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LETTERS TO THE EDITOR

Phase-Transfer Catalyzed Alkylation of Morpholine with 1,2-Dichloroethane

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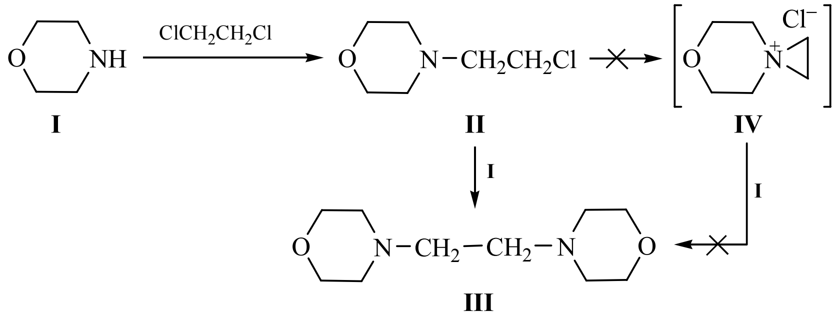
Piperazine was found to react with 1,2-dichloroethane to give first 1-(2-chloroethyl)piperazine, and then 3-azonio-6-azospiro[2,5]octane chloride as confirmed by experimental data and ^{1}H, ^{13}C, ^{15}N spectroscopy [1]. The 3-azonio-6-azospiro[2,5]octane chloride reacts with piperazine to form dipiperazinylethane. This suggests that it would not be possible to direct the reaction toward the production of the monosubstituted product while suppressing the formation of the disubstituted product. This is also observed in the case of the reaction of 1,2-dichloroethylene with morpholine in aqueous alkaline medium in the presence of triethylbenzylammonium chloride (TEBACH) to give 1,2-bismorpholinoethylene in 65.5% yield [2].

Aiming at the synthesis of 1-(2-chloroethyl)morpholine **II,** in the present work we carried out the alkylation of morpholine **I** with dichloroethane in a liquid-liquid system in the presence of triethylbenzylammonium chloride as a phase-transfer catalyst.

Our studies on the alkylation of morpholine **I** with 1,2-dichloroethane showed that the course of this simple reaction depends on the sequence of the reagents addition. Thus, when the reagents were added simultaneously, the alkylation of morpholine **I** with 1,2-dichloroethane (molar ratio 1:10) results in 1,2-bismorpholinoethane **III** in 70% yield. In this case 1-(2-chloroethyl)morpholine **II** was not detected in the reaction mixture. When morpholine was added dropwise within several hours at the same reagents ratio the reaction products were 1-(2-chloroethyl)morpholine **II** and 1,2-bismorpholinoethane **III** (2:1).

Based on these data, we can assume that the reaction of 1-(2-chloroethyl)morpholine **II** with morpholine **I** occurs as a direct nucleophilic substitution of the chlorine atom by the S_N1 mechanism [3], but not through the formation of an intermediate compound **IV** [1, 4].



1-(2-Chloroethyl)morpholine (II). Into a three-neck flask equipped with a thermometer, a reflux condenser, and a mechanical stirrer were placed 1 mol of dichloroethane, 0.5 mol of NaOH in 25 ml of water, and 2 g of TEBACH. To the mixture 0.05 mol of morpholine was added dropwise with vigorous stirring. The reaction mixture was stirred at 70–80°C for 2.5 h. After cooling, to the reaction mixture was added the second portion of alkali (0.5 mol of NaOH in 25 ml of water) and 0.05 mol of morpholine. The stirring was continued at 70–80°C for 2.5 h. Then the reaction mixture was cooled, extracted with chloroform, dried over magnesium sulfate, concentrated, and distilled in a vacuum. Yield 4.5 g (30%), bp 65°C (2 mm Hg), n_D^{20} 1.4789. IR spectrum, ν, cm^{-1}: 1100 (CH_2–O–CH_2). ^1H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 2.50 m [4H, $N(CH_2)_2$], 2.70 t (2H, NCH_2, *J* 7.9), 3.54 t (2H, CH_2Cl, *J* 7.0), 3.68 m [4H, $O(CH_2)_2$]. Found, %: C 47.25; H 7.66; N 9.00; Cl 24.46. $C_6H_{12}ClNO$. Caclulated, %: C 47.84; H 7.97; N 9.30; Cl 24.25. Yield of 1,2-bismorpholinoethane **III** is 2.2 g (22%).

1,2-Bismorpholinoethane (III) was prepared similarly from 8.7 g of morpholine **I**, 1 mol of dichloroethane and 1 mol of the base. Yield 7 g (70%), bp 110°C (3 mm Hg), mp 63–64°C (hexane). IR spectrum, ν, cm^{-1}: 1100 (CH_2–O–CH_2). ^1H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 2.38 m [8H, $N(CH_2)_4$], 2.40 s [4H, $N(CH_2)_2$], 3.56 m [8H, $O(CH_2)_4$]. Found, %: C 59.12; H 9.24; N 13.65. $C_{10}H_{20}N_2O_2$. Calculated, %: C 60.00, H 10.00, N 14.00.

The NMR spectra were registered on a Varian Mercury-300 spectrometer (300 MHz) in DMSO-d_6 or $CDCl_3$ solution. The IR spectra were obtained on a Specord 75-IR instrument (thin layer).

REFERENCES

1. Borisenko, V.S., Bobylev, V.A., and Tereshchenko, G.F., *Zh. Obshch. Khim.,* 1988, vol. 58, no. 1, p. 206.
2. Khachikyan, R. Dzh., Davtyan, S.L., and Indzhikyan, M.G., *Khim. Zh. Arm.,* 2006, vol. 59, no. 1, p. 93.
3. Ingold, K., *Teoreticheskiye osnovy organicheskoi khimii* (Theoretical Bases of Organic Chemistry), Moscow: Mir, 1973, p. 1054.
4. Leonard, N.J. and Paukstelis, J.V., *J. Org. Chem*., 1965, vol. 30, p. 821.