A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

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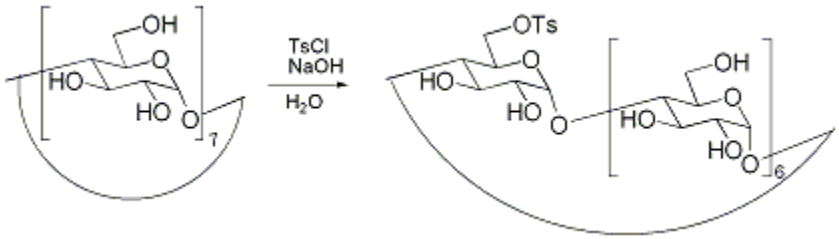
6^{A}-O-p-TOLUENESULFONYL-β-CYCLODEXTRIN

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



Submitted by Bernadette Brady, Nuala Lynam, Thomas O'Sullivan, Cormac Ahern, and Raphael Darcy[1] .
Checked by Kevin M. Shea and Rick L. Danheiser.

1. Procedure

A 3-L, three-necked, round-bottomed flask equipped with a large magnetic stirring bar and thermometer is charged with β-cyclodextrin hydrate (50 g, 44 mmol) (Note 1) and a solution of 25 g of sodium hydroxide in 1.5 L of water. The solution is stirred at 0-5°C in an ice-water bath while p-toluenesulfonyl chloride (20 g, 105 mmol) (Note 2) is added in one portion. The reaction mixture is stirred vigorously for 2 hr at 0-5°C (Note 3), and then another portion of p-toluenesulfonyl chloride (30 g, 157 mmol) (Note 4) is added and the reaction mixture is stirred at this temperature for 3 hr further. The reaction mixture is filtered through Celite in a fritted glass funnel to separate unreacted tosyl chloride (Note 5). The filtrate is cooled at 0-5°C while 10% aqueous hydrochloric acid (HCl, 350 mL) is added. The resulting solution is stored overnight in a refrigerator at 0°C, and then filtered. The product is dried to constant weight over Drierite in a vacuum desiccator to yield 27-28 g of a white solid. This material is recrystallized (three times) by dissolving it in 175-200 mL of water at the boiling point and then cooling to room temperature (Note 6). Storage in a refrigerator overnight provides 14.0 g (25%) of 6^{A}-O-p-toluenesulfonyl-β-cyclodextrin as a white solid, mp 163-168°C (dec.) (Note 7).

2. Notes

1. β-Cyclodextrin hydrate was purchased from Aldrich Chemical Company, Inc. and used without further purification.
2. p-Toluenesulfonyl chloride (99%) was purchased from Aldrich Chemical Company, Inc. , and used without further purification.
3. The progress of the reaction can be monitored by TLC by working up a sample of the reaction mixture: filter through Celite, cool to 0°C, and acidify to pH 1 with 10% aqueous HCl . The solid that precipitates is isolated by filtration and dissolved in dimethylformamide (DMF) for TLC analysis on Merck precoated-silica gel 60 plates with methyl ethyl ketone-methanol-water (4:1:1) as eluent, developed by dipping in 5% sulfuric acid-ethanol and heated to 450°C (e.g., with a Bunsen burner). R_F values are 0.25 for β-cyclodextrin, 0.5 for monotosylate and 0.65 for a second product, probably ditosylate.
4. Monitoring by TLC indicates that the second addition of reagent is necessary to complete the reaction within a reasonable time. Most of the tosyl chloride does not dissolve.
5. Unreacted reagent may be washed with water and reused.
6. Dissolving and cooling to 60°C should be rapid, since significant hydrolysis can occur above this temperature (J. Defaye, personal communication to submitters).
7. Lit.[2] mp 160-162° (dec.). TLC shows a weak spot for ditosylate, and ^{1}H NMR integration (aromatic region) shows this impurity to be 8-9%. The physical properties are as follows: ^{1}H NMR (500 MHz, DMSO-d_6) δ: 2.42 (s, 3 H), 3.20-3.67 (m, 40 H), 4.16-4.20 (m, 1 H), 4.32 (d, 1 H, J = 9), 4.37-4.39 (m, 1 H), 4.45-4.48 (m, 2 H), 4.52-4.53 (m, 3 H), 4.77 (d, 2 H, J = 3.4), 4.83-4.84 (m, 5 H), 5.64-5.85 (m, 14

H), 7.42 (d, 2 H, J = 8.2), and 7.75 (d, 2 H, J = 8.2) ; ^{13}C NMR (125 MHz, DMSO-d_6) δ: 21.3, 59.3, 59.6, 60.0, 69.0, 69.8, 71.9, 72.1, 72.2, 72.4, 72.5, 72.8, 73.0, 73.1, 80.8, 81.2, 81.4, 81.5, 81.7, 101.3, 101.9, 102.0, 102.3, 127.6, 129.9, 132.7, 144.9 ; $[\alpha]_D^{20}$ +131° (dimethyl sulfoxide, *c* 4).

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

Cyclodextrin monotosylate is the most important derivative of this host molecule for access to modifications on the primary hydroxyl side of the macrocycle.[3] While there is preferential tosylation of the primary sugar hydroxyl groups,[4] the problem of selective derivatization of one of the seven glucose units remains, and this requires that the reaction be monitored to avoid over tosylation. Apart from lack of details for this procedure, previous methods have used pyridine instead of water as solvent; have required dry conditions, which if rigorous, cause formation of a cyclodextrin-pyridine gel;[5] and have not avoided the risk of chlorination during work-up.[2] The method described here uses water as solvent; the lower yield is offset by simplicity and by recovery of excess reagent and larger scale. The method is adapted from a procedure that was originally thought to give 2-monotosylate;[6] this was later corrected.[7]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 10, 690

References and Notes

1. Laboratory for Carbohydrate and Molecular Recognition Chemistry, Department of Chemistry, National University of Ireland, University College, Dublin 4, Ireland.
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6. Onozuka, S.; Kojima, M.; Hattori, K.; Toda, F. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 3221.
7. Ueno, A.; Breslow, R. *Tetrahedron Lett.* **1982**, *23*, 3451.

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

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

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

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

N,N-Dimethylformamide: CANCER SUSPECT AGENT:
Formamide, N,N-dimethyl- (8,9); (68-12-2)