Tetrahedron Letters 49 (2008) 6707–6708

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Practical reduction of oxazolines to alcohols

Anna Bernardi, Stéphane G. Ouellet *, Remy Angelaud, Paul D. O'Shea

Department of Process Research, Merck Frosst Centre for Therapeutic Research, 16711 Trans-Canada Hwy., Kirkland, Québec, Canada, H9H 3L1

ARTICLE INFO

Article history:
Received 13 November 2007
Revised 9 September 2008
Accepted 10 September 2008
Available online 15 September 2008

ABSTRACT

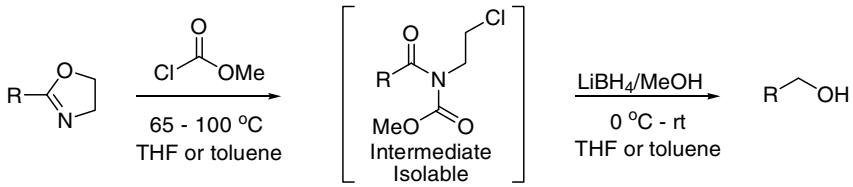
A two-step, one-pot procedure using methyl chloroformate and lithium borohydride was developed to transform 2-substituted-oxazolines into alcohols. This methodology is compatible with a wide range of substrates including heterocyclic, aromatic, and aliphatic functionalized 2-oxazolines. Best results are obtained with electron-rich and *ortho* substituted 2-aryl-oxazolines.

The first synthesis of an oxazoline was reported in 1884, but it was not until 1970s that its synthetic utility was developed.[1] Since then oxazolines have been used in many synthetic applications including heteroatom-facilitated lithiation,[2] transition-metal catalyzed C–H activation,[3] and aza-enolate carbanion chemistry.[4] Oxazolines can also serve as precursors to various functional groups including ketones, aldehydes, carboxylic acids, and alcohols.[5] Unfortunately, known methods to access alcohols are not readily transferable to large-scale synthesis. In light of this, a practical and scalable method was developed for the direct reduction of oxazolines to alcohols.

Work by Meyers et al. has described the use of chloromethyl methyl ether (MOMCl) or (trimethylsilyl) ethoxymethyl chloride as electrophile, to access a putative tertiary amide intermediate, which was then reduced to the corresponding alcohol using Dibal-H or lithium aluminum hydride.[6] The reagents used in this protocol are not amenable to large-scale synthesis (carcinogenicity of MOMCl and problematic work-ups associated with aluminum-based hydride sources). Furthermore, the lack of chemoselectivity of $LiAlH_4$ limits the scope of this transformation.

Herein, we report our efforts to develop a new methodology for the selective conversion of oxazolines to primary alcohols. In order to circumvent the need for highly reactive reductants, we decided to investigate the possibility of generating a more reactive tertiary amide intermediate. It is known that *N*-acylcarbamates possess an enhanced susceptibility toward reduction.[7] To this end, we have demonstrated that 2-phenyl-oxazoline is efficiently converted in situ to the related *N*-acylcarbamate upon treatment with methyl chloroformate.[8] Treatment of the *unisolated* intermediates with lithium borohydride afforded the desired alcohol in good yield (Scheme 1). Thus, *as the N-acylcarbamate was not isolated*, this affords a mild and efficient two-step, one-pot method to access alcohols from oxazolines.

We next investigated the scope of this reaction; our results are summarized in Table 1.[9] In all cases, 2-aryl-oxazolines were reduced efficiently using this method, irrespective of the presence of electron-donating (entries 2, 3, and 5) or electron-withdrawing groups (entries 4, 7, 8, and 11) on the aryl moiety. However, we did note that certain substrates (entries 4, 6–8) were slow to activate to the *N*-acylcarbamate. We postulated that the presence of electron-withdrawing groups, such as CF_3, resulted in a decrease in the nucleophilicity of the oxazoline. In order to address the lower reactivity, we increased both the reaction temperature and number of equivalents of chloroformate which resulted in a

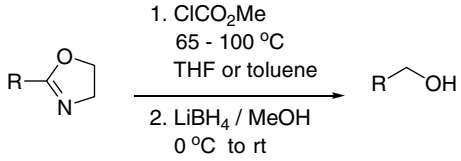


Scheme 1. Reduction of oxazolines to alcohols.

* Corresponding author.
E-mail address: stephane_ouellet@merck.com (S. G. Ouellet).

0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.09.061

Table 1



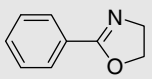
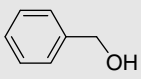
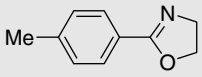
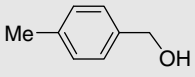
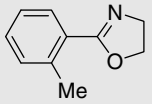
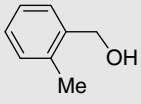
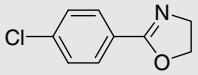
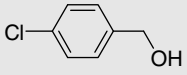
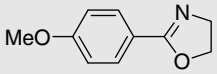
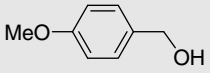
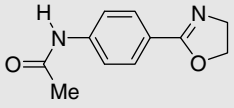
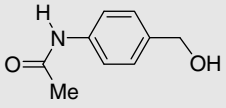
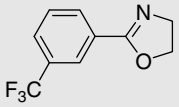
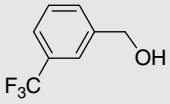
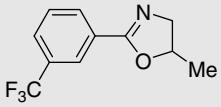
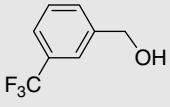
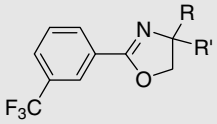
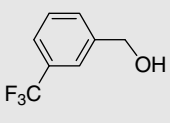
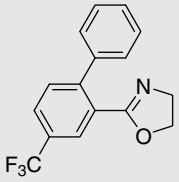
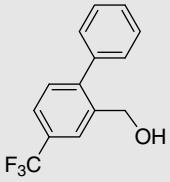
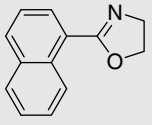
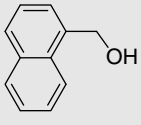
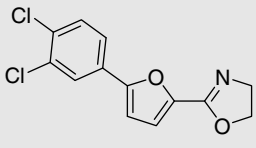
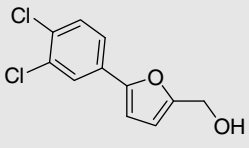
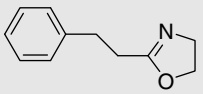
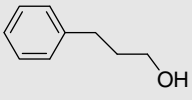
Entry	Starting material	Product	Yield[a] (%)
1			68[b]
2			74[b]
3			96[b]
4			54[c]
5			91
6			78[c]
7			75[c]
8			80[c]
			
9	R = H, R′ = Me		NR
10	R = R′ = Me		NR
11			80
12			73
13			75

Table 1 (*continued*)

Entry	Starting material	Product	Yield[a] (%)
14			63[b,c]

[a] Typical conditions: MeOCOCl (2 equiv), $(i\text{-Pr})_2$NEt (0.2 equiv) in THF at 65 °C then $LiBH_4$ (3 equiv) and MeOH (3 equiv) at room temperature.
[b] Assay yield determined by HPLC analysis.
[c] Increased temperature (from 65 °C in THF to 100 °C in toluene) and amount of MeOCOCl (4–5 equiv) required for activation.

complete activation. Interestingly, the presence of an *ortho*-substituent on the aryl ring increased the susceptibility of the substrate toward activation. This can be seen by comparing entries 7 and 11, where the addition of the phenyl at the *ortho*-position allowed for the use of lower reaction temperatures (65 °C vs 100 °C) and fewer equivalents of methyl chloroformate. This method is also applicable to 2-heteroaryl-oxazolines (entry 13) to afford the related alcohol in 75% isolated yield. This method was also applied successfully to a 2-alkyl-oxazoline (entry 14).

The use of the mild reductant (lithium borohydride) allows this method to be used in cases where chemoselectivity is required. For example, the oxazoline was converted to an alcohol in presence of an *N*-acylaniline (entry 6) without any over-reduction observed. However, we did note that this method is not effective for activation/reduction of oxazolines bearing substituents at carbon 4 of the oxazoline (entries 9 and 10).

In summary, we have developed a practical two-step one-pot method for the conversion of oxazolines to alcohols. In comparison with previous methods, this process required the use of a less-toxic activating agent and milder reductant. Thus, this new protocol is more operator friendly and has greater potential for use in chemoselective transformations.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.09.061.

References and notes

1. Wong, G. S. K.; Wu, W. In *Oxazoles: Synthesis, Reactions, and Spectroscopy*; Palmer, D. C., Ed.; The Chemistry of Heterocyclic Compounds; John Wiley & Sons: New Jersey, 2004; Vol. 60, pp 331–417.
2. For recent examples, see: Wanbin, Z.; Fang, X.; Shigeaki, M.; Yuji, I.; Toshiyuki, K.; Yohji, N.; Isao, I. *Tetrahedron: Asymmetry* **2006**, *17*, 767–777.
3. For recent examples, see: (a) Oi, S.; Aizawa, E.; Ogino, Y.; Inoue, Y. *J. Org. Chem.* **2005**, *70*, 3113–3119; (b) Ackermann, L.; Althammer, A.; Born, R. *Angew. Chem., Int. Ed.* **2006**, *45*, 2619–2622.
4. Meyers, A. I.; Mihelich, E. D. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 270–281.
5. Mayryanoff, B. E. In *Oxazoles and Oxazolines in Organic Synthesis*; Turchi, I. J., Ed.; Chemistry of Heterocyclic Compounds: Oxazoles; John Wiley & Sons: New York, 1986; Vol. 45, pp 964–996.
6. Meyers, A. I.; Shimano, M. *Tetrahedron Lett.* **1993**, *34*, 4893–4896.
7. Ragnarsson, U.; Grehn, L.; Monteiro, L. S.; Maia, H. L. S. *Synlett* **2003**, *15*, 2386–2388.
8. Laaziri, A.; Uziel, J.; Jugé, S. *Tetrahedron: Asymmetry* **1998**, *9*, 437–447.
9. *Typical procedure*: A 25 mL round-bottomed flask was charged with the oxazoline (2.5 mmol), THF (2.5 mL), Hünig's base (0.087 mL, 0.5 mmol), and methyl chloroformate (0.39 mL, 5.0 mmol). The reaction mixture was then heated to 65 °C and stirred at this temperature for 30 min (found to be complete by HPLC) before being cooled to 0 °C. Then, $LiBH_4$ (3.75 mL, 2 M in THF, 7.5 mmol) was added slowly followed by methanol (0.3 mL, 7.5 mmol) and the reaction was warmed to room temperature. After completion of the reaction, the reaction mixture was cooled to 0 °C and carefully quenched with 1 N HCl (2.5 mL) and then with water (2.5 mL). After 15 min of stirring, the reaction mixture was diluted with MTBE and water before being transferred to an extractor, whereupon the aqueous layer was removed. The aqueous layer was back-extracted with MTBE and the combined organic layers were washed with brine and dried over Na_2SO_4 prior to being concentrated under reduced pressure. The product was purified by column chromatography.