Tetrahedron Letters 53 (2012) 3049–3051

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

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

A straightforward one-pot synthesis of biologically important imidazolyl alcohols via catalytic epoxide ring-opening reactions

M. Abdul Jalil [a,*], Shah Md. Masum [b]

[a] School of Engineering, Presidency University, 10 Kemal Ataturk Avenue, Banani, Dhaka 1213, Bangladesh
[b] Department of Applied Chemistry and Chemical Engineering, University of Dhaka, Dhaka 1000, Bangladesh

ARTICLE INFO

Article history:
Received 20 February 2012
Revised 25 March 2012
Accepted 4 April 2012
Available online 12 April 2012

Keywords:
Imidazolyl alcohol
Antifungal
Epoxide
Catalyst
Solvent-free

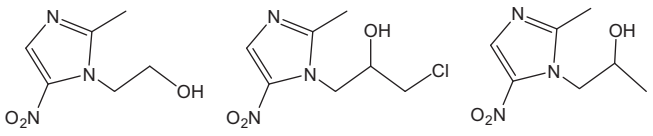
ABSTRACT

A general and efficient method for the preparation of biologically important imidazolyl alcohols via ring-opening of epoxides with N-silylated imidazole catalyzed by LiBr under solvent-free conditions is reported.

The imidazole group is an important residue found in a wide variety of biologically active and medicinally significant molecules, comprising several classes of derivatives that can be found in fungicides,[1] histamine H_2-receptor antagonists,[2] and anticancer agents.[3] Among bioactive imidazole derivatives, imidazolyl alcohols are a very important class of compounds that show a wide spectrum of activity and are used as important building blocks for drug synthesis. For instance, metronidazole, ornidazole, and secnidazole (Fig. 1) are effective antiprotozoal drugs of this family, which have been used for the treatment of amebic dysentery and other fungal infections. Miconazole and econazole are clinically used representative antifungal drugs derived from imidazolyl alcohols and several related compounds are currently undergoing clinical trials.[4]

Apart from their excellent bioactivities, imidazolyl alcohols are also used as ligands for catalytic reactions.[5] Some of them are used as bidentate N-heterocyclic carbene ligands (NHC) after alkylating the imidazole ring.[6] Also, higher oxidation state complexes provide enhanced stabilities to metal catalysts.[7] Moreover, their use as ionic liquids have also been reported.[8] Therefore, the development of an efficient route that can be applied to the large scale synthesis of this important class of molecules is an important goal.

Epoxides are very useful synthons in organic synthesis because they are susceptible to attack by nucleophiles and are readily accessible in optically pure form.[9] Catalytic ring-opening of epoxides by amines is a straightforward method to prepare β-amino alcohols.[10] Surprisingly, no effective catalytic methods for the ring-opening reaction of an epoxide with an imidazole have been described to date. Only a few uncatalyzed methods for the preparation of imidazolyl alcohols via ring-opening of an epoxide by imidazole are reported.[5,11] However, these methods suffer from one or more disadvantages such as long reaction times, elevated temperature and pressure, moderate yields, are not viable industrially, and lack generality. Here we report an efficient and general epoxide ring-opening reaction, using silylated imidazole catalyzed by LiBr at room temperature under solvent-free conditions, to afford a cost-effective and environmentally friendly process for the synthesis of imidazolyl alcohols. It has been established that solvent-free reactions are generally fast, give high selectivity and yields, and usually require easier work-up procedures and simpler equipment.[12] We chose four different epoxide systems as representatives, alkyl, aryl, functional and internal, to generalize our method.

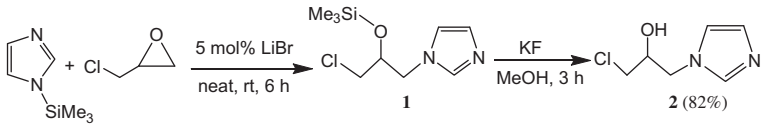


metronidazole ornidazole secnidazole

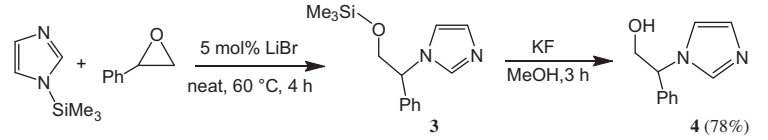
Figure 1. Examples of antiprotozoal drugs.

* Corresponding author. Tel.: +880 2 9899049x114; fax: +880 2 8831184.
E-mail addresses: drmajalil@yahoo.com, jalil_a@presidency.edu.bd (M. Abdul Jalil).

0040-4039/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2012.04.019



Scheme 1. Synthesis of imidazolyl alcohol from epichlorohydrin.



Scheme 2. Synthesis of imidazolyl alcohol **4** using an aryl-substituted unsymmetric epoxide.

To initiate our study we first chose the synthetically more important functionalised epoxide epichlorohydrin. The reaction of neat epichlorohydrin with an equimolar amount of silylated imidazole in the presence of a catalytic amount of LiBr (5 mol %) resulted in clean conversion into the ring-opened product **1**, which on treatment with KF in wet methanol gave the respective alcohol **2** in 82% isolated yield (Scheme 1). Similarly, we also prepared the optically pure imidazolyl alcohol (*R*)-**2** which was isolated as a white solid by starting from (*R*)-epichlorohydrin.[13] In contrast, the racemic imidazolyl alcohol **2** was a viscous colorless liquid.

The progress of the reaction was monitored by ^{1}H NMR spectroscopy and showed that **1** was the sole product resulting from nucleophilic attack at the terminal carbon of the epoxide. No product arising from nucleophilic displacement of chlorine could be detected through NMR and GC–MS analyses of the reaction mixture. We conducted the same reaction in the absence of LiBr to ascertain its role in the reaction. No significant amount of imidazolyl silyl ether **1** was formed in the absence of LiBr under the same reaction conditions even after prolonged stirring. It has been reported that the strong oxophilicity of a lithium ion can activate oxygen-containing electrophiles to nucleophilic attack.[14] We also conducted the LiBr-catalyzed reaction using 1*H*-imidazole instead of silylated imidazole under both solvent-free conditions and in anhydrous DMF. In both cases the conversion was rather disappointing. Yields of only 20–25% imidazolyl alcohol were obtained after purification. Therefore, silylated imidazole proved to be a more effective nucleophile than 1*H*-imidazole for efficient ring-opening of epoxides. This might be due to the enhanced nucleophilicity of the silylated imidazole. The other advantages in using silylated imidazole are: (i) it is widely soluble in most organic solvents, (ii) the reaction can be carried out conveniently under solvent-free conditions, and (iii) it is easy to convert the O-silylated product into its respective alcohol. We found that a significant amount of the imidazole silyl ethers were hydrolyzed to their respective alcohols during column chromatography using silica gel. Therefore, it was better to conduct the desilylation step on the crude product before performing column chromatography in order to obtain the pure imidazolyl alcohol as the sole product.

Next, we evaluated the regioselective outcome of the LiBr-catalyzed epoxide ring- opening with silylated imidazole using styrene oxide as a representative unsymmetrical epoxide. The reaction under mild heating at 60 °C gave only regioisomer **4** in 78% isolated yield (Scheme 2). At room temperature the reaction was slow and required 40 h to complete.

No regioisomer was formed as a result of attack of the nucleophile at the benzylic position. The regioselectivity was determined by ^{1}H NMR spectroscopy of the crude imidazolyl silyl ether and its respective alcohol. In both cases, only one set of signals was observed and that was identified as regioisomer **3** and its

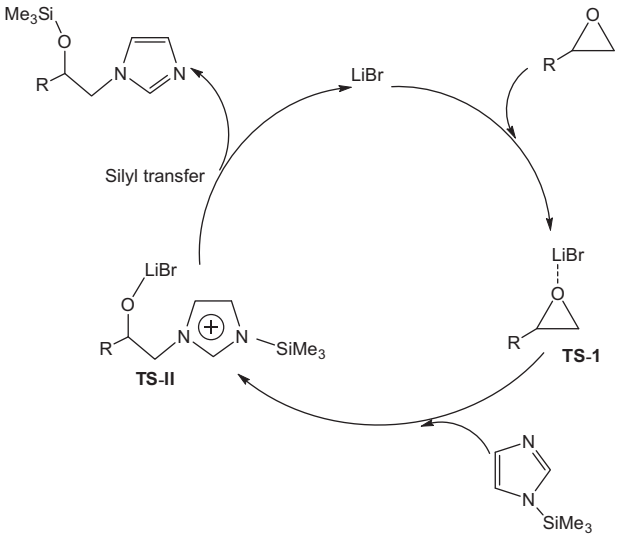
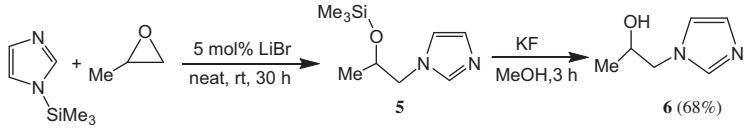


Figure 2. A plausible mechanism.

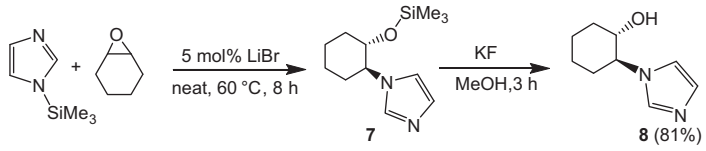
corresponding alcohol **4**. The ^{1}H and ^{13}C NMR spectra for **4** were identical to those reported.[5] The formation of the regioisomer **4** was further confirmed by determining the MS (EI) of the crude imidazolyl alcohol. In the MS, the presence of a daughter ion at *m*/*z* (M^+ 106) due to the loss of PhCHO from **4** and the absence of a daughter ion at (M^+ 31), a diagnostic feature of the alternative regioisomer, due to loss of CH_2OH, revealed the formation of regioisomer **4**, exclusively. Although the phenyl group in styrene oxide assists in the stabilization of the carbocationic character at the benzylic carbon in transition state **TS-I** (Fig. 2), the preferential attack at the terminal carbon of styrene oxide can be explained due to the enhanced nucleophilicity and hard nature of the silylated imidazole favoring a more S_N2-like process.

We next turned our attention to the conversion of an alkyl-substituted unsymmetric epoxide into the corresponding imidazolyl alcohol using propylene oxide as our model substrate. Reaction of propylene oxide with silylated imidazole in the presence of a catalytic amount of LiBr followed by desilylation with KF gave the corresponding ring-opened product **6** in 68% yield (Scheme 3). Spectroscopic analysis confirmed that no regioisomer was formed in this reaction.

Finally, we examined the efficiency of this method to prepare an imidazolyl alcohol by using a symmetric internal epoxide. An excellent 81% yield of product **8** was obtained from cyclohexene oxide on treatment with silylated imidazole under mild heating at 60 °C in the presence of 5 mol % LiBr (Scheme 4).



Scheme 3. Synthesis of imidazolyl alcohol **6** using an alkyl-substituted unsymmetric epoxide.



Scheme 4. Synthesis of an imidazolyl alcohol using a symmetric internal epoxide.

The stereochemistry of the ring-opened product **8** was found to be *trans*. The spectral data (^{1}H and ^{13}C) were similar to those of the reported compound.[5,15]

A plausible mechanism for the LiBr-catalyzed epoxide ring-opening with silylated imidazole is depicted in Figure 2.

Coordination of the epoxide oxygen to Li^+ (**TS-I**) renders the epoxide susceptible to nucleophilic attack by the silylated imidazole leading to **TS-II**. Subsequent intra or intermolecular silyl transfer resulted in formation of the imidazolyl silyl ether and liberation of the catalyst.

In conclusion, we have described an efficient general catalytic method for the preparation of biologically important imidazolyl alcohols via an epoxide ring-opening reaction. The advantages of this method are that the reactions are carried out under mild conditions in short times, with excellent stereo- and regioselectivity, using an inexpensive, user friendly, non-toxic catalyst. The solvent-free reaction conditions combined with simple experimental and product isolation procedures is expected to contribute to the development of an environmentally friendly (assuming no toxic organic solvents are used in the work-up/column chromatography) process for the synthesis of biologically and catalytically important imidazolyl alcohols.

Acknowledgment

We gratefully thank Dr. Tapan Kumar Chakraborti of the Presidency University for his support.

Supplementary data

Supplementary data (synthetic and spectroscopic data for compounds **2**, **4**, **6**, and **8**) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.04.019.

References and notes

1. Rosello, A.; Bertini, S.; Lapucci, A.; Macchia, M.; Martinelli, A.; Rapposelli, S.; Herreros, E.; Macchia, B. *J. Med. Chem.* **2002**, *45*, 4903–4912; (b) Sheehan, D. J.; Hitchcock, C. A.; Sibley, C. M. *Clin. Microbiol. Rev.* **1999**, *12*, 40–79; (c) Lartey, P. A.; Moehle, C. M. In *Annual Reports in Medicinal Chemistry*; Bristol, J. A., Ed.; Academic Press: New York, 1997; Vol. 32, pp 151–169; (d) Botta, M.; Corelli, F.; Gasparrini, F.; Messina, F.; Mugnaini, C. *J. Org. Chem.* **2000**, *65*, 4736–4739.
2. (a) Eicher, T.; Hauptmann, S. *The Chemistry of Heterocycles*; Georg Thieme Verlag: New York, 1995; (b)*Medicinal Chemistry: Principles and Practice*; King, F. D., Ed.; Royal Society of Chemistry: Cambridge, England, 1994; pp 191–202.
3. (a) Freyne, D.; Raeymaekers, A.; Venet, M.; Sanz, G.; Wouters, W.; De Coster, R.; Wauwe, J. V. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 267–272; (b) Njar, V. C. O.; Nnane, I. P.; Brodie, A. M. H. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1905–1908; (c) Aelterman, W.; Lang, Y.; Willemsens, B.; Vervest, I.; Leurs, S.; De Knaep, F. *Org. Process Res. Dev.* **2001**, *5*, 467–471; (d) Pouget, C.; Fagnere, C.; Basly, J. P.; Habrioux, G.; Chulia, A. J. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2859–2861.
4. (a) Godefroi, E.; Heeres, J.; Van Cutsem, J.; Janssen, P. *J. Med. Chem.* **1969**, *12*, 784; (b) Armando, R.; Simone, B.; Annalina, L.; Marco, M.; Adriano, M.; Simona, R.; Esperanza, H.; Bruno, M. *J. Med. Chem.* **2002**, *45*, 4903; (c) Polak, A. *Arzneim.-Forsch.* **1982**, *32*, 17–24; (d) Polak, A. *Sabouradia* **1983**, *21*, 205–213; (e) Gabriella, De M.; Guiseppe, La R.; Di Alessandra, P.; Rino, R.; Alberto, B.; Chiara, C.; Anna, S.; Giovanni, M.; Emmanuele, C.; Marino, A.; Romano, S. *J. Med. Chem.* **2005**, *48*, 4378.
5. (a) Kotsuki, H.; Wakao, M.; Hayakawa, H.; Shimanouchi, T.; Shiro, M. *J. Org. Chem.* **1996**, *61*, 984; (b) Kotsuki, H.; Wakao, M.; Hayakawa, H.; Shimanouchi, T.; Shiro, M. *J. Org. Chem.* **1996**, *61*, 8915; (c) Kotsuki, H.; Hayakawa, H.; Wakao, M.; Shimanouchi, T.; Ochi, M. *Tetrahedron: Asymmetry* **1995**, *6*, 2665.
6. Arnold, P. L.; Rodden, M.; Davis, K. M.; Scarisbrick, A. C.; Black, A. J.; Wilson, C. *Chem. Commun.* **2004**, 1612.
7. (a) Arnold, P. L.; Scarisbrick, A. C.; Black, A. J.; Rodden, M.; Wilson, C. *Chem. Commun.* **2001**, 2340; (b) Arnold, P. L.; Mungur, S. A.; Black, A. J.; Wilson, C. *Angew. Chem., Int. Ed.* **2003**, *42*, 5981.
8. Demberelnyamba, D.; Yoon, S. J.; Lee, H. *Chem. Lett.* **2004**, *33*, 560.
9. (a) Johnson, R. A.; Sharpless, K. B. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: New York, 1993. Chapter 4.1; (b) Jacobsen, E. N. Ibid. Chapter 4.2.
10. See for examples: (a) Yamamoto, Y.; Asao, N.; Meguro, M.; Tsukade, N.; Nemoto, H.; Adayari, N.; Wilson, J. G.; Nakamura, H. *J. Chem. Soc., Chem. Commun.* **1993**, 1201–1203; (b) Meguro, M.; Asao, N.; Yamamoto, Y. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2597; (c) Chini, M.; Crotti, P.; Favero, L.; Macchia, F.; Pineschi, M. *Tetrahedron Lett.* **1994**, *35*, 433; (d) Auge, J.; Leroy, F. *Tetrahedron Lett.* **1996**, *37*, 7715; (e) Rampalli, S.; Chaudhari, S. S.; Akamanchi, K. G. *Synthesis* **2000**, 7; (f) Curini, M.; Epifano, F.; Marcotullio, M. C.; Rosati, O. *Eur. J. Org. Chem.* **2001**, 4149; (g) Harrak, Y.; Pujol, M. D. *Tetrahedron Lett.* **2002**, *43*, 819; (h) Reddy, L. R.; Reddy, M. A.; Bhanumathi, N.; Rao, K. R. *Synthesis* **2001**, 831–832.
11. Glas, H.; Thiel, W. R. *Tetrahedron Lett.* **1998**, *38*, 5509.
12. (a) Tanaka, K.; Toda, F. In *Solvent-free Organic Synthesis*; Wiley-VCH, 2003; (b) Cave, G. W. V.; Raston, C. L.; Scott, J. L. *Chem. Commun.* **2001**, 2159–2169; (c) Varma, R. S. *Pure Appl. Chem.* **2001**, *73*, 193–198; (d) Tanaka, K.; Toda, F. *Chem. Rev.* **2000**, *100*, 1025–1074; (e) Varma, R. S. *Green Chem.* **1999**, 43–55; (f) Metzger, J. O. *Angew. Chem., Int. Ed.* **1998**, *37*, 2975–2978.
13. *Synthesis of (R)-**2**:* A 2-necked flask equipped with a stopper and a rubber septum was charged with LiBr (0.022 g, 5 mol %) in a glove box. It was then connected to a vacuum line and heat applied using a heating gun with occasional shaking of the flask in order to accumulate LiBr at the bottom of the flask. The flask was then filled with N_2 and epichlorohydrin (0.46 g, 2.5 mmol) was added via syringe and the mixture stirred for 10 min. Silyl imidazole (0.70 g, 2.5 mmol) was added via syringe and stirring was continued for 6 h at room temperature. KF (2.7 mmol) and MeOH (10 ml) were added and the mixture stirred for 3 h. The solvents were removed in vacuo and the remaining oily residue was purified by column chromatography using silica gel (CH_2Cl_2/MeOH = 9:1). Yield 82% (white solid); mp 89.0–91.0 °C; IR (KBr, cm^{-1}) *v*; 3117, 1597, 1511, 1440; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.27 (m, 1H; C*H*$_2$Cl), 3.40 (m, 1H, C*H*$_2$Cl), 3.90 (m, 2H, ImC*H*$_2$ and C*H*OH), 4.05 (m, 1H, ImC*H*$_2$), 5.54 (br d, 1H, O*H*), 6.74 (s, 1H, NC*H*N), 6.84 (s, 1H, NC*H*), 7.31 (s, 1H, NC*H*), ^{13}C NMR (100 MHz, $CDCl_3$): δ = 45.41 (s, *C*H$_2$Cl), 50.28 (s, ImCH$_2$), 70.00 (s, *C*HOH), 120.15 (s, NCH), 127.90 (s, NCH), 137.60 (s, NCH); MS (ESI): *m*/*z* (%): 161.1 (M+, 90), 90.9 (20), 68.97 (100); Anal. Calcd for $C_6H_9ClN_2O$: C 44.87, H 5.65, N 17.44. Found: C 44.67, H 5.72, N 17.09.
14. (a) Basak, A.; Nayak, M. K.; Chakraborti, A. K. *Tetrahedron Lett.* **1998**, *39*, 4883–4886; (b) Chakraborti, A. K.; Basak, A.; Grover, V. *J. Org. Chem.* **1999**, *64*, 8014–8017; (c) Chakraborti, A. K.; Rudrawar, S.; Kondaskar, A. *Eur. J. Org. Chem.* **2004**, 3597–3600.
15. Murabayashi, A.; Mukisumi, Y. *Heterocycles* **1990**, *31*, 537.