Pergamon

Tetrahedron Letters, Vol. 37, No. 27, pp. 4781-4784, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)00934-3

AN OXAZOLINE-MEDIATED SYNTHESIS OF FORMYL EPOXIDES

Saverio Florio,* Vito Capriati, and Renzo Luisi

Dipartimento Farmaco-Chimico, Università di Bari, Via Orabona 4, 70125 - Bari, Italy

Abstract: α,β-epoxy aldehydes have been prepared by deblocking of oxazolinyl oxiranes, which in turn have been synthesized on treatment of 4,4-dimethyloxazolinylchloromethyllithium with aldehydes.

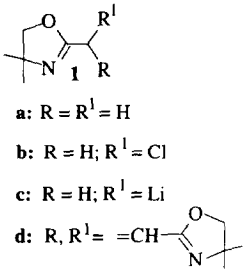
The epoxide functionality, which affords chemists an opportunity to manipulate two adjacent functionalized carbons has been demonstrated to be a versatile and useful moiety for organic synthesis. Among epoxides, α,β-epoxy aldehydes are particularly attractive substrates. Indeed, they are useful intermediates for the preparation of epoxy vinyl iodides,[1] α,β-unsaturated aldehydes,[2] functionalized butyrolactones and furanones,[3] chiral α,β-epoxy imines, useful precursors for the asymmetric synthesis of β-lactam antibiotics,[4] β,γ-epoxy alcohols[5] and chiral, non racemic,1,2-cyclohexanediols.[6]

α,β-Epoxy aldehydes, mainly β-alkyl derivatives, are currently prepared by oxidation of the corresponding epoxy alcohols,[7] even in high enantiomeric[8] and diastereomeric excess.[9] An alternative route relies on the oxidation of the corresponding α,β-unsaturated aldehydes.[10] The reduction of α,β-epoxy amides has also been reported.[11]

As far as we know, there is no report on the synthesis of α,β-epoxy aldehydes based on the elaboration of masked formyl groups present on the oxiranyl ring. We have recently disclosed that certain α-chloroheteroarylalkyllithiums behave as Darzens reagents adding to carbonyl compounds and imines to give heteroaryl oxiranes and aziridines.[12] We envisioned employing the above oxiranes as precursors of functionalized epoxides in the event that the deblocking reaction of the heteroaryl moiety could be carried out, leaving the oxiranyl group unaffected.

We report in this paper the first synthesis of α,β-epoxy aldehydes which is based on the preparation of oxazolinyl oxiranes and subsequent deblocking of the oxazolinyl moiety.

2-Cloromethyl-4,4-dimethyloxazoline **1b** was prepared by chlorination of 2,4,4-trimethyloxazoline **1a** with *tert*-butyl hypochorite. Lithiation of **1b** with lithium diisopropyl amide (LDA) at -78 °C gave oxazolinylchloromethyllithium **1c**, which is extremely reactive as it undergoes a very fast homocoupling reaction to give the dioxazolinyl ethene **1d**. However, under suitable conditions, **1c** could be generated and trapped with electrophiles. Indeed, when a solution of **1b** (1 equiv.) and benzophenone (1 equiv.) was added to a solution of LDA at -100 °C, the chlorohydrin **2a** formed in a very good yield. Treatment of **2a** with NaOH in isopropanol afforded the oxazolinyl epoxide **3a** quantitatively. We were happy to find that epoxide **3a** could be converted in very good yield to formyl epoxide **4a**, upon methylation with methyl triflate, reduction with $NaBH_4$ and deblocking with oxalic acid, according to the Meyers procedure.[13] Similarly, **1c** reacted cleanly with adamantanone to give the chlorohydrin **2b**, which was subsequently cyclized to the oxazolinyl epoxide **3b**, the deblocking of which afforded the formyl epoxide **4b**. Comparable results were obtained with other ketones such as acetone and cyclohexanone (See Table).



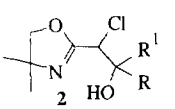
1

a: R = R^1 = H

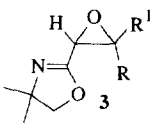
b: R = H; R^1 = Cl

c: R = H; R^1 = Li

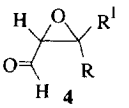
d: R, R^1 = =CH–



2



3



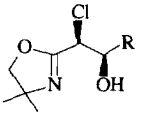
4

a: R, R^1 = Ph

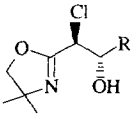
b: R, R^1 =

c: R = R^1 =

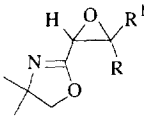
d: R = R^1 = Me



5



6



7a: R = Ph; R^1 = H

8a: R = H; R^1 = Ph

7b: R = p-ClPh; R^1 = H

8b: R = H; R^1 = p-ClPh

7c: R = p-MePh; R^1 = H

8c: R = H; R^1 = p-MePh

7d: R = p-OMePh; R^1 = H

8d: R = H; R^1 = p-OMePh

7e: R = o-OMePh; R^1 = H

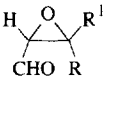
8e: R = H; R^1 = o-OMePh

7f: R = p-CF_3Ph; R^1 = H

8f: R = H; R^1 = p-CF_3Ph

7g: R = o-ClPh; R^1 = H

8g: R = H; R^1 = o-ClPh



9a: R = Ph; R^1 = H

10a: R = H; R^1 = Ph

9b: R = p-ClPh; R^1 = H

10b: R = H; R^1 = p-ClPh

9c: R = p-MePh; R^1 = H

10c: R = H; R^1 = p-MePh

9f: R = o-CF_3Ph; R^1 = H

9g: R = o-ClPh; R^1 = H

10g: R = H; R^1 = o-ClPh

a : R = Ph

b: R = p-ClPh

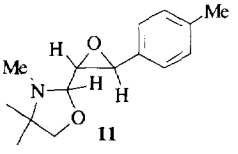
c: R = p-MePh

d: R = p-OMePh

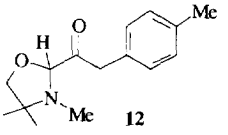
e: R = o-OMePh

f: R = p-CF_3Ph

g: R = o-ClPh



11



12

The addition of a solution of **1b** and benzaldehyde to a solution of LDA led to the diastereomeric chlorohydrins *syn* and *anti* **5a** and **6a**. Their mixture was, then, cyclized to the corresponding epoxides **7a** and **8a** (NaOH/ i-PrOH). The epoxides **7a** and **8a**, after chromatographic separation, were converted into formyl epoxides **9a** and **10a** respectively, by following the Meyers procedure. Comparable results were obtained when *p*-chlorobenzaldehyde was used as the electrophile to give the diastereomeric chlorohydrins **5b** and **6b**; cyclization gave oxazolinyl oxiranes **7b** and **8b**, and deblocking afforded formyl epoxides **9b** and **10b** (See Table). In the case of *p*-tolualdehyde we did obtain the chlorohydrins **5c** and **6c** and the oxiranes **7c** and **8c**, but only the *cis* epoxide **7c** could be deblocked to the formyl epoxide **9c**. In contrast, the attempted conversion of the *trans* isomer **8c** into the expected oxirane **10c** failed furnishing, instead, the oxazolidinyl ketone **12**, probably derived from the oxazolidinyl epoxide **11** after $NaBH_4$-promoted isomerization. The sodium borohydride promoted rearrangement of aryl epoxides has precedents.[14] The reaction of **1c** with *p*-anisaldehyde did provide the halohydrins **5d** and

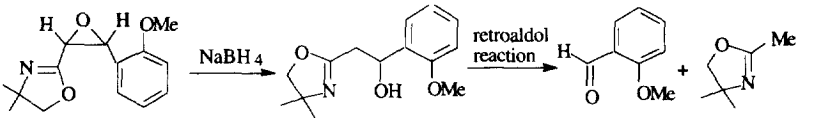
6d and then the oxazolinyl epoxides **7d** and **8d**. Comparable results were obtained in the reaction of **1c** with *o*-anisaldehyde which led to chlorohydrins **5e** and **6e** and then oxazolinyl epoxides **7e** and **8e**.The conversion of the epoxides **7d**, **8d** and **8e** into the expected formyl oxiranes failed leading to a mixture of unidentified products.[15]

Table. Reaction of oxazolinylchloromethyillithium **1c** with carbonyl compounds in THF at -100°C

Carbonyl Compound	Chlorohydrins[a] (% yield)	Oxazolinyl epoxides[b] (% yield)	Formyl epoxide (% yield)[c]
Ph_2CO	**2a** (78)	**3a** (100)	**4a** (82)
Adamantanone	**2b** (87)	**3b** (>95)	**4b** (80)
Cyclohexanone	**2c** (86)	**3c** (>95)	**4c** (84)
Acetone	**2d** (84)	**3d** (>95)	**4d**
PhCHO	**5a** + **6a** (50)	**7a** (49) **8a** (71)	**9a** (74) **10a** (56)
p-ClC_6H_4CHO	**5b** + **6b** (42)	**7b** (71) **8b** (99)	**9b** (73) **10b** (60)
p-MeC_6H_4CHO	**5c** + **6c** (52)	**7c** (82) **8c** (92)	**9c** (80)
p-$OMeC_6H_4CHO$	**5d** + **6d** (74)	**7d** (50) **8d** (70)	
o-$OMeC_6H_4CHO$	**5e** + **6e** (65)	**7e** (20) **8e** (100)	
p-$CF_3C_6H_4CHO$	**5f** + **6f** (50)	**7f** (66) **8f** (80)	**9f** (72)
o-ClC_6H_4CHO	**5g** + **6g** (65)	**7g** (70) **8g** (86)	**9g** (68) **10g** (76)

[a] The diastereomeric chlorohydrines formed in all cases in a 1 to 1 ratio as ascertained by ^1H NMR. [b] The *cis* and *trans* oxazolinyl epoxides were separated by column chromatography and yields refer to isolated purified compounds.[c]All new compounds showed consistent ^1H NMR, ^{13}C NMR, GC-MS, FTIR data and satisfactory analytical data.

Epoxide **7e** has been found to decompose in the presence of $NaBH_4$ to give the starting aldehyde, the formation of which might be explaned by assumption that $NaBH_4$ causes the ring opening of the epoxide, followed by a retroaldol reaction of the resulting alcohol.



Typical procedure: the reaction of **1c** with benzophenone is here described as an example. A solution of **1b** (1.0 g, 4.06 mmol) and benzophenone (5.68 mmol) in 6 mL of THF at -100 °C under nitrogen atmosphere was added dropwise to a solution of LDA (5.68 mmol) in 6 mL of THF. The reaction mixture was held at -100 °C for 4h, then allowed to warm to -40 °C and finally quenched with aqueous sat. solution of NH_4Cl. Extraction with Et_2O (3 x 30 mL), drying over anhydrous Na_2SO_4 and evaporation of the solvent under reduced pressure gave chlorohydrin **2a** (78 % yield),[16] which was treated with 1% NaOH (15 mL) in ^iPrOH (15 mL) with stirring. After 5 min, the solution was poured into H_2O and exctracted with Et_2O (3 x 30 mL). The crude product was purified by flash chromatography (silica gel, petroleum ether / Et_2O 1:1 as the eluent) to give the oxirane **3a** (oil, 930 mg, quantitative yield from **2a**). Deblocking of **3a**: to a solution of **3a** (0.98 mmol) in dry CH_2Cl_2 (4 mL)

was added at 0 °C, under N_2 and stirring, $CF_3SO_3CH_3$ (1.37 mmol). After 30 min, a solution of $NaBH_4$ (0.61 mmol) in dry THF (4 mL) and dry EtOH (1 mL) was added dropwise at -80 °C. The mixture was allowed to warm to -40 °C and quenched with a sat. solution of NH_4Cl. Usual work up gave a residue which was treated under stirring with a solution of oxalic acid (0.56 mmol) in THF (4 mL) and H_2O (1 mL). After 3h, usual work up and column chromatogrphy on silica gel (petroleum ether /Et_2O 9:1) gave 82% of 3,3-diphenyloxirane carboxaldehyde **4a** as a white waxy solid (mp 70-72 °C).

In conclusion, in this paper we have disclosed a new facet of the reactivity in the α-position of the oxazolinyl system. We have also shown how such a reactivity can be exploited for the preparation of oxazolinyl epoxides and how the oxazolinyl part of the latter can be deblocked without affecting the oxirane functionality to give formyl epoxides. Work is underway to make the above route to oxazolinyl and formyl epoxides enantioselective.

Acknowledgement: We thank the Italian Ministero dell'Università e della Ricerca Scientifica e Tecnologica (MURST) and CNR for financial support of this research.

References

1. Scheeren, J. W.; Lange, J. *Tetrahedron Lett.* **1984**, *25*, 1609.
2. Evans, D. A.; Williams, J. M. *Tetrahedron Lett.* **1988**, *29*, 5065.
3. Takeda, Y.; Matsumoto, T.; Sato, F. *J. Org. Chem.* **1986**, *51*, 4728; Howe, G. P.; Wans, S.; Procter, G. *Tetrahedron Lett.* **1987**, *28*, 2629.
4. Molander, J. A.; Shubert, D. C. *J. Am. Chem. Soc.* **1987**, *109*, 576.
5. Parikh, J. R.; von Doering, W. E. *J. Am. Chem. Soc.* **1967**, *89*, 5505.
6. Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165.
7. Tomioka, H.; Suzuki, T.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1982**, *23*, 3387; Narura, A. S. *ibid.* **1982**, *23*, 5579.
8. Payne, G. B. *J. Org. Chem.* **1961**, *26*, 250; Chapman, O. L.; Hess, T. C. *J. Org. Chem.* **1979**, *44*, 962.
9. Bestman, H. J.; Rippel, H. C.; Dostalek, R. *Tetrahedron Lett.* **1989**, *30*, 5261.
10. Mandal, A. K.; Mahajan, S. W. *Tetrahedron* **1988**, *44*, 2293.
11. Hayashi, M.; Terashima, S.; Koga, K. *Tetrahedron* **1981**, *37*, 2797.
12. Florio, S.; Troisi, L. *Tetrahedron Lett.* **1992**, *33*, 7953; Florio, S.; Troisi, L. *Tetrahedron Lett.* **1994**, *35*, 3175; Florio, S.; Capriati, V.; Troisi, L. *J. Org. Chem.*, **1995**, *60*, 2279; Florio, S.; Troisi, L. *J. Org. Chem.* **1996**, in press.
13. Meyers, A. I.; Shipman, M. *J. Org. Chem.* **1991**, *56*, 7098.
14. Wu, S.; Zhang, Y.; Wang, W. *Gazz. Chim. Ital.* **1991**, *121*, 519.
15. The presence of the electron-donating group -OMe in the benzene ring of the epoxides **7d**, **8d** and **8e** might be responsible for this failure.
16. We had substantial reduction of the used aldehyde to the corresponding benzylic alcohol in all the reactions in which the solution of the aldehyde and **1b** was added to the solution of LDA. The reduction of aldehydes by LDA is well documented. See Majeski, M.; Cleave, D. M. *J. Organomet. Chem.* **1994**, *470*, 1.

(*Received in UK* 10 *April* 1996; *revised* 14 *May* 1996; *accepted* 17 *May* 1996)