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Substituted 2,2′-bipyridines by nickel-catalysis: 4,4′-di-*tert*-butyl-2,2′-bipyridine

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Abstract

A simple, ligand-free synthesis of the important bipyridyl ligand 4,4′-di-*tert*-butyl-2,2′-bipyridine is presented. 5,5′-bis(trifluoromethyl)-2,2′-bipyridine is also synthesized by the same protocol. The syntheses efficiently couple the parent 2-chlorpyridies by a nickel-catalyzed dimerization with manganese powder as the terminal reductant.

Keywords

nickel; 4,4′-di-*tert*-butyl-2,2′-bipyridine; pyridine; catalysis; reductive

Bipyridine ligands have long been used with transition-metals in both catalysis and materials applications, but their chemistry is less well studied than the more frequently employed mono- and bisphosphines.[1] Among many recent applications, 4,4′-di-*tert*-butyl-2,2′-bipyridine (**3a**) has been found to be useful in the iridium-catalyzed C-H borylation reaction,[2] a variety of nickel-catalyzed cross-electrophile coupling reactions,[3] the nickel-catalyzed cross-coupling of tertiary alkyl bromides with organoboron reagents,[4] the copper-mediated trifluoromethylation of aryl iodides,[5] the manganese-catalyzed reduction of CO_2,[6] and in iridium dyes used in photocatalysis and OLED.[7] At the same time that the utility of 4,4′-di-*tert*-butyl-2,2′-bipyridine has become increasingly evident, the ligand has become more difficult to obtain commercially.[8] Aldrich, the sole supplier in the United States, was continually backordered for a period of 6 months in 2012. The limited availability prompted us to consider alternate synthetic routes and we present here our results with a nickel-catalyzed reductive homocoupling.

Of the methods reported for the synthesis of **3a** (Figure 1), the most convenient is reported to be that of McGill, which heats a mixture of 4-*tert*-butylpyridine with sodamide at 145 °C to form **3a** in 8-15% yield.[9] The other reported method is the dehydrogenative coupling of 4-*tert*-butylpyridine catalyzed by either nickel[10] or palladium[11] at elevated temperature. Reported yields range from <10% up to 64% yield, but vary considerably. In our hands, the reported procedures were inconvenient because they often suffered from low conversions

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that required distillation of the remaining, valuable 4-*tert*-butylpyridine, and because the dehydrogenative conditions provided inconsistent yields. The limited availability of **3a** may be related to the difficulties associated with these procedures.

A number of substituted bipyridines have been synthesized by the nickel[12] or palladium[13] catalyzed reductive homocouplings of 2-halogenated pyridines. Most of the methods require high catalyst loadings (up to 30 mol% nickel, up to 10 mol% palladium), ancillary ligands, and/or additives, such as Cp_2ZrCl_2.

We provide here a simple route to **3a** that is reliable and scalable (Scheme 1). Reaction of 4-*tert*-butylpyridine with peracetic acid forms the *N*-oxide. This then reacts with $POCl_3$ to form 4-*tert*-butyl-2-chloropyridine (**2a**).[14] Dimerization of **2a** is achieved by nickel catalysis (0.5 mol %) with manganese as the terminal reducing agent. No added ligand is required and purification is achieved by simple aqueous work-up and sublimation (Table 1). Additionally, 2-chloro-5-trifluoromethylpyrdine (**2b**) dimerized to form **3b** in 70% yield. This bipyridine has been reported as a ligand in ruthenium dyes[15] and for catalysis,[16] but has not been extensively explored in either arena. Previous syntheses were lower yielding or required expensive palladium catalysts.[17] Lastly, simple 2-chloropyridine (**2c**) dimerized in 86% yield with only 0.2 mol% nickel catalyst.

Vital to the success of these new, ligand-free dimerization conditions is the use of manganese powder as the reducing agent. Replacing manganese with zinc dust results in quantitative hydrodehalogenation of the chloropyridine. If $NiBr_2•3H_2O$ is not available, $NiCl_2•6H_2O$ also formed product in similarly high yield. Reactions in toluene, butanol, acetone, or ethanol did not form product at all, but a reaction in 1:3 DMF:THF worked as well as a reaction in pure DMF. Finally, although nickel hydrate salts were effective pre-catalysts, reactions run in DMF from an open-bottle off the shelf (measured to be ~10000 ppm H_2O) were half as fast as our standard reaction in dry DMF (85 ppm H_2O).

Although no ligand is added to these reactions, the first turnover of the catalyst generates a suitable ligand for the coupling reaction. Reactions of halopyridines that do not form bidentate ligands, such as 3-bromopyridine, do not consume starting material unless an external ligand is added.

Mechanistically, we have not conducted any investigations, but we currently favor the disproportion mechanism proposed by Osakada and Yamamoto.[18]

We expect that this method will provide improved and reliable access to **3a**. The low catalyst loading, ligand- and additive-free reaction conditions combined with high substrate concentrations makes this route particularly useful for large-scale laboratory experiments.

4,4′-di-*tert*-butyl-2,2′-bipyridine [72914-19-3] (3a)[19]

On the benchtop, a 50 mL round bottom flask equipped with a 1/2 inch Teflon coated magnetic stir bar was charged with $NiBr_2·3H_2O$ (401 mg, 1.47 mmol) and DMF (20.0 mL). The vessel was stoppered with a rubber septum and heated to 60 °C until a green homogenous solution resulted (approx. 20 min). Once homogeneity was achieved, the vessel

was removed from the heat and allowed to cool to room temperature. Once at room temperature 4-*tert*-butyl-2-chloropyridine (**2a**) (4.99 g, 29.4 mmol) and manganese powder (−325 mesh, 3.30 g, 60.0 mmol) were added, and the vessel was resealed with the septum, purged with argon, and heated again to 60 °C for the duration of the reaction. Reaction progress was monitored by GC analysis of aliquots of crude reaction mixture. In general the reaction turns very dark brown or black in color when complete, and the color change is a reliable indicator for the reaction endpoint. Upon completion, the reaction was cooled to room temperature, diluted with ether (80 mL) and filtered through a short pad of celite (approx. 2 in × 2 in × 2 in) that had been wetted with ether to remove metal salts. The reaction vessel was washed with ether (2 × 40 mL) and the washes were then passed through the filter. The filtrate was transferred to a separatory funnel and washed with 1M sodium hydroxide (200 mL). A brown emulsion formed in the separatory funnel during the work-up that slowly separated. Care was taken to keep the brown emulsion with the organics. Once separated, the aqueous layer was extracted with additional ether (3 × 150 mL). The combined organic extracts and brown emulsion were washed with brine (500 mL). Again care was taken to keep the brown emulsion with the organics. The organics were dried with copious amounts of $MgSO_4$. The solid drying agent was removed by filtration, ground into a fine powder and washed with additional ether (3 × 150 mL). The filtrate was evaporated to dryness to give **3a** (3.57 g) as faintly yellow crystals in 90% yield. This material was judged analytically pure by NMR and combustion analysis. If necessary the product can be further purified by sublimation (140 °C, 300 mtorr). Analytical data reported below is for material that was not sublimed.

^{1}H-NMR (400 MHz; $CDCl_3$): δ 8.60 (d, *J* = 5.2 Hz, 2H), 8.41 (d, *J* = 1.0 Hz, 2H), 7.30 (dd, *J* = 5.2, 1.7 Hz, 2H), 1.39 (s, 18H).

^{13}C-NMR (126 MHz; $CDCl_3$): δ 161.1, 156.7, 149.2, 120.8, 118.4, 35.1, 30.8.

Anal. Calc. for $C_{18}H_{24}N_2$ requires: C, 80.55; H, 9.01; N, 10.44; **found:** C, 80.29; H, 9.12; N, 10.44%.

MP = 157 -158 °C (lit.[19] = 159 -160 °C).

5,5′-Bis(trifluoromethyl)-2,2′-bipyridine [142946-80-3] (3b)[15, 17]

The procedure for **3a** was followed on 15.0 mmol scale and with 1M ammonium hydroxide in place of 1M sodium hydroxide. The product was purified by sublimation (110 °C, 200 mtorr) to give **3b** (1.54 g) as white solid in 70% yield.

^{1}H-NMR (500 MHz; $CDCl_3$): δ 8.96 (s, 2H), 8.62 (d, *J* = 8.3 Hz, 2H), 8.08 (dd, *J* = 8.3, 1.8 Hz, 2H).

^{13}C-NMR (126 MHz; $CDCl_3$): δ 157.9, 146.47 (q, *J* = 4.3 Hz), 134.47 (q, *J* = 3.2 Hz), 127.31 (q, *J* = 33.3 Hz), 123.67 (q, *J* = 272.8 Hz), 121.4.

^{19}F-NMR (376 MHz; $CDCl_3$): δ −0.1.

Anal. Calc. for $C_{12}H_6F_6N_2$ requires: C, 49.39; H, 2.07; N, 9.59; **found:** C, 49.60; H, 2.15; N, 9.59%.

MP = 128-130 °C (lit.[17] = 124-126 °C (hexanes)).

2,2′-bipyridine [366-18-7] (3c)[20]

The procedure for **3a** was followed on 15.0 mmol scale with 0.2 mol% nickel, and with 1M ammonium hydroxide in place of 1M sodium hydroxide. The product was purified by sublimation (95 °C, 100 mtorr) to give **3c** (1.00 g) as white solid in 86% yield.

^{1}H-NMR (500 MHz; $CDCl_3$): δ 8.69 (d, *J* = 4.6 Hz, 2H), 8.40 (d, *J* = 8.0 Hz, 2H), 7.82 (td, *J* = 7.7, 1.6 Hz, 2H), 7.31 (ddd, *J* = 7.4, 4.8, 1.0 Hz, 2H).

^{13}C-NMR (126 MHz; $CDCl_3$): δ 156.2, 149.2, 137.0, 123.8, 121.1.

Anal. Calc. for $C_{10}H_8N_2$ requires: C, 76.90; H, 5.16; N, 17.94; **found:** C, 76.72; H, 5.08; N, 17.93%.

MP = 70-72 °C (lit.[21] = 71-72 °C).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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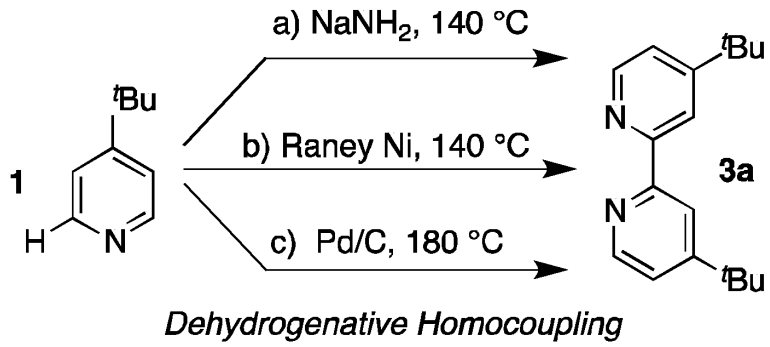
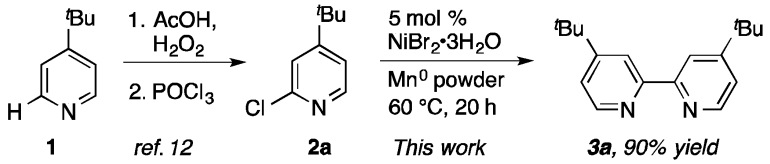


Figure 1.
Literature methods for the synthesis of 4,4′-di-*tert*-butyl-2,2′-bipyridine (**3a**).

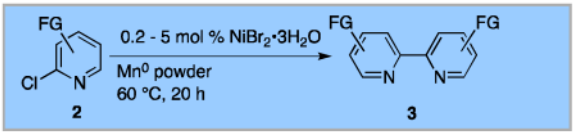


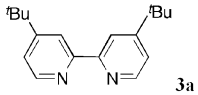
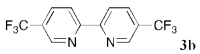
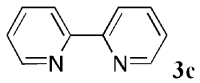
Scheme 1.

Improved and convenient synthesis of 4,4′-di-*tert*-butyl-2,2′-bipyridine (**3a**).

Table 1

Nickel-catalyzed reductive dimerization of 2-chloropyridines.[a]



Entry	3	Yield (%)[b]
1	 3a	90
2[c]	 3b	70
3[d]	 3c	86

[a] Reaction conditions: **2a** (4.99g, 29.4 mmol), $NiBr_2 \cdot 3H_2O$ (401 mg, 1.47 mmol), DMF (20 mL), and manganese powder (−325 mesh, 3.30 g, 60.0 mmol) were heated under argon for 20 h.

[b] Yield of isolated and purified product.

[c] Reaction run on 15.0 mmol scale with **2b**.

[d] Reaction run on 15.0 mmol scale with **2c** with 0.2 mol% $NiBr_2 \cdot 3H_2O$ for 18 h.