Pergamon

Tetrahedron Letters 43 (2002) 7739–7742

TETRAHEDRON LETTERS

An unexpected base-promoted isomerization of oxazolinylaryl oxiranes: synthesis of oxazolinylaryl alkanones

Filippo M. Perna, Vito Capriati, Saverio Florio* and Renzo Luisi

C.N.R., Istituto di Chimica dei Composti OrganoMetallici 'ICCOM', Sezione di Bari, DipartimentoFarmaco-Chimico, Università di Bari, Via E. Orabona 4, I-70126 Bari, Italy

Received 1 August 2002; revised 28 August 2002; accepted 29 August 2002

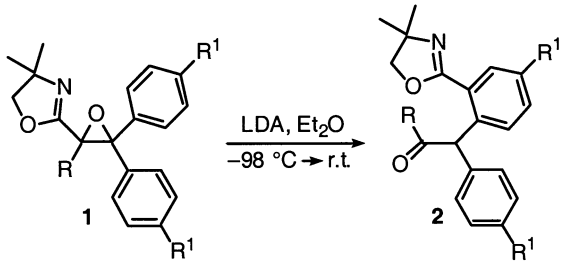
Abstract—Aryl substituted oxazolinyloxiranes **1a–g** have been found to undergo smooth isomerization into oxazolinyl substituted aryl alkanones **2a–g** upon treatment with LDA in Et_2O at –98°C, warming to room temperature and quenching with satd aq. NH_4Cl. A mechanism involving an oxazoline-assisted *ortho* lithiation of the aryl group (*cis* to the oxazoline system) of oxiranes **1** is proposed. © 2002 Published by Elsevier Science Ltd.

Oxiranes are versatile synthetic intermediates.[1] Their reactions generally involve cleavage of the strained oxirane ring and include a wide range of nucleophilic ring openings and acid- and base-induced isomerizations.[2] The chemistry of oxiranes under basic conditions has been extensively investigated, including: (a) α-deprotonation to give an oxiranyl anion, which, in turn, can be captured by an electrophile, dimerize to generate alkenediols, ring open to give an enolate or a carbene, or undergo a C–H insertion reaction;[3] and (b) β-elimination to furnish an allylic alcohol.[4] In previous papers we have reported that oxiranes bearing a stabilizing group on the oxirane ring can be easily deprotonated with lithium bases and resulting lithiated species could isomerize to acyloxazolines in the absence of external electrophiles[5] or be trapped with electrophiles yielding more functionalized oxiranes.[6] Quite recently, such an oxiranyl anion methodology has been successfully applied to the synthesis of highly enantioenriched styrene oxides[7] and epoxylactones.[8] In connection with such studies, we have also found that alkyl-substituted oxazolinyloxiranes, in which no oxirane ring hydrogen can be abstracted, are very prone to undergo β-elimination to give oxazolinyl allylic alcohols.[9]

In the present paper we report a novel base-mediated isomerization reaction of oxazolinylaryl oxiranes which begins with an oxazoline-assisted *ortho* lithiation. Treatment of ethyl oxazolinyl diphenyl oxirane **1a** (Table 1), easily available from lithiated α-(1-chloropropyl)-4,4-dimethyl-2-oxazoline and benzophenone as similarly reported,[10] with 1.5 equiv. of LDA in Et_2O at –98°C followed by warming to room temperature afforded a very good yield of a new compound which was assigned the structure of **2a** on the basis of spectroscopic data including ^1H and ^{13}C NMR, IR, GC–MS and elemental analysis.[11]

On the other hand, lithiation of methyl oxirane **1b** under the same experimental conditions provided only a small amount (about 10% yield) of ketone **2b** beside

Table 1. Synthesis of oxazolinylaryl alkanones **2**



Compound	R	R^1	Yield (%)[a]
a	Et	H	85
b	Me	H	10[b]
c	Et	Cl	95
d	Et	F	79
e	Et	Me	85
f	Et	OMe	88
g	*n*-Pr	H	85

[a] Isolated yield.

[b] The main reaction product was allylic alcohol **3**.

* Corresponding author. Tel.: +39.080.5442749; fax: +39.080.5442231; e-mail: florio@farmchim.uniba.it

0040-4039/02/$ - see front matter © 2002 Published by Elsevier Science Ltd.
PII: S0040-4039(02)01837-3

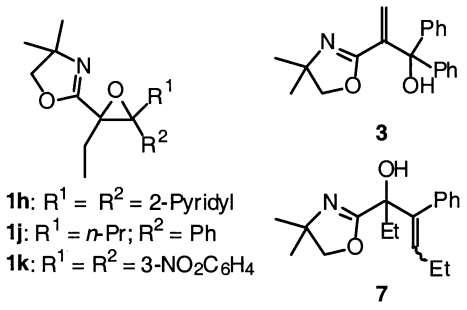


Chart 1.

the allylic alcohol **3** (75% yield) (Chart 1). A plausible explanation for the formation of **2a** is shown in Scheme 1. Lithiation of **1a** would generate the seven-membered chelated *ortho* lithiated intermediate **4**,[12] which would then evolve by an intramolecular addition to the C–N double bond of the oxazoline ring thus giving the oxazolidinyl derivative **5**. Isomerization involving reformation of the oxazoline system and opening of the oxirane ring would lead to the enolate **6** and then to **2a**. Attempts, however, to trap intermediate **4** or **5** have failed so far. A concerted, synchronous mechanism might be operating in the **1a**→**2a** conversion. The different behavior of **1a** and **1b** towards LDA could be explained by the fact that usually abstraction of protons from a methyl proceeds faster than from a methylene group for steric and electronic effects, so that β-elimination prevails in the case of **1b** affording allylic alcohol **3**. The use of LDA as the base is crucial for the **1a**→**2a** transformation. Indeed, no such a rearrangement occurred when $KN(SiMe_3)_2$ or *s*-BuLi with or without TMEDA were used for the metalation reaction.

The tendency of oxirane **1a** to isomerize to the ketone **2a** upon treatment with LDA is common to other alkyl aryl oxazolinyloxiranes. As shown in Table 1, in fact, oxiranes **1c**–**g** converted into ketones **2c**–**g** in very good yields upon treatment with LDA. A substituent effect was observed: oxiranes bearing electron-withdrawing groups in the aryl group isomerized faster than those with electron-donating groups. No such base-promoted isomerization occurred when ethyl oxazolinyl bis(2-pyridyl)oxirane **1h** was reacted with LDA. Such a failure is, reasonably, to be ascribed to the fact that the more acidic hydrogen in the pyridine ring (*ortho* to the nitrogen) is too far from the oxazoline group and the resulting lithiated intermediate cannot cyclize on the C–N double bond of the oxazoline ring. Several unidentified compounds formed when **1h** was treated with 1.5 equiv. of LDA. A complex mixture of several unidentified compounds was obtained also when bis(3-nitrophenyl)oxirane **1k** was reacted with LDA.

The need for the *cis* arrangement of the aryl and oxazolinyl groups for the isomerization reaction to occur is demonstrated by the following experiment. When (3*R**,4*S**)-3-oxazolin-2-yl-4-phenyl-3,4-epoxyheptane **1j**[13] was treated with LDA a diastereomeric mixture (81% yield; *E*/*Z* ratio: 9/1) of allylic alcohols **7** formed exclusively.[14] This is clear evidence that no *ortho* lithiation occurs when the aryl group is *trans* with respect to the oxazoline ring. A strong acceleration of the isomerization reaction of **1** into **2** was observed when the combination LDA/TMEDA was used. In fact, the isomerization **1e**→**2e** takes about 4 h to go to completion with LDA alone, but it takes about 1 h to be over at −40°C in the presence of TMEDA.

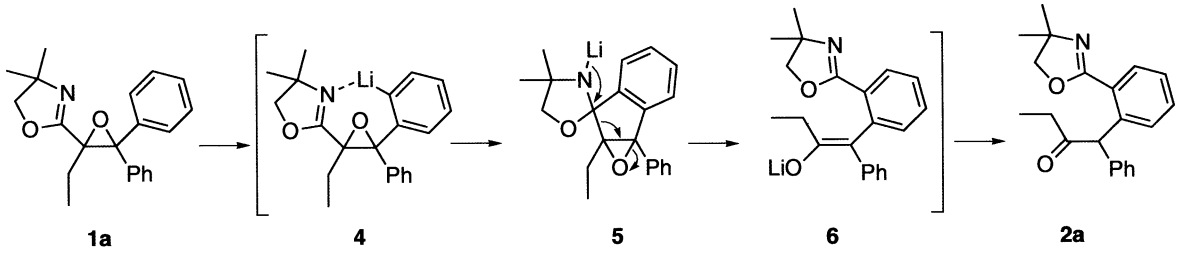
In conclusion, this paper reports a useful transformation of easily available oxazolinylaryl oxiranes **1** into novel oxazolinyl substituted aryl alkanones **2**, which look susceptible of further synthetic elaboration. Work is in progress in our laboratory for a more detailed mechanistic elucidation of the isomerization reaction above.

Acknowledgements

This work was carried out under the framework of the National Project 'Stereoselezione in Sintesi Organica. Metodologie ed Applicazioni' supported by the Ministero dell'Università e della Ricerca Scientifica e Tecnologica (MURST, Rome), by the University of Bari and CNR (Rome) and by C.I.N.M.P.I.S. (Consorzio Interuniversitario Nazionale Metodologie e Processi Innovativi di Sintesi).

References

1. Erden, I. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V., Eds.; Pergamon: Oxford, 1996; Vol. 1, pp. 97–171.
2. (a) Jonhson, R. A.; Sharpless, K. B. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2000; pp. 231–285; (b) Katsuki, T. In *Cata-*



Scheme 1.

lytic Asymmetric Synthesis, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2000; pp. 287–325; (c) Jacobsen, E. N.; Wu, M. H. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N.; Pfalz, A.; Yamamoto, H., Eds.; Springer: Berlin, 1999; pp. 649–677.

3. For two good reviews on oxiranyl anions see: (a) Satoh, T. *Chem. Rev.* **1996**, *96*, 3303–3325; (b) Mori, J. *Rev. Heteroat. Chem.* **1997**, *17*, 183–210.
4. (a) Södergren, M. J.; Andersson, P. G. *J. Am. Chem. Soc.* **1998**, *120*, 10760–10761; (b) Nilsson Lill, S. O.; Arvidsson, P. I.; Ahlberg, P. *Tetrahedron: Asymmetry* **1999**, *10*, 265–279; (c) Asami, M.; Ogawa, M.; Inoue, S. *Tetrahedron Lett.* **1999**, *40*, 1563–1564; (d) O'Brien, P. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1439–1457; (e) Hodgson, D. M.; Gibbs, A. R.; Lee, G. P. *Tetrahedron* **1996**, *52*, 14361–14384; (f) Cox, P. J.; Simpkins, N. S. *Tetrahedron: Asymmetry* **1991**, *2*, 1–26.
5. Capriati, V.; Florio, S.; Luisi, R.; Russo, V.; Salomone, A. *Tetrahedron Lett.* **2000**, *41*, 8835–8838.
6. (a) Florio, S.; Ingrosso, G.; Troisi, L.; Lucchini, V. *Tetrahedron Lett.* **1993**, *34*, 1363; (b) Florio, S.; Capriati, V.; Di Martino, S. *Tetrahedron Lett.* **1998**, *39*, 5639–5642; (c) Florio, S.; Capriati, V.; Di Martino, S.; Abbotto, A. *Eur. J. Org. Chem.* **1999**, 409–417; (d) Abbotto, A.; Capriati, V.; Degennaro, L.; Florio, S.; Luisi, R.; Pierrot, M.; Salomone, A. *J. Org. Chem.* **2001**, *66*, 3049–3058.
7. Capriati, V.; Florio, S.; Luisi, R.; Salomone, A. *Org. Lett.* **2002**, *4*, 2445–2448.
8. Capriati, V.; Degennaro, L.; Favia, R.; Florio, S.; Luisi, R. *Org. Lett.* **2002**, *4*, 1551–1554.
9. Unpublished results.
10. α-(1-Chloropropyl)oxazoline has been prepared by chlorination with *t*-butyl hypochlorite (Capriati, V.; Degennaro, L.; Florio, S.; Luisi, R.; Tralli, C.; Troisi, L. *Synthesis* **2001**, *15*, 2299–2306) of the corresponding 2-propyl derivative (Meyers, A. I.; Temple, D. L.; Nolen, R. L.; Mihelich, E. D. *J. Org. Chem.* **1974**, *39*, 2778–2783).
11. Typical procedure for the synthesis of 1-[4-chloro-2-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)phenyl]-1-(4-chlorophenyl)butan-2-one **2c**. To a precooled (–98°C with a methanol/liquid nitrogen bath) solution of LDA (0.75 mmol) in dry Et_2O (4 mL) and under N_2, a solution of oxazolinylepoxide **1a** (195 mg, 0.5 mmol) in 3 mL of Et_2O was added slowly and the resulting mixture stirred at this temperature for 20 min. After this time the mixture was allowed to warm to room temperature, further stirred for 2 h, quenched with satd aq. NH_4Cl, extracted with Et_2O (3×10 mL) and concentrated in vacuo. Flash chromatography on silica gel (petroleum ether/AcOEt: 9/1) afforded the product **2c** as a colorless oil (185 mg, 95% yield). ^1H NMR (300 MHz, $CDCl_3$) δ 1.02 (t, $J=7.3$ Hz, 3H), 1.34 (s, 3H), 1.37 (s, 3H), 2.41–2.54 (m, 1H), 2.65–2.78 (m, 1H), 4.02 (s, 2H), 6.38 (s, 1H), 6.80–6.85 (m, 1H), 7.11–7.38 (m, 5H), 7.88–7.90 (m, 1H). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 8.0, 28.3, 28.6, 35.5, 59.5, 68.7, 78.0, 128.2, 129.1, 130.0, 130.5, 131.2, 131.5, 132.8, 133.4, 136.3, 137.8, 160.1, 208.8. GC–MS (70 eV) *m*/*z* (%) 391 (M^++2, 7), 389 (M^+, 10), 374 (7), 372 (10), 360 (100), 333 (59), 280 (24), 278 (37), 227 (17), 190 (26), 57 (13). FT-IR (film cm^{-1}) 2970, 2932, 1720 (C=O), 1645 (C=N), 1593, 1489, 1351, 1189, 1092, 1046, 808. Anal. calcd for $C_{21}H_{21}Cl_2NO_2$: C, 64.62; H, 5.42; N, 3.59. Found: C, 64.90; H, 5.66; N, 3.59. All other new compounds showed the following data: **2a**: white solid, mp 121–123°C (Et_2O), 85%. ^1H NMR (300 MHz, $CDCl_3$) δ 1.05 (t, $J=7.4$ Hz, 3H), 1.36 (s, 3H), 1.39 (s, 3H), 2.48–2.60 (m, 1H), 2.69–2.80 (m, 1H), 4.03 (s, 2H), 6.39 (s, 1H), 6.92–6.96 (m, 1H), 7.21–7.40 (m, 7H), 7.87–7.90 (m, 1H). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 8.0, 28.4, 28.7, 35.5, 60.9, 68.4, 78.0, 126.6, 126.8, 127.2, 128.8, 129.9, 130.3, 130.5, 138.2, 139.8, 161.4, 209.4. GC–MS (70 eV) *m*/*z* (%) 321 (M^+, 10), 304 (12), 292 (100), 265 (50), 210 (41), 165 (33). FT-IR (film cm^{-1}) 3062, 2970, 2932, 1717 (C=O), 1644 (C=N), 1493, 1308, 1043, 703. Anal. calcd for $C_{21}H_{23}NO_2$: C, 78.47; H, 7.21; N, 4.36. Found: C, 78.69; H, 7.17; N, 4.35. **2b**: white solid, mp 104–105°C (Et_2O/hexane), 10%. ^1H NMR (300 MHz, $CDCl_3$) δ 1.36 (s, 3H), 1.38 (s, 3H), 2.26 (s, 3H), 4.02 (s, 2H), 6.36 (s, 1H), 6.85–6.89 (m, 1H), 7.17–7.47 (m, 7H), 7.88–7.92 (m, 1H). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 28.3, 28.6, 29.7, 62.1, 68.5, 78.0, 126.6, 127.3, 127.8, 128.1, 128.9, 129.9, 130.1, 130.5, 137.5, 139.7, 161.5, 209.5. GC–MS (70 eV) *m*/*z* (%) 307 (M^+, 10), 292 (49), 290 (100), 265 (32), 210 (40), 165 (43), 43 (90). FT-IR (film cm^{-1}) 3065, 2971, 2920, 1716 (C=O), 1644 (C=N), 1449, 1190, 752, 700. Anal. calcd for $C_{20}H_{21}NO_2$: C, 78.15; H, 6.89; N, 4.56. Found: C, 77.89; H, 7.17; N, 4.55. **2d**: colorless oil, 79%. ^1H NMR (300 MHz, $CDCl_3$) δ 1.03 (t, $J=7.2$ Hz, 3H), 1.35 (s, 3H), 1.38 (s, 3H), 2.43–2.56 (m, 1H), 2.65–2.77 (m, 1H), 4.02 (s, 2H), 6.28 (s, 1H), 6.84–6.89 (m, 1H), 6.95–7.08 (m, 3H), 7.15–7.35 (m, 2H), 7.58–7.62 (m, 1H). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 8.0, 28.3, 28.6, 35.5, 59.3, 68.7, 78.0, 116.1 (d, $^2J_{C\text{-}F}=21.8$ Hz), 117.2 (d, $^2J_{C\text{-}F}=24.1$ Hz), 117.4 (d, $^2J_{C\text{-}F}=24.2$ Hz), 129.2, 131.6 (d, $^3J_{C\text{-}F}=8.1$ Hz), 132.1 (d, $^3J_{C\text{-}F}=8.0$ Hz), 134.0, 135.8, 160.4, 161.5 (d, $^1J_{C\text{-}F}=246.3$ Hz), 162.3 (d, $^1J_{C\text{-}F}=246.1$ Hz) 209.3. GC–MS (70 eV) *m*/*z* (%) 357 (M^+, 7), 340 (10), 328 (100), 301 (49), 300 (25), 273 (12), 246 (49), 228 (18), 201 (829), 150 (13), 57 (11). FT-IR (film cm^{-1}) 2970, 2920, 1720 (C=O), 1646 (C=N), 1586, 1512, 1352, 1229, 1180, 1041, 836. Anal. calcd for $C_{21}H_{21}F_2NO_2$: C, 78.47; H, 7.21; N, 4.36. Found: C, 78.69; H, 7.17; N, 4.35. **2e**: colorless oil, 85%. ^1H NMR (300 MHz, $CDCl_3$) δ 1.03 (t, $J=7.2$ Hz, 3H), 1.34 (s, 3H), 1.37 (s, 3H), 2.30 (s, 3H), 2.34 (s, 3H), 2.43–2.72 (m, 2H), 4.01 (s, 2H), 6.28 (s, 1H), 6.81–6.84 (m, 1H), 7.03–7.51 (m, 5H), 7.66–7.72 (m, 1H). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 8.0, 20.8, 21.0, 28.3, 28.6, 35.4, 60.2, 68.2, 78.0, 129.5, 129.7, 130.1, 130.4, 131.2, 131.6, 135.3, 136.2, 136.7, 136.9, 161.7, 209.8. GC–MS (70 eV) *m*/*z* (%) 349 (M^+, 12), 332 (12), 320 (100), 292 (33), 265 (9), 248 (10), 222 (26), 178 (12), 146 (12). FT-IR (film cm^{-1}) 2970, 2926, 1720 (C=O), 1644 (C=N), 1512, 1352, 1119, 1046, 814. Anal. calcd for $C_{23}H_{27}NO_2$: C, 79.05; H, 7.79; N, 4.01. Found: C, 79.34; H, 7.77; N, 4.01. **2f**: colorless oil, 88%. ^1H NMR (300 MHz, $CDCl_3$) δ 1.02 (t, $J=7.2$ Hz, 3H), 1.34 (s, 3H), 1.37 (s, 3H) 2.44–2.55 (m, 1H), 2.63–2.76 (m, 1H), 3.77 (s, 3H), 3.79 (s, 3H) 4.01 (s, 2H), 6.20 (s, 1H), 6.84–6.96 (m, 4H), 7.10–7.46 (m, 3H). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 8.0, 28.3, 28.6, 35.3, 55.2, 55.3, 59.4, 68.4, 78.0, 114.2, 114.8, 116.4, 127.6, 130.4, 130.8, 131.3, 132.3, 157.8, 158.7, 161.3, 210.0. GC–MS (70 eV) *m*/*z* (%) 381 (M^+, 25), 364 (14), 352 (100), 324 (97), 252 (23), 162 (19), 121 (7). FT-IR (film cm^{-1}) 2967, 2931, 1718 (C=O), 1644 (C=N), 1510,

1249, 1108, 1035, 817. Anal. calcd for $C_{23}H_{27}NO_4$: C, 72.42; H, 7.13; N, 3.67. Found: C, 72.54; H, 7.27; N, 3.61. **2g**: colorless oil, 88%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87 (t, $J=7.6$ Hz, 3H), 1.36 (s, 3H), 1.39 (s, 3H), 1.54–1.64 (m, 2H), 2.47–2.52 (m, 1H), 2.65–2.73 (m, 1H), 4.03 (s, 2H), 6.41 (s, 1H), 6.96–6.99 (m, 1H), 7.22–7.38 (m, 5H), 7.86–7.90 (m, 1H). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 13.7, 17.1, 28.3, 28.6, 44.4, 60.8, 68.4, 78.0, 126.6, 126.9, 127.1, 128.2, 130.0, 130.3, 130.5, 138.3, 139.6, 161.4, 208.9. GC–MS (70 eV) m/z (%) 335 (M^+ 11), 318 (8), 292 (100), 265 (83), 264 (27), 210 (48), 193 (23), 178 (11), 165 (36), 132 (15), 91 (7), 43 (9). FT-IR (film cm^{-1}) 3027, 2967, 2928, 1717 (C=O), 1643 (C=N), 1451, 1363, 1259, 1042, 750, 703.

12. That the oxazoline moiety is an *ortho* director in the lithiation of benzene derivatives is well established: (a) Gant, T. G.; Meyers, A. I. *Tetrahedron* **1994**, *50*, 2297–2360; (b) Gschwend, H. W.; Rodriguez, H. R. In *Heteroatom Facilitated Lithiation*. *Organic Reactions*; Burke, S.; Grieco, P. A.; Gschwend, H. W.; Rodriguez, H. R., Eds.; Wiley: New York; 1979; Vol. 26, pp. 1–360. In the case of **1a**, the lithium cation coordinative assistance is provided from far in a seven-membered cyclic intermediate such as **4**, while a five-membered cyclic structure is actually involved when the oxazolinyl group is directly linked to a benzene ring.
13. The configuration to **1j** (in which the oxazoline and the *n*-propyl group are on the same side of the epoxide ring), obtained as a single diastereoisomer in the reaction of lithiated α-(1-chloropropyl)oxazoline with butyrophenone, was assigned by analogy to similar trisubstituted aryl methyl oxazolinyloxiranes as reported in Ref. 6d.
14. The *Z* or *E* configuration to allylic alcohols **7** was assigned on the basis of the vinylic protons chemical shifts: 5.41 vs 5.87 δ, respectively. If bulky substituent groups are in fact present on the double bond *gem* to aromatic rings these will adopt a twist conformation and a shielding of vinylic protons in *cis* positions will occur, as reported (Gaudemar, A. In *Stereochemistry: Fundamentals and Methods*; Kagan, H. B., Ed; Georg Thieme Publishers,1 Stuttgart, 1977; Vol. 1. Determination of configurations by spectrometric methods, pp. 48–50).