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Reductive opening of aziridines with polymethylhydrosiloxane †

S. Chandrasekhar * and Moinuddin Ahmed

Indian Institute of Chemical Technology, Hyderbaad 500007, India

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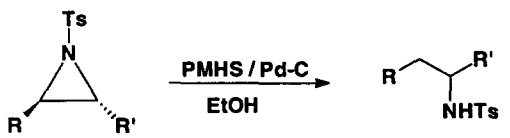
Abstract

Regio and chemoselective reductive opening of aziridines is achieved using catalytic palladium on charcoal and polymethylhydrosiloxane (PMHS) as a soluble hydrogen source.

Keywords: PMHS; aziridine opening; unusual amino acids.

The discovery of the aminohydroxylation reaction[1] by Sharpless et al. has allowed easy entry into chiral, as well as non-chiral, aziridines by a simple Mitsunobu reaction[2] of the resultant aminoalcohol. Previously, aziridines were prepared by multistep processes.[3,4] Due to the strained nature of aziridines, ring opening reactions are a dominant feature of this class of compounds. This feature has attracted various organic chemists and opening of aziridines with various nucleophiles has been studied.[5] A careful literature search, however, has revealed that reductive opening of this class of compounds is not addressed well.

The reports which deal with opening of aziridines with hydride sources such as $LiAlH_4$, DIBAL-H and Red-Al rely on neighbouring group assistance of an -OH group for regiocontrol.[6] Herein, we report our latest findings on the reductive opening of aziridines with PMHS as a soluble hydrogen source and Pd–C as catalyst (Eq. 1).[7]



(1)

The regioselectivities achieved, cost efficiency, safety and easy accessibility of PMHS makes this protocol most desirable. The readily accessible 2-phenyl-*N*-tosyl aziridine **1** (entry 1) was reduced with PMHS and 5% Pd–C in ethanol as solvent at room temperature to furnish 2-phenyl-*N*-tosyl ethylamine **1a** in 96% isolated yield after standard work up. Prior to this, some Lewis acids were tried as PMHS activators which include $ZnCl_2$, $AlCl_3$ and $TaCl_5$ but without much success. Encouraged by this finding,

* Corresponding author. Tel: +91 40 7170512; fax: +91 40 7173387; e-mail: srivaric@iict.ap.nic.in

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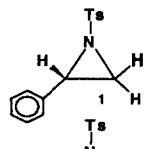
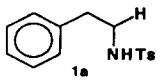
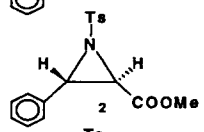
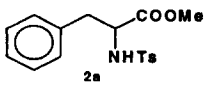
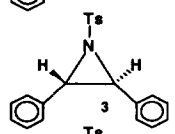
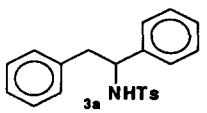
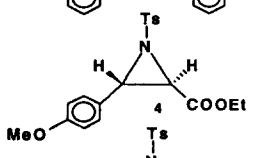
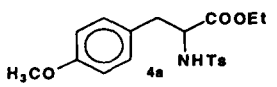
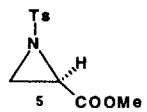
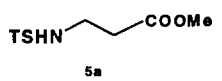
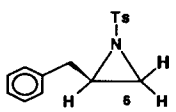
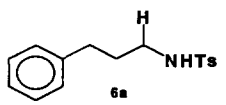
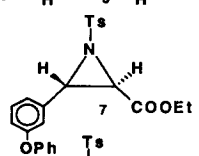
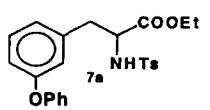
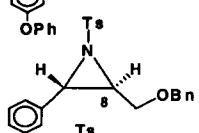
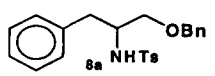
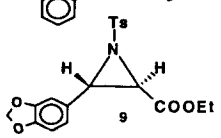
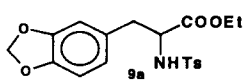
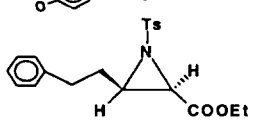
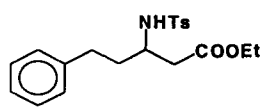
Table 1

Entry	Substrate	Product	Yield %
1			96
2			95[a]
3			97
4			93
5			80[b]
6			60
7			90[a]
8			75
9			80
10			85[b]
	10	10a	

a) Asymmetric aminohydroxylation products were utilized for aziridine preparation

b) Two regioisomers were isolated in the ratio of 8:2 with **5a** and **10a** being the major ones. [8]

a few aziridine substrates (Table 1) were prepared by a Sharpless aminohydroxylation and Mitsunobu sequence and were subjected to the present protocol. Entry 2, which has an ester moiety on the aziridine ring, underwent regioselective opening to furnish a phenyl alanine derivative **2a** in 95% yield. Similarly *p*-methoxy-phenyl derivative **4** (entry 4) yielded the corresponding α-amino ester **4a** in 95% yield. The stilbene derivative **3** (entry 3) also responded well to furnish the 1,2-diphenyl-*N*-tosyl ethylamine **3a** in 97% yield. Substrates in which there is no phenyl group on the aziridine ring (entries 5, 6 and 10) also

underwent smooth reductive opening.[8] Entry 7 describes *m*-phenoxy-phenylalanine[9] synthesis in 90% yield.

In conclusion, an efficient procedure for the reduction of aziridines is described. The products thus formed, especially the α-aminoesters (entries 2, 4, 7 and 9), find wide application as unusual amino acids in peptide chemistry.[10] Also, PMHS is a safe and soluble hydrogen source and is utilized for the first time for the reductive opening of aziridines. Other reductions using this protocol are currently being investigated.[11]

Typical experimental procedure:

To a stirred solution of 2-phenyl-*N*-tosylaziridine **1** (0.819 g, 3 mmol) and PMHS (0.7 ml) in ethanol (25 ml), was added 5% Pd–C (0.07 g), under a nitrogen atmosphere. After stirring for 6 h at ambient temperature, the catalyst was removed by filtration and the solvent was removed under reduced pressure. Water (50 ml) was added to the crude product and the mixture was stirred for further 4 h. The product was extracted from the aqueous mixture with diethyl ether (3×25 ml), washed with water (25 ml), brine (25 ml) and dried over Na_2SO_4. The solvent was removed in vacuo and pure product was isolated by column chromatography to yield **1a** (0.792 g, 96%).

Acknowledgements

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8. In the case of entries 5 and 10, Raney-Ni is used as the catalyst.
9. The substrate **7** is prepared by Wittig reaction of *m*-phenoxy benzaldehyde with ethyl triphenyl phosphorane followed by aminohydroxylation and Mitsunobu reaction.
10. (a) Wagner, I.; Musso, H. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 816. (b) See: Amino Acids, Peptides and Proteins. Specialist periodical reports, *Chem. Soc.* London, 1968–1981, Vol. 1–14.
11. All products were characterized by ^{1}H NMR, mass and HRMS. ^{1}H NMR data of **2a**: ($CDCl_3$, 200 MHz): 2.42 (s, 3H), 3.03 (d, J=6.6 Hz, 2H), 3.48 (s, 3H), 4.10–4.24 (m, 1H), 4.96 (br d, 1H, N*H*), 7.05–7.30 (m, 7H), 7.62 (d, J=9 Hz, 2H). **6a**: 1.63 (m, 2H), 2.46 (s, 3H), 2.85 (t, J=10.5 Hz, 2H), 3.35–3.75 (m, 2H), 4.72–4.88 (br m, 1H, N*H*), 7.00–7.29 (m, 7H), 7.68 (d, J=9 Hz, 2H).