

A SELECTIVE SYNTHESIS OF UNSYMMETRICAL 1,1'-METHYLENEBISDIAZOLES
BY SOLID-LIQUID PHASE TRANSFER CATALYSIS

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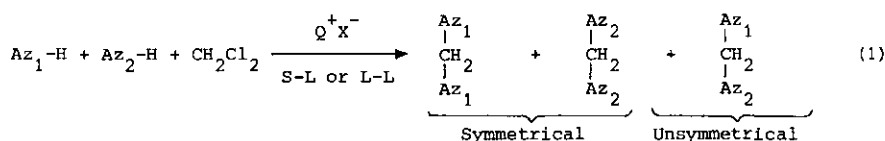
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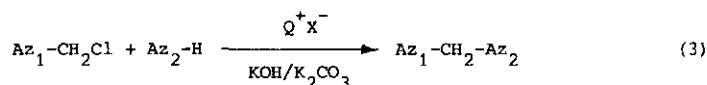
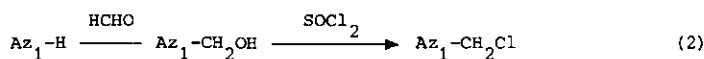
Abstract- 1,1'-Methylenebisdiazoles $Az_1-CH_2-Az_2$, Az_1 and Az_2 being two different diazoles, can be prepared selectively in three steps, through 1-hydroxymethyl- and 1-chloromethyldiazoles, by solid-liquid (S-L) phase transfer catalysis.

Symmetrical 1,1'-methylenebisdiazoles are useful ligands in organometallic chemistry.¹⁻⁵ Surprisingly enough, unsymmetrical 1,1'-methylenebisdiazoles are almost unknown compounds. So far, the only possible way to obtain these products is represented in eq. 1 (L-L means liquid-liquid).



Following this procedure, the unique representative of unsymmetrical 1,1'-methylenebisdiazoles, namely 1-pyrazolyl-1'-imidazolylmethane **6**, was synthesized.⁶ The obvious problem is that **6** was obtained mixed with the two symmetrical 1,1'-methylenebisdiazoles, the yield on crude product being low (32%) and compound **6** difficult to isolate and purify.

We report here a selective synthesis of unsymmetrical 1,1'-methylenebisdiazoles, summarized in eq. 2 and 3.



From the following diazoles (Az_1-H), pyrazole **1a**, 3,5-dimethylpyrazole **1b**, benzimidazole **1c**, 2-methylbenzimidazole **1d**, and indazole **1e**, the corresponding 1-hydroxymethyl derivatives **2** were prepared (Table 1) and transformed into the hydrochlorides of 1-chloromethyldiazoles **3** (Table 2). These last compounds were hygroscopic; the corresponding free bases were unstable.

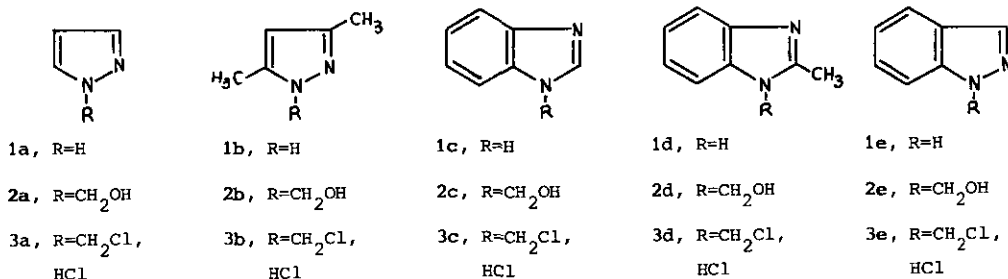


Table 1. 1-Hydroxymethyl diazoles 2 prepared

Product	Yield [%]	m p [°C]	Molecular formula ^a or Lit. m p [°C]	I.R. (KBr) ν [cm ⁻¹]	U.V. (C ₂ H ₅ OH) $\lambda_{\max}$ (log ϵ)	¹ H-N.M.R. (CDCl ₃) δ [ppm]	MS m/z (70 eV)
2a	74	89-90	88 ⁷	3400-2700, 1525	210 (3.57)	5.4 (s, 2H, CH ₂); 6.2 (t, 1H, H ₄); 7.3 (s, 1H, OH) 7.45 (d, 2H, H ₃ , H ₅); J ₃₅ =J ₄₅ = 2 Hz	98 (M ⁺) (2.5%)
2b	81	109	109 ⁷	3500-2700, 1550	214 (3.69)	2.2 (s, 3H, CH ₃); 2.3 (s, 3H, CH ₃); 5.35 (s, 2H, CH ₂); 5.8 (s, 1H, H ₄); 7.0-7.5 (bs, 1H, OH)	126 (M ⁺) (35%)
2c	90	142-143	141-143 ⁸	3500-2700, 1610	244 (3.74) 272 (3.72) 279 (3.76)	5.45 (s, 2H, CH ₂); 6.5-7.0 (bs, 1H, OH); 7.0-7.8 (m, 4H _{arom}); 7.9 (s, 1H, H ₂) ^b	117 (M ⁺ -31) (100%)
2d	97	152-153	C ₉ H ₁₀ N ₂ O (162.2)	3500-2700, 1610	243 (3.65) 274 (3.67) 280 (3.72)	2.55 (s, 3H, CH ₃); 3.0-3.5 (s, 1H, OH); 5.5 (s, 2H, CH ₂); 7.0-7.8 (m, 4H _{arom}) ^c	131 (M ⁺ -31) (100%)
2e	75	113-114	115 ⁹	3500-3000 1610	251 (3.61) 287 (3.61)	5.8 (s, 2H, CH ₂); 7.0-7.8 (m, 4H _{arom} + OH); 8.0 (s, 1H, H ₃)	148 (M ⁺) (20%)

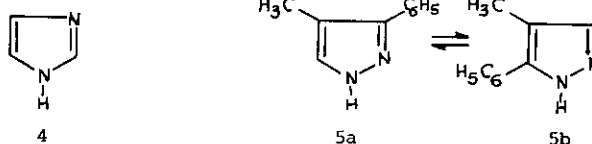
^aSatisfactory microanalysis obtained: C $\pm$ 0.23, H $\pm$ 0.15, N $\pm$ 0.02; ^bDMSO-d₆; ^cCD₃COCD₃

Table 2. 1-Chloromethyl diazoles 3 prepared (isolated as hydrochlorides)

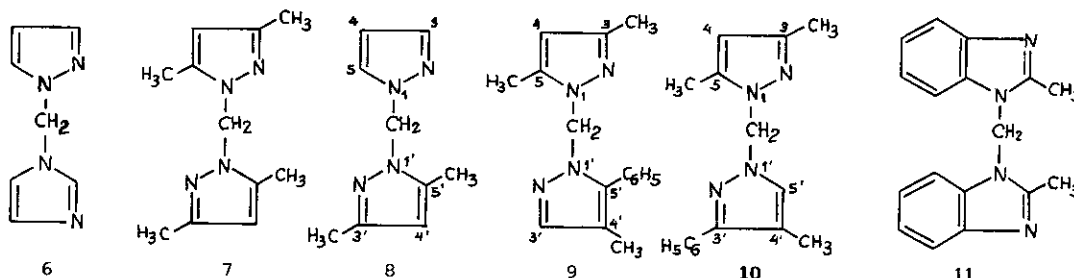
Product	Yield [%]	m p [°C]	I.R. (film) ν [cm ⁻¹]	¹ H-N.M.R. (CDCl ₃) δ [ppm]	MS m/z (70 eV)
3a^b	90	oil	2700-2000, 1515	5.9 (s, 2H, CH ₂); 6.3 (t, 1H, H ₄); 7.6 (d, 2H, H ₃ , H ₅), J ₃₅ =J ₄₅ = 2 Hz	116, 118 (M ⁺)
3b^c	98	100-105	2900-2000, 1620 ^d	2.55 (s, 3H, CH ₃); 2.6 (s, 3H, CH ₃); 6.3 (s, 3H, CH ₂ + H ₄)	144, 146 (M ⁺)
3c	99	174-175 ^e	2800-2500, 1610	6.7 (s, 2H, CH ₂); 7.5-8.3 (m, 5H _{arom}) ^f	166, 168 (M ⁺)
3d	98	oil	3000-2400, 1615	3.1 (s, 3H, CH ₃); 6.3 (s, 2H, CH ₂); 7.2-7.8 (m, 4H _{arom})	180, 182 (M ⁺)
3e	85	43-44 ^{g,h}	2800-2000, 1610	6.3 (s, 2H, CH ₂); 7.0-7.9 (m, 4H _{arom}); 8.1 (s, 1H, H ₃)	166, 168 (M ⁺)

^aThe 100% intensity peak always correspond to M⁺-35 (M⁺-37), the reported peaks have intensities below 30%; ^bThe hydrochloride of 3a was described by Pinar and Utting (yield, 80%¹⁰) without physical characteristics or analysis; ^cThe hydrochloride of 3b was described by Rüfenacht (yield 99%¹¹) without mp or analysis; ^dKBr; ^eLit. mp 173-174°C¹²; ^fDMSO-d₆; ^gFree base; ^hLit. mp (free base) 45-47°C⁹.

Solid-liquid phase-transfer catalysis was used to carry out the second step (eq. 3) using $\text{KOH}/\text{K}_2\text{CO}_3$ as a base. Table 3 contains the results we obtained. In addition to the above *N*-unsubstituted diazoles 1 (used now as $\text{Az}_2\text{-H}$), imidazole 4 and 3(5)-phenyl-4-methylpyrazole 5 were employed in this second step.



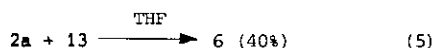
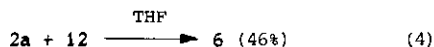
In this way, the following 1,1'-methylenebisazoles were prepared and characterized (Table 3):



The structure of the pair of isomers 9 and 10 was determined by nuclear magnetic resonance spectroscopy. The chemical shifts (both ^1H and ^{13}C)^{13,14} and the ^1H - ^1H coupling constants¹⁵ are similar to those of the corresponding *N*-methyl pyrazoles.

Symmetrical derivatives, 7 and 11, were prepared to check the method. Compound 8 is an unsymmetrical derivative; no traces (TLC) of the symmetrical compounds, 1,1'-methylenebispyrazole⁶ and 7, were found in the crude mixture. The reaction between 3b and 5 yields two isomers, 28% 9 and 35% 10 (the methylation of 5 also gives a major proportion of the 3-phenyl-4-methyl isomer).¹³

Compound 6 obtained previously in low yield and mixed with the two symmetrical isomers, was now isolated in pure form in 65% yield (Table 3). To check if the method here described is the best one to prepare unsymmetrical 1,1'-methylenebisdiazoles, compound 6 was prepared from 1-hydroxymethylpyrazole 2a and *N,N'*-sulfonyldiimidazole 12 or *N,N'*-carbonyldiimidazole 13 following a procedure described by Ogata and Matsumoto¹⁶ for benzylic alcohols (eq. 4 and 5).



This method avoids the preparation of the unstable 1-chloromethyldiazoles 3, but the yields are lower and both reagents, 12 and 13, delicate to handle. Moreover, eq. 4 and 5 are only known for imidazole derivatives.

In conclusion, the method via 1-chloromethyldiazoles is the best procedure available to obtain unsymmetrically substituted 1,1'-methylenebisdiazoles.

Table 3. 1,1'-Methylenebisdiazoles 6-11 prepared

Product	Yield [%]	Starting materials	m p [°C]	Molec. formula or Lit. m p [°C]	I.R. (KBr) ν [cm ⁻¹]	U.V. (C ₂ H ₅ OH) $\lambda_{\max}$ (log ϵ)	¹ H N.M.R. δ [ppm]	¹³ C N.M.R. δ [ppm]	MS m/z (70 eV)
6 ^b	65	3a + 4	77	77 ⁶	-----	-----	-----	-----	-----
7 ^b	85	3b + 1b	105	105 ⁶	-----	-----	-----	-----	-----
8 ^c	55	3a + 1b	85-86	C ₉ H ₁₂ N ₄ (176.2)	1550, 1400	222 (4.09)	{ 2.15 (s, 3H, CH ₃); 2.35 (s, 3H, CH ₃); 5.75 (s, 1H, H ₄); 6.15 (s, 2H, CH ₂); 6.20 (t, 1H, H ₄); 7.45 (d, 1H, H ₃); 7.55 (d, 1H, H ₅); J ₃₄ =J ₄₅ = 2 Hz	11.0 (CH ₃ -5'); 13.4 (CH ₃ -3'); 62.7 (CH ₂); 106.8 (C ₄ , C _{4'}); 129.2 (C ₅); 140.0 (C ₃); 140.3 (C ₅); 149.2 (C ₃) ^d	176 (M ⁺) (37%) 108 (M ⁺ -68) (100%)
8 ^c	65	3b + 1a	85-86	C ₉ H ₁₂ N ₄ (176.2)					
9 ^e	28	3b + 5	105-107	C ₁₆ H ₁₈ N ₄ (266.4)	{ 3030, 3020, 1560, 1380	< 210	{ 1.93 (s, 3H, CH ₃ -4'); 2.03 (s, 3H, CH ₃ -3); 2.32 (d, 3H, CH ₃ -5); J ₄₅ = 0.7 Hz; 5.78 (m, 1H, H ₄); 6.00 (s, 2H, CH ₂); 7.40 (s, 1H, H ₃); 7.45- 7.65 (m, 5H _{arom}) ^f	8.6 (CH ₃ -4'); 10.6 (CH ₃ -5); 13.2 (CH ₃ -3); 59.3 (CH ₂); 105.4 (C ₄); 114.2 (C _{4'}); 128.5, 128.6, 129.3, 130.1 (Aromatic); 140.2 (C ₅); 140.4 (C ₃); 140.5 (C ₅); 147.2 (C ₃) ^f	266 (M ⁺) (72%) 108 (M ⁺ -158) (100%)
10 ^e	35	3b + 5	131-133	C ₁₆ H ₁₈ N ₄ (266.4)					
11 ^b	95	3d + 1d	249	249 ⁶	-----	-----	-----	-----	-----

^aSatisfactory microanalysis obtained: C $\pm$ 0.31, H $\pm$ 0.21, N $\pm$ 0.12; ^bPurified as in reference 6; ^cPurified by column chromatography over Kieselgel using ether-benzene (1:1) as eluent (TLC, R_f = 0.40); ^dCDCl₃; ^eBoth isomers were separated by column chromatography over Kieselgel using ether-benzene (1:1) as eluent, followed by crystallization in *n*-hexane (TLC, 9, R_f = 0.84, 10, R_f = 0.70); ^fDMSO-d₆.

EXPERIMENTAL

1-Hydroxymethyldiazoles (2); General Procedure. The suitable diazole 1a-1e (0.04 mol) in 20 ml of ethanol and 5 ml of 40% formalin was refluxed during 1 h with stirring. The stirring was continued at room temperature for 12 h. The precipitate (in the case of pyrazoles 2a and 2b it was necessary to add 40 ml of cold water) was filtered off and purified by crystallization from ethanol-water. The yields in Table 1 are ones isolated as pure compounds.

1-Chloromethyldiazoles (3); General Procedure. In a 100 ml round bottom flask, provided with a magnetic stirrer, a condenser, and a calcium chloride stopper, 0.02 mole of the corresponding 1-hydroxymethyldiazole 2a-2e in 50 ml of chloroform were placed. After solution, 6.5 ml of thionyl chloride were added at room temperature. After stirring for 3 h at room temperature, the solution is evaporated to dryness in vacuo. The residue is the hydrochloride of 1-chloromethyldiazole which can be used without further purification. The hydrochloride solidifies in some cases (3b, 3c).

Methylenebisdiazoles (6-11); General Procedure. In a round bottom flask, provided with a magnetic stirrer, a condenser, and a calcium chloride stopper, were placed 0.01 mole of 1-chloromethyldiazole hydrochloride 3, 0.01 mole of *N*-unsubstituted diazole, 0.03 mole of powdered potassium hydroxide, 0.01 mole of anhydrous potassium carbonate, 0.0005 mole of tetrabutylammonium hydrogensulfate in 50 ml of anhydrous benzene. After reflux for 8 h and 16 h at room temperature, both with vigorous stirring, the solid was filtered and washed carefully with boiling benzene (2 x 25 ml). The solvent was evaporated under reduced pressure and the residue purified. The yields in Table 3 are in pure compounds.

1-Pyrazolyl-1'-imidazolylmethane (6). The synthesis according to eq. 4 and 5 follows exactly the procedure of Ogata and Matsumoto.¹⁶ The purification was carried out according to reference 6.

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Received, 11th April, 1986