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β-Cyclodextrin-Catalyzed Monosulfonylation of Amines and Amino Acids in Water

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Abstract: A mild and efficient procedure has been developed for the first time under biomimetic conditions for the monosulfonylation of various amines and amino acids catalyzed by β-cyclodextrin in water at room temperature to afford the corresponding sulfonamides in high yields.

Keywords: amines; amino acids; β-cyclodextrin; sulfonamides; sulfonyl chlorides; water

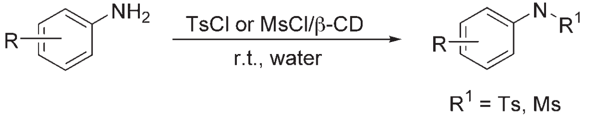
Sulfonamides are diverse group of medicinally important compounds widely used as anticancer, antibacterial, anticonvulsants, HIV protease inhibitors, anti-inflammatory, antitumor and antiviral agents.[1,2] Pharmaceutically important examples include the protease inhibitor amprenavir, the analgesic celecoxib, sildenafil for erectile dysfunction and the antimigraine agent sumatriptan.[3]

Although many efforts have been made towards the development of novel sulfonamides,[4] the conventional synthesis involves the reaction of amino compounds with sulfonyl chlorides.[5] However, these procedures involve the use of organic solvents, base and elevated temperatures, especially for less reactive aniline substrates. For sterically hindered primary amines with electron-withdrawing substituents, bis-sulfonylation is a common side reaction which requires further monodesulfonylation.[6] Although Diang and Mani recently reported[7] a synthesis of sulfonamides in water, it requires dynamic pH control with Na_2CO_3 and isolation of the products involves acidification up to pH 2 with HCl. This methodology has some drawbacks such as the limitation of utilizing mostly water-soluble amines like aminobenzoic acids and sluggish reactions with insoluble amines like aniline with yields only up to 30% of the desired product even after three days.

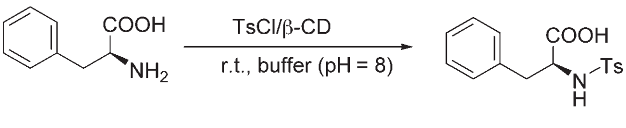
Therefore, there is a clear need for the development of a generally applicable, environmentally benign and mild methodology for the synthesis of sulfonamides in water. Organic reactions in aqueous media have recently become the focus in organic synthesis since they overcome the harmful effects of organic solvents and are environmentally benign.[8] These aqueous reactions can be made more sophisticated if they can be performed under supramolecular catalysis. In continuation of our interest in the use of cyclodextrins as mild and efficient biomimetic catalysts in promoting various transformations,[9] we have attempted the sulfonylation of amines in water in the presence of cyclodextrin.

Cyclodextrins (CDs) are cyclic oligosaccharides possessing hydrophobic cavities, which bind substrates selectively and catalyze chemical reactions with high selectivity. They promote reactions by supramolecular catalysis involving reversible formation of host-guest complexes by non-covalent bonding as seen in enzymes. We describe herein the remarkable catalytic activity of β-cyclodextrin in the reaction of various amines and amino acids with *p*-toluenesulfonyl chloride and methanesulfonyl chloride, to give exclusively the monosulfonamides (Scheme 1 and Scheme 2).

In general, the reactions were carried out by dissolving β-cyclodextrin in water and then adding the



Scheme 1.



Scheme 2.

Table 1. Sulfonamide synthesis in water/in buffer catalyzed by β-cyclodextrin.

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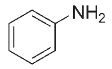
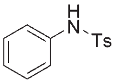
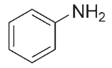
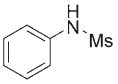
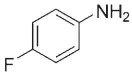
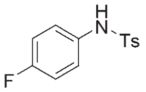
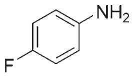
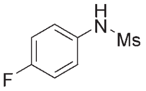
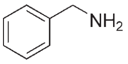
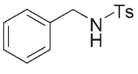
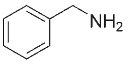
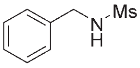
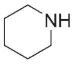
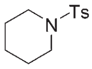
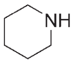
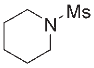
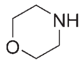
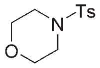
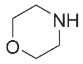
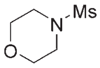
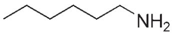
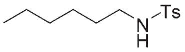
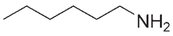
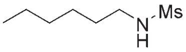
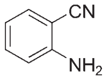
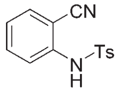
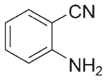
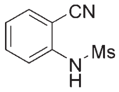
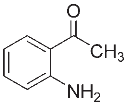
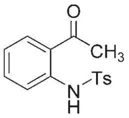
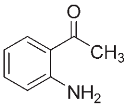
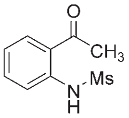
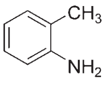
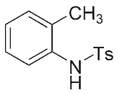
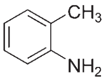
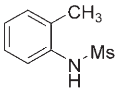
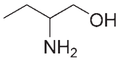
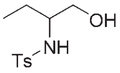
1			25	95
2			35	91
3			30	90
4			35	85
5			25	89
6			35	87
7			30	90
8			40	87
9			30	92
10			35	87
11			35	90
12			40	89
13			60	76
14			55	79
15			40	88
16			35	87
17			45	92
18			40	90
19			40	89

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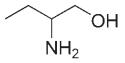
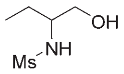
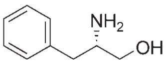
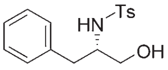
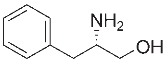
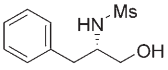
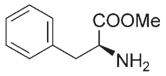
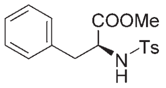
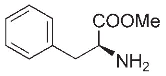
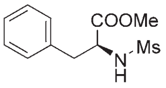
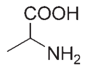
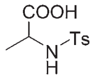
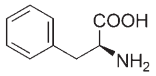
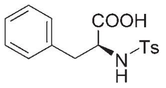
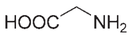
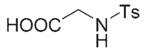
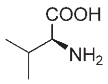
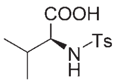
20			40	86
21			45	89
22			40	87
23			45	90
24			55	87
25			50	88
26			55	88
27			45	85
28			50	87

[a] All products were identified by IR, NMR and mass spectroscopy.

[b] Yields of products isolated after column chromatography.

amine followed by the addition of *p*-toluenesulfonyl chloride or methanesulfonyl chloride at room temperature to get the corresponding sulfonamides in high yields (76–95 %,). The reactions were rapid with all the amines studied (25–60 min). This method was also compatible with various types of primary and secondary amines. No bis-sulfonylated product formation was observed even with sterically hindered and electron-deficient anilines (entries 13–16, Table 1). High enantioselectivity was also observed in the case of amino alcohols (entries 19–22, Table 1). β-CD can be recovered and reused. All the products were isolated and characterized by ^{1}H NMR, mass and IR spectroscopy and by comparison with the known compounds.[4–6,10]

The successful monosulfonylation of amino compounds with TsCl and MsCl prompted us to attempt this reaction with amino acids. These reactions were attempted at pH 8 using a mild carbonate buffer (0.1 M) with β-cyclodextrin as the catalyst. Surprisingly, the reactions with TsCl were complete in 45–

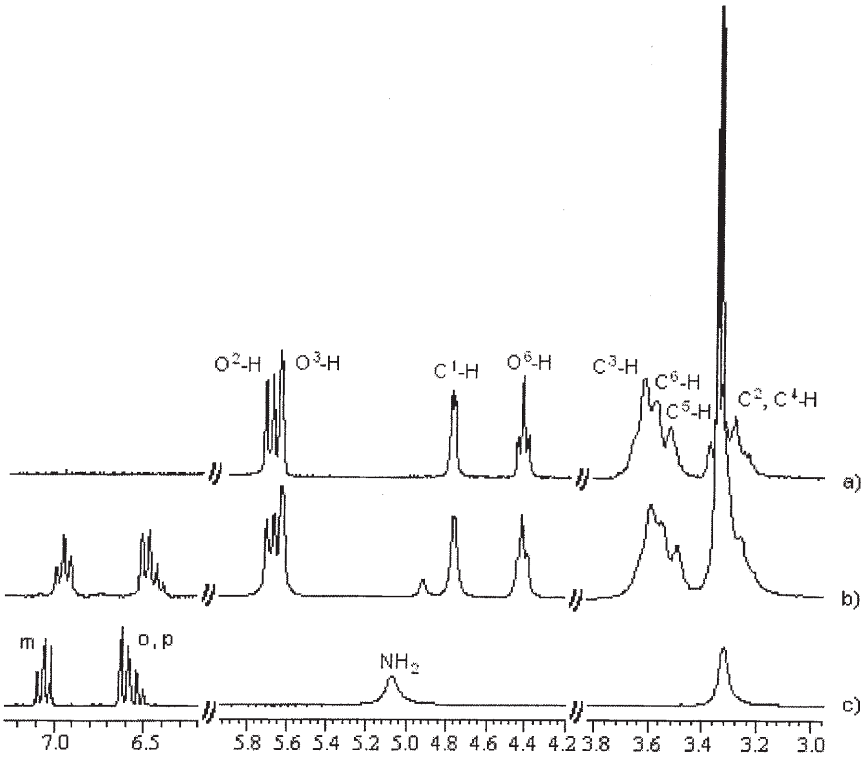


Figure 1. ^{1}H NMR spectra (200 MHz, DMSO-d_6) of **a**) β-CD, **b**) aniline:β-CD complex and **c**) aniline.

Table 2. 200 MHz (DMSO-d_6) ^{1}H NMR chemical shifts of aniline and β-CD protons in free and complexed states.[a]

Protons	Aniline	β-CD	β-CD-Aniline complex	Δ δ
H-*meta*	1410.7		1396.6	14.1
H-*ortho,para*	1295.9 – 1330.4	-	1277.1 – 1323.7	12.7
-NH_2	1013.8	-	995.7	18
C_1-H	-	964.0	963.2	0.8
C_2-H	-	667.9	668.4	–0.5
C_3-H	-	725.7	711.8	6
C_4-H	-	658.5	658.9	–0.4
C_5-H	-	706.2	695.0	11.2
C_6-H	-	716.4	713.0	2.6
O_2-H	-	1148.4	1149.0	–0.6
O_3-H	-	1137.5	1137.9	–0.4
O_6-H	-	839.7	895.4	–1.6

[a] Chemical shifts are expressed in Hertz with reference to DMSO-d_6 signal.

55 min at room temperature giving yields of 85–88 %, whereas no product formation was observed with MsCl due to rapid hydrolysis. No racemization was observed during these reactions.

The catalytic activity of cyclodextrin for this sulfonylation of amines and amino acids is established by the fact that no reaction was observed in the absence of cyclodextrin. Evidence for complexation between the amine and cyclodextrin is supported by ^{1}H NMR spectroscopy. Although all these reactions were carried out with a catalytic amount of β-CD, these studies were undertaken with β-CD-aniline (1:1) complex as a representative example, as cylcodextrins catalyze reactions by supramolecular catalysis involving reversible formation of host-guest complexes. A comparison of ^{1}H NMR spectra of aniline, β-CD and the β-CD-aniline complex was undertaken. All aromatic and NH_2 protons of aniline are shifted upfield due to the inclusion of aniline inside of β-CD cavity (Figure 1, Table 2).[11] There is also a clear upfield shift of H-3 (0.03 ppm) and H-5 (0.05 ppm) of cyclodextrin in the β-CD-aniline complex in comparison to β-CD indicating the formation of an inclusion complex of aniline with β-CD (Figure 1, Table 2).[11] Formation of hydrogen bonding between the hydroxy groups of the top torus in the β-CD molecule and aniline was already established by molecular dynamics studies.[12] Here, β-CD not only forms the inclusion complex with the amine but is also involved in intermolecular hydrogen bonding with the guest to promote the reaction.

In conclusion, we have presented an elegant and simple methodology for the monosulfonylation of various amines and amino acids in the presence of β-cyclodextrin in water. This straightforward methodology may find widespread applications in organic and medicinal chemistry.

Experimental Section

General Information

^{1}H NMR spectra were recorded on a Gemini-200 MHz or an Avance-300 MHz spectrometer in $CDCl_3$ or DMSO-d_6 with TMS as internal standard. Mass spectra were recorded on a Finnigan MAT 1020 mass spectrometer operating at 70 eV. IR spectra were recorded on Nicolet FT-IR. spectrometer. Melting points were recorded on Büchi R-535 apparatus and are uncorrected.

General Procedure for Synthesis of *N*-Tosylbenzeneamine or *N*-Mesylbenzeneamine

β-Cyclodextrin (0.1 mmol) was dissolved in water (15 mL) at room temperature and the amine (1 mmol) dissolved in acetone (1 mL) was added dropwise with stirring. To this suspension *p*-toluenesulfonyl chloride (1.2 mmol) or methanesulfonyl chloride (1.5 mmol) was added and the mixture stirred at room temperature until the reaction was complete (Table 1). The reaction mixture was extracted with ethyl acetate, dried over Na_2SO_4 and concentrated under reduced pressure and the resulting product was further purified by passage over a column of silica gel. β-Cyclodextrin was recovered (95 %) after lyophilization of the aqueous phase.

General Procedure for Synthesis of *N*-(*p*-Toluenesulfonyl)amino Acids

β-Cyclodextrin (0.1 mmol) was dissolved in 0.1 M carbonate buffer (pH 8) (10 mL) at room temperature, then the amino acid (1 mmol) was added and the mixture stirred for 5 min. Then TsCl (1.2 mmol) was added and stirring was continued at room temperature until the reaction was complete (Table 1). The reaction mixture was extracted with ethyl acetate, the organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed under vacuum to yield the product. These products were purified by silica gel chromatography.

Preparation of β-CD-Aniline Inclusion Complex

β-CD (1 mmol) was dissolved in water (15 mL) by warming to 60 °C until a clear solution was formed, and then aniline (1 mmol) dissolved in acetone (1 mL) was added dropwise and the mixture was allowed to come to room temperature. It was cooled to 15 °C for 5 h and the white solid precipitate was filtered and dried.

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