PHASE TRANSFER CATALYSIS WITHOUT SOLVENT. SYNTHESIS OF BISAZOLYLALKANES

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Abstract- The reaction of azoles and benzazoles with dihalomethanes and dihaloethanes was performed in the absence of solvent. This method provides a general procedure for the synthesis of bisazolylmethanes and ethanes. No solvent was used during the reaction and, when possible, during the work-up.

Polyazolylborate anions have been widely used as complexation agents.[1] As an extension *N*-polyazolylmethanes and -ethanes have a growing interest as neutral ligands.[2] However, complex synthesis of the azolylalkanes and low yields reduced the usefulness of these compounds. The application of Phase Transfer Catalysis (P.T.C.) provided a useful method for the preparation of azolylmethanes.[3] This method was extended to various azoles, pyrazoles,[4] 1,2,4-triazoles,[4] imidazoles,[5] benzotriazoles[6] and also to tris- and tetrakisazolylmethanes[6,7] and bisazolylethanes.[8] The advantages of P.T.C. were, more readily available and less toxic reagents, easier experimental procedures, higher yields and a wider scope than previous methods.[6]

●=CH or N

Scheme 1

We are interested in the use of azolylmethanes and -ethanes, in coordination chemistry, in deprotonation followed by electrophilic addition reactions and in the synthesis of azapentalene systems (Scheme 1).

We report the synthesis of bisazolylmethanes and -ethanes by Solid-Liquid Phase Transfer Catalysis in the absence of solvent. This technique[9] has been used in the last ten years with a great variety of substrates, providing an increase in the reactivity and sometimes a change in the selectivity in comparison with classical P.T.C. methods.
Results obtained in the reaction of pyrazole, imidazole, 1,2,4-triazole, benzimidazole and benzotriazole with dichloromethane or dibromomethane and 1,2-dichloroethane are gathered in Tables 1 and 2, together with the comparison with literature results.

Table 1

Synthesis of Bisazolylmethanes

Az = Azole
X = Cl or Br

Azole	Time (h)	Yield (%)[a]	Yield (%)[b]	Lit.[c]	Lit.[d]
Pyrazole[e]	5	93	97	88 [3]	77 [3]
Imidazole[e]	13	100	92	96 [5]	----
1,2,4 -Triazole[f]	48	77	48	61 [3]	0 [3]
Benzotriazole[g]	48	77	--	----	60 [6]
1,1-		40	--	----	30.4
1,2-		31	--	----	24.4
2,2-		6	--	----	5.0
Benzimidazole[g]	48	83	--	----	48 [5]

[a] Isolated by extraction; [b] Isolated by sublimation; [c] Liquid-Liquid P.T.C.; [d] Solid-Liquid P.T.C.; [e] Alkylation agent, dichloromethane, 1 eq.; [f] Alkylation agent, dibromomethane, 1.5 eq.; [g] Alkylation agent, dibromomethane, 1 eq.

BISAZOLYLMETHANES

Preparation of bisazolylmethanes was performed by reacting one equivalent of the azole and dichloromethane or dibromomethane with two equivalents of potassium hydroxide in the presence of tetra-n-butylammonium bromide (TBAB, 3%). Reactions were performed at room temperature and bisazolylmethanes were isolated by extraction (method A) or when possible, by direct sublimation from the crude mixture (method B). In the later no solvent was used during the reaction and during the work-up.

Table 2

Synthesis of Bisazolylethanes

$$AzH + Cl\text{-}CH_2CH_2\text{-}Cl \xrightarrow[base]{TBAB} Az\text{-}CH_2CH_2\text{-}Az$$

Az = Azole
base = KOH or K_2CO_3

Azole	Yield (%)[a]	Yield (%)[b]	Lit.[c]	Lit.[d]
Pyrazole	82	--	80	--
Imidazole	56	--	45	--
1,2,4-Triazole	52	67	45	40
Benzotriazole	8	51	25	100
1,1-	3	23	10	55
1,2-	4	24	15	45
2,2-	1	4	--	--
Benzimidazole	55	59	70	--

[a] Method A, base, KOH; [b] Method B, base, K_2CO_3; [c] Liquid-Liquid P.T.C.[8]; [d] Solid-Liquid P.T.C.[8]

Comparison with classical P.T.C. methods indicates the usefulness of Phase Transfer Catalysis without solvent in the synthesis of bisazolylmethanes. The advantages are higher yields and milder conditions by this method. Moreover, P.T.C. in the absence of solvent is a general procedure for the preparation of bisazolylmethanes while in classical methods solid-liquid or liquid-liquid P.T.C. are used depending on the azole and this fact could not be rationalized.[3] Finally, the absence of solvent permits the use of dibromomethane with the less reactive azoles because the alkylation agent is used in an equimolecular amount and not in a large excess (as a solvent).

Nevertheless, the regioselectivity obtained by our method is similar to that described by classical methods. The reaction did not stop in the monoazolylmethane because the 1-halomethylazole obtained in the first alkylation is a benzylic halide. 1,2,3-Triazole was alkylated exclusively in the more nucleophilic 1-nitrogen while benzotriazole afforded all the three possible products in a similar ratio than classical methods (Table 2).

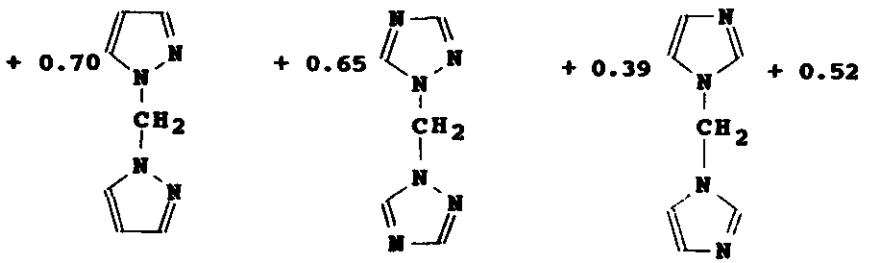
BISAZOLYLETHANES

Bisazolylethanes were prepared by reaction with 1,2-dichloroethane. The reaction proceeds in mild conditions (40-60°C) and final products were isolated by column chromatography.

The principal problem in the preparation of 1,2-bisazolylethanes is the β-elimination in the alkylation agent or in the intermediate β-haloethylazole. This reaction may account by the lack of reactivity of 1,2-bromoethane and of the presence of variable amounts of 1-ethenylazoles. In order to minimize the elimination, reactions were performed by addition of base and alkylation agent in two steps (method A). However, this method gave poor results with the more acidic azoles, due to the stability of the intermediate anion, the alkylation is slow and the competitive β-elimination is an important side reaction. In this cases β-elimination was minimized by using potassium carbonate (method B).

Direct synthesis of unsymmetrically 1,2-bisazolylethanes could not be achieved because it was impossible for us to stop the reaction in the intermediate β-haloethylazole. However, 1-β-chloroethylbenzimidazole was prepared in good yield (88 %) by reaction of benzimidazole with 1,2-dichloroethane by classical solid-liquid Phase Transfer Catalysis. This permited the use of 1-β-chlororethylbenzimidazole as an alkylation agent in the synthesis of unsymmetrical 1,2-bisazolylethanes in the absence of solvent. As an example, 1-benzimidazol-1-yl-2-imidazol-1-ylethane was prepared by this method.

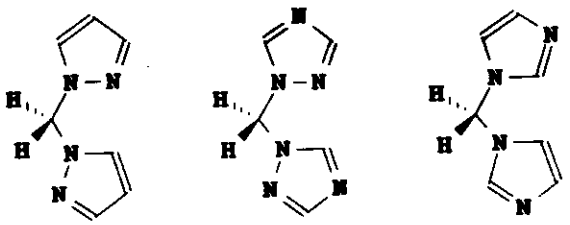
Comparison of the ^{1}H-nmr spectra of bisazolylmethanes and -ethanes shows a low field shift in the nmr signals of H-2 and H-5 in bisazolylmethanes (Scheme 2) and produce an inversion in the relative position of H-3 and H-5 signals in bispyrazol-1-yl and bis-1,2,4-triazol-1-ylmethanes.



Scheme 2

Low field shift in H-2 and H-5 from bisazolylethanes to bisazolylmethanes.

This deshielding may be explained considering the coplanar conformation shown in Scheme 3. This conformation has been previously proposed considering deshielding observed with Eu(fod)$_3$.[4]



Scheme 3

Assignment of the nmr signals was performed by considering the coupling constants between the heteroaromatic protons, literature results[4] and measuring the enhancement of the azole signals on irradiation of the "benzylic" CH_2, by NOE difference spectroscopy.[10]

In conclusion, the use of Phase Transfer Catalysis in the absence of solvent permits the synthesis of bisazolylmethanes and bisazolylethanes, in mild and economic conditions and in higher yields than previously reported methods, being also a method of general application to these substrates.

ACKNOWLEDGMENTS

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EXPERIMENTAL

Starting compounds were of commercial quality. Mp's were determined on a Gallenkamp MFB-595 and are uncorrected. Ir spectra were recorded on a PHILIPS 9500. ^{1}H-Nmr spectra ($CDCl_3$) were recorded on a Bruker AW-80. NOE difference spectra were recorded on a Bruker AMX 500.

Synthesis of bisazolylmethanes (Table 1)

General Procedure

In a 25 ml closed vessel,[11] the appropriate azole (20 mmol), finely ground potassium hydroxide (2.24 g, 40 mmol) and TBAB (193 mg, 0.6 mmol) were stirred for 1 h.* The appropriate dihalomethane (10 mmol) was added and the stirring was continued at room temperature for the time indicated in Table 1. Isolation of the azoles was performed by extraction with the suitable solvent followed by column chromatography or by direct sublimation from the crude.

* Using 1,2,4-triazole, benzimidazole or benzotriazole, water (0.15 ml) was added at this point.

Reaction with pyrazole

Method A: The crude was extracted with ethanol (3 x 20 ml) and chromatographed on silica gel (13 g). Elution with ethyl acetate afforded bispyrazol-1-ylmethane (Rf 0.49, 1.37 g, 93%). mp 107-108°C (light petroleum), lit.,[3] 108°C. δ(ppm) 6.28 (dd, J=1.8, 2.7, 2H); 6.32 (s, 2H); 7.55 (d, J=1.8, 2H); 7.65 (d, J=2.7, 2H).

Method B: Sublimation from the crude (100°C/10^{-4} mbar) afforded 1.44 g of bispyrazol-1-ylmethane (97%).

Reaction with imidazole

Method A: The crude was extracted with ethanol (3 x 20 ml) and chromatographed on silica gel (60 g). Elution with chloroform:ethanol (1:1) afforded bisimidazol-1-ylmethane (Rf 0.42, 1.48 g, 100%). mp 166-167°C (dichloromethane), lit.,[3] 168°C. δ(ppm) 6.00 (s, 2H); 6.95 (t, J=1.2, 2H); 7.10 (m, 2H); 7.65 (m, 2H).

Method B: Sublimation from the crude (165°C/10^{-4} mbar) afforded 1.36 g of bisimidazol-1-ylmethane (92%).

Reaction with 1,2,4-triazole

Method A: The crude was extracted with dichloromethane (5 x 20 ml) and chromatographed on silica gel (13 g). Elution with ethyl acetate afforded bis-1,2,4-triazol-1-yl-methane (Rf 0.18, 1.15 g, 77%). mp 142-143°C (toluene) lit.,[3] 127°C. δ(ppm) 6.40 (s, 2H); 8.00 (s, 2H); 8.40 (s, 2H).

Method B: Sublimation from the crude (135°C/10^{-4} mbar) afforded 0.72 g of bis-1,2,4-triazol-1-yl methane.

Reaction with benzotriazole

Method A: The crude was extracted with dichloromethane (5 x 20 ml) and chromatographed on silica gel (100 g). Elution with dichloromethane afforded a first fraction that contained bisbenzotriazol-2-ylmethane (Rf 0.75, 0.14 g, 6%). mp 152-153°C (tetrachloromethane) lit.,[6] 153-154°C. δ(ppm) 7.41 (s, 2H); 7.25-8.00 (AA'BB' pattern, J=3.2 and 6.6, 8H). The second fraction (Rf 0.45) that contained a mixture of the other two isomers was rechromatographed on silica gel (100 g). Elution with light petroleum:ethyl ether (1:1) afforded a first fraction that contained benzotriazol-1-yl-benzotriazol-2-ylmethane (Rf 0.28, 0.78 g, 31%). mp 165-166°C (tetrachloromethane) lit.,[6] 153-154°C. δ(ppm) 7.39 (s, 2H); 7.25-7.44 (m, 3H); 7.73-7.96 (m, 1H); 7.30-8.15 (AA'BB' pattern, J=3.2 and 6.7, 4H). The third fraction (Rf 0.16) contained bisbenzotriazol-1-ylmethane (1 g, 40%) mp 191-192°C (tetrachloromethane) lit.,[6] 188°C. δ(ppm) 7.41 (s, 2H); 7.30-8.10 (m, 8H).

Reaction with benzimidazole

Method A: The crude was extracted with ethanol (5 x 20 ml) and chromatographed on silica gel (30 g). Elution with ethyl acetate afforded bisbenzimidazol-1-ylmethane (Rf 0.42, 2.06 g, 83%). mp 246-247°C (dichloromethane) lit.,[3] 245°C. δ(ppm) 6.45 (s, 2H); 7.23-7.48 (m, 6H); 7.70-7.93 (m, 2H); 8.11 (s, 2H).

Synthesis of bisazolylethanes (Table 2)

Method A: In a 10 ml flask provided with a reflux condenser, the appropriate azole (20 mmol), finely ground potassium hydroxide (1.34 g, 24 mmol) and TBAB (193 mg, 0.6 mmol) were stirred at room temperature for 1 h. 1,2-Dichloroethane (0.76 ml, 10 mmol) was added and the stirring was continued at 40°C for 24 h. The whole process was repeated with a new addition of potassium hydroxide (0.67 g, 12 mmol) and 1,2-dichloroethane (0.79 ml, 10 mmol). Extraction with the suitable solvent followed by column chromatography afforded the pure bisazolylethane.

Method B: In a 25 ml flask provided with a reflux condenser, the appropriate azole (10 mmol), potassium carbonate (2.76 g, 20 mmol), TBAB (97 mg, 0.3 mmol) and 1,2-dichloroethane (0.40 ml, 5 mmol) were stirred at 60°C for 48 h. Extraction with the suitable solvent followed by column chromatography afforded the pure bisazolylethane.

Reaction with pyrazole

Method A: The crude was extracted with ethanol (3 x 20 ml) and chromatographed on silica gel (13 g). Elution with ethyl acetate afforded 1,2-bispyrazol-1-ylethane (Rf 0.47, 1.33 g, 82%). mp 39-41°C (108°C/10^{-4} mbar). δ(ppm) 4.50 (s, 4H); 6.11 (dd, J=1.9 and 2.2, 2H); 6.94 (d, J=2.2, 2H); 7.53 (d, J=1.9, 2H).

Reaction with imidazole

Method A: The crude was extracted with ethanol (3 x 20 ml) and chromatographed on silica gel (60 g). Elution with chloroform:ethanol (17:3) afforded 1-vinylimidazole (Rf 0.75, 0.2 g, 10%) as a yellow oil. δ(ppm) 4.64 (dd, J=1.5 and 8.2, 1H); 5.04 (dd, J=1.5 and 16.0, 1H); 6.66 (dd, J=8.2 and 16.0, 1H); 6.85 (s, 1H); 6.93 (s, 1H); 7.44 (s, 1H). The second fraction contained 1,2-bisimidazol-1-ylethane (Rf 0.47, 0.91 g, 56%). mp 155-156°C (light petroleum: ethyl acetate) lit.,[8] 141-144°C. δ(ppm) 4.50 (s, 4H); 6.67 (t, J=1.3, 2H); 7.07 (d, J=1.3, 2H); 7.27 (d, J=1.3, 2H).

Reaction with 1,2,4-triazole

Method A: The crude was extracted with dichloromethane (5 x 20 ml) and chromatographed on silica gel (13 g). Elution with acetone afforded 1,2-bis-1,2,4-triazol-1-ylethane (Rf 0.31, 0.86 g, 52%). mp 164-166°C (toluene) lit.,[8] 157-159°C. δ(ppm) 4.65 (s, 4H); 7.75 (s, 2H); 7.95 (s, 2H).

Method B: Similar to method A. Elution with acetone afforded 1-vinyl-1,2,4-triazole (Rf 0.78, 0.6 g, 32%) as a yellow oil. δ(ppm) 5.05 (dd, J=1.4 and 8.8, 1H); 5.78 (dd, J=1.4 and 15.6, 1H); 7.11 (dd, J=8.8 and 15.6, 1H); 8.00 (s, 1H); 8.30 (s, 1H). The second fraction contained 1,2-bis-1,2,4-triazol-1-ylethane (0.55 g, 67%).

Reaction with benzotriazole

Method A: The crude was extracted with dichloromethane (5 x 20 ml) and chromatographed on silica gel (100 g). Elution with light petroleum:ethyl acetate (1:1) afforded 2-vinylbenzotriazole (Rf 0.85, 0.5 g, 17%) as a yellow oil. δ(ppm) 5.33 (dd, J=1.3 and

9.0, 1H); 6.35 (dd, J=1.4 and 15.6, 1H); 7.57 (dd, J=9.0 and 15.6, 1H); 7.23-7.99 (AA'BB' pattern, J=3.3 and 6.5, 4H). The second fraction contained 1-vinylbenzotriazole (Rf 0.72, 0.34 g, 12%) as a yellow oil. δ(ppm) 5.24 (dd, J=1.4 and 8.4, 1H); 5.93 (dd, J=1.4 and 15.4, 1H); 7.98-8.18 (m, 1H); 7.21-7.80 (m, 4H). The third fraction contained 1,2-bisbenzotriazol-2-ylethane (Rf 0.66, 28 mg, 1%). mp 145-148°C (light petroleum:tetrachloromethane). δ(ppm) 5.40 (s, 4H); 7.22-7.92 (AA'BB' pattern, J=3.2 and 6.4, 8H). The fourth fraction contained 1-benzotriazol-1-yl-2-benzotriazol-2-ylethane (Rf 0.32, 96 mg, 4%). mp 136-137°C (light petroleum:tetrachloromethane) lit.,[8] 136-137°C. δ(ppm) 5.30 (s, 4H); 7.22-7.89 (AA'BB' pattern, J=3.2 and 6.6, 4H); 7.12-7.34 (m, 3H); 7.89-8.08 (m, 1H). Finally, the fifth fraction contained 1,2-bisbenzotriazol-1-ylethane (Rf 0.12, 76 mg, 3%). mp 164-165°C (toluene) lit.,[8] 161°C. δ(ppm) 5.20 (s, 4H); 6.77-6.97 (m, 2H); 7.05-7.30 (m, 4H), 7.77-7.97 (m, 2H).

Method B: Similarly to method A, 2-vinylbenzotriazole (0.13 g, 9%), 1-vinylbenzotriazole (0.03 g, 2%), 1,2-bisbenzotriazol-2-ylethane (0.051 g, 4%), 1-benzotriazol-1-yl-2-benzotriazol-2-ylethane (0.32 g, 24%) and 1,2-bisbenzotriazol-1-ylethane (0.3 g. 23%) were obtained.

Reaction with benzimidazole

The crude was extracted with dichloromethane (5 x 20 ml) and chromatographed on silica gel (60 g). Elution with chloroform:ethanol (1:1) afforded 1-vinylbenzimidazole (Rf 0.69, 0.2 g, 7%) as a yellow oil. δ(ppm) 5.05 (dd, J=1.4 and 9.2, 1H); 5.48 (dd, J=1.4 and 16.0, 1H); 7.12 (dd, J=9.2 and 16.0, 1H); 7.24-7.64 (m, 3H); 7.74-7.90 (m, 1H); 8.12 (s, 1H). The second fraction contained 1,2-bisbenzimidazol-1-ylethane (Rf 0.41, 1.44 g, 55%). mp 226-227°C (light petroleum: chloroform) lit.,[8] 225-226°C. δ(ppm) 4.58 (s, 4H); 7.15-7.35 (m, 6H); 7.45 (s, 2H); 7.70-7.80 (m, 2H).

Synthesis of 1-β-chloroethylbenzimidazole

In a 50 ml flask provided with a reflux condenser, benzimidazole (1.18 g, 10 mmol), finely ground potassium hydroxide (1.12 g, 20 mmol) and water (0.2 ml) were stirred at room temperature for 1 h. 1,2-Dichloroethane (25 ml) and TBAB (96 mg, 0.30 mmol) were added and the mixture was stirred at room temperature for 48 h. The mixture was filtered off and the residue was washed with dichloromethane (50 ml). The combined organic solutions were dried (anhydrous magnesium sulphate), the solvent removed on vacuo and the crude chromatographed on silica gel (13 g). Elution with ethyl acetate afforded 1-β-chloroethylbenzimidazole (Rf 0.31, 1.58 g, 88%). mp 84-86°C (sublimation 84°C/10^{-4} mbar). δ(ppm) 3.83 (t, J=6.0, 2H); 4,50 (t, J=6.0, 2H); 7.18-7-92 (m, 4H); 7.98 (s, 1H). Anal. Calcd for $C_9H_8N_2Cl$: C, 59.83; H 4.99; N, 15.51; Cl 19.67. Found: C, 59.70; H, 4.78; N, 15.25; Cl, 19.50.

Synthesis of 1-benzimidazol-1-yl-2-imidazol-1-ylethane

In a 10 ml closed vessel,[10] imidazole (0.068 g, 1 mmol), finely ground potassium hydroxide (0.067 g, 1.2mmol) and TBAB (10 mg, 0.03 mmol) were stirred at room

temperature for 1 h. 1-β-Chloroethylbenzimidazole (0.181 g, 1 mmol) was added and the mixture was stirred at room temperature for 48 h. The mixture was extracted with dichloromethane (5 x 10 ml), dried (anhydrous magnesium sulphate), the solvent removed on vacuo and the crude product was chromatographed on silica gel (25 g). Elution with dichloromethane:ethyl acetate (1:1) afforded 1-benzimidazol-1-yl-2-imidazol-1-ylthane (Rf 0.34, 0.12 g, 57%). mp 120-121°C (chloroform:light petroleum). δ(ppm) 4.24 (s, 4H); 6.56 (t, J=1.3, 1H); 7.01 (d, J=1.3, 1H); 7.21 (d, J=1.3, 1H); 7.16-7.41 (m, 3H); 7.49 (s, 1H); 7.70-7.91 (m, 1H). Anal.Calcd for $C_{12}H_{12}N_4$: C, 67,90; H, 5.70; N, 26,40. Found: C, 68.09; H, 5.80; N, 26.02.

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