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One-pot synthesis of a thioureido-β-cyclodextrin dimer

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Abstract

The present work describes a one-pot synthesis of a thioureido-β-cyclodextrin isolated in good yield (32%) by the 'phosphinimine' approach.

Keywords: β-cyclodextrin; Staudinger reaction; carbon disulphide; phosphinimine.

Pursuing developments of the 'phosphinimine' approach for direct access to abiotic receptors on the basis of cyclodextrins (Cds), we have recently reported studies leading to ureido Cds dimers[1,2] and oligomers.[3] Some of the published compounds have shown interesting biomimetic catalysis, and luminescent properties.[3] The present work describes an extension of the 'phosphinimine' approach for general access to thioureido-Cd derivatives (Scheme 1). The one-pot condensation of the per-*O*-acetyl-6-monoazido-6-monodeoxy-β-cyclodextrin[4] **1** with triphenyl phosphine (10 equiv.), hexamethylene diamine **2**, (0.6 equiv.) and CS_2 in anhydrous DMF as solvent, readily gives the acetylated *bis*-cyclodextrin ligand **3** in a good overall yield (32%) after 24 h of reaction and purification by chromatography on silica gel (CH_2Cl_2:MeOH, 98:2). The unprotected product **4** is obtained after a Zemplén deacetylation step (93%). The reaction could be also performed from the unprotected 6-monoazido-monodeoxy-β-Cd giving **4** under the same conditions in one step. The structures of new compounds **3–4** were fully analysed by IR, NMR and FABMS. The collected data are in agreement with the proposed structures.[5] IR spectra of new compounds show characteristic ν (*CS*–NH) thiocarbonyl and amine ν (CS–*NH*) of thiourea functions. The mechanism is, probably, analogous to that determined in a previous work[6] which suggests in situ formation of isothiocyanate-Cd intermediate during the reaction. Recently, literature has reported the reaction of nucleophilic amine with Cd-isothiocyanate applied to the synthesis of thioureido-Cds.[7]

Here, the 'phosphinimine' approach offers the advantage of a one-pot procedure leading to a wide variety of possible thio-derivatives without using hazardous reagents as isothiocyanates and thiophosgene.

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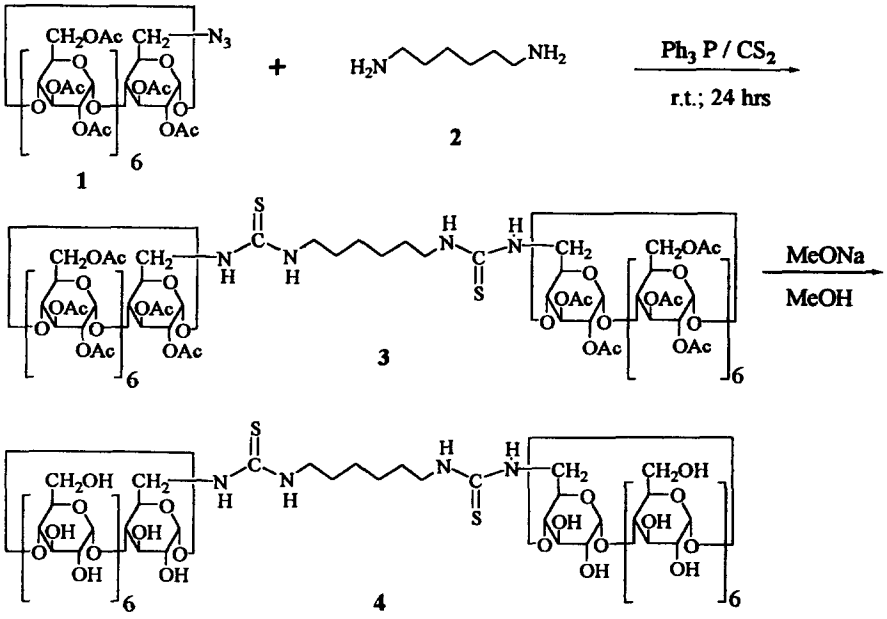

Scheme 1.

The above synthesised dimer **4** will be further explored for its potential biomimetic catalytic activity and metal complexation properties.

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5. Structures of all compounds were assigned by ^{1}H and ^{13}C NMR on a Bruker DRX-400 spectrometer, FTIR spectra were recorded on a Perkin–Elmer 1600 and mass spectra were recorded in FAB positive mode on a ZAB-SEQ mass spectrometer. The new compounds gave satisfactory analytical and spectroscopic data. **3**: Bis-{[hexakis(2,3,6-tri-*O*-acetyl)]-2,3-di-*O*-acetyl-cyclomaltoheptaosyl)-6-thioureido)]-1,6-hexamethylenediamine obtained by condensation of **1** (0.5 mmol, 1.0 g, 1.2 equiv.), **2** (0.25 mmol, 0.029 g, 0.6 equiv.), carbon disulphide in large excess (40 mL) and triphenylphosphane (4.2 mmol, 1.09 g, 10 equiv.). White powder (0.33 g, 32%); TLC (CH_2Cl_2:MeOH, 90:10): R_f=0.3; IR: 3626–3800 (N–H), 1732 (C=S); ^{1}H NMR ($CDCl_3$, 25°C) δ (ppm): 5.40–5.20, 4.90–4.70, 4.20–3.95 (m, 21H (H_a2, H_a3, H_a5, H_b2, H_b3, H_b5)); 5.18–4.95 (m, 14H (H_a1, H_b1, H_a4, H_b4)); 4.60–4.40, 4.40–4.20 (m, 14H (H_a6, H_b6)); 3.65–3.60

(m, 2H, CH_2, alkyl chain); 3.30 (m, 2H, CH_2, alkyl chain); 2.30–2.00 (m, 60H, CH_3CO); 1.30 (m, 2H, CH_2, alkyl chain); ^{13}C NMR ($CDCl_3$, 25°C) δ (ppm): 172–171 (CH_3CO); 170 (NH-*C*=S); 97 (C_1a, C_1b); 78–77 (C_4a, C_4b); 72–70 (C_2a, C_3a, C_5a, C_2b, C_3b, C_5b); 30 (*C*H_2 alkyl); 40 (*C*H_2 alkyl); 20 (*C*H_3CO); FABMS (NBA) : 3977 [M–4[*C*H_3*CO*]+3H$^+$]$^+$; Anal. calcd for $C_{172}H_{234}N_4O_{108}S_2$: C, 49.78; H, 5.68; N, 1.35; S, 1.54; found: C, 48.59; H, 5.66; N, 1.03; S, 1.45. **4**: Bis-[cyclomaltoheptaosyl-6-thioureido]-1,6-hexamethylenediamine. White powder (0.182 g, 93%); TLC (dioxane:NH3 25%, 10:7 v/v): R_f=0.8; IR: 3708–3384 (N–H, O–H); 1731 (C=S); ^{1}H NMR ($CDCl_3$, 25°C) δ (ppm): 5.40–5.20, 4.90–4.70, 4.20–3.95 (m, 21H (H_a2, H_a3, H_a5, H_b2, H_b3, H_b5)); 5.18–4.95 (m, 14H (H_a1, H_b1, H_a4, H_b4)); 4.60–4.40, 4.40–4.20 (m, 14H (H_a6, H_b6)); 3.65–3.60 (m, 2H, CH_2 C1-C6 alkyl chain); 3.30 (m, 2H, CH_2 C2-C5 alkyl chain); 1.30 (m, 2H, CH_2 C3-C4 alkyl chain); ^{13}C NMR (D_2O, 25°C) δ (ppm): 170 (NH-*C*=S); 97.1 (C_1a, C_1b); 78–77 (C_4a, C_4b); 72–70 (C_2a, C_3a, C_5a, C_2b, C_3b, C_5b); 62 (C_6a, C_6b); 46 (*C*H2 C_1,C_6 alkyl); 40 (*C*H2 C_2, C_5 alkyl); 30 (*C*H2 C_3,C_4 alkyl); FABMS (thioglycerol): 1379 [M–[*NH–CH$_2$–Cd*]+2Na$^+$]$^+$, 1199 [*Cd–CH$_2$–NH–CS*]+Na$^+$]$^+$, 1176 [*Cd–CH$_2$–NH–CS*]$^+$.

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