

## 2-Aminoethanols in Transacetalization Reactions

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**Abstract**—Symmetric and mixed nitrogen-containing acetals and enol ethers were synthesized in an overall yield of 46–63% by reactions of *N,N*-dialkylaminoethanols with diethyl acetals derived from cyclohexanone, cyclopentanone, and acetophenone.

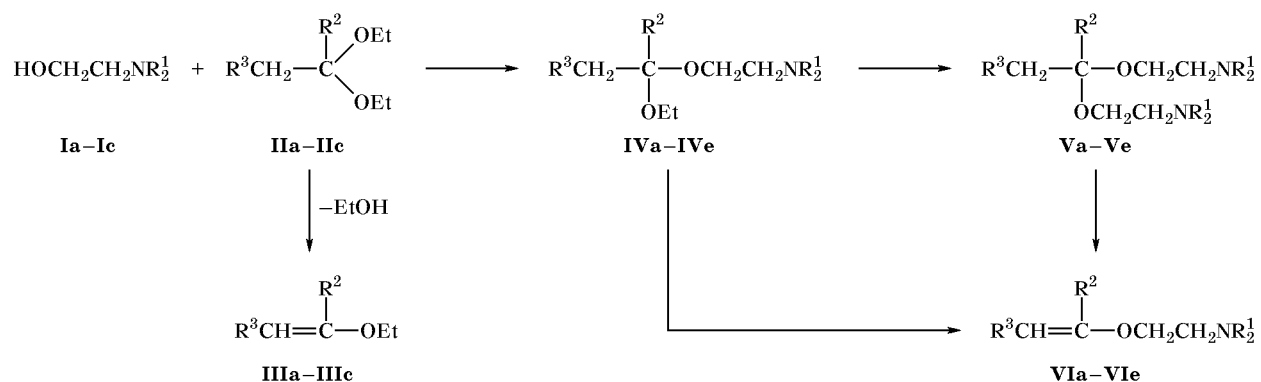
Transacetalization is widely used in the synthesis of various symmetric and mixed acetals [1]. However, published data on such reactions with amino alcohols and their derivatives are very limited. Amino alcohols having a secondary amino group [2] and their *N*-acyl derivatives [3, 4] are known to react with acetals, affording cyclic O,*N*-acetals (oxazolidines). On the other hand, acetals possessing amino alcohol moieties are promising intermediate products in organic synthesis, and some derivatives exhibit versatile biological activity [1–3].

In the present work we studied reactions of ketone diethyl acetals with *N,N*-dialkylaminoethanols with the goal of establishing the preparative potential of transacetalization reaction for the synthesis of symmetric and mixed nitrogen-containing acetals. We have found that heating of a mixture of *N,N*-diethyl-

2-aminoethanol (**Ia**) and cyclohexanone diethyl acetal (**IIa**) (molar reactant ratio 2:1) for 8 h at the boiling point in the absence of a catalyst and without removal of ethanol results in partial dealcoxylation of **IIa** to cyclohexenyl ethyl ether **IIIa**, while the expected nitrogen-containing acetals **IVa** and **Va** are formed only in trace amounts (according to the GLC data).

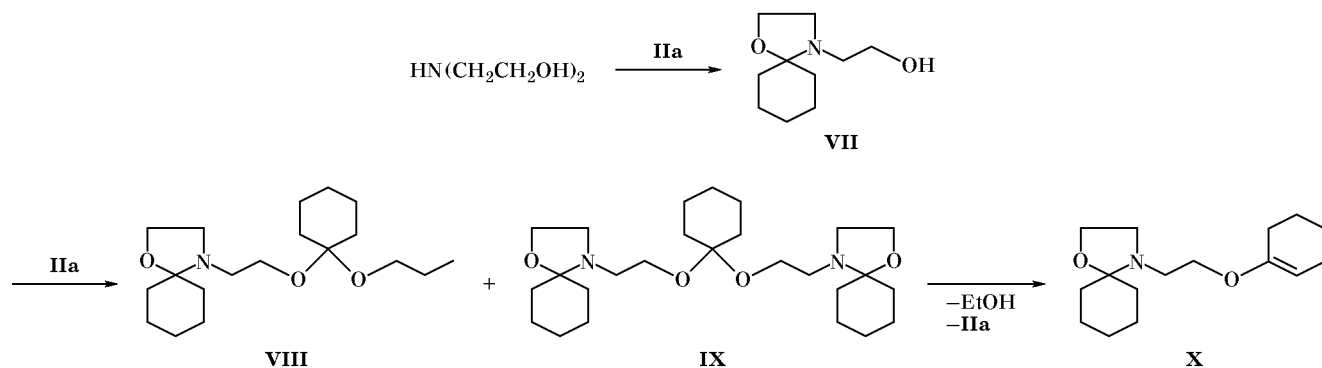
When the reaction was carried out with simultaneous removal of ethanol (by distillation), mixed (**IVa**) and symmetric (**Va**) acetals were isolated in addition to ether **IIIa**. If the theoretical amount of ethanol was distilled off, the overall yield of acetals **IVa** and **Va** was 61.4%, the molar ratio **IVa**:**Va** being 1:2.5. If the amount of distilled ethanol was a half of the theoretical, the overall yield of acetals **IVa** and **Va** was 43% (molar ratio 3.1:1). The yield of acetals **IVa** and **Va** decreased to 33% when the

Scheme 1.



**I**, R<sup>1</sup> = Et (**a**), Me (**b**), CH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>CH<sub>2</sub> (**c**); **II**, **III**, R<sup>2</sup>R<sup>3</sup> = (CH<sub>2</sub>)<sub>4</sub> (**a**), (CH<sub>2</sub>)<sub>3</sub> (**b**), R<sup>2</sup> = Ph, R<sup>3</sup> = H (**c**); **IV–VI**, R<sup>1</sup> = Et, R<sup>2</sup>R<sup>3</sup> = (CH<sub>2</sub>)<sub>4</sub> (**a**), R<sup>1</sup> = Me, R<sup>2</sup>R<sup>3</sup> = (CH<sub>2</sub>)<sub>4</sub> (**b**), R<sup>1</sup> = CH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>CH<sub>2</sub>, R<sup>2</sup>R<sup>3</sup> = (CH<sub>2</sub>)<sub>4</sub> (**c**); R<sup>1</sup> = Me, R<sup>2</sup>R<sup>3</sup> = (CH<sub>2</sub>)<sub>3</sub> (**d**), R<sup>1</sup> = Me, R<sup>2</sup> = Ph, R<sup>3</sup> = H (**e**).

Scheme 2.



reaction was performed in the presence of 5 mol % of *p*-toluenesulfonic acid with removal of ethanol. In this case, the major product was ether **IIIa**.

Taking into account that the best yields of acetals were obtained in the absence of acid catalyst upon distillation of the theoretical amount of ethanol, the reactions between other amino alcohols **Ia–Ic** and diethyl acetals **IIa–IIc** were carried out under the same conditions. Apart from the corresponding symmetric and mixed acetals, we isolated enol ethers **VIb**, **VIc**, and **VIe**. GLC analysis of the reaction mixtures showed that in all cases both kinds of nitrogen-containing acetals **IVa–IVe** and **Va–Ve** and enol ethers **VIa–VIe** were formed. However, we succeeded in isolating by fractional distillation only several of these compounds as pure substances. This is explained by thermal instability of some compounds, as well as by formation of azeotropic mixtures.

According to published data [2–4], transacetalization of cyclohexanone diethyl acetal (**IIa**) with bis-

(2-hydroxyethyl)amine should afford oxazolidine **VII**. In fact, the reaction between equimolar amounts of acetal **IIa** and bis(2-hydroxyethyl)amine gave 87% of oxazolidine **VII**. The product possesses a hydroxy group; therefore, we expected that the reaction with excess acetal **IIa** could afford acetals **VIII** and **IX** (Scheme 2). However, from the reaction of bis(2-hydroxyethyl)amine with 4 equiv of acetal **IIa** we isolated only 4-[2-(1-cyclohexenyloxy)ethyl]-1-oxa-4-azaspiro[4.5]decane (**X**) in 43.2% yield. No expected acetals **VIII** and **IX** were detected in the reaction mixture by GLC; presumably, these compounds undergo thermal decomposition during the process.

## EXPERIMENTAL

The  $^1\text{H}$  NMR spectra were recorded on a Jeol FX 90Q spectrometer (90 MHz) at 30°C using HMDS as internal reference. The reaction mixtures were analyzed, and the purity of compounds was checked,

**Table 1.** Yields, boiling points, densities, refractive indices, and elemental analyses of compounds **IVa**, **IVd**, **Va**, **Vb**, **Vd**, **Ve**, **VIb**, **VIc**, **VIe**, and **X**

Comp. no.	Yield, %	bp, °C ( <i>p</i> , mm)	$d_4^{20}$	$n_D^{20}$	Found, %			Formula	Calculated, %		
					C	H	N		C	H	N
<b>IVa</b>	18	116–118 (5)	0.9301	1.4581	69.18	12.02	5.87	$\text{C}_{14}\text{H}_{29}\text{NO}_2$	69.09	12.01	5.75
<b>IVd</b>	16	120–122 (20)	0.9252	1.4440	65.47	11.71	6.43	$\text{C}_{11}\text{H}_{23}\text{NO}_2$	65.63	11.52	6.96
<b>Va</b>	44	160–162 (3)	0.9361	1.4692	69.02	12.23	8.38	$\text{C}_{18}\text{H}_{38}\text{N}_2\text{O}_2$	68.74	12.18	8.91
<b>Vb</b>	40	109–110 (2)	0.9366	1.4620	65.40	11.83	10.76	$\text{C}_{14}\text{H}_{30}\text{N}_2\text{O}_2$	65.07	11.70	10.84
<b>Vd</b>	48	102–104 (3)	0.9470	1.4570	63.98	11.25	11.02	$\text{C}_{13}\text{H}_{28}\text{N}_2\text{O}_2$	63.89	11.55	11.46
<b>Ve</b>	32	122–124 (2)	0.9785	1.4962	68.28	10.46	9.58	$\text{C}_{16}\text{H}_{28}\text{N}_2\text{O}_2$	68.53	10.06	9.99
<b>VIb</b>	23	66–70 (2)	0.9242	1.4735	70.84	11.53	8.14	$\text{C}_{10}\text{H}_{19}\text{NO}$	70.96	11.31	8.28
<b>VIc</b>	38	146–149 (4)	1.0320	1.4945	67.98	10.07	6.99	$\text{C}_{12}\text{H}_{21}\text{NO}_2$	68.21	10.02	6.63
<b>VIe</b>	35	130–132 (8)	0.9761	1.5205	75.44	8.61	7.17	$\text{C}_{12}\text{H}_{17}\text{NO}$	75.35	8.96	7.32
<b>X</b>	43	190–191 (5)	1.0469	1.5032	72.83	10.07	5.17	$\text{C}_{16}\text{H}_{27}\text{NO}_2$	72.41	10.25	5.28

**Table 2.**  $^1\text{H}$  NMR spectra of compounds **IVa**, **IVd**, **Va**, **Vd**, **Vb**, **Ve**, **Vlb**, **Vlc**, **Vle**, and **X**

Comp. no.	Chemical shifts $\delta$ , ppm ( $J$ , Hz)
<b>IVa</b>	1.02 t (6H, $2\text{NCH}_2\text{CH}_3$ , $^3J = 7.4$ ), 1.16 t (3H, $\text{OCH}_2\text{CH}_3$ , $^3J = 6.9$ ), 1.49 m [10H, $(\text{CH}_2)_5$ ], 2.57 m [6H, $\text{CH}_2\text{N}(\text{CH}_2)_2$ ], 3.45 m (4H, $2\text{OCH}_2$ )
<b>IVd</b>	1.17 t (3H, $\text{OCH}_2\text{CH}_3$ , $^3J = 7.2$ ), 1.69 m [8H, $(\text{CH}_2)_4$ ], 2.25 s [6H, $\text{N}(\text{CH}_3)_2$ ], 2.46 t (2H, $\text{NCH}_2$ , $^3J = 6.4$ ), 3.48 m (4H, $2\text{OCH}_2$ )
<b>Va</b>	1.02 t (12H, $4\text{NCH}_2\text{CH}_3$ , $^3J = 7.4$ ), 1.50 m [10H, $(\text{CH}_2)_5$ ], 2.58 m (8H, $2\text{CH}_2\text{NCH}_2$ ), 3.49 t (4H, $2\text{OCH}_2$ , $^3J = 6.7$ )
<b>Vb</b>	1.51 m [10H, $(\text{CH}_2)_5$ ], 2.25 s (12H, $4\text{CH}_3$ ), 2.46 t (4H, $2\text{NCH}_2$ , $^3J = 6.2$ ), 3.50 t (4H, $2\text{OCH}_2$ , $^3J = 6.2$ )
<b>Vd</b>	1.70 m [8H, $(\text{CH}_2)_4$ ], 2.25 s (12H, $4\text{CH}_3$ ), 2.47 t (4H, $2\text{NCH}_2$ , $^3J = 6.3$ ), 3.53 t (4H, $2\text{OCH}_2$ , $^3J = 6.3$ )
<b>Ve</b>	1.56 s (3H, $\text{CH}_3$ ), 2.24 s [12H, $2\text{N}(\text{CH}_3)_2$ ], 2.51 t (4H, $2\text{NCH}_2$ , $^3J = 6.3$ ), 3.47 m (4H, $2\text{OCH}_2$ ), 7.29–7.51 m (5H, $\text{C}_6\text{H}_5$ )
<b>Vlb</b>	1.58 m (4H, $\text{C}=\text{CHCH}_2\text{CH}_2\text{CH}_2\text{CH}_2$ ), 2.03 m (4H, $\text{C}=\text{CHCH}_2\text{CH}_2\text{CH}_2\text{CH}_2$ ), 2.26 s [6H, $\text{N}(\text{CH}_3)_2$ ], 2.58 t (2H, $\text{NCH}_2$ , $^3J = 5.6$ ), 3.71 t (2H, $\text{OCH}_2$ , $^3J = 5.6$ ), 4.59 t (1H, $\text{C}=\text{CH}$ , $^3J = 3.3$ )
<b>Vlc</b>	1.56 m (4H, $\text{C}=\text{CHCH}_2\text{CH}_2\text{CH}_2\text{CH}_2$ ), 2.00 m (4H, $\text{C}=\text{CHCH}_2\text{CH}_2\text{CH}_2\text{CH}_2$ ), 2.46–2.60 m [6H, $\text{CH}_2\text{N}(\text{CH}_2)_2$ ], 3.64 m (6H, $\text{OCH}_2$ , $\text{CH}_2\text{OCH}_2$ ), 4.54 t (1H, $\text{C}=\text{CH}$ , $^3J = 3.3$ )
<b>Vle</b>	2.34 s [6H, $\text{N}(\text{CH}_3)_2$ ], 2.76 t (2H, $\text{NCH}_2$ , $^3J = 5.9$ ), 3.97 t (2H, $\text{OCH}_2$ , $^3J = 5.9$ ), 4.19 d (1H, $\text{OC}=\text{CH}-\text{Z}$ , $^2J = 2.5$ ), 4.57 d (1H, $\text{OC}=\text{CH}-\text{E}$ , $^2J = 2.5$ ), 7.26–7.56 m (5H, $\text{C}_6\text{H}_5$ )
<b>X</b>	1.49–1.62 m [14H, $(\text{CH}_2)_5$ , $\text{C}=\text{CHCH}_2\text{CH}_2\text{CH}_2\text{CH}_2$ ], 2.03 m (4H, $\text{C}=\text{CHCH}_2\text{CH}_2\text{CH}_2\text{CH}_2$ ), 2.78 t (2H, $\text{NCH}_2$ , $^3J = 6.4$ ), 3.05 t (2H, $\text{NCH}_2$ , $^3J = 6.9$ ), 3.73–3.86 m (4H, $2\text{OCH}_2$ ), 4.46 t (1H, $\text{C}=\text{CH}$ , $^3J = 3.4$ )

by GLC using an LKhM-80 chromatograph equipped with a thermal conductivity detector; carrier gas helium;  $3000 \times 3$ -mm steel column packed with 3% of OV-17 on Inerton Super (0.160–0.200 mm); oven temperature programming from 30 to  $250^\circ\text{C}$  at a rate of 4 deg/min.

**Reaction of amino alcohols Ia–Ic with diethyl acetals IIa–IIc (general procedure).** A mixture of 1 mol of diethyl acetal and 2 mol of amino alcohol was heated in a flask equipped with an adapter filled with ethanol as cooling fluid with continuous removal of ethanol. When 116.5 ml (2 mol) of ethanol was distilled off, the mixture was subjected to fractional vacuum distillation through a Vigreux column with an efficiency of 10 theoretical plates. The reaction of bis(2-hydroxyethyl)amine with cyclohexanone diethyl acetal was carried out in a similar way, but the amino alcohol-to-acetal ratio was 1:1 and 1:2.

From 17.2 g (0.1 mol) of diethyl acetal **IIa** and 10.5 g (0.1 mol) of bis(2-hydroxyethyl)amine we obtained 16.1 g (87%) of 4-(2-hydroxyethyl)-1-oxa-4-azaspiro[4.5]decane (**VII**), bp  $148\text{--}150^\circ\text{C}$  (14 mm),  $d_4^{20} = 1.0920$ ,  $n_D^{20} = 1.4970$ ; published data [5]: bp  $165\text{--}167^\circ\text{C}$  (24 mm).

From 172 g (1 mol) of diethyl acetal **IIa** and 52.5 g (0.5 mol) of bis(2-hydroxyethyl)amine we obtained 57.3 g (43.2%) of 4-[2-(1-cyclohexenyloxy)ethyl]-1-oxa-4-azaspiro[4.5]decane (**X**).

The yields, physical constants, analytical data, and  $^1\text{H}$  NMR spectra of the newly synthesized compounds are given in Tables 1 and 2.

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