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DESIGN AND SYNTHESIS OF A SERIES OF FACIALLY COORDINATING TRIDENTATE LIGANDS CONTAINING AN N_2O DONOR ATOM SET

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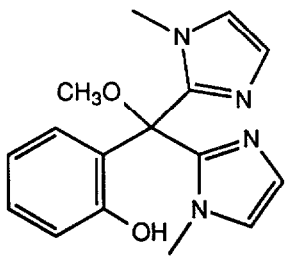
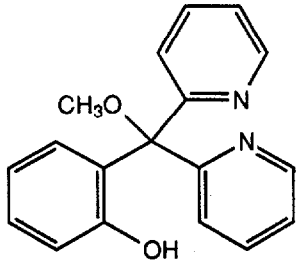
Summary: The preparation of a series of facially coordinating tridentate ligands is described. The N_2O ligands contain a phenol and either two imidazole, two pyridine or two pyrazole donor atoms.

Metalloprotein active sites in which the metal ion is coordinated to both the phenolate donor atom of the amino acid tyrosine and the imidazole donor atom of the amino acid histidine occur throughout biological systems.[1] In particular, the purple acid phosphatases may have an active site where a triply bridged diiron unit is capped by a combination of phenolate and imidazole donor atoms.[2] The elaboration of synthetic models for this class of metalloproteins requires polydentate ligands which contain both phenolate and heterocyclic nitrogen donor atoms.

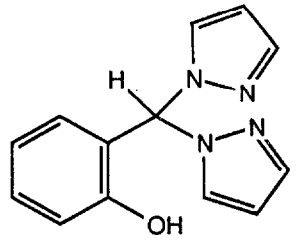
We wish to report the synthesis of a series of N_2O ligands, 1-3, which are capable of binding to the facial coordination sites of an octahedron. The oxygen donor atom is a phenol (phenoxide), and the nitrogen donor atoms are systematically varied from imidazole to pyridine to pyrazole.



1



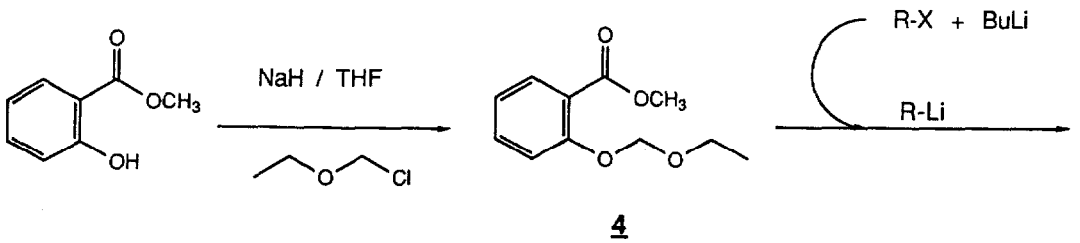
2



3

The synthesis of 1 followed the strategy of Breslow, et al.[3] for the construction of polyimidazole ligands. Ligand 2 was prepared by a similar strategy, except that lithiated pyridine replaced lithiated N-methylimidazole. Ligand 3 was prepared by converting the ethylene acetal to the dipyrazolyl alkane.[4]

SCHEME I



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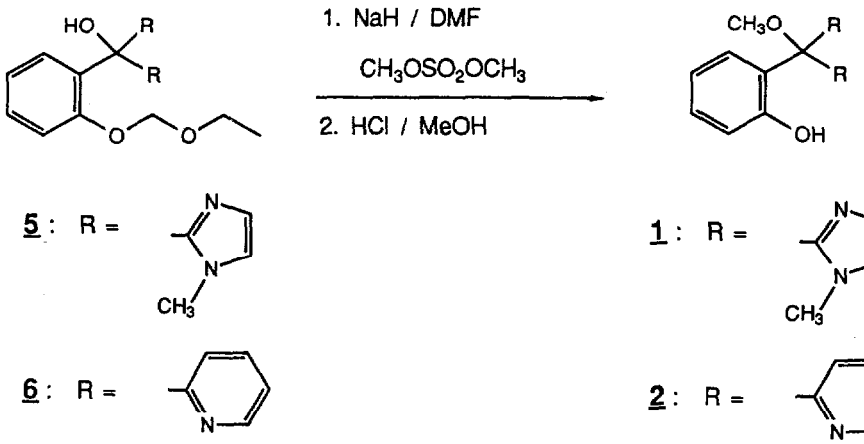
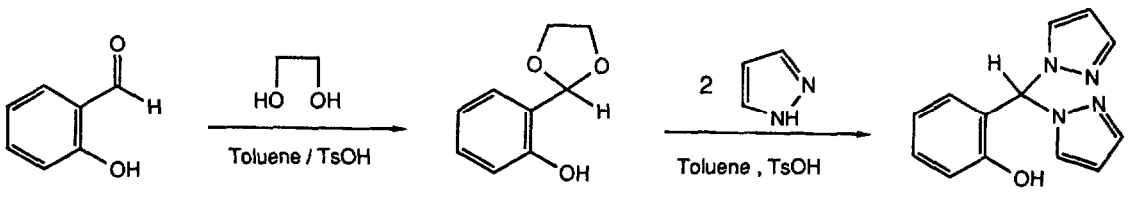


SCHEME II



7 **3**

The common intermediate in the synthesis of 1 and 2 is the ethoxymethyl ether 4, which was prepared by treating the sodium salt of methyl salicylate in THF with chloromethyl ethyl ether.[5] Treatment of the ester with 2 equivalents of 2-lithio-N-methylimidazole in THF (-78 °C) gave the alcohol 5 as an oil, which was purified by column chromatography (neutral alumina/ethyl acetate). In order to prevent any ambiguity regarding potential donor atoms, the alcohol (which at higher pH may bind metals as an alkoxide) was converted to a methyl ether using sodium hydride and dimethyl sulfate in THF/DMF. The protecting group was removed in the same pot by removal of solvent and treatment with conc. HCl/MeOH (1/3). Ligand 1 was isolated as a crystalline solid following column chromatography (neutral alumina/ethyl acetate).[6]

Ligand 2 was prepared by a similar route, except that 2-lithiopyridine was substituted for 2-lithio-N-methylimidazole. The alcohol 6, an oil, was purified by column chromatography (neutral alumina/toluene followed by ethyl acetate). The methylation and deprotection was performed in one pot and ligand 2 was isolated as a crystalline solid following chromatography (alumina/methylene chloride).

Salicylaldehyde was converted to the ethylene acetal 7 using ethylene glycol in the presence of a catalytic amount of p-toluenesulfonic acid. Treatment of 6 with excess pyrazole in the presence of a catalytic amount of p-toluenesulfonic acid afforded the aminal 3.

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References and Notes

1. Que, L., Jr. Coord. Chem. Rev. (1983), 50, 73-108.
2. Averill, B. A.; Davis, J. C.; Burman, S.; Zirino, T.; Sanders-Loehr, J.; Loehr, T. M.; Sage, J. T.; Debrunner, P. G. J. Am. Chem. Soc. (1987), 109, 3760-3767.
3. a) Tang, C. C.; Davalian, D.; Huang, P.; Breslow, R. J. Am. Chem. Soc. (1978), 100, 3918-3922; b) Breslow, R.; Hunt, T. L.; Smiley, R.; Tarnowski, T. J. Am. Chem. Soc. (1983), 105, 5337-5342.
4. Trofimenko, S. J. Am. Chem. Soc. (1970), 92, 5118-5126.
5. The structures of all of the compounds reported herein (except 4 and 7) were determined by ^{1}H (80 MHz) and ^{13}C (20 MHz) NMR ($CDCl_3$ solvent and chemical shift measured in ppm vs. TMS). Elemental analyses are reported for the target ligands. 4: bp 90-92 °C (1 mm); yield 88%; ^{1}H NMR 1.13 (t, 3H, $CH_2\underline{CH_3}$), 3.69 (q, 2H, $\underline{CH_2}CH_3$), 3.79 (s, 3H, OCH_3), 5.20 (s, 2H, OCH_2O), 6.8-7.8 (m, 4H, ArH).

5: oil; yield 55%; ^{1}H NMR 1.12 (t, 3H, $CH_2\underline{CH_3}$), 3.49 (q, 2H, $\underline{CH_2}CH_3$), 3.49 (s, 6H, NCH_3), 5.05 (s, 2H, OCH_2O), 6.85 (d, 2H, ImH), 6.89 (d, 2H, ImH), 6.3-7.5 (m, 4H, ArH); ^{13}C NMR 14.97, 34.75, 64.30, 75.78, 93.66, 115.83, 121.71, 122.91, 126.32, 128.17, 129.86, 130.96, 147.94, 155.59.

1: mp 171-172 °C; yield 66%; ^{1}H NMR 3.24 (s, 3H, OCH_3), 3.42 (s, 6H, NCH_3), 6.84 (d, 2H, ImH), 7.00 (d, 2H, ImH), 6.7-7.4 (m, 4H, ArH), 10.0 (br s, 1H, OH); ^{13}C NMR 34.56, 53.38, 81.72, 119.15, 119.86, 123.64, 124.37, 126.44, 127.02, 130.20, 145.37, 156.10. Anal. Calcd for $C_{16}H_{18}N_4O_2$: C, 64.42; H, 6.08; N, 18.77. Found: C, 64.25; H, 6.25; N, 18.53.

6: oil; yield 31%; ^{1}H NMR 1.06 (t, 3H $CH_2\underline{CH_3}$), 1.72 (br s 1H, OH), 3.28 (q, 2H, $\underline{CH_2}CH_3$), 4.78 (s, 2H, OCH_2O), 6.6-8.6 (m, 12H, ArH and PyH); ^{13}C NMR 14.90, 63.79, 80.15, 93.09, 114.75, 115.53, 121.13, 121.83, 122.68, 129.25, 135.14, 136.19, 147.34, 155.71, 163.51.

2: mp 160-161 °C; yield 58%; ^{1}H NMR 3.08 (s, 3H, OCH_3), 6.9-8.5 (m, 12H, ArH and PyH), 11.6 (br s, 1H, OH); ^{13}C NMR 52.77, 86.52, 119.60, 119.86, 122.51, 122.66; 126.82, 128.54, 129.39, 136.83, 147.62, 155.69, 161.82. Anal. Calcd for $C_{18}H_{16}N_2O_2$: C, 73.96; H, 5.52; N, 9.58. Found: C, 74.19, H, 5.63; N, 9.66.

7: mp 66-68 °C; yield 75%; ^{1}H NMR 4.05 (m, 4H, CH_2CH_2), 5.91 (s, 1H, CH), 6.75-7.40 (m, 4H, ArH), 7.70 (br s, 1H, OH).

3: mp 154-155 °C; yield 68% ^{1}H NMR 6.27 (t, 2H, PzH), 6.5-7.2 (m, 4H, ArH), 7.52 (d, 2H, PzH), 7.60 (t, 2H, PzH), 7.70 (s, 1H, CH), 10.91 (s, 1H, OH); ^{13}C NMR 77.91, 106.28, 119.55, 120.18, 121.08, 130.38, 130.55, 131.96, 140.62, 155.34. Anal Calcd for $C_{13}H_{12}N_4O$: C, 64.99; H, 5.04; N, 23.31. Found: C, 64.92; H, 5.12; N, 23.35.

6. Ligand 1 has been prepared by a slightly modified route: Borovik, A. S., Ph.D. Thesis, The University of North Carolina at Chapel Hill (1986).

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