Research Article

Synthesis of New Bitopic Tetra(pyrazolyl)-Ligands with Neopentane and O-Xylene Backbones

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Several new bitopic pyrazole-containing ligands were prepared from the corresponding pyrazoles and tetrahalogen or tetratosyloxy derivatives of o-xylene and neopentane in a superbasic medium (KOH-DMSO).

1. Introduction

Bitopic ligands are compounds possessing two separate metal binding cites [1]. These ligands can act as building blocks for syntheses of homo- and heterobimetallic coordination compounds, as well as coordination polymers. These types of compounds are interesting due to their potential catalytic activity and diverse supramolecular architecture (Figure 1).

Ligands bearing two bis(pyrazol-1-yl)methane units linked by aliphatic and aromatic spacers were first prepared by Daniel Reger and are referred to as the third-generation scorpionates [2].

In this communication we report the synthesis of two new types of bis(pyrazol-1-yl)alkane bitopic ligands. In one of them two 1,3-bis(pyrazol-1-yl)propane moieties are linked together directly without a spacer. In the other ligand two bis(pyrazol-1-yl)methane units are linked by an ortho-phenylene spacer forming a previously unavailable sterically hindered compound.

2. Materials and Methods

Elemental analyses were carried out on a Carlo Erba analyzer. NMR spectra were recorded on Bruker AV300 instrument operating at 300 MHz for ¹H and 75 MHz for ¹³C. EI MS measurements were carried out using TRACE DSQ (Thermo Electron Corporation, USA) instrument.

DFT calculations were carried out at RI DFT BP86 [3] level of theory and TZVPP [4] basis set (TZVJ auxiliary basis set [5, 6]) using ORCA 2.8.0.2 package [7].

1,3-Dibromo-2,2-bis(bromomethyl)propane [8] and 1,2-bis(dibromomethyl)benzene [9] were prepared using literature methods. Pentaerythritol tetrasulfate was prepared from pentaerythritol and p-toluenesulfonfyl chloride in acetonitrile–aqueous NaOH by adopting a procedure from [10].

Tetrakis[(pyrazol-1-yl)methyl]methane (1). A suspension of 0.5 g (7.35 mmol) of pyrazole, 0.823 g (14.7 mmol) of powdered KOH in 7 mL of DMSO was stirred at 80°C for 30 minutes. After that, 0.714 g (1.84 mmol) of 1,3-dibromo-2,2-bis(bromomethyl)propane were added in three equal portions every 30 minutes. Stirring was continued for 24 hours at 80°C, then 70 mL of water were added, the solution was neutralized with hydrochloric acid and extracted with chloroform (5 × 10 mL). The extract was washed with water (2 × 10 mL), dried over calcium chloride and evaporated in vacuo. Product yield 0.224 g (36%), colorless crystals, m.p. 192–194°C (EtOH). NMR ¹H (CDCl₃), δ, ppm: 4.23 (s, 8H, CH₂), 6.27 (t, 4H, J = 1.8 Hz, H₄), 7.58 (d, 4H, J = 1.8 Hz, H₃), 7.76 (d, 4H, J = 1.8 Hz, H₂). NMR ¹³C (CDCl₃), δ, ppm: 45.9 (C(CH₂)₄), 52.1 (CH₂), 105.3 (C₁-Pz), 132.4 (C₂-Pz), 139.9 (C₃-Pz). Anal. found, %: C 60.32; H 5.90; N 33.04.

C₁₇H₂₀N₈. Calculated, %: C 60.70; H 5.99; N 33.31.
**3,3-Bis(pyrazol-1-ylmethyl)oxetane (2).** A suspension of 0.5 g (7.35 mmol) of pyrazole, 0.823 g (14.7 mmol) of powdered KOH in 5 mL of DMSO was stirred at 80°C for 30 minutes. After that, 1.38 g (1.84 mmol) of pentaerythritol tetratosylate were added in three equal portions every 30 minutes. Stirring was continued for 24 hours at 80°C, then 50 mL of water were added, the solution was neutralized with hydrochloric acid and extracted with chloroform (5 × 10 mL). The extract was washed with water (2 × 10 mL), dried over calcium chloride, and evaporated in vacuo. Product yield 0.315 g (79%), colorless oil. NMR 1H (CDCl3), δ, ppm: 4.30 (s, 4H, CH2–O), 4.67 (s, 4H, CH2–Pz), 6.22 (t, 4H, J = 1.5 Hz, H4), 7.58 (d, 4H, J = 1.5 Hz, H3), 7.76 (d, 4H, J = 1.5 Hz, H5).

**NMR 13C (CDCl3), δ, ppm:** 45.0 (C(CH2)4), 54.0 (CH2–O), 77.4 (CH2–Pz), 105.1 (C–Pz), 130.8 (C5–Pz), 139.9 (C3–Pz).

3,3-Bis(3,5-dimethylpyrazol-1-ylmethyl)oxetane (3). It was prepared similarly to compound 2 from 0.5 g (5.21 mmol) of 3,5-dimethylpyrazole, 0.98 g (1.30 mmol) of pentaerythritol tetratosylate, and 0.58 g (10.4 mmol) of KOH in 5 mL of DMSO. Yield 0.315 g (67%), colorless crystals, 98–100°C. NMR 1H (CDCl3), δ, ppm: 1.86 (s, 6H, 3–CH3), 2.17 (s, 6H, 5–CH3), 4.14 (s, 4H, CH2–O), 4.79 (s, 4H, CH2–Pz), 5.72 (s, 2H, H3), NMR 13C (CDCl3), δ, ppm: 10.4 (5–CH3–Pz), 13.5 (3–CH2–Pz), 44.8 (C(CH2)4), 50.0 (CH2–O), 78.6 (CH2–Pz), 104.4 (C1–Pz), 139.9 (C3–Pz), 147.7 (C5–Pz). MS (EI, 70 eV), m/z (I, %): 274 (2%, [M]+), 244 (55%, [M-2CH3]+), 165 (48%, [M-PzCH2]+), 109 (100%, [PzCH2]+).

**1,2-Bis(bis(pyrazol-1-yl)methyl)benzene (4).** It was prepared similarly to compound 1 from 0.5 g (7.35 mmol) of pyrazole, 0.82 g (14.7 mmol) of KOH, and 0.78 g (1.84 mmol) 1,2-bis(dibromomethyl)benzene in 10 mL of DMSO, reaction duration 7 hours. Yield 0.377 g (55%), colorless crystals, m.p. 98–99°C (i-PrOH). NMR 1H (CDCl3), δ, ppm: 6.35 (t, 4H, J = 2 Hz, H4–Pz), 6.63 (d, 2H, J = 3 Hz, H3–Ph), 7.44 (d, 2H, J = 3 Hz, H4–Ph), 7.59 (d, 4H, J = 2 Hz, H3–Pz), 7.63 (s, 2H, Pz2CH), 7.68 (d, 4H, J = 2 Hz, H5–Pz). Anal. found, %: C 64.42; H 5.18; N 29.10. C20H18N8. Calculated, %: C 64.85; H 4.90; N 30.25.

**3,3-Bis(3,5-dimethylpyrazol-1-ylmethyl)oxetane (2).** A suspension of 0.5 g (7.35 mmol) of pyrazole, 0.823 g (14.7 mmol) of powdered KOH in 5 mL of DMSO was stirred at 80°C for 30 minutes. After that, 1.38 g (1.84 mmol) of pentaerythritol tetratosylate were added in three equal portions every 30 minutes. Stirring was continued for 24 hours at 80°C, then 50 mL of water were added, the solution was neutralized with hydrochloric acid and extracted with chloroform (5 × 10 mL). The extract was washed with water (2 × 10 mL), dried over calcium chloride, and evaporated in vacuo. Product yield 0.315 g (79%), colorless oil. NMR 1H (CDCl3), δ, ppm: 4.30 (s, 4H, CH2–O), 4.67 (s, 4H, CH2–Pz), 6.22 (t, 4H, J = 1.5 Hz, H4), 7.58 (d, 4H, J = 1.5 Hz, H3), 7.76 (d, 4H, J = 1.5 Hz, H5).

**NMR 13C (CDCl3), δ, ppm:** 45.0 (C(CH2)4), 54.0 (CH2–O), 77.4 (CH2–Pz), 105.1 (C–Pz), 130.8 (C5–Pz), 139.9 (C3–Pz).

**Scheme 1:** Synthesis of tetrakis[(pyrazol-1-yl)methyl]methane 1.
3. Results and Discussion

Previously unknown bitopic ligand 1 was prepared by the reaction of 4 equivalents of pyrazole (PzH) with neopentane tetrabromo derivative (1,3-dibromo-2,2-bis(bromomethyl)propane) (NTB) in a superbasic KOH-DMSO medium (Scheme 1). The moderate yield of 36% could not be improved by varying the reagents ratio (PzH : NTB : KOH) or reaction temperature (from 20 to 120°C), which is probably due to steric reasons. In agreement with this, more bulky 3,5-dimethylpyrazole did not give substitution product at all and only starting materials were recovered.

In an attempt to improve product yield we tried to change the bromo leaving group to toslyoxy moiety. Unexpectedly, no tetra-pyrazolyl substituted product was obtained in this case. Instead, bis(pyrazolymethyl) derivatives of oxetane were obtained, apparently as a result of intramolecular cyclization (Scheme 2). Similar cyclizations under the action of strong bases were reported previously for tri- and tetratosylates of pentaerythritol [11].

Scheme 2: Formation of 3,3-bis(pyrnol-1-ylmethyl)oxetanes 2, 3 as a result of intermolecular cyclization.

Synthesis of unsubstituted pyrazole compound 2 from potassium pyrazolidine and corresponding 3,3-dimethyloxetane derivative has been reported earlier [12]. The method of synthesis proposed here is more convenient and allowed to prepare previously unknown dimethyl derivative 3.

Compounds 2 and 3 are interesting as ligands for coordination chemistry and as semiproducts for synthetic organic chemistry, since the reactive oxetane cycle can be opened by different basic agents with the formation of a variety of polyfunctional compounds.

We have also prepared a new bitopic ligand with o-phenylene spacer. Compound 4 was obtained by the reaction of α, α, α', α'-tetrabromo-o-xylene with pyrazole in a superbasic medium (Scheme 3). Previously we have used this method for the preparation of ligands with p-phenylene spacer [13].

In case of p-xylene derivative, tetryrazolyl ligands were obtained for both unsubstituted and 3,5-dimethylsubstituted pyrazole [13]. In contrast, o-xylene derivative reacted only with unsubstituted pyrazole, while in case of 3,5-dimethylpyrazole only starting materials were recovered, which is
Table 1: Relative energies of bis(bis(pyrazol-1-yl)methyl)benzene derivatives.

| Structure | \( E_{\text{rel}} \), kcal/mol |
|-----------|-----------------------------|
| \( \text{Pz} \) | 2.53                        |
| \( \text{PzMe}_2 \) | 4.81                        |

Notes: Pz = pyrazol-1-yl; PzMe₂ = 3,5-dimethylpyrazol-1-yl; energies are computed at RI BP86 level of theory using TZVPP basis set.

Figure 2: Molecular models of compound 4 (a) and its dimethylsubstituted derivative obtained at DFT BP86 level of theory using TZVPP basis set.

4. Conclusion

In summary, we have prepared several new bitopic pyrazole-derived ligands that are interesting as building blocks for supramolecular chemistry and crystal engineering.

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