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A polymer-supported 'one-pot' phosphine imide reaction on cyclodextrins

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Abstract—The present work describes the first example of a polymer-assisted 'one-pot' phosphine imide reaction using a polymer-bounded triphenylphosphine. The syntheses were performed from the 6-monoazido-β-peracetylated cyclodextrin or from the heptakis-(6-deoxy-6-azido)-β-cyclodextrin and lead to, monosubstituted, polysubstituted or dimer of β-cyclodextrin in good yields (64–43%). The repeatability of the reaction and the polymer regeneration step were investigated.

On screening the literature for direct, simple and efficient reactions involving cyclodextrins (CDs), the phosphine imide method previously developed by some of us[1] appeared to be a versatile and interesting method for the synthesis of either functionalised, multi-hosted, or tethered CDs derivatives.[2–5] Also, some applications of this method in the separation sciences have been recently reported.[6] An extension of the method using CS_2 in place of CO_2 has allowed the obtention of dimers[7] and tethered thiorureido-CDs.[8] We now discuss another aspect of this approach dedicated to the reaction transfer on a solid phase using a polymer-bounded triphenylphosphine. The goal was to resolve one major problem related to the production of the triphenylphosphine oxide (TPO) by-product, which readily forms strong inclusion complexes with CDs and also to perform a powerful continuous synthetic process including the polymer regeneration step. In order to check the validity of the proposal, the polymer-assisted syntheses of different ureido-CDs were realised following the synthetic Scheme 1 and were compared to the results obtained in solution.

All the reactions have been conducted in the same conditions as in solution (rt/DMF) in a particular reactor for solid-phase peptide synthesis dimensioned for 1 g of resin and equipped with a CO_2 line inlet. The reaction works as well as in solution and gives in a 'one-pot' process the expected urea derivatives **3**, **4** from the 6-monoazido-β-peracetylated cyclodextrin **1** or from heptakis-(6-deoxy-6-azido)-β-cyclodextrin **2**, depending on the nucleophile. The final products are obtained in medium yields, slightly lower than in solution but without unfavourable traces of triphenylphosphine oxide during the purification. As shown, in Scheme 1 the triphenyl phosphine oxide polymer is easily regenerated in a second step by refluxing for 3 h into a trichlorosilane[9]/toluene solution.[11] The reaction repeatability was also investigated. Using as model the benzylamine nucleophile synthesis, it was possible to perform the reaction five times with the same polymer sample. The overall yield of the fifth run was 55%, that correspond to less than a 10% decrease which seems to be better attributed to losses during the purification steps than to a decreasing efficiency of the polymer itself.

Further, in DMF as the solvent and without the presence of any other nucleophile (Scheme 1) the dimer **5** (48%) was obtained. It appears also interesting to compare the reaction in anhydrous toluene. Like observed in solution,[10] the isocyanate **6** is readily obtained in a medium yield (43%). The formation of a small amount of **5** (9%) has been demonstrated by us recently[10] and was attributed to the side reaction between the phosphine imide intermediate and the isocyanate **6** affording the corresponding bis-cyclodextrin carbodiimide and then finally the bis-urea **5**.

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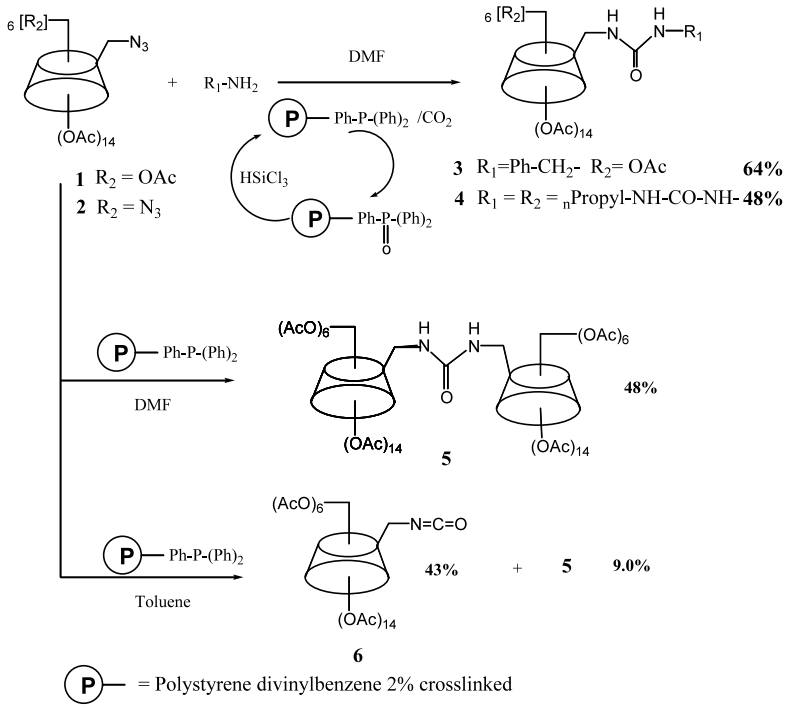

Scheme 1.

In this work, we prove that the 'one-pot' phosphine imide reaction could be easily performed with a good repeatability using the triphenylphosphine-grafted polymer assistance. In these conditions, the possibility of building an automated continuous synthetic process with a recyclable polymer reagent should be considered. Attempts to transfer the reaction in supercritical CO_2 as, solvent and reagent, are presently in progress. The proposed method is of outstanding interest in the cyclodextrin series because it greatly reduces the purification steps, avoiding loss of product and giving multi-Cds derivatives free of TPO traces. The main consequence for the future will be an easier access to pure and novel sophisticated multi-CDs hosts, foreseen to study as new vectors of drugs.

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11. Structures of all compounds were assigned by ^1H and ^{13}C NMR on a Bruker-DRX 400 spectrometer, H^A were designed as protons of the substituted CD-glucosyl residue and $H^{B–G}$ are those of the unsubstituted glucosyl units. FTIR spectra were recorded on a Bruker-Vector 22 spectrometer. Mass spectra were recorded on a Fisons-ZABIISEQ and on a Thermo-Finnigan Mat. MALDI-FTICR-MS; laser Nd Yag (355 nm). Polymer-bounded triphenylphosphine (~3 mmol/g) is from FLUKA.
Urea 3: DMF (30 mL), 6-monoazido-β-peracetylated cyclodextrin **1** (0.2 g, 0.1 mmol),[10] polystyrene bounded triphenylphosphine resin (1.0 g, 3 mmol) and benzylamine (0.053 g, 0.5 mmol) are placed in a solid-phase peptide synthesis reactor. The resulting mixture was stirred for 29 h at rt under continuous bubbling of CO_2, then 24 h more without the CO_2 stream. After filtration the polymer was washed three time by DMF, the solvent evaporated and the white solid residue chromatographed on silicagel (CH_2Cl_2/MeOH; 93/7). A pure white powder

(0.133 g, 0.63 mmol, 64%) was obtained. TLC (CH_2Cl_2/MeOH): $R_f = 0.45$; IR: 3423 cm^{-1} (NH), 1747 cm^{-1} (C=O, ester), 1654 cm^{-1} (C=O, urea). ^1H NMR ($CDCl_3$): 7.33–7.28 (m, 5H, Ar); 5.51 (t, 1H, NHBn); 5.39–5.21 (m, 7H, H-3^{A-G}); 5.16 (d, 1H, H-1^B); 5.13–5.11 (m, 4H, H-1^{C-F}); 5.08 (d, 1H, H-1^B); 5.00 (d, 1H, H-1^A); 4.95 (t, 1H, NH); 4.92–4.77 (m, 6H, H-2^{B-G}); 4.72 (dd, 1H, H-2^A); 4.71–4.48 (m, 6H, H-$6a^{B-G}$); 4.42–4.01 (m, 13H, H-5^{A-G}, H-$6b^{B-G}$); 3.81–341 (m, 11H, H-4^{A-G}, H-$6a^A$, H-$6b^A$, CH_2Ph); 2.19–2.02 (20s, 60H, MeCO); ^{13}C NMR ($CDCl_3$): 170.9–169.7 (Me*C*O); 158.5 (NH*C*ONH); 140.1 (Cq Ar); 128.9–127.5 (Ar); 97.8 (C-1^A); 97.3–96.8 (C-1^{B-G}); 79.2–76.1 (C-4^{A-G}); 71.9–69.5 (C-2,3,5^{A-B}); 63.5–60.8 (C-6^{B-G}); 44.8 (CH_2); 41.9 C-6^A); 21.4–21.1 (*Me*CO); ESMS (*m*/*z*): 2106.61$[M]^+$. Anal. calcd for: $C_{90}H_{118}N_2O_{55}$ C, 50.78; H, 5.61; N, 1.33. Found: C, 50.69; H, 5.61; N, 1.29.

Urea 4: Same procedure as **3** but with DMF (30 mL), heptakis-(6-deoxy-6-azido)-β-cyclodextrin **2** (0.131 g, 0.1 mmol),[10] polystyrene bounded triphenyl phosphine resin (1.0 g, 3 mmol) and *n*-propylamine (0.413 g, 7 mmol), reaction time 29 h. A pure white powder was obtained (0.084 g, 0.045 mmol, 48%) ^1H NMR (DMSO-d_6): 6.50 (t, unresolved, 1H, N*H*); 6.10 (t, unresolved, 1H, N*H*); 4.84 (s, H-1-Cd); 3.62–2.93 (m, unresolved, 56H, H-2 to H-6 Cd and OH-Cd); 1.34 (m, 14H, CH_2 propyl); 0.83 (m, 21H, CH_3 propyl). ^{13}C NMR (DMSO-d_6): 159.2 (CONH); 103.1 (C_1); 84.8 (C_4); 73.3 (C_3); 71.9 (C_2); 59.0 (C_5); 41.9 (C_6); 23.9 (CH_2); 12.1) (CH_3); IR: 3367 cm^{-1} (NH, OH); 2961–2875 (C-H propyl), 1637 (*CO*NH). MALDI (FTICR-MS), (*p*-nitroaniline) *m*/*z*: 1746 $[M+Na]^+$; 1660 $[M+Na-86]^+$. Anal. calcd for: $C_{70}H_{126}N_{14}O_{35}{\cdot}7H_2O$ (1849.9): C, 45.45; H, 7.63; N, 10.60. Found: C, 45.77; H, 7.15; N, 10.20.

Ureido bis-cyclodextrin 5: Same procedure as **3** but with DMF (40 mL), **1** (0.5 g, 0.25 mmol), polystyrene bounded triphenylphosphine resin (5.0 g, 7.5 mmol), reaction time 40 h. A pure white amorphous powder was obtained (0.240 g, 0.060 mmol, 48%). Mp 168–175; IR: 1755 cm^{-1} (C=O, ester), 1680 (C=O, urea); ^1H NMR ($CDCl_3$): 5.35–5.25 (m, 7H, (H3)); 5.18 (d, 1H, *J* = 2, H-1^A); 5.07 (m, 1H, (NH)); 5.11–5.01 (m, 6H, (H-1^{B-G})); 4.88–4.73 (m, 7H, (H-2)); 4.60–4.48 (m, 6H, (H-6^{B-G})); 4.35–4.22 (m, 6H, (H-$6'^{B-G}$)); 4.21–4.11 (m, 6H, (H-5^{B-G})); 3.99 (m, 1H, H-5^A)); 3.82 (m, 1H, (H-6^A)); 3.77–3.65 (m, 7H, (H-4^{A-G})); 3.48 (m, 1H, H-$6'^A$)); 2.16–2.03 (several s, 60H, 20 CH_3CO)). ^{13}C NMR ($CDCl_3$): 180.0–170.4, 169.6–169.3 CH_3CO; 158.2 (NH-*C*O-NH); 96.9–96.6 (C1); 77.9–76.5 (C4); 71.3–69.4 (C2, C3, C5); 62.9–62.4 (C-6^{B-G}); 40.4 (C-6^A); 20.9–20.8 (CH_3CO). FAB$^+$-MS (NBA) *m*/*z*: 3976.4 ($M+H^+$). Anal. calcd for: $C_{165}H_{220}N_2O_{109}$ (3975.6): C, 49.85; H, 5.58; N, 0.70. Found: C, 50.30; H, 5.50; N, 0.70.

Peracetyl-6-deoxy-6-isocyanato-β-cyclodextrin 6: A solution of **1** in toluene (8 mL) was dropped in 2 h to a suspension of polystyrene bounded triphenyl phosphine resin (0.66 g, 1.5 mmol) in toluene (20 mL) under gently bubbling CO_2. The mixture was then stirred under CO_2 atmosphere for a further 24 h. After filtration and washing of the polymer, the solvent was evaporated and the white solid residue chromatographed on silicagel (CH_2Cl_2/MeOH; 93/7) to give isocyanate as a white powder (0.057 g, 0.028 mmol, 43%). R_f (EtOAc–EtOH 95:5) 0.7, (EtOAc) 0.35. Mp 140–145°. $[\alpha]_D$ +122 (*c* 1, $CHCl_3$). IR: 2267 (N=C=O), 1757 cm^{-1} (AcO). ^1H NMR ($CDCl_3$): 5.34–5.20 (m, 7H, H-C(3^{A-G})); 5.16–5.04 (m, 7H, H-C(1^{A-G})); 4.87–4.76 (m, 7H, H-C(2^{A-G})); 4.63–4.52 (m, 6H, H-C($6a^{B-G}$)); 4.32–4.02 (m, 13H, H-C(5^{A-G}), H-C($6b^{B-G}$)); 3.87–3.67 (m, 9H, H-C(4^{A-G}), H-C(6a,b^A)); 2.15–2.04 (several s, 60H, CH_3CO). ^{13}C NMR ($CDCl_3$): 170.7–169.3 (CH_3CO); 125.0 (N=*C*=O); 96.9–96.5 (C(1)); 77.4–76.4 (C(4)); 71.1–69.4 (C(2), C(3), C(5)); 62.7–62.3 (C(6^{B-G})); 43.6 (C(6^A)); 20.8–20.7 (CH_3CO). ESMS (*m*/*z*): 2002.4 $[M]^+$.

Polymer regeneration procedure. A suspension of the triphenylphosphine oxide bounded resin (1.0 g, 3 mmol), trichlorosilane (1.598 g, 11.8 mmol) and triethylamine (1.194 g, 11.8 mmol) in argon degassed toluene (30 mL) was refluxed for 3 h under an argon atmosphere. The reaction medium was cooled in an iced water bath. A solution of NaOH (2 M, 75 mL) was added and the mixture was stirred (mechanical stirring) for 10 min at 0–4°C, filtered on a sintered glass funnel under argon, three times washed with water then, two times with a acetone/toluol 2/1 mixture and finally two times with toluene only. The regenerated resulting polymer was then dried under vacuum and ready for a new reaction.