Chemistry of Heterocyclic Compounds, Vol. 41, No. 11, 2005

NEW MORPHOLINE DERIVATIVES

E. G. Mesropyan, G. B. Ambartsumyan, A. A. Avetisyan, A. S. Galstyan, and A. N. Kirakosyan

A study was carried out on the reaction of morpholine with 2,5-di(chloromethyl)-p-xylene, 4,6-di(chloromethyl)-m-xylene, 4,5-di(chloromethyl)-o-xylene, 4,4′-bis(chloromethyl)diphenyl, 4,4′-bis-(chloromethyl)diphenyl ketone, and 4,4′-bis(chloromethyl)diphenyl sulfide.

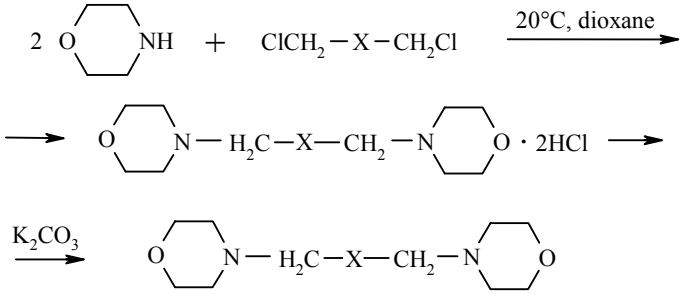
Keywords: 4,4'-bis(chloromethyl)diphenyl, 4,4'-bis(chloromethyl)diphenyl ketone, 4,4'-bis-(chloromethyl)diphenyl sulfide, 2,5-di(chloromethyl)-*p*-xylene, 4,5-di(chloromethyl)-*o*-xylene, 4,6-di(chloromethyl)-*m*-xylene, morpholine.

Systems containing a morpholine fragment hold interest for possible biological activity [1-4].

In the present study, we developed a synthesis for new aralkyl morpholine derivatives.

A method is proposed for the synthesis of 2,5-dimorpholinomethyl-*p*-xylene (**1a**), 4,6-dimorpholino-methyl-*m*-xylene (**1b**), 4,5-dimorpholinemethyl-*o*-xylene (**1c**), 4,4'-bis(morpholinomethyl)diphenyl (**1d**), 4,4'-bis(morpholinomethyl)diphenyl ketone (**1e**), and 4,4'-bis(morpholinomethyl)diphenyl sulfide (**1f**).

The best yields of the desired products were obtained when the reaction was carried out in dioxane at room temperature with a 2:1 mole ratio of the reagents. Hydrochlorides **1**·2HCl are formed initially. Subsequent treatment of these salts with saturated aqueous sodium carbonate gives bases **1a-f**.



1a–f

1 a X = 2,5-$Me_2C_6H_2$-1,4; **b** X = 4,6-$Me_2C_6H_2$-1,3; **c** X = 4,5-$Me_2C_6H_2$-1,2; **d** X= 4,4'-C_6H_4–C_6H_4; **e** X= 4,4'-C_6H_4–COC_6H_4; **f** X = 4,4'-C_6H_4–S–C_6H_4

The ^{1}H NMR spectra of **1a-1f** show singlets for the four CH_2Ar group protons at 3.31-3.51 ppm, triplets for the eight $\underline{CH_2}$–O protons of the morpholine fragments at 2.35-2.40 ppm, eight $\underline{CH_2}$–N group protons at 3.59-3.65 ppm, and the corresponding multiplets for the aromatic ring protons at 6.93-7.80 ppm. Furthermore, the spectra of **1a-c** show singlets for the six protons of the two methyl groups at 2.28 ppm.

Yerevan State University, 375049 Yerevan, Republic of Armenia, e-mail: mag_union@yahoo.com.
Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 11, pp. 1691-1692, November, 2005. Original article submitted July 3, 2003.

 0009-3122/05/4111-1424

TABLE 1. Characteristics of Compounds **1a-f**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C (hydrochloride)	R_f (eluent ratio)	Yield, %
		C	H	N			
1a	$C_{18}H_{28}N_2O_2$	70.90 71.05	9.30 9.21	9.05 9.21	126 (180, dec.)	0.54 (1:0.6:0.4)	98
1b	$C_{18}H_{28}N_2O_2$	71.15 71.05	9.40 9.21	8.99 9.21	115-116 (168)	0.48 (1:0.6:0.4)	97
1c	$C_{18}H_{28}N_2O_2$	70.98 71.05	9.29 9.21	9.00 9.21	311 (360, dec.)	0.58 (0.9:0.7:0.5)	95
1d	$C_{22}H_{28}N_2O_2$	75.03 75.00	7.90 7.95	7.91 7.95	175 (250, dec.)	0.51 (1:0.7:0.3)	92
1e	$C_{23}H_{28}N_2O_3$	72.56 72.63	7.09 7.37	7.21 7.37	156 (172, dec.)	0.54 (1:0.5:0.1)	90
1f	$C_{22}H_{28}N_2O_2S$	68.50 68.75	7.35 7.29	7.00 7.29	213 (239)	0.54 (1:0.5:0.2)	93

EXPERIMENTAL

The ^{1}H NMR spectra were taken on a Varian Mercury-300 spectrometer at 300 MHz in DMSO-d_6. The purity of the products was monitored by thin-layer chromatography on Silufol UV-254 plates using chloroform–acetone–hexane as the eluent.

2,5-Dimorpholinomethyl-*p*-xylene (1a). A sample of dioxane (15 ml) was added to 2,5-di(chloromethyl)-*p*-xylene (2.03 g, 0.01 mol). After dissolution of the solid, morpholine (1.74 g, 0.02 mol) was added in small portions. The mixture was left for 12 h at room temperature. Crystals of hydrochloride **1a**·2HCl were separated, washed with ether, and then treated with saturated aqueous potassium carbonate. The crude product was washed with water and dried in the air to give **1a**.

Morpholine Derivatives 1b-1f were obtained analogously.

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