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Tetrahedron Letters 45 (2004) 7995–7997
Tetrahedron Letters

A facile regioselective ring opening of aziridines to haloamines using tetrabutylammonium halides in the presence of β-cyclodextrin in water☆

M. Narender, K. Surendra, N. Srilakshmi Krishnaveni, M. Somi Reddy and K. Rama Rao*

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

Received 8 July 2004; revised 27 August 2004; accepted 2 September 2004
Available online 21 September 2004

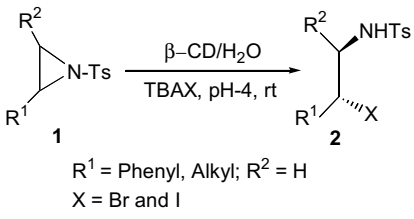
Abstract—A variety of *N*-tosylaziridines undergo regioselective ring opening with tetrabutylammonium halides in the presence of β-cyclodextrin in water at pH 4 and room temperature to afford the corresponding haloamines in excellent yields.

N-Activated aziridines are versatile intermediates for the synthesis of many biologically active compounds.[1] Aziridines can be easily prepared and the inherent ring strain leads to high reactivity with various nucleophiles.[2] A variety of nucleophiles have been developed for the ring opening of aziridines such as silyl nucleophiles,[3] organometallic reagents,[4] Wittig reagents,[5] amines,[6] hydroxyl compounds.[7] Metal halides such as InX_3,[8] NaX or $MgBr_2$,[9] $CeCl_3{\cdot}7H_2O/NaI$[10] and TMSI.[11] However, many of these methods have limitations such as long reaction times, high temperatures, the formation of regioisomers, etc. It is thus important to look for the development of a mild, efficient and convenient protocol for the regioselective synthesis of haloamines.

In continuation of our investigation on organic reactions involving β-cyclodextrin in aqueous medium, we have explored the regioselective ring opening of aziridines to afford β-haloamines by using the simple, readily available, environment friendly and easy to handle reagents, the tetrabutylammonium halides. They are widely known as phase transfer catalysts and have been extensively employed in various chemical transformations as nucleophilic halide sources.[12] However, tetrabutylammonium halides have not yet been explored for aziridine ring opening to the highly versatile haloamines. Herein, we describe an efficient ring opening of aziridines to vicinal haloamines in the presence of β-cyclodextrin in water at pH 4 (Scheme 1).

Tetrabutylammonium halides are nontoxic, easy to transport, lead to nonpolluting by-products and cost-effective processes. Tetrabutylammonium halides have been utilized for the first time in the present investigation under biomimetic conditions involving β-cyclodextrin for the regioselective ring opening of aziridines. Our earlier expertise in the field of biomimetic modelling of organic reactions involving cyclodextrins[13] prompted us to attempt the regioselective ring opening of aziridines with tetrabutylammonium halides in the presence of β-cyclodextrin (β-CD) as this is a useful synthetic transformation with a variety of applications.[9,14]

Cyclodextrins, which are cyclic oligosaccharides, have excited much interest as enzyme models due to their



Scheme 1.

Keywords: Aziridines; Haloamines; Tetrabutylammonium halide; β-Cyclodextrin; Water.
☆ IICT Communication No. 040820.
* Corresponding author. Tel.: +91 40 27193164; fax: +91 40 27160757; e-mail: ramaraok@iict.res.in

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doi:10.1016/j.tetlet.2004.09.014

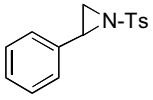
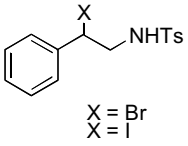
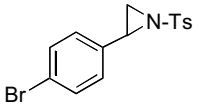
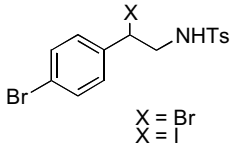
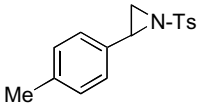
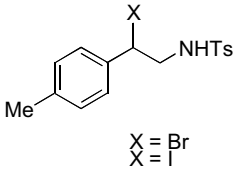
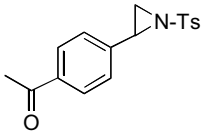
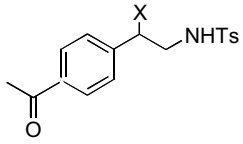
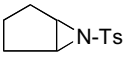
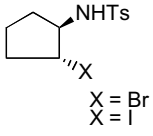
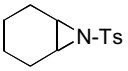
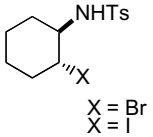
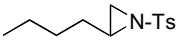
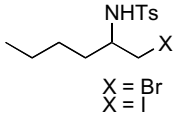
Table 1. Ring opening of styrene aziridine with TBAX

	Aziridine	Reagent	Time (h)	Yield (%)
With β-CD in water at pH4	Styrene aziridine	TBABr	5.0	85
		TBAI	3.5	88
With β-CD in water	Styrene aziridine	TBABr	15	30
		TBAI	12	55
Without β-CD in water	Styrene aziridine	TBABr	18	15
		TBAI	15	20
Without β-CD in water at pH4	Styrene aziridine	TBABr	24	25
		TBAI	20	35

ability to bind substrates selectively and catalyze chemical reactions by supramolecular catalysis involving the reversible formation of host–guest complexes with the substrates by noncovalent bonding as seen in enzyme complexation processes. Complexation depends on the size, shape and hydrophobicity of the guest molecule.

Reactions were carried out by the in situ formation of a β-cyclodextrin complex with aziridine **1** in water followed by the addition of the tetrabutylammonium halide at pH4 to give the corresponding haloamines **2** in impressive yields (Table 2).[15] The yields were optimum at pH4. The reaction goes smoothly at room temperature without the formation of by-products or rearranged products. The rate of haloamine formation decreased in the order n-$Bu_4NI > n$-$Bu_4NBr > n$-Bu_4NCl reflecting the decrease in softness of the halide ion. In the case of n-Bu_4NCl the yields were very low

Table 2. β-Haloamines from aziridines and tetrabutylammonium halides in the presence of β-CD

Entry	Substrate	Reagent	Product[a]	Time (h)	Yield (%)[b]
1		TBABr	 X = Br	5.0	85
2		TBAI	X = I	3.5	88
3		TBABr	 X = Br	5.5	87
4		TBAI	X = I	3.5	90
5		TBABr	 X = Br	5.5	85
6		TBAI	X = I	4.0	92
7		TBABr	 X = Br	6.0	84
8		TBAI	X = I	4.5	86
9		TBABr	 X = Br	5.0	92
10		TBAI	X = I	4.0	95
11		TBABr	 X = Br	5.0	94
12		TBAI	X = I	3.5	96
13		TBABr	 X = Br	5.5	90
14		TBAI	X = I	4.0	92

[a] All the products were identified by IR, NMR and mass spectroscopy.
[b] Yields of products isolated after column chromatography.

(<20%). All the products were characterized by ^{1}H NMR, IR and mass spectroscopy.

To study the scope of the reaction, we extended it to various cyclic, acyclic and aryl substituted aziridines. In the case of 2-phenylaziridines (entries 1–8) the product formed was the one from the attack of the nucleophile at the benzylic carbon atom (internal attack). In the case of acyclic terminal aziridines (entries 9–14) the reaction was highly regioselective with the formation of only one product from attack of the nucleophile at the less hindered terminal carbon.

Here, the role of cyclodextrin appears to be not only to activate the aziridine but also to promote highly regioselective ring opening due to inclusion complex formation. This mimicking of biochemical selectivity, which is due to orientation of the substrate by complex formation positioning only certain regions for favourable attack, is superior to chemical selectivity, which involves attack due to the intrinsic reactivity of the substrate at different regions. A comparative study has been carried out by taking styrene aziridine as an example in the presence and absence of β-CD under acidic and neutral conditions (Table 1). Higher yields in the presence of acid may be attributed to the facile abstraction of proton by the intermediate anion from the acidic medium than from water.

In conclusion, we have demonstrated for the first time that the ring-opening reactions of aziridines can be promoted by tetrabutylammonium halides, so opening a novel entry into using these reagents for the synthesis of vicinal haloamines. Formation of unwanted by-products and low regioselectivities can also be avoided by using this methodology.

Acknowledgements

We thank CSIR, New Delhi, India, for fellowships to M.N., K.S. and M.S.R.

References and notes

1. (a) *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Ress, C. W., Eds.; Pergamon: Oxford, 1984; Vol. 7, p 47; (b) Kump, J. E. G. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; 7, p 469.
2. (a) Tanner, D. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 599; (b) Mc Coull, W.; Davis, F. A. *Synthesis* **2000**, 1347.
3. Wu, J.; Hou, X.-L.; Dai, L.-X. *J. Org. Chem.* **2000**, *65*, 1344.
4. (a) Kozikowski, A.; Ishida, H.; Isobe, K. *J. Org. Chem.* **1979**, *44*, 2788; (b) Osborn, H. M. I.; Sweeney, J. B.; Howson, B. *Synlett* **1993**, 676.
5. (a) Baldwin, J. E.; Adlington, R. M.; Robinson, N. G. *J. Chem. Soc., Chem. Commun.* **1987**, 153; (b) Ibuka, T.; Nakai, K.; Habashita, H.; Fujii, N.; Garrido, F.; Mann, A.; Chounan, Y.; Yamamoto, Y. *Tetrahedron Lett.* **1993**, *34*, 7421.
6. Meguro, M.; Asao, N.; Yamamoto, Y. *Tetrahedron Lett.* **1994**, *35*, 7395.
7. Prasad, B. A. B.; Sekar, G.; Singh, V. K. *Tetrahedron Lett.* **2000**, *41*, 4677.
8. Yadav, J. S.; Reddy, B. V. S.; Mahesh Kumar, G. *Synlett* **2001**, *9*, 1417.
9. Giuliana Righi; Raffaella D'Achille *Tetrahedron Lett.* **1996**, *37*, 6893.
10. Gowravaram Sabitha; Satheesh Babu, R.; Rajkumar, M.; Srinivas Reddy, Ch.; Yadav, J. S. *Tetrahedron Lett.* **2004**, *42*, 3955.
11. Upender, K. N.; Arora, A.; Basu, N. *Indian J. Chem., Sec. B* **1992**, 353.
12. (a) Yadav, V. K.; Fallis, A. G. *J. Org. Chem.* **1986**, *51*, 3372; (b) Young-Ger, S. U. H.; Bon-Am, K. O. O.; Jung-Ae, K. O.; Youn-Sang, C. H. O. *Chem. Lett.* **1993**, 1907; (c) Koenig, K. E.; Weber, W. P. *Tetrahedron Lett.* **1974**, *26*, 2275; (d) Enxue, S.; Chengxin, P. *Synth. Commun.* **2004**, *34*, 1285; (e) Zahalka, H. A.; Sasson, Y. *Synthesis* **1986**, 763; (f) Ochiai, M.; Oshima, K.; Masaki, Y. *Tetrahedron Lett.* **1991**, 7711; (g) Binkly, R. W.; Ambrose, M. G.; Heheman, D. G. *J. Org. Chem.* **1980**, *45*, 4387; (h) Badri, M.; Brunet, J. J.; Perron, R. *Tetrahedron Lett.* **1992**, *33*, 4435; (i) Nezhad, A. K.; Soltani Rad, M. N.; Khoshnood, A. *Synthesis* **2003**, 2552.
13. (a) Krishnaveni, N. S.; Surendra, K.; Rao, K. R. *Adv. Synth. Catal.* **2004**, *346*, 346; (b) Surendra, K.; Krishnaveni, N. S.; Nageswar, Y. V. D.; Rao, K. R. *J. Org. Chem.* **2003**, *68*, 4994; (c) Surendra, K.; Krishnaveni, N. S.; Reddy, M. A.; Nageswar, Y. V. D.; Rao, K. R. *J. Org. Chem.* **2003**, *68*, 2058; (d) Surendra, K.; Krishnaveni, N. S.; Reddy, M. A.; Nageswar, Y. V. D.; Rao, K. R. *J. Org. Chem.* **2003**, *68*, 2018.
14. (a) Righi, G.; Franchini, T.; Bonini, C. *Tetrahedron Lett.* **1998**, *39*, 2385, and references cited therein; (b) Reetz, M. T.; Jaeger, R.; Drewlies, R.; Hubel, M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 103.
15. *Typical procedure*: β-Cyclodextrin (1 mmol) was dissolved in water (15 mL) at 60 °C, the aziridine (1 mmol) dissolved in acetone (1 mL) was added slowly with stirring and the mixture cooled to room temperature. To this solution, acetic acid was added and the pH was adjusted to 4. After addition of tetrabutylammonium halide (1.5 mmol), stirring was continued at room temperature (Table 2). After completion of the reaction the organic material was extracted with ethyl acetate, the organic phase was separated, filtered and washed with $NaHCO_3$ and brine. The organic phase was then dried (Na_2SO_4), filtered and the solvent was removed under vacuum. The crude product was purified by silica gel column chromatography using ethyl acetate–hexane (2:8) as eluent.