THE SYNTHESIS OF TETRAPYRAZOLE SUBSTITUTED PHENOLS

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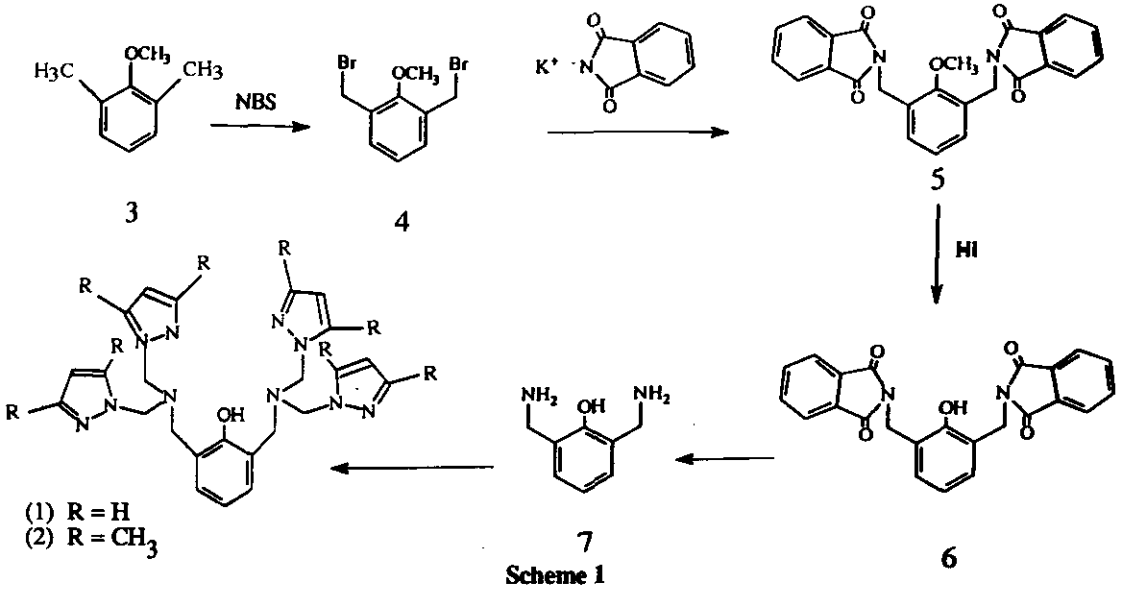
Abstract - The synthesis of two new potentially dinucleating tetrapyrazole substituted phenols is described. The compounds 2,6-bis[(bis(pyrazol-1-ylmethyl)amino)methyl] phenol (**1**) and 2,6-bis[(bis(3,5-dimethylpyrazol-1-ylmethyl)amino)methyl]phenol (**2**) were prepared via the pyrazolylmethylation of amines.

Organic compounds which can bind to two metal ions and lead to cooperative interactions between the metal centers are of considerable current interest. This is primarily a consequence of the existence of naturally occurring dinuclear proteins and enzymes such as those found in the copper-containing systems hemocyanin[1] and tyrosinase,[2] the copper-zinc enzyme superoxide dismutase,[3] the manganese ions in photosystem II,[4] and the iron atoms in hemerythrin.[5] Dinuclear systems are also of critical importance in biological catalysis and as catalysts for non-biological substrate oxidations.[6] Therefore, considerable effort has been directed towards the rational synthesis of ligands capable of holding two metal ions at distances between 2.0-4.0 Å.[7] By judicious choice of the donor atoms and the steric features, compounds can be designed which will drastically alter the physical and chemical properties of the metal complexes and should allow them to bind small molecules between the metal ions or act as multi-electron catalysts.

In order to enhance the ligand sets available for complexation to metal ions, we have synthesized the novel pyrazole containing compounds 2,6-bis[(bis(pyrazol-1-ylmethyl)amino)methyl]phenol (**1**) and 2,6-bis-[(bis(3,5-dimethylpyrazol-1-ylmethyl)amino)methyl]phenol (**2**). These molecules are capable of binding to two metal ions *via* donation of two pyrazole nitrogens and one aliphatic nitrogen per metal, along with a bridging phenol oxygen. Direct interaction between the two metal ions can be facilitated by this bridging group. The incorporation of the methyl groups onto the pyrazole rings in **2** will provide a more hydrophobic environment for subsequent metal complexes.

As shown in Scheme 1, compounds (**1**) and (**2**) were prepared in five steps from 2,6-dimethylanisole.



Scheme 1

The synthesis commenced with the free-radical bromination of 2,6-dimethylanisole (**3**) with N-bromosuccinimide and benzoyl peroxide which gave compound (**4**) as a crystalline compound in 61% yield. When **4** was treated with potassium phthalimide in DMF, the nitrogen protected compound (**5**) was isolated. Demethylation of the anisole (**5**) with refluxing hydriodic acid gave the substituted phenol (**6**). Deprotection of the amine protecting group in **6** with hydrazine hydrate resulted in formation of **7**, which was isolated in 68% yield as it's hydrochloride salt. The target compounds (**1**) and (**2**) were prepared using a modification of the procedure of Driessen[8] for the addition of pyrazole-1-methylene units to amines. The condensation of **7** with four equivalents of 1-(hydroxymethyl)pyrazole gave compound (**1**), while treatment with 1-(hydroxymethyl)-3,5-dimethylpyrazole gave **2**.

EXPERIMENTAL

All reagents and solvents were purchased from commercial sources and used as received. 1-Hydroxymethylpyrazole and 1-hydroxymethyl-3,5-dimethylpyrazole were prepared by the literature method.[8] Melting points were obtained with the use of Fisher-Johns apparatus and are uncorrected. Chemical analyses were performed at Desert Analytical, Tucson, AZ. Mass spectra were run at the Midwest Center for Mass Spectrometry in Lincoln, NE. ^{1}H Nmr were recorded on a Bruker WM 250 instrument.

2,6-Bis(bromomethyl)anisole (4). To a stirred solution of 30.0 g (0.22 mol) of 2,6-dimethylanisole (**3**) in 400 ml of CCl_4 was slowly added 78.4 g (0.44 mol) of N-bromosuccinimide. Benzoyl peroxide

(1.5 g) was added and the solution was refluxed for 6 h. The solution was filtered hot and the filtrate was evaporated under reduced pressure. The resultant oil was crystallized from hexane to yield 39.4 g (61%) of light orange crystals, mp 74-75 °C. ^{1}H Nmr 4.00 (3 H, s, OCH_3), 4.52 (4 H, s, CH_2Br), 7.22-7.45 (3 H, m, Ar-H). *Anal.* Calcd for $C_9H_{10}Br_2O$: C, 36.97; H, 3.45. Found: C, 37.12; H, 3.64.

2,6-Bis(phthalimidomethyl)anisole (5). To a stirred suspension of 48.1 g (0.26 mol) of potassium phthalimide in 400 ml of DMF was slowly added 38.0 g (0.13 mol) of **4**. The mixture was stirred for 48 h at 50 °C, cooled to room temperature, and filtered. The white solid collected was crystallized from $CHCl_3$ to give 18.0 g of white crystals. Additional product was obtained by evaporating the filtrate and crystallizing the residue resulting in an additional 5.0 g of product. Total yield 41%, mp 224-226 °C. ^{1}H Nmr 4.01 (3 H, s, OCH_3), 4.93 (4 H, s, CH_2N), 7.13-7.34 (3 H, m, Ar-H), 7.65-7.89 (8 H, m, Ar-H). *Anal.* Calcd for $C_{25}H_{18}N_2O_5$: C, 70.41; H, 4.26; N, 6.57. Found: C, 70.28; H, 4.40; N, 6.83.

2,6-Bis(phthalimidomethyl)phenol (6). Hydriodic acid (120 ml) was stirred while compound **(5)** (9.20 g, 0.021 mol) was slowly added. The solution was refluxed for 5 h, cooled to room temperature, and extracted with 3 x 50 ml $CHCl_3$. The extracts were successively washed with water and a 5% sodium thiosulfate solution until the coloration disappeared. The solution was dried over $MgSO_4$ and filtered. Upon evaporation of the solvent under reduced pressure, 3.55 g (41.0%) of a white precipitate formed (mp 209-212 °C). ^{1}H Nmr 4.82 (4 H, s, CH_2N), 7.18-7.32 (3 H, m, Ar-H), 7.65-7.89 (8 H, m, Ar-H). *Anal.* Calcd for $C_{24}H_{16}N_2O_5$: C, 69.89; H, 3.92; N, 6.79. Found: C, 69.26; H, 4.27; N, 6.62.

2,6-Bis(aminomethyl)phenol dihydrochloride (7). A mixture of 11.0 g (0.027 mol) of **6** and 3.0 g (0.059 mol) of hydrazine hydrate in 200 ml of CH_3OH was refluxed for 2.5 h. To the mixture was added 75 ml of H_2O and the CH_3OH was evaporated. Concentrated HCl (100 ml) was added, the solution was refluxed for 2 h, cooled in ice, filtered, and the residue washed with water. The washings and the filtrate were combined and evaporated. The residue was dissolved in 175 ml of C_2H_5OH followed by 75 ml of ether which resulted in precipitation of a white solid. The solid was dried in *vacuo*; mp 178-180 °C, yield 2.79 g (68%). ^{1}H Nmr (in D_2O) 4.28 (4 H, s, CH_2N), 7.18-7.32 (3 H, m, Ar-H). *Anal.* Calcd for $C_8H_{14}Cl_2N_2O$: C, 42.68; H, 6.28; N, 12.44. Found: C, 42.61; H, 6.10; N, 12.34.

2,6-Bis[(bis(pyrazol-1-ylmethyl)amino)methyl]phenol (1). To a stirred solution of 2.25 g (10.0 mmol) of **7** in 40 ml of CH_3OH was added 1.13 g (20.0 mmol) of KOH dissolved in 15 ml of

CH_3OH. The resultant solution was stirred for 0.5 h and filtered into a solution of 3.92 g (40.0 mmol) of 1-hydroxymethylpyrazole dissolved in 50 ml of acetonitrile and stirred for 72 h. The acetonitrile was separated from the water produced, dried over Na_2SO_4, filtered, and the solvent evaporated under reduced pressure. *Flash chromatography using a 2:1 ethyl acetate/hexane yielded 2.89 g (61.1%) of* **1** *as a colorless* oil. ^1H Nmr 4.68 (8 H, s, CH_2N), 5.32 (4 H, s, $pzCH_2$), 6.23 (4 H, t, pz-H), 7.16 (3 H, s, Ar-H), 7.60 (8H, d, pz-H) Ms, m/z 472 (M^+). *Anal.* Calcd for $C_{24}H_{28}N_{10}O$: C, 61.00; H, 5.98; N, 29.63. Found: C, 61.12; H, 5.88; N, 29.42.

2,6-Bis[(bis(3,5-dimethylpyrazol-1-ylmethyl)amino)methyl]phenol (2). To a stirred solution of 1.13 g (5.00 mmol) of **7** in 20 ml of CH_3OH was added 0.57 g (10.0 mmol) of KOH dissolved in 10 ml of CH_3OH. The resultant solution was stirred for 0.5 h and filtered into a solution of 2.52 g (20.0 mmol) of 1-hydroxymethyl-3,5-dimethylpyrazole dissolved in 30 ml of acetonitrile and stirred for 72 h. The acetonitrile was separated from the water produced, dried over Na_2SO_4, filtered, and the solvent was evaporated under reduced pressure. Flash chromatography using a 1:1 ethyl acetate/hexane yielded 1.99 g (68.2%) of **2** as a colorless oil. ^1H Nmr 1.99 (12 H, s, CH_3), 2.20 (12 H, s, CH_3), 4.90 (8 H, s, CH_2N), 5.40 (4 H, s, $pzCH_2$), 5.79 (4 H, s, pz-H), 7.24 (3 H, s, Ar-H). Ms, m/z 584 (M^+). *Anal.* Calcd for $C_{32}H_{44}N_{10}O$: C, 65.72; H, 7.60; N, 23.94. Found: C, 65.54; H, 7.38; N, 24.02.

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