

Debenzylation of Tertiary Amines using Phosgene or Triphosgene (BTC): an Efficient and Rapid Procedure for the Preparation of Carbamoyl Chlorides and Unsymmetrical Ureas. **Application** in Carbon-11 Chemistry

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General experimental methods.

Tetrahydrofuran (THF) was dried by reflux over sodium/ benzophenone and diethyl ether over LiAlH₄ before distillation under a nitrogen atmosphere. Toluene, CH₂Cl₂ and all amines used were distilled from CaH₂. Compounds **1**, **4**, **8**, **9**, **10**, **16**, pipercolate, **nipecotate** esters and all other reagents or catalysts were used as obtained from commercial sources (purity > 98%). PhMgBr was titrated before use. Carbamate **30**^{1,2} and amide **31**^{2,3} were prepared according to standard procedures. Thin layer chromatography (TLC) was performed on silica gel 60 F-254 plates (0.1 mm) with iodine and/or UV detection. Chromatographic separations were achieved on silica gel columns (40-63 μm) **according to a described procedure**.⁴ Liquid chromatographic analysis (LC) was performed with a gradient pump and a variable-wavelength UV detector

in series with a scintillation detector. ^1H NMR and ^{13}C NMR spectra were recorded at 250 MHz (^1H) or 62 MHz (^{13}C) using TMS and CDCl_3 as the reference and solvent respectively unless otherwise indicated. Mass spectra were obtained on a Nermag Riberg R10 RH (EI, 70 eV) and high resolution mass spectra (HRMS) on a Jeol JMSD 300 or a Jeol AX 500. IR spectra were recorded with a FT-IR Perkin-Elmer 16 PC instrument. Elemental analyses were obtained from a ThermoQuest CHNS-O instrument. Melting points were measured on a Gallenkamp capillary melting point apparatus and are reported uncorrected.

I. Synthesis of tertiary amines

2-Methyl 1,2,3,4-tetrahydroisoquinoline (13a). To tetrahydroquinoline **1** (2.63 g, 19.75 mmol) in toluene (30 mL) cooled to 0°C were simultaneously added ethylchloroformate (2.68 g, 24.68 mmol) and 4.1 M NaOH solution (1.25 mL). The reaction mixture was warmed to rt, stirred for 12 h and extracted with CH_2Cl_2 (2 x 20 mL). The combined organic extracts were dried over MgSO_4 . Evaporation of the solvent gave the carbamate (4.0 g, 98%) as a colorless liquid which was analyzed by ^1H NMR¹ and then used without any purification. To a LiAlH_4 (2.13 g, 56.00 mmol) suspension in THF (25 mL) was added dropwise the above carbamate (3.64 g, 17.76 mmol) in THF solution (5 mL). The reaction mixture was refluxed for 36 h then cooled to rt. Aqueous NaOH (1 mL, 3.75 M) was added and the mixture was stirred for 30 min. The solid was removed by filtration and the mother liquor dried over MgSO_4 . Evaporation of the solvent gave pure amine **13a** (2.48 g, 94%) which spectral properties are identical to that previously described.^{5, 6}

2-(Phenylmethyl)-1,2,3,4-tetrahydroisoquinoline (13b). Reduction of N-Benzoyl-tetrahydroisoquinoline (5.81 g, 24.49 mmol) under the conditions described for compound **13a** gave the tertiary amine **13b**⁷ (3.41 g, 62%): mp 37°C (hydrochloride: mp 168°C).

Reductive amination⁸

2-[(4-Methoxyphenyl)methyl]-1,2,3,4-tetrahydroisoquinoline (13c). To 4-methoxybenzaldehyde (1.22 g, 8.94 mmol) in 1,2-dichloroethane (40 mL) was added, at rt, tetrahydroisoquinoline **1** (1.19 g, 8.94 mmol) then NaHB(OAc)₃ (2.87 g, 13.40 mmol). The reaction mixture was stirred for 12 h. Water (20 mL) was added and the amine was extracted with CH₂Cl₂. The combined organic layers were dried over MgSO₄ and the solvent was evaporated. CH₂Cl₂ (2 mL) and diethyl ether (50 mL) were added to the residue and the solution was saturated with gaseous HCl. The solid which precipitated was filtered and washed with diethyl ether. After **recrystallization** from isopropanol, amine **13c**, as its hydrochloride, was obtained as white crystals (2.01 g, 77%): mp 211°C.

Data for the free amine **13c**: mp 62°C; ¹H NMR δ 2.78 (t, *J* = 6.1 Hz, 2H), 2.91 (t, *J* = 6.1 Hz, 2H), 3.70 (s, 2H), 3.73 (s, 2H), 3.84 (s, 3H), 6.87 - 7.1 (m, 4H), 7.25 (t, 7.4 Hz, 1H), 7.44 (dd, *J* = 7.4, *J* = 1.6 Hz, 1H); ¹³C NMR δ 29.1, 50.5, 55.3, 56.0, 62.1, 113.7, 125.6, 126.1, 126.6, 128.7, 130.3, 134.4, 158.8; IR (CHCl₃): 3010, 2922, 2836, 1600, 1588, 1492, 1464, 1242, 1216 cm⁻¹; MS (EI) *m/z* 253 (M⁺, 17.9), 132 (19.6), 104 (25.2), 84 (79.7), 77 (63.5), 49 (100); Anal. Calcd for C₁₇H₁₉NO: C, 70.46; H, 6.96; N, 4.83. Found: C, 70.13 ; H, 7.03; N, 4.86.

2-[(2,4-Dimethoxyphenyl)methyl]-1,2,3,4-tetrahydroisoquinoline (13d). To a solution of 2,4-dimethoxybenzaldehyde (3.65 g, 21.96 mmol) in 1,2-dichloroethane (50 mL) was added, at rt, tetrahydroisoquinoline **1** (2.93 g, 11.37 mmol) then NaHB(OAc)₃ (7.04 g, 32.94 mmol). The mixture was stirred for two days. Aqueous saturated NaHCO₃ solution (100 mL) was added and the mixture was extracted with CH₂Cl₂ (2 x 20 mL). The combined organic extracts were dried over MgSO₄ and the solvent was evaporated. Purification of the residue by flash chromatography on silica gel using pentane-ethyl acetate (90:10) as the eluent to gave amine **13d** as a white solid (4.69 g, 75 %): mp 48°C. which spectral properties are identical to those previously described.⁹

2[(4-Dimethylaminophenyl)methyl]-1,2,3,4-tetrahydroisoquinoline (13e). Using the procedure described for amine **13d**, reductive amination of 4-dimethylaminobenzaldehyde (1.902 g, 12.77 mmol) with

tetrahydroisoquinoline **1** (1.699 g, 12.76 mmol), led to amine **13e** (2.770 g, 81 %) as a white solid: mp 70°C; ¹H NMR δ 2.76 (t, *J* = 5.9 Hz, 2H), 2.92 (t, *J* = 5.9 Hz, 2H), 2.98 (s, 6H), 3.63 (s, 2H), 3.65 (s, 2H), 6.76 (d, *J* = 8.5 Hz, 2H), 7.29 (d, *J* = 8.5 Hz, 2H), 7.0-7.1 (m, 4H); ¹³C NMR δ 29.1, 40.7, 50.4, 56.0, 62.3, 112.4, 125.5, 126.0, 126.1, 126.6, 128.6, 130.1, 134.5, 135.1, 149.9; IR (KBr) 3062, 3022, 2986, 2900, 1944, 1908, 1614, 1442, 1320 cm⁻¹; HRMS (EI) calcd for C₁₈H₂₂N₂ 266.17828, found 266.17829.

1-(Phenylmethyl)-4-[(4'-methoxyphenyl)methyl]piperazine (15). Using the procedure described for amine **13d**, reductive amination of 4-methoxybenzaldehyde (9.816 g, 72.18 mmol) with *N*-benzylpiperazine **4** (12.718 g, 72.18 mmol) led to amine **15**¹⁰ (17.52 g, 82 %) as a white solid: mp 81°C; ¹H NMR δ 2.46 (br s, 8H), 3.44 (s, 2H), 3.50 (s, 2H), 3.79 (s, 3H), 6.83 (d, *J* = 8.5 Hz, 2H), 7.21 (d, *J* = 8.5 Hz, 2H), 7.1-7.3 (m, 5H); ¹³C NMR δ 53.0, 53.1, 55.2, 62.4, 63.1, 113.5, 126.93, 128.1, 129.2, 130.2, 130.4, 138.2, 158.7; IR (CHCl₃) 3012, 2936, 2812, 1612, 1512, 1456, 1248, 1216 cm⁻¹; MS (EI) *m/z* 296 (M⁺, 75), 295 (18), 205 (38), 175 (100), 148 (23), 121 (97), 91 (71). Anal. Calcd for C₁₉H₂₄ON₂ C, 76.99; H, 8.16; N, 9.40. Found: C, 76.76; H, 8.09; N, 9.55.

***N,N*-[(4-Methoxyphenyl)methyl]methyl aniline (17).** To Na₂CO₃ (4.43 g, 41.84 mmol) in CH₂Cl₂-water (95:5) were added *N*-methyl aniline (1.491 g, 13.94 mmol) then 4-methoxybenzyl chloride **16** (2.183 g, 13.94 mmol). The mixture was stirred for 3 days at rt. The solid was filtered over celite and the filtrate extracted with CH₂Cl₂ (2 x 20 mL). The combined organic extracts were dried over MgSO₄ and evaporation of the solvent gave a mixture of *N*-methylaniline, 4-methoxybenzyl chloride and the expected amine **17** (relative ratios from ¹H NMR: 33:38:52). Flash chromatography on silica gel using pentane-triethylamine (90:10) as the eluent gave pure **17** (0.791 g, 25 %). Its spectral characteristics are identical to those previously described.¹¹ Aniline **17** was transformed into its hydrochloride salt which was recrystallized from isopropanol. White solid: mp 99-101°C.

1-[(4-Methoxyphenyl)methyl]-piperidine-3-carboxylic acid ethyl ester (25).¹² To 15 mL of a 2/1 mixture of CH₂Cl₂/saturated aqueous solution of Na₂CO₃ were added ethyl nipecotate (0.786 g, 5 mmol) then 4-methoxybenzyl chloride **16** (1.174 g, 7.5 mmol). The mixture was stirred vigorously at rt for 15 h.

The mixture was diluted with 20 mL of CH_2Cl_2 and washed with 20 mL of brine, dried (MgSO_4) and filtered. After evaporation of the solvent under reduced pressure, the tertiary amine 25 was purified by flash chromatography on silica gel (Hexane/EtOAc 9:1) as a pale yellow oil (1.302 g, 94%): ^1H NMR δ 1.23 (t, $J = 7.1$ Hz, 3H), 1.3-1.75 (m, 3H), 1.87-1.91 (m, 1H), 2.09 (td, $J = 11.0$ Hz, $J = 3.1$ Hz, 1H), 2.25 (t, $J = 10.6$ Hz, 1H), 2.59 (tt, $J = 10.6$ Hz, $J = 3.8$ Hz, 1H), 2.78 (br d, $J = 11.3$ Hz, 1H), 3.01 (dd, $J = 11.2$ Hz, $J = 3.4$ Hz, 1H), 3.57 (s, 2H), 3.81 (s, 3H), 4.10 (q, $J = 7.1$ Hz, 2H), 6.84-6.96 (m, 2H), 7.19-7.37 (m, 2H); ^{13}C NMR δ 14.1, 24.5, 26.8, 41.9, 53.5, 55.3, 55.4, 56.1, 60.0, 110.3, 120.2, 126.3, 127.7, 130.1, 157.6, 174.2; IR (film) 2940, 2834, 1732, 1600, 1588, 1492, 1464, 1242 cm^{-1} ; MS (EI) m/z 277 (M^+ , 37), 248 (20), 232 (26), 204 (20), 156 (100), 121 (95), 91 (53); HRMS (EI) calcd for $\text{C}_{16}\text{H}_{23}\text{O}_3$ 277.1677, found 277.1712.

1-[(4-Methoxyphenyl)methyl]-piperidine-2-carboxylic acid ethyl ester (27). To 15 mL of a 2/1 mixture of CH_2Cl_2 /saturated aqueous solution of Na_2CO_3 were added ethyl pipercolate (0.685 g, 4.36 mmol) then 4-methoxybenzyl chloride **16** (1.024 g, 6.54 mmol). The mixture was stirred vigorously at rt for 24 h. The mixture was diluted with 20 mL of CH_2Cl_2 and washed with 20 mL of brine, dried (MgSO_4) and filtered. After evaporation of the solvent under reduced pressure, the product was purified by flash chromatography on silica gel (Hexane/EtOAc 9:1) as a pale yellow oil (0.990 g, 82%): ^1H NMR δ 1.29 (t, $J = 7.1$ Hz, 3H), 1.30-1.41 (m, 1H), 1.52-1.86 (m, 5H), 2.12-2.25 (m, 1H), 3.0 (dt, $J = 12.0$ Hz, $J = 5.0$ Hz, 1H), 3.15 (dd, $J = 8.2$ Hz, $J = 4.2$ Hz, 1H), 3.69 (s, 2H), 3.78 (s, 3H), 4.15-4.27 (m, 2H), 6.82-6.96 (m, 2H), 7.21-7.41 (m, 2H); ^{13}C NMR δ 14.2, 22.5, 25.2, 29.7, 50.2, 53.4, 55.1, 60.1, 64.3, 110.1, 120.2, 126.2, 127.8, 130.6, 157.7, 174.0; IR (film) 2936, 2856, 1732, 1600, 1588, 1490, 1464, 1240 cm^{-1} ; MS (EI) m/z 277 (M^+ , 2), 248 (4), 204 (100), 121 (70), 91 (20); HRMS (EI) calcd for $\text{C}_{16}\text{H}_{23}\text{O}_3$ 277.1677, found 277.1621.

II. Synthesis of carbamoyl chlorides

Typical procedure for the preparation of carbamoyl chlorides.

Method A. From BTC and secondary amines.

1,2,3,4-Tetrahydroisoquinoline-2-carbonyl chloride¹³ (**2**). To bis(trichloromethyl)carbonate (triphosgene or BTC, 9.0 g, 30.24 mmol) in CH₂Cl₂ (100 mL) at -78°C were added pyridine (6.82 g, 86.36 mmol) then tetrahydroisoquinoline **1** (11.50 g, 86.4 mmol) over a period of 10 min. The reaction mixture was warmed to RT, stirred for 2 h then hydrolyzed with 1N HCl (50 mL). The product was extracted with CH₂Cl₂ and the combine organic extracts were washed with aqueous NaHCO₃ then dried over MgSO₄. Evaporation of the solvent then purification of crude **2** by flash column chromatography on silica gel (Pentane/AcOEt 95:5) gave pure carbamoyl chloride **2** as a white solid (14.86 g, 88%). Mp 36°C; R_f 0.3, Pentane/AcOEt 95:5; IR (NaCl) : 3066, 3026, 1736, 1496, 1280, 1182 cm⁻¹; ¹H NMR δ 2.7-2.8 (m, 2H) 3.66 (t, *J* = 6.0 Hz, 1H), 3.73 (t, *J* = 6.0 Hz, 1H), 4.56 (s, 1H), 4.66 (s, 1H), 6.93 -7.10 (m, 4H); ¹³C NMR (2 conformers) δ 28.2, 28.5, 44.0, 46.1, 47.7, 49.6, 125.8, 125.9, 126.4, 126.9, 128.2, 128.3, 131.4, 131.7, 133.6, 148.1; MS (EI) *m/z* 197 (M⁺, 32), 195 (M⁺, 94.4), 160 (58.3), 117 (28.5), 104 (100), 77 (24.8); Anal. Calcd for C₁₀H₁₀ClNO C, 61.39; H, 5.15; N, 7.16. Found: C, 60.83; H, 5.21; N, 7.16.

2-[2-(methylcarboxylate)piperidine]carbonyl chloride (10).¹⁴

Using the same procedure, from methyl pipercolate (0.40 g, 2.79 mmol), BTC (0.33 g, 1.12 mmol), pyridine (0.22 g, 1 eq., 2.79 mmol), carbamoyl chloride **10** was obtained in 81% yield (0.47g). It partially decomposed on silica gel column. Colorless oil. R_f 0.8, Pentane/AcOEt 8:2; IR (NaCl) 1735, 1725 cm⁻¹; ¹H NMR δ 1.1-1.8 (m, 5H), 2.1-2.3 (m, 1H), 3.07 and 3.28 (2 dt, 2 conformers, *J* = 3.1 and 11.3, 1H), 3.78 and 3.80 (2s, conformers 3H), 4.2-4.3 (m, 1H), 5.0-5.1 (m, 1H); ¹³C NMR (2 conformers) δ 20.5, 20.6, 21.5, 21.6, 24.4, 24.8, 25.6, 26.6, 27.0, 43.7, 44.6, 46.6, 52.6, 52.7, 53.2, 56.2, 59.0, 168.6, 171.2, 170.5. MS (EI) *m/z* 206 (M⁺+1, 26), 148 (35), 147 (10), 146 (100), 142 (27), 67 (27).

Method B. From tertiary amines and BTC. To a mixture of 2-[(4-methoxyphenyl)methyl]-1,2,3,4-tetrahydroisoquinoline **13c** (1.19 g, 4.71 mmol) in dichloromethane (5 mL) was added BTC (0.56 g, 1.88 mmol) in dichloromethane (5 mL). The reaction mixture was stirred for 1 h then hydrolyzed by addition of water (20 mL). The crude product was extracted with dichloromethane. The combined organic extracts were dried over MgSO₄. Evaporation of the solvent then purification of crude **2** by flash chromatography as described above gave pure carbamoyl chloride **2** (0.56 g, 60 %).

Method C. From tertiary amines and phosgene. The same experimental procedure than method B was used with phosgene in toluene. Reaction of 2-[(4-methoxyphenyl)methyl]-1,2,3,4-tetrahydroisoquinoline **13c** with phosgene (2.1 mL, 3.16 mmol) in toluene, yielded, after purification, pure carbamoyl chloride **2** (0.4 g, 65 % yield).

4-(Phenylmethyl)-1-piperazine carbonyl chloride¹⁵ (5). Method A. 4-(Phenylmethyl) piperazine **4** (3.13 g, 17.74 mmol) gave carbamoyl chloride **5** (2.06 g, 48%).

Method B. 1-[4-Methoxyphenyl)methyl]-4-(phenylmethyl) piperazine **15** (0.74 g, 2.48 mmol) yielded carbamoyl chloride **5** as a white solid (0.95 g, 53%). This compound is prone to decomposition and must be kept at 0°C under nitrogen. Mp 92°C; R_f 0.3 (Pentane/NEt₃, 90:10); ¹H NMR δ 2.33 (t, J = 5.1 Hz, 4H), 3,40 (s, 2H), 3.47-3.59 (m, 4H), 7.17-7.21 (m, 5H); ¹³C NMR (2 conformers) δ 46.0, 48.4, 51.8, 52.3, 62.2, 127.1, 128.1, 128.8, 137.1, 147.8; MS (EI) m/z 240 (M⁺, 26), 239 (26), 238 (M⁺, 58), 237 (17), 203 (57), 202 (20), 175 (22), 161 (13), 147 (39), 146 (20) 91 (100).

(*N*-Methyl-*N*-chlorocarbonyl-1,2,3,4-tetrahydroisoquinolinyl)ammonium chloride (14a). Brown solid; mp 224°C; IR (NaBr) 3406, 3924, 2316, 2254, 2220, 1724, 1604, 1468 cm⁻¹; ¹H NMR δ 2.94 (s, 3H), 2.8-4.7 (m, 6H), 7.0-7.3 (m, 4H); ¹³C NMR δ 24.6, 42.0, 50.6, 53.8, 126.5, 126.5, 127.2, 127.3, 128.8, 130.0, 135.2.

[(*N*-(Phenylmethyl)-1,2,3,4-tetrahydroisoquinolinyl)chlorocarbonyl ammonium chloride (14b). White solid; mp 269°C; ¹H NMR δ 2.9-3.1 (m, 1H), 3.3-3.6 (m, 1H), 3.1-3.2 (m, 1H), 3.6-3.7 (m, 1H), 4.0-4.1 (m, 1H), 4.2-4.5 (m, 3H), 7.0-7.1 (m, 1H), 7.1-7.2 (m, 3H), 7.4-7.5 (m, 3H), 7.6-7.7 (m, 2H); ¹³C NMR δ 24.1, 48.1, 51.2, 58.0, 126.5, 126.9, 127.4, 128.4, 128.4, 128.9, 129.3, 130.1, 130.4, 131.2.

II. Synthesis of ureas

1,1'-Carbonyl-bis(1,2,3,4-tetrahydroisoquinoline) (3). To a solution of tetrahydroisoquinoline **1** (0.778 g, 5.85 mmol) in CH₂Cl₂ (25 mL) was added, at rt, BTC (0.130 g, 0.44 mmol) in CH₂Cl₂ (5 mL).

The reaction mixture was stirred for 1 h and 1N HCl (25 mL) was added. The urea was extracted with CH₂Cl₂ (2 x 20 mL). The combined organic layers were dried over MgSO₄. The solvent was evaporated and the residue was purified by recrystallization from ethanol-ether to give urea **3** as a white solid (0.358 g, 93 %): mp 103°C; ¹H NMR δ 2.95 (t, *J* = 5.8 Hz, 4H), 3.56 (t, *J* = 5.8 Hz, 4H), 4.49 (s, 4H), 7.0-7.3 (m, 8H); ¹³C NMR δ 28.7, 44.7, 48.8, 126.1, 126.3, 126.4, 128.8, 133.8, 134.6, 164.2; IR (KBr) 3062, 2938, 1638, 1424, 1238 cm⁻¹; MS (EI) *m/z* 292 (M⁺, 32), 187 (14), 160 (13), 142 (18), 132 (100), 91 (5). Anal. Calcd for C₂₀H₂₀N₂O C, 78.05; H, 6.89; N, 9.58. Found: C, 78.00; H, 7.09; N, 9.53.

General procedure for the synthesis of ureas.

Method A: a carbamoyl chloride is condensed at rt in CH₂Cl₂ with a primary or secondary amine to afford the urea. The amine may be used alone in excess (5 to 10 eq.) or in combination with triethylamine.

Method B: the carbamoyl chloride was generated in situ in CH₂Cl₂ at -10°C by the action of BTC (BTC) on the corresponding tertiary amine. Then a primary or secondary amine was added at rt to afford the urea. The amine may be used alone in excess (5 to 10 equivalents) or in combination with triethylamine.

1,1'-carbonyl-bis-[4-(phenylmethyl)]piperazine¹⁶ (6). Method A: To carbamoyl chloride **5** (0.163 g, 0.68 mmol) in CH₂Cl₂ (30 mL) were added, at rt, *N*-benzyl piperazine **4** (0.120 g, 0.68 mmol) then triethylamine (0.069 g, 0.68 mmol). The mixture was stirred for 12h. A saturated aqueous NaHCO₃ solution (10 mL) was added and after extraction with CH₂Cl₂ (2 x 20 mL), the combined organic layers were dried over MgSO₄. Evaporation of the solvent and purification of the product by flash chromatography on silica gel (pentane/EtOAc/Et₃N 7:2:1) gave urea **6** as a white solid (0.167 g, 65 %).

Method B: To tertiary amine **15** (0.152 g, 0.512 mmol) in CH₂Cl₂ (10 mL) was added at -10°C BTC (0.054 g, 0.18 mmol) in one portion. Then the reaction mixture was stirred at rt for 1h. *N*-benzyl piperazine **4** (0.271 g, 1.54 mmol) then triethylamine (0.156 g, 1.54 mmol) were added and the mixture was stirred for 15h. A saturated aqueous NaHCO₃ solution (10 mL) was added and after extraction with CH₂Cl₂ (2 x 10 mL), the combined organic layers were dried over MgSO₄. Evaporation of the solvent and purification of the product by flash chromatography on silica gel (pentane/EtOAc/Et₃N 7:2:1) gave urea **6** as a white solid (0.170 g, 88 %): mp 122°C; ¹H NMR δ 2.41 (t, *J* = 4.9 Hz, 8H), 3.25 (t, *J* = 4.9 Hz, 8H), 3.50 (s, 4H),

7.20-7.31 (m, 10 H); ^{13}C NMR δ 46.7, 52.8, 63.1, 127.1, 128.2, 129.2, 137.7, 163.7; IR (CHCl_3) 3006, 2938, 2812, 1636, 1474, 1420, 1218 cm^{-1} ; MS (EI) m/z 378 (M^+ , 31), 287 (22), 232 (30), 203 (25), 174 (46), 146 (22), 91 (100); HRMS (EI) calcd for $\text{C}_{23}\text{H}_{30}\text{N}_4\text{O}$ 378.2419, found 378.2403.

***N,N*-Diethyl-*N'*-tetrahydroisoquinolinyl urea (7).** According to method A, using carbamoyl chloride **2** (0.642 g, 3.25 mmol) and diethylamine (2.340 g, 32.55 mmol) in CH_2Cl_2 (20 mL), urea **7** was obtained as a colorless liquid (0.702 g, 93 %).

According to method B, using tertiary amine **13c** (0.205 g, 0.8 mmol), BTC (0.085 g, 0.28 mmol) in CH_2Cl_2 (10 mL), then diethylamine (0.292 g, 4 mmol) urea **7** was obtained as a colorless liquid (0.165 g, 89 %). ^1H NMR δ 1.15 (t, $J = 7.1$ Hz, 6H), 2.91 (t, $J = 5.8$ Hz, 2H), 3.25 (q, $J = 7.1$ Hz, 4H), 3.47 (t, $J = 5.8$ Hz, 2H), 4.39 (s, 2H), 7.0-7.3 (m, 4H); ^{13}C NMR δ 11.4, 23.5, 29.1, 41.1, 42.7, 45.5, 126.3, 126.3, 126.6, 128.4, 133.5, 135.2, 157.6; IR (film): 3064, 2974, 2934, 1670, 1602, 1428, 1278 cm^{-1} ; MS (EI) m/z 232 (M^+ , 87), 203 (21), 160 (21), 142 (20), 132 (100), 117 (15), 103 (14), 72 (46); HRMS (EI) calcd for $\text{C}_{14}\text{H}_{20}\text{N}_3\text{O}$ 232.1575, found 232.1575.

***N*-Propyl-*N'*-tetrahydroisoquinolinyl urea (19).** According to method A, using carbamoyl chloride **2** (0.551 g, 2.79 mmol) and n-propylamine (1.498 g, 25.4 mmol) in CH_2Cl_2 (20 mL), urea **19** was obtained as a **viscous oil** (0.578 g, 95%).

According to method B, using tertiary amine **13c** (0.205 g, 0.8 mmol), BTC (0.085 g, 0.28 mmol) in CH_2Cl_2 (10 mL), then n-propylamine (0.236 g, 4 mmol) urea **19** was obtained as an oil which slowly solidified (0.159 g, 91 %): ^1H NMR δ 0.94 (t, $J = 7.3$ Hz, 3H), 1.54 (sext, $J = 7.3$ Hz, 2H), 2.88 (t, $J = 5.9$ Hz, 2H), 3.25 (dt, $J = 6.9$ and 7.3 Hz, 2H), 3.62 (t, $J = 5.9$ Hz, 2H), 4.48 (br s, 1H), 4.54 (s, 2H), 7.1-7.2 (m, 4H); ^{13}C NMR δ 11.5, 23.4, 23.7, 29.3, 43.0, 45.9, 126.1, 126.5, 126.7, 128.2, 133.4, 135.3, 156.5; IR (CHCl_3) 3346, 2964, 2932, 2874, 1624, 1540, 1456, 1394, 1254 cm^{-1} ; MS (EI) m/z 218 (M^+ , 82), 203 (11), 174 (10), 160 (21), 132 (100), 104 (48); HRMS (EI) calcd for $\text{C}_{13}\text{H}_{18}\text{N}_2\text{O}$ 218.1419, found 218.1388.

***N*-Phenylmethyl-*N'*-tetrahydroisoquinolinyl urea (20).** According to Method A, using carbamoyl chloride **2** (0.640 g, 3.24 mmol), benzylamine (0.347 g, 3.24 mmol) and triethylamine (0.327 g, 3.24 mmol) urea **20** was obtained as a white solid (0.672 g, 78%).

According to Method B, using tertiary amine **13c** (0.205 g, 0.8 mmol), BTC (0.085 g, 0.28 mmol) in CH₂Cl₂ (10 mL), then benzylamine (0.094 g, 0.88 mmol) and triethylamine (0.242 g, 2.40 mmol) urea **20** was obtained as a white solid (0.176 g, 83%): mp 118°C; ¹H NMR δ 2.86 (t, *J* = 5.9 Hz, 2H), 3.62 (t, *J* = 5.9 Hz, 2H), 4.46 (d, *J* = 5.5 Hz, 2H), 4.55 (s, 2H), 4.8-4.9 (br s, 1H), 7.0-7.3 (m, 9H); ¹³C NMR δ 29.0, 41.2, 45.0, 45.5, 126.3, 126.4, 126.7, 127.3, 127.8, 128.4, 128.6, 133.3, 135.1, 139.5, 157.4. IR (KBr) 3062, 3030, 2938, 1720, 1692 cm⁻¹; MS (EI) *m/z* 266 (M⁺, 95), 175 (75), 132 (100), 104 (38), 91 (46); HRMS (EI) calcd for C₁₇H₁₈N₂O 266.1419, found 266.1411.

***N*-Phenyl-*N'*-tetrahydroisoquinolinyl urea (21).** According to Method A, using carbamoyl chloride **2** (0.640 g, 3.24 mmol), **aniline** (0.603 g, 6.48 mmol) and triethylamine (0.654 g, 6.48 mmol) urea **21** was obtained as a white solid (0.580 g, 71%).

According to Method B, using tertiary amine **13c** (0.205 g, 0.8 mmol), BTC (0.085 g, 0.28 mmol) in CH₂Cl₂ (10 mL), then aniline (0.149 g, 1.60 mmol) and triethylamine (0.242 g, 2.40 mmol) urea **21** was obtained as a white solid (0.145 g, 72%): mp 146-147°C (heptane:CHCl₃); ¹H NMR δ 2.87 (t, *J* = 5.7 Hz, 2H), 3.68 (t, *J* = 5.7 Hz, 2H), 4.63 (s, 2H), 6.67 (br s, 1H), 6.98-7.41 (m, 9H); ¹³C NMR δ 28.9, 41.5, 45.7, 120.2, 123.0, 126.2, 126.4, 126.7, 128.3, 128.7, 133.1, 134.9, 139.0, 155.0; IR (CHCl₃) 3320, 3018, 1652, 1526, 1444, 1216 cm⁻¹; MS (EI) *m/z* 252 (M⁺, 100), 208 (10), 160 (64), 142 (23), 132 (44); HRMS (EI) calcd for C₁₆H₁₆N₂O 252.1263, found 252.1246.

***N*-Propyl-*N'*-(phenylmethylpiperazinyl)-urea (22):** According to Method A, using carbamoyl chloride **5** (0.419 g, 1.74 mmol) and n-propylamine (1.026 g, 17.4 mmol) urea **22** was isolated as a white solid (0.359 g, 79 %).

According to Method B, using tertiary amine **15** (0.605 g, 2.04 mmol), BTC (0.220 g, 0.74 mmol) in CH₂Cl₂ (10 mL), then n-propylamine (1.206 g, 20.4 mmol), urea **22** was obtained as a white solid (0.515 g, 96 %): mp 110°C; ¹H NMR δ 0.91 (t, *J* = 7.4 Hz, 3H), 1.25 (sext, *J* = 7.4, 2H), 2.44 (m, 4H), 3.18 (dt, *J* = 7.4 Hz, *J* = 7.0 Hz, 2H), 3.37 (m, 4H), 3.53 (s, 2H), 4.43 (br s, 1H), 7.2-7.3 (m, 5H); ¹³C NMR δ 11.4, 23.4, 42.6, 43.7, 52.7, 63.0, 127.2, 128.3, 129.1, 137.7, 157.8; IR (KBr) 3344, 3030, 2934, 1616, 1540,

1264 cm^{-1} ; MS (EI) m/z 261 (M^+ , 52), 243 (53), 236 (8), 231 (100); HRMS (EI) calcd for $\text{C}_{15}\text{H}_{23}\text{N}_3\text{O}$ 261.1841, found 261.1841.

***N,N*-Diethyl-*N'*-(phenylmethylpiperazinyl)-urea¹⁷ (23)**: According to Method A, using carbamoyl chloride **5**, (0.221 g, 0.92 mmol) and diethylamine (0.672 g, 9.21 mmol), urea **23** was obtained as a colorless oil (0.21 g, 81 %).

According to Method B, using tertiary amine **15** (0.152 g, 0.50 mmol), BTC (0.053 g, 0.178 mmol) in CH_2Cl_2 (10 mL), then diethylamine (0.365 g, 5.0 mmol) urea **23** was obtained as a colorless oil (0.128 g, 93 %): ^1H NMR δ 1.1 (t, $J = 7.1$ Hz, 6H), 2.43 (t, $J = 4.9$ Hz, 4H), 3.2 (q, $J = 7.1$ Hz, 4H), 3.21 (t, $J = 4.9$ Hz, 4H), 3.51 (s, 2H), 7.2-7.3 (m, 5H); ^{13}C NMR δ 11.6, 40.2, 45.4, 51.4, 61.6, 125.6, 126.7, 127.6, 136.3, 162.9; IR (CHCl_3) 2998, 2936, 1628, 1422, 1216 cm^{-1} ; MS (EI) m/z 275 (M^+ , 42), 203 (11), 175 (11), 159 (35), 146 (94), 134 (74), 132 (53), 129 (37), 91 (100); HRMS (EI) calcd for $\text{C}_{16}\text{H}_{25}\text{N}_3\text{O}$ 275.1997, found 275.1995.

***N*-(*N*-Phenylmethylpiperazine)-*N'*-tetrahydroisoquinoline urea (24)**. According to Method A, using carbamoyl chloride **5** (1.135 g, 4.76 mmol), triethylamine (0.48 g, 4.76 mmol), and tetrahydroisoquinoline **1** (0.63 g, 4.76 mmol), urea **24** was obtained as a white solid (1.08 g, 68%).

According to Method B, using tertiary amine **15** (0.152 g, 0.51 mmol), BTC (0.054 g, 0.18 mmol) in CH_2Cl_2 (10 mL), then tetrahydroisoquinoline **1** (0.075 g, 0.56 mmol) and triethylamine (0.158 g, 1.54 mmol), urea **24** was obtained as a white solid (0.149 g, 87%): mp 82°C; ^1H NMR δ 2.46 (t, $J = 4.9$ Hz, 4H), 2.89 (t, $J = 5.8$ Hz, 2H), 3.32 (t, $J = 4.9$ Hz, 4H), 3.50 (t, $J = 5.8$ Hz, 2H), 3.53 (s, 2H), 4.42 (s, 2H), 7.0-7.3 (m, 9H); ^{13}C NMR δ 28.6, 44.7, 46.6, 48.8, 52.8, 63.1, 126.1, 126.4, 126.4, 127.1, 128.2, 128.8, 129.1, 133.8, 134.6, 137.7, 163.9; IR (CHCl_3) 3012, 2934, 2813, 1632, 1454, 1424, 1216 cm^{-1} ; MS (EI) m/z 335 (M^+ , 82), 203 (18), 160 (21), 146 (42), 132 (50), 91 (100); HRMS (EI) calcd for $\text{C}_{21}\text{H}_{25}\text{N}_3\text{O}$ 335.1997, found 335.2007; Anal. Calcd for $\text{C}_{21}\text{H}_{25}\text{N}_3\text{O}$ C, 75.19; H, 7.51; N, 12.53. Found: C, 74.80; H, 7.43; N, 12.55.

1-Phenylmethylcarbamoyl-piperidine-3-carboxylic acid ethyl ester (26). According to Method B, using tertiary amine **25** (0.277 g, 1.0 mmol), BTC (0.104 g, 0.35 mmol) in CH₂Cl₂ (10 mL), then benzylamine (0.536 g, 5.0 mmol), urea **26** was obtained as a colorless oil (0.220 g, 76%): ¹H NMR δ 1.23 (t, *J* = 7.1 Hz, 3H), 1.45-2.05 (m, 4H), 2.50 (sept, *J* = 4.6 Hz, 1H), 3.15-3.27 (m, 2H), 3.52 (dt, *J* = 13.4 Hz, *J* = 4.6 Hz, 1H), 3.87 (dd, *J* = 13.4 Hz, *J* = 3.7 Hz, 1H), 4.12 (q, *J* = 7.1 Hz, 2H), 4.38-4.41 (m, 2H), 5.03 (br s, 1H), 7.23-7.33 (m, 5H); ¹³C NMR δ 14.0, 23.9, 26.9, 40.9, 44.1, 44.7, 46.0, 60.5, 126.9, 127.4, 128.3, 139.5, 157.3, 173.3; IR (CHCl₃) 3352, 3062, 2986, 2940, 1728, 1632, 1523, 1230 cm⁻¹; MS (EI) *m/z* 290 (M⁺, 95), 245 (13), 217 (36), 156 (100), 106 (80), 91 (62); HRMS (EI) calcd for C₁₆H₂₂N₂O₃ 290.1630, found 290.1632.

1-Phenylmethylcarbamoyl-piperidine-2-carboxylic acid ethyl ester (28). According to Method B, using tertiary amine **27** (0.277 g, 1.0 mmol), BTC (0.104 g, 0.35 mmol) in CH₂Cl₂ (10 mL), then benzylamine (0.536 g, 5.0 mmol), urea **28** was obtained as a colorless oil (0.150 g, 51%): ¹H NMR δ 1.24 (m, 4H), 1.29-1.73 (m, 4H), 2.24 (br d, *J* = 11.4 Hz, 1H), 3.16 (td, *J* = 12.1 Hz, *J* = 3.2 Hz, 1H), 3.51 (br d, *J* = 12.1 Hz, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 4.44 (s, 2H), 4.91-5.03 (m, 2H), 7.22-7.33 (m, 5H); ¹³C NMR δ 14.2, 20.4, 24.7, 26.7, 41.2, 44.8, 53.7, 60.9, 127.1, 127.5, 128.5, 139.4, 158.6, 172.2; IR (CHCl₃) 3378, 3014, 2942, 1730, 1636, 1522, 1216 cm⁻¹; MS (EI) *m/z* 290 (M⁺, 9), 244 (54), 217 (88), 149 (11), 91 (48), 84 (100); HRMS (EI) calcd for C₁₆H₂₂N₂O₃ 290.1630, found 290.1633.

1-Oxo-3,4,4a,8a-tetrahydro-1H-isoquinoline-2-carboxylic acid propylamide (29) ¹H NMR δ 0.98 (t, *J* = 7.2 Hz, 3H), 1.63 (sext, *J* = 7.2 Hz, 2H), 2.98 (m, 2H), 3.33 (q, *J* = 6.8 Hz, 2H), 4.17 (t, *J* = 6.3 Hz, 2H), 7.24 (d, *J* = 7.4 Hz, 1H), 7.37 (t, *J* = 7.4 Hz, 1H), 7.50 (t, *J* = 7.4 Hz, 1H), 8.07 (d, *J* = 7.7 Hz, 1H), 9.51 (br s, 1H); ¹³C NMR δ 11.4, 22.7, 27.9, 41.6, 42.3, 127.0, 127.2, 129.0, 129.3, 133.1, 139.8, 154.9, 167.4; IR (CHCl₃) 3286, 3014, 2964, 2934, 1702, 1650, 1604, 1540, 1470, 1460, 1394, 1320, 1228, 1216 cm⁻¹; MS (EI) *m/z* 232 (M⁺, 69), 203 (100), 174 (80), 147 (54), 146 (55), 130 (50), 118 (38), 103 (20), 91 (34).

III - Radiochemistry

[¹¹C]Phosgene was prepared according to a described method¹⁸ from [¹¹C]methane produced in the ¹⁴N(p, α)¹¹C nuclear reaction at the Cyceron Center of Caen (CGR MeV 325 cyclotron). A mixture of chlorine and [¹¹C]methane was passed through an empty quartz tube heated at 560°C and [¹¹C]Carbon tetrachloride formed in the reaction was oxidized on line (Fe/320°C) into [¹¹C]phosgene. A typical bombardment (5 μA; 5-10 min, 16 MeV protons) gave 555 - 1850 GBq (15-50 mCi) of [¹¹C]phosgene. Radioactivity was measured in an ion chamber. Identification of the labeled compounds and measures of the radiochemical purities were determined by radio-TLC using a Berthold automatic TLC-linear analyser and authentic stable isotope samples as reference.

To optimize rapidly the synthesis, a careful adjustment of TLC parameters was achieved (Table S1). The eluents were chosen in order to separate all the ¹¹C-labelled compounds able to be present in the crude reaction mixture (phosgene, carbamoyl chloride, symmetrical urea, and eventually unsymmetrical urea, carbamate and amide).

[¹¹C]Chlorocarbamates.

Method A. [¹¹C]Phosgene was trapped in toluene, THF or CH₂Cl₂ (1.5 mL) cooled to -78°C. After 5 min at -78°C, the cooling bath was removed and the mixture was diluted by addition of a co-solvent (1.5 mL). For the different attempts, a fraction of this solution (100 - 400 μL) containing 10-70 MBq of [¹¹C]phosgene was transferred, at rt, through a septum, into a vial (l: 400 mm, d: 10 mm) containing the tertiary amine in a solvent. The mixture was stirred for 5 min at a given temperature. The reaction was stopped by addition of aqueous ammonium chloride (200 μL). A rapid liquid-liquid extraction using CH₂Cl₂, separated basic from non-basic components. The radioactivity of the organic and aqueous layers were measured and each fraction was analyzed by radio-TLC and/or by LC.

Method B. [¹¹C]Phosgene was trapped in a solution of tertiary amine (15 mg) in CH₂Cl₂ or THF (1.5 mL) cooled to -78°C. After 5 min at -78°C, the cooling bath was removed and the ¹¹C-chlorocarbamate (0.55 - 1.85 GBq, 15 - 50 mCi) was either analyzed by TLC (or LC) and immediately used in further reactions.

1,2,3,4-Tetrahydroisoquinoline-2-([¹¹C]-carbonyl) chloride ([¹¹C]2).

Method A: From tertiary amine **13d** (53 μmol), CH₂Cl₂, [¹¹C]phosgene (1.9 MBq, 78.9 mCi), the target compound [¹¹C]2 (756MBq, 20.4 mCi) was obtained in 45 % decay corrected (16 min total synthesis time from [¹¹C]CH₄), purity > 98%). LC R_t = 12.7 min (column: Nucleosil 100 5-CN, 300 x 7.8 mm), λ: 264 nm, eluent: hexane/CH₂Cl₂ (v:v 85/15), flow: 0.5 mL.min⁻¹.

4-(Phenylmethyl) piperazine-1-([¹¹C]-carbonyl) chloride ([¹¹C]5). Using the same procedure, starting from piperazine **15**, and [¹¹C]phosgene (2.1 GBq, 58.6 mCi) ([¹¹C]5 was isolated (734 MBq, 19.8 mCi) in 58 % yield (decay corrected from EOB, 16 min total synthesis time, 96% radiochemically pure). LC R_t = 12.7 min (column: Nucleosil 100 5-CN, 300 x 7.8 mm), λ: 254 nm, eluent: hexane/CH₂Cl₂ (v:v 90/10), flow: 1 mL.min⁻¹

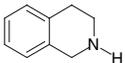
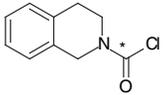
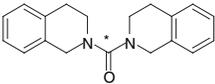
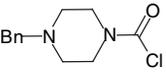
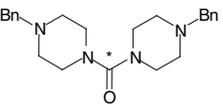
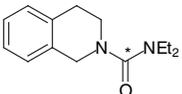
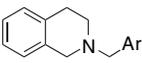
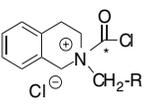
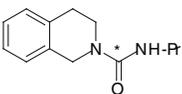
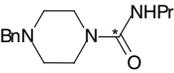
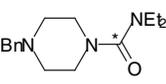
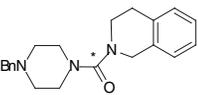
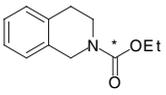
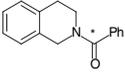
Typical procedure for the preparation of [¹¹C]ureas . To a solution of amine (1 mmol) in CH₂Cl₂ (0.150 mL) was added carbamoyl chloride [4 - 400 MBq.(1 - 1.1 mCi)] in THF-CH₂Cl₂ (v:v 50/50, 0.3 mL). After 5 min at rt, an aqueous ammonium chloride solution (saturated, 0.200 mL) was added. The mixture was extracted with CH₂Cl₂ (2 x 0.5 mL) and the radioactivity in both layers was counted to afford the crude radiochemical yield (decay corrected to EOB, 25 min). Analysis by radio-TLC, co-elution with reference compounds under different conditions, showed two radioactive spots: the unreacted [¹¹C]carbamoyl chloride and the expected [¹¹C]urea when it was formed. The conditions of radio-TLC analysis, and the *R_f* of the compounds that could be observed in the reaction, are given in Table S1.

N-Ethoxy-[¹¹C-carbonyl]-1, 2, 3, 4-tetrahydroisoquinoline] ([¹¹C]30). To a solution of sodium ethanoate (10 mg, 0.15 mmol) in ethanol (0.2 mL) was added carbamoyl chloride [¹¹C]2 2.3 MBq (0.064 mCi) in THF-CH₂Cl₂ (50:50). The mixture was allowed to react for 5 min at rt. Addition of aqueous ammonium chloride (saturated, 0.2 mL) and rapid extraction with CH₂Cl₂ (2 x 0.5 mL) gave an organic layer containing 80% of the starting activity with carbamate [¹¹C]30 (74%) and unreacted starting material [¹¹C]2 (26%).

Typical procedure for the reaction of PhMgBr or Ph₂CuMgBr.BrMgCN with carbamoyl chloride [¹¹C]2.

N-([¹¹C]benzoyl)-1,2,3,4-tetrahydroisoquinoline ([¹¹C]31). To a solution of carbamoyl chloride [¹¹C]2 (3.7 MBq, 0.1 mCi) in THF (0.350 mL) cooled to -30°C was added a solution of the organometallic (PhMgBr: 0.1 -0.2 mL, c = 0.6 mol.L⁻¹, 70 - 140 μmol; Ph₂CuMgBr.BrMgCN: 0.2 mL, 56 μmol, 0.3 mol.L⁻¹). The mixture was allowed to react for 5 min at -30°C. Addition of aqueous ammonium chloride (saturated, 0.2 mL) and rapid extraction with CH₂Cl₂ (2 x 0.5 mL) gave, the amide [¹¹C]31 with unreacted starting carbamoyl chloride [¹¹C]2 (relative ratio: 54/46) in the organic layer [1.99 MBq (0.054 mCi) or 52% of the starting activity, decay corrected]).

Table S1. TLC data (silica gel)

Compound	Eluent v:v:v	A: pentane/AcOEt/NEt ₃ 7/2/1	B: pentane/AcOEt 1/1	C: pentane/AcOEt 8/2
1		0.8	0.65	
2		0.5	0.85	
3			0.6	
5			0.67	
6		0.25		
7		0.65		
13c or 13d			0.3 - 0.4	
14c or 14d			0.1- 0.2	
19		0.2	0.3	
22		0.2	0.15	
23		0.6		
24		0.45	0.2	
30			0.9	0.55
31			0.9	0.6

References

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