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An Efficient Synthesis of Oxiranyl Oxazolines and Elaboration to Acyl Oxiranes

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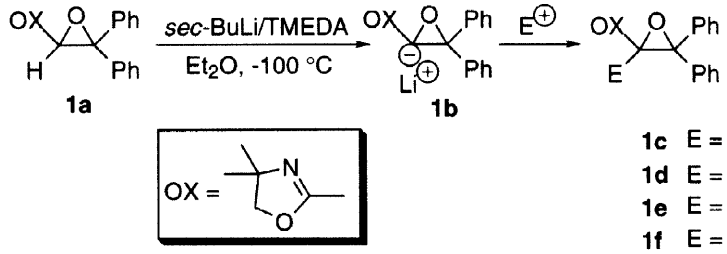
Abstract: Deprotonation of oxazolinyl oxirane **1a** with *sec*-BuLi/TMEDA at -100 °C in Et_2O furnished oxazolinyl oxiranyllithium **1b**, which could be trapped with electrophiles to give oxiranes **1c-g**. The reaction of **1b** with aldehydes produced diastereomers *syn* (**2a-d**) and *anti* (**3a-d**). Oxiranyllithium **1i** from *trans*-1-oxazolinyl-2-*p*-tolyl epoxy ethane **1h** was found to be configurationally stable while oxiranyllithium **1l**, generated from the *cis* isomer **1k**, was not. Oxazolinyl epoxides **1d**, **1j** and **1m** could be deblocked to acyl oxiranes **5a-e** through oxazolidines **4a-e**.

Keywords: deprotonation; oxiranyl oxazoline; oxazolinyl oxiranyllithium; oxazolidine; acyl oxirane

Oxiranyl oxazolines are particularly attractive intermediates in synthetic organic chemistry. Indeed, the deblocking reaction of the oxazolinyl moiety would lead to acyl oxiranes, which can be converted into a variety of useful compounds [1-9], while the elaboration of the oxiranyl group would provide oxazolines suitably functionalized in the side chain. In spite of such a synthetic potential, routes to oxiranyl oxazolines are quite limited and mainly based on the Darzens reaction of certain halogenoalkyl oxazolines [10-12].

As part of our work concerning the chemistry of 1,3-azoles [13-15], we have developed an efficient synthetic procedure to oxiranyl oxazolines based on the deprotonation-alkylation sequence of simpler and easily available oxiranyl oxazolines. Such a strategy relies on the presence in the epoxide moiety of the oxazolinyl group which is capable of stabilizing the oxiranyllithium generated by deprotonation [16]. Some oxiranyllithiums have been reported as synthetically useful in the functionalization of oxiranes [17-23]. The advantage of such a procedure is that a variety of functionalized oxiranyl oxazolines can be prepared from a common starting material.

Scheme 1



1c E = Me_3Si (95 %)
1d E = Me (62 %)
1e E = CH_2=$CHCH_2$ (76 %)
1f E = $(CH_3)_2COH$ (67 %)
1g El = $(CH_2)_5COH$ (79 %)

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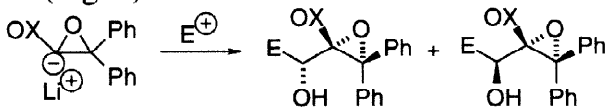
When treated with *sec*-butyllithium/TMEDA in Et_2O at -100 °C, the oxiranyl oxazoline **1a**, prepared from 4,4-dimethyl-2-chloromethyl-2-oxazoline as described in [11], underwent rapid lithiation which was complete in a few minutes to generate **1b**, which was stable and could be trapped with Me_3SiCl to give **1c**. The alkylation of **1b** with MeI and allyl bromide led to compounds **1d** and **1e**, respectively, and the reaction with acetone and cyclohexanone afforded epoxy alcohols **1f** and **1g**, respectively (Scheme 1).

The coupling reaction of **1b** with acetaldehyde furnished diastereomeric hydroxyethyl oxazolinyl epoxides **2a** and **3a**, which could be easily separated by column chromatography. The first eluted isomer **2a**, which was assigned the *syn* configuration (see below), had a less polar character than the *anti* isomer **3a** (ΔR_f=0.37 on TLC). This could be ascribed to the intramolecular hydrogen-bonding between the OH and the epoxy group [24]. The *syn* isomer **2a** (IR $5.0 \cdot 10^{-3}$ M in CCl_4, broad strongly bonded OH band at 3411 cm^{-1}, no frequence shift at higher concentrations and in KBr) should exist intramolecularly associated while the hydrogen-bonded conformation of the *anti* isomer **3a** (sharp band at 3616 cm^{-1} to be ascribed to a free OH [24, 25], shifted at 3236 cm^{-1} in KBr) should be disfavoured for experiencing a higher steric compression (Fig. 1).

Scheme 2

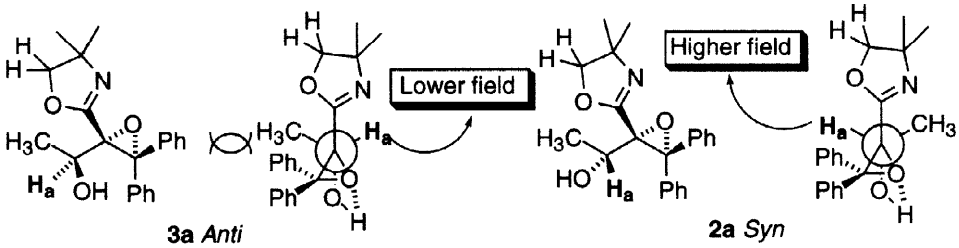


1b **2a-d** *Syn* **3a-d** *Anti*

			Overall yield %	d.r. *Syn/Anti*[a]
2a	E = Me	**3a**	68 %	1.3/1
2b	E = $(Me)_2CH$	**3b**	65 %	1.2/1
2c	E = C_6H_5	**3c**	83 %	1/1
2d	E = *p*-Tolyl	**3d**	70 %	1.8/1

[a]Diastereomeric ratio, determined after column chromatography

Figure 1

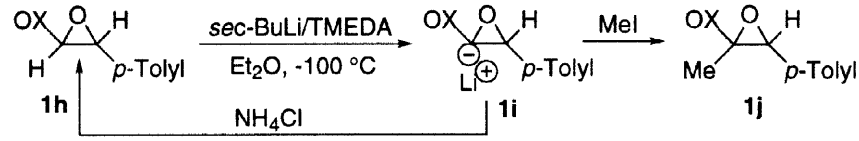


3a *Anti* **2a** *Syn*

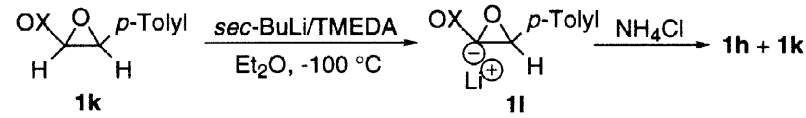
Support to the above considerations came from the ^{1}H-NMR chemical shift analysis. In the case of the *syn* isomer, which is probably intramolecularly hydrogen bonded, the hydroxyl proton resonance was strongly downfield (4.5 δ *versus* 2.4-2.7 δ for the *anti* isomer) [26]. On the other hand, the characteristic H_a proton (Fig. 1) of the *anti* isomer **3a** absorbs at lower field than that of the *syn* isomer **2a**, as reported for similar epoxy alcohols [27]. Moreover, the two geminal protons of the oxazoline ring showed a chemical shift difference in hertz (Δν) much larger than the coupling constant ($\Delta\nu/J > 10$, AX system); the *anti* isomer showed two doublets with a $\Delta\nu/J < 10$ (AB system). This probably could be due to the anisotropy of the methyl group on the same side of the two methylene protons that creates different magnetic environments for them (Fig. 1).

Comparable results were obtained when **1b** was treated with other aldehydes. Indeed, the reaction with isobutyraldehyde, benzaldehyde and *p*-tolualdehyde gave the diastereomeric epoxy alcohols **2b-d** and **3b-d** (Scheme 2).

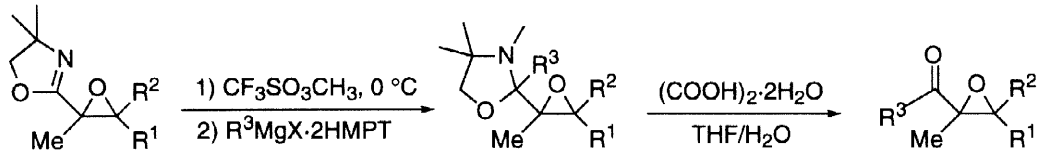
It was interesting to observe that the deprotonation of *trans*-1-oxazolinyl-2-*p*-tolyl epoxyethane **1h** gave the oxiranyllithium **1i** which was configurationally stable for at least 1 h at -100 °C. Starting *trans* epoxide **1h** was quantitatively recovered upon quenching of **1i** with NH_4Cl and the reaction with MeI gave the *E* oxirane **1j** (93 % yield) [28]. In contrast, lithiated intermediate **1l** from the *cis* isomer **1k** furnished a mixture of the isomers **1h** and **1k** upon acidic quenching. This clearly indicates that lithiated intermediate generated from **1k** is configurationally unstable. Such a different configurational stability has been reported for other oxiranyl anions [16-17] (Scheme 3).



Scheme 3



The oxazolinyl oxiranes above could be deblocked to acyl oxiranes. Indeed, treatment of **1d** first with CF_3SO_3Me and then with PhMgBr·2HMPT afforded oxazolidine **4a** (diasteromeric mixture) that could be elaborated to benzoyl oxirane **5a** upon hydrolysis with aq. oxalic acid. Similarly, methylation of **1d** with CF_3SO_3Me followed by the addition of MeMgBr·2HMPT gave oxazolidine **4b** (diastereomers) which was subsequently deblocked to acetyl oxirane **5b**. The reaction of *N*-methylated **1d** with cyclohexylMgCl·2HMPT led to oxazolidine **4c** (substantially one diastereomer) which was converted into formyl oxirane **5c**. The methylation-addition-deblocking sequence applied to oxazolines **1j** and **1m** [28] afforded acetyl oxiranes **5d** and **5e**, respectively, going through oxazolidines **4d** and **4e**. In both cases, the stereochemistry at the oxirane moiety was completely preserved (Scheme 4).



Scheme 4

	4a	$R^1 = R^2 = R^3 = Ph$	(77 %, d.r.1.5/1)	**5a**	$R^1 = R^2 = R^3 = Ph$ (69 %)
1d $R^1 = R^2 = Ph$	**4b**	$R^1 = R^2 = Ph$; $R^3 = Me$	(95 %, d.r. 4/1)	**5b**	$R^1 = R^2 = Ph$; $R^3 = Me$ (77 %)[a]
1j $R^1 = p$-Tolyl; $R^2 = H$	**4c**	$R^1 = R^2 = Ph$; $R^3 = H$	(51 %, d.r. ≥95/5)	**5c**	$R^1 = R^2 = Ph$; $R^3 = H$ (77 %)
1m $R^1 = H$; $R^2 = p$-Tolyl	**4d**	$R^1 = p$-Tolyl; $R^2 = H$; $R^3 = Me$	(95 %, d.r. 4/1)	**5d**	$R^1 = p$-Tolyl; $R^2 = H$; $R^3 = Me$ (40 %)
	4e	$R^1 = H$; $R^2 = p$-Tolyl; $R^3 = Me$	(78 %, d.r. ≥95/5)	**5e**	$R^1 = H$; $R^2 = p$-Tolyl; $R^3 = Me$ (40 %)

[a]Yield determined on the crude reaction mixture by ^1H NMR [29].

In conclusion, in this paper we show how variously substituted oxazolinyl oxiranes can be efficiently prepared upon deprotonation of their simpler parent epoxides and the resulting oxazolinyl oxiranes can be deblocked to acyl oxiranes. More work is in progress to apply this methodology to an asymmetric synthesis of acyl epoxides.

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Typical Procedure. The conversion **1a ->1d ->4a ->5a** is described as an example. To a solution of **1a** (1 mmol) and TMEDA (1.2 mmol) in 15 mL of dry Et_2O, under N_2 at -100 °C, 1.26 M *sec*-BuLi(1.2 mmol) was added dropwise. The resulting yellow solution of the putative oxiranyl anion **1b** was stirred at -100 °C for 2 h. MeI (1.3 mmol) in 3 mL of Et_2O was then added slowly and the mixture stirred at -100 °C for an additional hour. Then the reaction mixture was allowed to warm to r.t., quenched with sat. aq. NH_4Cl and extracted with Et_2O (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel; petroleum ether/Et_2O 8/2) to give **1d** (m.p. 103-104 °C from hexane, 62 % yield). To a solution of **1d** (1 mmol) in dry THF (2 mL), under N_2 at 0 °C, methyl triflate (1.5 mmol) was added directly. After 30 min, to the resulting oxazolinium salt a complex between PhMgBr (3.0 M in Et_2O, 1.1 mmol) and HMPT (2.2 mmol) in THF (1.5 mL) was added dropwise at r.t. The reaction mixture was stirred for 50 min, then quenched with sat. aq. NH_4Cl and extracted with Et_2O (3 x 10 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography (8/2 petroleum ether/Et_2O) to give **4a** (waxy solid, 77%) as an inseparable 1.5:1 mixture of diastereomers (checked by ^1H NMR and ^{13}C NMR analyses). Oxazolidine **4a** was deblocked to benzoyl oxirane **5a** (oil, 69 %) according to the procedure reported in Ref. [11]. All new compounds showed satisfactory IR, MS, ^1H NMR, ^{13}C NMR data and elemental analyses.

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