

Study of *N,N'*-Diazolymethanes

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Thirteen *N,N'*-diazolymethanes, including derivatives of pyrazole, imidazole, 1,2,4-triazole, benzimidazole and indazole were prepared by reaction of azoles with methylene chloride under phase transfer catalysis conditions. The relative amounts of isomeric mixtures obtained with 'asymmetric' azoles or with equimolar mixtures of azoles are compared with literature results on monoalkylation of azoles. Proton and carbon-13 nmr spectra of the *N,N'*-diazolymethanes are discussed.

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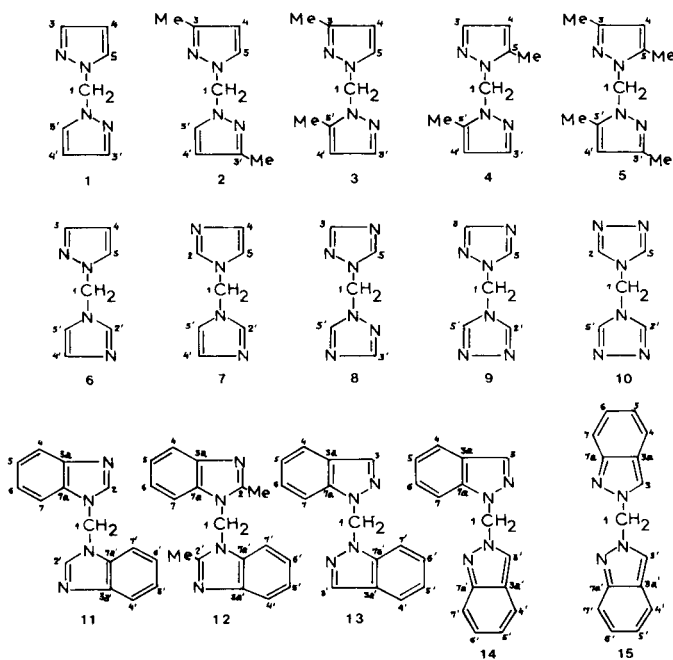
N,N'-Diazolymethanes are a class of heterocyclic derivatives which have received little attention. A careful survey of the literature showed that only five compounds were already known: *N,N'*-dipyrazolymethane (**1**), *N,N'*-di-(3,5-dimethyl)pyrazolymethane (**5**), *N,N'*-diimidazolymethane (**7**), *N,N'*-dibenzimidazolymethane (**11**) and *N,N'*-diindazolymethane (**13**). All of them are 'symmetrical' compounds (*i.e.* both azoles are identical) prepared by classical methods. Compound **1** was prepared by heating

was prepared as for **1** but using imidazole and methylene chloride (**2**). Compound **11** was obtained from benzimidazole using either methylene bromide (**3**) or methylene chloride (**4**) in basic medium. Compound **13** was obtained mixed with the *N*-CH₂OH derivative from indazole, formalin and hydrochloric acid (**5**).

The yields were moderate to poor (Table I) except in the case of **5** (1). In some cases the diazolymethane was obtained mixed with other products (4,5). Some experimental conditions were not fully satisfactory. These are use of autoclaves (1,2), potassium salts (1,4), methylene iodide (1) or methylene bromide (1,3) instead of the cheaper and less toxic methylene chloride. Thus for all of these reasons, it was of interest to study the possibility of preparation of *N,N'*-diazolymethanes using methylene chloride under phase transfer conditions. Methylene chloride is often used in phase transfer catalysis as an inert solvent (6,7) and in some cases (preparation of ROCH₂OR and RSCH₂SR derivatives) as a double alkylating agent (6). Even if there are no reports in the case of heterocycles, the fact that one can obtain *N,N'*, *N''*-triazolymethanes from chloroform under phase transfer catalysis conditions (8,9) justified our hypothesis.

The results reported in Table I show that indeed phase transfer catalysis is an excellent method to obtain *N,N'*-diazolymethanes. The effectiveness of the phase transfer

catalysis procedure is demonstrated in a blank experiment without any catalyst. Under these conditions using pyrazole as the substrate, no product of dialkylation (**1**) was isolated by solid-liquid or liquid-liquid procedures. The only question that we cannot rationalize at this time is, depending on the azole, why the liquid-liquid or the solid-liquid procedure gives the best results. In some cases, such as in pyrazole and 3,5-dimethylpyrazole both methods give



pyrazole and methylene bromide in an autoclave (1). Compound **5** was prepared from the potassium salt of 3,5-dimethylpyrazole and methylene iodide (1). Compound **7**

Table I
Synthesis of *N,N'*-Diazolylmethanes

Starting azole	Conditions (a)	Total yield (b)	Relative amounts (b)	Literature yield
Pyrazoles	{ L-L S-L	93% 81%	100% 1	} 46% (1)
3(5)-Methylpyrazole	L-L	96%	27%, 2 , 50% 3 , 23% 4	
3,5-Dimethylpyrazole	{ L-L S-L	78% 89%	100% 5	} 82% (1)
Equimolar mixture of pyrazole and imidazole	{ L-L S-L	66% 62%	32% 1 , 49% 6 , 19% 7 28% 1 , 50% 6 , 22% 7	
Imidazole	{ L-L S-L	73% (c)	100% 7	
1,2,4-Triazole	{ L-L S-L	62% (c)	100% 8	
Benzimidazole	{ L-L S-L	30% (d) 89%	100% 11	} 64% (3), 35% (4)
2-Methylbenzimidazole	S-L	94%	100% 12	
Indazole	L-L	79%	50% 13 , 41% 14 , 9% 15	15% 13 (5)

(a) L-L: liquid-liquid, S-L: solid-liquid. (b) Calculated from residue by proton nmr; the yields of chromatographically pure products are gathered in Table IV (see experimental part). (c) Incomplete reaction, yield not calculated. (d) Reaction time, 66 hours.

Table II

¹H NMR Data for *N,N'*-Diazolylmethanes (solvent: deuteriochloroform)

Compound No.	H ₁	H ₂ (Me ₂)	H ₃ (Me ₃)	H ₄	H ₅ (Me ₅)	H ₆	H ₇	H ₂ '(Me ₂ ')	H ₃ '(Me ₃ ')	H ₄ '	H ₅ '(Me ₅ ')	H ₆ '	H ₇ '
1 (a)	6.30	—	7.50	6.30	7.61	—	—	—	7.50	6.30	7.61	—	—
2 (b)	6.22	—	(2.30)	6.14	7.64	—	—	—	(2.30)	6.14	7.64	—	—
3 (c)	6.12	—	(2.22)	5.99	7.45	—	—	—	7.39	6.01	(2.42)	—	—
4 (d)	6.20	—	7.35	5.90	(2.48)	—	—	—	7.35	5.90	(2.48)	—	—
5 (e)	6.01	—	(2.13)	5.73	(2.38)	—	—	—	(2.13)	5.73	(2.38)	—	—
6	6.12	—	7.52	6.29	7.52	—	—	7.66	—	7.14	7.14	—	—
7	6.18	7.78	—	7.15	7.05	—	—	7.78	—	7.15	7.05	—	—
8	6.37	—	7.87	—	8.33	—	—	—	7.87	—	8.33	—	—
11 (g)	6.98	8.87	—	—	7.3 to 8.1	—	—	8.87	—	—	7.3 to 8.1	—	—
12	6.15	(2.52)	—	7.75	— 7.1 to 7.4	—	—	(2.52)	—	7.75	— 7.1 to 7.4	—	—
13 (f)	6.73	—	7.88	—	7.0 to 7.8	—	—	—	7.88	—	7.0 to 7.8	—	—
14	6.68	—	7.92	—	6.8 to 7.7	—	—	—	7.92	—	6.8 to 7.7	—	—
15	6.73	—	8.18	—	6.8 to 7.6	—	—	—	8.18	—	6.8 to 7.6	—	—

Coupling constants: (a) 1.7 (H₃H₄), 2.45 (H₄H₅), 0.45 (H₃H₅). (b) 0.3 (Me₃H₄), 2.4 (H₄H₅), 0.25 (Me₃H₅). (c) 2.4 (H₄H₅), 1.5 (H₃H₄'), 0.9 (H₄'Me₃'), 0.35 (H₃'Me₅'). (d) 1.5 (H₃H₄), 0.9 (H₄'Me₃'), 0.35 (H₃'Me₅'). (e) 0.8 (H₄'Me₃'). (f) 0.8 Hz (H₃H₄'). (g) Solvent: DMSO-d₆.

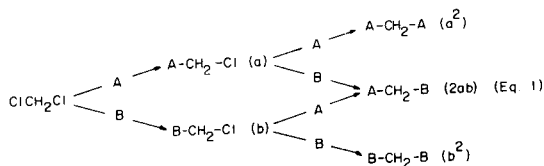
comparable yields, while in others, one procedure is more effective: liquid-liquid for imidazole and 1,2,4-triazole and solid-liquid for benzimidazole. However, one should be cautious about these conclusions because they correspond to non-optimized experimental procedures.

Another aspect of the results of Table I is worth noting.

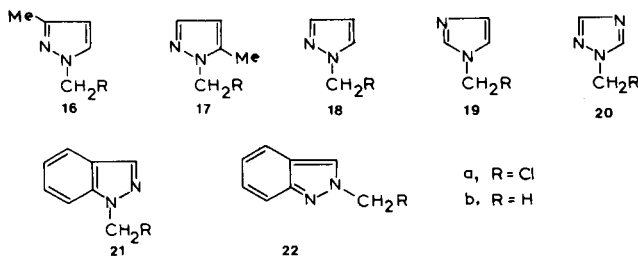
The first 'asymmetric' diazolylmethanes **3** and **14** starting from 'asymmetric' azoles like 3(5)-methylpyrazole or indazole were obtained and **6** starting from an equimolar mixture of two 'symmetric' azoles, pyrazole and imidazole were obtained.

Finally it seems of interest to discuss the question of the

relative amounts of isomeric diazolylmethanes. We have checked carefully that in the reaction between 1,2,4-triazole and methylene chloride, compounds **9** and **10** are not formed. Considering that an azole can exist in two tautomeric structures (or working with a mixture of two 'symmetrical' azoles) A and B, we could write the following sequence of reactions (Equation 1).



If it is assumed that the ratio a/b is the same in the two steps, then the final mixture must correspond to $(a + b)^2$. With remarkable accuracy the relative amounts of isomers in Table I follow this pattern. This fact allows the calculation of the relative amounts of $N\text{-CH}_2\text{Cl}$ precursors, **16a** to **22a** (Equations 2 to 5).



(Eq. 2) 3(5)-methylpyrazole \rightarrow 52% **16a** + 48% **17a**
 \rightarrow 27% **2** + 50% **3** + 23% **4**

(Eq. 3) an equimolar mixture of pyrazole and imidazole \rightarrow 56% **18a** + 44% **19a** \rightarrow 32% **1** + 49% **6** + 19% **7**

(Eq. 4) 1,2,4-triazole \rightarrow 100% **20a** \rightarrow 100% **8**

(Eq. 5) indazole \rightarrow 71% **21a** + 29% **22a** \rightarrow 50% **13** + 41% **14** + 9% **15**

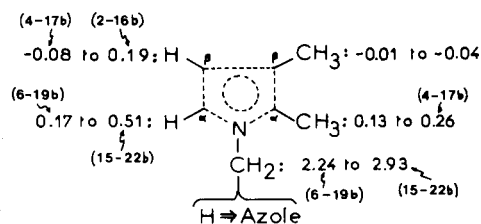
It is now possible to compare the first step proportions with literature results concerning the N -methylation of azoles. Methylation of 3(5)-methylpyrazole gives a 50:50 mixture of **16b** and **17b** (10) or a slight predominance of the 3-methyl isomer **16b** (11). Methylation of 1,2,4-triazole gives exclusively the isomer **20b** (12). Methylation of indazole gives a 50:50 mixture of **21b** and **22b** (13,14). Only in this case a difference appears between methylene chloride and methyl iodide (or dimethyl sulfate) as alkylating agents. The fact that pyrazole reacts faster than imidazole (56:44, Eq. 3) parallels the yields of 'symmetrical' **1** (93%) and **7** (73%).

Proton Magnetic Resonance Studies.

All the products were studied by ^1H nmr spectroscopy.

The chemical shifts (in ppm) and some coupling constants (in Hz) are reported in Table II. The structures of groups of isomers, **2-3-4**, **1-6-7**, **8-9-10**, **13-14-15**, were established without ambiguity using the chemical shifts values (δ) and coupling constants (J).

Comparison with ^1H nmr spectra of N -methylazoles (12,13,15,16,17,18) shows firstly that the coupling constants are almost identical. Secondly, it allows the calculation of the effect produced by the replacement of an hydrogen atom of the N -methyl group by an azole. The values depend both on the position, α or β , and on the nature, H or Me, of the substituent, the order being $\text{CH}_2(\textit{ipso}) > \text{H}_\alpha > \text{Me}_\alpha > \text{H}_\beta > \text{Me}_\beta$. This order corresponds to the number of bonds that separate the proton from the azole.



Carbon-13 Magnetic Resonance Studies.

A carbon-13 nmr study was carried out with the thirteen diazolylmethanes (Table III). The assignment was straightforward due to the previous experience in N -methylazoles (19,20), whose chemical shifts, almost unchanged, were found in the diazolylmethanes, providing that there is only a slight effect of one ring upon the other. The most interesting signal is that corresponding to C_1 , which is very sensitive to the nature of both rings.

If the thirteen chemical shifts of C_1 carbons are factored in two additive parts, we obtain the following values for each ring: pyrazole, 32.5; 3-methylpyrazole, 32.3; 5-methylpyrazole, 30.4; 3,5-dimethylpyrazole, 30.2; imidazole, 28.2; 1,2,4-triazole, 29.5; benzimidazole, 26.2; 2-methylbenzimidazole, 22.1; indazole, 30.0; isoindazole, 33.4. These values correlate with the chemical shifts of the N -Me groups in the corresponding N -methylazoles (21): $\delta(N\text{-Me}) = -3.15 + 1.28 \delta(N\text{-CH}_2)$, $n = 10$, $\text{CC}^2 = 0.999$ (n being the number of points and CC^2 the squared correlation coefficient).

EXPERIMENTAL

All melting points were uncorrected. The nmr spectra were recorded on a Varian EM-390 (^1H at 90 MHz) and on a Bruker WP-60-DS (^{13}C at 15.1 MHz) spectrometers using tetramethylsilane as an internal standard.

Table III
¹³C NMR Data for *N,N'*-Diazolymethanes
 Chemical Shift (δ ppm)

Compound	Solvent	C ₁	C ₂	C ₃	C ₄	C ₅	C ₆	C ₇	C _{8a}	C _{7a}	C _{8b}	C _{7b}	C ₉	C _{4'}	C _{5'}	C _{6'}	C _{7'}	C _{8a'}	C _{7a'}	C _{8b'}	C _{9'}	Me _{8(15)'}	Me _{10(14)'}	Me _{11(15)'}		
1	deuterio- chloroform	65.1	—	140.6	107.0	129.5	—	—	—	—	—	—	140.6	107.0	129.5	—	—	—	—	—	—	—	—	—	—	—
1	DMSO-d ₆	64.4 (a)	—	140.1 (b)	106.3 (c)	130.5 (d)	—	—	—	—	—	—	140.1 (b)	106.3 (c)	130.5 (d)	—	—	—	—	—	—	—	—	—	—	—
2	deuterio- chloroform	64.9	—	149.9	106.8	130.4	—	—	—	—	—	—	149.9	106.8	130.4	—	—	—	—	—	—	—	—	13.5	—	—
3	deuterio- chloroform	62.7	—	149.5	106.8	130.1	—	—	—	—	—	—	139.9	106.2	139.4	—	—	—	—	—	—	—	13.5	11.1	—	—
4	deuterio- chloroform	61.0	—	139.5	106.6	139.5	—	—	—	—	—	—	139.5	106.6	139.5	—	—	—	—	—	—	—	—	—	—	11.2
5	deuterio- chloroform	60.5	—	148.3	106.4	140.5	—	—	—	—	—	—	148.3	106.4	140.3	—	—	—	—	—	—	—	—	13.5	11.2	—
6	deuterio- chloroform	60.7	—	141.2	107.6	129.1	—	—	—	—	—	—	136.9	130.4	118.6	—	—	—	—	—	—	—	—	—	—	—
7	deuterio- chloroform	56.4	136.6	—	131.1	118.1	—	—	—	—	—	—	136.6	—	131.1	118.4	—	—	—	—	—	—	—	—	—	—
8	DMSO-d ₆	59.0	—	152.1	—	144.9	—	—	—	—	—	—	152.1	—	144.9	—	—	—	—	—	—	—	—	—	—	—
11	DMSO-d ₆	52.4	143.5	—	119.8	121.0	122.3	110.6	144.2	132.6	—	—	143.5	119.8	121.0	122.3	110.6	144.2	132.6	—	—	—	—	—	—	—
12	DMSO-d ₆	44.2	151.8	—	118.8	121.9	122.2	109.8	142.1	—	—	—	151.8	118.8	121.9	122.2	109.8	142.1	—	—	—	—	—	—	—	—
13	deuterio- chloroform	60.1	—	134.4	121.4 (e)	121.0 (e)	127.0	110.0	122.3	139.6	—	—	134.4	121.4 (e)	121.0 (e)	127.0	110.0	122.3	139.6	—	—	—	—	—	—	—
14	DMSO-d ₆	63.4	—	134.3	121.4	120.8	126.6 (e)	110.2	—	139.2	—	—	124.0	121.4	124.0	126.2 (e)	117.2	120.8	148.4	—	—	—	—	—	—	—
15	DMSO-d ₆	66.9	—	125.0	121.3	123.5	126.5	117.2	121.0	148.7	—	—	125.0	121.3	123.5	126.5	117.2	121.0	148.7	—	—	—	—	—	—	—

a) ¹J = 155.0, ²J = 8.4, ³J = 6.0, (c) ¹J = 176.8, ²J = 10.2, ³J = 8.8, (d) ¹J = 188.9, ²J = 9.3, ³J = 4.6, ⁴J = 2.5 (with the CH₃ protons), (e) Assignments may be reversed.

Table IV
Physical Constants of N,N'-Diazoylmethanes

Compound No.	Melting Point	Literature mp, °C	Yield (%) of pure compounds		Formula	Analysis %						UV, λ max (log ε)
			liquid-liquid	solid-liquid		Calculated			Found			
						C	H	N	C	H	N	
1	108°	111-112 (1)	88 (a)	77 (a)	C ₇ H ₈ N ₄	56.74	5.44	37.82	56.62	5.31	37.40	220 (3.90)
2	80°		22 (b)	—	C ₉ H ₁₂ N ₄	61.34	6.87	31.80	61.28	6.87	32.01	
3	58°		40 (b)	—	C ₉ H ₁₂ N ₄	61.34	6.87	31.80	61.52	6.92	31.79	
4	95°		18 (b)	—	C ₉ H ₁₂ N ₄	61.34	6.87	31.80	61.40	7.03	31.77	
5	105°	83-84 (1)	73 (a)	84 (a)	C ₁₁ H ₁₆ N ₄	64.67	7.90	27.43	64.89	8.08	27.43	
6	77°		30 (c)	(d)	C ₇ H ₈ N ₄	56.74	5.44	37.82	56.89	5.42	37.90	215 (3.84)
7	168°	170-171 (2)	60 (a,e)	(d)	C ₇ H ₈ N ₄	56.74	5.44	37.82	57.01	5.63	37.50	215 (3.91)
8	127°		61 (f)	0	C ₈ H ₆ N ₆	39.99	4.03	55.98	40.18	4.13	55.62	
11	245°	244-245 (3)	(d)	21 (a)	C ₁₅ H ₁₂ N ₄	72.56	4.87	22.57	72.80	4.65	22.33	245 (4.09), 272 (3.81), 280 (3.78)
12	249°		—	80 (g)	C ₁₇ H ₁₆ N ₄	73.89	5.84	20.28	73.89	5.81	20.42	
13	144°	143-144 (5)	—	23 (h)	C ₁₅ H ₁₂ N ₄	72.56	4.87	22.57	72.66	4.68	22.32	220 (4.29), 255 (4.02), 290 (3.96)
14	107°		—	7 (h)	C ₁₅ H ₁₂ N ₄	72.56	4.87	22.57	72.39	4.72	22.61	215 (3.93), 255 (3.26), 290 (3.38)
15	176°		—	5 (h)	C ₁₅ H ₁₂ N ₄	72.56	4.87	22.57	72.41	4.90	22.63	220 (4.12), 275 (3.87)

(a) Purified by vacuum sublimation. (b) Separated by column chromatography (kieselgel) using chloroform as eluent (order of elution: 4-3-2). (c) Purified by column chromatography (kieselgel) using methylene chloride-acetone 1:2 followed by sublimation. (d) Pure compounds have not been isolated in these experiments. (e) Order of elution: 1-6-7. (f) Separated by column chromatography (kieselgel) using acetone as eluent. (g) Purified by column chromatography (kieselgel) using 2-propanol as eluent. (h) Purified by column chromatography (kieselgel) using methylene chloride as eluent (order of elution: 13-14-15) followed by sublimation.

Liquid-Liquid General Procedure.

In a 25 ml round-bottom flask provided with a reflux condenser and a magnetic stirrer were introduced 8.4 mmoles of azole, 0.42 mmoles of TBAB (tetrabutylammonium bisulfate, 0.14 g), 10 ml of methylene chloride and 5 g of 50% aqueous sodium hydroxide (62.5 mmoles). The mixture was vigorously stirred and refluxed during 8 hours. The two layers were separated, the aqueous one was extracted continuously with ether and the ethereal solutions mixed with the methylene chloride solution and dried over anhydrous magnesium sulfate. The solvent was evaporated under vacuum. The residue was studied by ¹H nmr and after this purified as indicated in Table IV.

Solid-Liquid General Procedure.

In a 50 ml round-bottom flask provided with a reflux condenser and a magnetic stirrer were introduced 8.5 mmoles of azole, 0.42 mmoles of TEBA (triethylbenzylammonium chloride, 0.095 g), 25 ml of methylene chloride, 8.4 mmoles of potassium carbonate (1.2 g) and 0.6 g of 84% potassium hydroxide (9 mmoles). The mixture was vigorously stirred and refluxed during 8 hours. The residue was washed twice with hot methylene chloride (2 × 100 ml) and the organic solutions were dried over anhydrous magnesium sulfate. The methylene chloride was evaporated under vacuum. The residue was studied by ¹H nmr and after this purified as indicated in Table IV.

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