Phase Transfer Catalyzed Preparation of 4-Methylbenzenesulfonyl Imidazole for Regioselective Synthesis of Mono-6-(4-methylbenzenesulfonyl)-β-cyclodextrin

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Abstract: *The preparation of 4-methylbenzenesulfonyl imidazole by using triethylamine as an effective phase-transfer catalyst (PTC) under mild biphasic conditions has been studied intensively. The method can be used for large-scale preparation with high purity and high yield of 4-methylbenzene-sulfonyl imidazole. The result in 4-methylbenzenesulfonyl imidazole has been successfully applied for the regioselective synthesis of mono-6-(4-methylbenzenesulfonyl)-β-cyclodextrin in an aqueous medium. This synthetic methodology concept, together with the synthetic versatility of PTC, provides a general and reliable general strategy for the practical and industrial regioselective synthesis of highly valuable mono-6-(4-methylbenzenesulfonyl)-β-cyclodextrin as a key intermediate for the single functional isomer mono-substituted cyclodextrin derivatives. As characterized by FTIR, NMR and mass spectrometry, mono-6-(4-methylbenzenesulfonyl)-β-cyclodextrin was obtained in high purity.*

Keywords: *phase transfer catalysis; 4-methylbenzenesulfonyl imidazole; regioselective synthesis; mono-6-(4-methylbenzenesulfonyl)-β-cyclodextrin*

■ INTRODUCTION

Cyclodextrins (CDs) are naturally occurring cyclic oligosaccharides consisting of six, seven, and eight glucopyranose units, which are termed α-, β-, and γ-cyclodextrins, respectively [1-2]. These oligosaccharides consist of α-1,4-connection of each α-D-glucopyranose unit to form cyclic structures and they are shaped like truncated cones rather than perfect cylinders. Native cyclodextrins have limited aqueous solubility. In particular, β-cyclodextrin (β-CD) forms intramolecular hydrogen bonds between secondary OH groups at C-2 and C-3 positions which detract from hydrogen bond formation with surrounding water molecules, resulting in less negative heat of hydration and significant lowering of solubility, i.e., 18.5 g/L at 25 °C [2]. In order to improve the solubility of β-cyclodextrin in aqueous media, it is necessary to modify β-cyclodextrin by substituting one OH group at either 2- or 6-position with other groups to give functionalized CD derivatives which are more soluble in water [3-4].

Mono-6-(4-methylbenzenesulfonyl)-β-CD is the most important precursor to further functionalize the primary hydroxyl groups (C-6) of β-CD, since 4-methylbenzenesulfonylate is a good leaving group and can be easily substituted by other nucleophiles [5-6]. The most convenient procedure to prepare mono-6-(4-methylbenzenesulfonyl)-β-CD is by using 4-methylbenzenesulfonyl imidazole as an important reagent reacting with β-CD in a basic medium [7]. The reported procedure for preparation of 4-methylbenzenesulfonyl imidazole employs an excess amount of imidazole, a lot of organic solvents, including dichloromethane (500 mL), a mixture of ethyl acetate-*n*-hexane (500 mL), ethyl acetate (50 mL), *n*-hexane (500 mL), 3.5 h reaction, and complicated purification process [7]. The synthetic methodology, in particular, the purification steps was challenging, used a lot of solvents, produced many waste materials, and resulted

in a long and expensive procedure. These wastes should be destroyed, disposed, or regenerated thus consuming a lot of energy and creating a serious and heavy burden on the environment. Therefore, it is of great importance to develop, provide and use new synthetic methodologies of 4-methylbenzene-sulfonyl imidazole that minimize these problems. Perhaps one of the most general, efficient, and effective methodologies that fulfill this requirement is phase-transfer catalysis (PTC) [8-10]. This PTC synthetic methodology is applicable to a great variety of reactions in which organic substrates react with organic and inorganic anions. It consists of the use of heterogeneous two-phase systems - one phase being a reservoir of reacting base or anions for the generation of organic anions in an aqueous system, whereas catalyst and organic reactants as the source of lipophilic cations are present in the other (organic) phase [9].

Here, we report a convenient and economical method for the preparation of 4-methylbenzene-sulfonyl imidazole by using PTC on a high scale with high yields. Moreover, the use of 4-methylbenzene-sulfonyl imidazole as a precursor in synthesis with β-cyclodextrin is described to obtain a highly pure mono-6-(4-methylbenzene sulfonyl)-β-cyclodextrin with an acceptable yield in the aqueous media.

■ EXPERIMENTAL SECTION

Materials

Imidazole was purchased from Merck. Triethylamine, β-cyclodextrin, sodium bicarbonate, sodium hydroxide, anhydrous magnesium sulfate, dichloromethane, acetone, and *n*-hexane were purchased from Sigma-Aldrich. The 4-methylbenzenesulfonyl chloride and ammonium chloride were purchased from Fluka. All chemicals were directly used without further purification.

Instrumentation

Melting points were determined with Büchi Melting Point B-540 apparatus. Elemental analyses were performed with a Perkin Elmer 240C elemental analyzer for C, H, N, and S determination. UV-Vis spectra were recorded by using Double Beam Spectrophotometer Shimadzu UV-1800. Infrared spectra were recorded with a Perkin Elmer 1600 spectrometer and samples were prepared as KBr pellets. Electron spray ion mass spectrometry (ESI MS) was performed on a Finningan TSQ7000 mass spectrometer. The ^{1}H and ^{13}C-NMR spectra were recorded with a Bruker ACF 300 Spectrometer. Samples were dissolved in deuterated solvents and chemical shifts (δ) are reported in parts per million (ppm) according to tetramethylsilane (TMS) as the internal standard.

Procedure

Synthesis of 4-methylbenzenesulfonylimidazole (BsIm)

Imidazole (136.16 g, 2.0 mol) and 4-methylbenzenesulfonyl chloride (381.28 g, 2.1 mol) were dissolved in dichloromethane (1500 mL) in an Erlenmeyer. Sodium bicarbonate (176.421 g, 2.1 mol) was added to the water (1500 mL) and followed by the addition of triethylamine (20 mL) as a PTC. The two-layer mixtures, aqueous and organic layers, were stirred at room temperature. Carbon dioxide gas was released during the reaction and the mixture was continuously stirred for 4 h until no more gas formed. The organic layer was separated and the aqueous layer was extracted with dichloromethane (3 × 1000 mL). The organic phases were combined and dried with anhydrous $MgSO_4$, then filtered, concentrated to approximately 750 mL, and added with *n*-hexane (150 mL). The mixture was allowed overnight to form a white crystal and the crystal was filtered and dried under vacuum to give the desired product (425.62 g, 93.5%) with a melting point of 77.5–78.5 °C (lit. 78.0–79.0 °C) [7].

FTIR (cm^{-1}, KBr): 3159, 3103, 3032, 1595, 1516, 1383, 1151. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.42 (s, 3H, CH_3), 7.07 (s, 1H, =CH-4$_{im}$), 7.28 (s, 1H, =CH-5$_{im}$), 7.34 (d, 2H, J = 8.43 Hz, =CH$_{meta}$), 7.81 (d, 2H, J = 8.01 Hz, =CH$_{ortho}$), 7.99 (s, 1H, =CH-2$_{im}$). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 21.5 (CH_3), 117.4 (C4), 127.2 (C$_{meta}$), 130.3 (C$_{ortho}$), 131.2 (C5), 134.8 (C$_{para}$), 136.5 (C2), 146.2 (C$_{ipso}$). ESI-MS (*m/z*): 223.03 $[M+H]^+$, calc. 223.05.

Synthesis of mono-6-(4-methylbenzenesulfonyl)-β-cyclodextrin

In this study, a modified reported procedure was used to synthesize mono-6-(4-methylbenzenesulfonyl)-β-cyclodextrin [7]. The 4-methylbenzenesulfonyl imidazole (12.22 g, 0.055 mol) was added to a suspension of β-cyclodextrin hydrate (67.55 g, 0.05 mol) in water (500 mL). The mixture was allowed to be stirred for 2 h. A solution of sodium hydroxide (20 g in 100 mL, 0.5 mol) was added and stirred for 10 min. The insoluble solid was removed by filtration. The filtrate was neutralized to pH value was approximately 7.0 by adding ammonium chloride. The white solid formed was collected by filtration and washed with cold water to give the product (27.5 g, 42.5%) with a melting point of 173 °C slow dec., (lit. 163–168 °C (dec.) [11].

FTIR (cm^{-1}, KBr): 3400, 2935, 1647, 1367, 1159, 1080, 1031, 582. ^{1}H-NMR (300 MHz, DMSO-$_{d6}$) δ : 2.43 (s, 3H, CH_3), 3.22-3.40 (overlap with HDO, m, 14 H, H-2 and H-4), 3.46–3.65 (m, 28H, H-5, H-3, and H-6), 4.16–4.22 (m, 1H, OH-6), 4.31–4.40 (m, 1H, OH-6), 4.45–4.53 (m, 4H, OH-6), 4.77 (d, 2H, J = 3.21 Hz, H-1), 4.84 (d, 5H, J = 3.24 Hz, H-1), 5.64–5.83 (m, 14H, OH-3 and OH-2), 7.43 (d, 2H, J = 8.4 Hz, =CH_{meta} aromatic), 7.75 (d, 2H, J = 8.4 Hz, =CH_{orto} aromatic). ^{13}C-NMR (75 MHz, DMSO-$_{d6}$) δ: 21.2 (CH_3), 59.9 (C-6), 68.9 (C-6'), 69.7 (C-5'), 72.0 (C-5), 72.4 (C-3), 73.0 (C-2), 80.7 (C-4'), 81.5 (m, C-4), 101.9 (C-1), 101.2 (C-1'), 127.6 (C_{meta}), 129.9 (C_{ortho}), 132.7 (C_{para}), 144.8 (C_{ipso}). ESI-MS (m/z): 1311.2 $[M+Na]^+$, calc. 1311.38. Microanalysis (%): C 45.3, H 6.1, S 2.4; calc., C 45.7, H 5.9, S 2.5.

Determination of binding constant of BsIm/β-CD inclusion complex

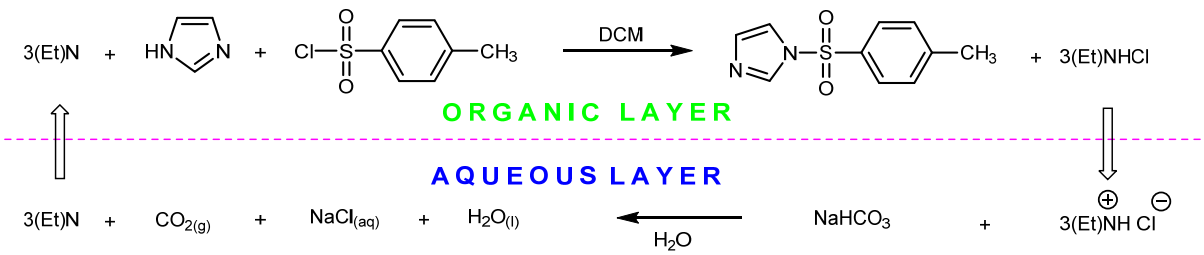
The binding constant of the inclusion complex was determined according to the reported procedure [12] with slight modification. The standard solution of 4-methylbenzenesulfonyl imidazole (BsIm) in water (5 mL, 5×10^{-5} M) and a volume (5 mL) of a standard solution of β-CD solution (2, 4, 6, and 8×10^{-3} M) were placed in a volumetric flask (10 mL). The volume was adjusted with deionized water and the mixture was stirred for 30 min to allow the formation of the complex. The absorbance of resultant solutions was determined using a UV-Vis spectrophotometer.

■ RESULTS AND DISCUSSION

Synthesis of 4-Methylbenzenesulfonylimidazole

The 4-methylbenzenesulfonylimodazole has been prepared from the 4-methylbenzenesulfonyl chloride by reaction with 2.26 equivalents of imidazole and 1.0 equivalent of triethylamine in dichloromethane [7]. For high-scale preparation or industrial purpose, the method is not convenient because consuming a lot of imidazole as substrate, triethylamine as a catalyst, dichloromethane, ethyl acetate and n-hexane as solvents, as well as long purification processes. Hence, we developed a new synthetic method by using PTC, and this method has advantages for industrial manufacturing as it is more effective and efficient. PTC reactions of organic anions use the inorganic phase contains bases such as concentrated aqueous or solid NaOH or KOH or solid K_2CO_3 as aqueous solutions whereas the organic phase contains the anion precursor, an electrophilic reactant, and eventually a solvent [8-10].

This methodology is efficiently applicable for the preparation of 4-methylbenzenesulfonyl imidazole. The mixture of 4-methylbenzenesulfonyl chloride, imidazole and triethylamine in a catalytic amount was dissolved in dichloromethane. The mixture was added with a saturated solution of sodium bicarbonate to form immiscible two-phase systems – the organic and aqueous phases. Since both phases are mutually immiscible, the reaction does not proceed unless the catalyst, usually a trialkylamine, R_3N is present. In the organic phase, in the presence of triethylamine, 4-methylbenzene-sulfonyl chloride reacts with imidazole to produce 4-methylbenzenesulfonyl imidazole and hydrochloric acid (HCl). The HCl further reacts with triethylamine to give quaternary ammonium salt which is soluble and transfers into an aqueous layer. In the aqueous phase, the ammonium salt then reacts with sodium bicarbonate and produces water, sodium chloride, carbon dioxide (CO_2) gas, and triethylamine (Scheme 1). The regenerated triethylamine returns to



Scheme 1. Synthesis of 4-methylbenzenesulfonyl imidazole using phase transfer catalysis method

the organic layer and the cycle continues until all of 4-methylbenzenesulfonyl chloride completely reacts with imidazole. The end of the reaction can be monitored from the absence of CO_2 bubbles.

The method used triethylamine in catalytic amount and could be used for high-scale preparation and gives a high yield. In this study, the synthetic method used 0.1 to 2.0 mol of imidazole and 4-methylbenzenesulfonyl chloride with a yield in the range of 93–94%. The comparison of the quantities of reactants, catalysts, solvents and products obtained in the preparation of 4-methylbenzenesulfonyl imidazole is given in Table 1. A similar reaction has been performed without phase transfer catalyst and the yield was 75–78%. This yield is lower than the reaction with a phase transfer catalyst, which is probably due to an incomplete reaction or equilibrium reaction.

This new synthetic method of making 4-methylbenzenesulfonyl imidazoles which are more efficient and effective used 4-methylbenzenesulfonyl chloride and imidazole reagents, tertiary amine as phase transfer catalyst, organic solvents, dichloromethane, and water to form two liquid phases and do not dissolve in each other. Upon completion of the reaction, the organic phases, dichloromethane layers, which contain the pure product, is separated by simple distillation and the product can be subsequently purified by crystallization. The dichloromethane obtained from distillation and aqueous phase upon separation of NaCl formed can be used again for another reaction process so the only waste is solid NaCl. Moreover, the 4-methylbenzenesulfonyl imidazole produced has been successfully used as a precursor in synthesis with β-cyclodextrin to obtain a highly pure mono-6-(4-methylbenzenesulfonyl)-β-cyclodextrin in an aqueous environment with an acceptable yield.

Synthesis of Mono-6-(4-methylbenzenesulfonyl)-β-cyclodextrin

Cyclodextrins are toroidal cyclic oligosaccharides with the primary C-6 hydroxyl group on the smaller open face and the secondary hydroxyls of glucose C-2 and C-3 on their more open face which can be modified with various functional groups. Chemical modifications of cyclodextrins influence the shape of the macrocyclic structure, the size of the molecular cavity, the ability to form hydrogen bonds, and in other physical properties. Therefore, the catalytic behavior and the binding properties can be controlled by the introduction of functional groups.

Table 1. The reactants ratio used and the yield of 4-methylbenzenesulfonyl imidazole

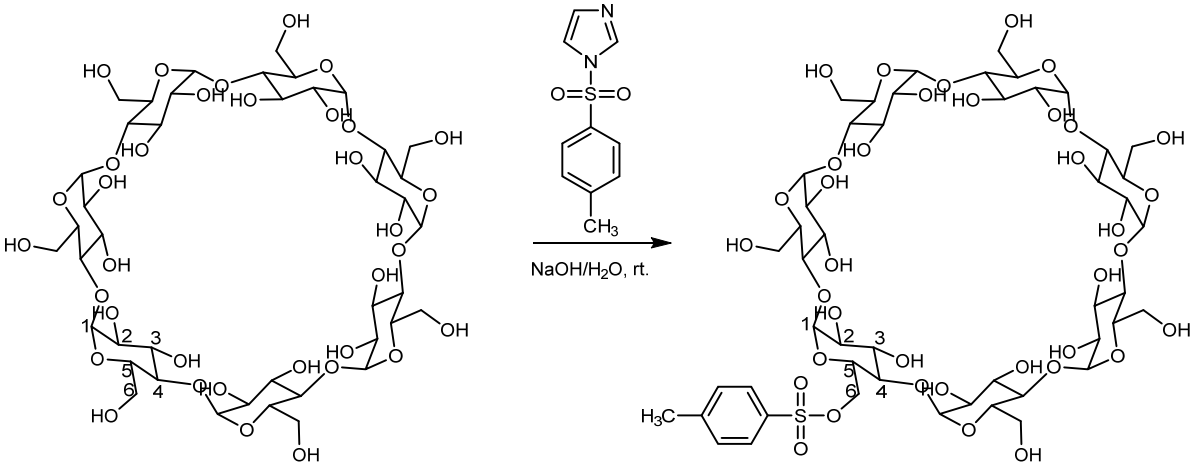
Imidazole (mol)	4-Methylbenzene-sulfonyl chloride (mol)	Et_3N (mL)	DCM (mL)	$NaHCO_3$ (mol)	H_2O (mL)	Yield g (%)
0.10	0.10	1.00	100	0.11	100	20.89 (94.00)
0.20	0.20	2.00	200	0.21	200	42.02 (94.50)
0.30	0.30	3.00	250	0.32	250	62.88 (94.30)
0.40	0.40	4.00	300	0.42	300	84.05 (94.50)
0.50	0.50	5.00	400	0.53	400	103.68 (93.30)
1.00	1.00	10.00	750	1.05	750	206.48 (92.90)
1.50	1.50	15.00	1200	1.58	1200	311.72 (93.50)
2.00	2.00	20.00	1500	2.10	1500	415.62 (93.50)

Establishing the synthetic approach for mono sulfonylation of one of the C-6 primary hydroxyl groups of β-cyclodextrin is an important step in providing a suitable intermediate for the introduction of a variety of other substituents or coupling of β-cyclodextrin at its primary hydroxyl group [13-16]. The selective chemical modification of cyclodextrins is possible by using the differences in reactivity of the three types of hydroxyl groups. The primary hydroxyl groups of the cyclodextrins are the most basic compared to the C-2- and C-3-hydroxyls which are secondary alcohols. They are also the most nucleophilic, as a consequence of which they may be selectively modified through their reaction with electrophilic species. While different synthetic methods for selectively functionalization, one single primary (C-6) hydroxyl group of cyclodextrins were reported and several by-products may be formed, requiring extensive subsequent purification procedures [17]. The most common synthetic strategies employed either organic or aqueous solvent/base systems.

Among numerous β-cyclodextrin derivatives, of particular interest is mono-6-(4-methylbenzenesulfonyl)-β-cyclodextrin [17]. The known methods of synthesis of this compound include acylation of β-cyclodextrin with 4-methylbenzenesulfonic hydride [18] and with 4-methylbenzenesulfonyl chloride in DMF [19], pyridine [20], aqueous acetonitrile [21], or sodium hydroxide solution [11]. These procedures utilize toxic solvents and are multistep and time- and energy-consuming.

In this study, mono-6-(4-methylbenzenesulfonyl)-β-cyclodextrin was synthesized using 4-methylbenzenesulfonyl imidazole (Scheme 2) and the yield was given in Table 2. It should be noted that the obtained mono-6-(4-methylbenzenesulfonyl)-β-cyclodextrin is characterized by high purity, so it can be used without additional purification.

As indicated in Scheme 2, a β-cyclodextrin molecule contains three types of hydroxyl groups, each including seven hydroxyl groups, in positions C-2, C-3 and C-6. The molecular structure of β-cyclodextrin has the form of a truncated cone, and unlike hydroxyl groups attached to the C-3 and C-6, the hydroxyl group is attached to the second carbon atom (OH-2) is oriented into the cavity of the cone and is thus not available for substitution



Scheme 2. Synthesis of mono-6-(4-methylbenzenesulfonyl)-β-cyclodextrin

Table 2. The yields and quantities of reactants and solvents used in the synthesis of mono-6-(4-methylbenzenesulfonyl)-β-cyclodextrin

No	β-CD	BsIm	Water	NaOH	Yield
1.	2.70 g (2 mmol)	0.47 g (2.10 mmol)	20 mL	0.80 g (20 mmol)	1.08 g (42.01%)
2.	13.51 g (0.01 mol)	0.47 g (0.01 mol)	100 mL	0.80 g (0.10 mol)	5.42 g (42.05%)
3.	27.02 g (0.02 mol)	4.90 g (0.02 mol)	200 mL	8.00 g (0.20 mol)	10.89 g (42.25%)
4.	67.55 g (0.05 mol)	12.22 g (0.05 mol)	500 mL	20.00 g (0.50 mol)	27.40 g (42.50%)

reactions with 4-methylbenzenesulfonyl imidazole. The mechanism of regioselective synthesis of mono-6-(4-methylbenzenesulfonyl)-β-cyclodextrin probably proceeds through the inclusion of complex formation between β-cyclodextrin and 4-methylbenzene-sulfonyl imidazole prior to sodium hydroxide addition. The β-cyclodextrin should form a 1:1 complex with 4-methylbenzenesulfonyl imidazole. This argument was supported by the observation of solid formation immediately when the solution of β-cyclodextrin was added with 4-methylbenzene-sulfonyl imidazole. This observation was consistent with the results obtained when mono-6-(4-methylbenzenesulfonyl)-β-cyclodextrin was made from β-cyclodextrin with 4-methylbenzenesulfonyl chloride [18] or 4-methylbenzenesulfonic anhydride [22].

In order to prove the inclusion of complex formation between 4-methylbenzenesulfonyl imidazole (BsIm) and β-CD, the BsIm/β-CD complex formed was isolated and the spectrometric experiment was performed. The UV absorption spectra of 4-methylbenzenesulfonyl imidazole and the BsIm/β-CD inclusion complex in aqueous solutions are shown in Fig. 1. A comparison of the UV spectra of BsIm and the BsIm/β-CD complex showed a distinct difference. The complexation of BsIm to β-CD causes a small red shift in the absorbance maximum and a large increase in the molar absorption coefficient. The increase in the molar absorption is presumably caused by the BsIm being complexed in the hydrophobic interior of the β-CD cavity. Therefore, the broad absorption at around 235 nm in Fig. 1 must be caused by the complex formation of β-CD with BsIm and not benzylated β-CD (β-CD-OBs).

Moreover, the complex formation of β-CD with BsIm may be confirmed by the determination of the binding constant (K_a). On the basis of the reliable Benesi-Hildebrand method for the 1:1 host-guest complex the double reciprocal plots have been drawn using Eq. (1) [12].

$$\frac{[H]_o[G]_o}{\Delta A} = \frac{1}{\Delta\varepsilon b K_a} + \frac{[H]_o}{\Delta\varepsilon b} \quad (1)$$

where $[H]_o$ and $[G]_o$ are the molar concentration of β-CD and BsIm, ΔA is the change in absorbance after the addition of β-CD, and Δε is the difference of the molar absorptivities for free and complexed BsIm. The binding constant for the 1:1 inclusion complex, K_a, can be calculated from Eq. (2).

$$Ka = \left(\frac{\text{slope}}{\text{intercept}}\right) \times 1000 \quad (2)$$

The Benesi-Hildebrand plots for β-CD with BsIM gave a straight line, Fig. 2. The K_a value for the complexes

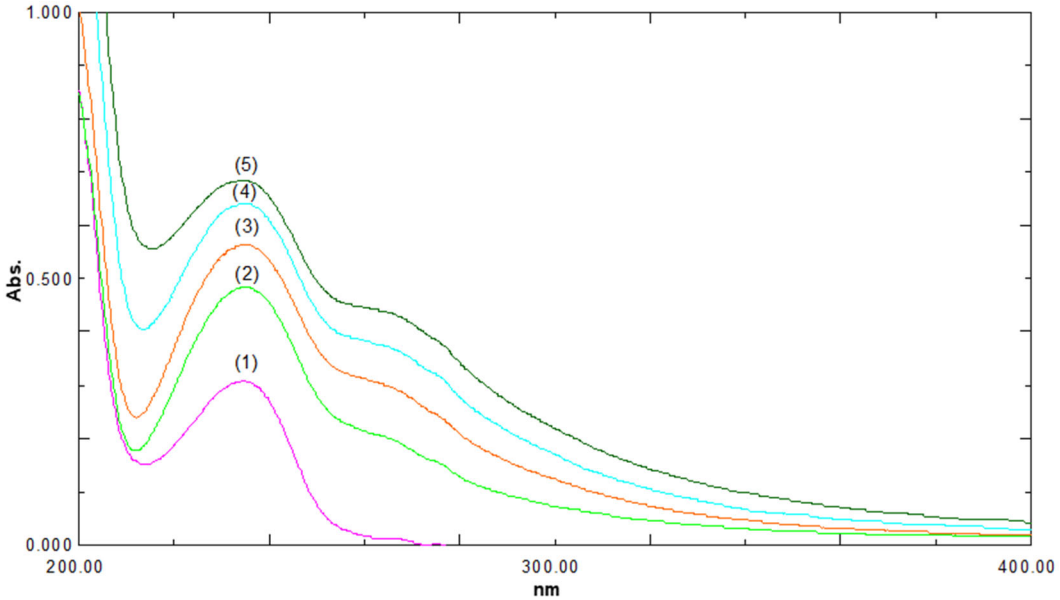


Fig 1. Spectrum of BsIm at varying β-CD concentration, aqueous, pH 7.0, 28 °C. [BsIm] is 2.5×10^{-4} M. [CD] is (1) 0 $\times 10^{-3}$, (2) 1×10^{-3}, (3) 2×10^{-3}, (4) 3×10^{-3}, (5) 4×10^{-3} M

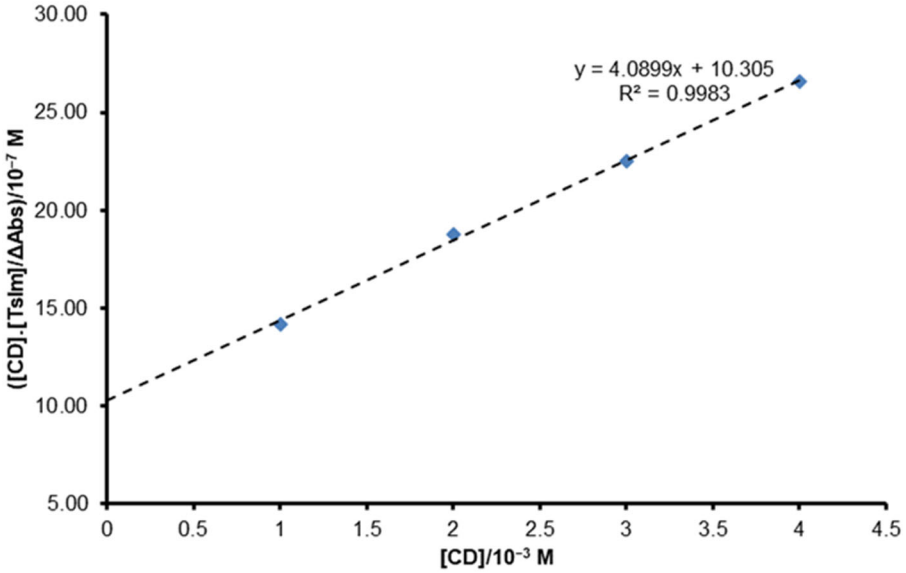


Fig 2. Benesi-Hildebrand plot for the mixture of β-CD and BsIm

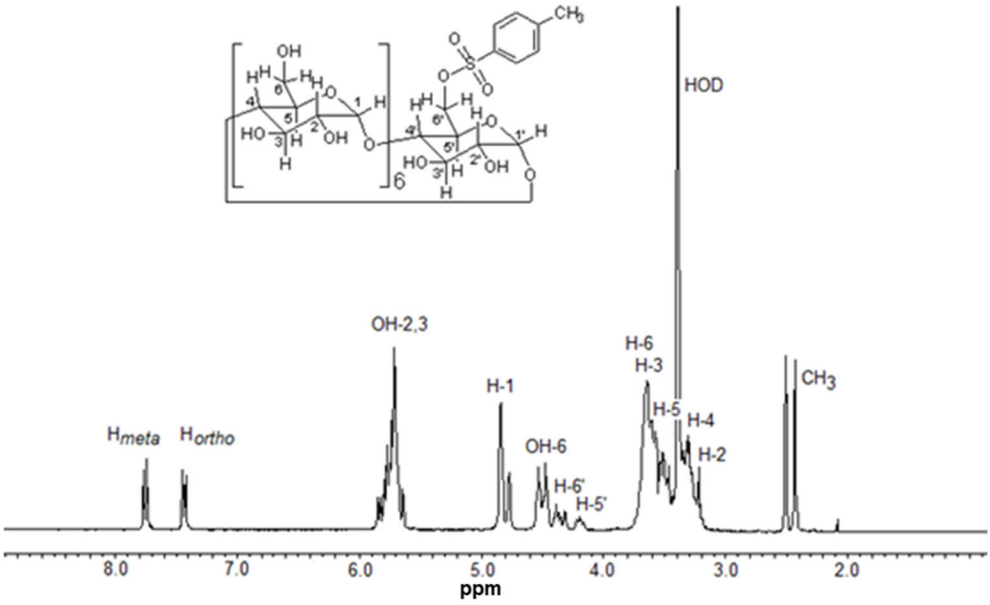


Fig 3. ^{1}H-NMR spectrum of mono-6-(4-methylbenzenesulfonyl)-β-CD in DMSO-d_6

of β-CD with BsIM, as calculated from the slope and intercept of this line, is 396.885 M^{-1}. This suggested that the mechanism of regioselective synthesis of mono-6-(4-methylbenzenesulfonyl)-β-CD proceeds through the formation of an inclusion complex between β-CD and BsIm with the 1:1 ratio.

The FTIR, NMR, and MS studies were conducted to identify and prove the structure of mono-6-(4-methyl benzene sulfonyl)-β-cyclodextrin. The functionalization of β-cyclodextrin with 4-methylbenzenesulfonyl group was confirmed by FTIR based on the peaks at 1159 cm^{-1} (S-O-R), which were not present in β-cyclodextrin or 4-methylbenzene-sulfonyl imidazole and could be attributed to alkyl substituted sulfonyl group. In addition, the comparison of ^{1}H-NMR spectra for the starting β-cyclodextrin and the product of its reaction with 4-methylbenzenesulfonyl imidazole determine the structural orientation of the reaction. The ^{1}H-NMR spectrum (Fig. 3) shows the resonance signals at 7.75 ppm (d, J = 8.4 Hz, 2 H_{ortho}), 7.43 ppm (d, J = 8.4 Hz, 2 H_{meta}),

and 2.43 ppm (s, 3H) for characteristic peaks of aromatic and CH_3 protons. A molar amount of > 99% of 4-methylbenzenesulfonyl group in the mono-6-(4-methylbenzenesulfonyl)-β-CD was detected by comparing the integral of the anomeric protons (H_1) at 4.85–4.76 ppm with that of benzene protons (-C_6H_4-CH_3) at 7.77–7.74 and 7.45–7.42 ppm, which stresses the high purity of the obtained product.

Furthermore, based on the integral ratios of the anomeric proton and the multiplet signal at 4.53–4.45 ppm (OH-6), which were calculated to be 7:6, it was confirmed that only one of the seven primary hydroxyl groups (C6-OH) of β-CD was replaced by 4-methylbenzenesulfonyl group. The 4-methylbenzenesulfonyl substituent causing unshielded effects resulted in a downfield peak shift at 4.37 ppm for the two protons of the derivatized C-6' and at 4.20 ppm for the adjacent C-5' proton, respectively. These facts gave information and proved the binding of the 4-methylbenzenesulfonyl group to the C-6' carbon. This result is consistent with previously reported ^{1}H-NMR data for mono-6-(4-methylbenzenesulfonyl)-β-cyclodextrin [23].

Fig. 4 shows the ^{13}C-NMR spectrum of mono-6-(4-methylbenzenesulfonyl)-β-CD and the assignments of resonance signals for the cyclodextrin region are as in inset. The ^{13}C-NMR spectrum shows important resonance signals at 144.8, 132.6, 129.8, 127.5, and 21.1 ppm for C_{ipso}, C_{para}, C_{ortho}, C_{meta} of the aromatic ring, and CH_3, respectively. The resonance signal for -CH_2- linked to 4-methylbenzenesulfonyl group is at 68.9 ppm. In the ^{13}C-NMR spectrum, peak shifts could be detected due to the functionalization of one (C-6') out of a total of seven C-6 carbons of β-cyclodextrin, namely, (i) a downfield shift of C-6' from 59.9 to 68.9 ppm, (ii) an upfield shift of adjacent C-5' from 71.8 to 69.6 ppm, and (iii) upfield shifts of C-4' (80.7 ppm) and C-1' (101.2 ppm). These values are consistence with Breslow's theory, which states that sulfonylation of the hydroxyl group causes a downward field shift of the carbon-carrying hydroxyl (the α-carbon), a small upward field shift of the β-carbon and a smaller upfield shift of the γ-carbon [24]. All ^{13}C-NMR peaks of non-functionalized carbon atoms showed the same chemical shift as the starting β-CD, supporting that a mono-functionalized product was obtained.

The mass spectrometry (MS) revealed a molecular weight of the molecular ion $[M+Na]^+$ of 1311.2 g mol^{-1}, which perfectly agreed with the calculated value (1311.38) for mono-6-(4-methylbenzenesulfonyl)-β-cyclodextrin. Importantly, compared to previous approaches to obtain mono-6-(4-methylbenzenesulfonyl)-β-cyclodextrin, the entire process, allowed to use of lower amounts of 4-methylbenzenesulfonyl imidazole and sodium hydroxide

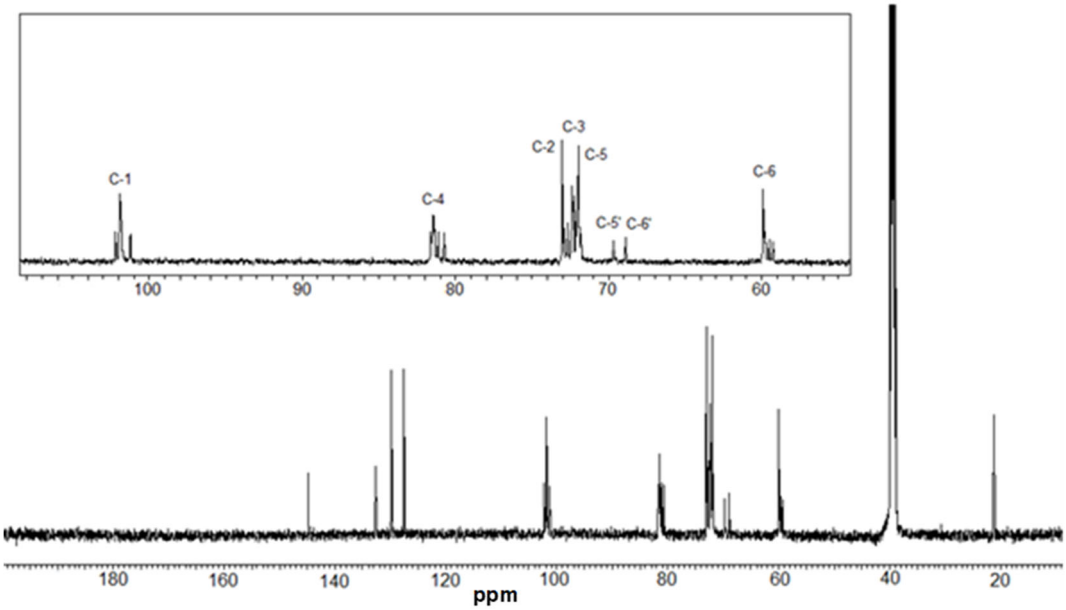


Fig 4. ^{13}C-NMR spectra of mono-6-(4-methylbenzenesulfonyl)-β-CD in DMSO-d_6

(molar ratio 4-methylbenzenesulfonylimidazole/β-cyclodextrin = 1.1 and NaOH/β-cyclodextrin = 10) in reasonable yield and high purity compared to the previously reported approach in NaOH/water environment [7].

■ CONCLUSION

The 4-methylbenzenesulfonyl imidazole has been prepared from the 4-methylbenzenesulfonyl chloride and imidazole by using phase transfer catalysis. This method can be used in the large-scale synthesis of 4-methylbenzenesulfonyl imidazole as it is easy to carry out and can produce a high percentage of yields. In addition, the method uses triethylamine in a catalytic amount and the solvent can be recycled and reused. It is a more effective and efficient synthetic methodology. Moreover, the 4-methylbenzene-sulfonyl imidazole produced has been successfully used as a precursor in regioselective synthesis with β-cyclodextrin to obtain a highly pure mono-6-(4-methylbenzenesulfonyl)-β-cyclodextrin in an aqueous environment with an acceptable yield. This synthetic methodology provides a reliable synthesis of mono-6-(4-methylbenzenesulfonyl)-β-cyclodextrin required for further synthesis of important single isomer mono-substituted β-cyclodextrin derivatives, containing just one substituent per β-CD molecule at the C-6 position.

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