Pergamon

Tetrahedron Letters 42 (2001) 8897–8899

TETRAHEDRON LETTERS

Mono-6-(*O*-2,4,6-triisopropylbenzenesulfonyl)-γ-cyclodextrin, a novel intermediate for the synthesis of mono-functionalised γ-cyclodextrins

Ronald Palin,* Simon J. A. Grove, Alan B. Prosser and Ming-Qiang Zhang

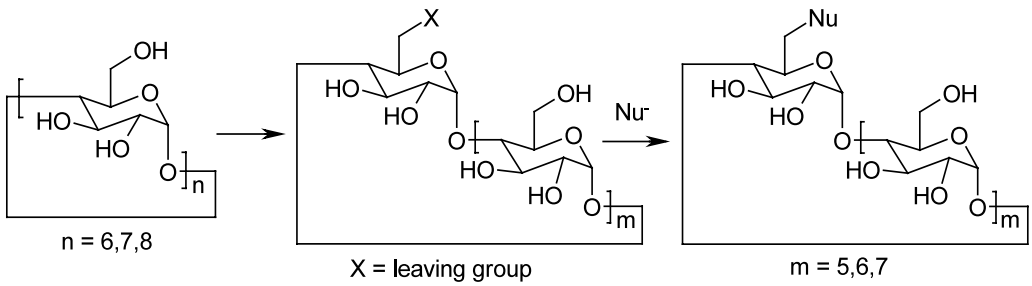
Department of Medicinal Chemistry, Organon Laboratories Ltd., Newhouse ML1 5SH, Scotland, UK

Received 13 July 2001; revised 1 October 2001; accepted 12 October 2001

Abstract—A reaction between γ-cyclodextrin (γ-CD) and 2,4,6-triisopropylbenzenesulfonyl chloride in pyridine gave mono-6-(*O*-2,4,6-triisopropylbenzenesulfonyl)-γ-cyclodextrin in good yield (~69%) and high purity (>98%). In contrast to other sulfonylations of γ-CD, this reaction did not give di- or tri-substituted side products and is thus useful for preparing pure mono-substituted γ-CD derivatives.

Cyclodextrins (CDs) have found wide utility in recent years in such fields as drug formulation,[1] waste management,[2] chromatographic supports[3] and artificial enzymes.[4] In order to expand these areas of industrial applications, the synthesis of functionalised CDs on a preparative scale is necessary. The purity of CDs is often one of the key factors for success, especially in the area of pharmaceutical applications.[1] Despite a considerable amount of synthetic effort,[5] several obstacles remain for selective CD derivatisation in an industrial scale with high purity. Firstly, only mono- and per-substitutions are feasible, and secondly, the yields are usually very low and purification requires tedious chromatographic work. Therefore, chemically modified CDs are expensive and at present only statistical mixtures are commercially available.

Mono-6-functionalised CDs are often prepared by nucleophilic displacement of an intermediate having one of the C(6) hydroxyls converted into a suitable leaving group such as sulfonate or halide[6–9] (Scheme 1). Reaction of α- or β-CD with *p*-toluenesulfonyl chloride in pyridine gives mixtures of mono-, di- and tri-adducts arising from polysulfonation of the primary face.[10] Extensive chromatography and crystallisation are necessary to yield the desired monotosylates with low yields (20–30%). It has been reported[6] that pyridine forms a pyridinium complex with the CD cavity and directs the reaction to the 6-position whereas in DMF sulfonation occurs on both faces of the CD. The bigger cavity size of γ-CD causes polysubstitution when reacted with *p*-toluenesulfonyl chloride.[11] Although mono-6-(2-naphthalenesulfonyl)-γ-CD is useful for selective C(6) mono-substitution, purification of this compound is not always easy, e.g. ion-exchange[12] or reverse phase HPLC.[13] We have experienced di- and tri-adduct formation when preparing mono-6-(2-naph-



Scheme 1.

Keywords: γ-cyclodextrins; mono-substitution; sulfonation.

* Corresponding author.

0040-4039/01/$ - see front matter
PII: S0040-4039(01)01934-7

thalenesulfonyl)-γ-CD according to literature procedures. Purification has been attempted using charcoal columns and crystallisation without success, which has prompted our efforts to find a more convenient route to the C(6) mono substituted γ-CDs.

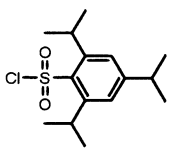
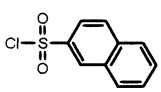
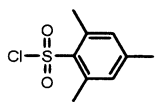
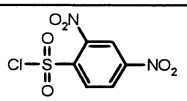
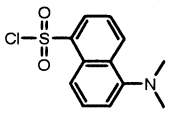
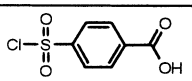
Here we report a convenient preparation of highly pure mono-6-(*O*-2,4,6-triisopropylbenzenesulfonyl)-γ-CD[14] in good yield. Several other arenesulfonylations were also investigated for comparison. The selection of these substrates is based on their potential for easy purification, e.g. a handle for ion-exchange chromatography, crystallisation, etc.

The results are shown in Table 1 for the six different arenesulfonylations investigated. It is interesting to note that reaction with 2-naphthalenesulfonyl chloride (entry 2) yielded considerable amount of di-substituted γ-CD even with reduced reaction times. The longer reaction times resulted in polysubstituted derivatives. Crystallisation of this mixture from water gave no pure mono-derivative.

The other sulfonyl chlorides used presented various problems. 4-(Chlorosulfonyl)benzoic acid (entry 6) for example substituted both the primary and secondary faces of γ-CD. '3,6-anhydro' formation also occurs, derived from one of the 3-hydroxyls displacing the C(6) sulfonate. Although some of the desired C(6) mono-derivative was formed, it was not possible to purify it using the amine based Sephadex DEAE-A25 resin chromatography. When dansyl chloride (entry 5) was the substrate some mono-derivative formed but purification proved fruitless with either the acid based Sephadex CM-25 or Dianion HP-20 resin chromatography. 2,5-Dinitrobenzenesulfonyl chloride (entry 4) provided no mono-substituted material and mesitylene chloride (entry 3) afforded a mixture of mono- and di-adducts inseparable after crystallisation.

Reaction of γ-CD with the sterically more hindered 2,4,6-triisopropylbenzenesulfonyl chloride (entry 1) efficiently produced the C(6) mono-derivative in good yield. In fact the only side product detected is the corresponding sulfonic acid, arising from the hydrolysis

Table 1. Sulfonation of γ-CD

Entry	Arenesulfonyl Chloride	Methods[a]	Yield[b]	LC-MS[c] (%)				
				γ-CD	**Mono-**	Di-	Tri-	Other
1		d	85.6	9.7	**57.7**	-	-	32.5[f]
		e	48.6	23.7	**22.4**	-	-	53.8[f]
2		d	12.6	1.7	**12.6**	35.9	34.5	1.3[g] 11.6[h] 2.4[l]
		e	45.0	11.5	**45.0**	35.9	7.5	-
3		d	21.3	3.1	**20.5**	53.8	-	3.9[f] 18.6[j]
		e	33.1	14.8	**29.7**	40.2	-	9.9[f] 5.4[g]
4		d	-	64.7	-	-	-	13.7[f] 21.5[k]
5		d	38.2	5.8	14.5	9.9	-	62.0[f] 5.3[g] 2.4[l]
6		d	20.8	30.5	**19.1**	-	-	8.3[f] 15.1[m] 9.7[n] 10.6[g] 6.4[o]

a) Reaction performed using 1.28 x 10^{-2} mol dm^{-3} of γ–CD in pyridine with 3 equivalents of arenesulfonyl chloride, b) estimated yield of mono-sulfonate by LC-MS based on γ-CD, c) LC-MS was obtained on a Perseptive Biosystem Mariner-TOF using the negative mode. Phenomenex Jupiter C18 column (150 mm x 4.6 mm, 5μ, 300Å) with CH_3CN/H_2O/Formic acid as solvent, d) 24 h @ RT, e) 3 h @ RT, f) corresponding sulfonic acid residue, g) *m/z* 1314, h) tetra substituted, i) penta substituted, j) *m/z* 1657, k) *m/z* 1357, l) *m/z* 1547, m) substituted with one sulfonate and one anhydro, n) mono regioisomer (bottom face), o) *m/z* 1497.

of the excess starting sulfonyl chloride on work-up. The C(6) mono sulfonate is conveniently separated from any impurities by treating with resin bound carbonate or crystallisation from water in high purity (>98%). This mono-derivative has been displaced with common nucleophiles such as azide[15] and thiophenol providing evidence that it is a suitable synthon for C(6) mono-functionalisation of γ-CD. Considering that the impurity present in this sample is the corresponding sulfonic acid, which is easily removed, we believe that this method provides the most convenient route to the C(6) mono-substituted γ-CD to date.

Acknowledgements

The authors would like to thank their colleagues in the Department of Analytical Chemistry, Organon Laboratories Ltd., for the measurement of LC–MS and various analyses.

References

1. Zhang, M.-Q.; Rees, D. C. *Exp. Opin. Ther. Patents* **1999**, *9*, 1697.
2. Szente, L.; Fenyvesi, J.; Szejtli, J. Proceedings of the Ninth International Symposium on Cyclodextrins 1998, p. 577.
3. Saenger, W. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 344.
4. Breslow, R.; Gabriele, G.; Yang, J. *Tetrahedron Lett.* **1998**, *39*, 2887–2890.
5. Uekuma, K.; Hirayama, T.; Irie, T. *Chem. Rev.* **1998**, *98*, 2045–2076.
6. Petter, R. C.; Salek, J. S.; Sikorski, C. T.; Kumaravel, G.; Lin, F.-T. *J. Am. Chem. Soc.* **1990**, *112*, 3860.
7. Mentzafos, D.; Terzis, A.; Coleman, A. W.; DeRango, C. *Carbohydr. Res.* **1996**, *282*, 125.
8. Nelles, G.; Weisser, M.; Black, R.; Wohlfart, P.; Wenz, G.; Mitter-Neher, S. *J. Am. Chem. Soc.* **1996**, *118*, 5039.
9. Omichi, K.; Matsushima *J. Biochem.* **1978**, *84*, 835.
10. Melton, L. D.; Slessor, K. N. *Carbohydr. Res.* **1971**, *18*, 29–37.
11. Djedaini-Pilard, F.; Azaroual-Bellanger, N.; Gosnat, M.; Vernet, D.; Perly, B. *J. Chem. Soc., Perkin Trans. 2* **1995**, 723.
12. Uekama, K.; Minami, K.; Hirayama, F. *J. Med. Chem.* **1997**, *40*, 2755–2761.
13. Fujita, K.; Tahara, T.; Imoto, T.; Koga, T. *Chem. Lett.* **1988**, 1329–1332.
14. *Mono-6-(O-2,4,6-triisopropylbenzenesulfonyl)-γ-CD*. To a dry round-bottomed flask was added pyridine (300 ml), followed by γ-CD (5.0 g, 3.85 mmol). After stirring for 30 min at room temperature under nitrogen, dissolution occurred. 2,4,6-Triisopropylbenzenesulfonyl chloride (3.5 g, 11.56 mmol) was added and stirred for 24 h. The mixture was evaporated to low volume and acetone (500 ml) added. The resulting precipitate was filtered and dried at 60°C under vacuum to leave 5.0 g of crude product (LC–MS taken at this point). 1.0 g of crude material was dissolved in DMF (10 ml) and stirred with resin-bound carbonate at room temperature for 24 h. The resin was filtered and the solution evaporated to low volume. Acetone (100 ml) was added and the resultant solid filtered and dried at 60°C under vacuum to leave mono-6-(*O*-2,4,6-triisopropylbenzenesulfonyl)-γ-CD (834 mg, 69%) as a white solid. ^{1}H NMR (D_2O)/DMSO) δ 7.36 (2H, s, Ar-H), 5.42 (1H, s, OH), 5.18–5.00 (8H, m, CyD H-1), 4.40–4.32 (1H, m, CH_2OSO$_2$Ar), 4.22–4.09 (2H, m, CH_2OSO$_2$Ar+CyD H-5), 4.23–3.45 (47H, m, CyD 2, 3, 4, 5′, 6-H+2×ArCH(CH$_3$)$_2$), 3.08–2.99 (1H, m, ArCH(CH$_3$)$_2$), 1.36–1.27 (18H, m, 6×CH$_3$). LC-ELSD = 98.28%. m/z (M−H)$^-$ = 1560.
In another experiment γ-CD (1.0 g, 0.77 mmol) was treated with 2,4,6-triisopropylbenzenesulfonyl chloride (0.70 g, 2.31 mmol) in the same manner as above. After precipitating the crude mixture from acetone the solid was crystallised from water to give mono-6-(*O*-2,4,6-triisopropylbenzenesulfonyl)-γ-CD (109 mg, 9%) as a white solid.
15. *Mono-6-azide-γ-CD*. To a stirred solution of sulfonate (430 mg, 0.27 mmol) in DMF (3 ml) was added sodium azide (27 mg, 0.41 mmol). The mixture was heated to 80°C and stirred for 24 h. Evaporated to dryness and water (1 ml) added and poured onto acetone (10 ml). The resultant solid was filtered and dried at 60°C under vacuum to leave mono-6-azido-γ-CD (340 mg, 94%) as a white solid. ^{1}H NMR (D_2O) δ 5.12–5.10 (8H, m, CyD H-1), 4.03–3.96 (1H, m, CyD CH_2N$_3$), 3.94–3.84 (30 H, m, CyD 3, 5, 6-H), 3.79–3.77 (1H, m, CH_2N$_3$), 3.67–3.57 (17 H, m, CyD 2, 4-H). LC-ELSD = 98.73%. IR (KBr) 2105 and 2037 cm^{-1} –N$_3$. m/z (M−H)$^-$ = 1321.