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AN IMPROVED, TWO-STEP SYNTHESIS OF 2,2':6',2"-TERPYRIDINE.

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Summary: The important tridentate ligand 2,2':6',2"-terpyridine has been synthesized in two steps in an overall yield of 47%. The reaction can be scaled up to provide multigram quantities of the ligand.

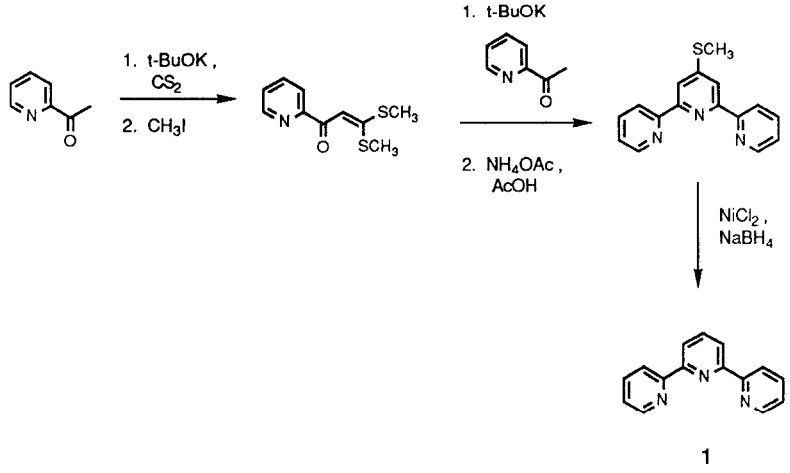
The 2,2':6',2"-terpyridine molecule (**1**) is widely used in transition metal chemistry as a meridionally coordinating, tridentate chelating ligand.[1] In addition, terpyridine serves as the starting material for a variety of substituted terpyridines.[2] The two common synthetic approaches to terpyridine involve the coupling of three pyridine units (via either oxidative coupling of pyridines[3,4] or by Ullman coupling of bromopyridines[5]) or syntheses in which the central pyridine ring is constructed.[6,7] The former strategy suffers from low yields and often involves the separation of intractable mixtures of different oligomers and regioisomers. The latter strategy, although more rational, is fairly lengthy and the reaction steps are often inconvenient. As part of a project directed toward the synthesis of substituted terpyridines, we required large amounts of the title ligand. Although terpyridine is commercially available, it is rather expensive. We wish to report a new, convenient, two-step synthesis which yields multigram quantities of terpyridine.

Potts, et al have reported a three step synthesis of terpyridine which features an α-oxoketene dithioacetal as the key synthetic intermediate (Scheme I).[7] A subsequent published modification required two steps.[8] Our synthesis, based on a variation of this strategy, is outlined in Scheme II.[9] The key intermediate is enaminone **2**, which is prepared in high yield by the reaction of 2-acetylpyridine with N,N-dimethylformamide dimethyl acetal.[10] The potassium enolate of 2-acetylpyridine is condensed with enaminone **2**, with subsequent loss of dimethyl amine. Closure of the resulting 1,5-enedione[11] (not isolated) with ammonium acetate gives terpyridine directly. The overall yield of the two step process is 47 %.[12]

Aside from the ready scale up of this method to afford large quantities of terpyridine, two additional advantages are obtained. The reaction of the potassium enolate of 2-acetylpyridine with the α-oxoketene dithioacetal (in Scheme I) causes the release of methanethiol, whose smell pervades the product (even after purification) as well as the reaction wastes. Secondly, the above procedure avoids the inconvenient

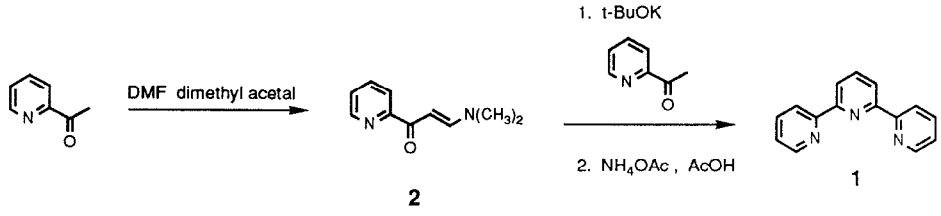
reductive removal of the thiomethyl group, which is a major obstacle to the scale-up of the procedure. This reduction step requires the use of 43 grams of nickel chloride and 20 grams of sodium borohydride for the isolation of 2.9 grams of terpyridine.[13] Efforts are currently underway to prepare a series of substituted terpyridines from the parent ligand.

Scheme I



1

Scheme II



2

1

EXPERIMENTAL

All reagents were purchased from Aldrich and were used as received. Anhydrous tetrahydrofuran was purchased from Aldrich in Sure-Seal bottles and was transferred to reaction flasks via cannula. Column chromatography was performed using neutral alumina (activity IV). Melting points are uncorrected. ^{1}H NMR (80 MHz) and ^{13}C NMR (20 MHz) spectra were recorded on an IBM NR-80 spectrometer. Spectra were run in $CDCl_3$ and chemical shifts are reported in parts per million (ppm) versus a TMS internal

standard.

β-(dimethylamino)vinyl 2-pyridyl ketone (2). A solution of 20.0 g (0.165 mol) of 2-acetylpyridine and 24.0 g (0.201) N,N-dimethylformamide dimethyl acetal in 100 mL of toluene was heated to reflux. Methanol was gradually removed by fractional distillation. The reaction was heated until no more methanol distilled over (ca. 8 h). The toluene was removed on a rotary evaporator and the product was crystallized by the addition of cyclohexane. Filtration afforded 24.9 g (86% yield) of yellow crystalline enaminone: mp 125-127 °C. The product was sufficiently pure to be used in the next step. ^{1}H NMR ($CDCl_3$) δ 3.06 (br s, 6H), 6.45 (d, 1H), 7.24-7.44 (m, 1H), 7.78 (d of t, 1H), 7.90 (d, 1H), 8.15 (d of m, 1H) 8.62 (d of d of d, 1H).

2,2':6',2"-terpyridine (1). A nitrogen-flushed 1-liter flask was charged with 22.4 g (0.20 mol) of potassium t-butoxide in 500 mL of anhydrous THF. To this solution was added 12.1 g (0.10 mol) of 2-acetylpyridine. The solution was allowed to stir for 2 h at room temperature and 17.6 g (0.10 mol) of β-(dimethylamino)vinyl 2-pyridyl ketone was added in a single portion. The solution, which gradually turned deep red, was allowed to stir at room temperature for 14 h. The mixture was treated successively with 77.0 g (1.0 mol) of ammonium acetate and 250 mL of acetic acid. The THF was removed by slow distillation over the course of 2 h. The remaining acetic acid was removed on a rotary evaporator, leaving a black residue which was treated with 500 mL of water. Solid sodium carbonate was added (carefully) until effervescing ceased and the mixture was extracted with 3 x 200 mL of methylene chloride. The combined organic phases were dried over magnesium sulfate, filtered and evaporated to a black oil. The oil was dissolved in 200 mL of toluene, leaving a black granular precipitate which was removed by filtration through Celite. The dark toluene filtrate was passed through a short (4.5 x 15 cm) column of neutral alumina and eluted with toluene. Evaporation of the eluent and crystallization from hexanes gave 12.8 g (55%) of tan crystals; mp 84-86 °C (lit mp 84-86°C [7]). ^{1}H NMR ($CDCl_3$) δ 7.29 (d of d of d, 2H), 7.81 (d of t, 2H), 7.93 (t, 1H), 8.45 (d, 2H), 8.62 (d, 2 H), 8.69 (d of m, 2H). ^{13}C NMR ($CDCl_3$) δ 121.0, 121.1, 123.7, 136.7, 137.8, 149.1, 155.4, 156.3.

The $Ru(terpy)_2(PF_6)_2$ complex was prepared and it exhibited a strong absorbance at 476 nm ($\varepsilon = 1.5 \times 10^4$)(lit.[14] : 476 nm ($\varepsilon = 1.6 \times 10^4$).

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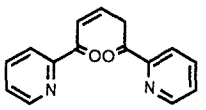
9. We have located at least one other example of a pyridine ring that has been constructed from an enaminone intermediate: Bell, T. W.; Firestone, A. *J. Am. Chem. Soc.* **1986**, 108, 8109.
10. A modification of a literature procedure was used; Lin, Y.; Lang, S. A., Jr. *J. Heterocycl. Chem.* **1977**, 14, 345.
11. The enedione intermediate has the following structure:



12. Compare with an overall yield of about 45% in reference 8.
13. The 4'-methylthioterpyridine is a useful intermediate for the preparation of other 4'-substituted terpyridines; see reference 8.
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