Pergamon

Tetrahedron Letters 42 (2001) 3955–3958

TETRAHEDRON LETTERS

Highly regioselective ring opening of epoxides and aziridines using cerium(III) chloride†

Gowravaram Sabitha,* R. Satheesh Babu, M. Rajkumar, Ch. Srinivas Reddy and J. S. Yadav

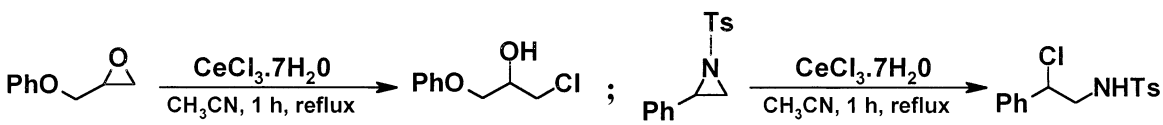
Organic Division I, Indian Institute of Chemical Technology, Hyderabad 500 007, India

Received 18 December 2000; accepted 11 April 2001

Abstract—A wide variety of epoxides and aziridines were converted to the corresponding β-halohydrins and β-haloamines using cerium(III) chloride and the cerium(III) chloride/NaI system in acetonitrile. The reactions were highly regioselective and efficient with excellent yields under mild and neutral reaction conditions. © 2001 Elsevier Science Ltd. All rights reserved.

Epoxides[1] and aziridines[2] have been recognized as most important and versatile synthetic intermediates in organic synthesis. They can be easily prepared and due to their ring strain and high reactivity, their reactions with various nucleophiles lead to highly regio- and stereoselective ring opened products. Therefore, there is significant current interest in the ring opening reactions of epoxides and aziridines. *vic*-Halohydrins have considerable importance[3] in the synthesis of halogenated marine natural products[4] and they can be utilized for some useful synthetic transformations.[5] These are generally prepared by ring opening of epoxides with hydrogen halides[6] or Lewis acids such as BF_3,[7] but these are limited by competing rearrangements and side reactions with other acid sensitive functional groups. Although they are conveniently prepared by addition of hypohalous acids and hypohalites to olefins,[8] the low regioselectivity of this addition makes this methodology less attractive. Iodohydrins can be also be prepared by iodomethylation of carbonyl compounds with CH_2I_2 in the presence of SmI_2[9] and elemental halogen.[10] Even though metal halides such as LiX[11] and the $TiCl_4{\cdot}LiX$[12] complex have been reported recently for this transformation, an excess of reagent is required and, particularly in the case of chlorohydrins, it takes several days for complete conversion. The hygroscopic nature of LiI limits its use in making iodohydrins. Similarly, a number of ring opening reactions of aziridines have been reported,[13] but the formation of chloroamines requires the addition of a catalyst to fasten the reaction. The ability of aziridines to undergo highly regio- and stereoselective ring opening reactions gives them great value in organic synthesis.[14] The regioselective conversion of epoxides and aziridines is a useful tool for stereospecific synthesis of various synthons. Since a large number of marine natural products possess halogenated skeletons, the development of a mild, efficient and convenient protocol which works with equal ease for epoxides and aziridines is desired for the synthesis of β-halohydrins and β-haloamines.

Recently cerium(III) chloride has been used for several regio- and chemoselective transformations,[15] since it is a very cheap, nontoxic and water tolerant reagent.[16] Addition of NaI makes this reagent very efficient.[17] Herein, we wish to report a highly efficient and regioselective ring opening of epoxides and aziridines with $CeCl_3{\cdot}7H_2O$ and the $CeCl_3{\cdot}7H_2O$/NaI system. These conversions are rapid and lead to the formation of the corresponding halohydrins and haloamines in excellent



Scheme 1.

Keywords: regioselective; cerium(III) chloride; epoxides; aziridines.

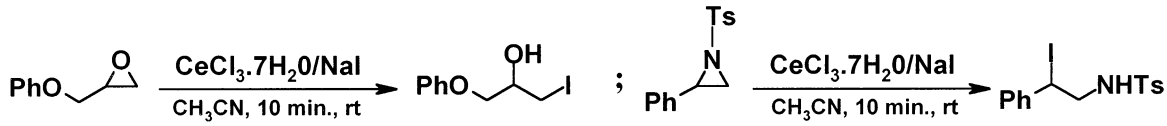
* Corresponding author.

† IICT Communication No. 4671.

PII: S0040-4039(01)00622-0

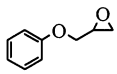
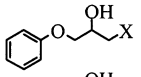
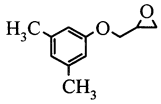
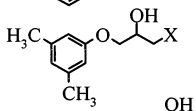
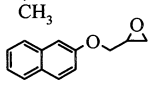
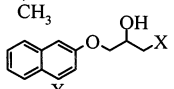
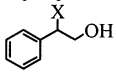
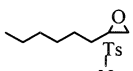
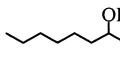
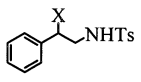
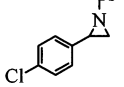
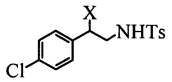
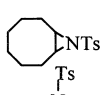
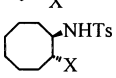
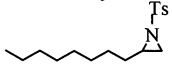
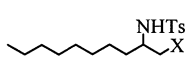
yields within a very short time. The mild reaction conditions, high efficiency and the use of a cheap, readily available and nontoxic reagent may open new access to β-halohydrins and β-haloamines (Schemes 1 and 2).

The reaction of phenyl glycidyl ether (Table 1, entry 1) was tested with 0.5 equiv. of $CeCl_3{\cdot}7H_2O$ in refluxing acetonitrile. Interestingly, complete conversion was achieved within 1 h to afford 1-chloro-3-phenoxy-2-propanol in 99% yield. This reaction failed to give any product at room temperature after prolonged time, whereas the ring opening reaction of the same compound, phenyl glycidyl ether (entry 1) with 0.5 equiv. of $CeCl_3{\cdot}7H_2O$ and 1 equiv. of NaI in acetonitrile, afforded the corresponding iodohydrin quantitatively at room temperature. The reaction was very fast and complete conversion was achieved within 10 minutes without any by-products. To test the generality of the reaction, several terminal epoxides were converted into the corresponding chlorohydrins and iodohydrins, respectively, as summarized in Table 1. In all cases, the



Scheme 2.

Table 1. Regioselective ring opening of epoxides and aziridines using cerium(III) chloride

Entry	Epoxide/Aziridine	Product [a]		Yield [b] %
1			X=Cl X=I	99 99
2			X=Cl X=I	97 99
3			X=Cl X=I	96 96
4			X=Cl X=I	84(8) 95
5			X=Cl X=I	90 91
6			X=Cl X=I	92 95
7			X=Cl X=I	90 96
8			X=Cl X=I	92 97
9			X=Cl X=I	93 90
10			X=Cl X=I	90 93
11			X=Cl X=I	92(5) 99
12			X=Cl X=I	91(5) 95
13			X=Cl X=I	92 96
14			X=Cl X=I	90 92
15			X=Cl X=I	95 97
16			X=Cl X=I	90 91

[a] The products obtained were characterized by IR, ^{1}H NMR and Mass spectra.

[b] Yield refers to the isolated pure products after column chromatography, yields in parantheses correspond to the diol in case of the epoxide and the aminoalcohol in case of the aziridine.

reaction was found to be highly regioselective giving the corresponding 1-chloro- and 1-iodo-2-alkanols exclusively in quantitative yields. This demonstrates the predominant attack of the reagent on the less hindered carbon of the epoxides. As expected in the case of styrene oxide (Table 1, entry 4), 2-chloro- and 2-iodo-2-phenylethanols were obtained as the major products due to the formation of the stabilized benzylic cation during the reaction. The corresponding diol was also isolated in 5–8% yield by refluxing in acetonitrile with $CeCl_3{\cdot}7H_2O$. The ring opening reaction of cyclic epoxides such as cyclopentene oxide, cyclohexene oxide and cyclooctene oxide was completely *anti*-stereoselective in both cases giving only the *trans* isomers.

Similarly as reported for the opening of epoxides, the ring opening reaction of *N*-substituted aziridines[18] proceeded very smoothly with 0.5 equiv. of $CeCl_3{\cdot}7H_2O$ in refluxing acetonitrile. Complete conversion was achieved within 1 h to afford the corresponding chloroamines in excellent yields, whereas the reaction of aziridines with 0.5 equiv. of $CeCl_3{\cdot}7H_2O$ and 1 equiv. of NaI in acetonitrile proceeded very cleanly to afford the iodoamines in quantitative yields. The reaction was very fast and complete conversion was observed within 10 minutes at room temperature. The ring opening of cyclic aziridines such as *N*-tosylcyclohexeneimine (Table 1, entry 13) gave the *trans* isomer and the stereochemistry of the iodoamine was deduced from the relevant coupling constants. To show the scope of the reaction, we extended it to a variety of cyclic and acyclic aziridines. In the case of acyclic terminal aziridines, the reaction was highly regioselective due to attack of chloride and iodide ions at the less hindered terminal carbon atom. The reaction of styrene *N*-tosylaziridine (Table 1, entry 11) occurred in reverse, the product formed was the one due to the attack at the benzylic carbon atom. Even though a single product, *N*-(2-iodo-2-phenylethyl)-4-methylbenzenesulfon amide, was isolated when styrene *N*-tosylaziridine (entry 11) was subjected to opening with the $CeCl_3{\cdot}7H_2O$/NaI system, two products, *N*-(2-chloro-2-phenylethyl)-4-methyl benzene sulfonamide and the corresponding amino alcohol were isolated in a 95:5 ratio with $CeCl_3{\cdot}7H_2O$ alone, as similarly observed in the case of styrene epoxide. This may be due to the fact that in these cases chloride ion competes with water, which is present in the reagent in refluxing conditions. It is interesting to note that in the absence of $CeCl_3$, the epoxides and aziridines were not cleaved with NaI alone after longer reaction times (24 h), instead the starting materials were recovered. Hence, this clearly indicates the role of $CeCl_3$ in the reactions.

In conclusion, we have demonstrated a highly efficient and regioselective conversion of epoxides and aziridines to the corresponding β-halohydrins and β-haloamines under neutral conditions[19] using water tolerant $CeCl_3{\cdot}7H_2O$ and the $CeCl_3{\cdot}7H_2O$/NaI system. Our methodology presents several advantages like the stability and availability of the catalyst, its ease of handling, shorter reaction times and excellent yields of the products. Further, the method is equally applicable to both epoxides and aziridines, hence we believe that this protocol makes a valuable addition to organic synthesis.

Acknowledgements

R.S.B. and M.R. thank CSIR and Ch.S.R. thanks UGC, New Delhi for the award of fellowships.

References

1. Parker, R. E.; Isaacs, N. S. *Chem. Rev.* **1959**, *59*, 737.
2. (a) Osborn, H. M. I.; Sweeney, J. *Tetrahedron: Asymmetry* **1997**, *8*, 1693; (b) Coleman, R. S. *Synlett* **1998**, 1031.
3. See for a review: Bartlett, P. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: Orlando, Fl, 1984; Vol. 3, p. 411.
4. For reviews, see: Moore, R. E. In *Marine Natural Products*; Scheuer, P. J., Ed.; Academic Press: New York, 1978; Vol. 1, Chapter 2; (b) Fenical, W. In *Marine Natural Products*; Scheuer, P. J., Ed.; Academic Press: New York, 1980; Vol. 2, p. 174; (c) Faulkner, D. *J. Nat. Prod. Pep.* **1984**, 25.
5. (a) Tarasow, T. M. *J. Org. Chem.* **1989**, *54*, 4966; (b) Corey, E. J. *Tetrahedron Lett.* **1982**, *23*, 4217; (c) Nace, H. R.; Crosby, G. A. *J. Org. Chem.* **1979**, *44*, 3105.
6. (a) Stewart, C. A.; Vander Werf, C. A. *J. Am. Chem. Soc.* **1954**, *76*, 1259; (b) Winstein, S.; Ingraham, L. L. *J. Am. Chem. Soc.* **1952**, *74*, 1160.
7. Coxon, J. N.; Hartshorn, M. P.; Rae, W. J. *Tetrahedron* **1970**, *26*, 1091.
8. For a review, see: Boguslavskaya, L. S. *Russ. Chem. Soc. Rev.* **1972**, *41*, 740.
9. Imamoto, T.; Takeyama, T.; Koto, H. *Tetrahedron Lett.* **1986**, *27*, 3243.
10. Sharghi, H.; Naeimi, H. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 1525.
11. (a) Kotsuki, H.; Shimanouchi, T. *Tetrahedron Lett.* **1996**, *37*, 1845; (b) Kotsuki, H.; Shimanouchi, T.; Ohshima, R.; Fujiwara, S. *Tetrahedron* **1998**, *54*, 2709.
12. Shimizu, M.; Yoshida, A.; Fujisawa, T. *Synlett* **1992**, 204.
13. (a) Wu, J.; Hou, X. L.; Dai, L. X. *J. Org. Chem.* **2000**, *65*, 1344; (b) Katagiri, T.; Takahashi, M.; Fujiwara, Y.; Ihara, H.; Uneyama, K. *J. Org. Chem.* **1999**, *64*, 7323.
14. Tanner, D. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 599.
15. (a) Ballini, R.; Marcantoni, E.; Perrella, S. *J. Org. Chem.* **1999**, *64*, 2954; (b) Alessandrini, S.; Bartoli, G.; Bellucci, M. C.; Dalpozzo, R.; Malavolta, M.; Marcantoni, E.; Sambri, L. *J. Org. Chem.* **1999**, *64*, 1986; (c) Liu, H.-J.; Shia, K.-S.; Shang, X.; Zhu, B.-Y. *Tetrahedron* **1999**, *55*, 3803 and references cited therein; (d) Denmark, S. E.; Nicaise, O. *Synlett* **1993**, 359; (e) Di Deo, M.; Marcantoni, E.; Torregiani, E.; Bartoli, G.; Bellucci, M. C.; Bosco, M.; Sambri, L. *J. Org. Chem.* **2000**, *65*, 2830.
16. Imamoto, T. *Lanthanides in Organic Synthesis*; Academic Press: New York, 1994.
17. (a) Bartoli, G.; Bellucci, M. C.; Bosco, M.; Cappa, A.; Marcantoni, E.; Sambri, L.; Orregiani, E. *J. Org. Chem.* **1999**, *64*, 5696; (b) Bartoli, G.; Bellucci, M. C.; Bosco, M.; Marcantoni, E.; Sambri, L.; Torregiani, E. *Eur. J. Org. Chem.* **1999**, 617; (c) Bartoli, G.; Bosco, M.; Marcantoni, E.; Sambri, L.; Torregiani, E. *Synlett* **1998**, 209; (d) Marcantoni, E.; Nobili, F.; Bartoli, G.; Bosco, M.; Sambri, L. *J. Org. Chem.* **1997**, *62*, 4183.

18. Ando, T.; Kano, D.; Minakata, S.; Ryu, I.; Komastu, M. *Tetrahedron* **1998**, *54*, 13485.

19. **General procedures for the regioselective opening of epoxides and aziridines: preparation of β-chlorohydrins and β-chloroamines**: To a solution of $CeCl_3 \cdot 7H_2O$ (0.5 mmol) and acetonitrile (10 mL), was added epoxide or aziridine (1 mmol) in acetonitrile (2 mL) and refluxed for 1 h. On completion, the solvent was removed under reduced pressure and extracted with EtOAc (2×10 mL) and washed with water and brine. After drying (Na_2SO_4) and solvent removal, the crude product was purified by column chromatography. The products obtained were characterized by IR, ^{1}H NMR and mass spectral data. **1-Chloro-3-phenoxy-2-propanol** (Table 1, entry 1): ^{1}H NMR ($CDCl_3$) δ 2.59 (d, 1H, $J=5.5$ Hz), 3.74 (m, 2H), 4.10 (m, 3H), 6.8–7.1 (m, 3H), 7.1–7.4 (m, 2H). ***N*-(2-Chlorocyclohexyl)-4-methylbenzenesulfonamide** (Table 1, entry 13): ^{1}H NMR ($CDCl_3$) δ 1.20–1.40 (m, 3H), 1.50–1.80 (m, 3H), 2.10–2.40 (m, 2H), 2.50 (s, 3H, CH_3), 3.00–3.20 (m, 1H) 3.60–3.8 (m, 1H), 4.95 (d, 1H, NH), 7.30 (d, $J=8.10$ Hz, 2H), 7.80 (d, $J=8.25$ Hz, 2H).

Preparation of β-iodohydrins and β-iodoamines: To a mixture of $CeCl_3 \cdot 7H_2O$ (0.5 mmol) and NaI (1 mmol) in acetonitrile (10 mL), was added epoxide or aziridine (1 mmol) in acetonitrile (2 mL) and stirred at room temperature for 10 minutes. On completion, the solvent was removed under reduced pressure and extracted with EtOAc (2×10 mL) and washed with water and brine. After drying (Na_2SO_4) and solvent removal, the crude product was purified by column chromatography. The products obtained were characterized by IR, ^{1}H NMR and mass spectral data. **2-Iodo-2-phenylethanol** (Table 1, entry 4): ^{1}H NMR ($CDCl_3$) δ 1.90 (brs, 1H), 4.1 (m, 2H), 5.18 (t, 1H, $J=7$ Hz), 7.35 (s, 5H). **2-Iodo-1-phenylethanol** (Table 1, entry 4): ^{1}H NMR δ 2.40 (brs, 1H), 3.39 (dd, 1H, $J=10$, 8 Hz), 3.5 (dd, 1H, $J=10$, 4.6 Hz), 4.8 (m, 1H), 7.35 (s, 5H). ***N*-(2-Iododecyl)-4-methylbenzenesulfonamide** (Table 1, entry 16): ^{1}H NMR ($CDCl_3$) δ 0.85 (t, $J=7.0$ Hz, 6.6 Hz, 3H), 1.05–1.6 (m, 14H), 2.45 (s, 3H), 2.9–3.0 (m, 1H), 3.10–3.30 (m, 2H), 4.55 (d, NH), 7.30 (d, $J=8.0$ Hz, 2H), 7.75 (d, $J=7.95$ Hz, 2H).