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Supercritical CO_2 improved phosphine imide reaction on peracetylated β-cyclodextrin

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This paper is dedicated to the memory of Professor Jòzef Szejtli 1933–2004

Abstract—Supercritical CO_2 (sCO_2) was successfully used as solvent and reagent in the 'one-pot' phosphine imide reaction. In sCO_2 smooth conditions and with or without assistance of triphenylphosphine-bounded polymer, the reaction efficiently leads to the desired urea β-Cd compounds in a short time, bringing an interesting alternative for solving problems of OVC and hazardous reagent substitution in the synthesis of ureido-Cds and, by extension, of urea derivatives.

In the development of new efficient synthetic processes, the replacement of organic volatile compounds (OVCs) such as hazardous organic solvents, or hazardous industrial reagents, appears as a major goal in the present-day challenge of so-called 'Green Chemistry'. In this sense, the general synthesis of ureas could represent a particularly sensitive problem in environmental protection. Ureas have a large range of uses including dyes for cellulose fibres, intermediates in carbamate synthesis, agrochemistry and wide sets of pharmaceuticals. As already reported in a recent review[1] on the subject it was well established that ureas have been traditionally synthesised by methodologies mainly based on the use of hazardous reagents such as phosgene (this concerns ca. 2×10^6 tonnes $year^{-1}$ of phosgene produced and used worldwide) and isocyanates. Thus, different phosgene substitutes have been utilised or proposed even recently[2] as safer reagents until the introduction of CO_2 first uses requiring drastic conditions of temperature and pressure or catalysis with expensive metals to obtain activation of CO_2.[1]

Elsewhere, the 'phosphine imide' strategy has been intensively developed in our group to achieve a rapid access to sophisticated cyclodextrin derivatives (urea, carbodiimides, isocyanates) from azides.[3a–d] More recently, we report by extension, a direct safe and soft general synthesis of ureas carrying the reaction in modified conditions from primary amines.[4] We estimate now that this strategy should lay the foundations for new processes using sCO_2 (supercritical carbon dioxide) as reagent and solvent in the syntheses of ureas and other sensitive compounds (e.g., carbamates, isocyanate carbodiimides…) as it works in smooth reaction conditions and without expensive catalysts. A wide industrial success of sCO_2 in the field of natural compound extraction and separation processes has been shown throughout the past decade and supports this idea. So it has become evident that it is high time to demonstrate the possible efficiency of sCO_2 in reactions as solvent or/and reagent as reported very recently in rare examples of the literature.[5]

In this sense, the present work was first attempted to observe the phosphine imide reaction in sCO_2 and in [sCO_2-polymer-assisted] conditions in place of gaseous CO_2 and DMF as the usual solvent of the reaction. The experiments were carried out in a customised stainless steel reactor (vol. 100 mL).[6] The reaction illustrated in Scheme 1 was performed in a 'one-pot' procedure from the 6-monoazido-peracetylated β-cyclodextrin **1** and four distinct nucleophilic amines **2**–**5** in two different conditions ('monophasic': all the components were checked as being totally soluble in sCO_2) and ('biphasic':

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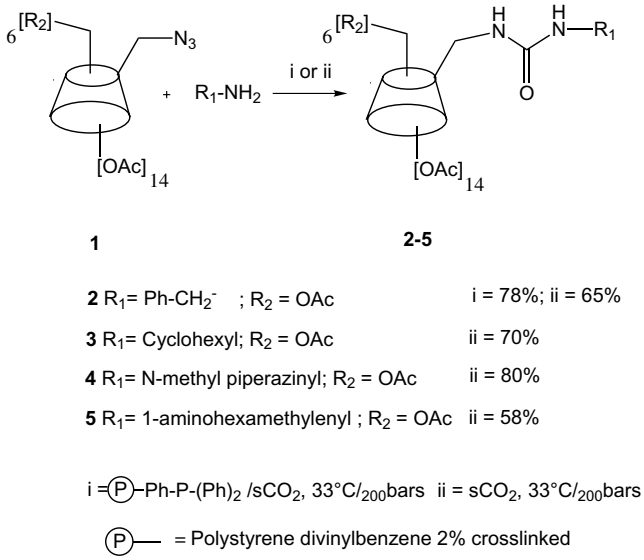

Scheme 1.

in this case Cd and amine components are soluble in sCO_2 except the triphenylphosphine grafted polymer which remains insoluble). In both situations, the amine nucleophile was introduced before closing the reactor. The mild reaction temperature of 33 °C was chosen to be as close as possible to those of reactions previously reported in DMF and compatible with the CO_2 working pressure to be in the supercritical phase.[5,3a–d] We observed the reaction gives the desired urea **2** in 78% and 65% yield[7] in monophasic and biphasic polymer assisted conditions, respectively (one should remember that the polymer catalyst could be easily regenerated as previously reported by us[3d]). Good yields (58–85%) are also obtained with **3**–**5** other nucleophiles (cyclic secondary amines and aliphatic primary diamine) in the same conditions.[7] Thus, the reaction could afford unsymmetrical monosubstituted or symmetrical disubstituted ureas as well, depending on the starting stoichiometry as illustrated by the obtention of monosubstituted compound **5** from hexamethylene diamine. These results also confirm an expected efficiency of sCO_2 on the reaction acceleration rate which was completed in only 8 h instead of currently 24 h in DMF at rt and atmospheric pressure conditions. The positive influence on the acceleration rate may be attributed to the high diffusion property of sCO_2 that probably occurs in the biphasic conditions especially with the polymer assisted reaction.

In conclusion, we have clearly demonstrated the phosphine imide reaction works perfectly in either mono phasic or biphasic supercritical CO_2 conditions with an acetylated Cd substrate. At present time, the moderate volume (100 mL) of our vessels did not allow us to carry out the reaction in bulk, a 1000 mL stainless steel new reactor is presently under manufacture and should resolve this limitation. Finally, we argued that it is of primary interest to develop such methodology which is potentially able to allow a significant improvement in the manufacture of simple or sophisticated ureas with concomitant reduction of waste at the source. This should be well represented by the application of supercritical carbon dioxide that combines the use of a non-toxic reagent, with the benefit of reducing the emission of CO_2 in a direct way by fixation of the molecule into products. In addition, it is also of current interest today to develop such methods to be able to propose in the near future pharmaceuticals totally free of solvent traces notably by coupling with a sCO_2 separation method. In this sense some other important urea drugs and derivatives are now currently under investigation.

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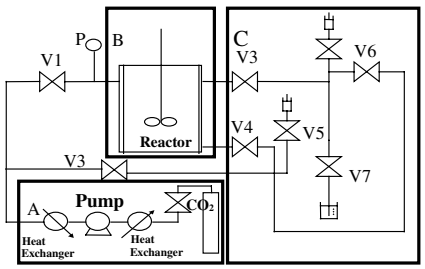
6. The reactor is a 100 mL stirred batch reactor in stainless steel (Top Industry). It was equipped with a three bladed turbine with a rotation speed from 300 rpm to 3000 rpm. The thermoregulation was obtained using a jacket through which water was circulating. The entire apparatus consists of three parts: a compression section, composed of the CO_2 tank, two heat exchangers and a pump (LEWA EKM-10); a reaction section, composed of the batch reactor where CO_2 can enter from the top or the bottom; a sampling section, composed of different valves which allow the recovery of the products at the end of the reaction. Whole apparatus used for the reaction under pressure: (A) compression modulus; (B) reaction modulus (batch reactor = I.D. = 4 cm, height = 8 m); Sampling modulus.



7. Structure of all compounds was assigned by ^{1}H and ^{13}C NMR on a Bruker-DRX 400 spectrometer, FTIR spectra

were recorded on a Bruker-Vector 22 spectrometer. The solvents were purified by standard methods. Polymer-bounded triphenylphosphine (~3 mmol/g) is from FLUKA Urea **2** (polymer-assisted, biphasic conditions): 6-monoazido-β-peracetylated cyclodextrin **1** (0.093 g, 0.047 mmol),[3b] benzylamine (0.46 mmol, 100 μL, 9.5 equiv) and polystyrene bounded triphenylphosphine resin (0.6 g, correspond to 40 equiv $P(Ph)_3$). The same conditions as below are applied to give the urea **2** as a pure white powder. Yield (%) 65 (0.064 g, 0.302 mmol) 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, 5 H, 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 (*multiple* s, 60H, *Me*CO); ^{13}C NMR ($CDCl_3$): 170.9–169.7 (*multiple* s, 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^AC-2,3,$5^{B–G}$); 63.5–60.8 (C-$6^{B–G}$); 44.8 (CH_2); 41.9 C-6^A); 21.4–21.1 (*multiple* s, *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. Ureas **2**–**5**. (sCO_2 monophasic conditions): 6-monoazido-β-peracetylated cyclodextrin **1** (0.093 g, 0.047 mmol),[3b] amine **2**–**5** (0.46 mmol, 9.5 equiv) and triphenylphosphine (0.488 g, 1.8 mmol, 40 equiv) were introduced in the stainless steel reactor. After sealing the latter the reactor was filled with liq. CO_2 and then heated at 33 °C during 8 h with a critical pressure of 200 bar. The reaction was stopped by slow release of the CO_2 and the fine white solid crude product was collected with small amounts of methanol. The solvent was evaporated and excess of triphenylphosphine and triphenylphosphine oxide by-product was extracted with hexane(50 mL) from the residue. After a chromatographic filtration on a silica gel column (CH_2Cl_2/MeOH, 9:1) the ureas **2**–**5** were obtained as pure white powders. Compound **2** Yield (%) 78 (0.077 g, 0.364 mmol). Compound **3** Yield (%) 70 (0.068 g, 0.143 mmol). IR: 1754 cm^{-1} (C═O, ester), 1650 cm^{-1} (C═O, urea). ^1H NMR ($CDCl_3$): 5.52–525 (m, 7H, H-$3^{A–G}$); 5.23–4.88 (m, 7H, H-$1^{A–G}$); 4.83–4.70 (m, 7H, H-$2^{A–G}$); 4.68–4.51 (m, 6H, H-$6a^{B–G}$); 4.49–3.90 (m, 8H, H-$5^{A–G}$, H-$6a^A$,); 3.88–3.41 (m, 15H, H-$4^{A–G}$, H-$6b^{B–G}$, H-$6b^A$, C*H cyclohexyl*), 2.18–1.90 (*multiple* s, 60H, CH_3–CO), 1.89–1.00 (m, 10H, CH_2 *cyclohexyl*). ^{13}C NMR ($CDCl_3$): 170.5–169.9 (*multiple* s Me*C*O); 97.1 (C-$1^{A–G}$); 73.5–70.0 (C-2,3,5 ^{A}, C-2,3,5 $^{B–G}$); 62.9 (C-$6^{B–G}$); 49.8 (C-6^A); 34.2; 32.4, 26.0, 25.3 (*cyclohexyl*); 21.2–20.9 (*multiple* s, MeCO). ESMS (*m*/*z*): 2100.6 $[M+H]^+$. **4** Yield (%) 80 (0.084 g, 0.190 mmol). IR: 1749 cm^{-1} (C═O, ester), 1655 cm^{-1} (C═O, urea). ^1H NMR ($CDCl_3$): 5.39–5.14 (m, 7H, H-$3^{A–G}$); 5.12–4.96 (m, 7H, H-$1^{A–G}$); 4.82–4.62 (m, 7H, H-$2^{A–G}$); 4.58–4.40 (m, 6H, H-$6^{B–G}$); 4.38–4.19 (m, 1H, H-6^A); 4.18–3.98 (m, 7H, H-$5^{A–G}$); 3.77–3.46 (m, 7H, H-$4^{A–G}$); 3.43–3.31 (m, 4H, CH_2 *piperazine*); 2.49–2.38 (m, 4H, CH_2 *piperazine*); 2.30 (s, 3H, CH_3–N); 2.18–1.90 (*multiple* s, 60H, CH_3–CO). ^{13}C NMR ($CDCl_3$): 171.1–168.4 (*multiple* s, Me*C*O); 95.5 (C-$1^{A–B}$); 69.9–68.5 (C-2,3,5^AC-2,3,$5^{B–G}$); 61.5 (C-$6^{B–G}$); 53.4 (C-6^A); 44.7 (*C*H_2 *piperazine*); 42.2 (*CH*$_2$ *piperazine*); 28.7 (*C*H_3–N); 21.2–19.8 (*multiple* s, *Me*CO). ESMS (*m*/*z*): 2263.3 $[M+H]^+$. **5** Yield (%) 58 (0.057 g, 0.121 mmol) IR: 1743 cm^{-1} (C═O, ester), 1655 cm^{-1} (C═O, urea). ^1H NMR ($DMSO_6$ D): 5.91–5.69 (s, *large*, NH_2); 4.91–4.78 (m, 7H, H-$1^{A–G}$); 4.41–3.54 (m, *complex unresolved*, 45H, H-2 to H-$6^{A–G}$); 3.01–2.98 (m, 2H, CH_2 *hexamethylene chain*); 2.02–1.97 (m, 2H, CH_2 *hexamethylene chain*); 1.40–1.37 (m, 4H, –CH_2–CH_2-*hexamethylene chain*); 1.35–1.18 (m, 4H, –CH_2–CH_2-*hexamethylene chain*). ^{13}C NMR ($DMSO_6$ D):170.0–169.3 (*multiple* s, Me*C*O); 82.5 (C-$1^{A–G}$); 73.4–72.4 (C-2, C-3, C-$5^{A–G}$); 69.4 (C-$6^{B–G}$); 63.5 (C-6^A); 60.3 (*C*H_2–NH_2); 32.0, 30.8, 29.5, 26.5, 22.9 (*CH*$_2$ *hexamethylene chain*); 20.9–20.3 (*multiple* s, *Me*CO). ESMS (*m*/*z*): 2118.0 $[M+H]^+$.