ChemComm

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COMMUNICATION

View Article Online
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Cite this: *Chem. Commun.*, 2013, **49**, 8193

Received 29th May 2013,
Accepted 29th July 2013

DOI: 10.1039/c3cc44046j

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# 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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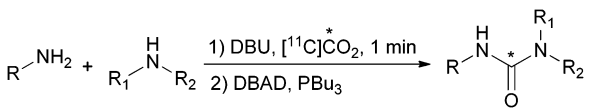
**A rapid urea radiolabelling methodology has been developed. [$^{11}$C]$CO_2$ was activated by 1,8-diazabicycloundec-7-ene (DBU) in the presence of aliphatic and aromatic amines and reacted with Mitsunobu reagents to produce asymmetric $^{11}$C radiolabelled ureas in high radiochemical yields.**

Positron emission tomography (PET) is a non-invasive molecular imaging technique that is used for medical diagnosis, drug development, and the understanding of normo- and pathophysiology.[1] Carbon-11 ($t_{1/2}$ = 20.4 min) is a commonly used radio-isotope for PET imaging, the ubiquity of carbon in all naturally occurring organic compounds making it an attractive radio-isotope for molecular imaging. Substituting carbon-12 ($^{12}$C) in biologically active molecules with radioactive $^{11}$C has no effect on the chemistry or the biological activity of the molecule.[2] Cyclotron-produced $^{11}$C is commonly prepared in the form of [$^{11}$C]carbon dioxide ([$^{11}$C]$CO_2$) by the $^{14}$N(p,α)$^{11}$C nuclear reaction. Due to its poor reactivity, [$^{11}$C]$CO_2$ is typically converted into more reactive synthons such as [$^{11}$C]methyl iodide or triflate and subsequently used to radiolabel molecules of biological interest.[3] Although these labelling synthons are useful, not all target molecules are accessible by these synthons and their preparation takes several minutes with a concomitant decrease in $^{11}$C radioactivity due to decay. The development of methods to efficiently label compounds directly with [$^{11}$C]$CO_2$ is therefore of significant interest.

To overcome the low reactivity of $CO_2$, bases such as 1,8-diazabicycloundec-7-ene (DBU) or 2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (BEMP) have recently been utilised as $CO_2$ activating agents in the synthesis of $^{11}$C-labelled organic molecules.[4,5] These methods, however, produce very poor yields for unreactive aromatic amines, or the reactions are limited to a specific product.[6]




**Scheme 1** Synthesis of [$^{11}$C]urea with [$^{11}$C]$CO_2$.

We report herein a rapid [$^{11}$C]$CO_2$ radiolabelling methodology which overcomes these limitations. DBU was used to trap the cyclotron-produced [$^{11}$C]$CO_2$ which was subsequently reacted with aliphatic, benzylic and aromatic amines (Scheme 1) to synthesise [$^{11}$C]ureas in a highly efficient manner.

Ureas are found in a plethora of biologically active molecules as has been extensively reported in the literature.[7] The method reported herein provides a methodology to label this class of compounds with carbon-11.

Model reactions were initially conducted using nonradioactive $CO_2$.[8] Compound **3** was subsequently chosen as the initial model reaction for optimisation with [$^{11}$C] $CO_2$.

[$^{11}$C]$CO_2$ from the cyclotron target was bubbled in a stream of helium gas at a flow rate of 1.4 ml min$^{-1}$ 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 for one minute prior to the addition of Mitsunobu reagents di-*tert*-butyl azodicarboxylate (DBAD) and tributylphosphine ($PBu_3$).

Initially, experiments were performed in a number of different solvents at 40 °C (Table 1, entries 1–3) with the aim of identifying the best solvent for the reaction. Acetonitrile trapped cyclotron-produced [$^{11}$C]$CO_2$ very efficiently when bubbled directly into the reaction mixture (>95%), while DMSO and DMF were slightly less efficient (80–90%).

Moderate radiochemical yields (46%) of the desired [$^{11}$C]ureas were observed using acetonitrile as a solvent while DMF and DMSO gave yields of 13% and 18% respectively, despite good [$^{11}$C]$CO_2$ trapping (Table 1). Acetonitrile was therefore selected as the solvent of choice for subsequent reactions.

RCY was determined by radio-HPLC and defined as the amount of labelled [$^{11}$C]urea as a percentage of the cyclotron-produced

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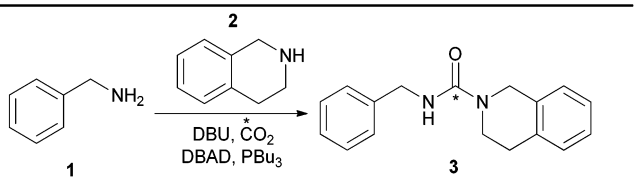
† Electronic supplementary information (ESI) available. See DOI: 10.1039/c3cc44046j

**Table 1** Reaction optimisation




| Entry[a] | Solvent | $T$ (°C) | Time (min) | RCY[b] (%) |
|---|---|---|---|---|
| 1 | MeCN | 40 | 5 | 46 ± 7 |
| 2 | DMF | 40 | 5 | 13 ± 3 |
| 3 | DMSO | 40 | 5 | 18 ± 6 |
| 4[c] | MeCN | 25 | 5 | 0 |
| 5 | MeCN | 25 | 5 | 8 ± 1 |
| 6 | MeCN | 60 | 5 | 26 ± 12 |
| 7 | MeCN | 50 | 5 | 95 ± 3 |
| 8 | MeCN | 50 | 1 | 96 ± 2 |

[a] Reaction conditions: primary amine (18.3 μmol), secondary amine (27.5 μmol), DBU (0.8 μmol), Mitsunobu reagents (36.6 μmol) in 400 μmol acetonitrile. $n$ = 3. [b] Determined by radio-HPLC. [c] Reduced concentration.[9]

$[^{11}C]CO_2$ trapped in solution obtained directly from the cyclotron and corrected for radioactive decay.

When the reactions were carried out at lower reagent concentrations (Table 1, entry 4), no $[^{11}C]$radiolabelled product was observed despite efficient $[^{11}C]CO_2$ trapping.[9]

The temperature dependency of the reaction was subsequently examined. Loss of $[^{11}C]CO_2$ from the reaction vial was observed when the reactions were performed at 60 °C. Reactions at 50 °C avoided these losses and resulted in over 95% incorporation of the $[^{11}C]CO_2$ into the target radiolabelled molecules (Table 1, entry 7). Reducing the reaction time from 5 to 1 minute still resulted in a RCY of 96% (Table 1, entry 8 and Fig. 1).

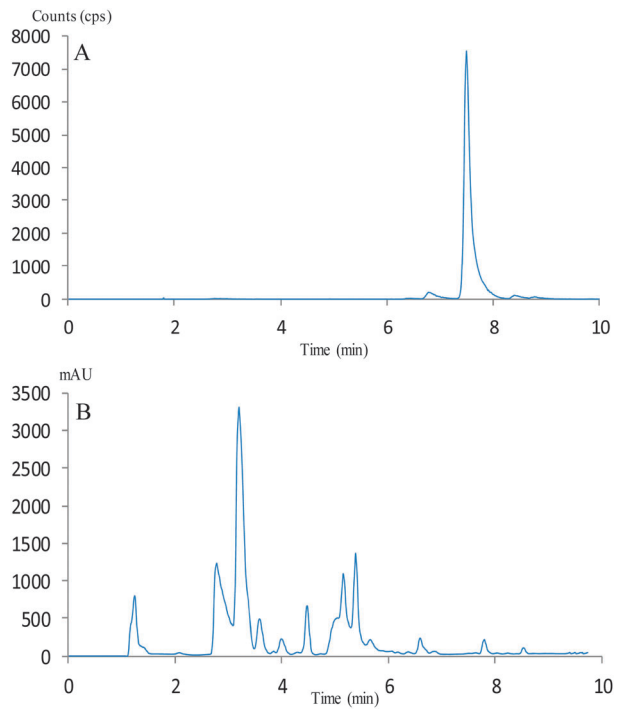
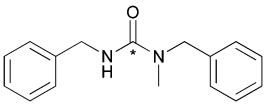
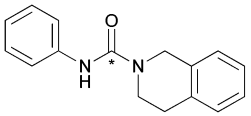
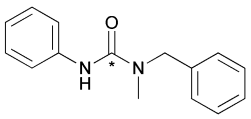
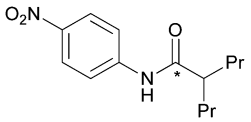
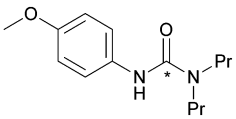
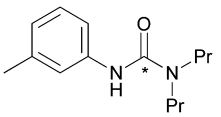
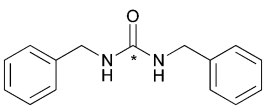



**Fig. 1** HPLC chromotogram of the crude radiolabelled product (Table 1, entry 8). (A) Radioactivity (counts per second) target compound **3** at $R_t$ 7.30 min. (B) UV absorption (254 nm) of compound **1** at $R_t$ 3.25 min, compound **2** $R_t$ 3.45 min and by-products at 5.00 min, 5.30 min and 5.50 min.

**Table 2** Radiolabelling various aliphatic, benzylic and aromatic amines with $[^{11}C]CO_2$

| Entry[a] | Product | RCY[b] (%) |
|---|---|---|
| 1 |  | 74 ± 9 |
| 2 |  | 94 ± 2 |
| 3 |  | 69 ± 6 |
| 4 |  | 85 ± 6 |
| 5 |  | 83 ± 5 |
| 6 |  | 80 ± 10 |
| 7 |  | 19 ± 15 |

[a] $n$ = 3. [b] Determined by radio-HPLC. Reaction conditions: $[^{11}C]CO_2$, primary amine (18.3 μmol), secondary amine (27.5 μmol), DBU (0.8 μmol) in 400 μmol acetonitrile heated at 50 °C for 1 min. Mitsunobu reagents (36.6 μmol) added and stirred for 1 min.

The conditions for the model reaction were subsequently applied to the radiosynthesis of various asymmetric ureas using a range of aliphatic, benzylic and aromatic amines (Table 2).

The reactions between benzylic primary amines and the secondary amine, tetrahydroisoquinoline (Table 1, entry 8) resulted in high RCY while the reaction with *N*-methylbenzylamine produced slightly lower yields of the $[^{11}C]$urea (Table 2, entry 1). The high yields for tetrahydroisoquinoline can be explained by the rigidity of the molecule, having a locked planer confirmation and less steric hindrance.

Interestingly, RCYs of similar magnitudes were observed when a less reactive aromatic primary amine was used in place of a benzylic amine to form the target radiolabelled molecules (Table 2, entries 2 and 3).

The effect of functional groups on aromatic amines was also studied. Reactions with the electron rich aromatic amines *m*-toluidine, and *p*-anisidine resulted in over 80% RCY (Table 2, entries 5 and 6) and even poor nucleophiles such as

4-nitroaniline reacted efficiently, producing high RCY of 85% (Table 2, entry 4). The reaction favours the formation of asymmetric [$^{11}$C]ureas despite primary amines being present in excess of [$^{11}$C]$CO_2$. In the absence of secondary amines, various by-products are observed resulting in reduced RCY (Table 2, entry 7).

In conclusion, a rapid and robust methodology for the radiosynthesis of ureas has been developed. The method incorporates [$^{11}$C]$CO_2$ directly into aliphatic, benzylic and aromatic amines producing the target radiolabelled ureas in high RCY. Overcoming limitations of previous methods, even poorly reactive aromatic amines gave excellent RCY's of asymmetric [$^{11}$C]ureas within one minute after the addition of Mitsunobu reagents.

This novel radiolabelling methodology opens up new possibilities for $^{11}$C radiolabelling molecules for *in vivo* molecular imaging applications.

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9 Reduced concentration conditions: primary amine (6.1 μmol), secondary amine (9.1 μmol), DBU (0.3 μmol), Mitsunobu reagents (12.2 μmol) and 400 μmol acetonitrile.