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Supramolecular Synthesis of Selenazoles Using Selenourea in Water in the Presence of β-Cyclodextrin under Atmospheric Pressure†

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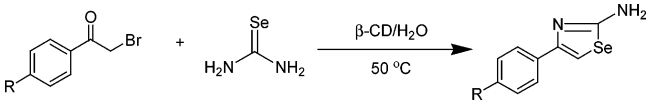

Selenazoles were synthesized from α-bromo ketones and selenourea in the presence of β-cyclodextrin in water at 50 °C under atmospheric pressure.

Selenazoles have been extensively studied as synthetic tools,[1] as well as for their biological significance.[2] Among them, 1,3-selenazoles are of pharmacological relevance due to their antibiotic and cancerostatic activity.[3] A prominent example is the C-glycosyl selenazofurin[3a] with antibacterial activity. 2-Amino-1,3-selenazoles are also good superoxide anion-scavengers.[4] A number of synthetic routes have been developed for the selenium-containing heterocyclic compounds because of their interesting reactivities.[5] These have been prepared mainly by the application of Hantzsch procedure.[6,7] The methods available have a number of drawbacks such as the use of anhydrous solvents, inert atmosphere, basic conditions,[8] longer reaction,[9] and low yields in the presence of water.[10] Apart from this, selenourea is air and light sensitive.[11] Thus, in view of these shortcomings, there is a need to develop a mild and ecofriendly synthetic methodology for these high value compounds by replacing organic solvents, most of which are flammable, toxic, or carcinogenic, with water using a recyclable activator as a part of green chemical approach.[12]

Water is a cheap, nontoxic, and most readily available reaction medium, making it an environmentally and economically attractive solvent.[13] However, the fundamental problem in performing reactions in water is that many organic substrates are hydrophobic and are insoluble in water. In our efforts to develop biomimetic approaches through supramolecular catalysis[14] and also to overcome some of the drawbacks in the existing methodologies for the synthesis of 2-amino-1,3-selenazoles from α-bromo ketones, we report herein, for the first time, the aqueous-phase synthesis of selenazoles from α-bromo ketones and selenourea in the presence of β-cyclodextrin (Scheme 1).

Cyclodextrins are cyclic oligosaccharides possessing hydrophobic cavities. They are torus-like macro-rings made up of glucopyranose units. As a consequece of the $^4C_1$ conformation of the glucopyranose units, all secondary hydroxyl groups are situated on one of the two edges of the ring, whereas all primary ones are placed on the other edge. The C-2-OH group of one glucopyranoside unit forms a hydrogen bond with C-3-OH group of the adjacent glucopyranose unit. Thus, the side where the secondary hydroxyl groups are situated, the diameter of the cavity is larger than on the side with the primary hydroxyls,

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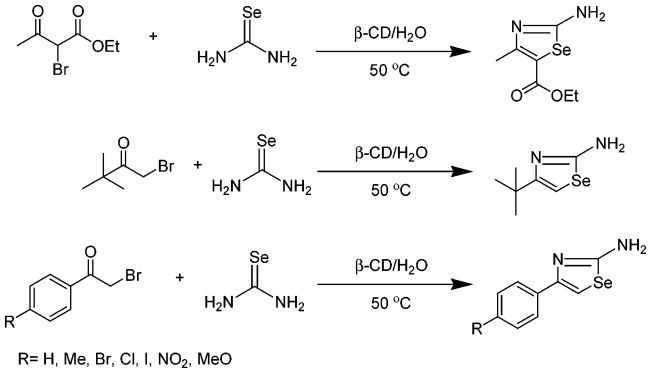
SCHEME 1

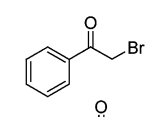
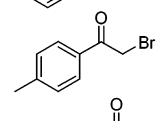
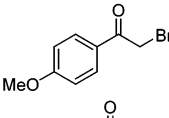
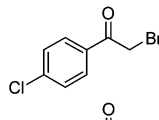
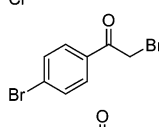
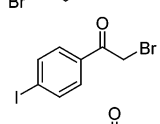
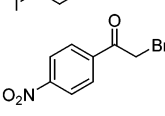
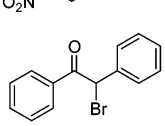
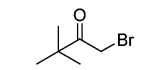
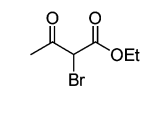


since the free rotation of the latter reduces the effective diameter of the cavity. They bind substrates selectively and catalyze chemical reactions by supramolecular catalysis involving the reversible formation of host−guest complexes with the substrates by noncovalent bonding as seen in enzyme complexation processes.[15] 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 the synthesis of a variety of selenazoles using the substrate-*β*-cyclodextrin complexes with selenourea in water.

In general, the reactions were carried out by the in situ formation of *β*-cyclodextrin complex of α-bromo ketone in water at 50 °C, followed by the addition of selenourea and stirring to give the corresponding selenazoles in almost quantitative yields (86−95%, Table 1). The yields of aromatic α-bromo ketones (phenacyl bromides) were comparatively higher than the aliphatic α-bromo ketones (Table 1, entries 9 and 10). When α-bromoethyl acetoacetate was reacted with selenourea, ethyl 2-amino-4-methyl-1,3-selenazole-5-carboxylate was obtained in 87% yield (Table 1, entry 10). These reactions proceed smoothly without the formation of any byproducts or rearranged products. All of the products were characterized by ^{1}H NMR, IR, and mass spectrometry and compared with the reported data.[16]

β-Cyclodextrin can be easily recovered and reused. These reactions do take place with α-cyclodextrin (α-CD); however, *β*-CD was chosen as the activator since it is inexpensive and easily accessible. Longer reaction (>12 h) and very low yields (25%) were seen in the absence of *β*-CD; in addition, water solubility problems arise with some compounds. Use of a catalytic amount of *β*-CD (0.1 mmol per mole of the substrate) had no impact on the reaction since the yields of the product obtained were the same as observed in the absence of *β*-CD. These experiments indicate the substantial role of cyclodextrin. The supramolecular catalysis of the reaction was established through ^{1}H NMR studies with phenacyl bromide (PB) as a representative example. The ^{1}H NMR (D_2O) of the *β*-cyclodextrin, *β*-cyclodextrin−phenacyl bromide complex, and freeze-dried reaction mixtures of *β*-cyclodextrin−phenacyl bromide−selenourea at 20 min and 40 min were studied (Table 2). It has been observed that there is an upfield shift of H_3 (0.067 ppm) and H_5 (0.069 ppm) protons of *β*-CD in the case of *β*-CD−PB complex as compared to *β*-CD due to the screening effect of the phenyl ring of phenacyl bromide included in the hydrophobic cavity of *β*-CD. These shifts indicate the formation of an inclusion complex of phenacyl bromide with *β*-CD.[17] After addition of selenourea (20 and 40 min), there is a further upfield shift of the H_3 (0.022 ppm) and H_5 (0.028 ppm) protons. This increase in the upfield character of H_3 (0.022 ppm) and H_5 (0.028 ppm) protons of *β*-CD as compared to *β*-CD−phenacyl bromide complex may be explained by the enhanced aromatic nature in the phenyl selenazole derivative. Thus, *β*-cyclodextrin

TABLE 1. Synthesis of Selenazoles in Water in the Presence of *β*-Cyclodextrin in Water

Entry	Substrate	Product[a]	Time(min)	Yield(%)[b]
1			40	92
2			45	94
3			40	95
4			50	93
5			50	92
6			50	90
7			35	94
8			45	91
9			60	86
10			55	87

[a] All of the products were identified by ^{1}H NMR, IR, and mass spectrometry and compared with the reported data.[16] [b] Isolated yields after purification.

TABLE 2. ^{1}H NMR Studies of *β*-CD Complexes and Reaction Mixtures

substrate	H_3 (δ)	H_5 (δ)
β-CD	4.014	3.902
β-CD−PB	3.947	3.833
β-CD−PB−selenourea, 20 min	3.925	3.805
β-CD−PB−selenourea, 40 min	3.909	3.792

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appears to activate the ketones, solubilize the reactants, and promote the reaction to completion in decreased reaction.

In conclusion, we have demonstrated for the first time that selenazole formation can be promoted by β-cyclodextrin in water. This methodology also overcomes the formation of unwanted byproducts, low yields, high temperatures, and inert atmosphere, thus making it a more user-friendly procedure. This methodology will be a useful addition to the modern synthetic methodology in the context of a higher demand for eco-compatible chemical processes and increasing interest in green chemistry.

Experimental Section

General Procedure for the Synthesis of Selenazoles. β-CD (1 mmol) was dissolved in water (20 mL) by warming to 50 °C until a clear solution was formed. Then, α-bromo ketone (1 mmol) dissolved in acetone (1 mL) was added dropwise followed by selenourea (1.2 mmol) and the mixture stirred at 50 °C until the reaction was complete (as monitored by TLC) (Table 1). The mixture was extracted with ethyl acetate, and the extract was filtered. The organic layer was dried over anhydrous Na_2SO_4, the solvent was removed under reduced pressure, and the resulting product was further purified by column chromatography. The aqueous layer was cooled to 5 °C to recover β-CD by filtration.

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Supporting Information Available: Characterization data for all compounds including ^{1}H NMR spectra and IR are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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