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SHORT COMMUNICATION

Microwave-assisted synthesis of 6-amino-β-cyclodextrins

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Abstract A general microwave-assisted procedure for the synthesis of 6-amino-β-cyclodextrins is reported. Mono-tosyl-β-cyclodextrin was used as the starting material in a one-pot route employing a solvent-free microwave-assisted reaction with a liquid amine. Shorter reaction times were observed for the formation of 6-amino-β-cyclodextrins using this novel microwave approach compared to the thermal procedure.

Keywords Microwave-assisted synthesis · 6-amino-β-cyclodextrins · Functionalised cyclodextrins · Mono-pendant cyclodextrins

Cyclodextrins (CDs) are extremely appealing for their applications in different fields in both pure and applied chemistry [1, 2]. CD derivatives can be structurally manipulated by exploiting the appropriate combination of the hydrophobic nature and different sizes of the CD cavity with the specific features of the substituents attached to it. Several CD derivatives have been synthesised and reported with substituents such as amines [3–5], amino acids [6–8], peptides [9–11] and aromatic systems [12–14]. The chemical modification of CDs offers enormous opportunities, but also challenges for chemists and much effort is being directed to developing new synthetic protocols.

Mono-substitution at the 6-position of β-CD has been reported extensively [15]. In particular, 6-amino-β-CDs can be synthesised from the corresponding liquid amines either by heating β-CD [16], 6-*O*-mono (*p*-toluenesulfonyl)-β-CD (6-tosyl-β-CD) [17] or 6-iodo-β-CD (β-CD-I) [18, 19] in an excess of the amine.

Herein a general microwave-assisted procedure for the synthesis of a nine-member library of 6-amino-β-CDs (β-CD-X) bonded through nitrogen to C6 carbon of the β-CD is reported. (Figure 1).

The use of microwave irradiation (MW) in organic chemistry is becoming increasingly important [20, 21]. Nevertheless, only a few papers reporting the use of MW for the modification of CDs have been published [22–26].

We report for the first time the synthesis of a library in which liquid amines displaces the tosyl group of the 6-tosyl-β-CD. Our one-pot procedure involves nucleophilic displace of the tosyl group of 6-tosyl-β-CD with liquid amines, or aqueous ammonia solution for **2a**, (in a microwave oven at 85 °C and 200 W for 30 min) yielding the corresponding mono-substituted amino-CD (β-CD-X). Shorter reaction times were generally found with the MW-assisted protocol compared to the thermal procedure.

Some of the prepared β-CD-X derivatives have been previously synthesised: **2a** [27], **2c** [16, 28–30], **2f** [31–35], **2g** [18].To the best of our knowledge, **2b**, **2d**, **2e**, **2h** and **2i** are synthesised and characterised for the first time.

An excess of liquid amine was reacted with 6-tosyl-β-CD (150:1) in a sealed tube yielding β-CDXs via the MW procedure (30 min, 200 W, 85 °C). Microwave reactions were carried out in a CEM Explorer. In the case of **2a** aqueous NH_3 solution (28% w/w) was used. Attempts to

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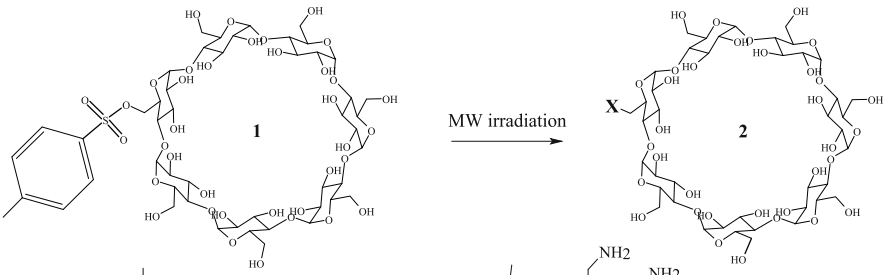

		X	NH2	NH	HN	HN	HN	HN	HN	N	N
			2a	2b	2c	2d	2e	2f	2g	2h	2i
MW 200 W/85 °C	30 min		60	65	>95	>95	>95	>95	>95	>95	>95
Thermal 85 °C	30 min		25	10	90	85	90	>95	>95	40	75
	1.5 h		40	15	>95	>95	>95	>95	>95	70	>95
	3.5 h		55	40	>95	>95	>95	>95	>95	90	>95

Yield (%)

Fig. 1 Schematic representation and yields of the cyclodextrin derivatives and reaction times

scale the reactions up often led to charring of the solution and poorer yields. Optimisation of the amount of amine was also explored. The reduction of the equivalents of amine led to more charring and lower yields since the amine is also the solvent. All final compounds were fully characterised by ^{1}H-NMR, ^{13}C-NMR, ESI–MS and HR-MS (see Electronic Supplementary Information). The precursor 6-*O*-mono (*p*-toluenesulfonyl)-*β*-CD (6-tosyl-*β*-CD) was synthesised according to the procedure reported in the literature [36].

The synthesis of 6-deoxy-6-isopropyl-amino-*β*-cyclodextrin (**2b**) illustrates the preparative aspects which generally apply to the other *β*-CDX considered.

6-Tosyl-*β*-CD (200 mg, 0.155 mmol) was dissolved in isopropylamine (2 mL, 150 fold excess) and the mixture was irradiated in a microwave oven (CEM Explorer) for 30 min at 200 W and 85 °C. After cooling, the solution was added to acetone (100 mL) and the resulting precipitate was collected by filtration. The crude precipitate was purified by Reversed Phase Chromatography RP8 (40–60 μm) with a gradient of $H_2O \rightarrow$ MeOH as eluent. The yields were calculated based on the isolated of final products.

6-Deoxy-6-amino-*β*-cyclodextrin (2a)

Rf (2PrOH: AcOEt: H_2O: NH_3/5:2:3:3) = 0.32.
ESI-MS (*m/z*) 1134.8 (M + H). HRMS-ES (*m/z*) found 1134.3928; calcd for $[C_{42}H_{71}NO_{34} + H]^+$ 1134.3936.

^{1}H-NMR (400 MHz, D_2O): 5.08 (s, 1H, H1), 4.04–3.78 (m, 26H, H3, H5, H6B–G), 3.72–3.52 (m, 13H, H2, H4B–G), 3.48 (t, 1H, $J_{4,5} = J_{3,4} = 9.11$ Hz, H4A), 3.12 (d, 1H, $J_{6A',6A''} = 14.0$ Hz, H6A′), 2.88 (m, 1H, H6A″).
^{13}C-NMR (100 MHz, D_2O): 102.0 (C-l), 83.0 (C-4A), 81.2 (C-4), 73.2 (C-2), 72.2 (C-5), 71.9 (C-3), 60.4 (C-6), 41.4 (C-6A).

6-Deoxy-6-isopropylamino-*β*-cyclodextrin (2b)

Rf (2PrOH: AcOEt: H_2O: NH_3/5:2:3:3) = 0.46.
ESI-MS (*m/z*) 1177 (M + H). HRMS-ES (*m/z*) found 1176.4386; calcd for $[C_{45}\ H_{77}\ NO_{34} + H]^+$ 1176.4400.
^{1}H-NMR (500 MHz, D_2O): 5.10 (d, 1H, $J_{1,2} = 3.52$ Hz, H1A), 5.05–4.92 (m, 6H, H1B-G), 3.94–3.67 (m, 26H, H3, H5, H6B–G), 3.60–3.43 (m, 13H, H2, H4B–G), 3.36 (t, 1H, $J_{4,5} = J_{3,4} = 9.32$ Hz, H4A), 3.04 (d, 1H, $J_{6A',6A''} = 10.7$ Hz, H6A′), 2.78 [m, 1H, N–CH(Me)$_2$], 2.68 (m, 1H, H6A″), 1.00 [m, 6H, (–CH_3)$_2$].
^{13}C-NMR (100 MHz, D_2O): 101.9 (C-l), 81.2 (C-4), 73.2 (C-2), 72.1 (C-5), 71.9 (C-3), 60.3 (C-6), 48.5 (C-6A), 47.3 ($CHMe_2$), 21.2 (–CH_3).

6-Deoxy-6-aminoethylamino-*β*-cyclodextrin (2c)

Rf (2PrOH: AcOEt: H_2O: NH_3/5:2:3:3) = 0.26.
ESI-MS (*m/z*) 1177.6 (M + H). HRMS-ES (*m/z*) found 1177.4339; calcd for $[C_{44}H_{76}N_2O_{34} + H]^+$ 1177.4352.

^{1}H-NMR (500 MHz, D_2O): 4.97 (s, 7H, H1), 3.90–3.71 (m, 26H, H3, H5, H6B–G), 3.60–3.43 (m, 13H, H2, H4B–G), 3.35 (t, 1H, $J_{3,4} = J_{4,5} = 9.17$ Hz, H4A), 2.95 (d, 1H, $J_{6A',6A''} = 11.0$ Hz, H6A′), 2.76–2.55 (m, 5H, H6A′, β–CD–CH_2–CH_2–NH_2).
^{13}C-NMR (100 MHz, D_2O): 102.0 (C-l); 84.0 (C-4A); 81.2 (C-4); 73.1 (C-2); 72.1 (C-5); 71.9 (C-3); 70.5 (C-5A); 60.4 (C-6); 50.2 (C-6A); 49.3 (–NH–CH_2–); 39.7(–CH_2–NH_2).

6-Deoxy-6-*N*,*N*′dimethyl-aminoethylamino-β-cyclodextrin (2d)

Rf (2PrOH: AcOEt: H_2O: NH_3/5:2:3:3) = 0.30.
ESI-MS (*m/z*) 1206 (M + H), 603.5 (M + 2)/2. HRMS-ES (*m/z*) found 1205.4677; calcd for $[C_{46}H_{80}N_2O_{34} + H]^+$ 1205.4671.
^{1}H-NMR (400 MHz, D_2O): 5.08 (s, 7H, H1), 4.02–3.78 (m, 26H, H3, H5, H6B–G), 3.72–3.53 (m, 13H, H2, H4B–G), 3.45 (t, 1H, $J_{4,5} = J_{3,4} = 9.49$ Hz, H4A), 3.09 (d, 1H, $J_{6A',6A''} = 11.9$ Hz, H6A′), 2.88–2.70 [m, 3H, H6A″ and –CH_2–N(Me)$_2$], 2.65–2.52 (m, 2H, CD–NH–CH_2–), 2.31 [s, 6H, –N(CH_3)$_2$].
^{13}C-NMR (100 MHz, D_2O): 102.0 (C-l); 81.3 (C-4); 73.2 (C-2); 72.2 (C-5); 72.0 (C-3); 60.4 (C-6); 57.3 [–CH_2–N(Me)$_2$]; 49.2 (C6A); 44.2 [–N(CH_3)$_2$].

6-Deoxy-6-*N*,*N*'diisopropyl-aminoethylamino-β-cyclodextrin (2e)

Rf (2PrOH: AcOEt: H_2O: NH_3/5:2:3:3) = 0.47.
ESI-MS (*m/z*) 1261.5 (M + H). HRMS-ES (*m/z*) found 1261.5272 calcd for $[C_{50}H_{88}N_2O_{34} + H]^+$ 1261.5291.
^{1}H-NMR (400 MHz, DMSO): 4.83 (s, 7H, H1), 3.77–3.48 (m, 26H, H3, H5, H6B–G), 3.44–3.18 (m, 13H, H2, H4B–G), 2.90 (m, 3H, H6A′, –N[CH(Me)$_2$]$_2$, 2.68 (m, 1H, H6A″), 2.44 [s, 4H, –(CH_2)$_2$], 0.91 (s, 12H, –CH_3).
^{13}C-NMR (100 MHz, DMSO): 104.8 (C-l), 86.6 (C-4A), 84.2 (C-4), 75.8 (C-2), 75.2 (C-5), 74.8 (C-3), 73.5 (C-5A), 62.6 (C-6), 52.9 (C-6A), 52.5 [–NCH(Me)$_2$]$_2$, 50.7 (CD–NH–CH_2–), 47.1(–CH_2–N–), 23.6 (–CH_3).

6-Deoxy-6{2-[bis(2-aminoethyl)amino]ethylamino}-β-cyclodextrin (2f)

Rf (2PrOH: AcOEt: H_2O: NH_3/5:2:3:3) = 0.2.
ESI-MS (*m/z*) 632.6 (M + 2H)/2. HRMS-ES (*m/z*) found 1263.5192; calcd for $[C_{48}H_{86}N_4O_{34} + H]^+$ 1263.5202.
^{1}H-NMR (400 MHz, D_2O): 5.02 (m, 7H, H1), 3.97–3.75 (m, 26H, H3, H5, H6B–G), 3.66–3.46 (m, 13H, H3, H4B–G), 3.39 (t, $J = 9.3$ Hz, H-4A), 3.03 (m, 1H, H-6A), 2.87 (m, 1H, H-6A′), 2.83–2.74 (m, 4H, CD–NH–CH_2–CH_2–N–), 2.70–2.52 [m, 8H, –N–(CH_2–CH_2–NH_2)$_2$].
^{13}C-NMR (100 MHz, D_2O): 102.0 (C-l), 83.6 (C-4A), 81.2 (C-4), 73.1 (C-2), 72.1 (C-5), 71.9 (C-3), 60.4 (C-6), 54.3 [–N(CH_2–CH_2NH_2)$_2$], 52.8 [–N(CH_2–CH_2NH–CD], 46.1 [–N(CH_2–CH_2NH–CD], 37.7 [–N(CH_2–CH_2NH_2)$_2$.

6-Deoxy-6-hydroxylethylamino-β-cyclodextrin (2g)

Rf (2PrOH: AcOEt: H_2O: NH_3/5:2:3:3) = 0.46.
ESI-MS (*m/z*) 1179 (M + H), 612 (M + 2Na)/2. HRMS-ES (*m/z*) found 1178.4188; calcd for $[C_{44}H_{75}NO_{35} + H]^+$ 1178.4198.
^{1}H-NMR (400 MHz, D_2O): 5.08 (m, 7H, H1), 4.03–3.79 (m, 26H, H3, H5, H6B–G), 3.76–3.53 (m, 15H, H3, H4B–G, β–CD–NH–CH_2–CH_2–OH), 3.45 (t, 1H, $J = 9.5$ Hz, H-4A), 3.09 (d, 1H, $J_{6A',6A''} = 10.6$ Hz, H-6A′), 2.83 (m, 1H, H-6A″), 2.78–2.71 (m, 2H, β-CD–NH–CH_2–CH–OH).
^{13}C-NMR (100 MHz, D_2O): 102.0 (C-l), 83.8 (C-4A), 81.3 (C-4), 73.2 (C-2), 72.2 (C-5), 71.9 (C-3), 70.6 (C-5A), 60.3 (C-6 and β-CD–NH–CH_2–CH_2–OH), 50.3 (C-6A), 49.4 (β-CD–NH–CH_2–CH_2–OH).

6-Deoxy-6-dihydroxyethylamino-β-cyclodextrin (2h)

Rf (2PrOH: AcOEt: H_2O: NH_3/5:2:3:3) = 0.48.
ESI-MS (*m/z*) 1222.6 (M + H). HRMS-ES (*m/z*) found 1222.4446; calcd for $[C_{46}H_{79}NO_{36} + H]^+$ 1222.4460.
^{1}H-NMR (400 MHz, D_2O): 5.02 (m, 7H, H1), 4.00–3.72 (m, 26H, H3, H5, H6B-G), 3.65–3.46 (m, 17H, H3, H4B–G, β-CD–NH–(CH_2–CH_2–OH)$_2$), 3.35 (t, 1H, $J = 9.5$ Hz, H-4A), 2.98 (d, 1H, $J_{6A',6A''} = 10.6$ Hz, H-6A′), 2.85 (m, 1H, H-6A″), 2.80–2.58 [m, 4H, CD–NH–(CH_2–CH_2–OH)$_2$].
^{13}C-NMR (100 MHz, D_2O): 101.9 (C-l), 83.6 (C-4A), 81.1 (C-4), 73.1 (C-2), 72.2 (C-5), 72.0 (C-3), 70.2 (C-5A), 60.4 (C-6), 59.1 [β-CD–NH–(CH_2–CH_2–OH)$_2$], 56.1 (β-CD–NH–(CH_2–CH_2–OH)$_2$), 49.6 (C-6A).

6-Deoxy-6-*N*-morpholine-β-cyclodextrin (2i)

Rf (2PrOH: AcOEt: H_2O: NH_3/5:2:3:3) = 0.50.
ESI-MS (*m/z*) 1204.8 (M + H), 637.6 (M + Na + HCOOH)/2 HRMS-ES (*m/z*) found 1204.4350; calcd for $[C_{46}H_{77}NO_{35} + H]^+$ 1204.4354.
^{1}H-NMR (400 MHz, DMSO): 5.98–5.60 (m, 14H, OH2, OH3), 4.95–4.76 (m, 7H, H1), 4.63–4.29 (m, 6H, OH6), 3.80–3.47 (m, 28H, H3, H5, H6), 3.47–3.17 [m, 18H, H2, H4, N(CH_2CH_2)$_2$O], 2.53–2.31 [m, 4H, N(CH_2CH_2)$_2$O].

^{13}C-NMR (100 MHz, DMSO): 102.7 (C-l), 84.4 (C-4A), 82.0 (C-4), 73.7 (C-2), 73.5 (C-5), 72.6 (C-3), 71.0 (C-5A), 66.8 [β-CD–N(CH_2–$\underline{C}H_2$)$_2$O], 60.5 (C-6), 54.9 [β-CD–N($\underline{C}H_2$–CH_2)$_2$O].

The microwave-assisted protocol for the synthesis of 6-amino-β-CDs gives rise generally to shorter reaction times compared to the thermal procedure. In particular, in the cases of **2a**, **2b** and **2h** we obtained considerably higher yields after 30 min. We also report for the first time the synthesis and characterisation of five 6-amino-CDs (**2b**, **2d**, **2e**, **2h** and **2i**).

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References

1. Szejtly, J.: Chem. Rev. **98**, 1743 (1998)
2. D'Souza, V.T., Lipkowitz, K.B.: Chem. Rev. **98**, 1741 (1998)
3. Bonomo, R.P., Pedotti, S., Vecchio, G., Rizzarelli, E.: Inorg. Chem. **35**, 6873 (1996)
4. Maccarrone, G., Rizzarelli, E., Vecchio, G.: Polyhedron **21**, 1531 (2002)
5. Cucinotta, V., Giuffrida, A., La Mendola, D., Maccarrone, G., Puglisi, A., Rizzarelli, E., Vecchio, G.J.: Chromatogr. Biomed. **127**, 800 (2004)
6. Donzé, C., Rizzarelli, E., Vecchio, G.: Supramol. Chem. **10**, 33 (1998)
7. Liu, Y., Han, B.-H., Sun, S.-X., Wada, T., Inoue, Y.: J. Org. Chem. **64**, 1487 (1999)
8. Ikeda, Nakamura, M., Ise, N., Oguma, N., Nakamura, A., Ikeda, T., Toda, F., Ueno, A.: J. Am. Chem. Soc. **118**, 10980 (1996)
9. Matsumura, S., Sakamoto, S., Ueno, A., Mihara, H.: Chem. Eur. J. **6**, 1781 (2000)
10. Pean, C., Creminon, C., Wijkhuisen, A., Grassi, J., Guenot, P., Jehan, P., Dalbiez, J.-P., Perly, B., Djedaini-Pilard, F.: J. Chem. Soc. Perkin Trans. **2**, 853 (2000)
11. Bonomo, R.P., Bruno, V., Conte, E., De Guidi, G., La Mendola, D., Maccarrone, G., Nicoletti, F., Rizzarelli, E., Sortino, S., Vecchio, G.: Dalton Trans. **23**, 4406 (2003)
12. Liu, Y., Zhang, Y.-M., Sun, S.-X., Li, Y.-M., Chen, R.-T.: J. Chem. Soc. Perkin Trans. **2**, 1609 (1997)
13. Puglisi, A., Tabbì, G., Vecchio, G.: J. Inorg. Biochem. **98**, 969 (2004)
14. Kawabara, T., Takamura, M., Matsushita, A., Ikeda, H., Nakamura, A., Ueno, A., Toda, F.: J. Org. Chem. **63**, 8729 (1998)
15. Khan, A.R., Forgo, P., Stine, K.J., D'Souza, V.T.: Chem. Rev. **98**, 1977 (1998)
16. Bonomo, R.P., Cucinotta, V., D'Alessandro, F., Impellizzeri, G., Maccarrone, G., Rizzarelli, E., Vecchio, G.: J. Incl. Phenom. Mol. **15**, 167 (1993)
17. Tabushi, I., Shimizu, N., Sugimoto, T., Shiozuka, M., Yamamura, K.: J. Am. Chem. Soc. **99**, 7100 (1977)
18. Van Hoof, N., Russel, N.R., McNamara, M., Darcy, R.: J. Incl. Phenom. Mol. **36**, 179 (2000)
19. Cucinotta, V., D'Alessandro, F., Impellizzeri, G., Maccarrone, G., Rizzarelli, E., Vecchio, G.: J. Chem. Soc. Perkin Trans. **2**, 1785 (1996)
20. Loupy, A. (ed.): Microwaves in Organic Synthesis. Wiley-VCH, Weinheim, (2006)
21. Kappe, C.O.: Angew. Chem. Int. Ed. **43**, 6250 (2004)
22. Trotta, F., Martina, K., Robaldo, B., Barge, A., Cravotto, G.J.: Incl. Phenom. Mol. **57**, 3 (2007)
23. Aime, S., Gianolio, E., Palmisano, G., Robaldo, B., Barge, A., Boffa, L., Cravotto, G.: Org. Biomol. Chem. **4**, 1124 (2006)
24. Cravotto, G., Bicchi, C., Tagliapietra, S., Costa, L., Di Carlo, S., Nervi, C.: Chirality **16**, 526 (2004)
25. Cravotto, G., Nano, G.M., Palmisano, G.J.: Carbohydr. Chem. **20**, 495 (2001)
26. Siu, M., Yaylayan, V., Belanger, J., Pare, J.: Tetrahedron Lett. **21**, 3737 (2005)
27. Melton, L.D., Slessor, K.N.: Carbohydr. Res. **18**, 29 (1971)
28. Matsui, Y., Yokoi, T., Moshida K. Chem. Lett. **5**(10), 1037 (1976)
29. Zhou, A.L., Lv, X.Y., Xie, Y.X., Liu, G.Q., Wang, H.X., Wang, X.S., Gao, R.Y.: Chromatographia **60**, 281 (2004)
30. May, B.L., Kean, S.D., Easton, C.J., Lincoln, S.F.: J. Chem. Soc. Perkin Trans. **1**, 3157 (1997)
31. Dong, S.D., Breslow, R.: Tetrahedron Lett. **39**, 9343 (1998)
32. Haskard, C.A., Easton, C.J., May, B.L., Lincoln, S.F.: Inorg. Chem. **35**, 1059 (1996)
33. Li, X., Liang, K., Wang, C., Bai, X., Xu, J., Shen, J., Liu, J.: J. Mol. Catal. A Chem. **295**, 47 (2008)
34. Tee, O.S., Bozzi, M., Clement, N., Gadosy, T.A.: J. Org. Chem. **60**, 3509 (1995)
35. Tee, O.S., Bozzi, M., Hoeven, J.J., Gadosye, T.A.: J. Am. Chem. Soc. **115**, 8990 (1993)
36. Baussanne, I., Benito, J.M., Mellet, C.O., García Fernández, J.M., Lawa, H., Defaye, J. Chem. Commun. **16**, 1489 (2000)