Electronic Supplementary Material (ESI) for Chemical Communications

Electronic Supplementary Information

Rapid and efficient synthesis of [^{11}C]ureas via the incorporation of [^{11}C]CO_2 into aliphatic and aromatic amines

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Contents:

General Method and materials:

All chemicals were purchased from Sigma-Aldrich and Alfa Aesar and used as received. Solvents were purchased from Fisher Scientific and Sigma-Aldrich. Thin-layer chromatography plates (TLC) were purchased from Merck, hexane: ethyl acetate were used as the mobile phase and detected by 254 nm UV light. Infra-Red spectra were acquired on a PerkinElmer spectrum 100FTIR. ^{1}H and ^{13}C-NMR spectra were obtained using a BRUKER DRX 400 MHz spectrometer. Mass spectroscopy was performed using on an Agilent 6520 Accurate-Mass Q-TOF LC/MS connected to an Agilent 1200 HPLC system with UV detector and autosampler.
HPLC Analysis was performed on an Agilent 1200 system with UV detector (254 nm) and radio-detector coupled in a series. Agilent Eclipse XDB-C18 reverse-phase column (4.6 x 150mm, 5µm) was used as column and flow rate of 1 ml/min.

General procedure for preparation of reference compounds:

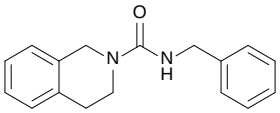
All reference compounds can be purchased from Sigma-Aldrich except for N-benzyl-3,4-dihydroisoquinoline-2(1H)-carboxamide and 1,3-dibenzyl-1-methylurea.

Reference compounds were synthesised using the procedure reported by Peterson *et. al.*[1] and Padiya *et. al.*[2]

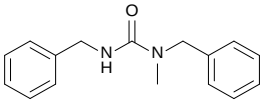
Procedure 1:
CO_2 gas was bubbled into a solution containing 10% DBU and a primary amine (1 mmol) in acetonitrile for 1 hour at room temperature. A secondary amine (1.5 mmol) was added to the reaction mixture and the vial was flushed with N_2. In a separate vial, PBu_3 (3 mmol) was added into a solution containing DBAD (3 mmol) in MeCN under nitrogen atmosphere. The solution was then added to the mixture dropwise and stirred at room temperature for 2 hours under nitrogen. The crude product was concentrated and purified by flash chromatography (hexane: ethyl acetate).

Procedure 2:

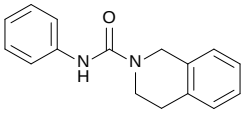
Amine (1 mmol) in water was stirred at 0 ^{o}C for 10 min. carbonyldiimidazole (1.2 mmol) was added and stirred for 1 hour at 0 ^{o}C. The reaction mixture was then warmed to room temperature and monitored by TLC. After complete conversion of amine to caronylimidazolide, an amine was added and the mixture stirred at room temperature for 3 hours. Reaction mixture was extracted with ethyl acetate and the organic layer was dried with MgSO4, concentrated, and purified by column chromatography.



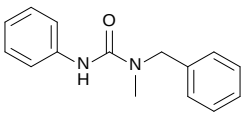
N-benzyl-3,4-dihydroisoquinoline-2(1H)-carboxamide; colourless solid; 48% yield; IR 3316.16, 2927.85, 1620.80 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 - 7.37 (m, 4H), 7.06 – 7.25 (m, 6H), 4.55 (s, 2H), 4.40 (d, J-5.7 Hz, 2H), 3.60 (t, J= 5.6 Hz, 2H), 2.8 (t, J=6.0, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.52, 139.75, 135.22, 133.58, 128.93, 128.66, 128.27, 127.66, 126.95, 126.53, 126.69, 45.82, 45.34, 41.42, 29.38; LCMS calculated for $C_{17}H_{18}N_2O$ $[M+H]^+$ = 267.1492; found 267.1502.



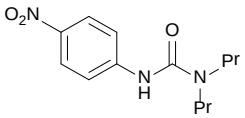
1,3-dibenzyl-1-methylurea; colourless solid; 46% yield; IR 3343.80, 2936.59, 1620.79 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.22 (m, 10H), 4.67 (s, 1H), 4.51 (s, 2H), 4.42 (s, 2H), 2.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.5, 139.8, 138.2, 128.9, 128.8, 127.8, 127.4, 127.4, 127.4, 52.5, 45.2, 34.7; HRMS calculated for $C_{16}H_{18}N_2O$ $[M+H]^+$ = 255.1492; found 255.1396.



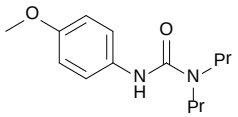
***N*-phenyl-3,4-dihydroisoquinoline-2-carboxamide**; IR 3252.26, 2913.06, 1631.83 cm^{-1}; ^{1}H NMR NMR (400 MHz, $CDCl_3$) δ7.35 (m, 9H), 4.40 (s, 2H), 3.50 (t, J= 6.0, 2H), 3.00 (T, J=5.9, 2H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.1, 139.2, 135.2, 133.3, 129. 2, 128.8, 127.4, 126.6, 126.1, 123.7, 120.2, 45.9, 41.4, 28.1; HRMS calculated for $C_{16}H_{16}N_2O$ $[M+H]^+$= 253.1335; found 253.1360.



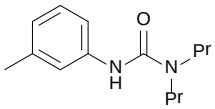
1-benzyl-1-methyl-3-phenylurea; IR 3278.14, 2918.03, 1643.22 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ7.40 – 7.00 (m, 10H), 6.30 (s, 1H), 4.58 (s, 2H), 3.00 (s, 3H); HRMS calculated for $C_{15}H_{16}N_2O$ $[M+H]^+$= 241.1335; found 241.1399.



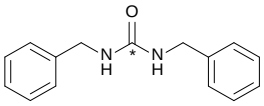
1,1-dipropyl-3-(4-nitropheyl)urea; IR 3315.14, 2961.03, 1630.22 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 – 8.15 (m, 2H), 7.35 – 7.45 (m, 2H), 3.25 (t, 6.9, 4H), 1.60 (s, J=6.4, 4H), 1.85 (t, 6.9, 6H); HRMS calculated for $C_{13}H_{19}N_3O_3$ $[M+H]^+$= 266.1426; found 266.1443.



3-(p-anisyl)-1,1-dipropylurea; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.52 (m, 2H), 6.62 – 6.78 (m, 2H), 3.72 (s, 3H), 3.25 (t, 6.9, 4H), 1.58 (s, J=6.4, 4H), 0.85 (t, 6.5, 6H); HRMS calculated for $C_{14}H_{22}N_2O_2$ $[M+H]^+$= 251.1681; found 251.1722.



1,1-dipropyl-3-(m-tolyl)urea; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (m, 1H), 7.24 (m, 2H), 6.94 (m, 1H), 3.21 (t, 6.9, 4H), 2.28 (s, 3H), 1.61 (s, J=6.4, 4H), 0.83 (t, 6.5, 6H); HRMS calculated for $C_{14}H_{22}N_2O$ $[M+H]^+$= 235.1732; found 255.1729.



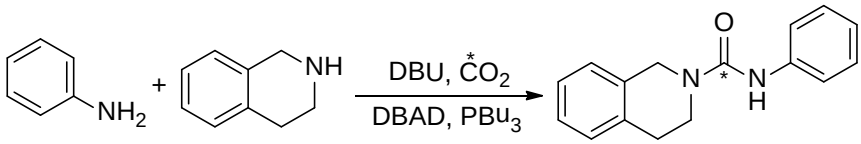
Dibenzylurea; colourless solid; yield = 65% yeild; IR 3343.80, 2936.59, 1620.79 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.26 (m, 10H), 4.33 (s, 4H); HRMS calculated for $C_{15}H_{16}N_2O$ $[M+H]^+$ = 241.1335; found 241.1377.

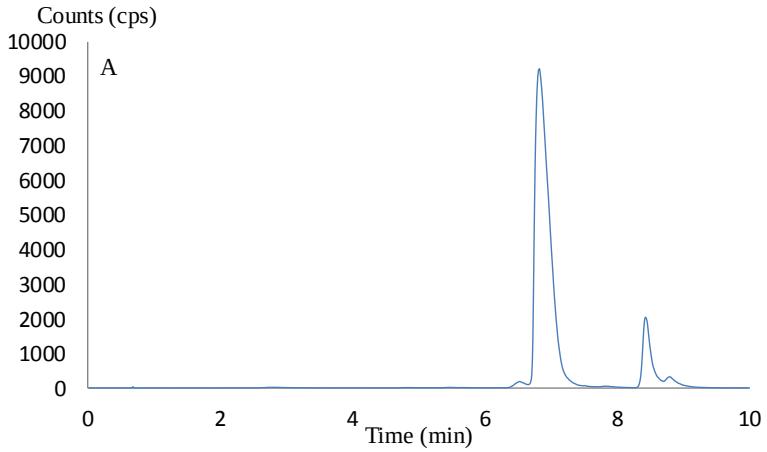
General radiolabelling procedure:

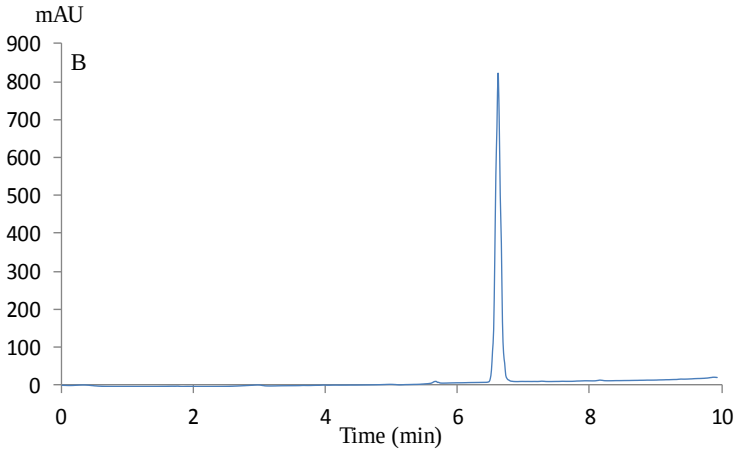
[^{11}C]CO_2 from the cyclotron target was bubbled in a stream of helium gas at a flow rate of 1.4 ml/min post target depressurisation directly into a solution containing a primary amine, a secondary amine and DBU in acetonitrile for one minute. The solution was stirred at 50 ^{o}C for one minute. Tributylphosphine was added to di-tert-butyl azodicarboxylate in acetonitrile under nitrogen atmosphere and the solution transferred to the reaction mixture. The crude product was analysed by HPLC (gradient, 5% to 95%,H_2O : MeOH).

The specific activity of the product were in the range of 50-60 GBq/µmol, similar in magnitude to other ^{11}C-labelled compounds produced at this laboratory.

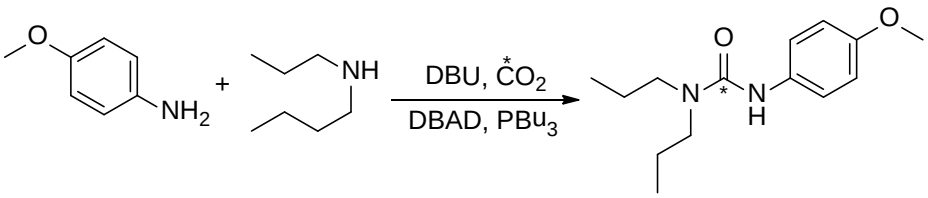
Similar Radiochemical yields were observed when secondary amines were added before bubbling [^{11}C]CO_2 and after [^{11}C]CO_2 however, bubbling [^{11}C]CO_2 in the presence of both amines trapped [^{11}C]CO_2 slightly more efficiently (92% and 95% respectively).

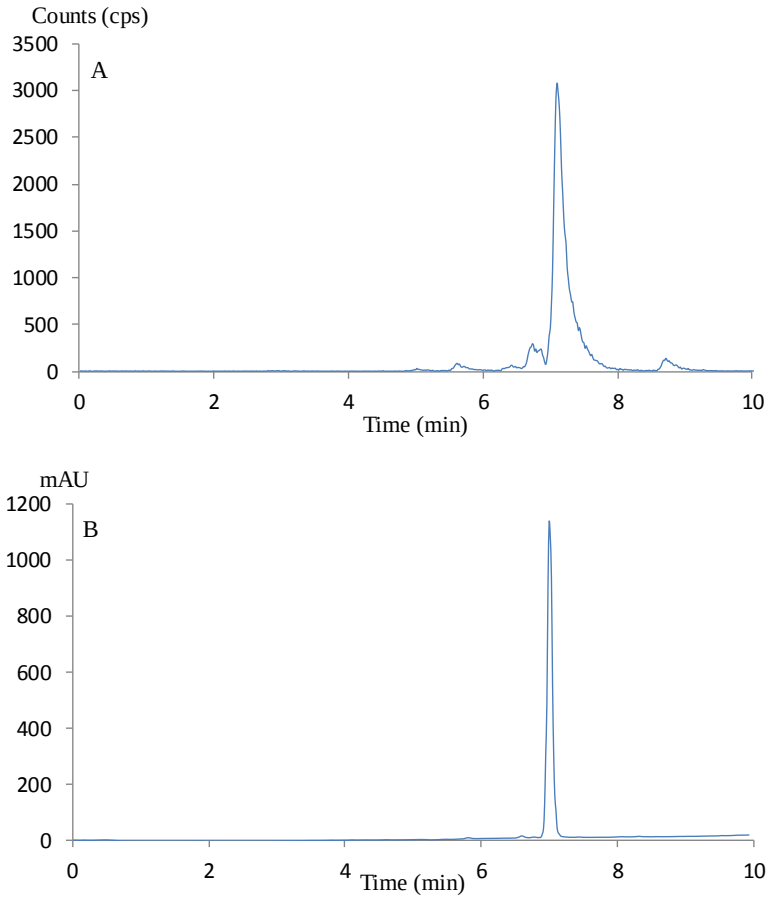






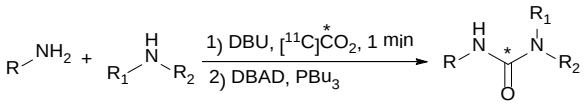
A) HPLC Radiochromatogram the crude product for the synthesis of [^{11}C]N-phenyl-3,4 dihydroisoquinoline-2-carboxamide. B) HPLC chromatogram of the reference compound *N*-phenyl-3,4-dihydroisoquinoline-2-carboxamide.

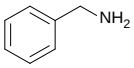
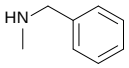
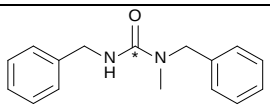
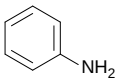
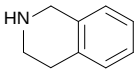
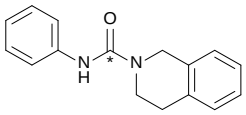
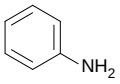
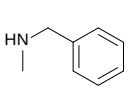
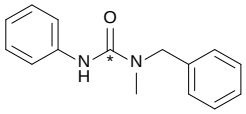
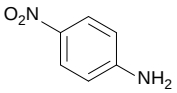
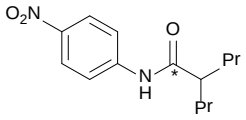
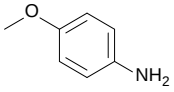
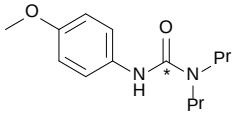
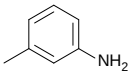
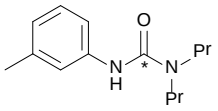
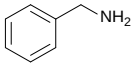
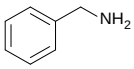
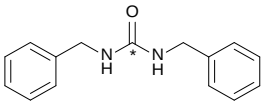




A) HPLC Radiochromatogram the crude product for the synthesis of [^{11}C] 3-(p-anisyl)-1,1-dipropylurea. B) HPLC chromatogram of the reference compound 3-(p-anisyl)-1,1-dipropylurea.

Radiolabelling various aliphatic, benzylic and aromatic amines with $[^{11}C]CO_2$.



Entry	R-NH_2	R_1NHR_2	Product	RCY (%)
1				74 ± 9
2				94 ± 2
3				69 ± 6
4				85 ± 6
5				83 ± 5
6				80 ± 10
7				19 ± 15

RCYs are determined by radio-HPLC.

References:

1. S. Peterson, S. Stucka, and C. Dinsmore, *Org. Lett.*, **2010**, *12*, 6, 1340.
2. K. Padiya, S. Gavade, B. Kardile, M. Tiwari, S. Bajare, M. Mane, V. Gaware, S. Varghese, D. Harel, and S. Kurhade, *Org. Lett.*, **2012**, *14*, 11, 2814.