REACTIVITY OF BIS(HETEROARYL)METHANES TOWARDS DOUBLE ELECTROPHILES. SYNTHESIS OF TWO NEW TRINUCLEAR [5.6.5]- AND [5.5.5]-HETEROCYCLIC SYSTEMS FROM BIS(PYRAZOL-1-YL)METHANE

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Abstract- Two new trinuclear [5.6.5]- and [5.5.5]-heterocyclic systems have been synthesized from bis(pyrazol-1-yl)methane. The scope of this process has been studied. A new desilylating-oxidating system [CuF_2/acetonitrile:pyridine (2:1)] is described.

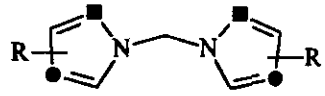
We have previously described the synthesis of bis(azol-1-yl)alkanes[1] by solvent-free phase transfer catalysis and their behaviour in metallation followed by reaction with electrophiles.[2] Substitution at the ring or bridge position is controlled by the nature of the electrophile and mono-or disubstitution can be easily achieved by a carefull choice of the reagents ratio.

We described the synthesis of [5.6.5]- and [5.5.5]-tricyclic systems by reaction with double electrophiles and, in the later, by oxidative coupling.

RESULTS AND DISCUSSION

Reactions with double electrophiles

Bis(pyrrol-1-yl)- (**1**), bis(pyrazol-1-yl)- (**2**), bis(3-methylpyrazol-1-yl)- (**3**), bis(4-methylpyrazol-1-yl)- (**4**) and bis(imidazol-1-yl)- (**5**) methanes have been used as the substrates. Reactions have been performed by deprotonation of the bis(heteroaryl)methanes (**1-5**) with n-butyllithium at 0°C and subsequent addition of the electrophile at room temperature followed by quenching with ammonium chloride.



1: ■,●= CH; R= H , **2**: ■=N,●= CH; R= H , **3**: ■= N, ●= CH; R= 3-Me

4: ■= N, ●= CH; R= 4-Me , **5**: ■= CH, ●= N; R= H

Dichlorosilanes were chosen as the electrophiles. Reaction with silyl electrophiles produced always substitution at the ring position.[2]

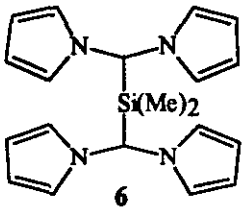
Depending on the nature of the starting material three different behaviours have been observed:

i) Bridge substitution (product **6**) with pyrrole derivative (**1**).

ii) Ring substitution (products **7-10**) with pyrazole derivatives (**2** and **3**).

iii) No reaction with pyrazole derivative (**4**) and imidazole derivative (**5**).

These diferences between are explained considering the relative acidities of the ring and bridge hydrogens as well as electronic and steris effects. Thus, in the bis(pyrrol-1-yl)methane with only one nitrogen atom at the ring, deprotonation at the benzylic position is favored.



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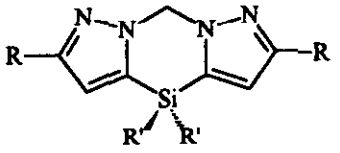


7: R= H; R'= Me; **8**: R= H; R'= Ph; **9**: R=R'=Me

Bis(pyrazol-1-yl)- (**2**) and bis(3-methylpyrazol-1-yl)methane (**3**) afforded the expected new tricyclic system, a dipyrazolo[5,1-*b*:1',5'-*e*]1,3,5-siladiazine (**7**, **8** or **9**).

The structures of 4,4-dimethyl-(**7**), 4,4-diphenyldipyrazolo[5,1-*b*:1',5'-*e*]1,3,5-siladiazine (**8**) and *9H-2,4,4,6-tetramethyldipyrazolo[5,1-b:1',5'-e]1,3,5-siladiazine* (**9**) were elucidated on the basis of their ^{1}H- and ^{13}C-nmr spectra. The assignment of carbon resonances could be stablished by a long range heteronuclear correlation experiment. Yield decrease to 11% using diphenylsilyl dichloride in agreement with the important influence of steric hindrance in silyl derivatives.[3] In the case of 4-methylpyrazole (**4**) and imidazole (**5**) derivatives the expected conformation for the cyclization process is impeded by steric interaction with the 4-methyl group in the first and electrostatic repulsion between the chlorine and the nitrogen lone pair of the imidazole in the later. (Figure 1).

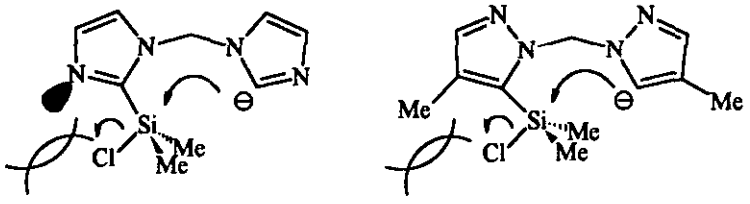


Figure 1

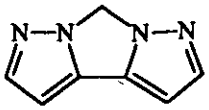
Reaction with trimethylsilyl chloride confirms that disubstitution is possible both in the pyrazole (**4**) (Experimental) and in the imidazole derivative (**5**).[2]

Oxidative cyclization

Oxidative coupling promoted by copper salts, has been used to prepare condensed heterocycles,[4] although low yields are always reported.[4,5] For example, bis(pyrrol-1-yl)methane is transformed in dipyrrolo[1,2-*c*:2'1'-*e*]-2*H*-imidazole in 24% by oxidation of the dianion.[5] Selected higher order cyanocuprates composed of one or two heteroaromatic ligands can be oxidatively coupled, at low temperature, in a inter- or intramolecular fashion to afford unsymmetrical biaryls.[6,7]

We have tried the preparation of a new [5.5.5] tricyclic system by oxidative coupling. Three starting materials have been employed: bis(pyrazol-1-yl)methane (**2**); 5,5'-(bistrimethylsilyl)bis(pyrazol-1-yl)methane (**11**) and 4,4-dimethyldipyrazolo[5,1-*b*:1',5'-*e*]1,3,5-siladiazine (**7**).

Oxidation of bis(pyrazol-1-yl)methane dianion with CuCN/TMEDA/O_2 in THF produces the expected 8*H*-dipyrazolo[5,1-*b*:1',5'-*e*]imidazole (**12**) in 5% yield. However, the starting material is recovered in the oxidative coupling of bistrimethylsilyl derivative (**11**) with CuF_2 in acetonitrile/pyridine. In both compounds the conformation of the starting material and the dianion is not the adequate to produce the cyclization. In the 4,4-dimethyldipyrazolo[5,1-*b*:1',5'-*e*]1,3,5-siladiazine (**7**), both pyrazole rings are in the appropriate disposition to produce the cyclization. Reaction of compound (**7**) with CuF_2 in acetonitrile/pyridine (2:1) afforded the desired [5.5.5] system, (**12**) in 15%.



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This new reagent (CuF_2 in acetonitrile/pyridine) produces oxidative coupling of silyl derivatives. It combines the good desilylation ability of fluoride ions with the oxidation ability of copper(II). The presence of pyridine is necessary to solubilize the inorganic salt and to activate copper(II) by coordination.[8]

EXPERIMENTAL

All reagents were of commercial quality from freshly opened containers. All solvents for reactions were distilled under a dry nitrogen atmosphere. THF was distilled from sodium benzophenone ketyl prior to use. Tetramethylethylenendiamine (TMEDA) was distilled from potassium hydroxide pellets and then redistilled from metallic sodium and stored over fresh-cut sodium. Pyridine was distilled from potassium hydroxide pellets and stored over molecular sieves. The acetonitrile was destilled from phosphorus pentoxide and stored over molecular sieves. CuCN was dried under high vacuum (10^{-3} mm Hg) at room temperature for 3 days and then stored in a stoppered flask. Oxygen gas was passed through H_2SO_4, $CaSO_4$ to remove traces of water. All reactions were carried out under an inert atmosphere of nitrogen. All glassware and stirring bars were dried overnight at *ca.* 140°C prior to use. CuF_2 and molecular sieves were dried under high vacuum (10^{-3} mm Hg) at 200°C for 3 days and then stored in a stoppered flask. Column chromatography was performed on silica gel 60 Merck (230-400 mesh). ^{1}H-Nmr spectra were recorded in chloroform-d_1 (TMS) solutions using a Varian Unity 300 MHz spectrometer.

General procedure of reaction of bis(heteroaryl)methanes with different electrophiles.

In a Schlenk tube, the appropriate bis(heteroaryl)methane was dissolved in dry tetrahydrofurane (THF) and the solution was cooled to 0°C. Under nitrogen, a 1.6 mol.dm^{-3} solution of butyllitium in hexane was added and the mixture was stirred at room temperature for 14 h. The reaction was quenched with solid ammonium chloride. After removal of solvents, the crude residue was elaborated as indicated in each case.

Bis(pyrrol-1-yl)methane (**1**)

Reaction with dimethylsilyl dichloride.

From bis(pyrrol-1-yl)methane (0.648 mmol, 100 mg), n-butyllithium (1.36 mmol, 0.85 ml) and dimethylsilyl dichloride (0.648 mmol, 0.082 ml).

The crude was extracted with chloroform (2 x 5ml) and by flash chromatography (CCl_4), 23 mg (10%) of dimethylbis[bis(pyrrol-1-yl)methyl]silane (**6**) was obtained, mp 123-124°C (from CCl_4-hexane) (Anal. Calcd for $C_{20}H_{24}N_4Si$: C, 68.9; H, 7.0; N, 16.1. Found: C, 68.9; H, 7.1; N, 16.1). ^{1}H-Nmr δ (ppm): 0.49 (s, 6H, $Si(CH_3)_2$); 5.34 (s, 2H, -CH-); 6.16 (t, 8H, J = 2 Hz, AA' part of a AA'BB'-system, H-3, H-3', H-4, H-4'); 6.62 (t, 8H, J = 2 Hz, BB' part of a AA'BB'-system, H-2, H-2', H-5, H-5'). ^{13}C-Nmr δ (ppm): -3.8 (CH_3); 64.7 (-CH-); 109.7 (C-3, C-3', C-4, C-4'); 120.7 (C-2, C-2', C-5, C-5').

Bis(pyrazol-1-yl)methane (**2**)

Reaction with dimethylsilyl dichloride

From bis(pyrazol-1-yl)methane (4.2 mmol, 592 mg), n-butyllithium (8.4 mmol, 5.26 ml) and dimethylsilyl dichloride (4.2 mmol, 0.52 ml).

The crude was extracted with chloroform (4x50 ml) and by flash chromatography [light petroleum-ethyl acetate (2:1)] 539 mg (63%) of *9H-4,4-dimethyldipyrazolo[5,1-b:1',5'-e]1,3,5-siladiazine* (**7**) was obtained, mp 86-87°C (sublimation at 64°C/10^{-3}mm. Hg). (Anal. Calcd for $C_9H_{12}N_4Si$: C, 52.9; H, 5.9; N, 27.4. Found: C, 52.5; H, 5.4; N, 27.6). ^{1}H-Nmr δ (ppm): 0.53 (s, 6H, $Si(CH_3)_3$); 6.40 (s, 2H, CH_2); 6.63 (d, J = 1 Hz, 2H, H-3, H-5); 7.65 (d, J = 1 Hz, 2H, H-2, H-6). ^{13}C-Nmr δ (ppm): -1.8 (q, J = 121.2 Hz, CH_3); 66.5 (t, J = 155.7 Hz, CH_2); 113.9 (dd, J = 185.5 and 6.3 Hz, C-3, C-5); 136.8 (d, J = 9.5 Hz, C-3a, C-4a); 139.5 (dd, J = 175.8 and 10.6 Hz, C-2, C-6).

Reaction with diphenylsilyl dichloride.

From bis(pyrazol-1-yl)methane (4.2 mmol, 592 mg), n-butyllithium (8.4 mmol, 5.26 ml) and diphenylsilyl dichloride (4.2 mmol, 0.88 ml).

Extraction of the crude residue with chloroform (4x50 ml) and flash chromatography [light petroleum-ethyl acetate (6:1)] afforded 134 mg (10%) of *9H-4,4-diphenyldipyrazolo[5,1-b:1',5'-e]1,3,5-siladiazine* (**8**), mp 119-120°C (from ethyl acetate-light petroleum). (Anal. Calcd for $C_{19}H_{16}N_4Si$: C, 69.5; H, 4.9; N, 17.1. Found: C, 69.1; H, 5.0; N, 17.0). ^{1}H-Nmr δ (ppm): 6.50 (s, 2H, CH_2); 6.72 (d, J = 1 Hz, 2H, H-3, H-5); 7.37-7.42 (m, 4H, H_{ortho}); 7.46-7.52 (m, 2H, H_{para}); 7.55-7.58 (m, 4H, H_{meta}); 7.71 (d, J = 1 Hz, 2H, H-2, H-6). ^{13}C-Nmr δ (ppm): 66.7 (t, J = 156.6 Hz, CH_2); 115.6 (dd, J = 176.8 and 10.0 Hz, C-3, C-5); 128.4 (dd, J = 102.0 and 6.5 Hz, C_{meta}); 129.9 (s, C_{ipso}); 131.0 (dt, J = 101.5 Hz, C_{para}); 134.5 (s, C-3a, C-4a); 135.0 (dt, J = 106.0 and 7.8 Hz, C_{ortho}); 139.8 (dd, J = 129.9 and 6.5 Hz, C-2, C-6).

Bis(3-methylpyrazol-1-yl)methane(**3**)

Reaction with dimethylsilyl dichloride.

Bis(3-methylpyrazol-1-yl)methane (0.54 mmol, 95 mg), n-butyllithium (1.08 mmol, 0.67 ml) and dimethylsilyl dichloride (0.54 mmol, 0.065 ml).

Extraction of the crude residue with chloroform (4x50 ml) and flash chromatography [light petroleum-ethyl acetate (5:1)] afforded a mixture of:

15 mg (12%) of *9H-2,4,4,6-tetramethyldipyrazolo[5,1-b:1',5'-e]1,3,5-siladiazine* (**9**), ^{1}H-nmr δ (ppm): 0.49 (s, 6H, $Si(CH_3)_2$); 2.33 (s, 6H, CH_3); 6.30 (s, 2H, CH_2); 6.39 (s, 2H, H-3, H-5). ^{13}C-Nmr δ (ppm): -1.7 (CH_3); 12.9 (CH_3); 65.9 (CH_2); 113.4 (C-3, C-5); 137.7 (C-3a, C-4a), 148.9 (C-2, C-6).

14 mg (14%) of *bis(3-methyl-5-chlorodimethylsilylpyrazol-1-yl)methane* (**10**), ^{1}H-nmr δ (ppm): 0.38 (s, 12H, $Si(CH_3)_2$); 2.26 (s, 6H, CH_3); 6.11 (s, 2H, CH_2); 6.38 (s, 2H, H-4, H-4'). ^{13}C-Nmr δ (ppm): 1.5 ($Si(CH_3)_2$); 13.1 (CH_3); 65.6 (CH_2); 115.1 (C-4, C-4'); 142.2 (C-3, C-3'), 149.2 (C-5, C-5').

Attemps of chromatographic purification produce product decomposition. Yields are calculated from nmr spectra.

Bis(4-methylpyrazol-1-yl)methane (**4**)

Reaction with trimethylsilyl chloride.

Bis(4-methylpyrazol-1-yl)methane (1.06 mmol, 187 mg), n-butyllithium (2.12 mmol, 1.32 ml) and trimethylsilyl chloride (2.12 mmol, 0.28 ml).

Extraction of the crude residue with chloroform (4x50 ml) and flash chromatography [light petroleum-ethyl acetate (20:1)] afforded 149 mg (44%) of *bis(4-methyl-5-trimethylsilylpyrazol-1-yl)methane*, mp 122-123°C (Anal. Calcd for $C_{15}H_{28}N_4Si_2$: C, 56.2; H, 8.8; N, 17.5. Found: C, 55.8; H, 8.8; N, 17.2). ^{1}H-Nmr δ (ppm): 0.46 (s,18H, $Si(CH_3)_3$); 2.10 (s, 6H, CH_3(C-4)); 6.28 (s, 2H, CH_2); 7.28 (s, 2H, H-3, H-3'). ^{13}C-Nmr δ (ppm): 0.4 ($Si(CH_3)_3$); 11.0 (CH_3); 64.9 (CH_2); 125.2 (C-4, C-4'), 139.4 (C-5, C-5'); 141.4 (C-3, C-3').

Synthesis of 8H-dipyrazolo[1,5-c:5',1'-e]imidazole (**12**)

Method A from bis(pyrazol-1-yl)methane. In a 100 ml two-necked flask, a solution of bis(pyrazol-1-yl)methane (2 mmol, 296 mg) in 10 ml of THF at 0°C was prepared. To this solution 2.63 ml (4 mmol) of n-butyllithium was adding. The mixture was then stirred for 1 h. At the same time, in a Schlenk tube a solution of dry CuCN (2 mmol, 180 mg) in 10 ml of THF at -40°C (acetonitrile/liquid nitrogen) was prepared. The solution of deprotonated bis(pyrazol-1-yl)methane was cooled to -95°C using a hexane/liquid nitrogen cooling bath in a Dewar flask. After that the CuCN suspension was transferred dropwise for 5-7 min. with a cannula to the flask containing the dilithium compound. The solution was stirred for an additional 8-10 min. Next, 1 ml of TMEDA was added dropwise over 3 min and the solution was stirred for an additional 7 min. The mixture was allowed to warm to 0°C. The nitrogen was shut off, and a strong flow of dry oxigen was bubbled through the reaction mixture. The color of the solution changes within minutes from orange to blacked green. After 1 h, the flask was evacuated under vacuum, purged with nitrogen, and the reaction was then quenched with 4 ml of a 1:1 mixture of methanol/saturated aqueous $NaHSO_3$ solution. The reaction mixture was then allowed to warm to room temperature and acidified with concentrated hydrochloric acid (2.5 ml). The solution was poured into a separatory funnel and extracted with CH_2Cl_2 (4x50 ml). The combined organic phases were dried with magnesium sulfate and filtered, and the solvent was evaporated in vacuo. The residue was filtered over silica gel using ethyl acetate as the eluent. The filtrated was flash chromatographed with acetonitrile/hexane (1:1) on silicagel and 15 mg. (5%) of *8H-dipyrazolo[1,5-c:5',1'-e]imidazole* (**12**) was obtained. mp103-104°C. (Anal.

Calcd for $C_7H_6N_4$: C,57.5; H, 4.1; N, 38.3. Found: C, 57.8; H, 4.3; N, 37.9). ^{1}H-Nmr δ (ppm): 6.05 (s, 2H, CH_2); 6.39 (d, J = 1.8 Hz, 2H, H-3, H-4); 7.66 (d, J = 1.8 Hz, 2H, H-2, H-5). ^{13}C-Nmr δ (ppm): 65.2 (t, J = 160.5 Hz, CH_2); 98.0 (dd, J = 180.5 and 11.5 Hz , C-3, C-4); 135.9 (d, J = 2.5 Hz, C-3a, C-3b); 143.9 (dd, J = 186.6 and 6.0 Hz, C-2, C-5).

Method B from 9*H*-4,4-dimethyldipyrazolo[5,1-*b*:1',5'-*e*]1,3,5-siladiazine. A mixture of 0.764 mmol (77.56 mg) of CuF_2 and 0.764 mmol (156 mg) of *9H-4,4-dimethyldipyrazolo[5,1-b:1',5'-e]1,3,5-siladiazine* placed in a 10 ml flask connected with a reflux condenser, were dissolved in 3 ml of acetonitrile:pyridine(2:1). After 150 min, was filtered off and washed with 5 ml of acetonitrile and the solvents were evaporated in vacuo. The residue was filtered over silicagel using acetonitrile as the eluent. The filtrated was chromatographed on silicagel with acetonitrile/hexane (1:1) and 16 mg (15%) of *8H-dipyrazolo[1,5-c:5',1'-e]imidazole* was obtained.

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