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Regioselective ring-opening of aziridines with potassium thiocyanate in the presence of β-cyclodextrin in water☆

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Abstract—Aziridines are cleaved regioselectively with KSCN in the presence of β-cyclodextrin in water at room temperature with excellent yields.

Aziridines, apart from being important precursors for the synthesis of many nitrogen-containing biologically active molecules, are attracting increasing attention as versatile intermediates in organic synthesis.[1] There is growing interest in the ring-opening reactions of aziridines with various nucleophiles[2,3] because of their high reactivity and ease of preparation. As a result, several procedures have been developed for the ring-opening of aziridines with nucleophiles such as hydroxy compounds,[4] organometallics,[5] Wittig reagents,[6] silyl nucleophiles[7] and amines.[8] Frequently the nucleophilic opening of aziridines requires harsh reaction conditions and most of these reactions need to be carried out in organic solvents. Hence, there is a need for new methodologies for the ring-opening of aziridines, especially using water as the solvent.

We have attempted the regioselective ring-opening of aziridines with potassium thiocyanate leading to versatile β-amino thiocyanates, since the thiocyanato group is emerging as a biologically important functionality.[9,10]

These reactions when carried out in organic solvents such as acetonitrile yield mixtures of products. However, regioselective ring-opening of arylaminocarbonyl aziridines at the benzylic carbon with HSCN in ether was reported by Weber et al.[11] In view of these findings, we attempted the ring-opening of aziridines, with KSCN, under supramolecular catalysis involving β-cyclodextrin, with water as the solvent. Potential advantages of using water as a solvent are its low cost, safety, ease of use and its environmentally benign nature.

Cyclodextrins, which are cyclic oligosaccharides, exert microenvironmental effects leading to selective reactions. They catalyze reactions by supramolecular catalysis through non-covalent bonding as seen in enzymes. Complexation depends on the size, shape and hydrophobicity of the guest molecule. Thus, cyclodextrins bind substrates by molecular recognition and catalyze reactions in a selective fashion. Our earlier expertise in the field of biomimetic modelling of organic reactions involving cyclodextrins,[12] prompted us to study the regioselective ring-opening of aziridines with potassium thiocyanate in the presence of β-cyclodextrin (β-CD) in water. The complexes were formed with β-CD since it is easily accessible and the least expensive among the cyclodextrins.

The reactions were carried out by dissolving β-CD in water at 60 °C followed by the addition of the aziridine. Then the reaction mixture was cooled to room temperature, KSCN was added and the mixture stirred until the reaction was complete (Schemes 1 and 2).[13] All the aziridines gave yields ranging from 78% to 90% (Table 1). In the case of cycloalkyl aziridines, the stereochemistry of the ring-opened products was assigned as the *trans*-configuration based on the coupling constants of the relevant ring protons as compared with similar disubstituted cycloalkanes.[8b] The role of β-CD leading to regioselective ring-opening through the formation of an

Keywords: β-Cyclodextrin; Potassium thiocyanate; Aziridines; Water; Biomimetic; β-Aminothiocyanates.

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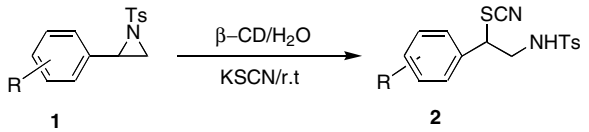
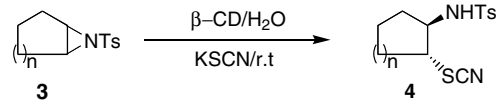


1 2

R = H, *p*-Cl, *p*-Br, *p*-OMe, *p*-Me and *p*-COMe

Scheme 1.

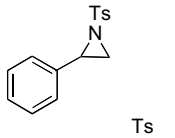
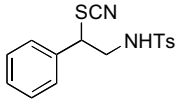
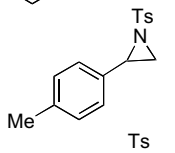
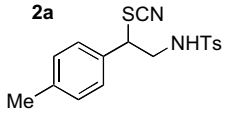
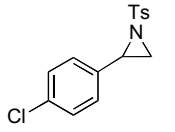
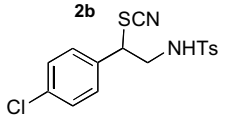
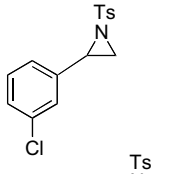
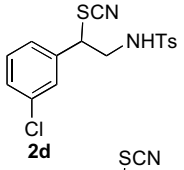
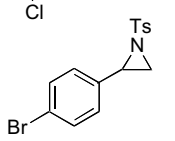
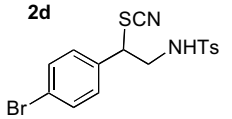
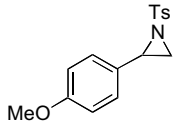
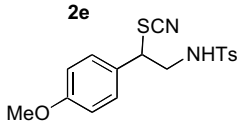
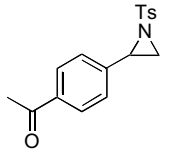
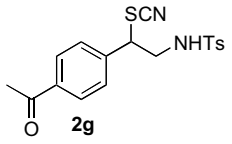
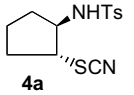
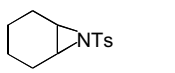
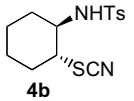


3 4

n=0,1

Scheme 2.

Table 1. Ring-opening of aziridines with KSCN

Entry	Substrate	Product[a]	Yield[b] (%)
1		 **2a**	90
2		 **2b**	90
3		 **2c**	85
4		 **2d**	88
5		 **2e**	87
6		 **2f**	90
7		 **2g**	86
8		 **4a**	80
9		 **4b**	78

[a] All the products were characterized by ^{1}H NMR, MS, IR spectroscopy and elemental analyses.

[b] Yields of products isolated after column chromatography.

inclusion complex of the aziridine was evident through our earlier ^{13}C NMR studies.[14] The deshielding of the methyl and tertiary carbons of the *p*-toluenesulfonyl group as well as the methylene carbon (β-position) of the aziridine ring indicated their inclusion in the hydrophobic cavity of the β-CD, thus exposing the α-position of the aziridine ring leading to the high regioselectivity. These reactions did not take place in the absence of the CD. All products were characterized by ^{1}H NMR, mass, IR and elemental analyses.

In summary, we have demonstrated a novel, mild and efficient method for the regioselective ring-opening of aziridines with KSCN using β-CD as the catalyst with water as the solvent.

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13. General procedure: To a solution of β-cyclodextrin (1 mmol) dissolved in distilled water (15 ml) at 60 °C, aziridine (**1** or **3**) (1 mmol) dissolved in acetone (2 ml) was added slowly with stirring. The mixture was cooled to room temperature, KSCN (2 mmol) was added then the reaction mixture was stirred at room temperature for 26 h and the product was extracted with ethyl acetate (3×50 ml). The organic phase was dried over anhydrous sodium sulfate and concentrated under vacuum. The crude product thus obtained was purified by column chromatography on silica gel (60–120 mesh) using ethyl acetate/hexane (85:15) as eluent.
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