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Efficient Synthesis of Tris(4-imidazolyl)methanol Derivatives

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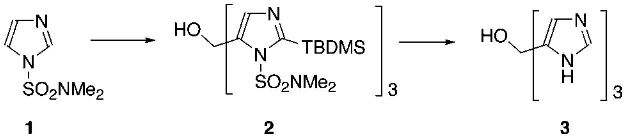
ABSTRACT



Biomimetic tris(4-imidazolyl)carbinol derivatives are prepared from imidazole in a short, high-yielding sequence via sulfonamide 1, which is converted to the 2-silylated carbinol 2 by one-pot, sequential 2-functionalization and then 4(5)-functionalization. Alcohol 2 can be transformed either to the parent carbinol 3 or to a desilylated sulfonamide derivative 4. The tripodal alcohol 3 is a convenient precursor to ethers by solvolysis and to metal complexes, as illustrated by the preparation of a bis-tripod complex with iron(III).

Polyimidazole coordination of metal ions to histidine residues is a pervasive feature of metalloproteins. Although many structural and spectroscopic models and some functional models for the active sites of poly(histidinyl)-metal enzymes have been prepared, almost all have incorporated polypyridine, -pyrazole, or -2-imidazole ligands rather than the biologically relevant poly(4-imidazole) ligand sets.[1] This stems in part from the lack of efficient synthetic methods for the regioselective functionalization of imidazoles, especially at the 4-position as found in the metal-bound histidines. Breslow first reported a multistep synthesis of tris(4-imidazolyl)carbinols featuring 2-thiophenyl protection of the imidazole unit that proceeded in five steps and 3−16% yield from imidazole.[2] Katritzky and co-workers produced 4-imidazolyl-substituted carbinols via 4-bromoimidazole in 25−35% overall yield (three synthetic steps) from imidazole.[3] Recently, the Collman group described a related sequence via metalation of 4-iodo-1-trityl imidazole (five steps, 14% from imidazole).[4]

Seeking biomimetic poly(4-imidazolyl)-metal complexes as catalysts, protein cofactors, and antibody haptens, we sought a more efficient and flexible entry to these ligands. We report here (1) a substantially improved route to tris(4-imidazolyl)carbinol derivatives featuring a three-pot sequence (56% overall) from imidazole, (2) a new method for producing the corresponding tripodal ethers and desilylated N-protected derivatives, and (3) the first structurally characterized metal complex of a tripodal tris(4-imidazolyl) ligand, **3**.

The doubly protected carbinol **2** can be efficiently prepared in one-pot from readily available sulfonamide **1** (one step, 91% from imidazole)[5] by adapting the regioselective lithiation method of Ngochindo and Chadwick (Scheme 1).[6] Thus, a THF solution of **1** was treated sequentially with *n*-BuLi (1.05 equiv, −78 °C), *t*-BuMe$_2$SiCl (1.1 equiv, −78 to 20 °C), *n*-BuLi (1.1 equiv, −78 °C), and finally diethyl carbonate (0.30 equiv, −78 to 20 °C). After aqueous workup, the carbinol **2** is easily isolated in pure form without chromatography (70% yield from **1**).[7] Conversion of **2** to the parent tripodal alcohol **3** was simply accomplished by heating in 1.5 M HCl; ion-exchange chromatography provided either the neutral alcohol **3a** (88%) or its hydrochloride

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[1] (a) Wu, L. P.; Yamagiwa, Y.; Ino, I.; Sugimoto, K.; Kuroda-Sowa, T.; Kamikawa, T.; Munukata, M. *Polyhedron* **1999**, *18*, 2047. (b) Kimblin, C.; Bridgewater, B. M.; Churchill, D. G.; Parkin, G. *J. Chem. Soc., Dalton Trans.* **2000**, 2191. (c) Champloy, F.; Benali-Cherif, N.; Bruno, P.; Blain, I.; Pierrot, M.; Reglier, M. *Inorg. Chem.* **1998**, *37*, 3910. (d) Kitajima, N.; Koda, T.; Iwata, Y.; Moro-oka, Y. *J. Am. Chem. Soc.* **1990**, *112*, 8833. (e) Sorrell, T. N.; Allen, W. E. *Inorg. Chem.* **1997**, *36*, 1732.

[2] Tang, C. C.; Davalian, D.; Huang, P.; Breslow, R. *J. Am. Chem. Soc.* **1978**, *100*, 3918.

[3] Katritzky, A. R.; Slawinski, J. J.; Brunner, F.; Gorun, S. *J. Chem. Soc., Perkin Trans. 1* **1989**, *6*, 1139.

[4] Collman, J. P.; Zhong, M.; Wang, Z. *Org. Lett.* **1999**, *1*, 949.

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[6] Ngochindo, R. I. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1645. Carpenter, A. J.; Chadwick, D. J. *Tetrahedron* **1986**, *42*, 2351.

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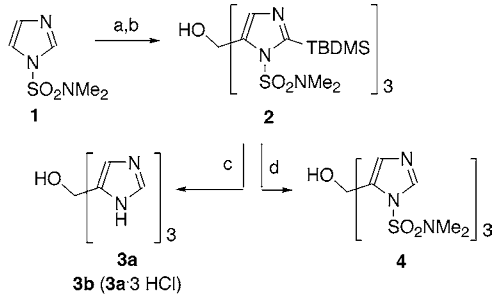
Scheme 1[a]

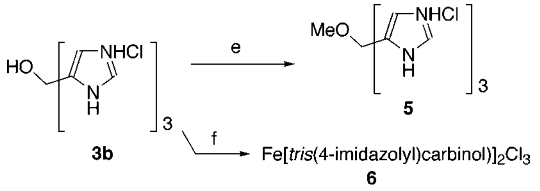


[a] Conditions: (a) BuLi, TBDMSCl; (b) BuLi, $(EtO)_2CO$; (c) 1.5 N HCl; (d) CsF.

salt **3b** (80%) depending on the eluant.[8] The protected tripodal alcohol **2** could also be selectively desilylated to give the N-protected tripod **4** upon treatment with CsF (H_2O/CH_3CN, reflux, 88%).[9]

Because the hydroxyl group of **2** and **3** is a potential site for metal ion interaction[2,10] and derivatives with O-spacer chains are of interest for various applications, we sought to establish a method to convert the tripodal alcohols to corresponding ethers. Surprisingly, conventional deprotonation/alkylation conditions (e.g., NaH/CH_3I/DMF) not only failed to produce the expected ether **5**, but caused retroaddition of **3** to bis(4-imidazolyl) ketone.[11] We found, however, that the hydrochloride salt **3b** could be quantitatively converted to the methyl ether hydrochloride **5** solvolytically, simply by refluxing it in dry methanol (Scheme 2).

Scheme 2[a]



[a] Conditions: (e) MeOH, 4 Å molecular sieves; (f) $FeCl_3$, pH 7.

Although the metal-binding capability of the tripodal (4-imidazolyl) ligands has been shown to be greater than for the corresponding (2-imidazolyl) ligands,[2] no metal complexes of the former have been isolated and characterized, perhaps because of the previously limited access to this class of ligands. Accordingly, carbinol **3a** was found to readily form a 2:1 complex **6** upon reaction with $FeCl_3$ (H_2O, pH 7, rt). The structure of **6**, established by X-ray diffraction (Figure 1), features a slightly distorted octahedral geometry.

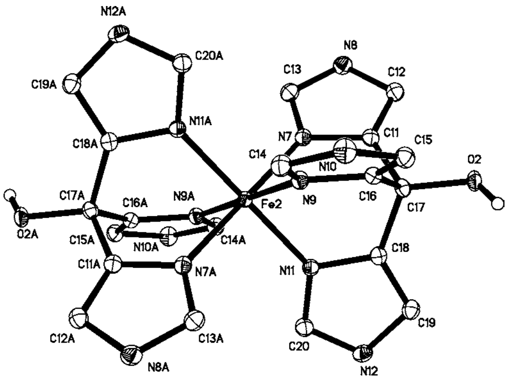


Figure 1. ORTEP diagram for the cation of **6**.

The bond lengths and angles around the iron center are quite similar to those found for the corresponding iron(III) complex of tris(2-imidazolyl)carbinol.[1a]

In summary, we have provided a substantially improved synthetic route to poly(4-imidazolyl)carbinol derivatives and have characterized a representative metal complex. With convenient access to these ligands now in hand, the structure, coordination properties, and the catalytic reactivity of their metal complexes can now be expeditiously examined.

Acknowledgment. We thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research.

Supporting Information Available: Experimental procedures and characterizational data for compounds **2**−**6** and crystallographic data for **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) **Protected Tripod 2.** 1-(Dimethylsulfamoyl)imidazole (1.85 g, 10.6 mmol) was dissolved in 90 mL of dry THF under argon. With vigorous stirring, the temperature was lowered to −78 °C and a solution of *n*-BuLi in pentane (11.1 mmol, 5.9 mL of 1.88 M) was added dropwise. After the solution was stirred for 30 min, a solution of *tert*-butyldimethylsilyl chloride (12.7 mmol, 1.91 g in 2 mL of THF) was added via cannula. The reaction was allowed to warm to room-temperature overnight. The mixture was then cooled to −78 °C, and a solution of *n*-BuLi (11.7 mmol, 6.2 mL, 1.88 M) was added dropwise. After the solution was stirred for 30 min, neat diethyl carbonate (3.0 mmol, 425 L) was added dropwise. The mixture was allowed to warm to room temperature over 24 h. Ethyl acetate (50 mL) was added, and the solution was washed three times with 20 mL of brine. The organic layer was dried over $MgSO_4$, and the solvent was rotary evaporated. During evaporation, a white solid precipitated, which was filtered off and washed with ethyl acetate. The filtrate was concentrated, and the procedure was repeated to afford 2.19 g of spectroscopically pure **2** as a white solid (70% yield). Characterizational data for all compounds is provided in Supporting Information.

(8) **Deprotected Tripod 3.** Carbinol **2** (1.60 g, 1.80 mmol) was refluxed in 50 mL of hydrochloric acid (1.5 M) for 90 min. The solvent was evaporated under reduced pressure. Chromatography of the residue on Dowex 50WX8-100 resin (20 mL) with water followed by 6 M hydrochloric acid yielded 487 mg (80% yield) of hydrochloride salt **3b** after solvent evaporation. If 6% NH_4OH was used as the eluant, 362 mg of the neutral alcohol **3a** was obtained (88% yield).

(9) Preparative and characterizational information for compounds **2**−**6** is provided in Supporting Information.

(10) Tagaki, W.; Ogino, K.; Fujita, T.; Yoshida, T.; Nishi, K.; Inaba, Y. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 140. Wu, L.-P.; Yamagiwa, Y.; Ino, I.; Sugimoto, K.; Kuroda-Sowa, T.; Kamikawa, T.; Munakata, M. *Polyhedron*, **1999**, *18*, 2047. Gorun, S. M.; Lippard, S. J. *J. Am. Chem. Soc.* **1985**, *107*, 4568.

(11) O-Alkylation of other tris(imidazolyl) carbinols has proven to be erratic under typical base-promoted conditions. Sorrell, T. N.; Borovik, A. S. *J. Am. Chem. Soc.* **1987**, *109*, 4255. Collman, J. P.; Zhong, M.; Wang, Z.; Rapta, M. *Org. Lett.* **1999**, *1*, 2121.