Synthesis of 2-substituted morpholines from dihydroxyalkylsulfamates

P. V. Bulatov, A. S. Ermakov, and V. A. Tartakovsky*

N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 47 Leninsky prosp., 117913 Moscow, Russian Federation. Fax: +7 (095) 135 5328. E-mail: secretary@ioc.ac.ru

2-Substituted morpholines and hexahydro-1,4-oxazepines were prepared by cyclodehydration of potassium dihydroxyalkylsulfamates in concentrated sulfuric acid.

Key words: sulfamates, cyclodehydration, 2-substituted morpholines, 2-substituted hexahydro-1,4-oxazepines.

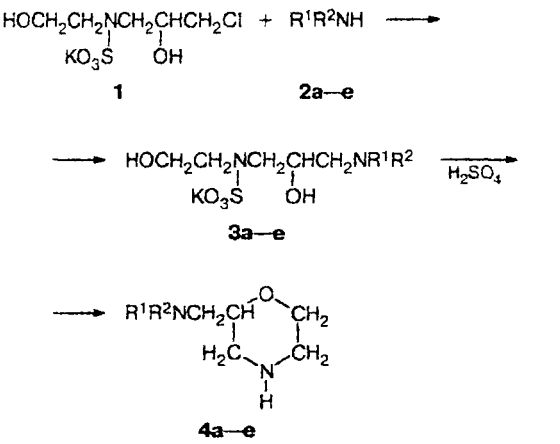
Various saturated nitrogen-containing heterocycles often serve as structural fragments of biologically active compounds. In particular, 2-substituted morpholines are components of antidepressants (Viloxazine)[1] and antibacterial drugs.[2] The synthesis of these morpholines involves cyclodehydration of the product of the reaction of epichlorohydrin with *N*-benzylethanolamine in concentrated sulfuric acid followed by the replacement of the chlorine atom by the functional group and the removal of the protection at the nitrogen atom in the morpholine ring.[2,3]

In the procedure proposed, the *N*-sulfo group is used as a protecting group. In this case, the closure of the morpholine ring and the removal of the sulfo group occur in one step. We proposed two ways of preparing morpholines. The pathway shown in Scheme 1 is based on the treatment of potassium *N*-(3-chloro-2-hydroxypropyl)-*N*-(2-hydroxyethyl)sulfamate (**1**), which has been prepared previously,[4] with amine **2**. The resulting aminosulfamate **3** is converted without isolation into the final morpholine **4** under the action of sulfuric acid. This scheme also allows one to prepare other XCH_2-substituted morpholines, where X is the functional group.

Another approach to the synthesis of morpholines as well as of hexahydro-1,4-oxazepines is based on the use of *N*-substituted potassium 3-chloro-2-hydroxypropylsulfamates (**5**), which have been prepared previously,[4] as the initial compounds (Scheme 2). The spectra of the synthesized morpholines and the related heterocycles can be extended (for example, to hexahydro-1,4-oxazepines (**4i,j**)) by replacing the chlorine atom in salts **5** by amino-alcoholic groupings and subjecting the corresponding amino derivatives **7** to cyclodehydration in concentrated sulfuric acid.

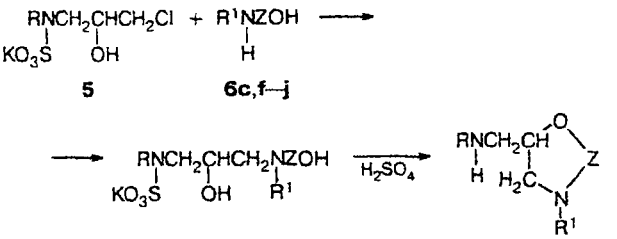
The preferential pathway of cyclodehydration of sulfamate **7k**, which contains more than two hydroxyl groups and which was prepared from potassium *N*-(3-chloro-2-hydroxypropyl)-*N*-methylsulfamate and diethanolamine according to a procedure proposed by us previously,[5] is worth consideration. Aminosulfamate

Scheme 1



	a	b	c	d	e
R^1	Me	Et	Me	$-(CH_2)_2O(CH_2)_2-$	$-(CH_2)_4CH(Me)-$
R^2	Me	Et	H	$-(CH_2)_2O(CH_2)_2-$	$-(CH_2)_4CH(Me)-$

Scheme 2



	R	R^1	Z
c	Me	H	CH_2CH_2
f	H	H	CH_2CH_2
g	H	Me	CH_2CH_2
h	Et	H	CH_2CHMe
i	H	H	$(CH_2)_3$
j	Me	H	$(CH_2)_3$

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Table 1. 2-Aminomethylmorpholines **4** prepared according to Scheme 1

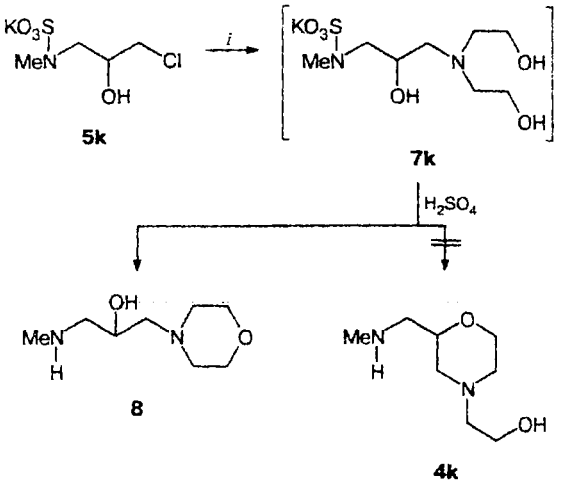
Compound	Yield (%)	B.p./°C* (*p*/Torr) M.p./°C	n_D^{20}	Empirical formula	Found / Calculated (%) C	H	N	^{1}H NMR, δ
4a	36.1	90—91 (13) [70—74 (6)]	1.4657	$C_7H_{16}N_2O$	—	—	—	
4b	34.1	112—113 (18) [100—101 (13)]	1.4665	$C_9H_{20}N_2O$	—	—	—	
4c**	33.1	179—181	1.4663	$C_6H_{14}N_2O \cdot 2HCl \cdot H_2O$	31.83 / 32.59	8.00 / 8.20	—	
4d	35.5	130—131 (11)	1.4923	$C_9H_{18}N_2O_2$	—	—	15.54 / 15.04	2.35—2.84 (m, 10 H, 5 CH_2N); 3.50—3.88 (m, 7 H, CH_2O, CHO)
4e	27	106—107 (2)	1.4907	$C_{11}H_{22}N_2O$	—	—	14.21 / 14.13	0.85 (d, 3 H, CH_3); 0.97—1.65 (m, 6 H, $CH_2CH_2CH_2$); 1.97—2.85 (m, 9 H, 4 CH_2N, CHN); 3.25—3.90 (m, 3 H, CH_2O, CHO)

* The published data are given in brackets.[2]

** In the case of compound **4c**, the melting point and the data of elemental analysis are given for dihydrochloride monohydrate; n_D is the value for free amine.

7k was subjected to cyclodehydration in sulfuric acid according to a standard procedure. In this case, either 1-methylamino-3-morpholinopropan-2-ol (**8**), which has been prepared previously according to an alternative procedure,[5] or 4-(2-hydroxyethyl)-2-(*N*-methylaminomethyl)morpholine (**4k**) can be formed (Scheme 3). It was demonstrated by ^{1}H NMR spectroscopy of the mixture (without separation) that morpholine **8** accounts for 85% of the resulting mixture of amines. This result indicates that cyclodehydration, as would be expected, proceeds more rapidly with the participation of sterically less hindered primary hydroxyl groups.

Scheme 3



i. $HN(CH_2CH_2OH)_2$

Hence, the proposed procedure for the synthesis using dihydroalkylsulfamates as the initial compounds allows one to prepare a series of functionally substituted saturated *N,O*-heterocycles.

Experimental

The ^{1}H NMR spectra were recorded on Bruker WM-250 and Bruker AM-300 instruments (250.13 and 300.13 MHz, respectively) in D_2O with HMDS as the internal standard (δ).

2-(*N,N*-Dimethylaminomethyl)morpholine (4a). A solution of KOH (0.92 g, 14 mmol) in H_2O (2 mL) and a 20% aqueous solution of dimethylamine (8 mL) were added to a solution of sulfamate **1** (4.1 g, 15 mmol) in H_2O (4 mL) and the reaction mixture was kept at ~20 °C for two days. Then the reaction mixture was concentrated and the residue was extracted with MeOH (30 mL). The extract was concentrated and 95% H_2SO_4 (9.2 g, 90 mmol) was added to the residue. Then the reaction mixture was kept at 150 °C for 3 h. After cooling, the reaction mixture was poured into water, and the pH was adjusted to 12.6 by adding a KOH solution. An equal amount of EtOH was added to the resulting solution, the precipitate was filtered off, the filtrate was concentrated, the residue was twice extracted with a mixture of EtOH (1 mL) and Et_2O (10 mL), and the extracts were concentrated. Compound **4a** was obtained in a yield of 0.78 g (36.1%), b.p. 90—91 °C (13 Torr). Compounds **4b**—e were prepared analogously (Table 1).

2-(*N*-Ethylaminomethyl)-6-methylmorpholine (4h). A solution of KOH (0.55 g, 9 mmol) in H_2O (1 mL) and 2-hydroxypropylamine (3 g, 40 mmol) were added to a solution of potassium *N*-(3-chloro-2-hydroxypropyl)-*N*-ethylsulfamate (2.56 g, 10 mmol) in H_2O (2 mL) and the reaction mixture was kept at ~20 °C for one day. Then KOH (0.2 g) was added to the reaction mixture, the mixture was concentrated, and the residue was extracted with MeOH (10 mL). The insoluble precipitate was filtered off, the filtrate was concentrated, and the residue was washed with a mixture of EtOH (3 mL) and Et_2O (10 mL) and dried *in vacuo*. Then 95% H_2SO_4 (7.5 g, 70 mmol) was added to the resulting aminosulfamate **7h** containing a small amount of inorganic salts and the mixture was kept at 150°C for 5 h. After cooling, the reaction mixture was poured into water, and the pH was adjusted to 12.5 by adding a

Table 2. 2-Aminomethylmorpholines and hexahydro-1,4-oxazepines **4** prepared according to Scheme 2

Compound	Yield (%)	B.p./°C* (*p*/Torr)	n_D^{20}	Empirical formula	Found / Calculated (%)			^{1}H NMR, δ
					C	H	N	
4c	57.7	92—93 (13)	1.4663	$C_6H_{14}N_2O$	—	—	—	—
4f	55.7	102—103 (19)	1.4861	$C_5H_{12}N_2O$	—	—	24.24	2.38—2.9 (m, 6 H, 3 CH_2N);
					—	—	24.12	3.42—3.90 (m, 3 H, CH_2O, CHO)
4g**	44.1	89—90 (20)	1.4704	$C_6H_{14}N_2O \cdot 2HCl \cdot 0.5H_2O$	34.01	7.91	13.55	2.22 (s, 3 H, MeN);
					33.97	8.08	13.21	1.83—2.8 (m, 6 H, 3 CH_2N);
								3.47—3.96 (m, 3 H, CH_2O, CHO)
4h	40.5	107—108 (15)	1.4688	$C_8H_{18}N_2O$	—	—	17.67	1.04—1.26 (m, 6 H, 2 Me);
							17.70	2.32—3.1 (m, 8 H, 4 CH_2N);
								3.64—4.07 (m, 2 H, 2 CHO)
4i	37.4	112—114 (28) [88—89 (10)]	1.4858	$C_6H_{14}N_2O$	—	—	—	—
4j	41.6	112—113 (22)	1.4742	$C_7H_{16}N_2O$	—	—	19.42	1.82—2.03 (m, 2 H, $CH_2\underline{CH_2}CH_2$);
							19.42	2.35 (s, 3 H, MeN);
								2.47—3.10 (m, 6H, 3CH_2N);
								3.62—3.86 (m, 2 H, CH_2O);
								3.92—4.10 (m, 1 H,CHO)

* The published data are given in brackets.[2]

** In the case of compound **4g**, the data of elemental analysis are given for dihydrochloride hemihydrate and the remaining characteristics are given for free amine.

solution of KOH. An equal amount of EtOH was added to the resulting solution, the precipitate that formed was filtered off, the filtrate was concentrated, the residue was twice extracted with a mixture of EtOH (1 mL) and Et_2O (10 mL), and the extracts were concentrated. Compound **4h** was obtained in a yield of 0.66 g (40.5%), b.p. 107—108 °C (15 Torr). Compounds **4c,f,g,i,j** were prepared analogously (Table 2).

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