DOI: 10.1002/adsc.200505391

C-3 Selective Ring Opening of 2,3-Aziridino Alcohols and their Derivatives with Nucleophiles in the Presence of β-Cyclodextrin in Water†

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Received: October 7, 2005; Accepted: February 7, 2005

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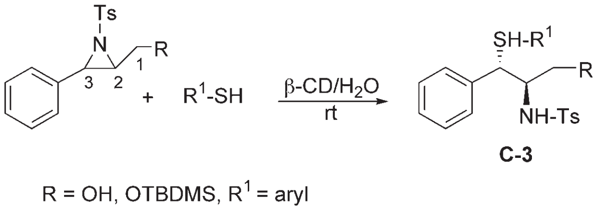
Abstract: For the first time a mild and efficient procedure has been developed for the C-3 selective ring opening, under biomimetic conditions, of 2,3-aziridino alcohols and their derivatives with nucleophiles such as aromatic thiols and amines catalyzed by β-cyclodextrin in water at room temperature to afford the corresponding β-amino sulfides and diamines with high regioselectivity in impressive yields. The use of cyclodextrin precludes the use of either acid or base and the catalyst can be recovered and reused.

Keywords: β-amino sulfides; aromatic amines; aromatic thiols; aziridines; β-cyclodextrin; diamines; water

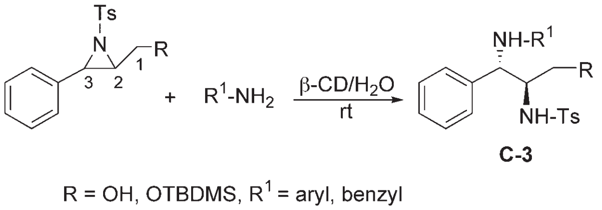
Aziridines are well known carbon electrophiles and their synthetic potential is enhanced by their ability to undergo regioselective ring opening reactions, especially for the synthesis of nitrogen-containing compounds such as amino acids,[1] heterocycles [2] alkaloids[3] etc. Although the ring opening of *N*-tosylaziridines has been studied with several nucleophiles,[4] little attention has so far been given to the chemistry of 2,3-aziridino alcohols and their derivatives. Only very few methods are known for the ring opening of 2,3-aziridino alcohols with nucleophiles[5] but no general methodology was reported on their reaction with thiols and amines. Regioselective cleavage of 2,3-aziridino alcohols and their derivatives with thiols and amines is interesting because the resulting amino sulfides and diamines are biologically and synthetically important classes of compounds in the field of pharmaceuticals,[6] especially for the synthesis of the hydroxy-amino-thiol moieties found in some HIV protease inhibitors.[7]

The straightforward synthesis of amino sulfides and diamines involves the ring opening of aziridines with thiols and amines. However, most of these ring openings of substituted aziridines require acid or base catalysis such as boron trifluoride · etherate, CAN, trifluoromethanesulfonic acids, sodium phosphate buffer etc.[8] Many of these Lewis acids are deactivated or sometimes decomposed by nitrogen-containing reactants and even when the desired reaction proceeds, more than stoichiometric amounts of the Lewis acids are required because the acids are trapped by nitrogen. In the case of reactions with thiols, large excesses of thiols are generally used.[9] Moreover, these reactions involve elevated temperatures and strict anhydrous conditions utilizing expensive and stoichiometric amounts of reagents with extended reaction times, undesirable side reactions and lower yields. The utility of these reactions is dependent on the regioselectivity at C-2 and C-3. Ring opening of 2,3-aziridino alcohols and their derivatives with thiols and amines show different ratios of C-2 and C-3 isomers.[8] In some cases selectivity was lost with reflux temperatures. Examples of higher C-3 selective ring opening have yet to be reported.

In view of these limitations, there is still need for a widely applicable approach for the C-3 selective ring opening of various substituted aziridines, preferably using water as solvent with a recyclable catalyst minimizing the use of harmful organic solvents as green chemistry is becoming a central issue in both academic and industrial research in the 21st century.[10] Thus, the development of environmentally benign and clean synthetic procedures is the goal of present day research thereby minimizing the cost of waste disposal. There is need for developing highly regioselective aziridine ring opening reactions in water without using any harmful organic solvents because water is a safe, economical and environmentally benign solvent.[11] In our efforts to develop biomimetic approaches for chemical reactions involving cyclodextrins in water,[12] we present herein the first C-3 selective thiolysis and aminolysis of 2,3-aziridino alcohols and their derivatives with aromatic thiols and amines catalyzed by β-cyclodextrin in water. This method provides facile and practical access to various β-amino sulfides and diamines (Schemes 1 and 2).



Scheme 1.

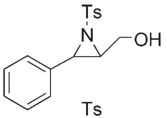
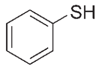
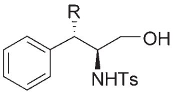
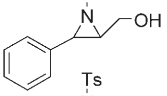
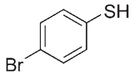
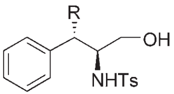
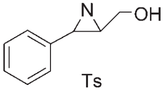
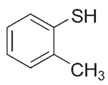
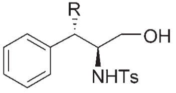
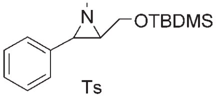
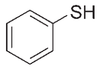
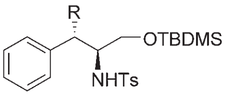
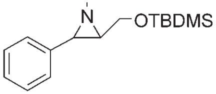
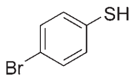
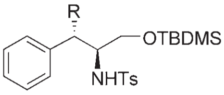
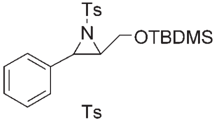
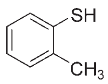
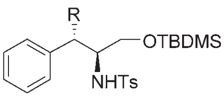
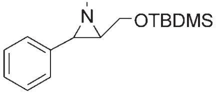
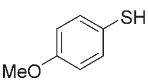
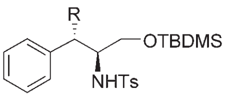


Scheme 2.

Cyclodextrins are cyclic oligosaccharides possessing hydrophobic cavities which bind substrates selectively and catalyze chemical reactions with high selectivity. They catalyze reactions by supramolecular catalysis involving reversible formation of host-guest complexes by non-covalent bonding as seen in enzymes. Complexation depends on the size, shape and hydrophobicity of the guest molecule. In this way they mimic biochemical selectivity which is due to orientation of the substrate by complex formation positioning only a certain region for favourable attack and thus will be superior to chemical selectivity, which involves random attack due to intrinsic reactivity of the substrate at different regions. These attractive features of cyclodextrins in the biomimetic modelling of chemical reactions prompted us to investigate the regioselective ring opening of 2,3-aziridino alcohols and their derivatives with aromatic thiols and amines in the presence of β-cyclodextrin (β-CD) as this is one of the most useful synthetic transformations with a variety of applications.

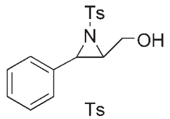
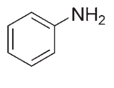
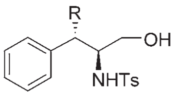
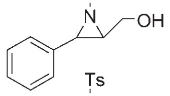
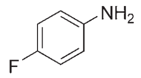
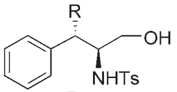
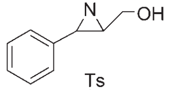
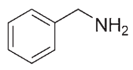
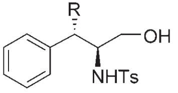
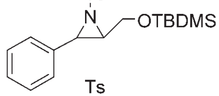
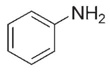
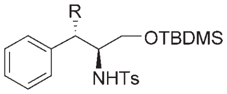
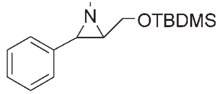
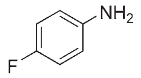
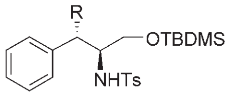
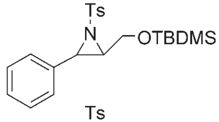
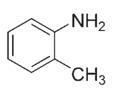
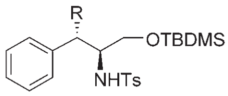
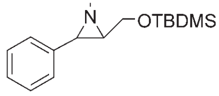
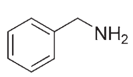
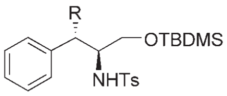
In general, the reactions were carried out by the *in situ* formation of the β-CD complex of 2,3-aziridino alcohols in water followed by the addition of thiophenol and stirring for 8 h at room temperature to give the corresponding β-amino sulfides (Scheme 1; Table 1) with C-3-opened product as the only isomer (as detected by ^{1}H

Table 1. Synthesis of β-amino sulfides from 2,3-aziridino alcohol derivatives in the presence of β-CD.

Entry	Substrate	Thiophenol (R)	Product[a]	Time [h]	Yield [%][b]
1				4	92
2				4	94
3				4	89
4				8	90
5				8	91
6				8	88
7				8	86

[a] Only one regioisomer could be detected by ^{1}H NMR spectroscopic analysis.
[b] Isolated yields.

Table 2. Synthesis of diamines from 2,3-aziridino alcohol derivatives in the presence of β-CD.

Entry	Substrate	Amine (R)	Product[a]	Time [h]	Yield [%][b]
1				8	90
2				8	92
3				8	86
4				12	88
5				12	88
6				12	84
7				12	84

[a] Only one regioisomer could be detected by ^{1}H NMR spectroscopic analysis.
[b] Isolated yields.

NMR spectroscopic analysis and comparison of the ^{1}H NMR spectra with those reported in the literature[4]) in impressive yields (86–94%). Similarly, amines were added after complexation to β-CD to give the diamines (Scheme 2; Table 2). Thus, it has been shown for the first time that β-amino sulfides and diamines of high synthetic potential can be made in a biomimetic fashion with high regioselectivity in the presence of β-cyclodextrin in water. The reaction proceeds smoothly at room temperature without the formation of any side products or rearrangements. These cyclodextrin-mediated, water-based reactions proceed under mild conditions without the need for organic solvents. The β-cyclodextrin can be easily recovered and reused. These reactions do not proceed in the absence of cyclodextrin.

The role of β-CD leading to regioselective ring-opening through the formation of an inclusion complex of the aziridine could be seen from our earlier ^{13}C NMR studies on a similar type of compounds in which the *p*-toluenesulfonyl group and C_2 carbon of the aziridine ring are deshielded, indicating their inclusion in the hydrophobic cavity of cyclodextrin.[13] This type of encapsulation of aziridine by β-CD exposes only the α position, i.e., the C_3 position for nucleophilic attack by thiols and amines leading to the high regioselectivity. Apart from this, it also leads to the formation of the more stable benzylic carbocation. Thus, the ring opening occurred exclusively at the benzylic position with the formation of only one regioisomer.

In some cases reported in literature, blocking of the free hydroxy group of the substrate with TBDMS led to much slower reactions (no ring opening occurred at or below room temperature) and elevated temperatures led to cleaving off of the TBDMS group along with ring opening,[5d] whereas in our reactions, apart from proceeding at room temperature, the TBDMS group also remained intact. The reaction conditions are mild and no side products or decomposition of the products are observed.

In conclusion, 2,3-aziridino alcohols and their derivatives have been opened in a C-3-selective fashion for the first time with various thiophenols and amines. This methodology represents a simple, convenient and highly efficient method for the synthesis of β-amino sulfides and diamines. The notable features of this method are cleaner reaction profiles, high yields and operational simplicity. Above all, these reactions are carried out in water. This methodology will be a useful addition to modern synthetic methodology with the ever-growing demand for eco-conscious chemical processes and increasing interest in green chemistry.

Experimental Section

Materials

The starting 2,3-aziridino alcohols and their derivatives were prepared from the corresponding epoxides in four steps: (a) ring opening of the epoxides with NaN_3;[14] (b) protection of the resulting azido alcohol with TBDMSCl;[15] (c) reduction of the protected azido alcohol using Ph_3P;[16] (d) protection of the amine as tosylate using TsCl.[17] The final aziridino-TBDMS alcohols are quite stable compounds. The TBDMS group was deprotected by TBAF whenever the free OH was required.[18]

General Procedure

β-Cyclodextrin (1 mmol) was dissolved in water (15 mL) at 60 °C, the 2,3-azidridino alcohol (1 mmol) dissolved in acetone (1 mL) was added slowly with stirring and the mixture was cooled to room temperature. This was followed by the addition of thiophenol or amine (1 mmol) and stirring was continued at room temperature. After completion of the reaction, the organic material was extracted with ethyl acetate, the organic phase was separated, filtered and washed with brine. The organic phase was then dried (Na_2SO_4), filtered and the solvent was removed under vacuum. Although seen as a single compound on TLC, the product was purified by silica gel column chromatography using ethyl acetate:*n*-hexane as eluent.

Acknowledgements

N. S. K. and K. S. thank CSIR, New Delhi, India, for the award of research fellowships.

References

† IICT communication no. 060121.

[1] a) D. Tanner, *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 599–619; b) W. McCoull, F. A. Davis, *Synthesis* **2000**, 1347.

[2] a) A. Dureault, I. Tranchepain, J. C. Depezay, *J. Org. Chem.* **1989**, *54*, 5324; b) D. Tanner, H. M. He, *Tetrahedron* **1992**, *48*, 6079.

[3] T. Hudlicky, H. Luna, J. D. Price, F. Rulin, *J. Org. Chem.* **1990**, *55*, 4683.

[4] T. K. Chakraborty, A. Ghosh, T. V. Raju, *Chem. Lett.* **2003**, *32*, 82 and references cited therein.

[5] a) D. Tanner, H. M. He, P. Somfai, *Tetrahedron* **1992**, *48*, 6069–6078; b) D. Tanner, R. O. Gautun, *Tetrahedron* **1995**, *51*, 8279; c) D. Tanner, H. M. He, *Tetrahedron*, **1992**, *48*, 6079; d) G, Righi, T. Franchini, C. Bonini, *Tetrahedron Lett.* **1998**, *39*, 2385; e) G. Righi, R. D. Achille, *Tetrahedron Lett.* **1996**, *37*, 6893; f) K. Nakai, T. Ibuka, A. Otaka, H. Tamamura, N. Fujii, *Tetrahedron Lett.* **1995**, *36*, 6247; g) J. Legters, J. G. H. Willems, L. Thijs, B. Zwanenburg, *Recl. Trav. Chim. Pays-Bas* **1992**, *111*, 59.

[6] a) R. Ingenitio, E. Bianchi, D. Fattori, *J. Am. Chem. Soc.* **1999**, 121, 11369; b) B. Adams, K. J. M. Beresford, S. M. Whyte, D. W. Young, *Chem. Commun.* **2000**, 619; c) M. T. Reetz, R. Jaeger, R. Drewlies, M. Hubel, *Angew. Chem. Int. Ed. Engl.* **1991**, **30**, 103 and references cited therein; d) *Drugs Future* **1999**, *24*, 1175; e) P. W. Smith, S. L. Sollis, P. D. Howes, P. C. Cherry, I. D. Starkey, K. N. Cobley, H. Weston, J. Scicinski, A. Merritt, A. Whittington, P. Wyatt, N. Taylor, D. Green, R. C. Bethell, S. Madar, R. J. Fenton, P. J. Morley, T. Patemann, A. J. Beresford, *J. Med. Chem.* **1998**, *41*, 787; f) P. W. Smith, J. E. Robinson, D. N. Evans, S. L. Sollis, P. D. Howes, N. Trivedi, R. C. Bethell, *Bioorg. Med. Chem. Lett.* **1999**, *9*, 601; g) D. Tanner, P. Somfai, *Tetrahedron Lett.* **1987**, *28*, 1211; h) D. Tanner, P. Somfai, *Tetrahedron* **1988**, *44*, 619.

[7] a) F. D. Deroose, P. J. DeClercq, *J. Org. Chem.* **1995**, *60*, 321; b) M. J. Mooknaar, W. N. Speckamp, H. Hiemstra, E. Poetsch, M. Casutt, *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2391; c) E. J. Corey, M. M. Megrotra, *Tetrahedron Lett.* **1988**, *29*, 57; c) P. Wipf, S. Venkatraman, *J. Org. Chem.* **1988**, *53*, 3154.

[8] a) J. Legters, L. Thijs, B. Zwanenburg, *Recl. Trav. Chim. Pays-Bas* **1992**, *111*, 16; b) O. Ploux, M. Caruso, G. Chassaing, A. Marquet, *J. Org. Chem.* **1988**, *53*, 3154; c) T. Katagiri, M. Takahashi, Y. Fujiwara, H. Ihara, K. Uneyama, *J. Org. Chem.* **1999**, *64*, 7323; d) Y. Hata, M. Watanabe, *Tetrahedron*, **1987**, *43*, 3881; e) see ref.[4]

[9] a) J. H. Bae, S. H. Shin, C. S. Park, W. K. Lee, *Tetrahedron*, **1999**, *55*, 10041; b) see ref.[7c]

[10] a) P. T. Anastas, J. C. Warner, *Green Chemistry, Theory and Practice*, Oxford University Press, Oxford, **1998**; b) *Green Chemistry, Frontiers in Benign Chemical Synthesis and Processes*, (Eds.: P. T. Anastas, T. C. Williamson), Oxford University Press, Oxford, **1998**; c) *Handbook of Green Chemistry & Technology*, (Eds.: J. Clark, D. Macquarrie) Blackwell Publishing, Oxford, **2002**; d) M. Eissen, J. O. Metzger, E. Schmidt, U. Schneidewind, *Angew. Chem. Int. Ed.* **2002**, *41*, 414.

[11] a) *Organic Synthesis in Water*, (Ed.: P. A. Grieco), Blackie Academic and Professional, London, **1998**; b) C.-J. Li, T.-H. Chan, *Organic Reactions in Aqueous Media*, Wiley, New York, **1997**.

[12] a) N. S. Krishnaveni, K. Surendra, K. R. Rao, *Chem. Commun.* **2005**, 669; b) K. Surendra, N. S. Krishnaveni, K. R. Rao, *Synlett* **2005**, 506; c) N. S. Krishnaveni, K. Surendra, K. R. Rao, *Adv. Synth. Catal.* **2004**, *346*, 346; d) N. S. Krishnaveni, K. Surendra, M. S. Reddy, Y. V. D. Nageswar, K. R. Rao, *Adv. Synth. Catal.* **2004**, *346*, 395; e) K. Surendra, N. S. Krishnaveni, M. A. Reddy, Y. V. D. Nageswar, K. R. Rao, *J. Org. Chem.* **2003**, *68*, 9119.

[13] M. S. Reddy, M. Narender, K. R. Rao, *Tetrahedron Lett.* **2005**, *46*, 1299.

[14] a) C. S. Behrens, K. B. Sharpless, *J. Org. Chem.* **1985**, *50*, 5696; b) Y. Kobayashi, T. Matsumoto, Y. Takemoto, K. Nakatani, Y. Ito, T. Kamijo, H. Harada, S. Terashima, *Chem. Pharm. Bull.* **1991**, *39*, 2550.

[15] S. Kajigaeshi, T. Kakinami, T. Okamoto, S. Fujisaki, *Bull. Chem. Soc. Jpn.* **1987**, *60*, 1159.

[16] a) Y. Ittah, Y. Sasson, I. Shahak, S. Tsaroom, J. Blum, *J. Org. Chem*. **1978**, *43*, 4271; b) R. Zambino, J. Rokach, *Tetrahedron Lett*. **1983**, *24*, 331.

[17] G. W. Kabalka, M. Varma, R. S. Varma, P. C. Srivastava, F. F. Knapp, *J. Org. Chem*. **1986**, *51*, 2386.

[18] E. J. Corey, A. Venkateswarlu, *J. Am. Chem. Soc*. **1972**, *94*, 6190.