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

Sebastian Juliá and Carlos Martínez-Martorell

Sección de Química Médica, Departamento de Química Orgánica, Instituto Químico de Sarriá, 08017 Barcelona, Spain

José Elguero*

Instituto de Química Médica, C.S.I.C., Juan de la Cierva 3, 28006 Madrid, Spain

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).

$$Az_1\text{-}H + Az_2\text{-}H + CH_2Cl_2 \xrightarrow[\text{S-L or L-L}]{Q^+X^-} \underbrace{Az_1\text{-}CH_2\text{-}Az_1 + Az_2\text{-}CH_2\text{-}Az_2}_{\text{Symmetrical}} + \underbrace{Az_1\text{-}CH_2\text{-}Az_2}_{\text{Unsymmetrical}} \qquad (1)$$

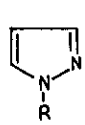
Following this procedure, the unique representative of unsymmetrical 1,1'-methylenebisdiazoles, namely 1-pyrazolyl-1'-imidazolylmethane **6**, was synthesized.[6] The obvious problem is that **6** was obtained mixed with the two symmetrical 1,1'-methylenebisdiazoles, the yield on crude product being 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.

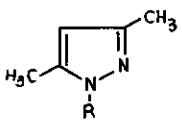
$$Az_1\text{-}H \xrightarrow{HCHO} Az_1\text{-}CH_2OH \xrightarrow{SOCl_2} Az_1\text{-}CH_2Cl \qquad (2)$$

$$Az_1\text{-}CH_2Cl + Az_2\text{-}H \xrightarrow[KOH/K_2CO_3]{Q^+X^-} Az_1\text{-}CH_2\text{-}Az_2 \qquad (3)$$

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.



1a, R=H



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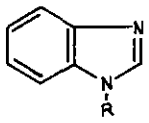

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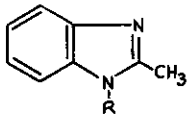

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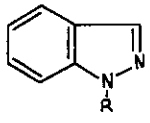


1e, R=H

2a, R=CH_2OH	**2b**, R=CH_2OH	**2c**, R=CH_2OH	**2d**, R=CH_2OH	**2e**, R=CH_2OH
3a, R=CH_2Cl, HCl	**3b**, R=CH_2Cl, HCl	**3c**, R=CH_2Cl, HCl	**3d**, R=CH_2Cl, HCl	**3e**, R=CH_2Cl, HCl

Table 1. 1-Hydroxymethyldiazoles 2 prepared

Product	Yield [%]	m p [°C]	Molecular formula[a] or Lit. m p [°C]	I.R. (KBr) ν [cm^{-1}]	U.V. (C_2H_5OH) λ_{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	$C_9H_{10}N_2O$ (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%)

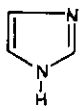
[a] Satisfactory microanalysis obtained: C ± 0.23, H ± 0.15, N ± 0.02; [b] DMSO-d_6; [c] CD_3COCD_3

Table 2. 1-Chloromethyldiazoles 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^+)

[a] The 100% intensity peak always correspond to M^+-35 (M^+-37), the reported peaks have intensities below 30%; [b] The hydrochloride of 3a was described by Finar and Utting (yield, 80%[10]) without physical characteristics or analysis; [c] The hydrochloride of **3b** was described by Rüfenacht (yield 99%[11]) without mp or analysis; [d] KBr; [e] Lit. mp 173-174°C[12]; [f] DMSO-d_6; [g] Free base; [h] Lit. mp (free base) 45-47°C[9].

Solid-liquid phase-transfer catalysis was used to carry out the second step (eq. 3) using KOH/K_2CO_3 as a base. Table 3 contains the results we obtained. In addition to the above N-unsubstituted diazoles 1 (used now as Az_2-H), imidazole **4** and 3(5)-phenyl-4-methylpyrazole **5** were employed in this second step.



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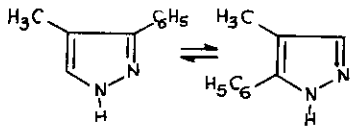
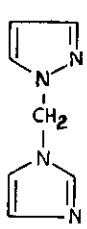


5a 5b

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



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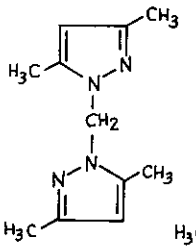

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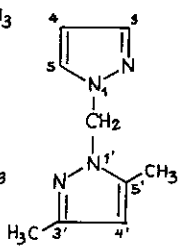

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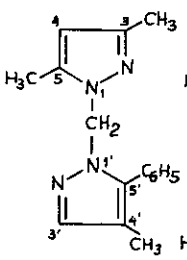

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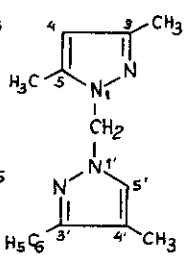

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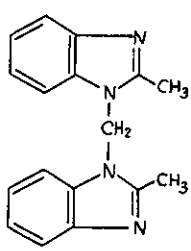

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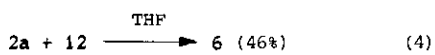
The structure of the pair of isomers **9** and **10** was determined by nuclear magnetic resonance spectroscopy. The chemical shifts (both ^1H and ^{13}C)[13,14] and the ^1H-^1H coupling constants[15] are similar to those of the corresponding N-methyl pyrazoles.

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'-methylenebispyrazole[6] 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 Matsumoto[16] for benzylic alcohols (eq. 4 and 5).



2a + **12** $\xrightarrow{THF}$ **6** (46%) (4)

2a + **13** $\xrightarrow{THF}$ **6** (40%) (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_2H_5OH) λ_{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	$C_9H_{12}N_4$(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	$C_9H_{12}N_4$(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 (C4'); 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)	3020, 1560, 1380	251 (4.04)	2.07 (s, 3H, CH_3-3); 2.16 (d, 3H, CH_3-4', J_{45}= 0.8 Hz); 2.42 (d, 3H, CH_3-5; J_{45}= 0.7 Hz); 5.83 (m, 1H, H_4); 6.20 (s, 2H, CH_2); 7.25-7.65 (m, 5H_{arom}); 7.70 (m, 1H, H_5)[f]	9.8 (CH_3-4'); 10.6 (CH_3-5); 13.2 (CH_3-3); 61.8 (CH_2); 105.9 (C_4); 113.7 (C_4'); 126.8, 127.2, 128.4, 133.7 (Aromatic); 130.8 (C_3'); 139.9 (C_5); 147.4 (C_3); 149.2 (C_5')[f]	266 (M^+)(68%) 108 (M^+-158) (100%)
11[b]	95	**3d** + **1d**	249	249[6]	-----	-----	-----	-----	-----

[a]Satisfactory microanalysis obtained: C ± 0.31, H ± 0.21, N ± 0.12; [b]Purified as in reference 6; [c]Purified by column chromatography over Kieselgel using ether-benzene (1:1) as eluent (TLC, R_f = 0.40); [d]$CDCl_3$; [e]Both 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); [f]DMSO-d_6.

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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