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ORIGINAL ARTICLE

Recent advances in the synthesis of cyclodextrin derivatives under microwaves and power ultrasound

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Abstract We describe improved syntheses of CD derivatives, like 6^I-monotosyl, 6^I-monoazido-6^I-monodeoxy, 6^I-monoamino-6^I-monodeoxy-βCD and 2^I-*O*-mono(methylamino)alkyl-βCDs, that were carried out under US or MW, to great advantage in terms of yield, purity and reaction time. In the search for more efficient procedures to prepare monosubstituted CDs, we applied MW and/or US to some fundamental preparations such as those of 6^I-amino-6^I-deoxy-βCD and a series of 2-monoaminomethyl-βCD derivatives.

Keywords Cyclodextrin derivatives · Microwave · Power ultrasound · Selective monosubstitution · Mannich aminomethylation

Introduction

Because of the irreplaceable roles they play in many physical and chemical processes, microwaves (MW) and power ultrasound (US) have seen their range of application expand enormously. Both techniques are being increasingly exploited in organic synthesis, and their combined use is one of the most promising innovations in this field [1].

Although the vast majority of organic chemists still cling to conductive heating as a means to promote reactions, major advances have recently been made in this regard. In many instances the effects of US and MW have been compared on the same system and a synergic effect has been observed when they were used in combination [2, 3]. These techniques, that often complement each other, have emerged as effective promoters of organic reactions, cutting down reaction times to minutes or even seconds rather than hours or days. A long way from pioneering approaches, when poorly standardized apparatus (domestic MW ovens and US cleaning baths) was employed, they are now currently used in reproducible, high-yield synthetic protocols [4, 5]. Despite the vast literature dealing with US- and MW-promoted reactions, only a couple of reports have so far concerned the modification of CDs under these non-conventional conditions [6, 7]. In some our recent papers several CD functionalizations carried out under US or MW were compared with those performed under conventional procedures, showing that the new techniques were very advantageous in terms of yields and reaction times [8–10]. Because many synthetic procedures require a modified reaction atmosphere, we have developed a new sonochemical apparatus in which a gas inlet is inserted into the top of the PTFE reactor and is joined to the horn by an elastomer sleeve coupling fixed to it with a tight seal [11].

Owing to problems of selectivity, efficiency and purification, the monosubstitution of CDs still remains a challenging target. We found that the synthesis of 6^I-monoamino-6^I-monodeoxy-βCD can be much improved under non-conventional conditions by means of US and MW (Scheme 1). Not only were the yields higher, but reaction times were dramatically cut down to few minutes in all three steps.

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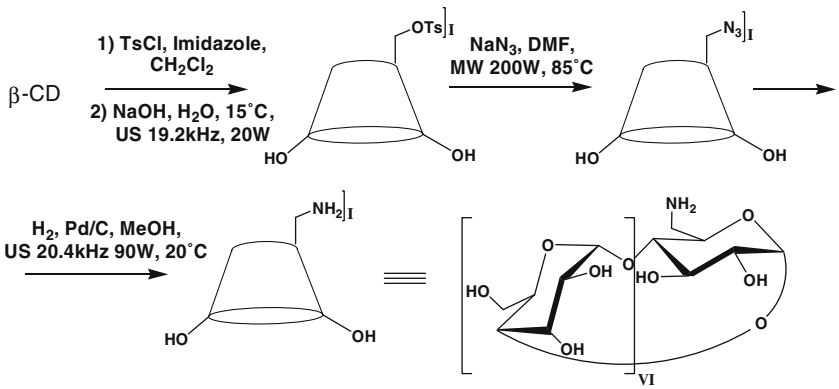
Scheme 1



The MW-promoted Mannich aminomethylation of 2^{I}-*O*-monopropargyl-6^{VII}-*O*-hepta-*t*BDMS-*β*CD proved to be an efficient method for selectively inserting one amino function in the molecule (Scheme 2).

Experimental

General

Reactions were monitored by TLC on Merck 60 F254 (0.25 mm) plates, in saturated chamber, which were visualized by UV inspection and/or by heating after a spray with 5% H_2SO_4 in ethanol. Merck silica gel was used for column chromatography (CC). IR spectra were recorded with a Shimadzu FT-IR 8001 spectrophotometer. Unless stated otherwise, NMR spectra were recorded on a Bruker 300 Avance (300 MHz and 75 MHz for ^{1}H and ^{13}C, respectively) at 25 °C; chemical shifts were calibrated to the residual proton and carbon resonance of the solvents: $CDCl_3$ ($\delta H = 7.26$, $\delta C = 77.0$) or DMSO-*d6* ($\delta H = 2.54$) or D_2O ($\delta H = 4.79$). Chemical shifts (δ) are given in ppm, and coupling constants (J) in Hz. MALDI-TOF MS spectra were measured on a Bruker Reflex III spectrometer and GC/MS analyses performed with a 6850 gas chromatograph with a 5973 mass-sensitive detector (Agilent Technologies). All sonochemical apparatus was developed in the author's laboratory, viz. a model with immersion horn [11] and a development of the cup-horn model we called ''cavitating tube'' because it features a thin titanium tube fixed onto the transducer [9]. Both reactors were equipped with an efficient cooling system; all critical parameters (power, frequency, reaction temperature and composition of the modified atmosphere) were continuosly monitored. MW-promoted reactions were carried out in a professional oven, MicroSYNTH-Milestone (Italy). Commercially available reagents and solvents were used without further purification unless otherwise noted. *β*CD was kindly provided by Wacker Chemie (Germany).

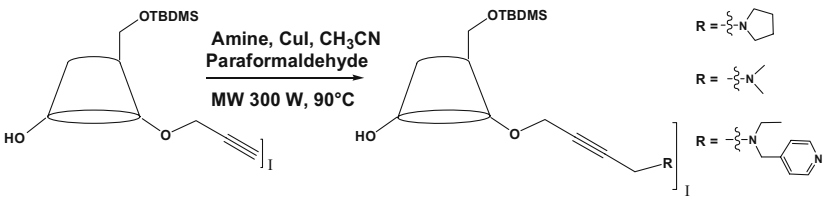
1-(p-toluensulfonyl)imidazole

To a solution of tosyl chloride (5 g, 26.3 mmol) in dichloromethane (DCM, 50 ml), imidazole (7.12 g, 104.5 mmol) was added. The mixture was left 2 h under magnetic stirring at room temperature, then it was diluted with more DCM (50 ml) and extracted with water (3 × 80 ml). The organic layer way dried over anhydrous Na_2SO_4 and evaporated to give the final product (5.17 g) as a white powder. Yield 89%; R_f: 0.57 ($CHCl_3$/MeOH 9:1); ^{1}H-NMR (300MHz, $CDCl_3$) δ: 8.02 (s, 1H), 7.84 (d, $J = 8.4$ 2H), 7.37 (d, $J = 8.4$ 2H), 7.31 (s, 1H), 7.10 (s, 1H), 2.46 (s, 3H); GC/MS (M + electron impact), m/z calc for $C_{10}H_{10}N_2O_2S$ 222.05, found 222.1, 155.5, 91.4.

6^{I}-O-mono(p-toluenesulfonyl)-*β*CD

*β*CD (1.3 g, 1.14 mmol) was dissolved in water (30 ml) and the solution was transferred to the cavitating-tube

Scheme 2



reactor. 1-(*p*-toluenesulfonyl)imidazole (1.01 g, 4.58 mmol) was then added and the mixture was sonicated for 10 min (19.2 kHz, 20W, formulation of the inclusion complex). 2 ml of aqueous NaOH (560 mg, 14 mmol) were then added dropwise over 10 min and after another 30 min the milky suspension was transferred to a flask and NH_4Cl (1.67 g, 31.5 mmol) was added. After one night the mixture was filtered and the collected solid washed with ice-cold water (5 ml) and acetone (5 ml), and finally dried under vacuum to yield the expected compound (0.82 g) as a white solid. Yield 55%; R_f: 0.37 (iPrOH/H_2O/EtOAc/NH_4OH 5:3:1:1); ^{1}H-NMR (300MHz, DMSO-*d6*) δ: 7.75 (d, J = 8 Hz, 2H), 7.42 (d, J = 8 Hz, 2H), 5.6–5.8 (m, 14H), 4.83 (br.s, 5H), 4.77 (br.s, 2H), 4.13–4.6 (m, 6H), 3.43–3.76 (m, 28H), 3.15–3.42 (m, overlaps with H_2O), 2.43 (s, 3 H); MALDI-TOF MS: m/z calcd. for $[M + Na]^+$ 1311.4 found 1311.4.

6^I-monoazido-6^I-monodeoxy-βCD

The reaction was carried out under magnetic stirring in the professional MW oven, the temperature being monitored with a fiber-optic thermometer. Sodium azide (0.181 g, 2.79 mmol) was suspended in 20 ml DMF (20 ml), and 6^I-O-mono(p-toluenesulfonyl)-βCD (2.0 g, 1.55 mmol) was added. The mixture was irradiated with MW (200W) for 2 min at 85 °C. Then acetone (20 ml) were added and the precipitate filtered off. When it was recrystallized from water/acetone 9:1, pure 6^I-monoazido-6^I-monodeoxy-βCD (1.35 g) was obtained. Yield 75%; R_f: 0.28 (CH_3CN/H_2O 3:1); IR: ν 3400, 2104 cm^{-1}; ^{1}H-NMR (300MHz, DMSO-*d6*) δ: 5.56–5.76 (m, 14H), 4.87 (shoulder, 1H), 4.81 (brs, 5H), 4.4–4.56 (m, 6H), 3.48–3.81 (m, 28H), 3.23–3.44 (m, overlaps with H_2O); MALDI-TOF MS: m/z calcd. for $[M + Na]^+$ 1182.4 found 1182.6.

6^I-monoamino-6^I-monodeoxy-βCD

The reaction was carried out in a sealed sonochemical reactor under H_2 (1 bar). 6^I-monoazido-6^I-monodeoxy-βCD (0.30 g) was dissolved in MeOH (4.5 ml) and water (0.5 ml), then Pd/C (40 mg, 10 % Pd on charcoal) was added. The suspension was sonicated under H_2 for 2 h (20.4 kHz, 80 W), then it was filtered and the clear filtrate was freeze-dried to give a white solid (0.25 g). Yield 88%; R_f: 0.19 (iPrOH/EtOAc/NH_4OH/H_2O 7:7:5:4); ^{1}H-NMR (300 MHz; D_2O) δ: 4.9–4.95 (m, 7H); 3.7–3.9 (m, 28H), 3.4–3.56 (m, 14H); MALDI-TOF MS m/z calcd. for $[M + Na]^+$ 1156.3; found 1156.4.

2^I-O-monopropargyl-6^{VII}-O-hepta-tBDMS-βCD

Following the procedure described in a previous paper of ours [9], we obtained 2^I-*O*-monopropargyl-6^{VII}-*O*-hepta-*t*BDMS-βCD in 40% yield as a white powder. R_f: 0.26 ($CHCl_3/CH_3OH$ 4:1); IR: ν 3420, 3325, 1473, 1254, 1086, 1040, 835 cm^{-1} ^{1}H-NMR ($CDCl_3$) δ: 4.9 (br.s, 7 H, H-1), 4.5 (br.qd, 2H, H-1′), 4.1–3.9 (m, 14H, H-3, H-6b), 3.8–3.5 (m, 28H, H-2, H-4, H-5, H-6a), 2.4 (t, 1H, H-3′), 0.88 (s, 63H, *t*-But), 0.05 (s, 42 H, Si-CH_3); ^{13}C-NMR($CDCl_3$) δ: 103.3–101.4 (7C1), 82.1–80.9 (7C4), 75.7 (C2′), 73.8, 73.4, 73.2, 72.6, (C3′, 7C2, 7C3, 7C5), 62.5–62.1 (14C6), 60.1 (C3′), 26.3 (3C-*Me*), 18.7 (*C*-Me), -5.0, -5.2 (2Si-*Me*); MALDI-TOF MS: m/z calcd. for $[M + Na]^+$ 1993.9; found 1994.0.

General procedure for MW-assisted Mannich aminomethylation

The reactions were carried out in the professional MW oven under magnetic stirring. In a 50 ml two-necked round-bottomed flask equipped with a condenser and a fibre-optic thermometer, paraformaldehyde (1 eq,) and acetonitrile (6 ml) were added to 1 eq of secondary amine (pyrrolidine, dimethylamine or *p*-(ethylaminomethyl)pyridine). The mixture was irradiated with MW (300 W) at 90 °C for 15 min. After it cooled down to 25 °C, 2^I-*O*-propargyl-6^{VII}-*O*-*t*BDMS-βCD (0.05 mmol) and copper iodide (CuI) (0.1 eq) suspended in THF (3 ml) were added and the mixture was further irradiated for 15–25 min (Table 2). The reaction was monitored by TLC, eluents $CHCl_3/CH_3OH$ 4:1 and EtOAc/CH_3OH/H_2O 40:7:5.

The reacted mixture was diluted with EtOAc, the precipitate washed with H_2O and brine, then dried (Na_2SO_4). The crude product was purified by CC ($CHCl_3/CH_3OH$ 19:1, 9:1, 4:1).

Adduct with pyrrolidine: an almost white powder (78 mg); yield 75%; R_f: 0.32 (EtOAc/CH_3OH/H_2O 40:7:5); R_f 0.19 ($CHCl_3/CH_3OH$ 4:1); IR: ν 3420, 1473, 1254, 1086, 1040, 835 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 4.9 (br.s, 7H, H-1), 4.5 (s, 2H, H-1′), 3.95–3.89 (m, 14 H, H-3, H-6b), 3.72–3.59 (m, 28H, H-2, H-4, H-5, H-6a, overlapped 2H-4′), 2.64 (br.t, 4H, H-pyrrol), 1.82 (br.t, 4H, H-pyrrol), 0.88 (s, 63H, *t*-But), 0.05 (s, 42H, Si-CH_3); ^{13}C-NMR ($CDCl_3$) δ: 103.3–101.8 (7C1), 82.1 (7C4), 82.2, 79.8 (C2′,C3′), 74.0, 73.8, 72.9 (7C2, 7C3, 7C5), 62.0(14C6), 60.2 (C1′), 53.1 (2Cpyrrol), 43.9 (C4′), 26.3 (3C-*Me*), 24.1 (2Cpyrrol), 18.2 (*C*-Me), -4.7, -4.8 (2Si-*Me*); MALDI-TOF MS: m/z calcd. for $[M + Na]^+$ 2077.6; found 2077.9.

Adduct with dimethylamine: yellow powder (53 mg); yield 52%. R_f: 0.34 (EtOAc/CH_3OH/H_2O 40:7:5); IR: ν

3420, 1471, 1254, 1086, 1040, 835 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 4.9 (brs, 7H, H-1), 4.5 (s, 2H, H-1′), 4.0–3.9 (m, 14H, H-3, H-6b), 3.7–3.6 (m, 28H, H-2, H-4, H-5, H-6a), 3.3 (s, 2H, H-4′), 2.3 (s, 6H, N-CH_3), 0.88 (s, 63H, *t*-But), 0.05 (s, 42H, Si-CH_3); ^{13}C-NMR ($CDCl_3$) δ: 102.3–99.8 (7C1), 80.0 (7C4), 79.1, 77.8 (C2′,C3′), 71.8, 71.1, 70.3 (7C2, 7C3, 7C5), 59.9 (14C6), 59.0 (C1′), 46.2 (C4′), 42.3 (N-CH_3), 26.3 (3C-*Me*), 18.2 (*C*-Me), –4.7, –4.8 (2Si-*Me*); MALDI-TOF MS: *m*/*z* calcd. for $[M + Na]^+$ 2051.1; found 2051.9.

Adduct with 4-(ethylaminomethyl)pyridine: yellow powder (89 mg), yield 84%; R_f: 0.46 ($EtOAc/CH_3OH/H_2O$ 40:7:5); R_f: 0.35 ($CHCl_3/CH_3OH$ 4:1); IR: ν 3420, 1474, 1254, 1040, 1086, 835 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 8.5 (d, J = 4.7 Hz, 2H, pyr), 7.3 (d, J = 4.7 Hz, 2H, pyr), 4.9 (br.s, 7H, H-1), 4.5 (s, 2H, H-1′), 4.1–3.9 (m, 14H, H-3, H-6b), 3.7–3.4 (m, 28H, H-2, H-4, H-5, H-6a, overlapped 2H, N-CH_2-pyr), 3.2 (s, 2H, H-4′), 2.5 (q, 2H, N-CH_2), 1.1 (t, 3H, NCH_2CH_3), 0.88 (s, 63H, *t*-But), 0.05 (s, 42H, Si-CH_3); ^{13}C-NMR ($CDCl_3$) δ: 149.7, 148.6, 124.0 (5C-pyr), 103.1–101.7 (7C1), 81.9, 80.8, 79.2(7C4, C2′,C3′), 73.9–72.5 (7C2, 7C3, 7C5), 62.1 (14C6), 59.9 (C1′), 56.9 (N-CH_2-pyr), 47.6 (C4′), 41.7 (N-CH_2CH_3), 26.0 (3C-*Me*), 18.4 (*C*-Me), 12.9 (N-CH_2CH_3), –3.4, –4.7 (2Si-*Me*); MALDI-TOF MS: *m*/*z* calcd. for $[M + Na]^+$ 2142.1; found 2142.9.

Results and discussion

Owing to problems of selectivity, efficiency and purification, the monosubstitution of CDs still remains a challenging target. We found that the synthesis of 6^I-monoamino-6^I-monodeoxy-βCD could be much improved by means of US and MW. A convenient, widely used synthon for the synthesis of 6^I-monoamino-6^I-monodeoxy-βCD is 6^I-mono(*p*-toluenesulfonyl)-βCD, generally prepared by reacting βCD with tosyl chloride (TsCl) in dry pyridine [12] or in water at alkaline pH [13, 14]. As polytosylation is the major drawback of this reaction, our efforts were directed to find milder conditions for it (Table 1). A sonochemical protocol with *p*-toluenesulfonyl imidazole (TsIm) in water at alkaline pH the yield increased to 55–60%. TsCl in water gave pure monotosyl derivative when no more than 1 eq of reagent was used; the yield however did not exceed 30–35%. Poor conversion was observed when TsCl was replaced with the corresponding anhydride (Ts_2O) in water at alkaline pH. The reaction with Ts_2O was much improved when it was carried out in anhydrous pyridine under MW irradiation. In spite of good conversion, product recovery proved particularly troublesome. According to the literature [15], the best reagent for the synthesis of the 6^I-*O*-mono(*p*-toluenesulfonyl)-βCD is be TsIm. Using 4.5 eq TsIm under US we obtained excellent yields in very short reaction times (Table 1). The formation of the βCD inclusion complex with TsIm, a crucial step for the monotosylation, was strongly promoted under US (10 min vs 1–2 h). In order to prepare the 6^I-monoazido-6^I-monodeoxy-βCD we displaced the tosylate group. On comparing results of this reaction under conventional heating and MW irradiation, we found that the latter dramatically promoted the nucleophilic substitution, cutting down the reaction time from several hours to 2 min; formation of side products was reduced as well. The reduction to amine of 6^I-monoazido-6^I-monodeoxy-βCD was achieved by catalytic hydrogenation in the presence of Pd/C; this was also dramatically sped up by US (reaction time fell from 18 h down to 20 min).

Table 1 Conditions and yields of monotosylation reactions

Reagent	Base	Solvent	Condition	Yield
TsCl	NaOH	Water	20 °C, 2 h	20–25%
Ts_2O	NaOH	Water	20 °C, 12 h	starting m.
Ts_2O	NaOH	Water	US, 3 h	starting m.
Ts_2O		Pyridine	20 °C, 3 h	traces
Ts_2O		Pyridine	MW, 80 W, 20 min	20%
TsIm	NaOH	Water	US, 20 W, 30 min	55–60%

Among the routes we explored to selectively insert one amino function on the secondary face of the CD, most efficient was the MW-promoted Mannich aminomethylation of a terminal alkyne. 2^I-*O*-monopropargyl-6^{VII}-*O*-hepta-*t*BDMS-βCD is a suitable substrate for the aminomethylation of terminal C(*sp*) with the putative methyliminium species originating from the condensation of formaldehyde with secondary amines such as pyrrolidine, dimethylamine and 4-(ethylaminomethyl)pyridine (Scheme 2). The same reactions carried out under conventional heating gave poorer yields even after many hours (Table 2).

Further improvement was achieved using a combined reactor featuring simultaneous US/MW irradiation [1] (work is in progress). The monoalkynyl CDs

Table 2 Reaction times and yields of Mannich aminomethylations

Amine	MW		Conventional heating	
	Time: min	Yield %	Time: h	Yield %
pyrrolidine	15	75	18	48
dimethylamine	25	52	22	37
4-(ethylaminomethyl)pyridine	15	84	22	44

used for the aminomethylation were prepared by reacting 6^{VII}-*O*-hepta-*t*BDMS-βCD in anhydrous THF under reflux with a stoichiometric amount of propargyl bromide in the presence of lithium hydride. Besides the 2^{I}-*O*-monoalkynyl-βCD the 3-monoalkynyl derivate was recovered as minor product.

Conclusion

US- and MW-promoted versions of well-known synthetic protocols were found to be well suited for selective chemical modification of CDs, among them the three-step preparation of 6^{I}-monoamino-6^{I}-monodeoxy-βCD and the Mannich aminomethylation of 2^{I}-*O*-monopropargyl-6^{VII}-*O*-hepta-*t*BDMS-βCD. In both cases US- and MW-assisted procedures proved very advantageous in terms of yields, reaction times and product purity.

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