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Convenient One-Pot Procedures for the Synthesis of 2,2′:6′,2″-Terpyridine

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Abstract: One-pot reactions to produce 2,2′:6′,2″-terpyridine (tpy) under mild conditions are described under both solventless and solvent-assisted conditions. Tpy can be obtained in 32% yield in a simple one-pot reaction, which can readily be scaled-up to give large quantities of tpy. These new approaches are superior to those previously described because of the fast and efficient synthesis and purification of tpy.

Keywords: Green chemistry, heterocycles, nitrogen ligands, one-pot reactions, terpyridine

Transition-metal complexes of 2,2′:6′,2″-terpyridine (tpy) and its substituted analogues possess interesting electrochemical, magnetic, and photophysical properties.[1–7] Although 4′-substituted terpyridines are more easily synthesized and functionalized, the parent tpy ligand remains a highly utilized component in organometallic and coordination assemblies.[8–10]

Tpy itself is commercially available; however, the compound remains relatively expensive considering the scale on which it is commonly used and therefore is typically prepared. Two common methods to synthesize tpy involve carbon–carbon bond-forming reactions[11–16] and ring-forming reactions,[17–18] of which the ring-forming reaction is more prevalent. In this respect, the methods developed by Hantzsch[17] and Potts et al.[18]

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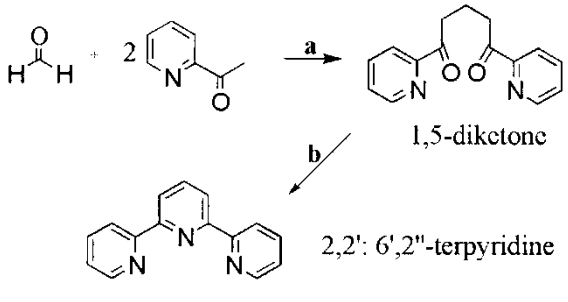
produce modest yields of unsubstituted terpyridines and involve multiple steps. More recently, Jameson reported a significant improvement in the yield of tpy via a two-step process in which a pyridyl-enaminone is generated first, followed by a ring-forming reaction to produce tpy.[19] Jameson's synthesis has undoubtedly become the preferred method to synthesize tpy; however, several factors make it less attractive than the methods proposed herein. The preparation and purification of the required pyridyl-enaminone and the variations in the final yield of the reaction due to the sensitivity of the potassium *t*-butoxide has led us to investigate more rapid procedures capable of producing consistently large quantities of tpy.

In our first attempts to produce a one-pot procedure to synthesize tpy, a 1,5-diketone was generated in situ from a basic methanolic solution of paraformaldehyde, 2-acetylpyridine, and potassium hydroxide (Scheme 1). After refluxing the mixture in the presence of ammonium acetate and filtering it through a plug of deactivated alumina, tpy was obtained in 10% yield in a solvent-assisted reaction (method A) and in 6% yield in a solventless reaction (method B). Although an excess of 2-acetylpyridine should favor the formation of the desired 1,5-diketone intermediate, 6 equiv of 2-acetylpyridine gave rise to a complex mixture that contained principally a cyclohexanol and a cyclohexanediol by-product analogous to those found for condensation reactions of 4′-aryl terpyridines.[20] Thus, a threefold excess of 2-acetylpyridine gave large amounts of the cyclohexanediol and no tpy; however, a twofold excess was found to give a 10% yield of tpy. Although the yields obtained are low, the reaction is very amenable to scale-up and multigram quantities of tpy can easily be prepared.

Considering a recent report on the efficient synthesis of substituted terpyridines via solventless condensation and subsequent Michael addition,[21] the same reaction was attempted under solventless conditions. Paraformaldehyde and a stoichiometric amount of 2-acetylpyridine in the presence of potassium hydroxide were ground for 30 min, and the mixture was then



Scheme 1. Synthesis of tpy from formaldehyde. Reagents and conditions: a) formaldehyde (33 mmol), 2-acetylpyridine (66 mmol), KOH (102 mmol), MeOH (150 mL) 16 h at rt, b) NH_4OAc (130 mmol), AcOH, reflux, 3 h.

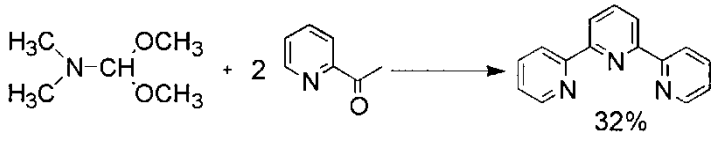
dissolved and heated to reflux in acetic acid containing ammonium acetate for 1.5 h. The reaction mixture was then filtered through a plug of deactivated alumina, and pure tpy was obtained in 6% yield. Although the yield was low as well, the short reaction time, the simplified experimental procedure, and the suitability of the reaction to scale-up make this a reasonable protocol for the synthesis of tpy. The main advantage of the solvent-assisted and solventless procedures mentioned previously is that reasonable quantities of tpy can be obtained quickly because of the shorter reaction times and the simplified purification procedures, filtration, and recrystallization, as opposed to the use of column chromatography to purify the tpy.

The highest yielding one-pot procedure has been optimized using a combination of Chichibabin and Jameson approaches (Scheme 2). As with the Jameson method, *N,N*-dimethylformamide dimethylacetal is reacted with 2-acetylpyridine to give an enaminone in situ for subsequent Michael addition. However, the enaminone is not isolated, and the enolate of 2-acetylpyridine is generated with a methanolic solution of potassium and ammonium hydroxide. The reaction conditions are less stringent than those of the Jameson reaction as anhydrous conditions are not required. Pure 2,2′:6′2″-terpyridine is obtained in 32% yield after stirring in EtOH at reflux for 24 h followed by column chromatography and recrystallization (method C). This improved one-pot reaction can also be scaled up to give 10 g of tpy following a similar protocol, albeit in a slightly lower yield (method D).

In conclusion, we have presented three different one-pot procedures for the synthesis of tpy, a useful synthon in coordination and supramolecular chemistry. The highest yielding reaction provides useful quantities of tpy in one single step.

EXPERIMENTAL

The properties of tpy prepared in the following methods were identical to those reported previously.[11–19] The reaction of tpy prepared in any of the methods with $RuCl_3$ gave a homoleptic $Ru(tpy)_2^{2+}$ complex with properties identical to those previously reported.[1]



Scheme 2. Generation of tpy from *N,N*-dimethylformamide dimethylacetal. Reagents and conditions: *N,N*-dimethylformamide dimethylacetal (10 mmol), 2-acetylpyridine (20 mmol), KOH (20 mmol), NH_4OH (30 mmol), EtOH (50 mL), 24 h reflux.

Method A: 2,2′:6′,2″-Terpyridine Synthesis

In a typical reaction, paraformaldehyde (1 g, 0.033 mol) was dissolved in methanol (150 mL) containing potassium hydroxide (5.74 g, 0.102 mol) and 2-acetylpyridine (16.2 g, 0.132 mol). The reaction mixture was stirred at room temperature for 16 h, after which time ammonium acetate (10 g, 0.130 mol) was added, and the mixture was stirred at reflux for 3 h. The methanol was removed under reduced pressure, and the remaining aqueous residue was washed with chloroform (100 mL × 3). The combined organic phases were dried, taken up in toluene, and purified by filtration through a plug of 5% deactivated alumina using toluene as eluent and ferrous ammonium sulfate as indicator. The desired fractions were collected and dried under vacuum at 70 °C to remove residual 2-acetylpyridine and gave 2,2′:6′,2″-terpyridine (0.775 g, 10%) after recrystallization from hexane. Elem. anal.: calc. C, 77.23; H, 4.75; N, 18.01; found C, 77.17; H, 4.77; N, 17.98.

Method B

In a typical reaction, paraformaldehyde (0.5 g, 0.0165 mol), 2-acetylpyridine (4.03 g, 0.033 mol), and potassium hydroxide (1.87 g, 0.033 mol) were ground in a mortar for 30 min. The resulting viscous residue was then dissolved in acetic acid (40 mL), to which was added ammonium acetate (5 g, 0.065 mol), and the mixture was stirred at reflux for 1.5 h. The crude mixture was then tipped into water (400 mL) to give a fine precipitate, which was isolated, dissolved in toluene, and purified by filtration through a plug of 5% deactivated alumina using toluene as eluent and ferrous ammonium sulfate as indicator. Evaporation of the combined tpy fractions and recrystallization of the crude product gave 2,2′:6′,2″ terpyridine (0.235 g, 6%). Elem. anal. calc. C, 77.23; H, 4.75; N, 18.01; found C, 77.02; H, 4.75; N, 17.91.

Method C

In a typical reaction, 2-acetylpyridine (2.42 g, 0.020 mol), *N,N*-dimethylformamide dimethylacetal (1.19 g, 0.010 mol), potassium hydroxide (1.54 g, 0.020 mol), and ammonium hydroxide (29 mL, 0.030 mol) were combined in absolute ethanol (50 mL). The solution was then heated to reflux for 24 h. After cooling, the ethanol was removed under reduced pressure, and the remaining aqueous solution was extracted with chloroform (30 mL × 3). The combined organic phases were dried, taken up in toluene, and applied to a short column of 5% deactivated alumina for purification using toluene as eluent and ferrous ammonium sulfate as indicator. Evaporation of the

combined tpy fractions and recrystallization of the residue from hexane affords 2,2′:6′,2″-terpyridine (0.74 g, 32%). Elem. anal.: calc. C, 77.23; H, 4.75; N, 18.01; found C, 77.08; H, 4.79; N, 17.89.

Method D

In a typical reaction, 2-acetylpyridine (60.6 g, 0.50 mol), *N,N*-dimethylformamide dimethylacetal (29.8 g, 0.25 mol), potassium hydroxide (32.6 g, 85%, 0.50 mol), and ammonium acetate (77 g, 1.0 mol) were combined in denatured alcohol (1.0 L; ethanol/methanol = 85:15). The solution was then heated to reflux for 24 h. After cooling, the solvent was removed under reduced pressure, and the remaining residue was extracted with chloroform (100 mL × 5). The organic phases were combined and dried, taken up in toluene, and applied to a short column of 5% deactivated alumina for purification using toluene as eluent and ferrous ammonium sulfate as indicator. Recrystallization from hexane affords 2,2′:6′,2″-terpyridine (10.4 g, 18%). Elem. anal.: calc. C, 77.23; H, 4.75; N, 18.01; found C, 76.88; H, 4.87; N, 17.76.

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