Synthesis of mono-6-tosyl-β-cyclodextrin, a key intermediate for the functional cyclodextrin derivatives

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Method Article

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Abstract

Mono-6-tosyl-β-cyclodextrin \(TsO-CD) is considered an important cyclodextrin \(CD) intermediate for easy introduction of various functional groups such as halides, azide, amine and imidazole groups to afford functionalized CD derivatives. This protocol describes the use 1-\(p-tosyl)-imidazole as the precursor to react with β-cyclodextrin, affording highly pure mono-substituted product with an acceptable yield.

Introduction

Mono-6-tosyl-β-cyclodextrin \(TsO-CD) is considered as an important cyclodextrin \(CD) intermediate for easy introduction of various functional groups such as halides, azide, amine and imidazole groups to afford functionalized CD derivatives[1,2,3]. This is especially so for mono-azido-CD which could serve as a precursor of Cu \(I) catalytic 1,3-dipolar cycloaddition \(click chemistry)[4,5]. However, the synthesis of TsO-CD often results in randomly substituted products, of which the separation of pure mono-substituted products can be difficult due to their similar physical properties. It is therefore attractive to use 1-\(p-tosyl)-imidazole as the precursor to react with β-cyclodextrin, affording highly pure mono-substituted product with an acceptable yield[6]. This reaction is described in this protocol.

Reagents

Triethylamine was purchased from Sigma-Aldrich \(T0886) p-Toluenesulfonyl chloride was purchased from Fluka \(89730) Imidazole was purchased from Merck \(436151) β-Cyclodextrin was purchased from Sigma-Aldrich \(C4805) Sodium bicarbonate was purchased from Sigma-Aldrich \(S6014) Sodium hydroxide was purchased from Sigma-Aldrich \(138701) Ammonium chloride was purchased from Fluka \(09725) Anhydrous magnesium sulfate was purchased from Sigma-Aldrich \(246972) Acetone was purchased from Sigma-Aldrich \(179124) Hexane was purchased from Sigma-Aldrich \(178918)

Equipment

Rotary evaporator \(Büchi, R205) Heidolph magnetic stirrer with thermal and speed controller Vacuum pump NMR spectrometer \(300 MHz; Bruker, ACF300) FTIR spectrometer \(FTS165) Vario EL universal CHNOS elemental analyzer Pressure-equalizing addition funnel Büchner funnel

Procedure

Synthesis of 1-\(p-tosyl)-imidazole \(3) 1] Add 300 mL dichloromethane into a 2 L erlenmeyer flask containing a Teflon-coated magnetic stirrer bar. 2] Add 25.5 g imidazole \(2) and 75 g p-toluenesulfonyl chloride \(1) into the erlenmeyer flask with stirring. 3] Dissolve 39 g sodium bicarbonate in 500 mL DI water to form a solution. 4] Add the solution obtained in Step 3 into the erlenmeyer flask. 5] Add 5.6 mL triethylamine into the flask as the phase transfer catalyst. 6] Stir the reaction mixture for 12 h at room

temperature. 7] Separate the dichloromethane layer from the aqueous layer. 8] Dry the dichloromethane using anhydrous magnesium sulfate. 9] Concentrate the dichloromethane to about 125 mL on a rotary evaporator. 10] Add 25 mL hexane into the resulted dichloromethane. 11] Allow the residual solution to stand overnight to form white crystals. **Synthesis of mono-6-tosyl-CD \(4)** 1] Add 450 mL DI water into a 1 L round bottomed flask containing a Teflon-coated magnetic stirrer bar. 2] Add 20 g dry β-CD into the flask with stirring. 3] Heat the mixture to 60 °C to form a clear solution. 4] Cool the solution to room temperature. 5] Add 15.5 g of 1-\(p-tosyl)-imidazole \(3) fine powder into the solution. 6] Stir the reaction mixture for 2 h. 7] Add a solution of 9 g sodium hydroxide in 25 mL DI water into the reaction solution after 20 min using a pressure-equalizing addition funnel. 8] Add 24 g ammonium chloride into the reaction solution with swirling to dissolve all the solids. 9] Concentrate the solution to half of its original volume by blowing a stream of air overnight. 10] Filter the reaction mixture and collect the white solid. 11] Wash the white solid using 100 mL ice water twice and then 200 mL acetone. 12] Dry the crude product under vacuum over calcium chloride to constant weight.

Timing

Synthesis of \(3): About 20 h. Synthesis of \(4) : About 24 h including the drying step.

Troubleshooting

Low yield of \(3): Concentrate the dichloromethane to below 125 mL. **Low yield of \(4):** Repeat reaction with highly dried β-CD. Grind the 1-\(p-tosyl)-imidazole into powder as fine as possible in Step 5.

Anticipated Results

Typical yield of \(4) with two synthetic steps is 29% \(yield of \(3) is 95%, yield of \(4) is 30%). Compound \(3), analytical data: Mp: 77-78 °C; ^{1}H NMR \($CDCl_3$)δ \(ppm): 2.46 \(s, 3H), 7.10 \(d, 2H), 7.31\(d, 2H), 7.35\(d, 1H), 7.83\(d, 1H), 8.03\(s, 1H); FTIR \(cm^{-1}, KBr): 3159, 3103, 3032, 1595, 1516, 1383, 1151; ESI-MS \(m/z): 223.03 \[M+H]$^{+}$, calcd 223.05. Compound \(4), analytical data: Mp: 165-167 °C \(dec); ^{1}H NMR \(DMSO-d6) δ \(ppm): 2.50 \(s, 3H), 3.31-3.62 \(overlap with HDO), 4.15-4.2 \(m, 1H), 4.28-4.35 \(m, 1H), 4.41-4.48 \(m, 4H), 4.76 \(m, 2H), 4.83 \(m, 5H), 5.62-5.84 \(m, 14H), 7.73-7.76 \(d, 2H), 7.41-7.44 \(d, 2H); FTIR \(cm^{-1}, KBr): 3400, 2935, 1647, 1367, 1159, 1080, 1031, 582; ESI-MS \(m/z): 1311.2 \[M+H]$^{+}$, calcd 1311.6. Microanalysis \(%): C 45.3, H 6.1, S 2.4; calcd, C 45.7, H 5.9, S 2.5

References

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Figures

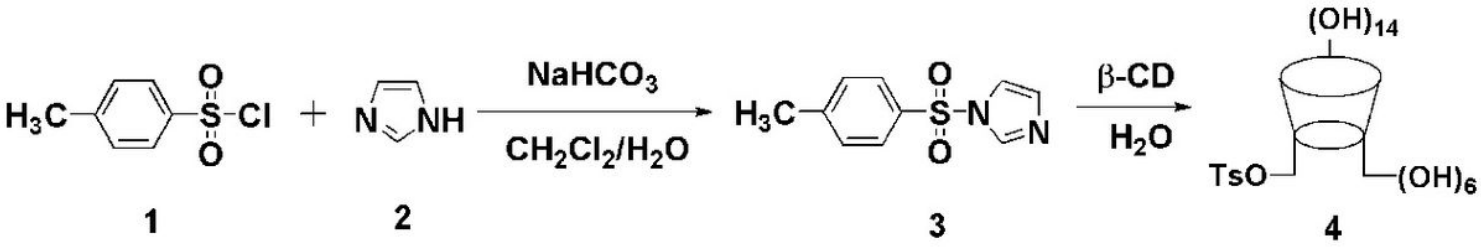

Figure 1

Scheme Synthesis of 1-(p-tosyl)-imidazole and mono-6-tosyl-CD