An Efficient Biomimetic Cleavage of Aziridines with Nucleophiles Catalyzed by β-Cyclodextrin in Water

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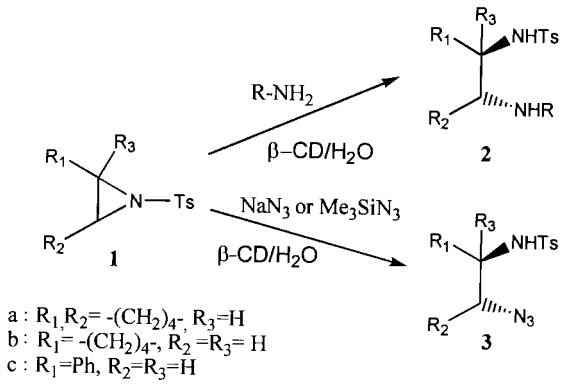
β-Cyclodextrin catalyzed for the first time a facile ring opening of aziridines with nucleophiles such as aromatic amines and azides in water at room temperature to afford diamines and azidoamines respectively in good yields.

Ring opening of aziridines with nucleophiles such as aromatic amines and azides gives rise to diamines and azidoamines respectively, which are synthetically important class of compounds in organic and medicinal chemistry.[1] The classical synthesis of these compounds consists of opening of aziridines in the presence of Lewis acids.[2] Later, a variety of metal triflates have been introduced to carryout aziridine opening at room temperature.[3] There is also a recent report of the opening of aziridines with trimethylsilyl azide triggered by tetrabutylammonium fluoride at 40 °C.[4] However, there are still some severe limitations with the literature methods such as use of anhydrous organic solvents, moisture sensitive catalysts, expensive and hazardous reagents etc. To overcome these limitations, we report herein, a novel, efficient and practical method for the ring opening of aziridines with nucleophiles catalyzed by β-cyclodextrin (β-CD) using water, which is an environmentally benign solvent.

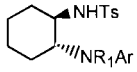
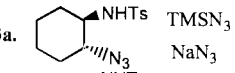
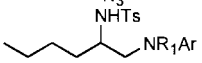
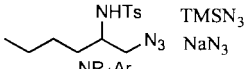
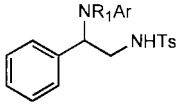
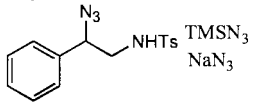


Scheme 1.

Cyclodextrins (CDs) which are cyclic oligosaccharides have excited much interest as enzyme models due to their ability to bind substrates selectively and catalyze reactions by supramolecular catalysis involving reversible formation of host:guest complexes with substrates by non-covalent bonding as seen in enzymes. Complexation processes in solution depend on the size, shape and hydrophobicity of guest molecules. Thus, the mimicking of biochemical selectivity which exhibits shape and substrate selectivity with the reactions being carried out in water will be superior to chemical selectivity and will also be environ friendly at the same time. Our earlier expertise in the field of biomimetic modelling of organic reactions,[5] prompted us to attempt the cleavage of aziridines with various nucleophiles using CDs, as this is one of the most useful synthetic transformations with varied applications.

The reaction was carriedout by dissolving β-CD in water followed by the addition of aziridine **1** and the nucleophile.[6] The optimum ratio of β-CD has been found to be 0.25 mole per mole of the substrate. The reaction mixture was stirred at room temperature for 24 h to give the corresponding diamines **2** or azido amines **3** in good yields (Table1). The catalyst can also be recovered and reused. These reactions do not take place in the absence of β-cyclodextrin. This aziridine opening reaction

Table 1. CD Catalysed aziridine opening with nucleophiles[a]

Entry	Product[b]	Yield / %[c]
		
1	**2a.** R_1=Me; Ar= Ph	86
2	**2b.** R_1=H; Ar= Ph	89
3	**2c.** R_1=H; Ar= C_6H_5-*p*-CH_3	90
4	**2d.** R_1=H; Ar = C_6H_5-*o*-CH_3	90
5	**2e.** R_1=H; Ar = C_6H_5-*p*-OCH_3	92
6	**2f** .R_1=H; Ar= C_6H_5-*o*-OCH_3	84
7	**2g.** R_1=H; Ar= C_6H_5-*p*-Cl	87
8	**2h** .R_1=H; Ar = α-naphthyl	78
9	 **3a.** $TMSN_3$ NaN_3	75 69
		
10	**2i.** R_1=H ; Ar= C_6H_5-*p*-CH_3	85
11	**2j.** R_1=H ; Ar= C_6H_5-*o*-OCH_3	89
12	**2k.** R_1=H ; Ar= α-naphthyl	78
13	 **3b.** $TMSN_3$ NaN_3	72 70
		
14	**2l.** R_1=H ; Ar= C_6H_5-*o*-CH_3	85
15	**2m.** R_1=H ; Ar= C_6H_5-*o*-OCH_3	79
16	**2n.** R_1=H ; Ar= α-naphthyl	73
17	 **3c.** $TMSN_3$ NaN_3	70 65

[a] The reaction was carried out as described in ref 6. [b] The products were identified by IR, ^{1}H NMR, mass spectrometry and elemental analysis. [c] Isolated yields.

tolerated a varying degree of steric hindrance with aromatic amines such as α-naphthylamine, *o*-methylaniline and *o*-methoxyaniline. The trans stereochemistry of the products (**2** and **3)** was deduced by ^{1}H NMR spectroscopy. All the compounds are fully characterized by ^{1}H NMR, IR, mass spectra and elemental analysis.[7]

To study the scope of the reaction, we extended it to various cyclic, acyclic and aryl substituted aziridines. In the case of acyclic terminal aziridines, the reaction was highly regioselective with the formation of only one product and it was due to attack of the nucleophile at the less hindered terminal carbon atom. In the case of 2-phenyl aziridines the situation was reverse, the product formed was the one due to the attack of nucleophile at the benzylic carbon atom (internal attack). In this biomimetic catalysis, even the opening of the aziridines with trimethylsilyl azide could be easily carriedout at room temperature.

Here, the role of the β-CD appears to be to activate the aziridines by formation of hydrogen bonding. The reaction though catalyzed by α-CD, β-CD will be the most preferred catalyst due to the easy accessibility and inexpensive nature. The unusual feature of this reaction is that aromatic amines, trimethylsilyl azide and sodium azide opened the aziridines, whereas aliphatic amines such as diethyamine, *n*-butylamine, benzylamine and pyrrolidine failed to react with the aziridines even after two days and also under alkaline conditions using aqueous sodium hydroxide solution.

Thus, these water solvent reactions apart from mild conditions are very useful because of economical and environmental concerns and also the practical convenience of not having to handle flammable and anhydrous organic solvents.

In conclusion we have demonstrated a novel and efficient method for the ring opening of aziridines with a variety of nucleophiles using CD as a catalyst. This novel method may find wide range of applications.

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References and Notes

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6 Typical Procedure**:** β-Cyclodextrin (0.0025 mole) was dissolved in distilled water (100 mL), then aziridine (0.01 mole) dissolved in acetone (1 mL) was added followed by the amine/azide (0.01 mole) in acetone (1 mL) at room temperature. Then the reaction mixture was stirred at room temperature for 24 h and the product was extracted with ethyl acetate (3 × 50 mL). The organic phase was dried over anhydrous sodium sulfate and removed in vacuum. The crude product was purified by column chromatography on silica gel (100–200 mesh) using ethyl acetate: hexane as eluent.

7 Representative data for compound **2e**: white solid. mp 172 °C. IR (KBr): 3270, 2935, 1597 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.95–1.15 (m, 1H), 1.20–1.40 (m, 3H), 1.60–1.75 (m, 2H), 2.05–2.30 (m, 2H), 2.45 (s, 3H), 2.91 (ddd, *J* = 9.1, 9.1, 3.6 Hz, 1H), 3.05–3.20 (m, 1H), 3.80 (s, 3H), 5.10 (d, 1H, *J* = 4.5 Hz), 6.50–6.60 (m, 1H), 6.65–6.85 (m, 3H), 7.30 (d, *J* = 8.5 Hz, 2H), 7.75 (d, *J* = 8.5 Hz, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz) : δ 21.4, 23.9, 24.0, 31.5, 32.3, 55.3, 55.7, 56.9, 109.9, 110.7, 117.1, 121.2, 127.1, 129.5.136.7, 137.5, 142.9, 147.3. MS: 374(M^+). Anal. Calcd for $C_{20}H_{26}N_2O_3S$ (MW 374.50): C, 64.14; H, 7.00; N, 7.48; S, 8.54%. Found: C, 64.13; H, 7.24; N, 7.34; S, 8.72%.

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