Chemoselective isomerization of amide-substituted oxetanes with Lewis acid to give oxazine derivatives or bicyclic amide acetals

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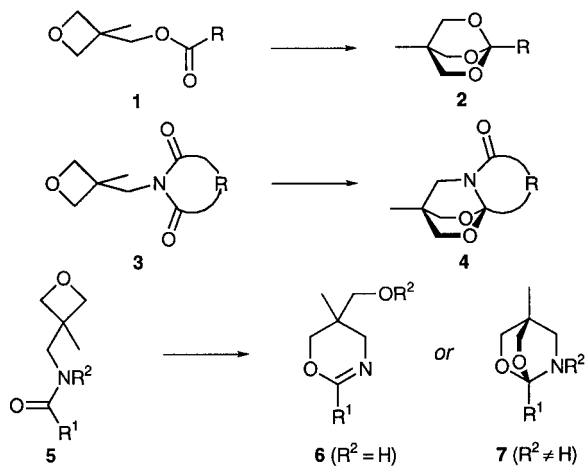
The Lewis-acid catalyzed isomerization of secondary and tertiary amide-substituted oxetanes takes place chemoselectively, giving 5-hydroxymethyl-5,6-dihydro-4*H*-1,3-oxazines and reactive amide acetals consisting of a bicyclo[2.2.2]octane skeleton, respectively.

Oxetane and its various derivatives are well known to be polymerizable cationically *via* conventional ring-opening processes.[1,2] As an exception, certain oxetanes carrying a carbonyl-containing substituent, however, can undergo Lewis-acid catalyzed intramolecular nucleophilic attack of the unsaturated oxygen atom, for example, ester-substituted oxetanes **1** give the bridged orthoesters **2**,[3] and cyclic imide-substituted oxetanes **3** give bicyclic acetals with a lactam ring **4**[4] (Scheme 1). Here we report a novel chemoselective isomerization of oxetanes having an amide group at their 3-positions. The isomerization of the amide-substituted oxetanes **5** with Lewis acid gives two quite different types of products, depending on the structure of amide group. One type is 5-hydroxymethyl-5,6-dihydro-4*H*-1,3-oxazines **6** produced from the secondary amides of **5** by a new mode of rearrangement involving the oxetanyl group. The other type is bicyclic amide acetals, *i.e.* 2,6-dioxa-7-azabicyclo[2.2.2]octanes **7**, which are produced from the tertiary amides of **5** by a similar mode to those in the already reported cases of **1** and **3**.



Scheme 1

Starting oxetane amides **5a**–**e** were prepared *via* acylation of oxetane amine **8** derived from **3** (phthalimide), and the resulting secondary amides were *N*-alkylated under phase-transfer catalyzed conditions[5] to give the tertiary amides **5f**–**k**.‡

The isomerization of **5** was successfully carried out in anhydrous chlorobenzene or CH_2Cl_2 using Lewis acids such as BF_3·OEt_2 and $AlMe_3$ (Table 1).§ Like **1** and **3** cycloacetalization occurred in the reactions of **5f**–**k**. The products (**7f**–**k**) obtained are a new series of bicyclic amide acetals.¶ Analogous amide acetals of the bicyclo[*n*.3.0] type (*n* = 3 or 4) have already been synthesized by intermolecular cycloaddition or transacetalization, and they have been reported to possess high susceptibility to nucleophiles.[6] Similarly compounds **7** were so sensitive to moisture that hydrolytic fission proceeded rapidly under normal conditions.‖ When the above isomerization was run for 24 h at 100 °C and above, most of the **7** produced was consumed. The final products were oligomers having a polyether backbone.

In sharp contrast, the isomerization of **5a** unexpectedly afforded 5-hydroxymethyl-5-methyl-2-phenyl-5,6-dihydro-4*H*-1,3-oxazine **6a** instead of a bicyclic amide acetal, and no polymerization took place.¶ The molecular structure of **6a** was established by X-ray analysis (Fig. 1).** The isomerization of the other secondary amides (**5b**–**e**) always gave oxazine derivatives (**6b**–**e**) in good yields (Table 1).¶ Compounds **6** were stable during distillation or recrystallization, but chromatographic manipulation over alumina often caused hydrolysis to propanediols with amide groups.

Table 1 Lewis-acid catalyzed isomerization of oxetane amides **5**[a]

Amide		Lewis acid				Product	
	(R^1,R^2)		(mol%)	*T*/°C	*t*/h		Yield (%)[b]
5a[c]	(Ph, H)	BF_3·OEt_2	(25)	35	96	**6a**	89
5b	(H, H)	$AlMe_3$	(50)	120	24	**6b**	50[d]
5c	(Me, H)	$AlMe_3$	(5)	120	24	**6c**	92
5d	(Pr^n, H)	$AlMe_3$	(5)	120	24	**6d**	89
5e	($PhCH_2$, H)	$AlMe_3$	(5)	120	24	**6e**	71
5f	(Ph, Et)	BF_3·OEt_2	(5)	120	1	**7f**	59
5g	(Ph, $PhCH_2$)	BF_3·OEt_2	(5)	130	1	**7g**	61
5h	(H, $PhCH_2$)	BF_3·OEt_2	(35)	70	96	**7h**	63
5i	(Me, Et)	BF_3·OEt_2	(5)	130	1	**7i**	55
5j	(Me, $PhCH_2$)	BF_3·OEt_2	(5)	130	1	**7j**	65
5k	(Pr^i, Et)	BF_3·OEt_2	(5)	130	1.5	**7k**	48

[a] In PhCl. [b] Isolated yield. [c] In CH_2Cl_2. [d] The reaction was quenched with Et_3N followed by MeOH containing a small amount of dilute NaOH.

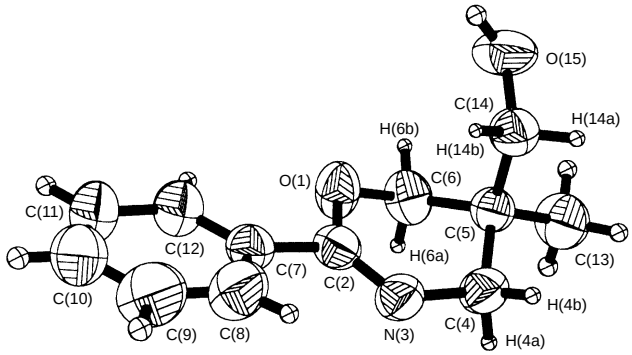
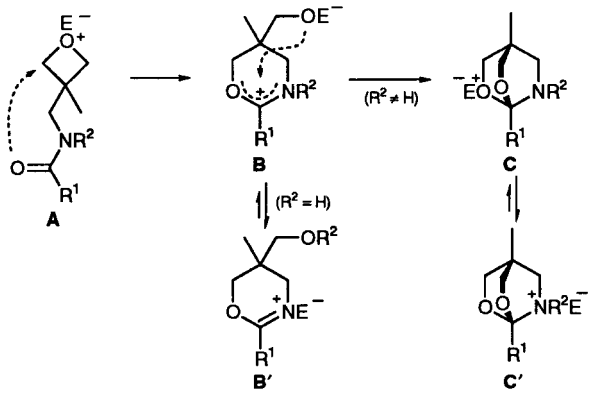


Fig. 1 ORTEP view of **6a** (30% probability thermal ellipsoids)

Although the secondary and tertiary amides of **5** are isomerized giving structurally different products, these reactions can be explained by the following mechanisms passing through a common intermediate **B** (Scheme 2). Both isomerizations begin with the coordination of Lewis acid E to oxetanyl oxygen atom of **5**, and then oxonium **A** undergoes intramolecular nucleophilic attack of the carbonyl oxygen atom by neighboring group participation. The fate of the resulting **B** determines the consequent chemoselection. For tertiary amides, subsequent ring closure of **B** gives an equilibrium mixture of **C** and **C′**. On the other hand, **B** is interconvertible to **B′** when R^2 is a hydrogen atom. The iminium and ammonium salts, **B′** and **C′**, are probably thermodynamically more stable than **B** and **C**, and the catalytic turnover of Lewis acid would decrease as the isomerization progresses. This was strongly supported by the observation that the isomerization rates of **5** steeply slowed down at increased yields of basic **6** and **7**. In order to force these reactions to completion, it was necessary to employ either high temperature or a very large amount of Lewis acid, or both (Table 1). Under such conditions, however, the yields of **7** began to decrease after reaching maxima at relatively early stages, because of inevitable polymerization as a competing reaction.

In the chemoselective isomerization of **5**, moderate to fairly good yields of **6** and **7** were obtained using simple operations. Like other bicyclic amide acetals,[6] compounds **7** are also interesting in a variety of chemical transformations not only as reactive amino ethers but also as ring-opening polymerizable monomers.[6,7] Numerous methods of preparing dihydro-1,3-oxazines appear in the literature.[8] The advantages (as well as differences) in the present reaction may be summarized as follows: (a) the preparation of dihydro-1,3-oxazines having a hydroxymethyl group, which is a useful functional group for further modification. (b) A general method for obtaining not only the phenyl- or alkyl-substituted oxzines at the 2-positions but also the unsubstituted oxazine.



Scheme 2

Footnotes and References

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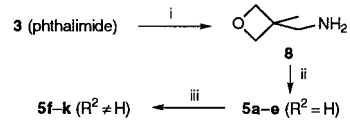

Reagents and conditions: i, 3-methyl-3-(phthalimidomethyl)oxetane[4] (1.0 equiv.), hydrazine hydrate (5 equiv.), in EtOH, 60 °C, 1.5 h, and then a catalytic amount of Raney Ni (*W*-2), vigorous reflux, 81% (GLPC purity 96%), bp 90–95 °C/100 mmHg; ii, acylating reagents: $(R^1CO)_2O$, HCO_2COMe, or R^1CO_2H (DCC coupling), 76–92%; iii, **5** (1.0 equiv.), R^2Br (1.1 equiv.), K_2CO_3 (1.0 equiv.), NaOH (2.5 equiv.), $Bu^n_4NHSO_4$ (0.10 equiv.), in benzene, 40 °C to reflux, 3–15 h, 55–78%.

§ *Typical experimental procedure*: To an anhydrous PhCl (1.0 ml) solution of **5c** (150 mg, 1.1 mmol) in a tube was added 1.0 mol l^{-1} $AlMe_3$ in hexane (0.05 mmol) under nitrogen. The resulting solution was allowed to react at 120 °C for 24 h. After the reaction was quenched by addition of Et_3N (0.1 ml) followed by MeOH (3.0 ml), the solvents were replaced by CH_2Cl_2 (10 ml). Distillation of the CH_2Cl_2-soluble part afforded **6c** in 92% yield, bp 100–110 °C/0.1 mmHg. Similarly, the isomerization of **5f** was carried out in a small distillation flask at 120 °C for 1 h. After the addition of anhydrous Et_3N (0.1 ml) followed by CaH_2 (*ca.* 50 mg), distillation of the resulting mixture afforded **7f** (0.12 g, 0.52 mmol) in 59% yield, bp 110–120 °C/0.1 mmHg. The product isolated was stable under nitrogen.

¶ All compounds were characterized by ^1H NMR and IR spectroscopy, although the IR spectra of **7** were always observed as a mixture of **7** and its hydrolysis product. *Selected data* for **6a**: mp 135–136 °C (CH_2Cl_2–hexane); ν_{max}(KBr)/cm^{-1} 3400 (OH), 1650 (C=N); the atomic numbering system refers to that used in Fig. 1; δ_H($CDCl_3$, *J*/Hz) 7.89 (dd-like, *J* 6.9, 1.5, 2 H, ArH_o), 7.44–7.33 (m, 3 H, $ArH_{m,p}$), 4.23 [dd, *J* 10.7, 2.4, 1 H, H(6b)], 3.92 [d-like, *J* 10.7, 1 H, H(6a)], 3.57, 3.47 [each d, *J* 10.7, 2 H, H (14a) and H (14b), 3.48 [dd, *J* 16.9, 2.2, 1 H, H (4b)], 3.27 [d-like, *J* 16.6, 1 H, H(4a)], 2.02 (br s, 1 H, OH), 1.02 [s, 3 H, C(13) H_3]; δ_C (100 MHz, $CDCl_3$) 155.0 [C(2)], 133.3 [C(7)], 130.5 [C(10)], 128.0 [C(9), C(11)], 127.0 [C(8), C(12)], 70.1 [C(6)], 65.8 [C(14)], 51.1 [C(4)], 32.7 [C(5)], 19.0 [C(13)]. HRMS: *m*/*z* 205.1115, calc. for $C_{12}H_{15}NO_2$: 205.1104. Analysis for $C_{12}H_{15}NO_2$, found (calc.): C, 69.96 (70.22); H, 7.33 (7.37); N, 6.76 (6.82%). For **7f**: δ_H(anhydrous $CDCl_3$ under nitrogen, *J*/Hz) 7.60 (dd, *J* 6.8, 3.2, 2 H, ArH_o), 7.38–7.29 (m, 3 H, $ArH_{m,p}$), 3.98 (s, 4 H, OCH_2), 2.99 (s, 2 H, NCH_2), 2.36 (q, *J* 7.2, 2 H, CH_2CH_3), 0.94 (t, *J* 7.3, 3 H, CH_2CH_3), 0.88 (s, 3 H, CCH_3). HRMS: *m*/*z* 233.1439, calc. for $C_{14}H_{19}NO_2$: 233.1417.

‖ The hydrolysis product is 2-ethylaminomethyl-2-hydroxymethylpropyl benzoate. The initially formed esters except for the benzoates and isobutyrate were spontaneously converted to the corresponding amide-substituted propanediols by acyl exchange.

** **6a**: Mp 135–136 °C (CH_2Cl_2–hexane). *Crystal data* for **6a**: space group $P2_1/c$, Z = 4, a = 11.044(1), b = 9.3865(8), c = 11.817(1) Å, β = 116.336(8)°, D_c = 1.242 g cm^{-3}. 2816 measured, 2685 independent reflections, of which 1813 were considered as observed [$I > 3.00\ \sigma(I)$]. R = 0.039, R_w = 0.035. CCDC 182/639.

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