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Lithium Trifluoromethanesulfonate-catalysed Aminolysis of Oxiranes

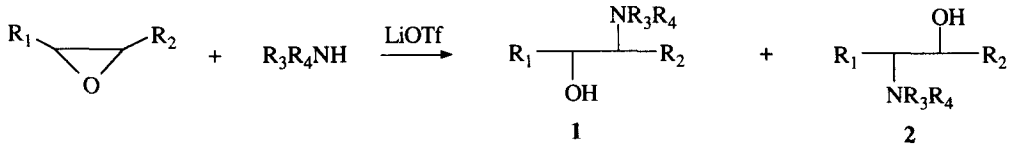
Jacques Augé* and Frédéric Leroy

Département de Chimie, Laboratoire des Réactivités Spécifiques,
Université de Cergy-Pontoise, 95031 Cergy-Pontoise Cedex, France

Abstract: The aminolysis of oxiranes was found to be catalysed by lithium trifluoromethanesulfonate in acetonitrile solutions. This salt turned out to be an excellent substitute for the unsafe lithium perchlorate. Copyright © 1996 Published by Elsevier Science Ltd

The aminolysis of oxiranes is a classical route to β-amino alcohols, an important class of compounds with pharmaceutical and biological properties.[1] Unfortunately, this ring-opening requires high temperatures or prolonged reaction times. A remarkable improvement was recently accomplished when metal salts, particularly lithium perchlorate, were recommended as promotors.[2]

This letter deals with the use of lithium trifluoromethanesulfonate (lithium triflate) as a surrogate of lithium perchlorate, which has been responsible for so many accidents, sometimes lethal.[3] Lithium triflate, easily prepared from an equimolecular mixture of lithium hydroxide and trifluoromethanesulfonic acid exhibits high conductivity, making it useful electrolyte in non-aqueous electrochemical cells.[4] By contrast, its use in organic chemistry was scarcely mentioned in the recent years.[5]



1 **2**

For the sake of comparison we first investigated the aminolysis of styrene oxide under the conditions described by Crotti.[6] When the reaction of diethylamine with styrene oxide was conducted in the presence of two equivalents of lithium perchlorate or zinc triflate, the conversion went up to 92% after 0.5 h.[7] With two equivalents of lithium triflate the reaction was almost complete (98%) after 20 min at room temperature. This encouraging result prompts us to further investigate the use of lithium triflate as catalyst. The table outlines reactions between various oxiranes and amines carried out mostly in acetonitrile, as recommended in the lithium perchlorate-promoted aminolysis of oxiranes. Acetone and tetrahydrofuran gave however similar results (compare runs 3-5) in terms of reaction rate. Dichloromethane or toluene poorly dissolved this lithium salt and the aminolysis was then investigated at low concentration, where the salt was completely soluble. Although lithium triflate is insoluble in toluene, the mixture containing the salt and the oxirane was made homogeneous as soon as morpholine was added. Since the rate of the aminolysis of oxiranes notably

increased with the amount of lithium triflate (see for example runs 6 and 7), acetonitrile which easily dissolved this salt appeared to us as an excellent solvent. With non aromatic oxiranes, the primary carbon is much more reactive towards amines than the secondary one; as usual in basic or neutral medium, we observed the "normal opening" so that the reaction is totally regioselective. With aromatic oxiranes the regioselectivity is lower, but the attack on the less hindered side of the epoxide remains preponderant.

Table: Aminolysis of Oxiranes[a]

Run	Oxirane R_1 , R_2	Amine[b]	Catalyst (eq)	Solvent	Yield[c]	Time (h)	Ratio[d] **1 / 2**
1	Ph , H	morpholine	LiOTf (0.05)	$PhCH_3$	79	24	2.8
2	"	"	LiOTf (0.1)	CH_2Cl_2	80	12	1.2
3	"	"	LiOTf (0.5)	CH_3CN	88	1	1.4
4	"	"	"	THF	85	1	1.2
5	"	"	"	$(CH_3)_2CO$	89	1	1.6
6	"	Et_2NH	"	CH_3CN	87	11.5	2.8
7	"	"	LiOTf (2)	"	98	0.33	2.8
8	"	"	$LiClO_4$ (0.5)	"	96[e]	0.5	1.3
9	"	"	$Zn(OTf)_2$	"	92[e]	0.5	0.8
10	"	"	$SmI_2(THF)_2$	CH_2Cl_2	63[f]	18	> 100
11	"	$PhCH_2NH_2$	LiOTf (0.5)	CH_3CN	83	3.5	1.5
12	"	$tBuNH_2$	"	"	80 (81°C)	1.5	2.6
13	CH_3CH_2 , H	morpholine	"	"	83	4	> 100
14	"	$PhCH_2NH_2$	"	"	83	18	g
15	"	$tBuNH_2$	"	"	71	21	> 100
16	$-(CH_2)_4-$	$PhCH_2NH_2$	"	"	86 (81°C)	3	
17	"	"	LiOTf (2)	"	84	9	
18	"	"	$Yb(OTf)_3$	THF	86 (66°C)[h]	10	
19	"	morpholine	LiOTf (2)	CH_3CN	92	8	
20	"	Et_2NH	"	"	80	48	
21	"	$tBuNH_2$	"	"	79	48	

[a]With the only exception of runs 12 and 16 the reactions were performed at room temperature; all the compounds were identified by ^1H- and ^{13}C NMR spectroscopy. [b]In our experiments, the concentrations of oxirane and amine are 4 and 4.2 M respectively except for the run 7 ([styrene oxide] = 2.5 M; [diethylamine] = 5 M). [c]Isolated yield (%). [d]The ratio **1/2** was determined by ^1H-NMR spectroscopy. [e]See ref 6. [f]See ref 7. [g]With 1.2 equivalent of benzylamine, the reaction led to 75% of the monoadduct and 25% of the bisadduct $(CH_3CH_2CHOH)_2$-NCH_2Ph; the amount of the bisadduct was reduced (14%) when using 2 equivalents of amine. [h]See ref 8.

Typical procedure for the preparation of an β-amino alcohol

A solution of ethyl epoxide (4 mmol) in acetonitrile (1 ml) was treated with anhydrous lithium trifluoromethanesulfonate (2 mmol). After stirring the mixture for 15 minutes, morpholine (4.2 mmol) was added and the solution was allowed to react for 4 hours. After the end of the reaction, a saturated solution of ammonium chloride was added and the adduct was extracted with ethyl acetate. The organic extracts were dried, filtered off and then evaporated. A flash chromatography yielded 2-hydroxybutylmorpholine (83%) as a pure compound.

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