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A mild and efficient synthesis of α-tosylamino ketones from aryl aziridines in the presence of β-cyclodextrin and NBS in water☆

M. Somi Reddy, M. Narender and K. Rama Rao*

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

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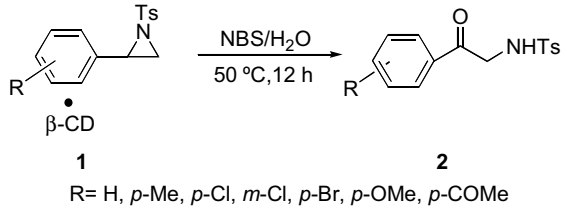
Abstract—NBS has been utilized for the first time for the oxidative cleavage of aryl aziridines involving β-cyclodextrin–aziridine complexes in water to give the corresponding α-amino ketones in high yields.

α-Amino aryl ketones are an important class of organic synthetic intermediates which have found use in organic and medicinal chemistry.[1] α-Amino arylketones also provide starting materials for the synthesis of biologically active β-aminoalcohols. Only a few direct methods are available for the preparation of these amino ketones.[2–4] These methods have various limitations such as the use of transition metal catalysts, organic solvents, controlled temperatures, long reaction times, and hazardous reagents. Thus, there is still a need to develop cleaner synthetic methodologies for the generation of α-amino ketones.

One of the goals of present day organic synthesis is to develop environmentally benign and clean synthetic procedures with high atom economy. For example, the development of chemical reactions in water shows advantages over the use of organic solvents since water is safe, economical, and environmentally benign. In continuation of our work on biomimetic modeling of chemical reactions[5] involving cyclodextrins in water, we report here for the first time the direct synthesis of α-tosylamino ketones from easily accessible and inexpensive aryl aziridines using NBS as a mild oxidizing agent in water as solvent (Scheme 1).



Scheme 1.

Cyclodextrins are cyclic oligosaccharides possessing hydrophobic cavities, which bind substrates selectively and catalyze chemical reactions with high regioselectivity. They promote reactions by supramolecular catalysis involving reversible formation of host–guest complexes using non-covalent bonding, as seen in enzymes. Complexation depends on the size, shape, and hydrophobicity of the guest molecule. These attractive features of cyclodextrins in the biomimetic modeling of chemical reactions prompted us to investigate a variety of oxidations using the substrate–β-cyclodextrin complexes with NBS in water. The complexes were prepared with β-cyclodextrin since it is easily accessible and least expensive among the cyclodextrins.

The *N*-tosylaziridines were synthesized as reported.[6] The β-cyclodextrin inclusion complexes of the aziridines were prepared in water as described by us earlier.[5] The reactions were carried out by the in situ formation of the β-cyclodextrin complex of the aziridine **1** in water followed by the addition of NBS[7] and stirring at 50 °C to give the corresponding α-tosylamino ketones **2** in very high yields (Table 1). All the compounds were characterized by ^{1}H NMR, mass and IR spectroscopy, and by elemental analysis or otherwise compared with data for known compounds.[8] β-Cyclodextrin can be easily recovered and reused a number of times. These reactions did

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* Corresponding author. Tel.: +91 40 27193164; fax: +91 40 27160757; e-mail: drkrrao@yahoo.com

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not take place in the absence of β-CD. Succinimide, obtained as a by-product, can be recycled to NBS as described earlier.[9] These cyclodextrin mediated water based reactions proceed under mild conditions and avoid flammable and anhydrous organic solvents.

The evidence for the inclusion complex of the aziridines with β-cyclodextrin was derived through ^{13}C NMR examination during our earlier studies.[10] It was observed that the methyl and tertiary carbons of the *p*-toluenesulfonyl group as well as the methylene carbon (β-position) of the aziridine ring are deshielded indicating their inclusion in the hydrophobic cavity of the cyclodextrin. Thus, only the α-position of the aziridine ring is exposed to attack leading to high regioselectivity. We suggest that water can attack only at the exposed α-position of the aziridine in the supramolecular complex and is facilitated through hydrogen bonding with β-CD to form a β-hydroxyamine, which is oxidized by NBS to yield α-amino ketones.

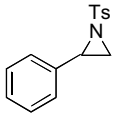
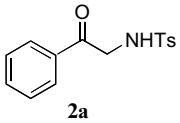
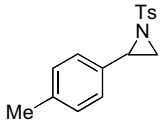
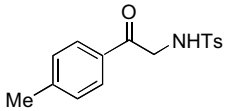
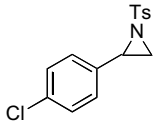
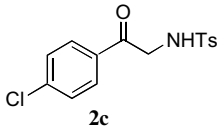
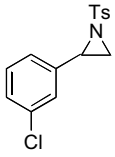
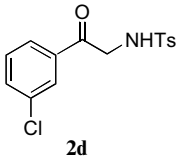
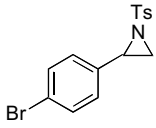
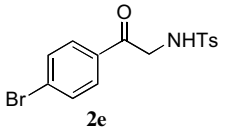
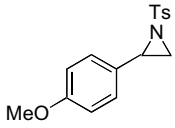
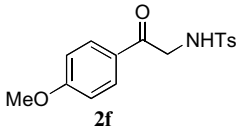
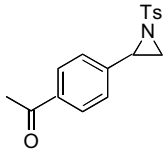
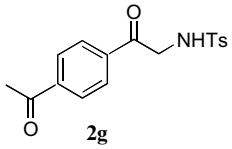
Thus, we have demonstrated that α-tosylamino ketones **2** can be generated directly from easily accessible aziridines in the presence of β-cyclodextrin and NBS in water. To our knowledge, this is the first report on the synthesis of α-tosylamino ketones directly from aziridines and NBS in a single step.

Physical data of novel compounds:

3-Chloro-1-(2-(4-methylphenylsulfonamino)acetyl)benzene (Table 1, entry 4): solid, mp: 116 °C, IR (neat): 3448, 2923, 1701 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 2.42 (s, 3H), 4.44 (d, $J = 4.5$ Hz, 2H), 5.50 (br s, 1H, NHTs) 7.20–7.40 (m, 4H), 7.60 (d, 1H, $J = 7.5$ Hz), 7.70–7.90 (m, 3H). LSIMS: *m/z*: 324 ($M^+ + 1$). Anal. Calcd for $C_{15}H_{14}O_3SNCl$ C: 55.64, H: 4.34, S: 9.90, N:4.33%; Found : C: 55.90, H: 4.25, S: 9.80, N: 4.38%.

4-Bromo-1-(2-(4-methylphenylsulfonamino)acetyl)benzene (Table 1, entry 5): solid, mp: 116 °C, IR (neat): 3447,

Table 1. Reaction of NBS with β-CD complexes of aziridines

Entry	Substrate	Product[a]	Yield (%)[b]
1		 **2a**	85
2		 **2b**	90
3		 **2c**	88
4		 **2d**	88
5		 **2e**	80
6		 **2f**	90
7		 **2g**	86

[a] All the products were characterized by ^1H NMR, mass and IR spectroscopy, and elemental analysis.
[b] Yields of isolated products after column chromatography.

2924, 1694 cm^{-1} ^1H NMR ($CDCl_3$, 300 MHz): δ 2.41 (s, 3H), 4.40 (d, $J = 3.7$ Hz, 2H), 5.50 (br s, 1H), 7.20–7.30 (m, 3H), 7.62 (d, $J = 8.3$, 2H), 7.70–7.80 (m, 3H). LSIMS: *m/z*: 367 (M^+). Anal. Calcd for $C_{15}H_{14}O_3SNBr$: C, 48.93; H, 3.83; S, 8.71; N,3.80. Found: C, 49.02; H, 3.62; S, 8.51; N, 3.92.

4-Acetyl-1-(2-(4-methylphenylsulfonamino)acetyl)benzene (Table 1, entry 7): white solid, mp: 115 °C, IR (neat): 3448, 2925 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 2.31 (s, 3H), 2.42 (s, 3H), 4.40 (d, $J = 4.2$ Hz, 2H), 5.51 (br s, 1H), 7.10–7.40 (m, 4H), 7.70–7.80 (m, 2H), 7.90 (d, $J = 8.6$ Hz, 2H). LSIMS: *m/z*: 332 ($M^+ + 1$); Anal. Calcd for $C_{17}H_{17}O_4SN$: C: 61.60, H: 5.17, S: 9.67, N: 4.23; Found: C: 61.40, H: 5.24, S: 9.78, N: 4.12.

Acknowledgements

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7. General procedure: β-Cyclodextrin (1 mmol) was dissolved in water (15 ml) at 60 °C, and the aziridine (1 mmol) dissolved in acetone (2 ml) was added slowly with stirring. After 15 min, NBS (1.0 mmol) was added and the mixture stirred for 12 h at 50 °C. The organic material was extracted with ethyl acetate. The organic phase was separated, filtered, and washed with brine then dried over sodium sulfate and the solvent removed under vacuum. The crude product was purified by column chromatography with ethyl acetate:hexane (20:80) as eluent. The aqueous layer was cooled to 5 °C to recover precipitated CD by filtration. The filtrate which contained succinimide was evaporated and the residue purified and converted to NBS.
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