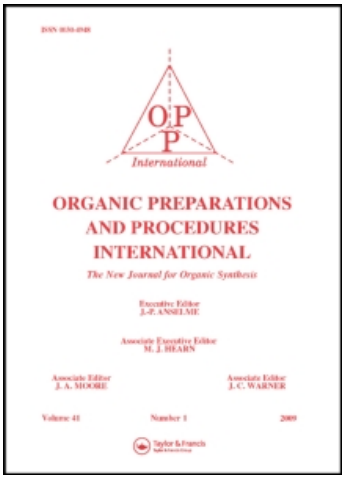

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IMPROVED SYNTHESIS OF POLYAZOLYLMETHANES UNDER SOLID-LIQUID PHASE-TRANSFER CATALYSIS

Sebastián Juliá[a]; José Ma del Mazo[a]; Luis Avila[a]; José Elguero[b]
[a] Departamento de Química Orgánica, Instituto Químico de Sarriá, Barcelona, SPAIN [b] Instituto de Química Médica, CSIC, Madrid, SPAIN

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IMPROVED SYNTHESIS OF POLYAZOLYLMETHANES UNDER SOLID-LIQUID PHASE-TRANSFER CATALYSIS

Sebastián Juliá, José M[a] del Mazo, Luis Avila

Departamento de Química Orgánica, Instituto Químico de Sarriá

Barcelona-17, SPAIN

José Elguero*

Instituto de Química Médica, CSIC, Juan de la Cierva, 3

Madrid-6, SPAIN

The chemistry of polyazolylmethanes has been rarely studied in spite of their interest in the context of heterocyclic chemistry; only few of these compounds are known. Moreover the yields and experimental conditions are not completely satisfactory (use of autoclaves, potassium salts, etc.).[1-6] Thus it was of interest to develop a general method of synthesis of polyazolylmethanes under phase-transfer conditions according to Eq. 1.

$$n\ Az\text{-}H + Cl_nCH_{4-n} \xrightarrow[Base]{Q^+X^-} (Az)_nCH_{4-n} + n\ HCl$$

n = 2-4, Az = Azole

We recently described[7] the first application of this method to the synthesis of several N,N'-diazolylmethanes under liquid-liquid (L-L) (50 % NaOH) or solid-liquid (S-L) ($KOH\text{-}K_2CO_3$) phase transfer catalysis (PTC) conditions, by reaction of the corresponding azole with CH_2Cl_2 in the presence of tetrabutylammonium bisulphate (TBAB). Table 1 reports the synthesis of new N,N'-diazolylmethanes under S-L PTC conditions (Eq. 2).

$$Az\text{-}H + Az'\text{-}H + CH_2Cl_2 \xrightarrow[K_2CO_3\text{-}KOH]{TBAB} Az\text{-}CH_2\text{-}Az + Az'\text{-}CH_2\text{-}Az' + Az\text{-}CH_2\text{-}Az' \quad (2)$$

Az = Az' "unsymmetric" (different position of N-alkylation)

The above conditions are not adequate for the preparation of N,N',N"-triazolylmethanes, since the generation of dichlorocarbene[4,8] and its reaction with the azole followed by a Plancher-type ring expansion is the predominant pathway.[5,6] In order to obviate this side-reaction, we designed another S-L PTC method, using solid K_2CO_3, as the base, instead the K_2CO_3-KOH mixture. A blank experiment showed that traces (1.5 %) of dichlorocarbene were indeed produced under these conditions. However, the nucleophilic reaction of the azolate anion with $CHCl_3$ did occur and the triazolylmethanes were obtained in higher yields than previously described. Results and spectroscopic data are shown in Tables 1 to 3. In contrast, the N,N'-diazolylmethanes cannot be obtained with only K_2CO_3 as base.

The major advantages of this method are: a) more readily available and less toxic reagents, b) easy experimental procedure, c) higher yields (entries 1, 2, 6, 7 of Table 1)(when the substrate is benzotriazole, entry 7, the four possible isomers have been identified[9] and three isolated), and d) wider scope. The method failed with imidazole and indazole. The alternative procedure of N-alkylation of sodium salt of azole with chloroform without base, under the same S-L PTC conditions afforded poor results. Finally, the procedure was applied to the synthesis of tetrapyrazolylmethane (entry 9) using K_2CO_3/KOH as base, by reacting pyrazole with CCl_4 under identical conditions.[10]

This method constitutes an excellent example of the synthetic possibilities of S-L phase-transfer catalysis by varying the solid base. A more detailed study of ^{13}C NMR spectroscopy[11] of these compounds and of the kinetics of these reactions will be described elsewhere.

ACKNOWLEDGMENTS.- Grants to L.A. and J.M. of Ministerio de Universidades e Investigación (Spain), are gratefully acknowledged.

TABLE 1. Polyazolylalkanes **1**—**15**

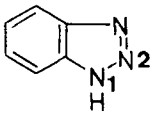
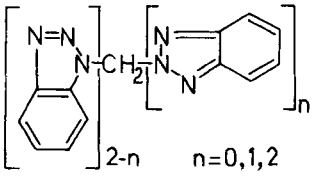
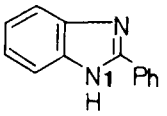
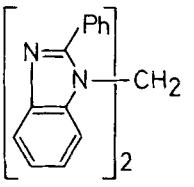
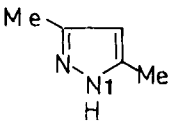
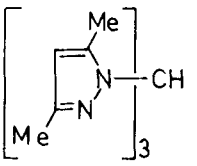
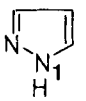
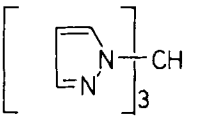
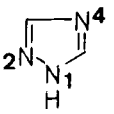
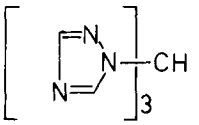
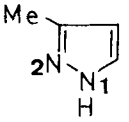
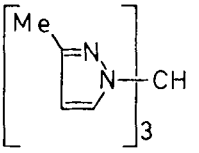
Entry	Substrate	Products	Isomer No	Purification (eluent)
		DIAZOLYLMETHANES		
1			2,2' (**1**) n = 2 1,2' (**2**) n = 1 1,1' (**3**) n = 0	Chromatography SiO_2 (1:100) (1, CH_2Cl_2, 2, 1:1 Hex-Ether)
2			1,1' (**4**)	Chromatography SiO_2 (1:100) (CH_2Cl_2)
		TRIAZOLYLMETHANES		
3			1,1',1"(**5**)	Chromatography SiO_2 (1:100) (1:1 Hex-Ether)
4			1,1',1"(**6**)	Chromatography SiO_2 (1:100) (1:1 Ether-CH_2Cl_2)
5			1,1',1"(**7**)	Chromatography SiO_2 (1:100) (AcOEt) and Cryst. MeOH
6			1,1',1"(**8**)	Chromatography SiO_2 (1:130) (1:2 Hex-Ether)

TABLE 1. Continued

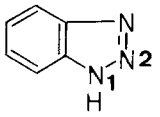
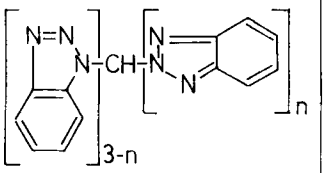
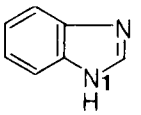
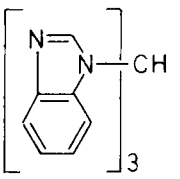
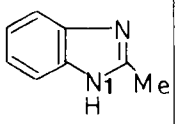
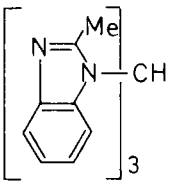
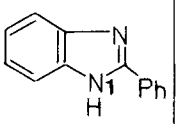
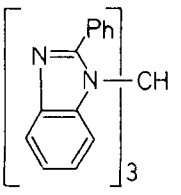
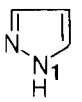
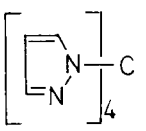
Entry	Substrate	Products	Isomer No	Purification (eluent)
7		 n = 0, 1, 2, 3	1,2',2" (**9**) n = 2 1,1',2" (**10**) n = 1 1,1',1" (**11**) n = 0	Chromatography SiO_2 (1:125) (CH_2Cl_2)
8			1,1',1" (**12**)	Crystallisation EtOH-H_2O
9			1,1',1" (**13**)	Crystallisation EtOH-H_2O
10			1,1',1" (**14**)	Chromatography SiO_2 (1:100) (CH_2Cl_2)
TETRAZOLYLMETHANES				
11			1,1',1",1''' (**15**)	Chromatography SiO_2 (1:100) (2:1 Cyclohexane-AcOEt)

TABLE 2. Yields and mp. of Compounds **1**—**15**

Compound	Yield (lit. yield)		mp. (°C)	Molecular formula[b] or Lit. mp. (°C)
	Crude[a]	Isolated		
1	71.5	5(--)	153-154	$C_{13}H_{10}N_6$ (250.3)
2		24(--)	165.5	$C_{13}H_{10}N_6$ (250.3)
3		30(--)	188	$C_{13}H_{10}N_6$ (250.3)
4	c	24(--)	98-99	$C_{27}H_{20}N_4$ (400.5)
5	62	42(17)[2]	152.5[d]	153-154[2]
6	72	62(34)[1]	105	106[1]
7	43	e(--)	159-160	$C_7H_7N_9$ (217.2)
8	69	e(--)	107-109	$C_{13}H_{16}N_6$ (256.3)
9	45	2(--)	188	$C_{19}H_{13}N_9$ (367.4)
10		10(--)	149	$C_{19}H_{13}N_9$ (367.4)
11		20(--)	191	$C_{19}H_{13}N_9$ (367.4)
12	75	56(4)[4](16.7)[5]	218	218[4]
13	43	27(14)[4]	110	108[4]
14	c	15(--)	233-234	$C_{40}H_{28}N_6$ (592.7)
15	c	20(12)[2]	146	146-147[2]

a) Total yield including all the isomers; crude yield determined by ^1H NMR. b) Satisfactory microanalysis obtained: C ± 0.25, H ± 0.09, N ± 0.19. c) Determination by ^1H NMR not possible. d) Sublimed 180°, 760 mmHg. e) Only an analytical sample was isolated for identification purposes.

TABLE 3. Spectroscopic Data of **1** — **15**[a]

Compd	NMR (δ)	IR (cm^{-1})	UV	MS
1	7.10-7.40 (m,2H) 7.41 (s,1H) 7.75-7.95 (m,2H)	3090, 3040 2980, 1560 1450, 850	282 (23500) 289 (23500)	250 (M^+,50) 77 (100)
2	7.25-7.65 (m,4H) 7.40 (s,2H) 7.80-8.10 (m,4H)	3060, 3040 2980, 1560 1450, 850, 750	279 (16880) 286 (15490)	250 (M^+,43) 132 (100)
3	7.25-7.65 (m,4H) 7.43 (s,2H) 7.85-8.15 (m,4H)	3090, 3010, 2960 1610, 1590, 1490 1450, 950, 750	254 (34500) 282 (7250)	250 (M^+,27) 104 (100)
4	6.7 (s,1H) 6.8-7.8 (m,9H)	3040, 2960, 1620 1590, 1530, 1460 1440, 1410, 740	-----	400 (M^+,30) 207 (100)
5	2.0 (s,9H) 2.2 (s,9H) 5.85 (s,3H) 8.1 (s,1H)	298, 2950, 2920 1555, 1270, 870 995, 710	223 (20300)	298 (M^+,20) 203 (100)
6	6.4 (q,3H) 7.63 (d,3H) 7.7 (d,3H) 8.5 (s,1H)	3120, 2985, 1520 1385, 1205, 1090 800, 750, 610[b]	218 (16800)	214 (M^+,15) 147 (100)
7	8.2 (s,3H) 8.85 (s,3H) 9.4 (s,1H)[c]	3140, 3100, 2970 1500, 1280, 1130 1010, 800, 670	-----	217 (M^+,8) 149 (100)
8	2.25 (s,9H) 6.08 (d,3H) 7.37 (d,3H) 8.11 (s,1H)	2920, 2980 1530, 1400 970, 800	-----	256 (M^+,20) 175 (100)

TABLE 3. Continued

9	7.25-7.45 (m,7H) 7.65-7.85 (m,4H) 8.3 (m,1H) 10.23 (s,1H)	3070, 2940 1560, 1450 1330, 1250 875, 740[b]	212 (48700) 282 (28500) 290 (27670)	367 (M^+,4) 166 (100)
10	7.30-8.30 (m,12H) 10.27 (s,1H)	3060, 2940 1610, 1590 1560, 1450 1330, 1270 825, 740	258 (18110) 282 (19750) 288 (18700)	367 (M^+,4) 77 (100)
11	7.20-7.40 (m,9H) 7.95-8.10 (m,3H) 10.21 (s,1H)	3080, 2940, 2910 2840, 1610, 1590 1450, 1350, 1290	253 (21370) 284 (10500)	367 (M^+,5) 77 (100)
12	7.0-7.5 (m,9H) 7.76 (s,3H) 7.8-8.0 (m,3H) 8.76 (s,1H)	3070, 1610, 1490 1450, 1410, 810 770, 750, 740	243 (26420) 281 (11730)	364 (M^+,22) 247 (100)
13	2.3 (s,9H) 6.1 (d,3H) 7.1 (t,3H) 7.3 (t,3H) 7.8 (d,3H) 8.53 (s,1H)	3040, 2980, 1610 1540, 1480, 1450 1340, 750	243 (27100) 274 (10460) 281 (9710)	406 (M^+,18) 275 (100)
14	6.3-8.1 (m,27H) 9.0 (s,1H)	3060, 2960, 1680 1480, 1450, 740	-----	593 (M^+,20) 387 (100)
15	6.3 (q,4H) 7.5 (d,4H) 7.7 (d,4H)	3150, 3120, 3100 1520, 1330, 1090 870, 750	218 (23000)	280 (M^+,51) 213 (100)

a) MS, m/e, relative intensity (%); IR (KBr); UV (CH_3OH), λmax, nm (ε); ^{1}H-NMR ($CDCl_3$). b) Film. c) In $(CD_3)_2SO_2$ solution.

EXPERIMENTAL SECTION

N,N'-Diazolylmethanes.- A mixture of 16.8 mmols of azole, 16.8 mmols of anhydrous K_2CO_3, 16.8 mmols of powdered KOH (85 %) and 0.85 mmols of $(Bu)_4N.HSO_4$ was vigorously stirred and refluxed in dry CH_2Cl_2 (25 mL) overnight. The the mixture was filtered and the residue washed with hot CH_2Cl_2 (2 x 25 mL). The combined organic solution was evaporated and the crude product purified by column chromatography (Table 1).

N,N',N"-Triazolylmethanes.- A mixture of 24 mmols of azole, 120 mmols of anhydrous K_2CO_3 and 1.2 mmols of $(Bu)_4N.HSO_4$ was vigorously stirred and refluxed in dry $CHCl_3$ (25 mL) overnight. Then the mixture was filtered and the residue washed with hot $CHCl_3$ (2 x 25 mL). The organic solution was evaporated and the crude product purified by column chromatography or crystallisation (Table 1).

N,N',N",N"' -Tetrapyrazolylmethane.- A mixture of 29.4 mmols (2.00 g) of pyrazole, 147 mmols (9.68 g) of powdered KOH (85 %), 29.4 mmols (4.05 g) of anhydrous K_2CO_3 and 1.45 mmols (0.49 g) of $(Bu)_4N.HSO_4$ was vigorously stirred and refluxed in anhydrous CCl_4 (25 mL) overnight. Then the mixture was filtered and the residue washed with hot CCl_4 (2 x 25 mL). The organic solution was evaporated and the crude product purified by column chromatography (Table 1).

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10. The preparation of tetrapyrazolylmethane was reported in higher yield from carbonyldipyrazole [K. I. Thé, L. K. Peterson and E. Kiehlmann, Can. J. Chem., 51, 2448 (1973)] . This complex procedure involves the purification of the carbonyldipyrazole by zone melting. In fact, in our hands, the method failed when we attempted to obtain tetrapyrazolylmethane from crude carbonyldipyrazole.

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