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Working with Hazardous Chemicals

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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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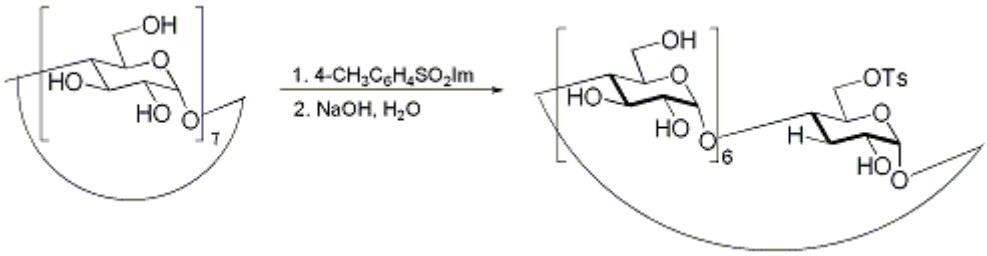
6^{A}-O-p-TOLUENESULFONYL-β-CYCLODEXTRIN

[β-Cyclodextrin, 6^{A}-(4-methylbenzenesulfonate)]



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Checked by Kevin M. Shea and Rick L. Danheiser.

1. Procedure

1-(p-Toluenesulfonyl)imidazole . A 1-L, three-necked, round-bottomed flask equipped with a thermometer, argon inlet adapter, pressure-equalizing addition funnel, and a magnetic stirbar is charged with a solution of imidazole (65 g, 0.95 mol) (Note 1) in 250 mL of dry dichloromethane (Note 2) and then cooled to 0°C. A solution of p-toluenesulfonyl chloride (80 g, 0.42 mol) in 250 mL of dichloromethane is added dropwise over 1.5 hr. The resulting mixture is allowed to warm to room temperature and then stirred vigorously for 2 hr. The reaction mixture is filtered through a pad of silica gel (100 g), which is washed with 500 mL of 1:1 ethyl acetate-hexane . The filtrate is concentrated under reduced pressure, leaving a residue to which is added 50 mL of ethyl acetate and then 500 mL of hexane . Filtration of the resulting suspension gives 83-84 g (89-90%) of 1-(p-toluenesulfonyl)imidazole as a white solid, mp 78.0-79.0°C (lit.[2] 77.0-78.5°C; lit.[2] 78-78.5°C) (Note 3).

6^{A}-O-Toluenesulfonyl-β-cyclodextrin. In a 2-L, three-necked, round-bottomed flask equipped with a thermometer, pressure-equalized dropping funnel, and a large magnetic stirbar, 40.0 g (35.2 mmol) of β-cyclodextrin hydrate (Note 4) is dissolved in 900 mL of water by heating to 60°C with vigorous stirring (Note 5). Stirring is continued as the solution is allowed to cool to room temperature (Note 6), and to the resulting milky suspension is added 31.3 g (141 mmol) of finely powdered 1-(p-toluenesulfonyl) imidazole in one portion (Note 7). After 2 hr, a solution of 18 g (0.45 mol) of sodium hydroxide in 50 mL of water is added over 20 min (Note 8). After 10 min, unreacted 1-(p-toluenesulfonyl)imidazole is separated by filtration through a sintered glass funnel (Note 9). The reaction is quenched by the addition of 48.2 g (0.90 mol) of ammonium chloride (NH_4Cl) with swirling to dissolve all the solids. The resulting mixture is concentrated to about half of its original volume by blowing a stream of air over its surface overnight (Note 10). The product begins to precipitate almost immediately as the mixture becomes more concentrated. The resulting suspension is filtered through a large sintered-glass funnel (ca. 2 hr), and the collected solid is washed with two 100-mL portions of ice water and one 200-mL portion of acetone and then dried to constant weight over calcium chloride in a vacuum desiccator to yield 18 g (40%) (Note 11) of the title compound as a white solid (Note 12).

2. Notes

1. p-Toluenesulfonyl chloride and imidazole were purchased from Aldrich Chemical Company, Inc. , and used as supplied.
2. Dichloromethane was stored over calcium hydride and distilled from calcium hydride immediately prior to use.
3. The physical properties are as follows: TLC (silica gel 60 F254 aluminum-backed plates) R_f = 0.48 (hexane/EtOAc 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.43 (s, 3 H), 7.08 (s, 1 H), 7.30 (s, 1 H), 7.35 (d, 2 H, J = 8.3), 7.83 (d, 2 H, J = 8.3), 8.02 (s, 1 H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.7, 117.4, 127.1, 130.3, 131.3, 134.7, 136.5, 146.2 ; GCMS (M^+ electron impact) m/e Calcd for $C_{10}H_{10}N_2O_2S$ 222.05,

found 222.05.
4. β-Cyclodextrin hydrate (≤ 14% H2O by weight) was purchased from Acros Organics, Fisher Scientific Company , and was used without further purification or drying (R_f = 0.41, 2-PrOH/H_2O/EtOAc/concd NH_4OH 5:3:1:1). If the β-Cyclodextrin contains more than ~ 14% H2O, the yield of the title compound is decreased. β-Cyclodextrin and the title compound were dissolved in water, spotted on silica gel 60 F254 aluminum-backed plates (EM Separations Technology), and dried on a hot plate prior to development in the solvent systems indicated.
5. The submitters swirled the mixture on a steam bath to effect dissolution of the cyclodextrin. A clear solution is obtained; otherwise, any undissolved materials, which may promote crystallization of cyclodextrin, should be removed by filtration of the hot solution through a sintered glass funnel.
6. In an alternative procedure (which resulted in approximately the same yield of the title compound), instead of cooling the solution to room temperature, the submitters adjusted the temperature to 45°C, and then added powdered 1-(p-toluenesulfonyl)imidazole with vigorous stirring.
7. Because of the heterogeneous nature of this reaction, 1-(p-toluenesulfonyl)imidazole was ground using a mortar and pestle before being added to the reaction mixture. Use of large particles of tosylimidazole resulted in lower yields.
8. The solution of sodium hydroxide should be cooled completely to room temperature before it is added. The yield is lower when the sodium hydroxide solution is added at temperatures below or above room temperature.
9. The solution must not be stirred for more than ca. 20 min after addition of the sodium hydroxide solution; otherwise some unreacted 1-(p-toluenesulfonyl)imidazole will undergo hydrolysis. In addition, on prolonged stirring some product does not crystallize, but instead forms an emulsion, and thus the product remains in the mother liquor. The submitters noted that the addition of a large volume of acetone to the mother liquor precipitates some of the product, which may be collected and recrystallized in water.
10. Difficulties were encountered when the solution was concentrated under reduced pressure using a rotary evaporator because of extensive formation of bubbles. Also, some product decomposed at elevated temperature. All the NH_4Cl must be dissolved before air-blowing. Overnight air-blowing is recommended; at longer times, hydrolysis of the product takes place.
11. The submitters obtained the title compound in 51-61% yield (23-28 g).
12. Characterization data for the title compound follows. The submitters report TLC R_f = 0.59 (2-PrOH/H_2O/EtOAc/concd NH_4OH 5:3:1:1) and R_f = 0.23 ($CHCl_3$/MeOH/H_2O 65:35:8); the checkers observed R_f values of 0.40 and 0.12, respectively, in these solvent systems and visualized the spots by dipping in 5% sulfuric acid-ethanol and heating to 450°C (e.g., with a Bunsen burner). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.49 (s, 3 H), 3.20-3.65 (overlap with HDO, m, 40 H), 4.15-4.20 (m, 1 H), 4.30-4.38 (m, 2 H), 4.44-4.57 (m, 2 H), 4.51 (br s, 3 H), 4.76 (br s, 2 H), 4.83 (br s, 4 H), 5.62-5.83 (m, 14 H), 7.42 (d, 2 H, J = 8.1), 7.73 (d, 2 H, J = 8.1) ; ^{13}C (100 MHz, DMSO-d_6) δ: 21.2, 59.3-59.9 (m), 68.9, 69.7, 72.0-73.1 (m), 80.8-81.5 (m), 101.3-102.3 (m), 127.6, 129.9, 132.7, 144.8 . The submitters observed $[\alpha]_D^{25}$ +141° to 146° (DMSO, *c* 0.28 to 0.35) and the checkers found $[\alpha]_D^{20}$ +131° (DMSO, *c* 4); [lit.[3] $[\alpha]_D^{20}$ +131° (DMSO, *c* 4)]. The submitters report the following HPLC data for the product: HPLC Alltech Econosphere amino column (5 mm, 4.6 × 250 mm); t_R = 4.4 min (mobile phase: 50% MeOH, 40% MeCN, 10% H_2O); Sedex 55 evaporative light scattering detection. Under these conditions, the t_R of β-cyclodextrin is 5.1 min.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

6^A-O-Toluenesulfonyl-β-cyclodextrin is used frequently to prepare functionalized β-cyclodextrins on a preparative scale. Examples of the wide variety of functional groups that have been introduced include 6-deoxyazido, amino, alkylamino, hydroxyamino, thio, thioalkyl, halo, and formyl.[4] Selective monotosylation of β-cyclodextrin without formation of a considerable amount of a mixture containing primary and secondary side multi-tosylated by-products has been difficult to achieve.[3,4] Monotosylation on the primary side has been accomplished in 61% yield by treatment of β-cyclodextrin in water with p-

toluenesulfonic anhydride (1.5 equiv), followed by addition of aqueous sodium hydroxide solution to the inclusion complex.[5] However, difficulty in preparing tosic acid-free p-toluenesulfonic anhydride frequently results in a lower yield of the title compound. To overcome this problem, 1-(p-toluenesulfonyl)imidazole is used here to synthesize the title compound. The use of the imidazolide of tosic acid as the sulfonating reagent rather than p-toluenesulfonyl chloride (TsCl) or p-toluenesulfonic anhydride (Ts_2O) has the following advantages: (1) the aqueous solubility of 1-(p-toluenesulfonyl) imidazole is higher than that of Ts_2O or TsCl; (2) tosylimidazole is more resistant to hydrolysis at room temperature[2] than are Ts_2O or TsCl, so less free tosic acid would be formed during the sulfonation reaction; and (3) significant multi-tosylation of β-cyclodextrin is not observed, even though 4 equiv of 1-(p-toluenesulfonyl)imidazole are used.

References and Notes

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

6ᴬ-O-Toluenesulfonyl-β-cyclodextrin:
β-Cyclodextrin, 6ᴬ-(4-methylbenzenesulfonate) (10); (67217-55-4)

1-(p-Toluenesulfonyl)imidazole:
Imidazole, 1-(p-tolylsulfonyl)- (8);
1H-Imidazole, 1-[(4-methylphenyl)sulfonyl] (9); (2232-08-8)

Imidazole (8);
1H-Imidazole (9); (288-32-4)

p-Toluenesulfonyl chloride (8);
Benzenesulfonyl chloride, 4-methyl- (9); (98-59-9)

β-Cyclodextrin hydrate:
β-Cyclodextrin, hydrate (10); (68168-23-0)