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Tetrahedron Letters
Tetrahedron Letters 46 (2005) 2809–2812

Synthesis of sterically hindered tris(4-imidazolyl)carbinol ligands and their copper(I) complexes related to metalloenzymes

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Received 1 December 2004; revised 23 February 2005; accepted 23 February 2005

Abstract—Tris(4-imidazolyl)carbinol, which has close coordination environment to the active site of metalloenzymes, has not been utilized as a biomimetic ligand because of its instability. We have synthesized stable tris(4-imidazolyl)carbinol derivatives having a methyl group as the NH protective group and a bulky substituent on the imidazole ring for stabilizing reactive species bound to the metal center. These ligands provide stable monomeric copper(I) complexes whose coordination environment are very close to the active site of metalloenzymes.

In non-heme metalloenzymes, imidazole rings of histidine residues often form part of the metal-binding site.[1] For example, in the active sites of hemocyanin (Cu),[1a] nitrite reductase (Cu),[1c] and carbonic anhydrase (Zn),[1e] three imidazoles coordinate to one metal ion (Fig. 1a). Because the coordination environment with three histidine imidazoles are generally occurred in many non-heme metalloenzymes, tripodal N-donor ligands such as hydrotris(2-pyrazolyl)borate and triazacyclononane have been used for synthetic model studies to mimic the active centers.[2] For biomimetic studies, ligands with imidazolyl units are more desirable to understand the nature of metalloenzymes. Especially, a tripodal ligand with three 4-imidazolyl units, e.g., tris(4-imidazolyl)carbinol,[3] is better suited because the coordination environment of this ligand is close to the active sites of metalloenzymes, as shown in Figure 1. Recently, Collman et al. succeeded in synthesis of tris(4-imidazolyl)carbinol by nucleophilic addition of 4-magnesio-1-tritylimidazole to methyl chloroformate.[4] However, the labile trityl protecting group and the absence of steric effect around the metal ion of this ligand prevent the application to biomimetic study. Actually, the absence of bulky substituents in tripodal ligands results in the formation of the complex coordinating two ligands to one metal ion or the intermolecular dimer bridged by the ligand.[2d] The use of appropriately positioned, large alkyl substituents on tripodal ligands is critical for enabling isolation of many reactive model complexes of enzyme intermediates.[2a,b] Therefore, it is desirable to synthesize tris(4-imidazolyl)carbinol with stable NH protecting group and sterically hindered substituent to mimic the reactive intermediates. Here, we report the synthesis of tris(4-imidazolyl)carbinol ligands having chemically stable methyl group as the NH protective group and bulky substituent (isopropyl or phenyl) for stabilizing reactive species bound to metal center. The copper complexes prepared from these ligands can reproduce the metal active site of copper enzymes and are suitable for biomimetic studies.

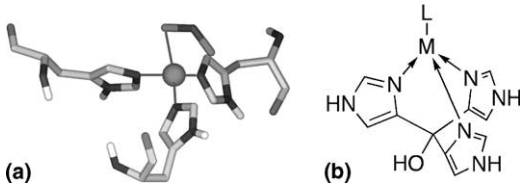

Figure 1. (a) Structure of the active site of copper-containing nitrite reductase. (b) Tris(4-imidazolyl)carbinol.

For the synthesis of new tris(4-imidazolyl)carbinol ligands we employed the nucleophilic addition of 4-magnesioimidazole derivatives to $ClCO_2Me$ (Scheme 1) in a similar way reported by Collman et al.[4] 4-Iodoimidazole compounds **1a** and **1b** were readily prepared from 2-substituted imidazoles in a large scale using the literature

Keywords: Imidazole; Tripodal ligand; Copper(I) complex.
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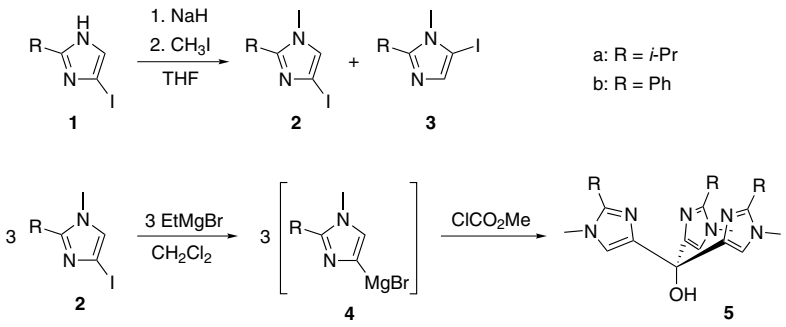
doi:10.1016/j.tetlet.2005.02.122



Scheme 1. Synthesis of tris(imidazolyl)carbinol ligand **5**.

method[5] in 78% and 84% yield, respectively. Methylation of **1** by using NaH–CH_3I procedure in THF generated the mixture of 4-iodo isomer **2** and 5-iodo isomer **3**, which were separated by silica-gel column chromatography (R = *i*-Pr: **2a** 42%, **3a** 40%. R = Ph: **2b** 43%, **3b** 42%).[6] Reaction of $ClCO_2Me$ with 3 equiv of 4-magnesioimidazole reagent **4** generated from **2** and EtMgBr in CH_2Cl_2 at room temperature afforded tris(4-imidazolyl)carbinol derivative $HOC(Im^{i\text{-}Pr})_3$ (**5a**) or $HOC(Im^{Ph})_3$ (**5b**), which were isolated by alumina column chromatography in 38% or 33% yield, respectively.[7] The structures of **5a** and **5b** were mainly confirmed by using ^1H NMR, ^{13}C NMR, and MS spectroscopy. In the ^1H and ^{13}C NMR spectra of **5a** and **5b**, one set of imidazolyl signals were observed together with the bridgehead (COH) signal in each case, indicating that three imidazolyl groups are in equivalent conditions. The MS analysis of **5a** and **5b** showed the meaningful peaks assigned for tertiary carbocation $[C(Im^{i\text{-}Pr})_3]^+$ and $[C(Im^{Ph})_3]^+$ generated by elimination of the bridgehead OH^- from **5a** and **5b**, respectively. The structures of these compounds were also confirmed by single crystal X-ray analysis of their copper(I) complexes (see below). Compound **5a** and **5b** are stable both in the solid and solution at room temperature.

By the use of **5a** and **5b** as supporting ligands, we prepared acetonitrile copper(I) complexes $[HOC(Im^{i\text{-}Pr})_3Cu(CH_3CN)]\cdot ClO_4$ (**6a**) and $[HOC(Im^{Ph})_3Cu(CH_3CN)]\cdot ClO_4$ (**6b**). Reaction of $Cu(CH_3CN)_4\cdot ClO_4$[8] with 1 equiv of **5a** or **5b** in CH_2Cl_2 gave **6a** or **6b** as colorless crystals in 68% or 75% yield, respectively.[9] The X-ray crystal structure showed that **6a** and **6b** are monomeric complexes having a distorted tetrahedral geometry with three imidazolyl groups of the ligand and an acetonitrile molecule coordinating to the central metal (Fig. 2).[10] The coordination environment in **6a** and **6b** are similar to the metal-binding site in copper enzyme. It has been reported that a non-substituted tripodal ligand such as tris-(2-imidazolyl)carbinol does not form the monomeric complex but the intermolecular copper(I) dimer bridged by the ligand,[2d,11] so the formation of the monomeric complexes **6a** and **6b** results from the steric effect of the isopropyl or the phenyl groups in each ligand. The crystal structures of both complexes **6a** and **6b** were very close to each other in respect of their bond lengths and angles around the copper(I) ions.[10] On the other hand, the average bond lengths of Cu–N(ligand) in **6a** and **6b** are shorter than those of acetonitrile complex of sterically hindered triazacyclononane and longer

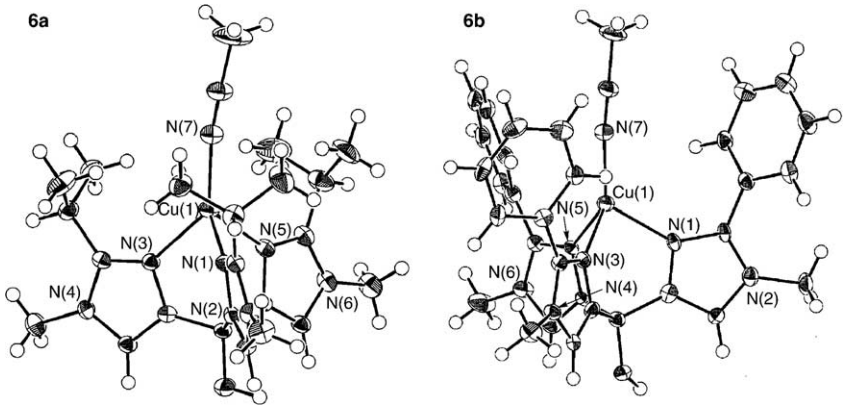


Figure 2. ORTEP view of $[HOC(Im^{i\text{-}Pr})_3Cu(CH_3CN)]^+$ in **6a** and $[HOC(Im^{Ph})_3Cu(CH_3CN)]^+$ in **6b** drawn with the thermal ellipsoids at the 50% probability level. Selected bond lengths (Å) and angles (deg): **6a**: Cu(1)–N(1), 2.100(3); Cu(1)–N(3), 2.075(3); Cu(1)–N(5), 2.130(3); Cu(1)–N(7), 1.896(4); N(1)–Cu(1)–N(3), 89.0(1); N(1)–Cu(1)–N(5), 91.3(1); N(1)–Cu(1)–N(7), 121.6(1); N(3)–Cu(1)–N(5), 89.2(1); N(3)–Cu(1)–N(7), 134.1(1); N(5)–Cu(1)–N(7), 120.1(1). Compound **6b**: Cu(1)–N(1), 2.072(8); Cu(1)–N(3), 2.105(6); Cu(1)–N(5), 2.108(7); Cu(1)–N(7), 1.883(6); N(1)–Cu(1)–N(3), 88.9(3); N(1)–Cu(1)–N(5), 90.4(3); N(1)–Cu(1)–N(7), 121.5(4); N(3)–Cu(1)–N(5), 87.5(3); N(3)–Cu(1)–N(7), 128.3(3); N(5)–Cu(1)–N(7), 128.2(3).

than that of sterically hindered hydrotrispyrazolylborate.[12] It is noteworthy that the terminal methyl groups of three isopropyl substituents in **6a** are directing to metal side. This behavior is in contrast to the other copper complexes bearing isopropyl-substituted tripodal ligands, in which the terminal methyl groups are directing to the opposite side of the metal center.[2a–c] The steric repulsion between the isopropyl group and the adjacent N-methyl group would direct the methyl group to the metal side. Because of this unique structure, the isopropyl group of **6a** functions as the *t*-butyl group and prevents the intermolecular dimer formation.[2d] ^{1}H NMR measurements of **6a** and **6b** indicated that these structures are retained even in solution. Especially, the strong NOE between the CH proton of the isopropyl group and the N-methyl group in **6a** suggest retention of the unique orientation of the isopropyl group in solution. The redox potential of **6a** for Cu(I)/Cu(II) was +0.56 V versus SCE, which was extremely lower than that (+0.93 V) of the hydrotrispyrazolylborate complex.[11] The neutral character of tris-(4-imidazolyl)carbinol ligand would stabilize Cu(II) oxidation state, leading to the decrease in the redox potential.

We have succeeded in synthesis of stable tris(4-imidazolyl)carbinol derivatives having methyl group at the 1-position and bulky substituent at the 2-position of each imidazolyl ring. These ligands are suitable for mimicking the metal-binding sites of non-heme metalloenzymes. Further studies with these new ligands are now underway.

Acknowledgements

This work was supported by Grants in Aids for Scientific Research from the Minister of Education, Culture, Sports, Science, and Technology, Japan.

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6. Procedure for **2** and **3**: To a THF suspension (100 mL) of NaH (1.43 g, 59.6 mmol) was added **1a** (14.2 g, 59.6 mmol) and the resultant mixture was stirred for 1 h at ambient temperature. To the mixture was titrated CH_3I (8.45 g, 59.5 mmol) and stirred for 12 h at ambient temperature. The mixture was concentrated and the residue was subject to silica-gel chromatography using CH_2Cl_2–acetone (9:1) as the eluent. Compounds **2a** (42%) and **3a** (40%) were obtained as colorless solid and oil, respectively. By the same procedure from **1b**, **2b** (43%) and **3b** (40%) were obtained as colorless solids. Spectroscopic data: ^{1}H NMR (400 MHz, $CDCl_3$) **2a**: 6.82 (1H, s), 3.55 (3H, s), 2.95 (1H, sept, J = 6.9 Hz), 1.28 (6H, d, J = 6.9 Hz). Compound **2b**: 7.61 (2H, d, J = 7.4 Hz), 7.48–7.44 (3H, m), 7.07 (1H, s), 3.74 (3H, s). Compound **3a**: 7.01 (1H, s), 3.52 (3H, s), 3.03 (1H, sept, J = 6.8 Hz), 1.27 (6H, d, J = 6.9 Hz). Compound **3b**: 7.59 (2H, d, J = 7.3 Hz), 7.50–7.43 (3H, m), 7.26 (1H, s), 370 (3H, s). ^{13}C NMR (100 MHz, $CDCl_3$) **2a**: 155.3, 125.7, 79.5, 32.4, 26.0, 21.2. Compound **2b**: 150.0, 129.3, 129.1, 128.7, 128.5, 127.6, 81.5, 34.4. Compound **3a**: 155.5, 134.4, 69.9, 33.2. 27.2, 21.1. Compound **3b**: 150.5, 136.0, 130.7, 129.1, 128.7, 128.6, 72.6, 35.5. GC–MS (*m*/*z*) **2a**; 250 (M^+). Compound **2b**: 284 (M^+).
7. Procedure for **5**: To a CH_2Cl_2 solution (100 mL) of **2a** (5.98 g, 23.9 mmol) was added 3 M EtMgBr (8.0 mL, 24 mmol) in diethyl ether and the resultant solution was stirred for 2 h at ambient temperature. To the mixture was added $ClCO_2Me$ (753 mg, 7.97 mmol) and stirred for 40 h at ambient temperature. The reaction was quenched by addition of saturated aqueous NH_4Cl (50 mL), and CH_2Cl_2 layer was concentrated. Purification of the residue by alumina column chromatography using CH_2Cl_2–acetone (3:1) as the eluent gave **5a** (38%) as yellow solid. By the same procedure from **2b**, **5b** (33%) was obtained as colorless solid. Spectroscopic data: ^{1}H NMR (500 MHz, $CDCl_3$) **5a**: 6.72 (3H, s), 4.72 (1H, br), 3.47 (9H, s), 2.94 (3H, sept, J = 6.9 Hz), 1.27 (18H, d, J = 7.1 Hz). Compound **5b**: 7.58 (6H, d, J = 8.1 Hz), 7.40–7.34 (9H, m), 7.08 (3H, s), 4.60 (1h, br), 3.63 (9H, s). ^{13}C NMR (125.7 MHz, $CDCl_3$) **5a**: 151.8, 144.4, 117.9, 70.3, 32.3, 26.2, 21.4. Compound **5b**: 147.1, 145.7, 130.8, 129.0, 128.3, 128.2, 120.4, 71.0, 34.3. MALDI TOF-MS (*m*/*z*) **5a**; 381.2 ($[M-OH^-]^+$). Compound **5b**: 483.1 ($[M-OH^-]^+$).
8. $Cu(CH_3CN)_4{\cdot}ClO_4$ was prepared by literature method: Hathaway, B. J.; Holah, D. G.; Postlethwaite, J. D. *J. Chem. Soc.* **1961**, 3215, **CAUTION!** Perchlorate salts are potentially explosive and should be handled with care.
9. Procedure for **6**: To a CH_2Cl_2 solution (10 mL) of **5a** (377 mg, 0.946 mmol) was added $Cu(CH_3CN)_4{\cdot}ClO_4$ (310 mg, 0.947 mmol) and the resultant solution was stirred for 1 h at ambient temperature. The mixture was concentrated followed by recrystallization from CH_3CN–diethyl ether afforded **6a** (68%) as colorless crystals. By the same procedure from **5b** and $Cu(CH_3CN)_4{\cdot}ClO_4$, **6b** (75%) was obtained as colorless crystals. Compound data: ^{1}H NMR (500 MHz, CD_3CN) **6a**; 6.77 (3H, s), 4.56 (1h, br), 3.51 (9H, s), 3.12 (3H, sept, J = 6.9 Hz), 1.95 (3H, s), 1.342 (18H, d, J = 6.8 Hz). **6b**; 7.65 (6H, d, J = 6.4 Hz), 7.51–7.48 (9H, m), 7.17 (3H, s), 5.00 (1H, br), 3.66 (9H, s), 1.95 (3H, s). Compound **6a**: Anal. Calcd for $C_{24}H_{37}N_7O_5ClCu{\cdot}CH_3CN$; C 48.52, H 6.26, N 17.41. Found: C 48.46, H 6.33, 17.52. Compound **6b**: Anal. Calcd for $C_{33}H_{31}N_7O_5ClCu{\cdot}CH_3CN$; C 56.37, H 4.60, N 15.03. Found: C 55.51, H 4.71, N 15.33.
10. Crystal data (wavelength 0.71070 Å): **6a** and acetonitrile; $C_{24}H_{37}N_7O_5ClCu{\cdot}C_2H_3N$. M = 643.65, monoclinic, space group $P2_1/c$, a = 11.855(3) Å, b = 8.955(1) Å, c = 30.19(1) Å, β = 93.71(3)°, V = 3197.8799 Å^3, Z = 4, D_c = 1.337 mg m^{-3}, R indices (all data) R_1 = 0.060,

$wR_2 = 0.080$. Reflections collected 5114 (CCDC 255619). Compound **6b** and acetonitrile: $C_{33}H_{31}N_7O_5ClCu{\cdot}C_2H_3N$. $M = 745.70$, monoclinic, space group $P2_1$, $a = 8.947(1)$ Å, $b = 16.625(3)$ Å, $c = 12.433(2)$ Å, $\beta = 99.705(3)°$, $V = 1822.8(5)$ Å^3, $Z = 2$, $D_c = 1.359$ mg m^{-3}. R indices (all data) $R_1 = 0.083$, $wR_2 = 0.214$, reflections collected 4218 (CCDC 255620).

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