13. P. R. Wells in: Progress in Physical Organic Chemistry, R. W. Taft (editor), Vol. 6, Interscience, New York—London (1968), p. 111.
14. J. B. Lambert, D. A. Netzel, H. Sun, and K. K. Lilianstrom, J. Am. Chem. Soc., 98, 3778 (1976).
15. A. F. Graefe, US Patent No. 3,173,910; Chem. Abs., 63, 580 (1965).
16. R. G. Kostyanovskii, Dokl. Akad. Nauk SSSR, 135, 853 (1960).
17. R. G. Kostyanovskii, O. A. Panshin, and V. F. Bystrov, Izv. Akad. Nauk SSSR, Ser. Khim., No. 5, 931 (1962).
18. H. Bestian, Annalen, 566, 210 (1950).
19. A. T. Bottini and J. D. Roberts, J. Am. Chem. Soc., 80, 5203 (1958).
20. A. F. Graefe and R. E. Meyer, J. Am. Chem. Soc., 80, 3939 (1958).
21. O. Scherer and H. Schmidt, Chem. Ber., 98, 2243 (1965).
22. R. G. Kostyanovskii and O. A. Panshin, Izv. Akad. Nauk SSSR, Ser. Khim., No. 4, 740 (1965).
23. P. T. Trapentsier, I. Ya. Kalvin'sh, É. É. Liepin'sh, and É. Ya. Lukevits, Khim. Geterotsikl. Soedin., No. 9, 1227 (1983).
24. S. A. Giller, A. V. Eremeev, I. Ya. Kalvin'sh, É. É. Liepin'sh, and V. G. Semenikhina, Khim. Geterotsikl. Soedin., No. 12, 1625 (1975).

SYNTHESIS AND LACTONIZATION OF 1-(2-HYDROXY-1,1-DIMETHYLETHYL)-AZIRIDINE-2-CARBOXYLIC ACID ESTERS

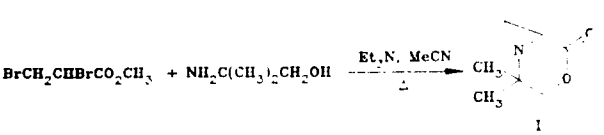
O. N. Krutius, F. D. Polyak, and A. V. Eremeev

UDC 547.717'464.3:542.97

The reaction of 2,3-dibromopropanoates with 2-amino-2-methyl-1-propanol in the presence of triethylamine gave a number of 1-(2-hydroxy-1,1-dimethylethyl)aziridine-2-carboxylic acid esters, which, under the influence of basic catalysts, were converted to a bicyclic lactone — 2,2-dimethyl-4-oxa-1-azabicyclo[4.1.0]heptan-5-one. The effect of the structure of the substrate and the nature of the lactonizing agent on the rate of cyclization was studied. Two new catalysts for the cyclization of hydroxy esters to lactones, viz., CsF/Al_2O_3 and Cs_2CO_3/18-crown-6, are proposed.

One of the most important methods for the synthesis of lactones is the cyclization of hydroxy esters. In the overwhelming majority of cases it is carried out under the influence of either strong mineral or organic acids or Lewis acids [1-4]. The lactonization of hydroxy esters under the influence of bases is rarely used (see [5-7] for the most typical methods), and the literature contains a limited amount of data on the use of basic reagents with no comparison of the effect of basic catalysts on the effectiveness of lactonization.

In a previous paper [8] it was reported that a bicyclic lactone — 2,2-dimethyl-4-oxa-1-azabicyclo[4.1.0]heptan-5-one — was obtained in the reaction of methyl 2,3-dibromopropanoate with 2-amino-2-methyl-1-propanol.



We have now isolated the intermediate in this reaction, viz., methyl 1-(2-hydroxy-1,1-dimethylethyl)aziridine-2-carboxylate (X), which gives lactone I under the influence of bases.

Institute of Organic Synthesis, Academy of Sciences of the Latvian SSR, Riga 226006.
Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 10, pp. 1340-1343, October, 1988. Original article submitted February 16, 1987; revision submitted March 28, 1988.

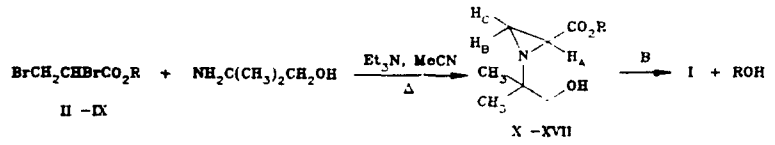
0009-3122/88/2410-1109$12.50

TABLE 1. PMR Spectra of X-XVII, δ, ppm

Compound	H_A*	H_B*	H_C*	CMe_2 (two s or s)	OH (br.s)	CH_2OH (s)	R
X	2.37	1.91	2.02	0.86; 0.93	2.67	3.44	3.73 (3H, s, Me)
XI	2.36	1.89	2.00	0.87; 0.93	2.64	3.42	1.27 (3H, t, CH_3) and 4.20 (2H, q, CH_2), J=7.0 Hz
XII	2.36	1.89	2.00	0.87; 0.93	2.78	3.42	0.91 (3H, t, CH_3); J=6.8 Hz; 1.18...1.80 (4H, m, CH_2—CH_2—CH_3); 4.15 (2H, t, OCH_2), J=6.9 Hz
XIII	2.27	1.82	1.93	0.87; 0.91	3.04	3.42	1.47 (9H, s, $(CH_3)_3$)
XIV	2.33	1.86	2.00	0.87; 0.93	2.73	3.42	1.25 (6H, d, $(CH_3)_2$) and 5.06 (1H, septet, CH), J=6.3 Hz
XV	2.24	1.73	1.82	0.71	3.02	3.24	4.96 (2H, s, CH_2); 7.16 (5H, s, Ph)
XVI	2.33	1.86	2.00	0.87; 0.93	2.89	3.42	1.03...1.82 (10H, m, $(CH_2)_5$); 4.82 (1H, m, CH)
XVII	2.29; 2.30	1.84	2.01	0.86; 0.91	2.64	3.37	0.97...1.73 (9H, m, ring protons and $CH(CH_3)_2$); 0.93 (6H, d, $(CH_3)_2CH$), J=6.5 Hz; 0.74 (3H, d CH_3CH), J=7.0 Hz; 4.71 (1H, m, OCH)

*Doublet of doublets; J_{AB} = 6.2-6.5 Hz, J_{AC} = 3.0 Hz, J_{BC} = 1.3-1.4 Hz.

Similarly, the reaction with 2-amino-2-methyl-1-propanol of other dibromopropanoates also led to aziridine-2-carboxylic acid esters X-XVII, which were then converted to lactone I under the influence of various bases (B).



II, X R=Me; III, XI R=Et; IV, XII R=Bu; V, XIII R=*t*-Bu; VI, XIV R=*i*-Pr; VII, XV R=CH_2Ph; VIII, XVI R=*cyclo*-C_6H_{11}; IX, XVII R= menthyl

To avoid the formation of lactone I the time of contact of starting esters II-IX with the amino alcohol was limited to 1 h; this, however, did not prevent obtaining rather high yields of aziridine derivatives X-XVII (Tables 1 and 2).

An analysis of the PMR and IR spectra (Tables 1 and 2) confirms the structures of hydroxy esters X-XVII unequivocally. (—)-Menthol ester XVII was isolated in the form of a pair of diastereomers that differ with respect to the absolute configuration of the asymmetric carbon atom of the aziridine ring. According to GLC data, the ratio of the diastereomers is 1:1.19, i.e., the asymmetric yield in this reaction is 8.7%.

A difference in the shielding of the two diastereomeric forms for the H_A proton of the aziridine ring, the OCH part of the methyl residue, and the protons of the CH_2OH groups is observed in the PMR spectrum of (—)-menthyl ester XVII; however, in all cases the difference in the chemical shifts is extremely small and, as a rule, leads only to broadening of the signals. Only the signals of the H_A protons of the two diastereomers are observed in the form of two doublets of doublets with $\Delta\nu \approx 1$ Hz, the integral intensity of which corresponds to the ratio of diastereomers obtained by GLC.

Attempts to use hydroxy esters X-XVII in the presence of organic acids or Lewis acids were unsuccessful because of the rapid decomposition of the starting compounds; however, these hydroxy esters were found to be extremely convenient subjects for the study of lactonization under the influence of bases. We initially investigated their cyclization at room temperature in acetonitrile under the influence of an equimolar amount of 1,8-diazabicyclo-[5.4.0]undec-5-ene (DBU). The rates of lactonization were evaluated from the time (obtained by monitoring by GLC) required for 99.5% conversion of the hydroxy esters to the lactone at a standard concentration of their solutions.

It was found that the hydroxy esters that contain a primary alcohol group (X-XII, XV) are cyclized considerably faster than the esters of secondary (XIV, XVI, XVII) and tertiary (XIII) alcohols (Table 2); the fastest leaving group among those investigated is $^-OCH_2Ph$.

TABLE 2. Physicochemical Characteristics of X-XVII

Compound	R_f	ν_{CH}*, cm^{-1}	δ*, cm^{-1}	$\nu_{C=O}$, cm^{-1}	ν_{OH}, cm^{-1}	M**	Yield, %	Lactonization time with DBU
X	0.45	3070	1200	1740	3380	173	73	8 h
XI	0.52	3070	1190	1740	3400	187	69	36 h
XII	0.59	3070	1180	1740	3420	215	66	48 h
XIII	0.61	3070	1180	1740	3400	215	61	—
XIV	0.58	3070	1200	1740	3400	201	70	110 h
XV	0.65	3070	1190	1740	3390	249	72	4.5 h
XVI	0.60	3060	1190	1740	3400	241	68	6 days
XVII***	0.74	3060	1190	1730	3450	297	76	35 days

*For the aziridine ring.
**Determined by mass spectrometry.
***$[\alpha]_D^{20} = -32.2°$ (EtOH, c = 1 g/100 ml EtOH).

The decrease in the rate of lactonization in the order X > XI > XII is evidently explained by an increase in the steric hindrance in the nucleophilic attack of the ester carbonyl group, which becomes even greater for secondary alcohol esters XIV, XVI, and XVII. In the case of tert-butyl ester XIII the result of steric hindrance is such that lactonization does not occur under the influence of DBU, although we were able to accomplish its conversion to the lactone after 50 min by the action of potassium tert-butoxide in dioxane.

A study of the relative reactivities of a number of bases and inorganic salts that are used as catalysts for the lactonization of hydroxy esters at room temperature was made in the case of methyl ester X. In addition to the form of the catalyst, we varied its amount and the solvent.

It was established that DBU is most effective in an equimolar amount; a decrease in the DBU concentration to 5 and 2 mole % leads to an increase in the reaction time from 8 h to 5 days and 24 days, respectively.

In the case of an equimolar amount of DBU replacement of acetonitrile by dimethylformamide does not change the cyclization time, but in dioxane the lactonization time increases to 11 days. In ethanol an equilibrium in which the reaction mixture contains 71% of the lactone is established 6 h after the start of the reaction. The reaction proceeded very rapidly in dioxane with KOH (a few seconds), in dioxane with potassium tert-butoxide (6 min), and in dioxane with sodium methoxide (10 min). When MeONa was used, an equilibrium that was shifted almost completely to favor the lactone (the residual methyl ester X constituted ~1%) was established 4 min after the start of the reaction when dioxane was replaced by methanol. The use of organic bases such as 1,4-diazabicyclo[2.2.2]octane, 4-(dimethylamino) pyridine, and tetrabutylammonium fluoride in acetonitrile did not give positive results.

An investigation of inorganic salts as lactonization catalysts led to the following results. Potassium fluoride in acetonitrile does not affect the lactonization, evidently because of its extremely low solubility. Potassium carbonate leads to 92% lactonization after 3.5 months; the addition of 18-crown-6 markedly shortens the reaction time (3.5 days).

Potassium fluoride in the presence of the same crown ether did not display catalytic activity. This result is surprising, since potassium fluoride applied to aluminum oxide lactonizes ester X after 2.5 h.

Finally, for the first time we have proposed inorganic cesium salts as catalysts for the lactonization of hydroxy esters. Cesium fluoride and carbonate led to the cyclization of X in acetonitrile in 4.5 days and 8 h, respectively.

As we assumed, the use of a crown ether significantly shortened the reaction time (to 7 h in the case of CsF/18-crown-6 and to 3 min in the case of Cs_2CO_3/18-crown-6), as did cesium fluoride applied to aluminum oxide (to 12 min). It must be noted that cesium salts are extremely hygroscopic, and this obliges one to make sure that all of the components of the reaction mixture are thoroughly anhydrous.

EXPERIMENTAL

The IR spectra were obtained with a Specord IR-75 spectrometer. The PMR spectra of 5% solutions of the compounds in $CDCl_3$ were recorded with a Bruker WH-90 spectrometer (90 MHz) with tetramethylsilane (TMS) as the internal standard.

The lactonization of hydroxy esters X-XVII was investigated by GLC with a Chrom-5 chromatograph; the phase was SE-30 (10%), the support was Chromosorb W AW (100-120 mesh, Fluka), the column dimensions were 1200 by 3.5 mm, the temperature conditions were isothermal (from 100 to 170°C, depending on the molecular mass of the hydroxy ester), the carrier gas was helium (50 ml/min), and the detector was a flame-ionization detector. The optical rotation of ester XVII was determined with an Autopol^R II polarimeter (Rudolf Research Corp.). The mass spectra were obtained with an MS-50 Kratos spectrometer. The R_f values were determined on Merck UV-254 plates for TLC (the thickness of the silica gel layer was 0.25 mm); the eluent was ethyl acetate, the path length of the solvent front was 6 cm, and the developer was iodine vapors.

General Method for the Synthesis of 1-(2-Hydroxy-1,1-dimethylethyl)aziridine-2-carboxylic Acid Esters X-XVII. A 2.8-ml (20 mmole) sample of triethylamine and 0.89 g (10 mmole) of 2-amino-2-methyl-1-propanol were added with stirring at room temperature to 10 mmole of the 2,3-dibromopropanoic acid ester in 50 ml of acetonitrile, and the mixture was stirred for 1 h at 70°C. The solvent was then removed by distillation in vacuo, and 250 ml of dry ether was added to the residue. The precipitated salt of triethylamine was removed by filtration, the filtrate was evaporated to a volume of 5 ml, and the concentrate was applied to a column (with a diameter of 3 cm and a height of 5 cm) packed with silica gel (40-100 μm).

The hydroxy esters were isolated by gradient chromatography. The column containing the applied mixture was initially eluted with petroleum ether (150 ml) at a rate of 0.5 ml/sec and subsequently at the same rate with a mixture of ether with hexane while gradually increasing the ether concentration from 5% to 35% and even to 60%. The chromatographically pure hydroxy esters (Tables 1 and 2) were isolated after evaporation of the combined portions of the eluate containing the desired products. However, satisfactory results of elementary analysis of X-XVII could not be obtained because of their highly hygroscopic character.

General Method for the Lactonization of Hydroxy Esters X-XVII. A 3-mmole sample of the catalyst was added to 1 mmole of the hydroxy ester in 5 ml of the solvent; the degree of conversion of the hydroxy esters to lactone I was determined by GLC. A 99.5% degree of conversion of the hydroxy ester to the lactone was taken as the criterion for completion of the reaction. The course of the cyclization was also monitored by means of TLC.

Potassium and cesium fluorides applied to aluminum oxide were used in the same molar ratio (based on the pure fluorides). The crown ether was used in the amount of 0.02 mole per mole of the substrate. The potassium and cesium fluorides were applied to the Al_2O_3 surface in the following way. The water was removed under reduced pressure from a mixture of water, the fluoride, and neutral aluminum oxide (Reanal) (10:1:1 by mass), and the resulting white powder, which was free-flowing in air, was then dried in vacuo (10^{-3} mm) at 100°C for 6 h.

LITERATURE CITED

1. J. Fujita, S. Watanabe, K. Suga, Y. Higuchi, and T. Sotoguchi, J. Org. Chem., 49, 1975 (1984).
2. M. Kato, H. Saito, and A. Yoshikoshi, Chem. Lett., No. 2, 213 (1984).
3. S. D. Burke, D. M. Armistead, and T. J. Schoenen, J. Org. Chem., 49, 4320 (1984).
4. A. Fadel and J. Salaun, Tetrahedron, 41, 1267 (1985).
5. J. W. Muskopt and R. M. Coates, J. Org. Chem., 50, 69 (1985).
6. M. Sciozaki, N. Ishida, T. Hiraoka, and H. Maruyama, Bull. Chem. Soc. Jpn., 57, 2135 (1984).
7. C. R. Johnson, R. C. Elliot, and N. A. Meanwell, Tetrahedron Lett., 23, 5005 (1982).
8. A. V. Eremeev, O. N. Krutius, A. F. Mishnev, Ya. Ya. Bleidelis, E. E. Liepin'sh, A. G. Odynets, D. A. Berzinya, and A. A. Kimenis, Khim. Geterotsikl. Soedin., No. 10, 1349 (1984).