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“Click” synthesis of monofunctionalized amino- and carboxylic acid-βCDs with low copper(I) catalyst loading

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Abstract

A series of monofunctionalized amino- and carboxylic acid-β-cyclodextrin monomers were prepared from mono-6-azido-6-deoxy-β-cyclodextrin (N_3βCD) by copper(I)-catalyzed azide-alkyne cycloaddition (CuAAC). The reduction of copper catalyst to 1 mol% proved to be effective in delivering the desired monomers selectively and in high yields. The use of chromatographic techniques was not needed, as the products were isolated by precipitation in acetone and their purity was confirmed by 1D NMR analyses.

Keywords

β-cyclodextrin; cyclodextrin derivatives; click chemistry; CuAAC; mono-functionalization.

Introduction

Cyclodextrins (CDs) are cyclic oligosaccharides composed of a variable number of glucose units bound together through α-(1→4) glycosidic linkages [1]. CDs gained noticeable attention within supramolecular chemistry over the last decades thanks to their numerous useful properties, which include edibility/nontoxicity, chemical stability, and the presence of a central cavity in their molecular structure. The latter has been extensively exploited to use them as supramolecular hosts for a variety of diverse applications as pharmaceutical, cosmetic, textile, and dietary products [2].

The seven glycosidic unit member of the CDs family, β-cyclodextrin (βCD), has been the most studied to date. βCDs can form host-guest inclusion complexes with different organic scaffolds via hydrophobic and hydrogen bonding interactions, an

ability that increases stability, water solubility, bioavailability, and biocompatibility of the formed products [3].

One of the most studied modifications of βCDs involves the formation of functionalized monomers and polymers from mono-6-azido-6-deoxy-β-cyclodextrin (N_3βCD) [4]. The latter allows prompt insertion of diverse substituents bearing a terminal alkynyl group via “click” reaction with the azido moiety. This reaction is known as Cu(I)-catalyzed azide-alkyne 1,3-dipolar cycloaddition (CuAAC) [5], where the oxidation state of copper(I) is stabilized via complexation with 1-(1-benzyl-1H-1,2,3-triazol-4-yl)-N,N-bis[(1-benzyl-1H-1,2,3-triazol-4-yl)methyl]-methanamine (TBTA) and its oxidation to copper(II) by O_2 is prevented by use of sodium ascorbate (NaAsc) as reducing agent.

The CuAAC reaction between N_3βCD and a suitable alkyne leads to the exclusive formation of 1,4-substituted triazole monomers, which are resistant to reduction, oxidation, and hydrolysis [6]. Among several copper-based catalysts investigated for the CuAAC reaction, we chose tetrakis(acetonitrile)copper(I) hexafluorophosphate ($Cu(CH_3CN)_4PF_6$), which appears to be the perfect catalyst candidate by effectively enhancing product formation in high yields [5, 7].

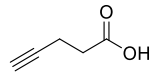
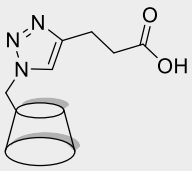
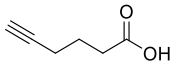
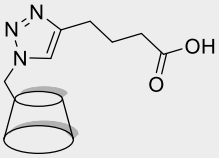
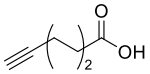
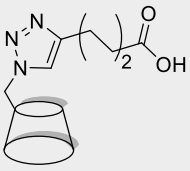
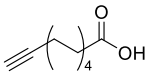
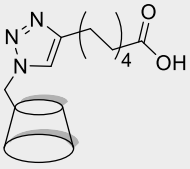
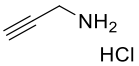
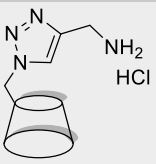
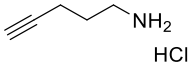
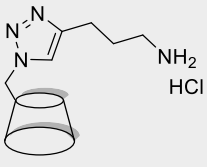
In this work, we present a facile protocol for the synthesis of diverse monosubstituted triazol-βCD-monomers in high to quantitative yields by use of low copper catalyst loading.

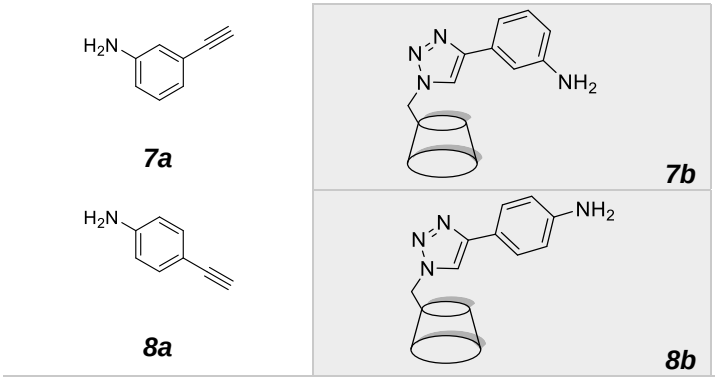
Results and Discussion

The monofunctionalization of N_3βCD by use of the catalytic system $Cu(CH_3CN)_4PF_6$, TBTA, and NaAsc was achieved using a slightly modified version of previously reported methods, which involved DMF as reaction solvent [7].

Moreover, the method implied a catalyst loading set at 4 mol%, which encouraged us to investigate the influence of the catalytic amount on the yield of the products. The investigation started with 10 mol% catalyst loading, which led to successfully preparing the desired 1,4-disubstituted triazole products in yields ranging between 81% and 92%. We repeated the reactions with 1 mol% catalyst loading, and the yields increased for all the products, rocketing to quantitative amounts for some of the substrates. [Table 1]

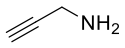
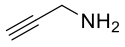
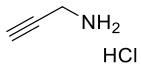
Table 1: Overview of the alkynes used in this study, the corresponding mono-6-functionalized products, and yields.

Alkyne structure	Product	Yield
 ***1a***	 ***1b***	84 %
 ***2a***	 ***2b***	88 %
 ***3a***	 ***3b***	82 %
 ***4a***	 ***4b***	99 %
 ***5a***	 ***5b***	99 %
 ***6a***	 ***6b***	97 %



Furthermore, we employed propargyl amine as both free-base and hydrochloride salt to explore how the amine form could impact the yields. As shown in Table 2, the use of propargyl amine hydrochloride salt **5a** led to one of the highest yields achieved in this study, which suggests that the lower reactivity of the amino moiety discouraged potential side products formation.

Table 2: Comparison of yields for propargyl amine substitution with 10 mol% and 1 mol% catalyst loading, its free-base, and hydrochloride form.

Propargyl amine form	Catalyst loading	Yield
	10 mol%	84 %
	1 mol%	92 %
	1 mol%	99 %

However, the lower reactivity of aromatic amines **7a** and **8a** makes superfluous the use of their salt form.

Conclusion

Eight monomers of monosubstituted triazol-βCD analogues were synthesized via CuAAC by use of 1 mol% copper(I) catalyst loading. Interestingly, decreasing the amount of catalyst from 10 to 1 mol% led to higher yields. The alkynes used were terminal amines and carboxylic acids with variable chain lengths, which were "clicked" to N_3βCD in DMSO/H_2O solvent system in high yields. The reaction was successful with both aliphatic primary amines and their hydrochloride forms, even though the yields improved when the latter were employed.

Experimental

Materials

NMR analyses of the products were conducted in D_2O (30 g/L) using a Bruker AVIII-600 MHz NMR spectrometer equipped with a CPP-TCI cryogenically cooled probe. ^1H spectra were calibrated using the residual water signal in accordance with literature [8] and processed with TopSpin 4.1.4 TLC analyses were performed on ALUGRAM SIL G/UV_{254} TLC plates with 0.2 mm silica gel and 2-PrOH/H_2O/EtOAc/NH_3 (5:3:1:1) solvent system. The plates were visualized with 5% H_2SO_4 ethanolic solution and heat gun drying. HPLC filters were Phenomenex Phenex PTFE membrane 0.45 µm, 25mm syringe filters. Solvents were HPLC grade and purchased from VWR Chemicals. Diethyl ether was dried by use of standard procedure. Ligands (**1a** – **5a**, **7a** – **8a**) and 4-pentynenitrile were purchased from Merck and used without further purification.

Synthesis of 4-pentyn-1-amine hydrochloride - *6a*

In a flame-dried 250 ml round bottom flask under Ar atmosphere, lithium aluminium hydride 1M solution in dry diethyl ether (40 ml) was added to dry diethyl ether (50 ml)

under stirring. After cooling the mixture to 0 ˚C, 4-pentynenitrile (1.8 ml, 20 mmol) was added dropwise and the vessel was allowed to reach RT over one hour. Once cooled to 0 ˚C, the mixture was quenched with H_2O (2.7 ml), NaOH 15% aqueous solution (2.7 ml), and H_2O (2.7 ml) under stirring. Once reached RT, the mixture was filtered through a pad of celite eluted with diethyl ether and extracted with diethyl ether (3 x 50 ml). The organic extracts were combined, dried over $MgSO_4$, and concentrated under reduced pressure to deliver 4-pentyn-1-amine as viscous orange oil (1.36 g, 16.4 mmol, 82%). The free-base product was dissolved in diethyl ether (50 ml) and precipitated as hydrochloride salt by dropwise addition of HCl 2M solution in diethyl ether under vigorous stirring. Product **6a** was collected by filtration and recrystallized in Et_2O:EtOH (1:1) solution as a yellow solid.

General method for the monofunctionalization of N_3βCD

In a 50 ml round bottom flask, 6-monodeoxy-6-monoazido-βCD (1.5 g, 1.3 mmol, 1 eq.), 1-(1-benzyl-1H-1,2,3-triazol-4-yl)-N,N-bis[(1-benzyl-1H-1,2,3-triazol-4-yl)methyl]methanamine (7.55 mg, 14.22 µmol, 0.011 eq.), sodium ascorbate (5.12 mg, 25.86 µmol, 0.02 eq.), and alkyne (**1a** - **8a**; 1.94 mmol, 1.5 eq) were dissolved in 20 ml of degassed H_2O/DMSO (1:1) solution. The mixture was degassed by use of Ar balloon under stirring for 5 minutes. Tetrakis(acetonitrile)copper(I) hexafluorophosphate (4.82 mg, 12.29 µmol, 0.01 eq.) was added to the vessel and the mixture was degassed for further 5 minutes. The vessel was sealed, heated to 50 ˚C, and stirred overnight. Once TLC analysis indicated the complete consumption of N_3βCD, the mixture was cooled to RT and Ambersep™ GT74 resin (500 mg) was added to remove residual copper. After 30 minutes in a tube rotator (20 rpm), the mixture was diluted with milli-Q H_2O and filtered through HPLC filters into a 100 ml round bottom flask. The residue was concentrated under reduced pressure and precipitated by slow addition of a 10-fold excess of acetone under stirring. The

precipitate was filtered, washed with acetone, and dried under high vacuum at 105 ˚C overnight.

3-(1-ethyl-1H-1,2,3-triazol-4-yl)propanoic acid-βCD (**1b**):

^{1}H-NMR (D_2O) δ 2.18 (1H, d, *J* = 0.66 Hz), 2.68 (2H, s), 2.70 (4H, m, *J* = 3.73 Hz), 2.82 (1H, d, *J* = 11.52 Hz), 2.98 (2H, t, *J* = 7.11 Hz), 3.14 (1H, d, *J* = 12.24 Hz), 3.57 (19H, m, *J* = 4.54 Hz), 3.75 (1H, q, *J* = 5.60 Hz), 3.88 (26H, m, *J* = 4.64 Hz), 4.11 (1H, q, *J* = 6.48 Hz), 4.96 (2H, q, *J* = 3.30 Hz), 5.03 (4H, t, *J* = 4.50 Hz), 5.13 (1H, d, *J* = 3.78 Hz), 7.75 (1H, s).

R_f = 0.35

4-(1-ethyl-1H-1,2,3-triazol-4-yl)butanoic acid-βCD (**2b**):

^{1}H-NMR (D_2O) δ 1.92 (2H, m, *J* = 7.46 Hz), 2.18 (1H, s), 2.35 (2H, m, *J* = 3.96 Hz), 2.68 (4H, s), 2.72 (2H, m, *J* = 3.30 Hz), 2.79 (1H, d, *J* = 10.92 Hz), 3.13 (1H, d, *J* = 12.36 Hz), 3.57 (28H, m, *J* = 4.62 Hz), 3.75 (2H, m, *J* = 4.51 Hz), 3.87 (44H, m, *J* = 4.53 Hz), 4.14 (1H, m, *J* = 4.16 Hz), 4.54 (1H, q, *J* = 7.92 Hz), 4.97 (2H, q, *J* = 3.08 Hz), 5.03 (8H, q, *J* = 3.58 Hz), 5.13 (1H, d, *J* = 3.78 Hz), 7.79 (1H, s).

R_f = 0.37

5-(1-ethyl-1H-1,2,3-triazol-4-yl)pentanoic acid-βCD (**3b**):

^{1}H-NMR (D_2O) δ 1.63 (6H, t, *J* = 18.78 Hz), 2.18 (1H, d, *J* = 0.72 Hz), 2.34 (3H, t, *J* = 6.81 Hz), 2.64 (3H, s), 2.68 (4H, d, *J* = 0.60 Hz), 2.76 (1H, t, *J* = 5.85 Hz), 3.08 (1H, d, *J* = 12.12 Hz), 3.46 (2H, d, *J* = 7.86 Hz), 3.60 (25H, m, *J* = 5.00 Hz), 3.83 (40H, m, *J* = 6.28 Hz), 4.05 (1H, t, *J* = 9.45 Hz), 4.98 (2H, q, *J* = 3.98 Hz), 5.03 (7H, q, *J* = 3.62 Hz), 5.13 (1H, d, *J* = 3.54 Hz), 7.89 (1H, s).

R_f = 0.39

9-(1-ethyl-1H-1,2,3-triazol-4-yl)nonanoic acid-βCD (**4b**):

^{1}H-NMR (D_2O) δ 1.21 (10H, d, *J* = 70.40 Hz), 1.58 (5H, d, *J* = 46.75 Hz), 2.37 (3H, s), 2.68 (22H, s), 3.23 (3H, d, *J* = 114.32 Hz), 3.70 (48H, m, *J* = 9.18 Hz), 4.99 (7H, d, *J* = 3.18 Hz), 5.04 (1H, m, *J* = 3.35 Hz), 5.16 (1H, s), 7.81 (1H, d, *J* = 192.34 Hz).

R_f = 0.40

(1-ethyl-1H-1,2,3-triazol-4-yl)methanamine hydrochloride-βCD (**5b**):

^{1}H-NMR (D_2O) δ 2.18 (5H, s), 2.68 (5H, s), 2.90 (1H, q, *J* = 5.58 Hz), 3.13 (1H, d, *J* = 11.94 Hz), 3.55 (24H, m, *J* = 7.15 Hz), 3.75 (35H, *J* = 5.40 Hz), 3.88 (1H, m, *J* = 5.65 Hz), 4.17 (1H, t, *J* = 9.39 Hz), 4.30 (2H, s), 4.97 (2H, q, *J* = 4.58 Hz), 5.03 (6H, t, *J* = 4.38 Hz), 5.14 (1H, d, *J* = 3.72 Hz), 8.12 (1H, s).

R_f = 0.26

2-(1-ethyl-1H-1,2,3-triazol-4-yl)propan-1-amine hydrochloride-βCD (**6b**):

^{1}H-NMR (D_2O) δ 2.18 (2H, m, *J* = 7.62 Hz), 2.97 (3H, q, *J* = 8.80 Hz), 3.19 (2H, t, *J* = 7.65 Hz), 3.31 (1H, d, *J* = 12.42 Hz), 3.75 (16H, m, *J* = 6.39 Hz), 3.90 (1H, q, *J* = 5.58 Hz), 4.06 (22H, m, *J* = 6.20 Hz), 4.34 (1H, t, *J* = 9.42 Hz), 5.13 (3H, m, *J* = 5.13 Hz), 5.21 (4H, d, *J* = 3.18 Hz), 5.31 (1H, d, *J* = 3.54 Hz), 7.99 (1H, s).

R_f = 0.21

3-(1-ethyl-1H-1,2,3-triazol-4-yl)aniline-βCD (**7b**):

^{1}H-NMR (D_2O) δ 2.18 (1H, s), 2.68 (6H, s), 2.83 (1H, d, *J* = 10.32 Hz), 2.99 (1H, d, *J* = 11.76 Hz), 3.29 (1H, d, *J* = 8.46 Hz), 3.54 (33H, m, *J* = 6.26 Hz), 3.77 (11H, m, *J* = 10.32 Hz), 3.96 (10H, m, *J* = 7.65 Hz), 4.34 (1H, t, *J* = 9.78 Hz), 4.87 (1H, d, *J* = 3.30 Hz), 4.96 (2H, q, *J* = 4.82 Hz), 5.03 (1H, t, *J* = 4.08 Hz), 5.07 (3H, d, *J* = 3.18 Hz), 5.13 (1H, d, *J* = 3.48 Hz), 6.90 (1H, d, *J* = 7.86 Hz), 7.09 (1H, d, *J* = 7.56 Hz), 7.30 (3H, q, *J* = 9.40 Hz), 8.54 (1H, s).

R_f = 0.50

4-(1-ethyl-1H-1,2,3-triazol-4-yl)aniline-βCD (**8b**):

^{1}H-NMR (D_2O) δ 1.09 (1H, t, *J* = 7.08 Hz), 2.13 (4H, s), 2.63 (6H, d, *J* = 0.00 Hz), 2.78 (1H, d, *J* = 11.46 Hz), 2.96 (1H, d, *J* = 10.86 Hz), 3.31 (1H, s), 3.51 (22H, m, *J* = 5.77 Hz), 3.82 (22H, m, *J* = 9.65 Hz), 4.13 (1H, s), 4.61 (2H, q, *J* = 14.30 Hz), 4.85 (1H, t, *J* = 5.01 Hz), 4.97 (6H, m, *J* = 8.83 Hz), 5.12 (1H, d, *J* = 3.78 Hz), 7.49 (2H, d, *J* = 8.22 Hz), 7.89 (2H, d, *J* = 8.46 Hz), 8.41 (1H, s).

R_f = 0.51

Supporting Information

1D NMR spectra are available in the Supporting Information file.

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