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An improved synthesis of hydroxymethyl bipyridines

Adam P. Smith, Perry S. Corbin and Cassandra L. Fraser *

Department of Chemistry, University of Virginia, Charlottesville, Virginia 22901, USA

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Abstract

This account describes quick and efficient syntheses of 4,4′-bis(hydroxymethyl)-2,2′-bipyridine and 4-hydroxymethyl-2,2′-bipyridine from 4,4′-dimethyl-2,2′-bipyridine and 4-methyl-2,2′-bipyridine, respectively, via (trimethylsilyl)methyl-, bromomethyl-, and acetoxymethyl- intermediates.

Keywords: nitrogen heterocycles; pyridines; alcohols; ligands.

Bipyridine reagents are widely used in many areas of chemistry including bioinorganic,[1] supramolecular[2] and polymeric materials[3] contexts. Of interest to us is the use of these heterocycles and their complexes as initiators[4] for various living/controlled polymerizations. Despite their prevalence, many simple bipyridine analogues have traditionally been difficult to conveniently synthesize in high yields.[5]

Among these are the hydroxymethyl derivatives.[6–12] For example, Beer et al. have described a synthesis of 4,4′-bis(hydroxymethyl)-2,2′-bipyridine **1**, from 4,4′-dimethyl-2,2′-bipyridine (4,4′-dimethyl bpy) by Jones' oxidation, subsequent Fischer esterification of the resulting diacid, and $NaBH_4$ reduction.[6] Although this sequence employs common organic transformations, it typically affords product in moderate yield and takes several days to complete on a large scale. Another common pathway to bis(hydroxymethyl)-2,2′-bipyridines is the reaction of a dimethyl bpy *N*-oxide with Ac_2O, followed by hydrolysis of the resulting diester.[7–9] Again, only moderate yields are reported for this transformation.

Herein we describe a quick and more efficient synthesis of **1** from 4,4′-dimethyl bpy. This procedure makes use of a high-yielding bis(halomethyl)-2,2′-bipyridine synthesis that proceeds via 4,4′-bis(trimethylsilyl)methyl-2,2′-bipyridine, **2**.[13] Following isolation of **2**, bromination was achieved by the addition of CsF and an electrophilic bromide source, BrF_2CCF_2Br, to afford 4,4′-bis(bromomethyl)-2,2′-bipyridine, **3** (Scheme 1).

Initial attempts to obtain **1** directly from **3** or the analogous bis(chloromethyl) bipyridine[13] afforded product in low yield. Specifically, 4,4′-bis(chloromethyl)-2,2′-bipyridine was refluxed with aqueous $CaCO_3$ in 1,4-dioxane.[14] All trials produced a mixture of products from which the alcohol was isolated in

* Corresponding author.

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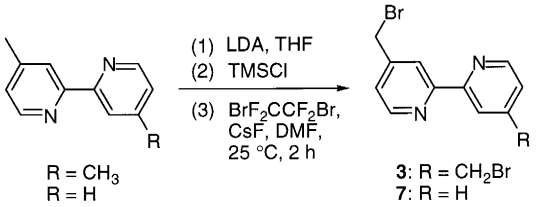
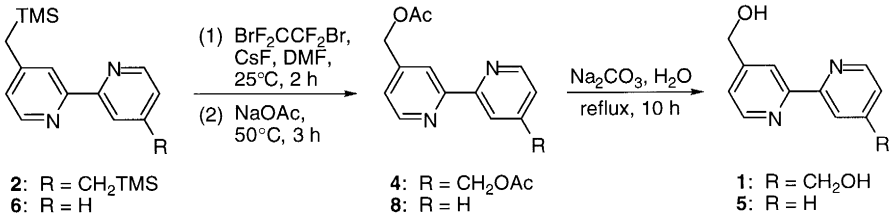


Scheme 1.

only 38% yield, at best. Likewise, poor yields of **1** (~30%) were obtained when 4,4′-bis(bromomethyl)- or 4,4′-bis(chloromethyl)-2,2′-bipyridine were reacted with NaOH in DMF, THF or H_2O. We speculate that the low yields and product mixtures may arise due to competing oligomerization by ether formation.

The use of an acetate nucleophile for the halogen displacement circumvented issues mentioned above and gave **1** after hydrolysis (Scheme 2).[15,16] Furthermore, it was not necessary to isolate **3** prior to addition of the acetate. After converting **2** to **3**, excess BrF_2CCF_2Br was removed in vacuo, and NaOAc was added to the reaction mixture to provide 4,4′-bis(acetoxymethyl)-2,2′-bipyridine **4**, after stirring for 3 h at 50°C. From this point, hydrolysis of the acetate was either conducted in situ or following isolation of **4**, with the latter case affording cleaner product in higher yield. Specifically, the acetate was isolated with an aqueous work-up, and, without further purification, hydrolysis was carried out with aqueous Na_2CO_3 in THF.



Scheme 2.

Isolation of product **1** was achieved in two steps. First, after concentrating the entire reaction mixture, the solid was redissolved in hot H_2O then filtered to remove any insoluble organic impurities. Following concentration of this aqueous solution, a solid extraction with hot EtOAc was performed to separate the diol from sodium salts. Concentration afforded 4,4′-bis(hydroxymethyl)-2,2′-bipyridine, **1**, in 85% yield from **2** as a white crystalline solid (>95% pure by ^{1}H NMR). The product may be further purified by EtOAc recrystallization.[17] For a representative preparation of **1**, see Ref. 16.

The versatility of this route was demonstrated by the synthesis of 4-hydroxymethyl-2,2′-bipyridine **5**, from 4-(trimethylsilyl)methyl-2,2′-bipyridine **6**.[18] Following purification via flash chromatography on silica gel (10% CH_3OH:90% $CHCl_3$), **5** was obtained in 70% yield as a pale yellow, oily solid.[19]

In summary, an efficient three-step synthesis of widely used hydroxymethyl bipyridine derivatives from methyl bpy precursors was developed. As compared with a common alternative route,[6] this straightforward approach reduces overall preparation time by ~2 days and generates products more conveniently and in higher overall yields.

Acknowledgements

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16. Representative synthesis of **1** via the acetate **4**: To 4,4′-bis[(trimethylsilyl)methyl]-2,2′-bipyridine **2**,[13] (1.00 g, 3.05 mmol) and BrF_2CCF_2Br (3.16 g, 12.17 mmol) in DMF (35 mL) was added dry CsF (1.85 g, 12.17 mmol). The heterogeneous reaction mixture was stirred at 25°C for 2 h. Volatiles ($F_2C{=}CF_2$, Me_3SiF, and excess BrF_2CCF_2Br) were removed in vacuo then NaOAc (3.87 g, 47.2 mmol) was added to the remaining DMF mixture. The suspension was stirred at 50°C for ~3 h and then was cooled to room temperature. Solvent was removed in vacuo, and the resulting solids were partitioned between CH_2Cl_2 and H_2O (~75 mL each). After extracting the aqueous layer with CH_2Cl_2 (3×25 mL), combined organic layers were concentrated to dryness to give the crude diacetate, **4**. Analytical data for 4,4′-bis(acetoxymethyl)-2,2′-bipyridine, **4**, are as follows: TLC R_f=0.66 (100% EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.18 (s, 1H), 5.20 (s, 2H), 7.29 (dd, *J*=0.8, 5.0 Hz, 2H), 8.38 (s, 2H), 8.67 (d, *J*=5.0 Hz, 2H). The acetate intermediate, **4**, was dissolved in THF (50 mL) and an aqueous solution of Na_2CO_3 (1.24 g, 11.66 mmol in 50 mL) was added. The reaction mixture was heated at reflux for 10 h, then concentrated to dryness. The crude product was redissolved in hot water and filtered to remove insoluble impurities. After concentration in vacuo, the resulting residue was extracted with hot EtOAc. Concentration of the EtOAc solution gave 4,4′-dihydroxymethyl-2,2′-bipyridine **1**, as a white solid: 570 mg (85%); Spectral properties were in accord with those previously reported.[10]
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19. ^{1}H NMR (CD_3OD, 300 MHz) δ 4.68 (s, 2H), 7.37 (m, 2H), 7.87 (m, 1H), 8.22 (m, 2H), 8.55 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 30.2, 119.2, 121.8, 122.0, 124.4, 137.7, 149.5, 149.6, 152.3, 156.3, 156.4.