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Cerium(III) Chloride Promoted Highly Regioselective Ring Opening of Epoxides and Aziridines Using NaN_3 in Acetonitrile: A Facile Synthesis of 1,2-Azidoalcohols and 1,2-Azidoamines†

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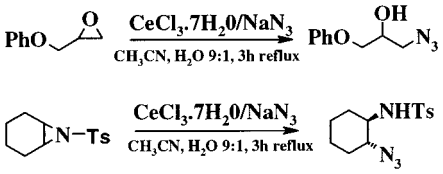
ABSTRACT



A convenient and efficient synthesis of 1,2-azidoalcohols and 1,2-azidoamines has been achieved by ring opening of epoxides and aziridines using cerium(III) chloride and sodium azide in acetonitrile. The reaction is highly regioselective and afforded the corresponding products in good to excellent yields under mild and neutral reaction conditions. The method is very rapid and equally compatible for both epoxides and aziridines.

1,2-Azidoalcohols are versatile intermediates in organic synthesis since they are very important precursors of β-amino alcohols and vicinal diamines, which are present in numerous natural products.[1] Further, their importance is significant in the chemistry of carbohydrates and nucleosides.[2] 1,2-Azidoamines are compounds of synthetic interest because of the reduced products, vicinal diamines which are biologically important compounds[3] and have varied applications in organic synthesis.[4] Therefore, there is significant current interest in the ring opening reactions of epoxides and aziridines using azide as nucleophile. Azidohydrins and azidoamines can be easily prepared from epoxides and aziridines by the ring opening reaction. Because of their ring strain and high reactivity, their reactions with various nucleophiles lead to high regio- and stereoselective ring-opened products.

Generally, azidohydrins are prepared through the ring opening of epoxides by using different azides in suitable solvents. Even though the classical protocol uses[2a,b,5] sodium azide and ammonium chloride, the azidolysis reaction requires a long reaction time (12−48 h) and the azidohydrin is often accompanied by isomerization, epimerization, and rearrangement of products.[6a] The reagents for azidohydrin

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(3) Reets, M. T.; Jaeger, R.; Drewlies, R.; Hubel, M. *Angew. Chem., Int. Ed. Engl*. **1991**, *30*, 103 and references therein.

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(6) (a) Fringuelli, F.; Piermatti, O.; Pizzo, F.; Vaccaro, L. *J. Org. Chem*. **1999**, *64*, 6094 and references therein. (b) Fringuelli, F.; Piermatti, O.; Pizzo, F.; Vaccaro, L. *J. Org. Chem*. **2001**, *66*, 4719.

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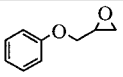
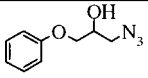
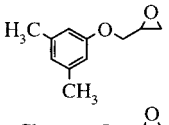
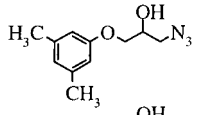
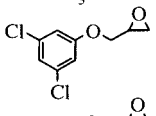
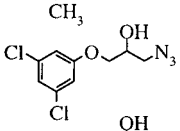
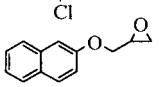
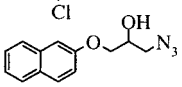
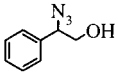
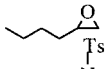
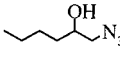
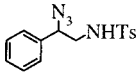
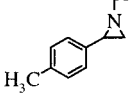
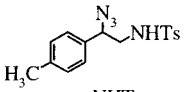
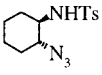
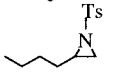
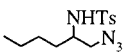
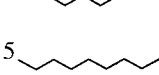
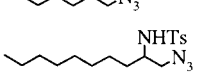
synthesis are the combined use of NaN_3 or $TMSN_3$ and a Lewis acid or a transition metal complex[7] or reaction in the presence of tetrabutylammonium salt.[8] Recently pH-controlled azidolysis of epoxides was also studied in water using various Lewis acids and NaN_3.[6] Similarly, 1,2-azidoamines are also compounds of synthetic interest in organic synthesis, because they are easily transformed to biologically important vicinal diamines. These *vic* azidoamines are generally prepared by ring opening reaction of aziridines. Yeung and co-workers reported the azidolysis of *N*-tosylaziridines with $TMSN_3$ in the presence of a chromium complex.[9,10] However, the results were not satisfactory regarding the yields and regioselectivity (1:1) with aziridines derived from terminal aliphatic compounds as well as styrene, and the reaction times were also too long (2−9 days). Azidolysis of aziridines was also reported with $TMSN_3$ but it requires tetrabutylammoniumfluoride[11] as a trigger. Another report describes the ring opening of nonactivated aziridines with $TMSN_3$ to yield the corresponding azidoamines.[12] Very recently, Lectka et al.[13] reported the azidolysis of *N*-benzylaziridine catalyzed by transition metal based complexes, which causes rearrangement to oxazolines. Although all the above methods and procedures have their own advantages, many of these procedures suffer from one or more drawbacks such as longer reaction times, strongly acidic conditions, unsatisfactory yields, and lack of regioselectivity, cost, and stability of the reagent. In this context, there is a great need to develop a mild and efficient method, which can be a valuable alternative for the synthesis of 1,2-azidoalcohols and 1,2-azidoamines.

In the context of our recent report in the regioselective ring opening of epoxides and aziridines[14] and the water-tolerant reagent[15] cerium(III) chloride, which has been used for several regio- and chemoselective transformations,[16] we herein disclose our results on regioselective azidolysis of epoxides and aziridines using a cerium(III) chloride and sodium azide system in a mixture of acetonitrile and water (9:1) (Schemes 1 and 2).

As a typical example, the reaction of phenyl glycidyl ether (1 mmol, entry 1, Table 1) was tested with a mixture of $CeCl_3 \cdot 7H_2O$ (0.5 mmol) and NaN_3 (1 mmol) in an acetonitrile and water mixture (9:1). After 3 h the complete conversion was achieved at acetonitrile reflux temperature to afford 1-azido-3-phenoxy-2-propanol in 99% yield. Because of the predominant attack of azide ion on the less hindered carbon of the epoxide, all the terminal epoxides gave highly regioselective azidohydrins in quantitative yields.

Table 1. Regioselective Ring Opening of Epoxides and Aziridines Using $CeCl_3 \cdot 7H_2O/NaN_3$

entry	epoxide/aziridine	product [a]	time h	yield [b] %
1			3	99
2			3	96
3			4	93
4			3	98
5			3	86(10)
6			5	93
7			3	98
8			4	95
9			6	92
10			6	96
11			3	94(3)
12			3	90(5)
13			3	97
14			6	90
15			6	95

[a] The products obtained were characterized by IR, ^1H NMR, and mass spectra. [b] Yield refers to the isolated pure products after column chromatography; yields in parantheses corresponds to the other isomer.

(7) (a) Birkofer, I.; Kaiser, W. *Liebigs Ann. Chem.* **1975**, 266. (b) Blandy, C.; Choukroun, R.; Gervais, D. *Tetrahedron Lett.* **1993**, *24*, 4189. (c) Caron, M.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 1560. (d) Nugent, W. A. *J. Am. Chem. Soc.* **1992**, *114*, 2768. (e) For a recent Review, see: Paterson, I.; Berrisford, D. J. *Organic Synthesis Highlights III*; Mulzer, J., Waldmann, H., Eds.; Wiley-VCH, 1998.

(8) Schneider, C. *Synlett* **2000**, *12*, 1840.

(9) Leung, W. H.; Yu, M. T.; Wu, M. C.; Yeung, L. L. *Tetrahedron Lett.* **1996**, *37*, 891.

(10) For aziridine opening with $TMSN_3$ catalyzed by a chiral chromium(III) complex, see: Li, Z.; Fernandez, M.; Jacobson, E. N. *Org. Lett.* **1999**, *1*, 1611.

(11) Wu, J.; Hou, X. L.; Dai, L. X. *J. Org. Chem.* **2000**, *65*, 1344.

(12) Chandrasekhar, M.; Sekar, G.; Singh, V. K. *Tetrahedron Lett.* **2000**, *41*, 10079.

(13) Ferraris, D.; Drury, W. J., III; Cox, C.; Lectka, T. *J. Org. Chem.* **1998**, *63*, 4568.

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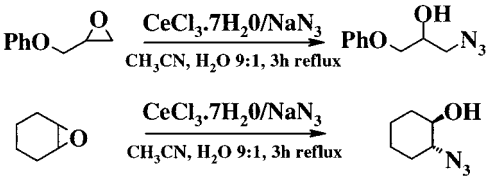
(15) Imamoto, T. *Lanthanides in Organic Synthesis*; Academic Press: New York, 1994.

(16) (a) Sabitha, G.; Satheesh Babu, R.; Rajkumar, M.; Srividya, R.; Yadav, J. S. *Org. Lett.* **2001**, *3*, 1149. (b) Ballini, R.; Marcantoni, E.; Perrella, S. *J. Org. Chem.* **1999**, *64*, 2954. (c) Alessandrini, S.; Bartoli, G.; Bellucci, M. C.; Dalpozzo, R.; Malavolta, M.; Marcantoni, E.; sambri, L. *J. Org. Chem.* **1999**, *64*, 1986. (d) Liu, H.-J.; Shia, K.-S.; Shang, X.; Zhu, B.-Y. *Tetrahedron* **1999**, *55*, 3803 and references therein. (e) Denmark, S. E.; Nicaise, O. *Synlett* **1993**, 359. (f) Di Deo, M.; Marcantoni, E.; Torregiani, E.; Bartoli, G.; Bellucci, M. C.; Bosco, M.; Sambri, L. *J. Org. Chem.* **2000**, *65*, 2830.

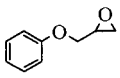
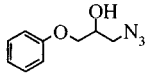
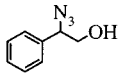
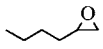
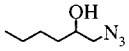
As expected in the case of styrene oxide (entry 5, Table 1), 2-azido-2-phenylethanol was obtained as the major product due to the formation of the stabilized benzylic cation during the reaction (Scheme 1). In the case of cyclic epoxides, the

Scheme 1



ring-opened products were completely *anti*-stereoselective, giving only the *trans* isomers. Comparison experiments were conducted for each epoxide classes (entries 1, 5, 7, and 10, Table 1) using classical procedure (NH_4Cl/NaN_3 in CH_3OH:H_2O 8:1) and the results are summarized in Table 2. This

Table 2. Comparative Study for Regioselective Ring Opening of Epoxides[a]

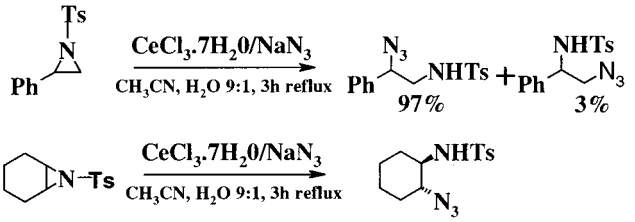
entry	epoxide	product	conditions	time h	yield [a] %
1			A	3	99
			B	12	93(1)
5			A	3	86(10)
			B	20	73(20)
7			A	3	98
			B	36	90
10			A	6	96
			B	36	89(5)

[a] **A:** 0.5 equiv of $CeCl_3$/1.1 equiv of NaN_3, CH_3CN:H_2O (9:1), reflux. **B:** 5 equiv of NH_4Cl/2.2 equiv of NaN_3, MeOH:H_2O (8:1), reflux. Yield refers to the isolated pure products after column chromatography; yields in parantheses corresponds to the other isomer.

indicates the superiority of our protocol in terms of regioselectivity, yields, and reaction times.

Similarly, the ring opening of *N*-substituted aziridines proceeded very smoothly with $CeCl_3 \cdot 7H_2O$ (0.5 mmol) and NaN_3 (1 mmol) in an acetonitrile and water mixture (9:1). Complete conversion was achieved in 3 h at acetonitrile reflux temperature to afford the corresponding azidoamines

Scheme 2



in good yields (Scheme 2). As described in the case of ring opening reactions of epoxides, high regioselectivity was achieved in the case of terminal acyclic aziridines, affording 1- and 2- azido products with a ratio of >99:1 (entries 14 and 15, Table 1) because of the attack of nucleophile on the less substituted aziridine carbon. In the case of cyclic aziridine (entry 13, Table 1), the reactions were completely *anti* stereoselective, affording *trans* azidoamines. As expected, the reaction of styrene *N*-tosylaziridine (entry 11, Table 1) afforded the 1- and 2-azido products with a selectivity of 97:3 due to attack at the benzylic carbon atom. It is compulsory to use the acetonitrile and water mixture (9:1) at acetonitrile reflux temperature for more than 2 h, because as described in our earlier communication,[14] in the absence of water the chlorohydrins and chloroamines were isolated as products. To determine the role of $CeCl_3$, this reaction was tested without use of cerium(III) chloride; the reaction failed to give any product, but after prolonged reaction time (12 h) ~10% diol was isolated.

In conclusion, we have described a novel and regioselective ring opening of epoxides and aziridines with the $CeCl_3$/NaN_3 system in an acetonitrile/water mixture (9:1) for the synthesis of 1,2-azidoalcohols and 1,2-azidoamines under mild and neutral reaction conditions. The advantages of the present protocol, such as shorter reaction times, simplicity in operation, the low cost of reagents, high yields of products, and its equally compatible reaction procedure for both epoxides and aziridines, make it a valuable alternative to the existing reagents reported in the literature.

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

Supporting Information Available: Spectral data for all compounds along with a detailed experimental procedure. This material is available free of charge via the Internet at http://pubs.acs.org.

OL016979Q

(17) **General procedure:** To a mixture of epoxide/aziridine (1 mmol) and $CeCl_3.7H_2O$ (0.5 mmol) in acetonitrile and water (9:1, 10 mL) was added NaN_3 (1.1 mmol), and the reaction mixture was stirred at acetonitrile reflux temperature for a specified time as required to complete the reaction (Table 1). After completion as indicated by TLC, the reaction mixture was extracted with ethyl acetate, the combined organic layers were washed with H_2O and brine, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The residue was subjected to flash chromatography on silica gel (eluent: hexane/ethyl acetate) to provide the pure azidohydrin/azidoamine.