Available online at www.sciencedirect.com

SCIENCE DIRECT®

Tetrahedron Letters 45 (2004) 2435–2438

Tetrahedron Letters

Efficient synthesis of chlorohydrins: ionic liquid promoted ring-opening reaction of epoxides and TMSCl

Li-Wen Xu, Lyi Li, Chun-Gu Xia* and Pei-Qing Zhao

State key laboratory of Oxo Synthesis and Selective Oxidation, Lanzhou Institute of Chemical Physics, Chinese Academy of Sciences, Lanzhou 730000, PR China

Received 25 December 2003; revised 7 January 2004; accepted 13 January 2004

Abstract—The environmentally benign, highly efficient synthesis of chlorohydrins by cleavage of epoxides using TMSCl in ionic liquid, bmimPF_6, has been studied.

Chlorohydrins and other halohydrins are an important class of organic compounds and versatile intermediates in the synthesis of a vast range of biologically active natural and synthetic products, unnatural amino acids, and chiral auxiliaries for asymmetric synthesis.[1] There is a continued interest in the synthesis of chlorohydrins and derivatives. Methodologies for preparing these chlorohydrins include (a) conversion of aldehydes to chlorohydrins through chloroallylboration,[2] (b) cleavage of cyclic ketal acids with phosphorus pentachloride, thionyl chloride, or pivaloyl chloride,[3] (c) reaction of diol with dry HCl or chlorotrimethylsilane,[4] (d) zinc–magnesium- and samarium-mediated reaction of dichloroacetates with carbonyl compounds,[5] (e) olefins are directly functionalized to chlorohydrins in one-pot by palladium catalyst[6] or the combination of BTSP, trimethylsilyl (TMS)X (X = Cl), a catalytic amount of Lewis acid,[7] and (f) ring opening of epoxides with different chloride ion sources.[8] Although chlorohydrins are conveniently by an addition of hypohalite-water to olefins and other substrates, none or low regiospecific addition was observed. It is therefore not surprising that the synthesis of chlorohydrins through ring-opening reaction have received considerable attention. But the most general method of preparing chlorohydrins by the ring opening of epoxides with hydrogen halides, metal chlorides, or other chloride compounds[9] also suffers from one or more disadvantages such as acidity, handling, and in situ preparation of reagent or relative long reaction times, pharmacologically inactive chlorohydrins, unwanted byproducts, and low regioselectivity. Although recent advances[10] have made this route more attractive, development of cheaper, simpler, and more efficient methods, especially environmentally benign, highly efficient procedure, is highly desirable.

To minimize the amount of harmful organic solvents used in chemical processes, much attention has been devoted to the use of alternative reaction media. Besides supercritical fluids, water, and solvent-free conditions, the use of room ionic liquids has been receiving more attention.[11] Room temperature ionic liquid such as bmimPF_6 are finding growing application as an alternative media for separation and organic transformations, and much attention has been focused on organic reactions promoted by ionic liquid.[12] The desirable advantages of ionic liquids such as the lack of vapor pressure, wide liquid range, and thermal stability have made them exceptional reaction media and environmentally benign solvents.[13] These factors are especially important in industry. In addition, several ionic liquids show enhancement in reaction rates and selectivity, compared to organic solvents with added benefit of ease of recovery and reuse of these ionic liquids. Surprisingly however, there is no report on ionic liquids promoted ring-opening reaction of epoxides with chlorides ion sources.

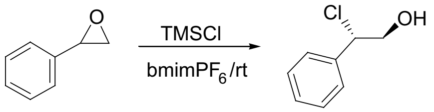
In view of the emerging importance of ionic liquids as novel reaction media, we wish to report the use of ionic liquid as efficient promoters for the synthesis of chlorohydrins or ring-opening reaction and other reaction.[14] In this letter, we try to explore the catalytic activities of

---

Keywords: Ionic liquid; Epoxide; Chlorohydrins; TMSCl.

* Corresponding author. Tel.: +86-0931-8276531; fax: +86-0931-827-7088; e-mail: cgxia@ns.lzb.ac.cn

0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.01.042



Scheme 1.

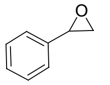
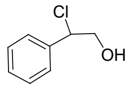
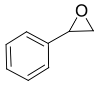
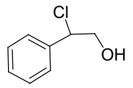
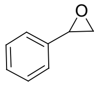
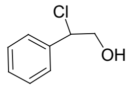
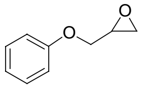
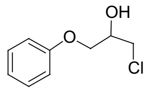
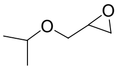
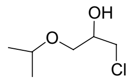
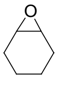
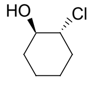
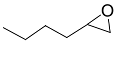
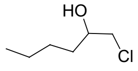
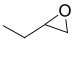
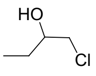
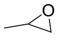
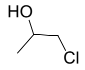
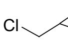
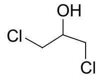
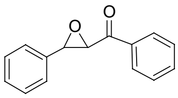
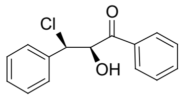
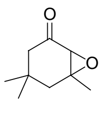
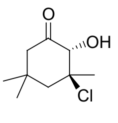
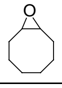
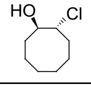
Scheme 2.

ionic liquid in the ring-opening reaction of epoxides with TMSCl (Schemes 1 and 2), and we reported the efficient and green synthesis of chlorohydrins through the first ionic liquid promoted ring-opening reaction of epoxides with TMSCl. Advantages of the protocol include high-yielding reaction that can be conducted at low temperature, high regio- and stereoselective ring opened products was obtained under environmental benign conditions.

Initially ring opening of styrene oxide (Scheme 1)[15] was investigated with TMSCl in ionic liquid bmimPF_6 and general organic solvents, such as CH_2Cl_2. Styrene oxide was treated with 1.1 equiv of TMSCl at room temperature in CH_2Cl_2, and few chlorohydrin products was obtained even for longer time (yield $\leqslant$ 10%). However, the ring opening of styrene oxide with TMSCl in bmimPF_6 gave clean conversion to the chlorohydrin, and styrene oxide was observed to yield chlorohydrin with chlorine at the more substituted α-carbon atom in high regioselectivity (99:1). Phosphine compound have been used in many reaction and include the ring-opening reactions.[16] However, the use of PF_6^- as catalyst has not been reported. We used $NaPF_6$ as a catalyst in the ring-opening reaction of TMSCl in CH_2Cl_2 and found the catalyst was poor in the reaction (low yield). This enhancement in the reactivity observed in ionic liquid could be attributed to the strong Lewis acidity of bmimPF_6 in comparison to other organic solvents. To our knowledge, the result represent one of the highest regioselectivity reported to date for the nucleophilic catalytic ring-opening epoxides in the presence of TMSCl and other chlorine nucleophiles.[10e]

We then turned our attentions to examining the substrate scope under the same reaction condition (Scheme 2). We found that ionic liquid bmimPF_6 catalyzed or promoted the ring opening of epoxides at high rates. In the first hour, the reaction was carried out completely. Presented in Table 1 are the results of combining various epoxides with TMSCl in ionic liquid bmimPF_6 followed by cleavage of the trimethylsilyl group with aqueous HCl. In all cases the corresponding chlorohydrins were obtained in excellent yields (96–100%) and chemoselectivity or regioselectivity. The expected two isomers could not be separated by general column chromatography. On each occasion, the regioselectivity was determined by GC–MS and ^{1}H NMR. The stereochemistry of ring

Table 1. Ring opening of various epoxides with TMSCl promoted by ionic liquid bmimPF_6

Entry[a]	Substrates	Chlorohydrins	Yields (%)[b]
1			98 (99:1)
2[c]			Trace
3[d]			97 (99:1)
4			100 (100:0)
5			100 (100:0)
6			98
7			98 (80:20)
8			98 (85:15)
9			97 (74:26)
10			99 (99:1)
11			96[e] (89:11)
12			89[e] (78:22)
13			96

[a] All reaction were performed in ionic liquids for 1 h except entry 2.

[b] Isolated yields, and the ratio of stereochemistry was determined by ^{1}HNMR and GC–MS.

[c] The reaction was performed in CH_2Cl_2 and no addition of any catalyst for 5 h.

[d] The yield after five runs.

[e] The reaction was performed at 0–5 °C.

opening had several expected and unique features. The aliphatic epoxides such as cyclic oxides were observed to yield products with exclusive inversion of stereochemistry (entries 6 and 13). And styrene oxide showed a strong preference for the opposite regioselective to that observed in the glycidyl aryl ethers and glycidyl alkyl ethers.

To check the efficiency of recycling ionic liquids ($bmimPF_6$), styrene oxide was subjected to the ring-opening reaction of TMSCl,[17] after five runs, the yield of corresponding chlorohydrin was very high (97%).

In summary, we have first demonstrated that the ring-opening reaction of epoxides with TMSCl could be promoted by simple recyclable $bmimPF_6$ ionic liquid. The present reaction with its mild reaction conditions opens a novel entry to synthesis of chlorohydrins compounds using recyclable ionic liquid. And the specific advantages are that the reactions are carried out under mild conditions with high stereo-, and chemoselectivity for the synthesis of chlorohydrin derivatives.

Acknowledgements

This study was supported in part by the Natural Science Founder of National for financial support of the work (No. 29933050 and 20373082).

References and notes

1. (a) Erden, I. In *Comprehensive Heterocyclic Chemistry*, 2nd ed.; Padwa, A., Ed.; Pergamon: Oxford, 1996; Vol. 1A, Chapter 1.03; (b) Watson, K. G.; Fung, Y. M.; Gredley, M.; Bird, G. J.; Jackson, W. R.; Gountzos, H.; Matthews, B. R. *Chem. Commun.* **1990**, 1018; (c) Kolb, H. C.; Sharpless, K. B. *Tetrahedron* **1992**, *48*, 10515; (d) Kwon, D. W.; Cho, M. S.; Kim, Y. H. *Synlett* **2003**, 959; (e) Akiyama, Y.; Fukuhara, T.; Hara, S. *Synlett* **2003**, 1530.
2. (a) Brown, H. C.; Racherla, U. S.; Liao, Y.; Khanna, V. V. *J. Org. Chem.* **1992**, *57*, 6608; (b) Jayaraman, S.; Hu, S.; Oehlschlager, A. C. *Tetrahedron Lett.* **1995**, *36*, 4765.
3. (a) Newman, M. S.; Chen, C. H. *J. Org. Chem.* **1973**, *38*, 1173; (b) Newman, M. S.; Chen, C. H. *J. Am. Chem. Soc.* **1972**, *94*, 2149; (c) Robins, M. J.; Mengel, R.; Jones, R. A. *J. Am. Chem. Soc.* **1973**, *95*, 4074.
4. (a) Derbesy, M.; Naudet, M. *Bull. Soc. Chim. Fr.* **1968**, 4531; (b) Eras, J.; Méndez, J. J.; Balcells, M.; Canela, R. *J. Org. Chem.* **2002**, *67*, 8631.
5. (a) Benincasa, M.; Forti, L.; Ghelfi, F.; Libertini, E.; Pagnoni, U. M. *Synth. Commun.* **1996**, *26*, 4113; (b) Curran, T. T. *J. Org. Chem.* **1993**, *58*, 6360; (c) Kim, K. S.; Qian, L. *Tetrahedron Lett.* **1993**, *34*, 7195; (d) Zhang, X. L.; Han, Y.; Tao, W. T.; Huang, Y. Z. *J. Chem. Soc., Perkin. Trans. 1* **1995**, 189; (e) Tanaka, H.; Yamashita, S.; Yamanoue, M.; Torii, S. *J. Org. Chem.* **1989**, *54*, 444; (f) Utimoto, K.; Takai, T.; Matsui, T.; Matsubara, S. *Bull. Soc. Chim. Fr.* **1997**, *134*, 365; (g) Castagner, B.; Lacombe, P.; Ruel, R. *J. Org. Chem.* **1998**, *63*, 4551.
6. El-Qisairi, A. K.; Qaseer, H. A.; Henry, P. M. *J. Organomet. Chem.* **2002**, *656*, 168.
7. (a) Sakurada, I.; Yamasaki, M.; Gottlich, R.; Lida, T.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2000**, *122*, 1245; (b) Larock, R. C. *Comprehensive Organic Transformations*; VCH: New York, 1989; pp 325–326.
8. (a) Andrews, G. C.; Crawford, T. C.; Contilio, L. G. *Tetrahedron Lett.* **1981**, *22*, 3803; (b) Loreto, M. A.; Pellacani, L.; Tardella, P. A. *Synth. Commun.* **1981**, *11*, 287.
9. (a) Eisch, J. J.; Liu, Z. R.; Ma, X.; Zheng, G. X. *J. Org. Chem.* **1992**, *57*, 5140; (b) Shimizu, M.; Yoshida, A.; Tamotsu, F. *Synlett* **1992**, 204; (c) Eisch, J. J.; Liu, Z. R.; Singh, M. *J. Org. Chem.* **1992**, *57*, 1618; (d) Azzena, F.; Calvani, F.; Crotti, P.; Gardelli, C.; Macchia, F.; Pineschi, M. *Tetrahedron* **1995**, *51*, 10601; (e) Ciaccio, J. A.; Heller, E.; Talbot, A. *Synlett* **1991**, 248.
10. (a) Garrett, C. E.; Fu, G. C. *J. Org. Chem.* **1997**, *62*, 4534; (b) Denmark, S. E.; Barsanti, P. A.; Wong, K. T.; Stavenger, R. A. *J. Org. Chem.* **1998**, *63*, 2428; (c) Ready, J. M.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1999**, *121*, 6086; (d) Reymond, S.; Brunel, J. M.; Buono, G. *Tetrahedron: Asymmetry* **2000**, *11*, 4441; (e) Wang, L. S.; Hollis, T. K. *Org. Lett.* **2003**, *5*, 2543.
11. (a) Tanaka, K.; Toda, F. *Chem. Rev.* **2000**, *100*, 1025–1074; (b) Adeyemi, O. G.; Coville, N. J. *Organometallics* **2003**, *22*, 2284; (c) Akiyama, T.; Sanada, M.; Fuchibe, K. *Synlett* **2003**, 1463; (d) Chancharunee, S.; Perlmutter, P.; Statton, M. *Tetrahedron Lett.* **2003**, *44*, 5683–5685; (e) Firouzabadi, H.; Iranpoor, N.; Nowrouzi, F. *Tetrahedron Lett.* **2003**, *44*, 5343; (f) Mitra, A. K.; Banerjee, K. *Synlett* **2003**, 1509.
12. (a) Welton, T. *Chem. Rev.* **1999**, *99*, 2071; (b) Wasserscheid, P.; Keim, W. *Angew. Chem., Int. Ed.* **2000**, *39*, 3773; (c) Sheldon, R. *Chem. Commun.* **2001**, 2399; (d) Zhang, S. B.; Ding, M. X.; Gao, L. X. *J. Org. Chem.* **2002**, *22*, 159; (e) Dupont, J.; de Souza, R. F.; Suarez, P. A. Z. *Chem. Rev.* **2002**, *102*, 3669; (f) Chandrasekhar, S.; Narasihmulu, C.; Jagadeshwar, V.; Reddy, K. V. *Tetrahedron Lett.* **2003**, *44*, 3629; (g) Li, Z.; Xia, C. G. *Tetrahedron Lett.* **2003**, *44*, 2069.
13. (a) Davis, J. H.; Fox, P. A. *Chem. Commun.* **2003**, 1209; (b) Davis, J. H.; Fox, P. A. *Chem. Commun.* **2003**, 4281; (c) Kabalka, G. W.; Venkataiah, B.; Dong, G.; Kim, D. W.; Song, C. E.; Chi, D. Y. *J. Org. Chem.* **2003**, *68*; *Tetrahedron Lett.* **2003**, *44*, 4673; (d) Chen, S.; Ji, S. L.; Loh, T. P. *Tetrahedron Lett.* **2003**, *44*, 2405; (e) Ranu, B. C.; Dey, S. S. *Tetrahedron Lett.* **2003**, *44*, 2865.
14. Xu, L. W.; Li, L.; Xia, C. G.; Zhou, S. L.; Li, J. W. *Tetrahedron Lett.*, **2004**, *45*, 1219.
15. General procedure: A mixture of the epoxide (2 mmol), TMSCl (2.2 mmol, freshly distilled: argon atmosphere, pyridine) and 2 mL of $bmimPF_6$, was stirred at room temperature for 1 h. After completion of the reaction, as indicated by TLC and GC, the reaction mixture was diluted with water and aqueous HCl or NH_4Cl, and extracted with diethyl ether. The combined organic layers were dried over anhydrous Na_2SO_4, concentrated in vacuo, and purified by column chromatography on silica gel (100–200 mesh, ethyl acetate–petroether) to afford corresponding chlorohydrin. All the known compounds were characterized by GC–MS (Agilent 6890N GC/5973N MS, HP-5MS) and usual spectral methods.
16. Some new examples of phosphine catalyzed reaction: (a) Lu, X. Y.; Zhang, C. M.; Xu, Z. R. *Acc. Chem. Res.* **2001**, *34*, 535; (b) Brown, P. M.; Kappel, N.; Murphy, P. J. *Tetrahedron Lett.* **2002**, *43*, 8707; (c) Wende, M.; Gladysz, J. A. *J. Am. Chem. Soc.* **2003**, *125*, 5861; (d) Stewart, I. C.; Bergman, R. G.; Toste, F. D. *J. Am. Chem. Soc.* **2003**, *125*, 8696; (e) Valentine, D. H., Jr.; Hillhouse, J. H.

Synthesis **2003**, 317; (f) Fan, R. H.; Hou, X. L. *Tetrahedron Lett.* **2003**, *44*, 4411; (g) Fan, R. H.; Hou, X. L. *J. Org. Chem.* **2003**, *68*, 726; (h) Shi, M.; Chen, L. H. *Chem. Commun.* **2003**, 1310; (i) Xu, L. W.; Xia, C. G.; Li, J. W.; Zhou, S. L. *Synlett* **2003**, 2246.

17. Recycling study of ionic liquid: After extraction with diethyl ether to separate the products, the ionic liquid layer was washed by aqueous $NaHCO_3$, water; the residue water was removed in vacuum, and the resulting ionic liquid layer was reused for the next run.