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Tetrahedron Letters 46 (2005) 1017–1019
Tetrahedron Letters

Synthesis of 6-hydroxymethyl-5,6-dihydro-4*H*-1,2-oxazines by one-pot-cyclization of dilithiated oximes with epibromohydrin

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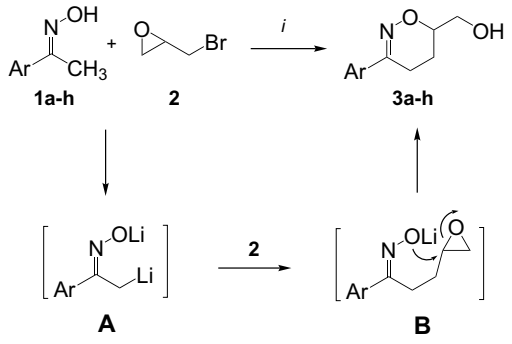
Received 3 November 2004; revised 3 December 2004; accepted 7 December 2004
Available online 22 December 2004

Abstract—6-Hydroxymethyl-5,6-dihydro-4*H*-1,2-oxazines were regioselectively prepared by one-pot cyclization of dilithiated oximes with epibromohydrin.

1,2-Oxazines are of pharmacological relevance and represent useful synthetic building blocks. They have been used, for instance, as intermediates during the synthesis of glycosidase inhibitor analogues[1,2] and of functionalized pyrroles.[3] Many syntheses of 1,2-oxazines rely on hetero-Diels–Alder reactions of alkenes with ene–nitroso compounds, derived from α-haloximes,[4a–d] or on hetero-Diels–Alder reactions of dienes with nitroso compounds.[1,4e] Other methods rely on cyclizations of alkenyl-substituted oximes in the presence of NBS,[5] diphenyldiselenide,[6a,b] or acid[7] or by photochemical activation.[8] In addition, 1,2-oxazines have been prepared by base-mediated cyclizations of γ-chloroximes[9] and γ-sulfonyloximes.[10] Other syntheses rely on the Lewis-acid catalyzed reaction of allenoximes,[11] acid-catalyzed cyclization of cyclopropyloximes[12] or cyclization of γ-nitroketones.[13] Despite the simplicity of the idea, the synthesis of functionalized oxazines based on cyclization reactions of 1,4-dianions of oximes[14,15] has, to the best of our knowledge, not yet been reported.[16,17] Herein, we wish to report the synthesis of 6-hydroxymethyl-5,6-dihydro-4*H*-1,2-oxazines by cyclization of dilithiated oximes with epibromohydrin.[18]

The reaction of the dianion of acetophenone oxime (**1a**), generated by *n*-butyllithium (2.5 equiv), with epibromohydrin (**2**) afforded the 1,2-oxazine **3a** (Scheme 1).[19] During the optimization of the reaction, the conditions of the deprotonation step proved to be important (1 h, −78 °C, then 10 min, 20 °C) to ensure a complete formation of the dianion of **1a**. The formation of **3a** can be explained by S_N2 reaction of the deprotonated CH_3 group of the dianion with the CBr functionality of **2** and subsequent cyclization via the oxygen atom or, alternatively, by attack of the dianion on the sterically less hindered carbon atom of the epoxide, Payne rearrangement and subsequent cyclization. The reaction proceeded with very good regioselectivity, due to the higher nucleophilicity of the carbanion compared to the alkoxide within the dianion.



Scheme 1. Synthesis of 1,2-oxazines **3a**–**h**. Reagents and conditions: (i) (1) *n*-BuLi (2.5 equiv), 1 h, −78 °C; (2) 10 min, 20 °C; (3) **2**, −78 → 20 °C, 16 h.

The preparative scope of the methodology was studied next (Scheme 1, Table 1). The cyclization of **2** with substituted acetophenone oximes **1b**–**f** afforded the aryl-substituted 1,2-oxazines **3b**–**f**. The 1,2-oxazines **3g**,**h** were prepared from acetonaphthone oximes **1g**,**h**.

Keywords: Cyclizations; Dianions; Epoxides; One-pot reactions; Oximes.
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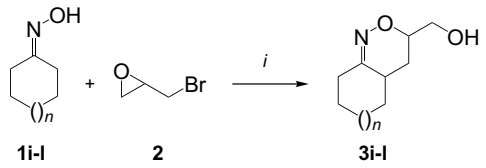
doi:10.1016/j.tetlet.2004.12.031

Table 1. Products and yields

3	R	%[a]
a	Ph	30
b	4-MeC_6H_5	81
c	4-$(MeO)C_6H_5$	73
d	3-MeC_6H_5	36
e	3-$(MeO)C_6H_5$	72
f	2-MeC_6H_5	33
g	1-Naphthyl	44
h	2-Naphthyl	42

[a] Yields of isolated products.

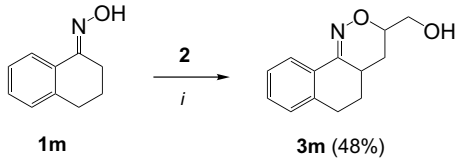


Scheme 2. Synthesis of bicyclic oxazines. Reagents and conditions: (i) (1) *n*-BuLi (2.5 equiv), 1 h, −78 °C; (2) 10 min, 20 °C; (3) **2**, −78 → 20 °C, 16 h.

Table 2. Products and yields

3	*n*	%[a]
i	1	38
j	2	51
k	3	49
l	7	52

[a] Yields of isolated products.



Scheme 3. Synthesis of 1,2-oxazine **3m**. Reagents and conditions: (i) (1) *n*-BuLi (2.5 equiv), 1 h, −78 °C; (2) 10 min, 20 °C; (3) **2**, −78 → 20 °C, 16 h.

The cyclization of **2** with oximes **1i–l**, prepared from cycloalkanones, afforded the corresponding 6,6-, 6,7-, 6,8- and 6,12-bicyclic 1,2-oxazines **3i–l** (Scheme 2, Table 2). The cyclization of tetralone-derived oxime **1m** with **2** afforded the tricyclic 1,2-oxazine **3m** (Scheme 3). All products **3i–m** were formed as 1:1 mixtures of diastereomers.

Acknowledgements

Financial support from the Deutsche Forschungsgemeinschaft is gratefully acknowledged.

References and notes

1. (a) Streith, J.; Defoin, A. *Synlett* **1996**, 189; (b) Defoin, A.; Sarazin, H.; Streith, J. *Tetrahedron* **1997**, *53*, 13769.
2. Bach, P.; Bols, M. *Tetrahedron Lett.* **1999**, *40*, 3460.
3. Miyashita, M.; Awen, B. Z. E.; Yoshikoshi, A. *Tetrahedron* **1990**, *46*, 7569.
4. For a review, see: (a) Gilchrist, T. L. *J. Chem. Soc., Chem. Rev.* **1983**, *12*, 53; see also: (b) Gilchrist, T. L.; Roberts, T. G. *J. Chem. Soc., Chem. Commun.* **1978**, 847; (c) Zimmer, R.; Reißig, H. U. *Liebigs Ann. Chem.* **1991**, 553; (d) Yoon, S. C.; Kim, K.; Park, Y. J. *J. Org. Chem.* **2001**, *66*, 7334; (e) Naruse, M.; Aoyagi, S.; Kibayashi, C. *Tetrahedron Lett.* **1994**, *35*, 595.
5. (a) Bowman, W. R.; Davies, R. V.; Slawin, A. M. Z.; Sohal, G. S.; Titman, R. B.; Wilkins, D. J. *J. Chem. Soc., Perkin Trans. 1* **1997**, 155; (b) Dondas, H. A.; Grigg, R.; Hadjisoteriou, M.; Markandu, J.; Kennewell, P.; Thornson-Pett, M. *Tetrahedron* **2001**, *57*, 1119.
6. (a) Tiecco, M.; Testaferri, L.; Tingoli, M.; Bagnoli, L.; Marini, F. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1989; (b) Grigg, R.; Hadjisoteriou, M.; Kennewell, P.; Markandu, J. *J. Chem. Soc., Chem. Commun.* **1992**, 1537.
7. Bishop, R.; Hawkins, S. C.; Quibuyen, T. A. O.; Brooks, P. R. *Tetrahedron Lett.* **1988**, *29*, 6805.
8. Armesto, D.; Austin, M. A.; Griffiths, O. J.; Horspool, W. M.; Carpintero, M. *J. Chem. Soc., Chem. Commun.* **1996**, 2715.
9. (a) Kaiser, A.; Mayer, K. K.; Sellmer, A.; Wiegrebe, W. *Monatsh. Chem.* **2003**, *3*, 343; (b) Ellames, G. J.; Hewkin, C. T.; Jackson, R. F. W.; Smith, D. I.; Standen, S. P. *Tetrahedron Lett.* **1989**, *26*, 3471.
10. Saiki, H.; Mukai, T. *Chem. Lett.* **1981**, 1561.
11. Lathbury, D.; Gallagher, T. *J. Chem. Soc., Chem. Commun.* **1986**, 1017.
12. Castin, V.; Rentzea, C. N. *Angew. Chem.* **1980**, *92*, 195.
13. Boberg, F.; Ruhr, M.; Garburg, K. H.; Garming, A. *J. Heterocycl. Chem.* **1986**, *23*, 759.
14. For reviews of dianions including oxime 1,4-dianions, see: (a) Kaiser, E. M.; Petty, J. D.; Knutson, P. L. A. *Synthesis* **1977**, 509; (b) Thompson, C. M.; Green, D. *Tetrahedron* **1991**, *47*, 4223.
15. For a review of cyclization reactions of dianions, see: Langer, P.; Freiberg, W. *Chem. Rev.* **2004**, *104*, 4125.
16. For the synthesis of isoxazoles by reaction of dilithiated oximes with esters, see: (a) Beam, C. F.; Dyer, M. C. D.; Schwarz, R. A.; Hauser, C. R. *J. Org. Chem.* **1970**, *35*, 1806; for the synthesis of isoxazolin-5-ones from oximes and carbon dioxide, see: (b) Griffiths, J. S.; Beam, C. F.; Hauser, C. R. *J. Chem. Soc. C* **1971**, 974.
17. For reactions of silyl enol ethers with α-chloroximes, see: (a) Reissig, H.-U.; Hippeli, C.; Arnold, T. *Chem. Ber.* **1990**, *123*, 2403; for reactions of allylsilanes with α-chloroximes, see: (b) Hippeli, C.; Reissig, H.-U. *Synthesis* **1987**, 77.
18. For other cyclization reactions of epibromohydrin from our laboratory, see: (a) Langer, P.; Freifeld, I. *Chem. Eur. J.* **2001**, *7*, 565; (b) Albrecht, U.; Langer, P. *Synlett* **2004**, 2200.
19. *Typical procedure for the preparation of dihydrooxazines* **3**: to a THF solution (10 ml) of oxime **1b** (0.298 g, 2.0 mmol) was added *n*-butyllithium (5.0 mmol, 2.5 M) at −78 °C. After stirring for 1 h at −78 °C, the mixture was warmed to 20 °C and stirred for 10 min. Subsequently, epibromohydrin (300 mg, 2.2 mmol) was added at −78 °C. After warming of the mixture to 20 °C for 16 h, a saturated aqueous solution of NH_4Cl (20 ml) was added. The organic and the aqueous layer were separated and the latter was extracted with ethyl acetate (3 × 30 ml). The combined organic layers were dried (Na_2SO_4), filtered and the solvent of the filtrate was removed in vacuo. The residue was purified by chromatography (silica gel, *n*-

hexane/EtOAc, 2:1) to give **3b** as a colourless solid (333 mg, 81%), mp 80 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.89–2.07 (m, 2H, CH_2), 2.12 (br, 1H, OH), 2.38 (s, 3H, CH_3), 2.55–2.76 (m, 2H, CH_2), 3.73–3.92 (m, 3H, CH_2, CH), 7.19 (dd, J = 6 Hz, J = 2 Hz, 2H, CH), 7.58 (dd, J = 6 Hz, J = 2 Hz, 2H, CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.4 (CH_2), 21.1 (CH_3), 21.3 (CH_2), 63.9 (CH_2), 75.3, 125.1, 128.1 (CH), 132.6, 139.4, 155.0 (C). MS (EI, 70 eV): m/z = 205 (M^+, 86), 174 (100), 146 (18), 131 (27), 118 (46). IR (KBr): $\tilde{\nu}$ = 3392 (s), 2964 (w), 2924 (m), 2869 (w), 1612 (w), 1511 (w), 1456 (w), 1444 (w), 1423 (w). UV–vis: λ_{max} (lg ε) = 202.49 (4.25), 252.46 (4.05). Anal. Calcd for $C_{12}H_{15}NO_2$ (205.25): C, 70.22; H, 7.37; N, 6.82; found: C, 70.35; H, 7.66; N, 7.10.