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Cyclization of Vinyl Ethers Derived from Amino Alcohols

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Abstract—Cyclization of vinyl ethers derived from linear and cyclic α- and β-amino alcohols, catalyzed by mercury(II) acetate gave 2-methyloxazolidines and 2-methylperhydro-1,3-oxazines in 37–94% yield.

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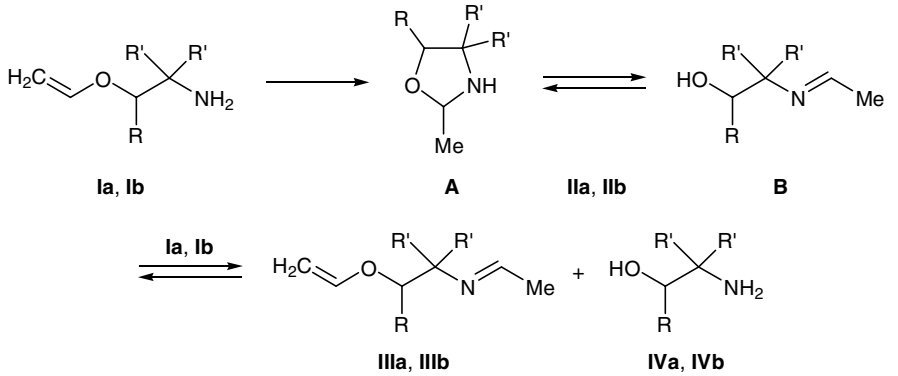
It is known that 2-vinyloxyalkanamines are capable of undergoing cyclization to 2-methyloxazolidines. On the basis of the available published data we can judge only on the effect of substituents on the nitrogen atom on this reaction. For example, various *N*-acyl derivatives of 2-vinyloxyethanamine readily undergo cyclization either by the action of protic acids [1] or on heating [2]. The cyclization of 2-(alkyl- and arylamino)alkanols successfully occurs only in the presence of soft acids (such as Hg^{2+} or Pd^{2+}) [3, 4]. There are no published data on the effect of the fragment connecting the amino and vinyloxy groups on the cyclization of vinyloxyalkanamines.

In the present work we examined the cyclization of α- and β-vinyloxy-substituted acyclic and cyclic aliphatic amines with a view to elucidate how the nature of the linking unit affects the cyclization process and estimate preparative potential of this reaction for the synthesis of 2-methylperhydro-1,3-oxazacycloalkanes. The reactions were carried out according to the procedure described in [4], i.e., by heating in benzene in the presence of 0.3 mol % of mercury(II) acetate. As we showed previously [3, 4], the cyclization of 2-vinyloxyethanamine gives 2-methyloxazolidine like **A** which undergoes ring–chain tautomeric transformation into 2-ethylideneaminoethanol **B**; exchange reaction of the latter with initial 2-vinyloxyethanamine leads to the formation of *N*-ethylidene-2-vinyloxyethanamine as the major product (yield 50%), while the yield of 2-methyloxazolidine is as poor as 20%.

It is known that introduction of a substituent into the bridging fragment increases the concentration of cyclic isomer in ring–chain tautomeric systems [5]. Therefore, we anticipated that cyclization of 2-vinyloxypropan-1-amine (**Ia**) and 1-vinyloxy-2-methylpropan-2-amine (**Ib**) will produce the corresponding oxazolidines **IIa** and **IIb** in higher yields than in the cyclization of 2-vinyloxyethanamine (Scheme 1). In

Scheme 1.

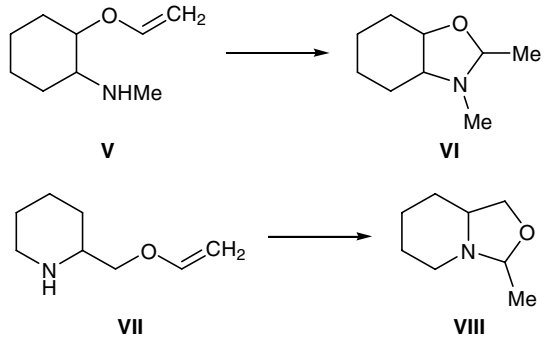


R = Me, R′ = H (**a**); R = H, R′ = Me (**b**).

fact, the expected products **IIa** and **IIb** were obtained in 37 and 83% yield, respectively. The yield of Schiff base **IIIa** was 31%, and that of **IIIb**, only 2%. Presumably, considerable increase in the yield of cyclic product **IIb**, as compared to the cyclization products obtained from 2-vinyloxyethanamine and 2-vinyloxypropan-1-amine (**Ia**), results from the *gem*-dialkyl effect [5].

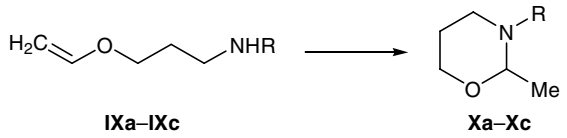
As a rule, increased rigidity of the linking fragment favors formation of the cyclic product [5]. We synthesized vinyl ethers of cyclic amino alcohols (compounds **V** and **VII**) containing exo- or endocyclic nitrogen atom and brought them into cyclization in the presence of mercury(II) acetate. The yields of fused oxazolidines **VI** and **VIII** were 89–91%, i.e., they were larger by 3–15% than in the cyclization of vinyl ethers derived from acyclic *N*-methyl α-amino alcohols [4] (Scheme 2). We failed to effect analogous cyclization of 2-vinyloxyamiline: the reaction was accompanied by strong tarring, and distillation of the reaction mixture gave 91% of *o*-aminophenol. This result resembles unsuccessful attempts [6] to obtain acetals by addition of alcohols to 2-vinyloxyaniline in the presence of protic or Lewis acids, where *o*-aminophenol and polymeric products were also formed.

Scheme 2.



The cyclization of 3-vinyloxypropan-1-amines **IXa**–**IXc** smoothly afforded the corresponding 2-methylperhydro-1,3-oxazines **Xa**–**Xc** in 67–94% yield (Scheme 3).

Scheme 3.



R = H (**a**), $NCCH_2CH_2$ (**b**), $PhCH_2$ (**c**).

The structure of the isolated compounds was confirmed by the IR and ^{1}H NMR spectra. The IR spectra of **IIa**, **IIb**, **VI**, **VIII**, and **Xa**–**Xc** contained no absorption bands typical of vinyloxy group in the initial vinyl ethers (1605, 1620 cm^{-1}), but bands in the regions 1080–1114, 1116–1139, and 1149–1185 cm^{-1} were present due to vibrations of the O–C–N fragment [7]. The ^{1}H NMR spectra of these compounds lacked olefinic proton signals, and protons in the $NCH(CH_3)O$ fragment resonated as a quartet at δ 3.84–4.66 ppm and a doublet at δ 1.23–1.33 ppm.

The ^{1}H NMR spectrum of the isomerization product of 2-vinyloxypropan-1-amine (**Ia**) was more complicated. It contained multiplets at δ 1.18, 1.32, and 4.60 ppm due to protons in the methyl groups in positions *5* and *2* of the oxazolidine ring (*cis* and *trans* isomers) and OCHN proton (structure **A**), respectively. In addition, there was a doublet at δ 1.97 ppm (N=CH) and a quartet at δ 7.72 ppm ($N{=}CHC\mathbf{H}_3$) belonging to structure **B**. In keeping with the signal intensities, the reaction gives an equimolar mixture of *cis* and *trans* isomers of oxazolidine **IIa**. The fraction of imino alcohol **B** was estimated at 21% on the basis of the intensities of the N=CH and OCHN signals and signals from methyl protons of tautomers **A** and **B**.

Thus the results of our study show that the cyclization of vinyl ethers derived from amino alcohols follows general relations found for the effect on such reactions of the fragment connecting the ether and amino groups and that this reaction may be used to synthesize 1,3-oxazacycloalkanes having various structures.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded at 30°C on a Jeol FX 90Q spectrometer at 90 MHz using HMDS as internal reference. The IR spectra were measured on a Specord 75 IR spectrophotometer from samples prepared as thin films (neat). The purity of the products was checked, and the reaction mixtures were analyzed, by GLC on an LKhM-80 chromatograph equipped with a thermal conductivity detector and a steel column, 3000×3 mm, packed with 3% of OV-17 on Inerton Super (0.160–0.200 mm); carrier gas helium, oven temperature programming from 50 to 250°C at a rate of 4 deg/min.

2-Methylperhydro-1,3-oxazacycloalkanes (*general procedure*)**.** A mixture of 0.1 mol of the corresponding vinyl ether and 0.005 mol of mercury(II) acetate in 50 ml of benzene was heated under reflux with stirring. Samples of the reaction mixture were

withdrawn intermittently and analyzed by GLC. When the initial vinyl ether disappeared, the mixture was subjected to fractional distillation under reduced pressure.

2,5-Dimethyloxazolidine (IIa, A) and 1-ethylideneaminopropan-2-ol (IIa, B). Yield 37%, bp 49–52°C (80 mm), d_4^{20} = 0.9529, n_D^{20} = 1.4350. IR spectrum, ν, cm^{-1}: 650, 795, 845, 905, 935, 1075, 1130, 1180, 1290, 1325, 1365, 1425, 1670, 2865, 2920, 2965, 3250, 3360. ^{1}H NMR spectrum, δ, ppm: **A**: 1.18 m (3H, 5-CH_3), 1.32–1.33 m (3H, 2-CH_3), 2.70 m and 3.33 m (2H, 4-H), 3.96 m (1H, 5-H), 4.60 m (1H, 2-H), 4.73 br.s (1H, NH); **B**: 1.20 m (3H, C**H**$_3$CHO), 1.97 d (3H, N=CHC**H**$_3$, ^3J = 4.4 Hz), 3.40 m (2H, NCH_2), 3.99 m (1H, OCH), 4.73 br.s (1H, OH), 7.72 q (1H, N=CH, ^3J = 4.4 Hz). Found, %: C 59.24; H 10.85; N 13.68. $C_5H_{11}NO$. Calculated, %: C 59.37; H 10.96; N 13.85.

2,4,4-Trimethyloxazolidine (IIb). Yield 83%, bp 39–43°C (45 mm), d_4^{20} = 0.9021, n_D^{20} = 1.4270. IR spectrum, ν, cm^{-1}: 590, 650, 805, 890, 985, 1010, 1055, 1120, 1135, 1180, 1220, 1305, 1375, 1435, 2850, 2930, 2955, 3280. ^{1}H NMR spectrum, δ, ppm: 1.21 s (3H, 4-CH_3), 1.25 s (3H, 4-CH_3), 1.30 d (3H, 2-CH_3, ^3J = 4.6 Hz), 2.89 s (1H, NH), 3.50 m (2H, 5-H), 4.66 q (1H, 2-H, ^3J = 4.6 Hz). Found, %: C 62.30; H 11.21; N 12.08. $C_6H_{13}NO$. Calculated, %: C 62.57; H 11.38; N 12.16.

***N*-Ethylidene-2-vinyloxypropan-1-amine (IIIa).** Yield 31%, bp 83–86°C (80 mm), d_4^{20} = 0.8625, n_D^{20} = 1.4371; published data [8]: bp 77–78°C (60 mm), d_4^{20} = 0.8627, n_D^{20} = 1.4378. IR spectrum, ν, cm^{-1}: 1600, 1615 (C=C), 1660 (C=N), 3105 (=C–H). ^{1}H NMR spectrum, δ, ppm: 1.24 m (3H, OCHC**H**$_3$), 1.97 d (3H, N=CHC**H**$_3$, ^3J = 4.5 Hz), 3.48 m (2H, NCH_2), 3.92–4.27 m (3H, OCH, *cis*-CH=C, *trans*-CH=C), 6.30 d.d (1H, OCH=C, $^3J_{cis}$ = 6.8, $^3J_{trans}$ = 14.1 Hz), 7.73 q (1H, N=CH, ^3J = 4.5 Hz). Found, %: C 66.02; H 10.44; N 11.17. $C_7H_{13}NO$. Calculated, %: C 66.11; H 10.30; N 11.01.

***N*-Ethylidene-2-methyl-1-vinyloxypropan-2-amine (IIIb).** Yield 3%, bp 60–63°C (45 mm), d_4^{20} = 0.8632, n_D^{20} = 1.4411; published data [8]: bp 64–68°C (48 mm), d_4^{20} = 0.8639, n_D^{20} = 1.4418. IR spectrum, ν, cm^{-1}: 1605, 1620 (C=C), 1655 (C=N), 3050, 3110 (=C–H). ^{1}H NMR spectrum, δ, ppm: 1.17 s (6H, CH_3), 1.96 d (3H, CHC**H**$_3$, ^3J = 4.2 Hz), 3.55 s (2H, CH_2O), 3.92 d.d (1H, *cis*-HC=C, ^2J = 2.1, ^3J = 6.7 Hz), 4.14 d.d (1H, *trans*-CH=C, ^2J = 2.1, ^3J = 14.0 Hz), 6.44 d.d (1H, OCH=C, $^3J_{cis}$ = 6.7, $^3J_{trans}$ = 14.0 Hz), 7.73 q (1H, N=CH, ^3J = 4.2 Hz). Found, %: C 67.92; H 10.51; N 9.71. $C_8H_{15}NO$. Calculated, %: C 68.04; H 10.71; N 9.92.

2,3-Dimethylperhydro-1,3-benzoxazole (VI). Yield 89%, bp 77–79°C (20 mm), d_4^{20} = 0.9563, n_D^{20} = 1.4658. IR spectrum, ν, cm^{-1}: 805, 817, 885, 923, 1000, 1075, 1100, 1120, 1140, 1180, 1200, 1315, 1330, 1345, 1365, 1440, 2755, 2840, 2920. ^{1}H NMR spectrum, δ, ppm: 1.31 d (3H, CH_3, ^3J = 4.7 Hz), 1.32–1.82 m (8H, CH_2), 2.25 s (3H, CH_3), 2.35 m (1H, 3a-H), 3.42 m (1H, 7a-H), 3.98 q (1H, 2-H, ^3J = 4.7 Hz). Found, %: C 69.52; H 11.12; N 8.95. $C_9H_{17}NO$. Calculated, %: C 69.63; H 11.04; N 9.02.

2-Methylperhydro[1,3]oxazolo[3,4-*a*]pyridine (VIII). Yield 91%, bp 90–91°C (50 mm), d_4^{20} = 0.9637, n_D^{20} = 1.4675. IR spectrum, ν, cm^{-1}: 600, 655, 675, 780, 820, 840, 850, 910, 930, 975, 1000, 1075, 1100, 1115, 1160, 1200, 1230, 1260, 1295, 1305, 1330, 1385, 1400, 1440, 2790, 2810, 2875, 2930. ^{1}H NMR spectrum, δ, ppm: 1.24 d (3H, CH_3, ^3J = 4.9 Hz), 1.74–2.11 m (6H, 6-H, 7-H, 8-H), 2.65 m (3H, 5-H, 8a-H), 3.43 m (2H, 1-H), 3.87 q (1H, 3-H, ^3J = 4.9 Hz). Found, %: C 68.28; H 10.84; N 9.71. $C_8H_{15}NO$. Calculated, %: C 68.04; H 10.71; N 9.92.

2-Methylperhydro-1,3-oxazine (Xa). Yield 67%, bp 37–38°C (20 mm), d_4^{20} = 0.9674, n_D^{20} = 1.4460; published data [9]: bp 68–70°C (100 mm), d_4^{20} = 0.948, n_D^{20} = 1.4382. IR spectrum, ν, cm^{-1}: 540, 600, 750, 805, 925, 975, 1065, 1080, 1145, 1170, 1240, 1290, 1390, 1430, 1445, 1460, 2840, 2935, 2975, 3280. ^{1}H NMR spectrum, δ, ppm: 1.23 d (3H, CH_3, ^3J = 5.2 Hz), 1.64 m (2H, 5-H), 2.89 m (2H, 4-H), 3.61 br.s (1H, NH), 3.90 m (2H, 6-H), 4,22 q (1H, 2-H, ^3J = 5.2 Hz). Found, %: C 58.99; H 10.65; N 13.71. $C_5H_{11}NO$. Calculated, %: C 59.37; H 10.96; N 13.85.

3-(2-Methylperhydro-1,3-oxazin-3-yl)propanenitrile (Xb). Yield 94%, bp 157–159°C (7 mm), d_4^{20} = 1.0420, n_D^{20} = 1.4709. IR spectrum, ν, cm^{-1}: 615, 645, 700, 860, 905, 920, 1045, 1105, 1120, 1175, 1230, 1295, 1330, 1395, 1445, 1460, 2240, 2860, 2945, 2975. ^{1}H NMR spectrum, δ, ppm: 1.31 d (3H, CH_3, ^3J = 5.4 Hz), 1.67–2.45 m (4H, 5-H, C**H**$_2$CN), 2.89 m (4H, 4-H, 4-CH_2), 3.91 m (2H, 6-H), 4,12 q (1H, 2-H, ^3J = 5.4 Hz). Found, %: C 62.79; H 9.32; N 18.01. $C_8H_{14}N_2O$. Calculated, %: C 62.31; H 9.15; N 18.17.

3-Benzyl-2-methylperhydro-1,3-oxazine (Xc). Yield 82%, bp 106–109°C (2 mm), d_4^{20} = 1.0259, n_D^{20} = 1.5190. IR spectrum, ν, cm^{-1}: 680, 710, 780, 800, 860, 905, 950, 1050, 1070, 1105, 1140, 1175, 1200, 1230, 1250, 1270, 1320, 1380, 1390, 1420, 1445, 1490, 2830, 2920, 2975, 3015, 3050, 3070. ^{1}H NMR spectrum, δ, ppm: 1.29 d (3H, CH_3, ^3J = 5.3 Hz), 1.68 m (2H, 5-H)

2.85 m (4H, 4-H, PhC**H**$_2$), 3.93 m (2H, 6-H), 4.29 q (1H, 2-H, ^3J = 5.3 Hz), 6.98–7.45 m (5H, Ph). Found, %: C 75.23; H 8.58; N 7.40. $C_{12}H_{17}NO$. Calculated, %: C 75.35; H 8.96; N 7.32.

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