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Boron-chelate assisted synthesis of di[pyrazol-3(5)-yl]methane and 1,1′,2,2′-tetra[pyrazol-3(5)-yl]ethane

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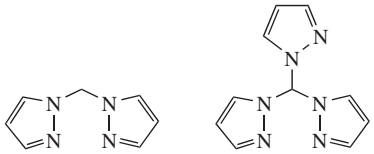
A boron-chelate assisted methodology was applied to the synthesis of di[pyrazol-3(5)-yl]methane and 1,1′,2,2′-tetra[pyrazol-3(5)-yl]-ethane from acetylacetone or tetraacetylethane, *N*,*N*-dimethylformamide dimethyl acetal and hydrazine hydrate.

Dipyrazolyl- and tripyrazolylmethanes are regarded as attractive polydentate ligands for the preparation of metal complexes. These compounds are recognized as structural isomers because different pyrazolic atoms may be bonded to methylene or methane carbon atom. Di(pyrazol-1-yl)methane **1** and tri(pyrazol-1-yl)-methane **2** and their derivatives are mostly studied among these ligands.[1] Both **1** and **2** have a similar structure to (pyrazol-1-yl)-borates,[2] in which boron atom occupies the carbon position, widely used in coordination chemistry.



1 **2**

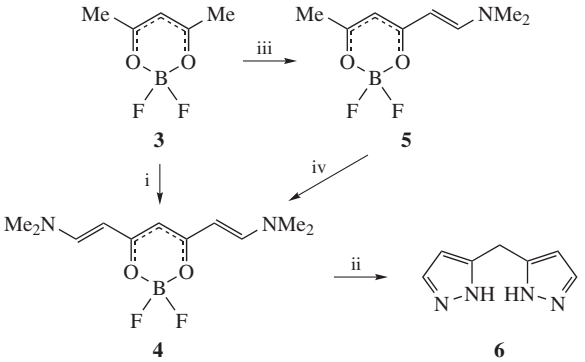
A series of publications concerned Pt complexes of 4,4′-di-pyrazolylmethane, which were tested for cytotoxic activity analoguos to the well known 'cisplatin'.[3]

In contrast, very little is known about dipyrazol-3(5)-ylmethane (DPM), which should be considered as potential chelating ligand. The only synthetic scheme for obtaining DPM was described.[4] It involves the nitrosation of *N*,*N*′-dibenzoyltrimethylenediamine followed by decomposition of the reaction product to afford bis(diazopropane) and further cyclization of the latter compound with acetylene under pressure.

Here we present a convenient synthesis of DPM and 1,1′,2,2′-tetra[pyrazol-3(5)-yl]ethane applying the boron-chelate assisted methodology. Recently, the ability of amide acetals to react with difluoroboron aroylacetonates at the exocyclic methyl group was used in the synthesis of 5-aroylmethylpyrazoles.[5] *N*,*N*-Dimethylformamide dimethyl acetal (DMF DMA) is able to condense at both methyl groups of difluoroboron acetylacetonate† under refluxing in toluene to result in the formation of bisdimethylaminovinyl derivative **4**. Note that DMF DMA condenses at methylene group of free acetylacetone to give 3-[(dimethylamino)methylene]pentane-2,4-dione.

Intermediate monocondensation product **5** can be isolated under the action of an equvalent of amide acetal on difluoroboron complex **3** in THF at room temperature and transformed into **4** by refluxing with DMF DMA in toluene (Scheme 1).‡

Compounds **4** and **5** are stable crystalline solids in air and are soluble in DMF, DMSO, pyridine, chloroform and acetone. Both of the ^{11}B NMR spectra show the signals for four coordinated B at ~0 ppm, and their mass spectra contain molecular ion peaks



Scheme 1 *Reagents and conditions*: i, 2 equiv. DMF DMA, toluene, reflux, 20 min; ii, $N_2H_4 \cdot H_2O$, EtOH, reflux, 3 h; iii, DMF DMA, THF, 20 °C, 2 h; iv, DMF DMA, toluene, reflux, 20 min.

† The starting chelate of acetylacetone was obtained using butoxydifluoroborane[6] as borylating agent prepared *in situ* from $BF_3 \cdot OEt_2$ and $(BuO)_3B$ in a 2:1 ratio. Tetraacetylethane was synthesized as described earlier.[7]

^{1}H and ^{13}C NMR spectra were recorded on a Bruker WM-250 instrument (250 and 63 MHz, respectively) at 25 °C. ^{11}B NMR spectra were recorded on a Bruker AC-200P instrument (64 MHz) with $BF_3 \cdot OEt_2$ as the internal standard. Mass spectra were measured on a Kratos MS-30 instrument (EI, 70 eV). IR spectra were obtained on a Specord M-82 instrument (KBr pellets).

For **3**: $BF_3 \cdot OEt_2$ (0.1 mol) was slowly added to a solution of acetylacetone (0.15 mol) and $(BuO)_3B$ (0.05 mol) in 10 ml of diethyl ether and the mixture was remained at room temperature for 16 h. The solvent was removed and the residue was cooled in the frost chamber. The sediment thus formed was filtered off and washed with 10 ml of light petroleum. White crystals of chelate **3** were obtained in 91% yield after sediment crystallization from diethyl ether; mp 43 °C (lit.:[8] mp 43 °C from chloroform–lygroin). ^{11}B NMR ($CHCl_3$) δ: 0.43.

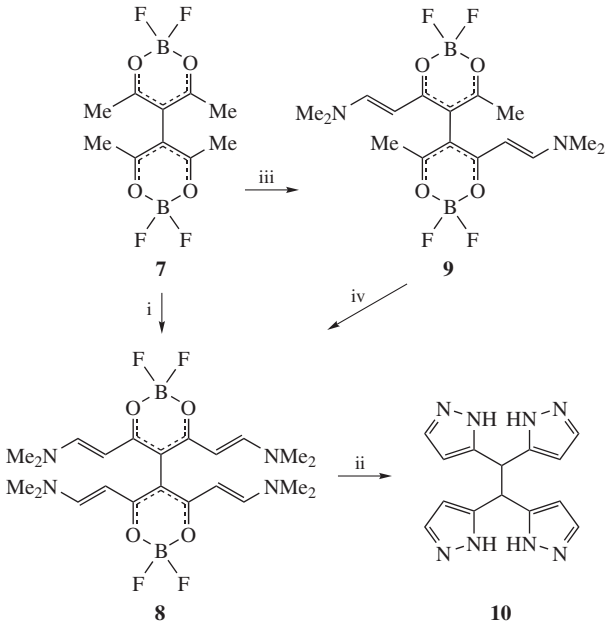
‡ For **4**: difluoroboron chelate **3** (10 mmol) was suspended in 15 ml of toluene containing DMF DMA (25 mmol). The suspension was refluxed for 20 min. The sediment thus formed was filtered off, washed with 5 ml of diethyl ether and purified by flash chromatography (silica gel Silpearl, eluent: acetonitrile). Yield 75%, mp 273–275 °C (toluene–acetonitrile). ^{1}H NMR ($CDCl_3$) δ: 2.92 (br. s, 12H, NMe_2), 4.75, 7.71 (2d, 4H, CH=, J 11.8 Hz), 5.18 (s, 1H, CH). ^{11}B NMR (MeCN) δ: 1.03. IR (ν/cm^{-1}): 2928, 1628, 1520. MS, m/z [I_{rel}(%)]: 258 [M]$^+$ (47), 239 (4), 214 (20). Found (%): C, 51.24; H, 6.61; N, 10.74. Calc. for $C_{11}H_{17}BF_2N_2O_2$ (%): C, 51.19; H, 6.64; N, 10.85.

For **5**: yield 90%, mp 130–131 °C (EtOH). ^{1}H NMR ($CDCl_3$) δ: 2.07 (s, 3H, Me), 2.99, 3.25 (2s, 6H, NMe_2), 4.84, 8.02 (2d, 2H, 2CH=, J 12.2 Hz), 5.43 (s, 1H, CH). ^{11}B NMR (MeCN) δ: 0.97. IR (ν/cm^{-1}): 2962, 1576. MS, m/z [I_{rel}(%)]: 203 [M]$^+$ (83), 188 [M – Me]$^+$ (23), 184 [M – F]$^+$ (39), 159 [M – NMe_2]$^+$ (93). Found (%): C, 47.62; H, 6.13; N, 6.54. Calc. for $C_8H_{12}BF_2NO_2$ (%): C, 47.34; H, 5.96; N, 6.90.

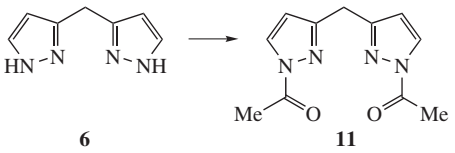
[M]$^+$. There is one set of signals in ^{1}H NMR spectra ($CDCl_3$) containing NMe_2 group protons singlets at ~3.0 ppm and CH group of chelate ring protons singlets at ~5.2–5.4 ppm. The coupling constants value for doublets at 4.8 and 7.7–8.0 ppm of dimethylaminovinyl group protons in compounds **4** and **5** is ~12 Hz that indicates the *E*-configuration of these enamines.

Chelate complex **4** reacts with 2 equiv. of hydrazine hydrate under refluxing in ethanol to form dipyrazolylmethane **6**.§ Compound **6** was isolated as white crystalline solid, which is well soluble in DMSO, acetonitrile, ethanol, ethyl acetate, dioxane and acetone, poorly soluble in chloroform and diethyl ether and insoluble in hexane. The ^{1}H NMR spectrum of **6** ([$^2H_6$]DMSO) shows CH_2 protons as a singlet at 3.91 ppm, the pyrazole ring protons H(3) and H(4) at 7.49 and 6.02 ppm, respectively, and the NH proton as a broad singlet at 12.5 ppm. Similar approach was applied to the synthesis of compound **10** containing four pyrazole rings. Tetraacetylethane was transformed into crystalline binuclear chelate **7**. Condensation of compound **7** with an excess of DMF DMA in DMF at 90 °C yielded **8** with four dimethylaminovinyl fragments in the molecule. (Intermediate chelate **9** was isolated under the action of 2 equiv. of acetal on bis-β-diketonate **7** in THF at room temperature.) Heterocyclization of **8** with the participation of all four dimethylaminovinyl fragments proceeds under refluxing in ethanol with an excess of hydrazine hydrate, delivering 1,1′,2,2′-tetra[pyrazol-3(5)-yl]ethane **10** (Scheme 2).¶

Compound **10** is insoluble in organic solvents other than DMSO. In its ^{1}H NMR spectrum ([$^2H_6$]DMSO) the aliphatic proton is shifted ~1 ppm downfield and the singlet appears at 4.97 ppm. Note that both of the signals for the pyrazole ring protons at 6.06 and 7.29 ppm and singlets for the NH protons are broadened due to the tautomerism of heterocyclic rings. This fact was confirmed by the narrow signals of the CH protons and broad signals of the NH protons while recording the ^{1}H NMR spectra under heating. Acylation of DPM under the action of an excess of acetic anhydride proceeds regioselectively to give symmetric diacetyl derivative **11** (Scheme 3).†† The location of both acetyl groups in the molecule of di(1-acetyl-pyrazol-3-yl)-methane **11** was proved with HMBC ^{1}H-{^{15}N} NMR spectroscopy. The correlation between the CH_2 protons at 3.99 ppm and the down shifted N atom at –80 ppm observed in HMBC spectra testifies that the N atom the nearest to CH_2 group has pyridine but not pyrrole character.



Scheme 2 *Reagents and conditions*: i, 4 equiv. DMF DMA, DMF, 90 °C, 3 h; ii, 4 equiv. $N_2H_4 \cdot H_2O$, EtOH, reflux, 3 h; iii, 2 equiv. DMF DMA, THF, 20 °C, 2 h; iv, 2 equiv. DMF DMA, DMF, 90 °C, 3 h.



Scheme 3 *Reagents and conditions*: Ac_2O, MeCN, reflux, 4 h.

Compounds **6**, **10** and **11** may be considered as potential bi- and tetradentate ligands for preparation of coordination compounds with metals. Furthermore, they are convenient blocks for the construction of heterocyclic systems. The first representative of new tricyclic system, 9-dimethylamino-4*H*,9*H*-dipyrazolo-[1,5-*c*:5′,1′-*f*]pyrimidine **12**, was synthesized from **6** and DMF DMA in the presence of DBU in 69% yield (Scheme 4).‡‡

The structure of **12** was confirmed by IR, ^{1}H and ^{13}C NMR spectroscopy and 2D {^{1}H-^{13}C} NMR spectroscopy. Thus, there

§ For **6**: chelate **4** (1 mmol) was suspended in 5 ml of ethanol containing hydrazine hydrate (0.2 ml). The suspension was refluxed for 3 h. After removal of ethanol, 10 ml of aqua was added to the residue and extracted with ethyl acetate (3×10 ml). The combined extracts were dried over Na_2SO_4, filtered and concentrated and the residue was crystallized from chloroform. Yield 52%, mp 128–129 °C (lit.:[3] mp 129 °C from dioxane). IR (ν/cm^{-1}): 3184, 3112, 2972, 2980, 1584, 1540, 1476. MS, *m*/*z* [I_{rel}(%)]: 148 [M]$^+$ (100), 119 [M – N_2]$^+$ (53), 94 [M – 2N_2]$^+$ (29). Found (%): C, 56.69; H, 5.62; N, 37.67. Calc. for $C_7H_8N_4$ (%): C, 56.74; H, 5.44; N, 37.81.

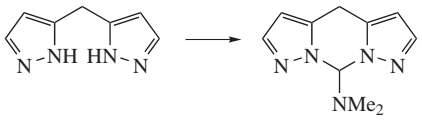
¶ Chelate **7** was synthesized analogously to **3** from tetraacetylethane (27.9 g, 0.15 mol), $(BuO)_3B$ (27 ml, 0.1 mol) and $BF_3 \cdot OEt_2$ (25 ml, 0.2 mol) in 10 ml THF. The sediment thus formed was filtered off and crystallized from acetonitrile. White crystals of **7** were obtained. Yield 40.5 g (92%), mp > 300 °C (decomp.). ^{1}H NMR ($CDCl_3$) δ: 2.25 (s, 4Me). ^{11}B NMR ($CHCl_3$) δ: 0.06. IR, (ν/cm^{-1}): 2936, 1584, 1492, 1360. MS, *m*/*z* [I_{rel}(%)]: 294 [M]$^+$ (9), 180 (20), 165 (55). Found (%): C, 41.15; H, 4.24. Calc. for $C_{10}H_{12}B_2F_4O_4$ (%): C, 40.88; H, 4.12.

For **8**: a solution of chelate **7** (0.5 mmol) and DMF DMA (2 mmol) in 5 ml DMF was stirred at 90 °C for 3 h. The solvent was removed, and the residue was purified by flash chromatography (silica gel Silpearl, eluent: acetonitrile) to give pure compound **8**. Yield 61%, mp > 300 °C (decomp.). ^{1}H NMR ([$^2H_6$]DMSO) δ: 2.71, 3.13 (2br. s, 24H, NMe_2), 4.70, 7.61 (d, 4H, CH=, *J* 12.2 Hz). ^{11}B NMR (MeCN) δ: 1.05. IR (ν/cm^{-1}): 2916, 1612, 1508. MS, *m*/*z* [I_{rel}(%)]: 514 [M]$^+$ (3), 400 (5). Found (%): C, 51.62; H, 6.18; N, 10.98. Calc. for $C_{22}H_{32}B_2F_4N_4O_4$ (%): C, 51.40; H, 6.27; N, 10.90.

For **9**: yield 76%, mp > 300 °C (EtOH, decomp.). ^{1}H NMR ($CDCl_3$) δ: 2.00 (s, 6H, Me), 2.97, 3.28 (2s, 12H, NMe_2), 4.90, 8.08 (2d, 4H, CH=, *J* 12.2 Hz). ^{11}B NMR (MeCN) δ: 0.92. IR (ν/cm^{-1}): 2920, 1520. MS, *m*/*z* [I_{rel}(%)]: 404 [M]$^+$ (3), 335 (5), 290 (10). Found (%): C, 47.32; H, 5.75; N, 5.58. Calc. for $C_{16}H_{22}B_2F_4N_2O_4$ (%): C, 47.57; H, 5.49; N, 5.73.

1,1′,2,2′-Tetra[pyrazol-3(5)-yl]ethane **10** was synthesized analogously to dipyrazolylmethane **6** from chelate **8** (257 mg, 1 mmol) and 0.5 ml of hydrazine hydrate. The bright-brown sediment thus formed after cooling of the reaction mixture was filtered off, washed with 5 ml of hot water followed by 5 ml of ethanol and dried in a vacuum. Crystalline **10** (72 mg) was obtained; yield 49%, mp ~270 °C (sublimation). ^{13}C NMR ([$^2H_6$]DMSO) δ: 41.6, 102.9, 131.8, 149.4. IR (ν/cm^{-1}): 3148, 3040, 2968, 2912, 1528, 1450. MS, *m*/*z* [I_{rel}(%)]: 294 [M]$^+$ (3), 147 [M/2]$^+$ (100). Found (%): C, 57.31; H, 4.53; N, 38.25. Calc. for $C_{14}H_{14}N_8$ (%): C, 57.13; H, 4.79; N, 38.07.

†† For **11**: a solution of **6** (148 mg, 1 mmol) and Ac_2O (0.3 ml, 3 mmol) in 3 ml of acetonitrile was refluxed for 4 h. Colourless needles of **11** thus formed after cooling of the reaction mixture were filtered off and washed with diethyl ether. Yield 70%, mp 154–155 °C. ^{1}H NMR ($CDCl_3$) δ: 2.60 (s, 6H, 2Me), 3.99 (s, 2H, CH_2), 6.24 [d, 2H, C(4), *J* 2.8 Hz], 8.10 [d, 2H, C(5), *J* 2.8 Hz]. ^{15}N NMR ($CDCl_3$) δ: –142, –80. IR (ν/cm^{-1}): 3136, 3112, 3016, 2936, 1728, 1548. MS, *m*/*z* [I_{rel}(%)]: 232 [M]$^+$ (9), 190 [M – Ac + H]$^+$ (78), 148 [M – 2Ac + 2H]$^+$ (100). Found (%): C, 56.80; H, 5.34; N, 24.35. Calc. for $C_{11}H_{12}N_4O_2$ (%): C, 56.89; H, 5.21; N, 24.12.



6 **12**

Scheme 4 *Reagents and conditions*: DMF DMA, DBU, toluene, reflux, 2 h.

are a weak molecular ion $[M]^+$ peak and an intensive $[M - NMe_2]^+$ ion peak in the mass spectrum. The singlet for NMe_2 protons at 2.29 ppm, two doublets of CH_2 protons at 4.11 and 4.29 ppm with coupling constant 20.5 Hz are observed in ^1H NMR spectra. Signal of H(9) is located at 7.00 ppm and both of H_α and H_β protons from two pyrazole rings appear as one set at 7.64 and 6.21 ppm. The ^{13}C NMR spectrum (the signals were ascribed according to HMBC method) shows the CH_2 carbon at 21.0 ppm, the NMe_2 carbons at 38.0 ppm and the CH carbons at 88.0 ppm. Downfield signals at 102.5 and 140.6 ppm are assigned to the pyrazole ring carbon atoms C(3), C(5) and C(2), C(6) respectively. Signal at 135.0 ppm is assigned to quaternary carbon atoms.

‡‡ *9-Dimethylamino-4*H,*9*H-*dipyrazolo[1,5-c:5',1'-f]pyrimidine* **12**. DPM **6** (148 mg, 1 mmol) was suspended in a solution of DMF DMA (0.2 ml, 1.5 mmol) in 3 ml of toluene and two drops of DBU were added. The mixture was refluxed for 2 h. After removal of the solvent, the residue was dissolved in $CHCl_3$ and filtered off through the thin layer of silica gel. Chloroform was removed and 152 mg of compound **12** as colourless needles were obtained by crystallization of the residue from hexane. Yield 69%, mp 115–116 °C. IR (ν/cm^{-1}): 3104, 2948, 2828, 2780, 1552, 1484, 1460. MS, *m*/*z* [I_{rel}(%)]: 203 $[M]^+$ (3), 159 $[M - NMe_2]^+$ (62). Found (%): C, 59.15; H, 6.51; N, 34.32. Calc. for $C_{10}H_{13}N_5$ (%): C, 59.10; H, 6.45; N, 34.46.

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