Notes

Synthesis of 6-Deoxychlorocyclodextrin via Vilsmeier–Haack-Type Complexes

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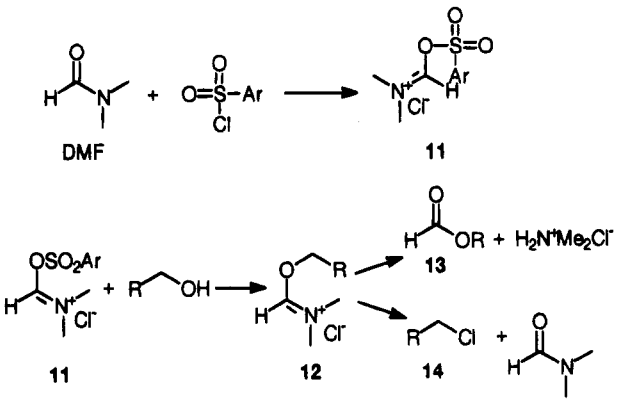
The primary hydroxyl groups of cyclodextrins have been substituted by halogens to produce 6-deoxyhalocyclodextrins for various synthetic purposes.[1-3] These are reactive intermediates in the formation of 6-halomaltoses and bifunctional cyclodextrins such as 6-amino- and 6-imidazolylcyclodextrins. They have generated a considerable interest because of their solubility and ability to form inclusion complexes.[4,5] Three types of deoxyhalogenated cyclodextrins, depending on the number of the primary hydroxyl groups (one = mono, two = di, and all = per) displaced by halogen atoms, are known. Mono 6-deoxyhalogenated cyclodextrins have been prepared by reacting α-cyclodextrin (**1**) with 1 equiv of tosyl chloride in pyridine to form mono(6-tosyl)cyclodextrin (**2**) which is converted to mono(6-chloro-6-deoxy)- (**3**), (6-bromo-6-deoxy)- (**4**), or (6-iodo-6-deoxy)cyclodextrin (**5**) by the reaction of tetramethylammonium chloride, lithium bromide, or aqueous sodium iodide, respectively.[6] However, sulfonation at the 6-position of cyclodextrins proceeds neither with good yield (40%) nor high selectivity.[4,7,8] Di- and perdeoxyhalogenated cyclodextrins have been synthesized by similar methods.[3,9]

The first direct method to brominate all the primary positions of cyclodextrins was reported by Takeo and coworkers.[10] Methanesulfonyl bromide converts α- (**1**), β- (**6**), and γ-cyclodextrins (**7**) to a mixture of 6-brominated and formylated products in a very high yield when heated in DMF at 65 °C for 18 h. Finally, these products are deformylated with sodium methoxide to afford hexakis(6-bromo-6-deoxy)-α- (**8**), heptakis(6-bromo-6-deoxy)-β- (**9**), and octakis(6-bromo-6-deoxy)-γ-cyclodextrins (**10**). The sulfonated compounds are formed during these reactions as side products along with compounds **8** and **9**.[11]

Compounds **8** and **9** can also be prepared[12,13] by heating cyclodextrins with triphenylphosphine dibromide in DMF at 80 °C for 15 h. The corresponding iodo compounds are synthesized by the same method using triphenylphosphine diiodide in DMF.[12,13] The formate esters formed during these reactions are destroyed by sodium methoxide. A simple direct method to covert all the primary hydroxyl groups of cyclodextrins into chloro groups in a very high yield without forming any side product is described in this report. These reactions are believed to proceed through a Vilsmeier–Haack-type complex which leads to the sequential displacement of the primary hydroxyl group by corresponding halogen atoms.[12]

Scheme 1



Results and Discussion

β-Cyclodextrin reacts with a mixture (1:1 molar) of methanesulfonyl chloride and imidazole to initially form a white gel-like precipitate which later turns into a clear solution and after appropriate workup affords heptakis(6-chloro-6-deoxy)-β-cyclodextrin (**17**) in 89.5% yield. The ^{1}H NMR spectrum shows the anomeric proton as a doublet at 4.95 ppm and the coupling constant, $J_{1,2}$, is 2.58 MHz. The ^{13}C NMR (DMSO-d_6) spectrum shows an upfield shift of 15.4 ppm for C-6 and a downfield shift of 1.65 ppm for C-4 whereas rest of the carbon atoms show a small change in their chemical shifts (see supplementary material).

It is known that sulfonyl chlorides and DMF form[14-19] a complex **11** (Scheme 1) which reacts with alcohols to give **12**. The intermediate **12** under anhydrous conditions gives the corresponding alkyl chloride **14** and under hydrolytic conditions affords the formate ester **13** along with ammonium salt.[20] As shown in Scheme 2, it is reasonable to propose that imidazole first forms a complex with methanesulfonyl chloride[21] which then attacks

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(21) A white gel-like precipitate is not formed in the absence of imidazole.

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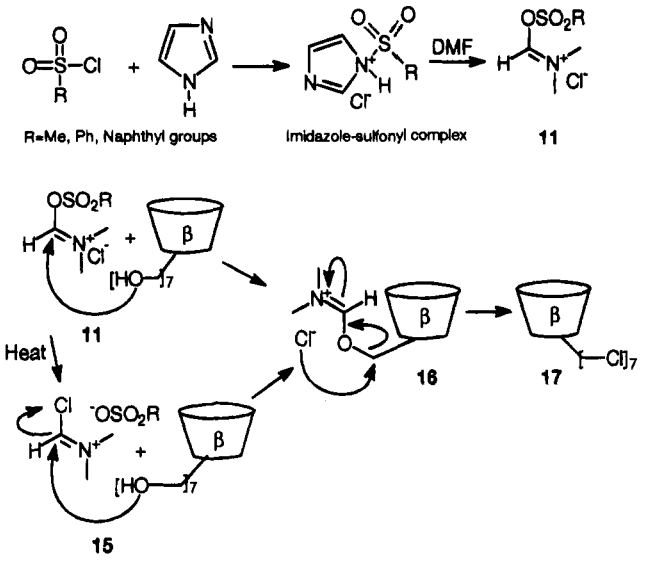
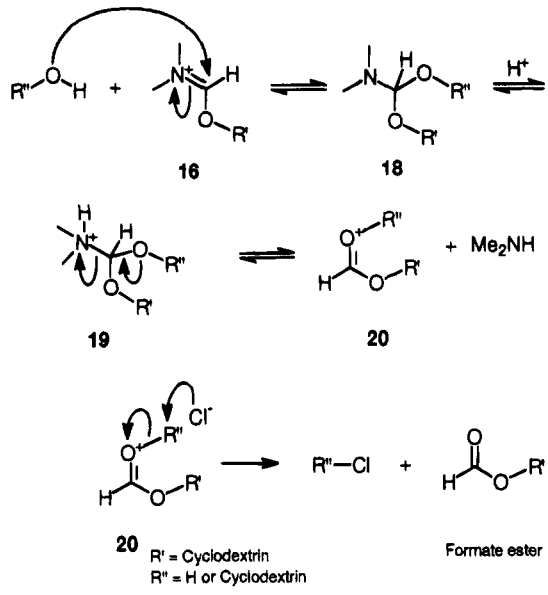
Scheme 2



Scheme 3



a DMF molecule to produce an adduct **11**. As per literature precedence, **11** can (Scheme 2) either directly[22] react, or undergo a thermal rearrangement[23] to **15** and then react, with the primary alcohol to give alkyl halides *via* the intermediate **16** whose structure is similar to **12**. The carbon atom at the 6-position of cyclodextrin in the intermediate **16** is thus activated and can undergo nucleophilic displacement by chloride ion to produce **17**. Due to steric interactions, it can be further proposed that there is sequential *in situ* generation of complex **16** at each primary hydroxyl group of cyclodextrin. Benzenesulfonyl and β-naphthalenesulfonyl chlorides also react with β-cyclodextrin under similar conditions to give the same product in 89% and 85% yield, respectively, suggesting that these two reagents follow an identical reaction pathway.

1. The Role of Imidazole. The early investigations of the reaction of cyclodextrins with sulfonyl halides (without imidazole) were reported to give a mixture of formylated and sulfonated products along with desired 6-halogenated compounds.[10,11] NMR spectra of the crude product obtained from our method (using imidazole in 1:1 molar ratio) do not show the presence of formylated or sulfonated compounds indicating that imidazole helps to prevent the side reactions. The possible role of imidazole in preventing the sulfonation and formylation side reactions is described below.

a. The Prevention of the Sulfonation Reaction. Imidazole used in a 1:1 molar ratio may react with sulfonyl chloride to give N-sulfonated imidazole which may further combine with DMF to form a Vilsmeier–Haack complex **11** (Scheme 2). The conversion of the intermediate **11** into the complex **15** and sulfonate ion may leave no free sulfonyl chloride in the reaction mixture to react with hydroxyl groups of cyclodextrins and give a sulfonated product. The intermediate **15** is converted to the complex **16** by combining with the hydroxyl group of cyclodextrin which ultimately produces halogenated cyclodextrin **17**.

b. The Prevention of the Formylation Reaction. As shown in Scheme 3, the intermediate **16** can produce a ketal **18** by combining with a second molecule of cyclodextrin (R″ = cylodextrin) which is transformed into another complex **19** by the protonation of a nitrogen atom. The intermediate **19** breaks up into dimethylamine and the oxonium ion **20** which is similar to a complex reported in the literature.[24] The chloride ion can attack the activated carbon atom of the intermediate **20** to produce 1 mol each of halogenated and formylated products. It is reasonable to propose that all these steps are reversible, and thus the forward reaction is facilitated in the presence of acid. Imidazole neutralizes the acid, hinders the conversion of complex **18** into **19**, and prevents the reaction from proceeding further to give formylated product. In order to test this hypothesis for the formation of an ester, experiments were carried out using undried cyclodextrin. If the water is present in the system, **16** would preferentially react with water rather than with cyclodextrin, due to steric reasons, leading to the formation of a formylated product. The production of the ester would be further facilitated by the deprotonation of **20** (R″ = H) by imidazole. However, this reaction affords a low yield of a partially 6-halogenated product as indicated by ^{13}C NMR spectra of the crude material without forming a formylated product. This can be attributed to water reacting with **15** and thus making the system anhydrous at the cost of this reagent.

It has been reported that the sulfonation proceeds at the 6-position of cyclodextrins in pyridine. When cyclodextrin is allowed to react with methanesulfonyl chloride containing an equivalent amount of imidazole or 4-(*N*,*N*-dimethylamino)pyridine in pyridine, the ^{13}C NMR spectrum of the crude product indicates sulfonated as well as 6-chlorinated compounds. From this observation, it is proposed that in this reaction, sulfonation takes place in the first step and the sulfonate groups are displaced by chloride ions in the subsequent step.

p-Toluenesulfonyl fluoride (**21**) or cyanide (**24**) do not react with cyclodextrin under similar conditions in DMF to give the corresponding 6-fluoro or cyano compound (Scheme 4). Compounds **21** and **24** can form Vilsmeier–Haack complexes **22** and **25** similar to **11** in DMF. The cyanide and fluoride ions are good nucleophiles in DMF,

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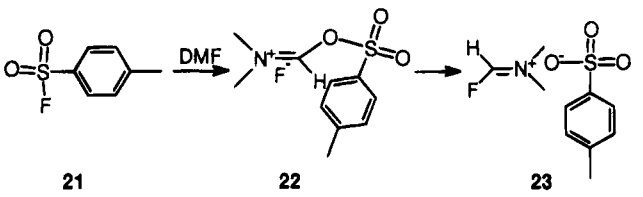
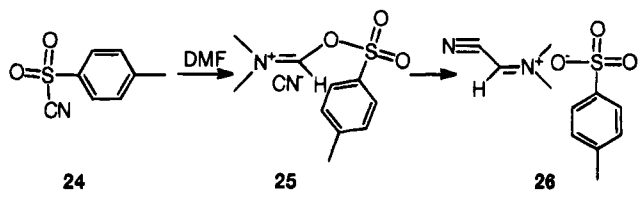
Scheme 4



21 22 23



24 25 26

Scheme 5

15 X = Br, I

as compared to the hydroxyl group,[25] and they can attack the activated carbon atoms of complex **22** and **25**, respectively, to form the stable intermediates **23** and **26**. Although these intermediate are analogous to **15**, they may not further react with cyclodextrin to produce the corresponding fluorinated or cyanated compound because of their stability. The stability of these intermediates **23** and **26**, as compared to **15**, is attributed to the poor leaving group character of fluoride and cyanide ions with respect to the chloride ion.[26] A stable compound similar to the intermediate **23** is reported in the literature,[27] and cyanide ion can also be expected to form a stable complex **26** analogous to **23**. An attempt to extend this method for the synthesis of 6-bromo- and 6-iodocyclodextrins was made by carrying out this reaction in the presence of sodium bromide or iodide with the expectations that bromide or iodide may displace the chloride ion from the complex **15** (Scheme 5). The formation of insoluble NaCl was not observed in these reactions, and upon workup no desired products were obtained leading to the conclusion that bromide or iodide ions do not displace chloride ions from the Vilsmeier–Haack complex **15**.

Sodium or potassium cyanide does not react with **17** to give the corresponding cyano compound in DMF or DMSO at elevated temperature. The reaction mixture of **17** and sodium or potassium cyanide in DMSO or DMF turns black at high temperature indicating the decomposition of the compound **17**. Compound **17** is only soluble in pyridine, DMF, or DMSO, and pyridine is not suitable for dissolving sodium or potassium cyanide salts. The sulfonation reaction performed on the secondary face of **17** with benzenesulfonyl chloride at 70 °C affords a black mixture suggesting the decomposition of a compound **17**. This reaction repeated in the presence of 4-(*N,N*-dimethylamino)pyridine as catalyst also gives decomposed products.

Conclusion. A simple method for synthesis of 6-chlorocyclodextrin directly from sulfonyl chloride in DMF in high yield and purity, without the contamination of sulfonated or formylated products, is now available. This reaction is believed to proceed through a Vilsmeier–Haack complex which results in sequential displacement of all the primary hydroxyl groups of cyclodextrin by chloro groups.

Experimental Section

General Procedure. NMR spectra were recorded on a Varian XL 300 NMR spectrometer in deuterated dimethyl sulfoxide, and the chemical shift values were reported in ppm with respect to the solvent used.

Thin layer chromatography was performed on plates (0.2 mm thickness, supported on Alumina, Merck) in the following solvent system: 1-butanol:ethanol:water (5:4:3, v/v) (A). β-Cyclodextrin was dried under high vacuum at 110 °C for 24 h in a drying piston under refluxing propanol. DMF and DMSO were dried over CaH_2 for several days and decanted before use. Methane- and benzenesulfonyl chlorides were purchased from Eastman, distilled, and stored in sealed bottles. β-Naphthalenesulfonyl chloride, *p*-toluenesulfonyl fluoride, and *p*-toluenesulfonyl cyanide were obtained from Aldrich and used immediately. Potassium bromide and potassium iodide were purchased from Fisher. Sodium hydride (60% in oil) was acquired from Aldrich. The elemental analysis was performed by the Galbraith laboratory.

Heptakis(6-chloro-6-deoxy)-β-cyclodextrin (17). Methanesulfonyl chloride (4.54 g, 39.68 mmol) was heated at 70 °C with β-cyclodextrin (3 g, 2.645 mmol) containing imidazole (2.7 g, 39.68 mmol) in DMF (90 mL) for 24 h. The solvent was removed under reduced pressure, and a large excess of water was added. The aqueous sodium hydroxide solution was added until the solution was completely basic and the resulting solution stirred for 2 h. The precipitate, after filtration, was first washed thoroughly with water and then with acetone. After the solid was dried under vacuum at 90 °C, a white colored compound (3 g) in 89.8% yield was obtained. Benzenesulfonyl and β-naphthalenesulfonyl chlorides react with β-cyclodextrin under the same conditions to give **17** in 89 and 85% yields, respectively. The sulfonated or formylated products were not observed in these reactions: ^{1}H NMR (DMSO-d_6) δ 4.95 (d, 1 H, 2.58 MHz $J_{1,2}$, H-1), 4.07 (d, 1 H, 10.4 MHz $J_{3,4}$, H-4), 3.81 (m, 2 H, H-2, H-3), 3.62 (m, 1 H, H-5), 3.35 (m, 2 H, H-6), 5.85 (br, OH); ^{13}C NMR (DMSO-d_6) δ 101.99 (C-1), 83.53 (C-4), 72.43 (C-2), 71.98 (C-3), 71.13 (C-5), 44.96 (C-6). Anal. Calcd for $C_{42}H_{63}O_{28}Cl_7 5H_2O$ (1354.19): C, 37.25; H, 5.43; Cl, 18.33. Found: C, 37.18; H, 5.46; Cl, 18.14.

Reaction of Methanesulfonyl Chloride with β-Cyclodextrin in the Presence of Potassium Bromide. Methanesulfonyl chloride (1.01 g, 8.81 mmol) was stirred overnight with β-cyclodextrin (1 g, 0.882 mmol) containing imidazole (0.600 g, 8.81 mmol) and potassium bromide (3.15 g, 26.49 mmol) in DMF (30 mL) at 70 °C. The solvent was evaporated under reduced pressure, and the residue was dissolved in acetone to filter out the insoluble salts. The clear filtrate was evaporated to dryness, and NMR spectra of the crude product indicated the recovery of β-cyclodextrin.

Reaction of Methanesulfonyl Chloride with β-Cyclodextrin in the Presence of Potassium Iodide. Methanesulfonyl chloride (1.01 g, 8.81 mmol) was heated with β-cyclodextrin (1 g, 0.882 mmol) containing imidazole (0.600 g, 8.81 mmol) and potassium iodide (4.3 g, 25.9 mmol) in DMF (30 mL) for 24 h at 70 °C. The solvent was evaporated under reduced pressure, and the residue was stirred with aqueous sodium hydroxide for 30 min in methanol. The white precipitate was filtered, washed with water, and air dried. NMR spectra of the crude product showed the presence of β-cyclodextrin.

Reaction of *p*-Toluenesulfonyl Fluoride with β-Cyclodextrin. *p*-Toluenesulfonyl fluoride (2.35 g, 13.22 mmol) was stirred at 70 °C with β-cyclodextrin (1 g, 0.882 mmol) containing imidazole (0.900 g, 13.22 mmol) in DMF (40 mL) for 24 h. The TLC of this reaction mixture showed no reaction in the solvent system A, and the reaction was further continued at this temperature. After several days, TLC of the reaction mixture showed no progress in the reaction.

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Reaction of *p*-Toluenesulfonyl Cyanide with β-Cyclodextrin. a. β-Cyclodextrin (1 g, 0.882 mmol) and imidazole (0.900 g, 13.12 mmol) were added to the solution of *p*-toluenesulfonyl cyanide (2.5 g, 13.12 mmol) in DMF (40 mL). The mixture was heated at 70 °C for 48 h, and the TLC of the reaction indicated no progress in the reaction in solvent system A. In another reaction, reactants were heated at 90 °C for 48 h and TLC indicated no reaction.

b. *p*-Toluenesulfonyl cyanide (0.900 g, 4.97 mmol) was heated in DMF (15 mL) at 90 °C for 3 h, and then β-cyclodextrin (0.500 g, 0.44 mmol) containing imidazole (0.34 g, 4.97 mmol) was added to the solution. The mixture was stirred further at 90 °C for 24 h. The precipitate was filtered after the addition of a large excess of water and air dried. The product was dissolved in acetonitrile (15 mL), and the insoluble component was filtered. After the solvent was removed, 0.45 g of the crude product was obtained. NMR spectra of this product were very complex and broad, indicating a complex mixture.

c. Compound **17** (1 g, 0.791 mmol) was heated at 100 °C with sodium cyanide (0.3 g, 6.122 mmol) in DMSO (20 mL) for 3 h. Under these conditions, the solution turned black, suggesting the decomposition of the starting material. The solvent was evaporated under reduced pressure at 70 °C, and NMR spectra of the crude residue also suggested the decomposed product.

d. Compound **17** (1 g, 0.791 mmol) was stirred at 100 °C with potassium cyanide (0.77 g, 11.85 mmol) in DMF (20 mL) for 24 h, and during this time, the solution turned black. The solvent was evaporated under reduced pressure, and NMR spectra of the residue indicated the decomposition of a starting material.

e. Compound **17** (1 g, 0.791 mmol) and benzenesulfonyl chloride (1.384 g, 7.84 mmol) were heated in pyridine (20 mL) at 70 °C for 24 h, during which time the solution turned black. The solvent was evaporated at 60 °C under vacuum, and NMR spectra of the crude residue indicated the presence of a decomposed material.

f. Benzenesulfonyl chloride (0.698 g, 3.96 mmol) and **17** (0.5 g, 0.395 mmol) were heated in pyridine (15 mL) with 4-(*N*,*N*-dimethylamino)pyridine (100 mg) at 70 °C. The solution turned black after 3 h, showing the decomposition of the material.

g. 4-(*N*,*N*-Dimethylamino)pyridine (1.91 g, 15.6 mmol) and **17** (1 g, 0.791 mmol) were stirred with benzenesulfonyl chloride (2.768 g, 15.68 mmol) in pyridine (30 mL) at 60 °C for 24 h. The solution became slightly black, suggesting a partial decomposition of **17**. Water was added to precipitate the product from the solution. This material was dissolved in ethyl acetate (40 mL) and washed with 5% HCl (20 mL × 2) and then with saturated sodium bicarbonate solution (20 mL). The solution was dried over anhydrous sodium sulfate, and finally the solvent was removed under reduced pressure. The product (with R_f value of 0.28) was purified by column chromatography by using ethyl acetate:hexane (1:1, v/v) as the eluent. NMR spectra of this product were very complex and broad indicating the decomposed material.

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Supplementary Material Available: ^1H and ^{13}C NMR (300 MHz) spectra of compound **17** (2 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.