Pergamon

Tetrahedron Letters, Vol. 35, No. 5, pp. 761-764, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $6.00+0.00

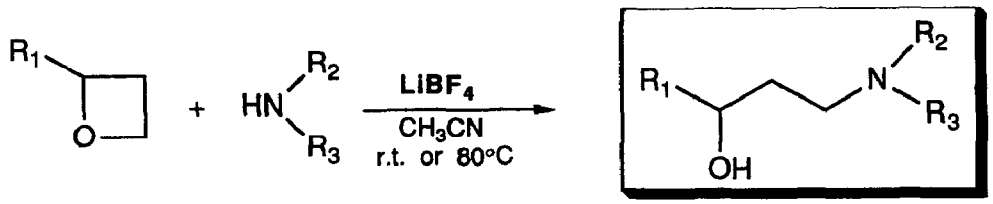
0040-4039(93)E0300-9

Mild $LiBF_4$-Promoted Aminolysis of Oxetanes

Marco Chini, Paolo Crotti,* Lucilla Favero, and Franco Macchia
Dipartimento di Chimica Bioorganica, Università di Pisa, via Bonanno 33, 56126 Pisa, Italy

Abstract: *$LiBF_4$ in acetonitrile efficiently catalyzes the aminolysis of trimethylene oxide and 2-octyl oxetane under mild conditions (r.t. or 80 °C) to give the corresponding γ-amino alcohols in very good yields.*

1,2-Epoxides (oxiranes) and 1,3-epoxides (oxetanes) are important classes of organic compounds useful in the synthesis of 1,2- and 1,3-functionalized alcohols, respectively, by nucleophilic ring opening reactions. However, oxiranes are much more widely used than their oxetane homologs. This difference in use may be largely ascribed to the different availability of the two systems and to the lower reactivity of oxetanes in the ring opening process, unless protic catalysis is used.[1] The reactions of oxetanes with amines to yield γ-amino alcohols are particularly difficult to obtain, even if unhindered oxetanes and amines are used.[1] For example, the reaction of primary and secondary amines with the simple unsubstituted trimethylene oxide (**1**) occurs in a sealed tube at 150 °C, giving only 45-67% yield of the desired 3-N-alkyl or 3-N,N-dialkylaminopropanols.[1,2] To our knowledge, no report other than this, and no more favorable method has been presented in the literature on this subject.



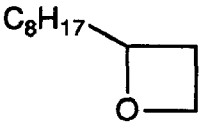
1, R_1=H
2, R_2= C_8H_{17}

3, R_1=R_2=H, R_3=C_4H_9
4, R_1=R_2=H, R_3=*t*-C_4H_9
5, R_1=H, R_2=R_3=C_2H_5
6, R_1=H, R_2=R_3=*i*-C_3H_7
7, R_1=R_2=H, R_3= Ph
8, R_1=H, R_2=Me, R_3=Ph
9, R_1=H, R_2 R_3= 
10, R_1=H, R_2 R_3= 

11, R_1=R_2=H, R_3=(3,4-diOMe)Bn
12, R_1=C_8H_{17}, R_2=H, R_3=*t*-C_4H_9
13, R_1=C_8H_{17}, R_2=R_3=C_2H_5
14, R_1=C_8H_{17}, R_2=R_3=*i*-C_3H_7
15, R_1=C_8H_{17}, R_2=H, R_3=Ph
16, R_1=C_8H_{17}, R_2 R_3= 

Recently, we found that simple readily available metal salts, such as $LiClO_4$ and $Zn(OTf)_2$ efficiently catalyze[3], among other reactions,[4] the direct aminolysis of a large variety of 1,2-epoxides in a non-protic solvent (CH_3CN), under very mild experimental conditions.[3] On this basis, we expected to be able to transfer

Table. $LiBF_4$-Promoted Aminolysis of Trimethylene Oxide (1) and 2-Octyloxetane (2) with Some Representative Amines in CH_3CN.

entry	oxetane	amine	reaction time (h) and temperature(°C)[a]	reaction product	yield %[b]
1	 1	$C_4H_9NH_2$	48 (r.t.)	3	92
2		*t*-$C_4H_9NH_2$	42 (r.t.)	4	95
3		$(C_2H_5)_2NH$	42 (r.t.)	5	92
4		(*i*-$C_3H_7)_2NH$	90 (r.t.)	6	89
5		$PhNH_2$	64 (r.t.)	7	93
6		PhNHMe	68 (r.t.)	8	88
7		piperidine	23 (r.t.)	9	93
8		morpholine	22 (r.t.)	10	89
9		(3,4-dimethoxy)Bn	68 (r.t.)	11	85
10	 2	*t*-$C_4H_9NH_2$	24 (80)	12	95
11		$(C_2H_5)_2NH$	18 (80)	13	88
12		(*i*-$C_3H_7)_2NH$	24 (80)	14	92
13		$PhNH_2$	18 (80)	15	98
14		morpholine	18 (80)	16	86

[a] For reaction conditions, see the General Procedure. [b] Yields based on weight, GC analysis and ^1H NMR examination of the isolated crude product.

this type of catalysis to the aminolysis of oxetanes. Unfortunately, treatment of trimethylene oxide (**1**) with amines in the presence of $LiClO_4$ or $Zn(OTf)_2$ under the same experimental conditions previously used for the corresponding reactions of 1,2-epoxides, led only to the recovery of the unreacted oxetane **1**, and when more drastic conditions (higher temperatures) were tried, only polimeric products were obtained (^1H NMR). However, when the reactions of different amines with the unsubstituted oxetane **1** or the 2-octyl substituted oxetane **2** [5] were carried out in the presence of $LiBF_4$ in CH_3CN at r.t (in the case of **1**) or at 80°C (in the case of **2**) quite interesting yields of the corresponding γ-amino alcohols were obtained in a few hours. The Table shows the results of the opening reactions of oxetanes **1** and **2** with some representative aliphatic and aromatic, primary and secondary amines. The reaction rate depends on the nucleophilicity of the amine, as shown by the reaction of **1** with the secondary hindered diisopropylamine, which requires a considerably longer reaction time. In the case of the opening reaction of **1**, the use of reaction temperatures higher than r.t .leads to lower overall yields of the γ-amino alcohol, because of the formation of polymeric products. The use of higher amounts of $LiBF_4$ also increases the amounts of polymeric products. As mentioned above, and as shown in

the Table, $LiBF_4$-promoted aminolysis of the 2-alkyl substituted oxetane **2** does not occur at r.t, and nice yields of γ-amino alcohols can be obtained only if the reactions are carried out in CH_3CN at 80°C. In the case of **2**, the opening reactions are completely regioselective with the attack of the amine on the less substituted oxetane carbon α to the ring oxygen. The promoting effect of $LiBF_4$ was definitely confirmed by control reactions of oxetanes **1** and **2** with amines carried out following the general procedure, without adding the lithium salt: in these cases, no trace of opening products was revealed, even after prolonged reaction times (5 days).

The catalysis previously observed in the metal salt (e.g. $LiClO_4$)-promoted aminolysis of 1,2-epoxides was ascribed to the ability of the metal ion to coordinate the oxirane oxygen.[4] The different behavior of these catalysts in the aminolysis of oxetanes (see above) suggests that a different mechanism should be operative in the case of $LiBF_4$-promoted reactions. It could be reasonable to admit that $LiBF_4$ operates, as already suggested for other reactions,[7,8] as a slow BF_3-releasing source mediated by the acetonitrile solvent. Then BF_3 acts by coordinating the oxetane oxygen, thus favoring the nucleophilic ring opening process which affords γ-amino alcohols. Moreover, the complete regioselectivity observed in the reactions of **2** suggests a low polarization of the oxetane C-O bond in the transition state.

In conclusion, this $LiBF_4$-promoted aminolysis of oxetanes appears to be quite a useful method for the synthesis of γ-amino alcohols, if compared with the corresponding uncatalyzed ring opening reactions of oxetanes, which occur, in low yields, only in protic solvents and at unfavorable high temperatures. Moreover, the use of a non-protic solvent (CH_3CN) makes this new methodology suitable to be applied also to protic solvent-sensitive substrates.

Studies are in progress in order both to evaluate the possible extension of this kind of catalysis and to find out new and more effective catalysts for the ring opening of oxetanes with nucleophiles.

General Procedure and Identification of γ-Amino Alcohols.

A solution of the oxetane (5.0 mmol) in anhydrous CH_3CN (5.0 ml) was treated at r.t. with the amine (10.0 mmol). $LiBF_4$ (10.0 mmol) was then rapidly added and the reaction mixture was stirred at r.t. (in the case of **1**) or at 80°C in the case of **2** for the time shown in the Table. Dilution with 36% aqueous NH_3 (20 ml) and saturated aqueous NaCl, extraction with $CHCl_3$ (3x40 ml) and evaporation of the washed (saturated aqueous NaCl) afforded a crude reaction product consisting of the corresponding γ-amino alcohols (^1H NMR) which was purified by distillation (amino alcohols from **1**) or by TLC (amino alcohols from **2**). The structure of all the γ-amino alcohols obtained was unequivocally determined by their ^1H and ^{13}C NMR spectra and confirmed by satisfactory microanalytical results (C,H,N, ±0.3 of the calculated value).

Compound **3**,[9] liquid, bp 115°C/1 mm ; ^1H NMR δ 3.77 (t, 2H, *J* =5.4 Hz), 2.84 (t,2H, *J*=5.9 Hz), 2.60 (t, 2H, *J*=7.0 Hz), 1.69 (tt, 2H, *J*=5.9 and 5.4 Hz), 1.25-1.54 (m, 4H), 0.91 (t, 3H, *J*=7.0 Hz). ^{13}C NMR δ 62.55, 49.22, 48.75, 31.67, 30.93, 20.08, 13.61.
Compound **4**, liquid, bp 55°C/1.5 mm ; ^1H NMR δ 3.76 (t, 2H, *J* =5.4 Hz), 2.80 (t, 2H, *J*=5.9 Hz), 1.68 (tt, 2H, *J*=5.4 and 5.9 Hz), 1.11 (s, 9H). ^{13}C NMR δ 63.26, 50.14, 41.83, 31.70, 28.44.
Compound **5**, liquid, bp 65°C/1 mm (lit.[2], bp 62-64°C/11 mm); ^1H NMR δ 3.78 (t, 2H, *J*=5.2 Hz), 2.65 (t, 2H, *J*=5.7 Hz), 2.53 (q, 4H, *J*=7.1 Hz), 1.68 (tt, 2H, *J*=5.2 and 5.7 Hz), 1.05 (t, 6H, *J*=7.2 Hz). ^{13}C NMR δ 63.99, 53.23, 46.51, 27.59, 11.32.
Compound **6**, liquid, bp 80°C/1 mm (lit.[2], bp 85-87°C/9 mm); ^1H NMR δ 3.81 (t, 2H, *J*=5.0 Hz), 3.13 (7 lines, 2H, *J*=6.6 Hz), 2.71 (t, 2H, *J*=5.7 Hz), 1.67 (tt, 2H, *J*=5.0 and 5.7 Hz), 1.05 (d, 12H, *J*=6.6 Hz). ^{13}C NMR δ 64.13, 46.66, 44.20, 26.27, 19.69.

Compound **7**, liquid bp 140°C/0.5 mm (lit.[2] bp 125-129°C/0.5 mm); ^{1}H NMR δ 7.13-7.21 (m, 2H), 6.59-6.74 (m, 3H), 3.74 (t, 2H, *J*=5.9 Hz), 3.23 (t, 2H, *J*=6.6 Hz), 1.83 (tt, 2H, *J*=5.9 and 6.6 Hz). ^{13}C NMR δ 148.10, 129.00, 117,34, 112,92, 60.72, 41.33, 31.47.
Compound **8**, liquid bp 160°C/0.5 mm (lit.[2] bp 120-122°C/1 mm); ^{1}H NMR δ 7.11-7.24 (m, 2H), 6.64-6.73 (m, 3H), 3.58 (t, 2H, *J*= 6.1 Hz), 3.35 (t, 2H, *J*=6.9 Hz), 2.84 (s, 3H), 1.73 (tt, 2H, *J*=6.1 and 6.9 Hz). ^{13}C NMR δ 149.30, 128.96, 116.37, 112.57, 60.36, 49.72, 38.16, 29.28.
Compound **9**, liquid bp 85°C/1 mm (lit.[2] bp 89°C/6 mm); ^{1}H NMR δ 3.76 (t, 2H, *J*=5.3 Hz), 2.54 (t, 2H, *J*=5.9 Hz), 2.44 (m, 4H), 1.70 (tt, 2H, *J*=5.3 and 5.9 Hz), 1.43-1.63 (m, 6H). ^{13}C NMR δ 63.82, 58.90, 54.37, 27.03, 25.67, 23.94.
Compound **10**, liquid bp 125°C/1 mm (lit.[2] bp 107°C/9 mm); ^{1}H NMR δ 3.76 (t, 2H, *J*=5.4 Hz), 3.70 (t, 4H, *J*=4.8 Hz), 2.58 (t, 2H, *J*=6.2 Hz), 2.51 (t, 4H, *J*=4.8 Hz), 1.73 (tt, 2H, *J*=5.4 and 6.2 Hz). ^{13}C NMR δ 66.50, 63.14, 58.09, 53.37, 26.95.
Compound **11**, liquid bp 185°C/1 mm; ^{1}H NMR δ 6.78-6.91 (m, 3H), 3.89 (s, 3H), 3.87 (s, 3H), 3.74-3.93 (m, 4H), 2.90 (t, 2H, *J*=5.7 Hz), 1.73 (tt, 2H, *J*=5.2 and 5.7 Hz). ^{13}C NMR δ 148.74, 147.93, 131.59, 120.14, 111.14, 110.76, 63.39, 55.63, 53.33, 46.52, 30.55.
Compound **12**, solid, mp 40.5-41°C; ^{1}H NMR δ 3.75 (m, 1H), 2.98 (tt, 1H, *J*=11.3 and 3.7 Hz), 2.66 (ddd, 1H, *J*=11.3 and 2.9 Hz), 1.59-1.63 (m, 1H), 1.11-1.52 (m, 15H), 1.08 (s, 9H), 0.85 (t, 3H, *J*=5.8 Hz). ^{13}C NMR δ 74.56, 51.10, 42.25, 38.62, 36.42, 32.46, 30.36, 30.19, 29.84, 29.29, 26.17, 23.23, 14.67.
Compound **13**, liquid; ^{1}H NMR δ 3.68-3.82 (m, 1H), 2.54-2.78 (m, 4H), 2.34 (6 lines, 2H, *J*=6.9 Hz), 1.10-1.60 (m, 16H), 1.05 (t, 6H, *J*=6.9 Hz), 0.87 (t, 3H, *J*=6.0 Hz). ^{13}C NMR δ 74.17, 53.41, 47.15, 38.57, 32.73, 32.51, 30.42, 30.25, 29.90, 26.26, 23.29, 14.71, 11.94.
Compound **14**, liquid; ^{1}H NMR δ 3.75 (m, 1H), 3.13 (7 lines, 2H, *J*=6.6 Hz), 2.59-2.78 (m, 2H), 1.18-1.67 (m, 16H), 1.10 and 0.98 (2d, 12H, *J*=6.6 Hz), 0.87 (t, 3H, *J*=6.0 Hz). ^{13}C NMR δ 74.63, 47.62, 44.44, 38.63, 33.17, 32.53, 30.46, 30.26, 29.93, 26.22, 23.30, 22.51, 18.74, 14.73.
Compound **15**, solid, mp 85.5-86°C; ^{1}H NMR δ 7.06-7.17 (m, 2H), 6.54-6.68 (m, 3H), 3.64-3.77 (m, 1H), 3.09-3.30 (m, 2H), 1.50-1.82 (m, 2H), 1.02-1.50 (m, 14H), 0.80 (t, 3H, *J*=6.7 Hz).^{13}C NMR δ 149.03, 129.88, 118.39, 113.91, 72.07, 42.58, 38.50, 36.95, 32.54, 30.31, 30.23, 29.94, 26.27, 23.32, 14.77.
Compound **16**, liquid; ^{1}H NMR δ 3.57-3.73 (m, 5H), 2.45-2.66 (m, 4H), 2.25-2.38 (m, 2H), 1.05-1.68 (m, 16H), 0.80 (t, 3H, *J*=6.1 Hz). ^{13}C NMR δ 74.01, 67.27, 58.64, 54.08, 38.19, 32.36, 31.75, 30.20, 30.09, 29.76, 26.10, 23.13, 14.58.

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*, 1789-2790.

3. a) Chini. M.; Crotti, P.; Macchia, F. *Tetrahedron Lett.* **1990**, *31*, 4661-4664; b) *J.Org.Chem.* **1991**, *56*, 5939-5944; 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. The 2-octyl oxetane (**2**), not previously described, was prepared (80% overall yield) by methylene transfer of dimethyloxosulfonium methylide to 1-decene oxide in accordance with the method of Okuma *et al.*[6] Oxetane **2** was purified by filtering on silica gel column and eluting with hexane. Oxetane **2**, liquid: ^{1}H NMR δ 4.81 (5 lines, 1H, *J*=6.9 Hz), 4.66 (tt, 1H, *J*=8.0 Hz), 4.49 (tt, 1H, *J*=5.7 Hz), 2.56-2.72 (m, 1H), 2.23-2.40 (m, 1H), 1.57-1.92 (m, 1H), 1,20-1.38 (m ,14H), 0.87 (t, 3H, *J*=6.5 Hz). ^{13}C NMR δ 83.36, 68.53, 38.60, 32.43, 30.14, 30.08, 29.80, 28.23, 24.60, 23.21, 14.61.

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

7. Lipshutz, B.H.; Pegram, J.J.; Morey, M.C. *Tetrahedron Lett.* **1981**, *22*, 4603-4606.

8. Smith, D.A.; Houk, K.N. *Tetrahedron Lett.* **1991**, *32*, 1549-1552.

9. Goldberg, D.S.; Whitmore, W.F. *J.Am.Chem.Soc.* **1937**, *59*, 2280-2283.

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

(*Received in UK* 20 *October* 1993; *revised* 23 *November* 1993; *accepted* 26 *November* 1993)