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Synthesis of N- (Aminoethyl) Azoles Under Phase Transfer Catalysis

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SYNTHETIC COMMUNICATIONS, 21(4), 535-544 (1991)

SYNTHESIS OF N-(AMINOETHYL)AZOLES UNDER PHASE TRANSFER CATALYSIS

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Abstract.- A convenient procedure is reported for the N-alkylation of azoles with 2-chloroethylamine under phase-transfer catalysis conditions.

N-(Aminoethyl)azoles **(2)** are well known as intermediates for the preparation of many interesting pharmacologically active compounds. Thus, N-imidazolyl derivatives have been used to prepare thromboxane synthetase inhibitors, useful as antihypertensive[1,2] The benzimidazolyl analogs have been used to prepare phenothiazines with antipyretic and sedative effects[3]

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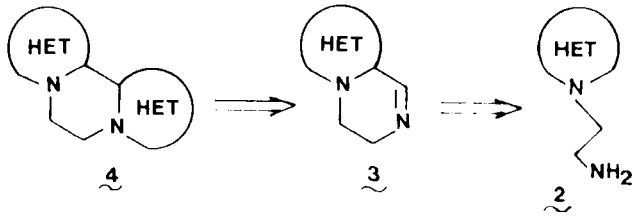

HET=Heteroaromatic

Scheme 1

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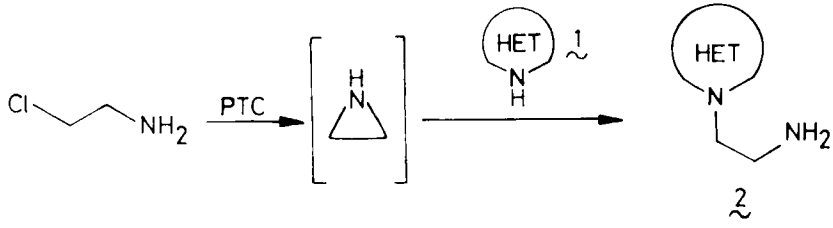
and ureas with diuretic, analgesic, antitumoral and cardiovascular properties[4-7]. Moderate histaminergic activities have also been described for 1-(N,N-dialkylaminoethyl)triazoles[8].

We became interested in the title compounds because of their potential utility as starting materials for the preparation of bridged derivatives of 2,2'-biazoles **(4)**, a class of biheteroaryl compounds with attractive properties as bridging ligands and redox systems[9].

Although the most widely used method of preparing N-(aminoethyl)azole derivatives **(2)**, consist on the alkylation of metalated azoles[7,8,10,11], the Michael reaction with acrylamide followed by Hoffmann rearrangement[12] and the Gabriel synthesis[1,2] have also been used as alternative procedures. We now report a general method of preparing N-(aminoethyl)azole deriva-



Scheme 2

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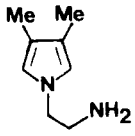
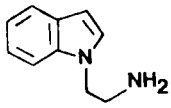
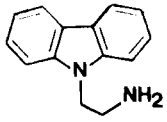
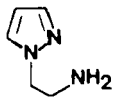
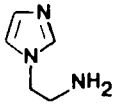
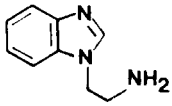
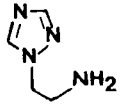
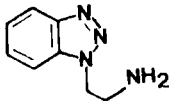
tives based on the alkylation of azoles under phase-transfer catalysis (PTC), which enables alkylation to occur by using an almost stequiometric amount of the highly toxic 2-chloroethylamine. Although an example of alkylation with 2-chloroethylamine of 1,2,4-triazol and pyrazol derivatives under PTC is known[13], the procedure has not been generally applied to other azoles. This method, simply involves a solid-liquid biphasic system and a phase-transfer catalyst in an aprotic solvent. In all cases, the reactions were conducted at reflux temperature and the alkylated azoles were isolated as hydrobromides. The best yields were obtained by using tetrabutylammonium hydrogensulphate (TBAS) as catalyst[14], sodium hydroxide as base[15] and toluene as organic phase being acetonitrile a better alternative when the hetero-aromatic substrate shows poor solubility in toluene.

Sonication was tested in the N-alkylation of benzo-triazole and benzimidazole, the two processes giving

TABLE. N-Alkylated derivatives from azoles

PRODUCT		METHOD	YIELD %
2a		A	65
2b		A	58 (ref 17)
2c		B	61
2d		B	68 (ref 13)
2e		B	60
2f		A	50 (ref 4)
2g		B	66 (ref 13)
2h		A	60

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the lowest yields. Although it is reported the important advantage of this technique in effecting some heterogeneous reactions[16], in the present case results were clearly disappointing and neither acceleration of reaction rate nor improvement of the yields were observed in comparison with unsonicated experiments (N-alkylated derivatives were obtained in 26-41 % yield after conventional sonication for 6 h).

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EXPERIMENTAL

All reagents were purchased from Aldrich Chemical Co. and used without further purification. 3,5-Dimethylpyrrole was prepared by a literature method[17]. Dry solvents were prepared according to literature. All products were characterized by their physical and spectral characteristics and/or by comparison with authentic samples. Full analytical and spectroscopic data are given for new compounds. Melting points were determined on a Buchi SMP-20 apparatus and are uncorrected. The ir spectra were recorded on a Perkin-Elmer 700 and 1310 spectrophotometers. ^{1}H-nmr spectra were obtained on a Varian FT-80 using TMS as internal reference.

N-Alkylation of Azoles. General Procedure.

To a mixture of the corresponding azole (0.08 mol) in dry toluene (50 ml, Method A) or acetonitrile (40 ml,

Method B) sodium hydroxide (11.51 g, 0.287 mol) was added and the mixture was stirred at room temperature for 30 min. Then, the tetrabutylammonium hydrogensulphate (TBAS) (1.08 g, 3.2 mmol) and the 2-chloroethylamine monohydrochloride (9.97 g, 0.086 mol) were added and stirring was continued at reflux temperature for 24 h. After cooling, the solid was separated by filtration and the filtrate evaporated under reduced pressure. The residual oil was treated with an excess of hydrobromic acid (48% solution) and triturated with ethyl acetate (Method A) or ethanol (Method B). Recrystallization afforded pure derivatives **(2a-e)** as hydrobromides.

1-(Aminoethyl)-3,4-dimethylpyrrole hydrobromide (2a). Brown powder. M.p. 208-210 °C (EtOH); Anal. Calcd. for $C_8H_{15}BrN_2.H_2O$: C, 40.5; H, 6.4; N, 11.8. Found: C, 40.3; H, 6.55; N, 11.6. Ir (KBr) ν_{max}: 3100-2600, 1600, 1450, 1360, 1260, 1180, 1125, 1090, 1070, 960 cm^{-1}. ^{1}H-Nmr δ (80 MHz, DMSO-d_6): 8.30 (broad, interchangeable with D_2O); 8.08 (s, 1H); 7.55(s, 1H); 3.93(m, 4H); 2.19 (s, 6H) ppm.

9-(Aminoethyl)carbazole hydrobromide (2c). White crystals. M.p. 320-322 °C (EtOH-Et_2O); Anal. Calcd. for $C_{14}H_{15}BrN_2.H_2O$: C, 54.4; H, 4.9; N, 9.1. Found: C, 54.6; H, 4.8; N, 9.4. Ir (KBr) ν_{max}: 3010-2650,

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1620, 1580, 1480, 1450, 1375, 1350, 1280, 1230, 1155, 1120, 1025, 995, 970 cm^{-1}. ^{1}H-Nmr δ (80 MHz, DMSO-d_6): 8.21(d, 2H, J=7.3 Hz); 7.8 (broad, interchangeable with D_2O); 7.72(d, 2H, J=8.3 Hz); 7.56(t, 2H, J=7.8 Hz); 7.33(t, 2H, J=7.3 Hz); 4.65(t, 2H, J=6.8 Hz); 3.27 (t, 2H, J=6.8 Hz) ppm.

1-(Aminoethyl)imidazole hydrobromide (2e). White crystals. M.p. 143-145 °C (EtOH); Anal. Calcd. for $C_5H_{10}BrN_3.2H_2O$: C, 26.3; H, 4.4; N, 18.4. Found, C, 25.9; H, 4.7; N, 18.45. Ir (KBr) ν_{max} 3100-2600, 1530, 1400, 1280, 1230, 1050, 950 cm^{-1}. ^{1}H-Nmr δ (80 MHz, DMSO-d_6): 9.31(s, 1H); 8.3(broad, interchangeable with D_2O); 7.90(d, 1H, J=1.2 Hz); 7.71 (d, 1H, J=1.2 Hz); 4.63(t, 3H, J=5.7 Hz); 3.54(t, 2H, J=5.7 Hz) ppm.

1-(Aminoethyl)benzotriazole (2h). White powder. M.p. 194-196 °C (EtOH); Anal. calcd. for $C_8H_{10}BrN_4.H_2O$: C, 36.9; H, 4.25; N, 21.5. Found, C, 36.55, H, 4.3; N, 21.3. Ir (KBr) ν_{max} 3000-2520, 1600, 1500, 1450, 1360, 1280, 1250, 1210, 1160, 1130, 1120, 1090, 1040 cm^{-1}. ^{1}H-Nmr δ (80 MHz, DMSO-d_6): 8.3 (broad, interchangeable with D_2O); 7.9-7.3 (m, 7H); 5.01(t, 2H, J=5.2 Hz); 3.43(t, 2H, J=5.2 Hz) ppm.

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