromatic resonances were unambiguously assigned from a double quantum filtered COSY spectrum. The new ligand was moderately soluble in chloroform or dichloromethane and also in mixtures of chlorinated solvents with alcohols. We are currently investigating the coordination behaviour of this and other aryl-functionalised 2,2':6',2'':6'',2''':6'''.2'''':6'''',2''''':6''''',2''''''-septipyridines.[7]

This septipyridine derivative has also been observed as the sole product in the attempted syntheses of a novi- and a decipyridine derivative (Scheme 4). This result can be explained by the chalcone undergoing a retro-Claisen reaction before it can react with the bispyridinium salts **10** and **11**. When a solution of the chalcone (**8**) is heated in methanol in the presence of an excess of ammonium acetate the septipyridine derivative (**9**) is obtained as the only product. This is consistent with the formation of the parent acetyl derivative under the reaction conditions, followed by Michael addition of **8** and further investigation of these observations are currently underway.



Scheme 4

EXPERIMENTAL

General: All reagents were used as supplied. IR spectra were recorded on a Mattson Genesis Fourier-transform spectrophotometer with samples in compressed KBr discs. Proton NMR spectra were recorded on Varian Gemini 300 MHz or Bruker AM 250 spectrometers. Electron-impact (EI) spectra were recorded on a MAT 12 spectrometer. Time of flight (MALDI) spectra were recorded using a PerSpective Biosystems Voyager-RP Biospectrometry Workstation.

2-Acetyl-6-(2-(2,5,5-trimethyl-1,3-dioxanyl))pyridine (1) and 2,6-bis((2-(2,5,5-trimethyl-1,3-dioxanyl)pyridine (2)

2,6-Diacetylpyridine (1.00 g, 6.1 mmol), 2,2-dimethyl-1,3-propanediol (1.0 g, 9.4 mmol) and Amberlyst resin 15 (2 g) were stirred in CH_2Cl_2 (30 ml) for 24 h at r.t. The resin was removed by filtration, washed with CH_2Cl_2 before concentrating the combined filtrates *in vacuo*. Cold ethanol (20 ml) was added to the resulting yellow oil and the bisketal **2** (0.16 g, 8%) filtered off as a white solid. The filtrate was concentrated to dryness and purified by column chromatography (silica gel, CH_2Cl_2) to afford unreacted 2,6-diacetyl pyridine (0.50 g, 50%) and **1** (0.58 g, 38%) as a pale yellow oil which slowly crystallised on standing. **1**: m.p. 72-73C. δ_H (300 MHz, $CDCl_3$) 0.70 (3H, s CH_3); 1.25 (3H, s CH_3); 1.65 (3H, s CH_3); 2.76 (3H, s CH_3); 3.50 (4H, AB, J = Hz, CH_2); 7.72 (1H, d J = 7.6 Hz, H_3); 7.88 (1H, t J = 7.6Hz, H_4); 7.98 (1H, d J = 7.6Hz, H_5). Anal. calcd for $C_{14}H_{19}NO_3$: C, 67.45; H, 7.68; N, 5.62. Found: C, 67.89; H, 7.75; N, 6.72. *m/z* (EI) 250 $(M+H)^+$. IR (KBr) 2994m, 2954s, 2874m, 2663m, 1701 1585m, 1473m, 1460m, 1353s, 1298s, 1278m, 1236m, 1214m, 1184s, 1155m, 1137m, 1112m, 1079s, 1039m, 1018s, 954m, 914m, 896m, 877m, 824m, 794m, 602m, 593m cm^{-1}.

2: m.p. 215-216°C. δ_H (300 MHz, $CDCl_3$) 0.64 (6H, s, CH_3); 1.22 (6H, s, CH_3); 1.59 (6H, s, CH_3); 3.45 (8H, AB, CH_2); 7.46 (2H, d J = 7.7 Hz, H_3); 7.75 (1H, t J = 7.7 Hz, H4). Anal. calcd for $C_{19}H_{29}NO_4$: C, 68.03; H, 8.71; N, 4.18. Found: C, 67.92; H, 8.90; N, 4.34. IR (KBr) 2993m, 2947m, 2859m, 1850m, 1474m, 1364m, 1275m, 1236m, 1179s, 1155m, 1139m, 1079s, 1038m, 1017m, 913m, 878m cm^{-1}. *m/z* (EI) 250 $(M)^+$.

2-(4-*tert*-Butylphenylcinnamoyl)-6-((2-(2,5,5-trimethyl-1,3-dioxanyl))pyridine (3)

4-*tert*-Butylbenzaldehyde (2.05 g 0.013 mol) and **1** (3.15 g, 0.013 mol) were dissolved in EtOH (30 ml) and aqueous NaOH (5 ml of a 1.5 M solution) added. The solution was stirred at r.t. for 4 h. Water (10 ml) was added to the orange solution before extracting with CH_2Cl_2 (3 x 20 ml). After drying ($MgSO_4$), the organic solution was concentrated *in vacuo* and purified by column chromatography (silica gel, CH_2Cl_2) to afford **3** as a yellow oil (3.68 g, 75 %). δ_H (300 MHz, $CDCl_3$) 0.70 (3H, s, CH_3); 1.28 (3H, s, CH_3); 1.35 (9H, s, ^{t}butyl); 1.69 (3H, s, CH_3); 3.54 (4h, AB, CH_2); 7.45 (2H, d J = 8.2 Hz, $H_{o/m}$); 7.67 (2H, d J = 8.2 Hz, $H_{o/m}$); 7.74 (1H, d J = 7.8 Hz, H_5); 7.92 (1H, t J = 7.8 Hz, H_4); 7.98 (1H, J = 16.2 Hz, H_a); 8.14 (1H, d J = 7.8 Hz, H_3); 8.34 (1H, d J = 16.2 Hz, H_b). *m/z* (EI) 393 $(M)^+$. IR (KBr) 2956s, 2867m, 1672s, 1601s, 1513m, 1472m, 1413m, 1366m, 1335s, 1268m, 1185s, 1108m, 1081m, 1037s, 992m, 817m, 746m, 642m cm^{-1}.

6-((2-(2,5,5-Trimethyl-1,3-dioxanyl))-4'-(4-*tert*-butylphenyl)-2,2':6',2''-terpyridine (5)

N-[2-(2-pyridyl)-2-oxoethyl]-pyridinium iodide [3] (**4**) (2.76 g, 8.5 mmol), ammonium acetate (4 g, excess) and **3** (3.34 g, 8.5 mmol) were heated at reflux in EtOH (20 ml) for 14 h. After cooling water (10 ml) was added and the off-white solid precipitated filtered off. Recrystallisation from ethanol afforded **5** (1.52 g, 37 %). δ_H (300 MHz, $CDCl_3$) 0.69 (3H, s, CH_3); 1.29 (3H, s, CH_3); 1.41 (9H, s, ^{t}butyl); 1.72 (3H, s, CH_3); 3.58 (4H, AB CH_2); 7.58 (1H, m, H_5); 7.55 (3H, m, H_m,$H_{4''}$); 7.88 (3H, m, H_o,H_4); 8.60 (1H, d, $H_{3''}$); 8.68 (1H, d, $H_{6''}$); 8.72 (2H, m, $H_{3/5}$, $H_{3'/5'}$); 8.82 (2H, m, $H_{3/5}$, $H_{3'/5'}$).Anal. calcd for $C_{32}H_{35}N_3O_2.CHCl_3$: C, 64.65; H, 5.93; N, 6.86. Found: C, 64.24; H, 6.37; N, 6.63. IR (KBr) 2361m, 2867m, 1580m, 1474m, 1459m, 1391m, 1365m, 1269m, 1183m, 1112m, 1080m, 821m, 748m, 668m cm^{-1}. *m/z* (TOFMS) 493 $(M)^+$.

6-Acetyl-4'-(4-*tert*-butylphenyl)-2,2':6',2''-terpyridine (6)

A solution of 6 M HCl (2 ml) was added to a suspension of **5** (1.52 g, 3.1 mmol) in methanol (20 ml) and the mixture stirred at room temperature for 6h. The solution was then neutralised with $NaHCO_3$ and the resulting precipitate isolated by filtration. Recrystallisation from EtOH afforded **6** as an off-white solid (1.15 g, 92 %). m.p. 174-175°C. δ_H (300 MHz, $CDCl_3$) 1.41 (9H, s, ^{t}butyl); 2.89 (3H, s, CH_3); 7.37 (1H, m, $H_{5''}$); 7.57 (2H, d J = 8.4 Hz, H_m); 7.86 (2H, d J = 8.4 Hz, H_o); 7.90 (1H, td J = 7.6 Hz, 1.5 Hz, $H_{4''}$); 8.02 (1H, t J = 7.6 Hz, H_4); 8.12 (1H, dd J = 7.6 Hz, 1.5 Hz, $H_{3''}$); 8.68 (1H, d J = 7.6 Hz, H_5); 8.75 (1H, m, $H_{6''}$); 8.78 (1H, d J = 1.5 Hz, $H_{3'/5'}$); 8.83 (1H, d J = 1.5 Hz, $H_{3'/5'}$); 8.87 (1H, dd J = 7.6 Hz, 1.5 Hz, H_3). Anal. calcd for $C_{27}H_{25}N_3O$: C, 79.58; H, 6.18; N, 10.31. Found: C, 79.67; H, 10.23; N, 4.34. *m/z* (TOFMS) 407. IR (KBr) 2961m, 1697s, 1603m, 1580m, 1459m, 1390m, 1362m, 1268m, 1113m, 993m, 820m cm^{-1}.

***N*-[2-(6-(4'-(4-*tert*-Butylphenyl)-2,2':6',2''-terpyridine))-2-oxoethyl]pyridinium iodide (7)**

6 (0.132 g, 0.032 mmol) was added to a solution of I_2 (0.08 g, 0.032 mmol) in dry pyridine (2 ml) and the solution heated at reflux for 2 h. The solvent was removed *in vacuo*, $CHCl_3$ (2 ml) added and **7** was filtered off as a light brown solid. (0.15 g, 77%). IR (KBr) 3055m, 2960m, 1718s, 1636m, 1594s, 1524m, 1488m, 1384s, 819m, 670m cm^{-1}.

4'-(4-*tert*-Butylphenyl)-6-(4-*tert*-butylphenylcinnamoyl)-2,2':6',2"-terpyridine (8)

(**6**) (0.100 g, 0.25 mmol) and *tert*-butylbenzaldehyde (0.040 g 0.25 mmol) were heated at reflux for 12 h in n-propanol (10 ml) containing diethylamine (1 ml). After cooling, water (10 ml) was added and the mixture extracted with CH_2Cl_2 (3 x 10 ml). The combined organic extractions were dried ($MgSO_4$) before concentrating in vacuo. Recrystallisation from ethanol afforded **8** as a light brown solid (0.075 mg, 55%). m.p. 135-136°C. δ_H (300 MHz, $CDCl_3$) 1.38 (9H, s, ^{t}butyl); 1.44 (9H, s, ^{t}butyl); 7.38 (1H, m, $H_{5''}$); 7.49 (2H, d J = 8.2 Hz, $H_{o'/m'}$); 7.62 (2H, d J = 8.2 Hz, $H_{o/m}$); 7.75 (2H, d J = 8.2 Hz, $H_{o'/m'}$); 7.91 (1H, td J = 7.5 Hz, 1.5 Hz, $H_{4''}$); 7.75 (2H, d J = 8.2 Hz, $H_{o/m}$); 8.03 (1H, AB J = 16 Hz, $H_{a/b}$); 8.08 (1H, t J = 7.4 Hz, H_4); 8.25 (1H, dd J = 7.5 Hz, 1.5 Hz, $H_{3/5}$); 8.57 (1H, AB J = 16 Hz, $H_{a/b}$); 8.71 (1H, d J = 8.2 Hz, $H_{3''}$); 8.76 (1H, m, $H_{6''}$); 8.82 (1H, d J = 1.5 Hz, $H_{3'}$); 8.88 (1H, dd J = 7.5 Hz, 1.5 Hz, $H_{3/5}$); 8.99 (1H, d J = 1.5 Hz, $H_{5'}$). *m/z* (TOFMS) 551. IR (KBr) 2963m, 1672s, 1607s, 1580m, 1565m, 1364m, 1330m, 1272m, 1030s, 983m, 817s, 793s, 756m, 546m cm^{-1}.

4',4''',4'''''-Tris(4-*tert*-butylphenyl)-2,2':6',2":6",2''':6''',2'''':6'''',2'''''-septipyridine (9):

A solution of **7** (30 mg, 0.05 mmol), **8** (43 mg, 0.07 mmol) and anhydrous NH_4OAc (50 mg, excess) were heated at reflux in methanol (5 ml) for 6 h. After cooling the pale brown was filtered off and recrystallised by the diffusion of diethyl ether into a chloroform solution of the solid. This afforded **9** as a white solid (32 mg, 68 %). δ_H (300 MHz, $CDCl_3$) 1.42 (18H, s, ^{t}butyl); 1.44 (9H, s, ^{t}butyl); 7.38 (2H, m, H_5); 7.62 (6H, m, H_o,$H_{o'}$); 7.94 (8H, m, H_4,H_m,$H_{m'}$); 8.08 (2H, t J = 7.6 Hz, $H_{4''}$); 8.75 (10H, m, H_3, H_6, $H_{3'}$,$H_{3''}$,$H_{5''}$); 9.05 (2H, s, $H_{5'/3''}$); 9.08 (2H, s, $H_{5'/3''}$). Anal. calcd for $C_{65}H_{59}N_7.5CHCl_3$: C, 54.77; H, 4.21; N, 6.39. Found: C, 54.42; H, 4.21; N, 6.39. IR (KBr) 2961m, 1608m, 1580s, 1569s, 1543m, 1462m, 1386m, 1273m, 1117m, 819m, 664m, 546m cm^{-1}. *m/z* (TOFMS) 937 (M^+).

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