Pergamon

Tetrahedron Letters, Vol. 35, No. 38, pp. 7089-7092, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01549-X

Aminolysis of Oxetanes: Quite Efficient Catalysis by Lanthanide(III) Trifluoromethansulfonates

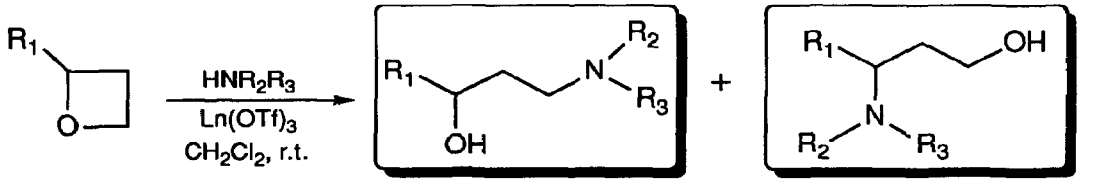
Paolo Crotti,* Lucilla Favero, Franco Macchia, and Mauro Pineschi

Dipartimento di Chimica Bioorganica, Università di Pisa, via Bonanno 33, 56126 Pisa, Italy

Dedicated to Prof.G.Berti on the occasion of his 70th birthday

Abstract: Ln(III)trifluoromethansulfonates in CH_2Cl_2 efficiently catalyze the aminolysis of trimethylene oxide, 2-octyl -, and 2-phenyloxetane, at r.t., to give the corresponding γ-amino alcohols in very good yields.

Although the structure and hybridization of orbitals in oxetanes and oxiranes are largely different, the reactivity of the two systems in the ring opening reactions under acid conditions is similar even if the oxetanes react slightly more slower.[1] Evidently, the lower degree of strain in oxetanes is at least partly offset by the greater basicity of the ring oxygen.[1] On the contrary, in ring opening reactions carried out in the presence of strong nucleophiles under basic or neutral conditions, oxetanes usually exhibit a scarce reactivity compared with oxiranes. In this sense, it is particularly difficult to obtain the direct reaction of oxetanes with amines even if unhindered oxetanes and amines are used.[1,2] By consequence, this reaction cannot be efficiently utilized as a general synthetic method for the preparation of γ-aminoalcohols.



1, R_1=H
2, R_1= C_8H_{17}
3, R_1=Ph

4, R_1=R_2=H, R_3=C_4H_9
5, R_1=H, R_2=CH_3, R_3=Ph
6, R_1=H, R_2=R_3=C_2H_5
7, R_1=C_8H_{17}, R_2=H, R_3=*t*-C_4H_9
8, R_1=C_8H_{17}, R_2=H, R_3=Ph
9, R_1=C_8H_{17}, R_2=R_3= C_2H_5
10, R_1=C_8H_{17}, R_2=R_3=*i*-C_3H_9

11, R_1=C_8H_{17}, R_2 R_3= 

12, R_1=Ph, R_2=R_3=C_2H_5

14, R_1=Ph, R_2 R_3= 

16, R_1=Ph, R_2 R_3= 

13, R_1=Ph, R_2=R_3= C_2H_5

15, R_1=Ph, R_2 R_3= 

17, R_1=Ph, R_2 R_3= 

In a program aimed at finding new, efficient catalysts for the ring opening of small ring heterocycles, we have found that common metal salts such as $LiClO_4$ are able to assist effectively the addition of a large variety of nucleophiles, including amines, to oxiranes.[3,4] We also found that $LiBF_4$ in a non-protic solvent (CH_3CN) efficiently promoted the direct aminolysis of oxetanes with a large variety of primary and secondary amines, while $LiClO_4$ turned out to be markedly less efficient in promoting this reaction.[5,6] More recently, we found that lanthanide(III) trifluoromethansulfonates (triflates) [$Ln(OTf)_3$] such as $Yb(OTf)_3$, $Gd(OTf)_3$ and $Nd(OTf)_3$ catalyze in an extraordinarily effective way the aminolysis of oxiranes in low polarity non-protic solvents such as CH_2Cl_2 or toluene.[7] We therefore tried to transfer the $Ln(OTf)_3$-catalysis also to the aminolysis of oxetanes. Actually, we found that the $Ln(OTf)_3$ promote in a more efficient way than $LiBF_4$ the direct aminolysis of some representative oxetanes [trimethylene oxide (**1**), 2-octyl- (**2**), and 2-phenyloxetane (**3**)] with primary and secondary, aliphatic and aromatic amines, to give the corresponding γ-amino alcohols in very good yields (see the Table). The reactions proceed smoothly using just 0.5 molar equivalent of the catalyst. The use of lower amounts of $Ln(OTf)_3$ somewhat lengthens the reaction times (entry 17, Table). The reactions occur nicely also using an hindered amine such as $(i\text{-Pr})_2NH$ (entry 19, Table). As in the $Ln(OTf)_3$-catalyzed aminolysis of oxiranes,[7] the use of a low polar non-protic solvent such as toluene or CH_2Cl_2 appears to give the best results; on the contrary, the use of a more coordinating solvent such as CH_3CN, makes the catalyst less effective (see entries 13 and 16, Table). The $Ln(OTf)_3$-promoted aminolysis of oxetanes effectively occurs also using an aryl-substituted substrate such as **3**, which didn't yield any addition product under $LiBF_4$-promoted aminolysis conditions.[5] The ring opening of the $Ln(OTf)_3$-catalyzed aminolysis of **2** is completely regioselective with the attack of the nucleophile on the less substituted carbon α to the oxetane oxygen. On the contrary, in the reactions of **3**, mixtures of the two possible regioisomers are obtained in a ratio which depends on the type of the amine; however, the regioisomer arising from the nucleophilic attack on the less substituted oxetane carbon α to the oxetane oxygen turns out to be, also in this case, the main product. Among the $Ln(OTf)_3$ tested, the order of effectiveness found is: $Yb(OTf)_3 > Gd(OTf)_3 >> Nd(OTf)_3$ (entries 2-4 and 8-10, Table). It is interesting to note that this order is different from the one observed in the corresponding reactions of oxiranes [$Yb(OTf)_3 \cong Gd(OTf)_3 > Nd(OTf)_3$].[7]

In accordance with previous proposals for the $Ln(OTf)_3$-promoted aminolysis of oxiranes,[7] the catalytic effect of the Ln(III) salts in the corresponding oxetane ring opening reactions appears to be ascribable to the strong oxophilicity of Ln(III), which allows the metal to coordinate tightly to the heterocyclic oxygen, thus favoring the nucleophilic ring opening process.

In conclusion, the $Ln(OTf)_3$-promoted aminolysis of oxetanes appears to be a useful and valuable general method for the synthesis of γ-aminoalcohols. Moreover, the successful application of this new methodology to the aminolysis of 2-phenyloxetane (**3**), makes this method to be applied also to an easy synthesis of phenyl-substituted 1,3-propanolamines.

General Procedure and Identification of γ-Amino Alcohols.

A solution of the oxetane (1.0 mmol) in anhydrous CH_2Cl_2, or toluene, (1.0 ml) was treated at r.t. with the amine (1.2 mmol). $Yb(OTf)_3$ (0.5 mmol) was then rapidly added and the reaction mixture was stirred at r.t. for the time shown in the Table. Dilution with Et_2O and evaporation of the washed (saturated

Table. Aminolysis of Some Representative Oxetanes (1-3) in the Presence of Ln(OTf)$_3$ [Yb(OTf)$_3$, Gd(OTf)$_3$ and Nd(OTf)$_3$], or Other Metal Salts.

entry	oxetane	salt[a]	amine	solvent	reaction time (°C)[b]	α attack[c]	β attack[d]	yield %[e]
1		Yb(OTf)$_3$ 50%	BuNH$_2$	CH_2Cl_2	3 h		*f*	90
2		Yb(OTf)$_3$ 50%	PhNHMe	CH_2Cl_2	4 h		*g*	99
3		Gd(OTf)$_3$ 50%	PhNHMe	CH_2Cl_2	18 h		*g*	99
4	**1**	Nd(OTf)$_3$ 50%	PhNHMe	CH_2Cl_2	48 h		*g*	96
5		$LiBF_4$ 2M	PhNHMe	CH_3CN	68 h		*g*	88*h*
6		$LiClO_4$ 5M	$NHEt_2$	CH_3CN	13 h (80)		*i*	95
7		$LiClO_4$ 5M	$NHEt_2$	CH_3CN	48 h		*i*	20
8		Yb(OTf)$_3$ 50%	*t*-BuNH$_2$	CH_2Cl_2	16 h	>99*j*	<1	99
9		Gd(OTf)$_3$ 50%	*t*-BuNH$_2$	CH_2Cl_2	16 h	>99*j*	<1	50
10		Nd(OTf)$_3$ 50%	*t*-BuNH$_2$	CH_2Cl_2	48 h	>99*j*	<1	7
11	C_8H_{17}	$LiBF_4$ 2M	*t*-BuNH$_2$	CH_3CN	24 h (80)	>99*j*	<1	95*h*
12		Yb(OTf)$_3$ 50%	*t*-BuNH$_2$	toluene	16 h	>99*j*	<1	99
13		Yb(OTf)$_3$ 50%	*t*-BuNH$_2$	CH_3CN	16 h	>99*j*	<1	75
14		Yb(OTf)$_3$ 50%	$PhNH_2$	CH_2Cl_2	2 h	>99*k*	<1	99
15		Yb(OTf)$_3$ 50%	$NHEt_2$	CH_2Cl_2	2 h	>99*l*	<1	99
16	**2**	Yb(OTf)$_3$ 50%	$NHEt_2$	CH_3CN	16 h	>99*l*	<1	70
17		Yb(OTf)$_3$ 20%	$NHEt_2$	CH_2Cl_2	48 h	>99*l*	<1	53
18		$LiClO_4$ 5M	$NHEt_2$	CH_3CN	4 days (80)	>99*l*	<1	99
19		Yb(OTf)$_3$ 50%	(*i*-Pr)$_2$NH	CH_2Cl_2	24 h	>99*m*	<1	90
20		Yb(OTf)$_3$ 50%	morpholine	CH_2Cl_2	7 h	>99*n*	<1	80
21	Ph	Yb(OTf)$_3$ 50%	$NHEt_2$	CH_2Cl_2	2 h	83*o*	17*p*	99
22		$LiClO_4$ 5M	$NHEt_2$	CH_3CN	48 h (80)	83*o*	17*p*	81
23		$LiClO_4$ 5M	$NHEt_2$	DMF	24 h (80)	83*o*	17*p*	50
24		$LiBF_4$ 2M	$NHEt_2$	CH_3CN	12 h (80)	no reaction		
25		Yb(OTf)$_3$ 50%	piperidine	CH_2Cl_2	12 h	75*q*	25*r*	90
26	**3**	Yb(OTf)$_3$ 50%	morpholine	CH_2Cl_2	2 h	65*s*	35*t*	98

[a] For reaction conditions, see the General Procedure. [b] Unless differently stated, the reactions were carried out at r.t. [c] Attack of the nucleophile on the less substituted carbon α to the oxetane oxygen. [d] Attack of the nucleophile on the more substituted carbon α to the oxetane oxygen. [e] Yields based on weight and ^{1}H NMR examination of the isolated crude reaction product. [f] Amino alcohol **4**. [g] Amino alcohol **5**. [h] See ref. 5. [i] Amino alcohol **6**. [j] Amino alcohol **7**. [k] Amino alcohol **8**. [l] Amino alcohol **9**. [m] Amino alcohol **10**. [n] Amino alcohol **11**. [o] Amino alcohol **12**. [p] Amino alcohol **13**. [q] Amino alcohol **14**. [r] Amino alcohol **15**. [s] Amino alcohol **16**. [t] Amino alcohol **17**.

aqueous NaCl) afforded a crude reaction product consisting of the corresponding γ-amino alcohols (^{1}H NMR) which was purified by distillation (amino alcohols from **1**) or by TLC (amino alcohols from **2**). In the Ln(OTf)$_3$-catalyzed aminolysis of **1** with primary amines, an excess of the amine (epoxide:amine=1:5) was used in order to suppress the over alkylation process. The regioisomeric couples of amino alcohols **12-13**, **14-15**, and **16-17** from oxetane **3** were separated by TLC (a 6:3:1 mixture of hexane, Et_2O and NEt_3 was used as the eluant). The structure of all the γ-amino alcohols obtained was unequivocally determined by their ^{1}H and ^{13}C NMR spectra and confirmed by satisfactory microanalytical results (C,H,N, ±0.3 of the calculated value).

The relative amounts of regioisomers from oxetane **3** were determined by ^{1}H NMR. Amino alcohols **4-11** have previously been described.[5] Oxetanes **2**[5] and **3**[8] were prepared as previously described.

Amino alcohol **12**, a liquid; ^{1}H NMR δ 7.15-7.42 (m, 5H), 4.92 (unresolved triplet, 1H, *J*=5.8 Hz), 2.43-2.87 (m, 6H), 1.79-1.88 (m, 2H), 1.10 (t, 6H, *J*=7.2 Hz). ^{13}C NMR δ 128.83, 127.49, 126.24, 76.11, 53.07, 47.32, 35.05, 11.99.

Amino alcohol **13** was not separated in the pure state due to the insufficient amount present in the crude reaction product and to difficulties in the TLC separation stage. However, its presence was substantiated by ^{1}H NMR analysis of the crude reaction product: ^{1}H NMR δ 4.02 (dd, 1H, *J*=11.6 and 2.9 Hz), 3.75-3.87 (m, 2H), 1.52 (dq, 1H, *J*=14.8 and 2.7 Hz), 1.96 (sextet, 1H, *J*=6.7 Hz).

Amino alcohol **14** a liquid; ^{1}H NMR δ 7.11-7.41 (m, 5H), 4.93 (unresolved t, 1H, *J*=5.7 Hz), 2.18-2.80 (m, 6H), 1.78-1.89 (m, 2H), 1.32-1.72 (m, 6H). ^{13}C NMR δ 128.78, 127.42, 126.18, 76.23, 58.35, 55.26, 34.30, 26.64, 24.85.

Amino alcohol **15**, a liquid; ^{1}H NMR δ 7.22-7.40 (m, 3H), 7.10-7.22 (m,2H), 3.82-3.94 (m, 3H), 2.44-2.80 (m, 2H), 2.10-2.44 (m, 2H), 1.48-1.72 (m, 5H), 1.18-1.41 (m, 3H). ^{13}C NMR δ 136.75, 129.50, 128.61, 128.30, 80.70, 71.97, 64.44, 31.87, 26.79, 24.80.

Amino alcohol **16**, a liquid; ^{1}H NMR δ 7.03-7.32 (m, 5H), 4.86 (unresolved triplet, 1H, *J*=5.7 Hz), 3.67 (t, 4H, *J*=4.6 Hz), 2.38-2.68 (m, 6H), 1.79 (q, 2H, *J*=5.8 Hz). ^{13}C NMR δ 128.87, 127.63, 126.12, 76.05, 67.53, 58.12, 54.27, 34.04.

Amino alcohol **17**, a liquid; ^{1}H NMR δ 7.14-7.40 (m, 5H), 3.59-3.91 (m, 7H), 2.22-2.70 (m, 5H), 1.71 (dq, 1H, *J*=14.6 and 3.7 Hz). ^{13}C NMR δ 137.16, 129.33, 128.78, 128.38, 71.23, 67.80, 63.84, 50.50.

References and Notes

1. Searles, S. Jr., *Heterocyclic Compounds with Three- and Four-Membered Rings* ; Weissberger, A., Ed; Interscience, New York, 1964, p 983-1068.

2. Searles, S. Jr.; Gregory, V.P. *J.Am.Chem.Soc.* **1954**, *76*, 1789-1790.

3. a) Chini. M.; Crotti, P.; Macchia, F. *Tetrahedron Lett.* **1990**, *31*, 4661-4664; b) *J.Org.Chem.* **1991**, *56*, 5939-5942; c) Chini, M.; Crotti, P.; Flippin, L.A.; Macchia, F. *J.Org.Chem.* **1991**, *56*, 7043-7048.

4. Chini, M.; Crotti, P.; Gardelli, C.; Macchia, F. *Synlett* **1992**, 673-676 and references cited therein.

5. Chini, M.; Crotti, P.; Favero, L.; Macchia, F. *Tetrahedron Lett.* **1994**, *35* , 761-764.

6. Contrary to previous reports by us,[5] we have now verified that $LiClO_4$ is able to promote the aminolysis of oxetanes. However, the promoting reactivity of $LiClO_4$ is much lower compared with $LiBF_4$[5]and $Ln(OTf)_3$ (present work). By way of comparison, some examples are given in the Table (entries 6,7,18,22 and 23).

7. Chini, M.; Crotti, P.; Favero, L.; Macchia, F.; Pineschi, M. *Tetrahedron Lett.* **1994**, *35* , 433-436.

8. Okuma, K.; Tanaka, Y.; Kaji, S.; Ohta, H. *J.Org.Chem.* **1983**, *48*, 5133-5134.

Acknowledgment. This work was supported by the Consiglio Nazionale delle Ricerche (CNR) and the Ministero dell'Università e della Ricerca Scientifica e Tecnologica (MURST), Roma.

(*Received in UK* 27 *May* 1994; *revised* 4 *August* 1994; *accepted* 12 *August* 1994)