A Convenient, High Yield Synthesis of 2,2′:6′,2″-Terpyridine and its Iron(II) Complex

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Abstract

2,2′:6′,2″-Terpyridine (**3**) is obtained in high yield (60%) from the condensation of *N*-{1-(2′-pyridyl)-1-oxo-2-ethyl}pyridinium iodide with 2-(2′-pyrrolidinopropionyl)-pyridine in the presence of ammonium acetate. The ligand is conveniently isolated as its iron(II) complex, from which it may be obtained in near-quantitative yield on treatment with alkali in oxidative conditions. Performing the condensation in the presence of an iron(II) template results in enhanced yields of the iron(II) complex, which is readily isolable as its hexafluorophosphate salt.

Introduction

Ligands such as 2,2′-bipyridine, 1,10-phenanthroline and 2,2′:6′,2″-terpyridine have played formative roles in the development of contemporary inorganic chemistry [1, 2]. The ligands possess vacant low-lying π^* orbitals capable of accepting electron density from a metal, and are widely used in the stabilization of low formal oxidation states. 2,2′:6′,2″-Terpyridine is also encountered as an analytical reagent, with particular application to the colorimetric determination of transition metal ions [2]. It has recently become apparent that transition metal complexes of these π-acceptor ligands exhibit a hitherto unsuspected chemistry; specific deuterium-exchange reactions of the coordinated ligands [3], adoption of cyclometallated C,N-bonding modes [4], unusual NMR properties [5], and accelerated ligand centred reactions [6]. It is also apparent that this class of ligands form stable complexes with Group IA and IIA metal cations [7]. There is, thus, considerable interest in methods for the synthesis of 2,2′:6′,2″-terpyridine and its derivatives. Although 2,2′-bipyridine and its derivatives are readily available, the ligands based upon 2,2′:6′,2″-terpyridine are expensive, and generally only available through low yield reactions, typical preparation of 2,2′:6′,2″-terpyridine have involved the reaction of pyridine, or mixtures of pyridine and 2,2′-bipyridine, with oxidizing agents (iron(III) chloride, iodine or bromine) or dehydrogenating agents (platinum, palladium or nickel); in all cases yields are low [8]. Newkome *et al.* have described the reaction of 2,2′-bipyridine with 2-lithiopyridine, in which reasonable yields of 2,2′:6′,2″-terpyridine are obtained, although it is unlikely that this synthesis would be readily adaptable to the preparation of a wide range of substituted derivatives [9]. In this paper we report a convenient, high yield, template synthesis of 2,2′:6′,2″-terpyridine (64% overall) via its iron(II) chelate.

Experimental

Preparations involving the use of iron(II) salts were conducted under an atmosphere of dinitrogen, all other reactions were performed in air. Ammonium acetate (B.D.H.), iron(II) chloride tetrahydrate (B.D.H.) and 'ruthenium trichloride' (Johnson-Matthey) were used as supplied; 2-(2′-pyrrolidinopropionyl)pyridine [10] and *N*-{1-(2′-pyridyl)-1-oxo-2-ethyl}pyridinium iodide [11] were prepared by the literature methods. NMR spectra were recorded on Bruker AM 400 or WM 250 spectrometers. Chromatographic separations were performed using a Chromatotron (Harrison Research Co., Paolo Alto, Calif.).

Preparation of 2,2′:6′,2″-Terpyridine

A suspension of 2-(2′-pyrrolidinopropionyl)pyridinium oxalate (1.47 g, 0.005 mol) and *N*-{1-(2′-pyridyl)-1-oxo-2-ethyl}pyridinium iodide (1.63 g, 0.005 mol) in aqueous methanol (25 cm^3, 1:1) was heated to reflux with ammonium acetate (5 g) for 4 h. After this period, the oxalate had dissolved and a

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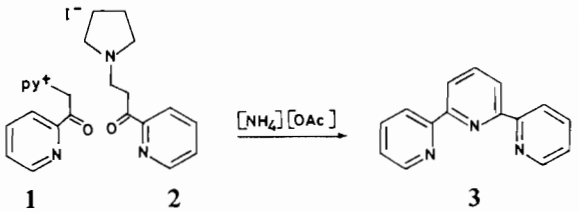
dark solution had been obtained. This was filtered hot, and the filtrate treated with $FeCl_2 \cdot 4H_2O$ (1.0 g, 0.005 mol) to give an intensely purple solution. This was treated with ammonium hexafluorophosphate (2.0 g) to give a purple microcrystalline precipitate of $[Fe(terpy)_2][PF_6]_2$, which was collected by filtration (2.03 g, 65%). *Anal.* Found: C, 44.5; H, 2.6; N, 10.5. Calc. for $C_{30}H_{22}F_{12}FeN_6P_2$: C, 44.3; H, 2.7; N, 10.3%.

A solution of $[Fe(terpy)_2][PF_6]_2$ (0.50 g, 0.62 mmol) in aqueous acetonitrile (10 cm^3, 1:1) was made alkaline by the addition of aqueous potassium hydroxide (0.6 g in 2 cm^3 H_2O) followed by the dropwise addition of aqueous hydrogen peroxide solution (30%) until the purple colour had been discharged. The suspension was filtered to remove iron oxides, and the filtrate extracted with chloroform (3×5 cm^3). The extracts were concentrated and chromatographed (Chromatotron, methanol, silica) to yield 2,2′:6′,2″-terpyridine as a pale yellow solid (0.23 g, 81%). *Anal.* Found: C, 77.4; H, 4.4; N, 18.2. Calc. for $C_{15}H_{11}N_3$: C, 77.25; H, 4.7; N, 18.05%; *m/z* 233, 100%, M^+; melting point (m.p.) 87 °C, m.p. (literature value) 88–89 °C [1]. Similar yields are obtained if the iron(II) chloride is added to the reaction mixture with the initial reactants, but the reaction time is reduced to about 1 h.

Discussion

The Kröhnke pyridine synthesis relies upon the *in situ* generation of a 1,5-dicarbonyl compound, which reacts with an amine or hydroxylamine to produce a 1,n-dihydropyridine or pyridine respectively [11]. Typically the 1,5-dicarbonyl compound is produced by the Michael condensation of a 1,2-unsaturated carbonyl compound with an active methylene compound. We have shown that this approach to the synthesis of pyridine derivatives is readily applicable to the preparation of 6,6″- or 4,4″-disubstituted or 4′-substituted 2,2′:6′,2″-terpyridines [12]. Our initial approach to the synthesis of the unsubstituted 2,2′:6 ,2″-terpyridine involved the reaction of 2-acetylpyridine with formaldehyde, to give either 2-(1-oxoprop-2-enyl)pyridine or 1,5-bis-(2′-pyridyl)-1,5-pentanedione. All attempts to prepare these compounds led to the formation of intractible tars, from which no characterized products were isolated. Highly coloured products were obtained in attempts to prepare the Mannich base of 2-acetylpyridine, by direct reaction with formaldehye in the presence of dimethylammonium chloride or pyrrolidinium chloride, under conditions in which 2,6-diacetylpyridine cleanly forms the appropriate Mannich product. However, the Mannich base could be isolated as its oxalate salt in 62% yield, using the literature procedure of treating methyl 4-(1-pyrrolidino)butyrate with 2-lithiopyridine, followed by treatment with oxalic acid [10]. This oxalate reacted with *N*-{1-(2′-pyridyl)-1-oxo-2-ethyl}pyridinium iodide and ammonium acetate in aqueous methanol to give a dark coloured solution. The addition of iron(II) chloride to this solution resulted in the formation of the characteristic deep purple coloration of the bis chelate, $[Fe(terpy)_2]^{2-}$. The high stability of this ion ($\log K_1 K_2 = 20.9$) [13] ensures the extraction of the ligand in near-quantitative yield. The addition of ammonium hexafluorophosphate results in the precipitation of $[Fe(terpy)_2][PF_6]_2$ as a purple solid. Typical yields of the complex were 60–65%, based on the organic starting materials (Scheme 1).



1 2 3

Scheme 1.

Although the stability of the iron(II) bis-chelate is high, that of the iron(III) complex is considerably lower, and it is known that iron(III) complexes of 2,2′-bipyridine and 2,2′:6′,2″-terpyridine are labile at high pH. Treatment of an alkaline solution of the iron(II) complex with hydrogen peroxide resulted in the evolution of dioxygen, and the precipitation of iron(III) oxides. Extraction of the aqueous phase with chloroform, followed by chromatography over silica (Chromatotron, methanol eluant) resulted in the isolation of 2,2′:6′,2″-terpyridine as a pale yellow solid in 80% yield (based on the iron(II) complex). The high stability of the iron(II) chelate of 2,2′:6′,2″-terpyridine prompted us to investigate the effect of added iron(II) salts upon the condensation of the Mannich base with the 'pyridacylpyridinium iodide'. It was found that the addition of half an equivalent of iron(II) chloride to the reaction mixture facilitated the dissolution of the oxalate of the Mannich base (1 h as opposed to 4 h), and resulted in the formation of an intensely purple solution, from which $[Fe(terpy)_2][PF_6]_2$ could be isolated in 60–65% yield. An attempt to use ruthenium(III) chloride as a template, to give a direct one-pot synthesis of $[Ru(terpy)_2]^{2-}$ salts was unsuccessful, the product being $[Ru(terpy)Cl_3]$. This modification of the synthesis, followed by treatment with alkaline hydrogen peroxide, enables 2,2′:6′,2″-terpyridine to be isolated in 60–65% yield overall, in a short, convenient synthesis.

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