Pergamon

Tetrahedron Letters 41 (2000) 8835–8838

TETRAHEDRON LETTERS

Oxiranyllithium based synthesis of α-keto-2-oxazolines

Vito Capriati, Saverio Florio,* Renzo Luisi, Vincenzo Russo and Antonio Salomone

CNR, Centro di Studio sulle Metodologie Innovative di Sintesi Organiche, Dipartimento Farmaco-Chimico, Università di Bari, Via E. Orabona 4, I-70125 Bari, Italy

Received 13 September 2000; accepted 14 September 2000

Abstract

α-Keto-2-oxazolines **5a–j** have been efficiently prepared by lithiation [*sec*-(or *n*-)BuLi/TMEDA, Et_2O, −100°C] and rearrangement of oxiranyl oxazolines **2a–j**. © 2000 Published by Elsevier Science Ltd.

Keywords: oxazolinyl oxiranes; oxiranyllithiums; α-keto-2-oxazolines; oxirane–ketone rearrangement.

α-Ketoheterocycles are very interesting and useful substances. Some of them, the peptidyl α-ketoheterocycles, have been reported to possess important biological activity such as the inhibition of human neutrophil elastase (HNE), a serine protease, which is believed to be involved in some pathological effects in pulmonary emphysema, rheumatoid arthritis, atherosclerosis and other inflammatory disorders.[1] Peptidyl α-ketoheterocycles have also been reported to act as potent inhibitors against prolyl endopeptidase[2] and thrombin.[3] Among the α-ketoheterocycles, α-keto-2-oxazolines are important members as peptidyl derivatives have been described as potent inhibitors of HNE.[4]

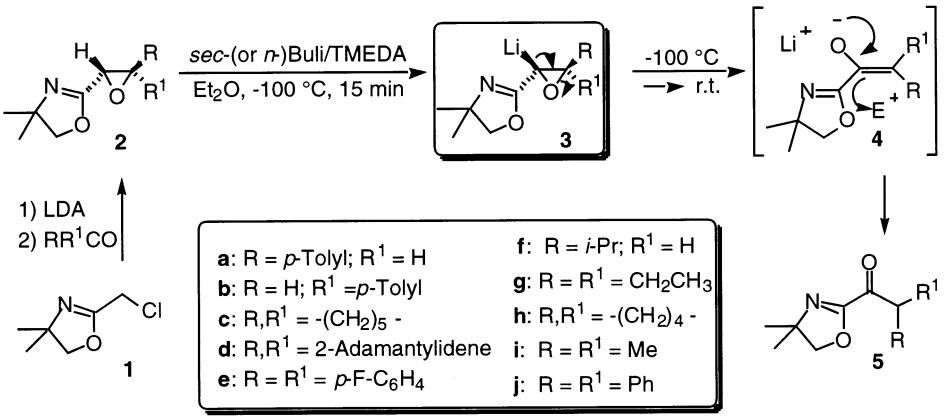
α-Keto-2-oxazolines have been reported to be the putative intermediates in the oxidative rearrangement of 2-alkyloxazolines to dihydrooxazinones and morpholinones[5] and useful precursors to enantiomerically pure α-hydroxy carboxylic acids.[6] There are few reports dealing with the synthesis of α-keto-2-oxazolines. Hansen[7] and Meyers[8] had reported that certain α-keto-2-oxazolines can be prepared by oxidation (O_2) of lithiated 2-alkyloxazolines. Quite recently a synthetic route to peptidyl α-keto-2-oxazolines has been published[4] which was based on the cyclodehydration oxidation of dipeptide derivatives by an extension of Wipf's protocol of 2-oxazolines.[9] As part of our continuing interest in oxazoline chemistry, in the present paper we

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

0040-4039/00/$ - see front matter © 2000 Published by Elsevier Science Ltd.
PII: S0040-4039(00)01558-6

report a synthetic procedure to α-keto-2-oxazolines based substantially on the deprotonation–rearrangement of oxazolinyl oxiranes.

The oxazolinyl oxiranes **2a–j**, needed for the rearrangement, were prepared by the Darzens-type reaction of lithiated 4,4-dimethyl-2-chloromethyl-2-oxazoline **1** with carbonyl compounds.[10] When treated with *sec*-BuLi/TMEDA in Et_2O at −100°C *trans*-oxiranyl oxazoline **2a** (Scheme 1) underwent rapid lithiation to give oxiranyllithium **3a** which was stable at that temperature and could be easily trapped with a number of electrophiles to give more substituted oxiranes.[11] The same oxiranyllithium **3a**, in the absence of an external electrophile and upon warming to room temperature and acid quenching, underwent a clean conversion to the oxazolinyl benzyl ketone **5a**, likely through the enolate **4a** (Scheme 1). Such a hypothesis was supported by the fact that there are precedents that, under basic conditions, oxiranes isomerize to carbonyl compounds via the relevant enolates.[12] The same ketone **5a** was obtained when oxiranyl oxazoline **2b** was isomerized under the experimental conditions above.



Scheme 1.

Similarly, oxazolinyl oxiranes **2c–h** could be converted into oxazolinyl ketones **5c–h** upon lithiation at low temperature followed by warming to room temperature and quenching with sat. aq. NH_4Cl (Scheme 1, Table 1).[†]

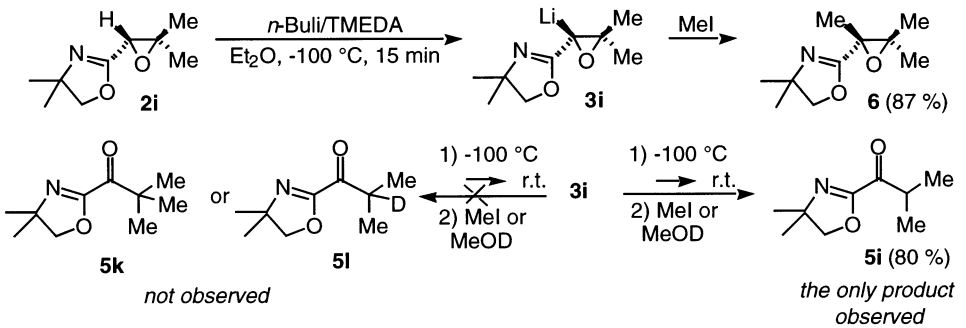
[†] **Typical procedure:** A solution of **2e** (117 mg, 0.35 mmol) and TMEDA (0.08 mL, 0.53 mmol) in 6 mL of Et_2O at −100°C and under N_2 was treated with *sec*-BuLi (0.45 mL, 0.53 mmol, 1.18 M in cyclohexane), and the resulting orange mixture was stirred for 15 min at −100°C. The mixture was then allowed to warm to room temperature and after 3 h (generally, when the putative enolate was formed, the reaction mixture became green from yellow) was quenched with sat. aq. NH_4Cl, extracted with EtOAc (3×10 μL) and concentrated in vacuo. Flash chromatography on silica gel (7:3 petroleum ether–EtOAc) afforded the keto oxazoline **5e** (70.2 mg, 60 %); mp 123–125°C (hexane). ^1H NMR (300 MHz, $CDCl_3$): δ 1.25 (s, 6H), 4.02 (s, 2H), 6.11 (s, 1H), 6.95–7.02 (m, 4H), 7.21–7.26 (m, 4H). GC–MS (70 eV) *m/z* (%): 329 (55.3) [M^+], 328 (14), 203 (100), 183 (40.7), 55 (10.5), 41 (2.17). FT-IR (KBr, cm^{-1}): 1717 (s, CO), 1633 (s, CN). Anal. calcd for $C_{19}H_{17}F_2NO_2$: C, 69.29; H, 5.20; N, 4.25. Found: C, 69.69; H, 5.45; N, 4.20.

Table 1
Synthesis of α-keto-2-oxazolines **5a**–**j** from oxazolinyl epoxides **2a**–**j**

Epoxides	Base used	α-Keto-2-oxazolines	Yield (%)[a,b]
2a	*sec*-BuLi	**5a**	67
2b	*sec*-BuLi	**5a**	67
2c	*sec*-BuLi	**5c**	62
2d	*sec*-BuLi	**5d**	60
2e	*sec*-BuLi	**5e**	60
2f	*sec*-BuLi	**5f**	30[c]
2g	*sec*-BuLi	**5g**	80
2h	*sec*-BuLi	**5h**	75
2i	*n*-BuLi[d]	**5i**	80
2j	*n*-BuLi[d]	**5j**	63[e]

[a] Isolated yields.
[b] All new compounds showed satisfactory microanalytical data (±0.4%) and consistent ^{1}H NMR, IR and MS data.
[c] In this case the anion **3f** was highly reactive giving rise to many by-products.
[d] Generally *n*-BuLi can also be used instead of *sec*-BuLi as in these examples.
[e] In this case the reaction was stopped at −10°C for the best yield.

Lithiation of 1-(4,4-dimethyl-2-oxazolin-2-yl)-2-methyl-1,2-epoxypropane **2i** (*n*-BuLi/TMEDA, Et_2O, −100°C) (Scheme 2) followed by quenching at −100°C (after 30 min) with MeI provided tetrasubstituted epoxide **6** in high yield (87%). Instead, lithiation of **2i**, under the same conditions, warming at room temperature for 2 h and quenching with excess MeI afforded the isopropyl ketone **5i** (80% yield) and not **5k** (Scheme 2). Attempted trapping of the putative enolate **4i** with MeOD to give deuterated ketone **5l** (Scheme 2) also failed, the undeuterated ketone **5i** being obtained (80% yield).



Scheme 2.

Equally unsuccessful was the attempt to capture the enolate **4j** derived from **3j**. Indeed, when epoxide **2j** was deprotonated under the above conditions, warmed to room temperature and then D_2O or allyl bromide added, the only product that could be obtained was **5j** (63% yield).

In conclusion, in this paper we report a new synthesis of α-keto-2-oxazolines, which are potentially useful synthetic intermediates, based on the deprotonation–rearrangement of oxazolinyl oxiranes. More work is under way in order to rationalize the observed results.

Acknowledgements

Work carried out in the framework of the National Project 'Stereoselezione in Sintesi Organica. Metodologie ed Applicazioni' was supported by the Ministero dell'Università e della Ricerca Scientifica e Tecnologica, Rome, and by the University of Bari. The authors would also like to thank the Italian CNR for financial support.

References

1. (a) Edwards, P. D.; Wolanin, D. J.; Andisik, D. W.; Davis, M. W. *J. Med. Chem.* **1995**, *38*, 76–85. (b) Edwards, P. D.; Zottola, M. A.; Davis, M.; Williams, J.; Tuthill, P. A. *J. Med. Chem.* **1995**, *38*, 3972–3982. (c) Edwards, P. D.; Meyer Jr., J. F.; Vijayalakshmi, J.; Tuthill, P. A.; Andisik, D. A.; Gomes, B.; Strimpler, A. *J. Am. Chem. Soc.* **1992**, *114*, 1854–1863.
2. (a) Tsutsumi, S.; Okonogi, T.; Shibahara, S.; Patchett, A. A. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 831–834. (b) Tsutsumi, S.; Okonogi, T.; Shibahara, S.; Ohuchi, S.; Hatsushiba, E.; Patchett, A. A.; Christensen, G. *J. Med. Chem.* **1994**, *37*, 3492–3502.
3. (a) Costanzo, M. J.; Maryanoff, B. E.; Hecker, L. R.; Schott, M. R.; Yabut, S. C.; Zhang, H.-C.; Andrade-Gordon, P.; Kauffman, J. A.; Lewis, J. M.; Krishnam, R.; Tulinsky, A. *J. Med. Chem.* **1996**, *39*, 3039–3043. (b) Tamura, S. Y.; Shamblin, B. M.; Brunck, T. K.; Ripka, W. C. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1359–1364. (c) Akiyama, Y.; Tsutsumi, S.; Hatsushiba, E.; Ohuchi, S.; Okonogi, T. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 533–538.
4. Dunn, D.; Chatterjee, S. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1273–1276.
5. (a) Shafer, C. M.; Molinsky, T. F. *J. Org. Chem.* **1996**, *61*, 2044–2050. (b) Shafer, C. M.; Morse, D. I.; Molinsky, T. F. *Tetrahedron* **1996**, *52*, 14475–14886.
6. Meyers, A. I.; Slade, J. *J. Org. Chem.* **1980**, *45*, 2912–2914.
7. Hansen, J. F.; Wang, S. *J. Org. Chem.* **1976**, *41*, 3635–3637.
8. Meyers, A. I.; Slade, J. *J. Org. Chem.* **1980**, *45*, 2785–2791.
9. Wipf, P.; Miller, C. P. *Tetrahedron Lett.* **1992**, *33*, 907–910.
10. Florio, S.; Capriati, V.; Luisi, R. *Tetrahedron Lett.* **1996**, *37*, 4781–4784. Similarly, **2e**, diastereomeric oxazolinyl epoxides **2f**–**h** were prepared with an overall yield of 63, 33, 65 and 66%, respectively.
11. (a) Florio, S.; Capriati, V.; Di Martino, S.; Abbotto, A. *Eur. J. Org. Chem.* **1999**, 409–417. (b) Florio, S.; Capriati, V.; Di Martino, S. *Tetrahedron Lett.* **1998**, *39*, 5639–5642.
12. Satoh, T. *Chem. Rev.* **1996**, *96*, 3303–3325 and references cited therein.