JOURNAL OF LABELLED COMPOUNDS AND RADIOPHARMACEUTICALS
J Label Compd Radiopharm 2006; **49**: 321–330.
Published online in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/jlcr.1052

Research Article

One-pot synthesis of [^{11}C]ureas via triphenylphosphinimines

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Summary

A series of ^{11}C-labeled ureas was prepared using a rapid and efficient one-pot procedure. First, the intermediate [^{11}C]phenylisocyanate was formed with phenyl-triphenylphosphinimine and [^{11}C]CO_2. A range of amines was then reacted with the [^{11}C]phenylisocyanate yielding the [^{11}C]urea derivatives in short synthesis times. This easy-to-handle method circumvents disadvantages of known procedures and generates the possibility to prepare other kinds of ^{11}C-labeled compounds using a variety of phenylphosphinimines in combination with different nucleophiles. The presented approach is an alternative to the use of established methods in ^{11}C-labeling chemistry. Copyright © 2006 John Wiley & Sons, Ltd.

Key Words: [^{11}C]CO_2; [^{11}C]isocyanates; phosphinimines; ^{11}C-labeled ureas

Introduction

Positron emission tomography (PET) is a powerful technique for determining noninvasively the *in vivo* biodistribution of compounds labeled with positron-emitting radionuclides. The demand for new radiolabeling methods is growing with the increasing use of PET throughout drug development processes and medical imaging. The radioisotope ^{11}C is very valuable for this purpose, since it permits the radiosynthesis of the native compound. However, one has to take into account that there is a relative limited number of labeled synthons (e.g. [^{11}C]CO_2, [^{11}C]CH_4) or those rapidly prepared from them (e.g. [^{11}C]CH_3I)[1] as well as a desire to introduce the radioisotope as late as possible during the synthesis, because of the half-life of ^{11}C (20.3 min). Since the molecular complexity and diversity of biologically active compounds have

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Received 19 December 2005
Revised 2 January 2006
Accepted 2 January 2006

increased, there is a need for new and simple methodologies that give access to ^{11}C-labeled pharmaceuticals in short synthesis times and in high yields. Preferably, these general methodologies are suitable for automation.

A structural element that can often be found in biologically active compounds is the urea group.[2–5] So far, ^{11}C labeling of ureas in the carbonyl function has been performed mainly starting from [^{11}C]phosgene. In this paper, an efficient synthesis of [^{11}C]ureas via triphenylphosphinimines and [^{11}C]CO_2 is described. This procedure appeared to be simple and fast and is therefore a powerful tool to circumvent the disadvantages of established methods that use phosgene ($COCl_2$) or its substitutes. The scope of this reaction was demonstrated with a diversity of amines.

Results and discussion

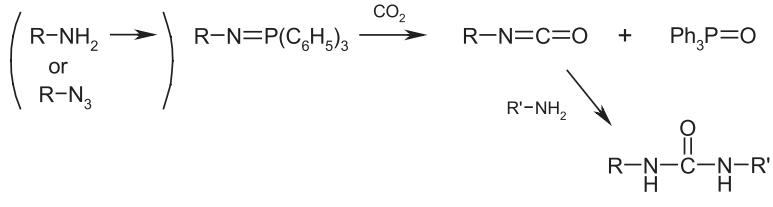
The most common procedure for the synthesis of ureas, with the ^{11}C label in the carbonyl function, requires the preparation of the intermediate [^{11}C]phosgene.[6–10] However, [^{11}C]phosgene is obtained via multistep syntheses in low radiochemical yields and with relatively long reaction times (approx. 20 min).[6,8,10] Synthetic routes to isocyanates and ureas with phosgene substitutes have also been described. Trichloromethyl chloroformate (diphosgene)[11] was one of the first substitutes affording certain unlabeled isocyanates in excellent yields. Carbon dioxide has also been used in methods that avoid the preparation of phosgene, for example, [^{11}C]urea has been prepared via [^{11}C]cyanamide[12] starting from [^{11}C]CO_2. More general syntheses of ureas have been done in three-step-reactions via dehydration of intermediary formed carbamate salts starting from [^{11}C]- or [^{14}C]CO_2[13,14] or via Mitsunobu chemistry starting from [^{12}C]CO_2.[15,16] More recently, [^{11}C]CO has gained more attention as a radioactive synthon.[17,18] Its major drawbacks (low reactivity and harsh reaction conditions) have been overcome by using known palladium-catalyzed carbonylation reactions in combination with [^{11}C]CO,[19,20] and selenium-mediated syntheses of ^{11}C-carbamoyl compounds.[21] But still, it has been proven to be difficult to trap [^{11}C]CO in a reaction mixture using conventional methods, i.e. by leading the radioactive precursor with a carrier gas into a solution.[22] Because of the low solubility of [^{11}C]CO, it has been necessary to develop a specific gas handling system for the preconcentration of [^{11}C]CO_2, the conversion to and recirculation of [^{11}C]CO.[19,21]

In this study, phosphinimines (iminophosphoranes)[23] were used for the synthesis of ^{11}C-labeled ureas, to circumvent the mentioned disadvantages of the described methods (i.e. the relatively large number of reaction steps, the use of catalysts or reagents such as Pd, Se or Sn reagents, and specific automation). The preparation of phosphinimines from either azides or primary amines has been described,[24–29] as well as their use in the

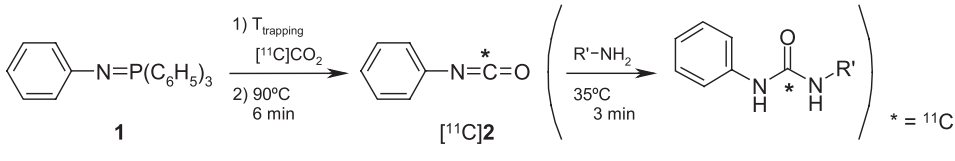
(inter- and intramolecular) synthesis of a variety of compounds.[29] The reaction of triphenylphosphinimines with carbon dioxide (Scheme 1), yielding isocyanate derivatives under mild conditions,[27,30] was particularly interesting. Here, this concept could be implemented by using [^{11}C]CO_2 instead of CO_2, for the development of a new and simple alternative method for labeling [^{11}C]ureas. Furthermore, a large versatility can be created since the phosphinimine of either the R–NH_2 or the R′–NH_2 can be prepared, depending on the ease of its preparation.

Triphenylphosphinimines have been described to have great differences in properties, from extremely hygroscopic and air sensitive to very stable (resonance-stabilized) ones.[24,26,28,30] Because of its stability[26] and commercially availability, phenyltriphenylphosphinimine (**1**, Scheme 2) was selected as the model phosphinimine to investigate the radiochemical scope of this method. The general idea was to react **1** with [^{11}C]CO_2 to obtain the ^{11}C-labeled intermediate phenylisocyanate [^{11}C]**2**, which in turn can react with different amines (R′–NH_2) to form the desired [^{11}C]urea derivatives.

The formation of the [^{11}C]phenylisocyanate ([^{11}C]**2**) intermediate was explored first. Compound [^{11}C]**2** was not isolated however, but with the aid of benzylamine (R′ = $CH_2C_6H_5$, Scheme 2) the radiochemical yield of the ^{11}C-labeled urea derivative was used as indication. [^{11}C]CO_2 was bubbled through a solution of **1** (19.6 μmol) in benzene at 15°C. This way, less than 5% of the [^{11}C]CO_2 was trapped in the reaction vial. Tetrahydrofuran (THF) was then tried as solvent, but still almost no [^{11}C]CO_2 was trapped at 15°C. Using THF in combination with a low trapping temperature of −60°C solved this problem (> 80% of the [^{11}C]CO_2 in the vial). After trapping the [^{11}C]CO_2, the mixture was heated for 6 min at 90°C (formation of [^{11}C]**2**), and finally



Scheme 1. Reaction of triphenylphosphinimines with CO_2[24,25,30]



Scheme 2. General scheme for the radiochemical synthesis of [^{11}C]ureas starting from [^{11}C]CO_2

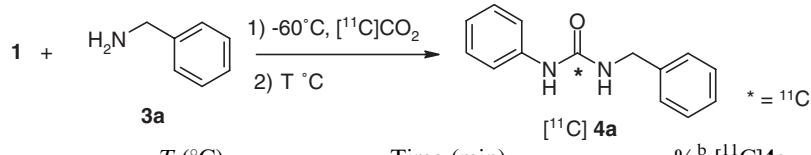
benzylamine was added (13 μmol) after which the solution was heated for another 3 min at 35°C. Urea [^{11}C]**4a** was obtained in a 33% overall yield.

Subsequently, a further simplification of the reaction conditions was explored. The possibility of having benzylamine already present in the reaction vial, together with **1**, before the trapping of the [^{11}C]CO_2, was investigated. This way, the formed isocyanate ([^{11}C]**2**) could react immediately with the amine, possibly speeding up the reaction (Table 1). The radioactivity was now trapped quantitatively in the vial (>99%), using THF at −60°C. An explanation could be the formation of a complex between the [^{11}C]CO_2 and the amine,[16] or the increased basicity of the solution due to the amine. The initial reaction temperature was chosen similar to that used earlier for the formation of [^{11}C]**2** (90°C, see Scheme 2), and these conditions gave the labeled urea [^{11}C]**4a** in a radiochemical yield of 44% (Table 1, entry 1).

With an elevated reaction temperature (110°C, Table 1, entry 2) it seemed that more product was formed in the solution. However, part of the [^{11}C]CO_2 evaporated from the solution and this caused an overall (small) decrease in the radiochemical yield. In fact, a reaction temperature of 60°C gave a comparable overall radiochemical yield of [^{11}C]**4a**, since more [^{11}C]CO_2 stayed in solution and was therefore available to react with **1** (entry 3). A reaction temperature of only 21°C decreased the radiochemical yield considerably (entry 4). Analyses of all final reaction mixtures showed that the remainder of radioactivity was mainly unreacted [^{11}C]CO_2, however, prolonged reaction times did not have a beneficial effect on the overall yields. So, trapping the [^{11}C]CO_2 at −60°C in a reaction vial containing both **1** and the amine in THF, with a subsequent reaction temperature of 60°C (6 min), appeared to be the most optimal conditions for the synthesis of [^{11}C]**4a**.

To explore the scope of this concept, the following other amines (R′–NH_2) were selected: aniline (**3b**), *n*-propylamine (**3c**) and 5-methoxy-tryptamine (**3d**). The latter amine was chosen with the view to prepare its biologically active

Table 1. Optimization of the one-pot reaction conditions



3a [^{11}C] **4a**

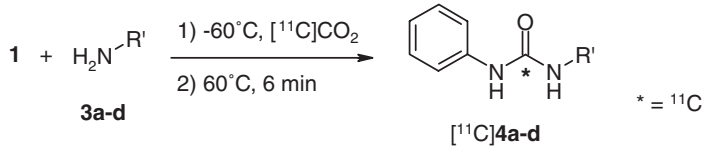
Entry[a]	*T* (°C)	Time (min)	%[b] [^{11}C]**4a**
1	90	6	44
2	110	6	43
3	60	6	45
4	21	6	21

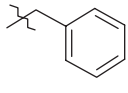
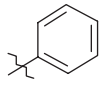
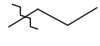
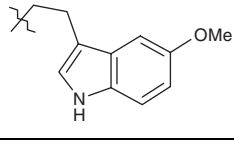
[a] 19.6 μmol **1** and 73 μmol **3a** were used, in 600 μl THF.
[b] Overall decay-corrected yield from [^{11}C]CO_2.

derivative in the future, since ureas containing a tryptamine moiety have been shown to act as antagonists to the melatonin receptor.[5] For identification purposes of the radiolabeled compounds, the unlabeled reference compounds were synthesized as well (**4a-d**, see Table 2 for corresponding labeled compounds). The asymmetric unlabeled ureas were obtained in good overall yields (70–90%) by reaction of phenylisocyanate with the corresponding primary amines in ether (rt, 0.5–3 h), according to a known literature procedure.[5] The labeled compounds [^{11}C]**4b-d** were synthesized under the same reaction conditions that were used for preparing [^{11}C]**4a**, without further optimization (Table 2). The aliphatic amines **3c** and **3d** displayed a similar behavior as our model amine **3a**, and [^{11}C]**4c** and [^{11}C]**4d** were synthesized in overall radiochemical yields of 49 and 45%, respectively. As expected, the aromatic aniline **3b** was less reactive under these conditions, giving [^{11}C]**4b** in a low yield of 8%.

In summary, [^{11}C]ureas **4a-d** were efficiently synthesized in an one-pot procedure, with decay-corrected yields ranging from 8 to 49%. This fast, simple and reproducible method includes leading the [^{11}C]CO_2 through a solution of phenyltriphenylphosphinimine (**1**) and the amine of interest in THF at −60°C, and a subsequent reaction temperature of 60°C for 6 min. In theory, a large number of triphenylphosphinimines can be used to form

Table 2. Radiosynthesis of the ^{11}C-labeled ureas



Amine	R′	μmol[a]	Product	%[b]
3a		73	[^{11}C]**4a**	46 ± 4
3b		66	[^{11}C]**4b**	8 ± 1
3c		120	[^{11}C]**4c**	49 ± 3
3d		13	[^{11}C]**4d**	45 ± 3

[a] **3a-d** (all amines in excess compared to [^{11}C]CO_2) + **1** (19.6 μmol) in 600 μl THF.
[b] Decay-corrected radiochemical yields from [^{11}C]CO_2 ($n = 3$).

intermediate [^{11}C]isocyanates using [^{11}C]CO_2. In fact, by using azides for the preparation of phosphinimines, a large variety of chemical structures can be chosen for R (or R′, depending on the starting point of the synthesis route, Scheme 1). Although not explored in this paper, it is obvious that other variations on the presented method may be possible as well. For example, the application of resin-bound triphenylphosphinimines,[27] subjection of amines on solid support[31,32] to the intermediate [^{11}C]isocyanate, as well as the use of a wide range of other nucleophiles that can lead to compounds other than ureas (i.e. thiols,[33–35] alkynes,[36,37] or alcohols/acids[38–41]). So, the present method generates great possibilities for the preparation of a large number of different ^{11}C-labeled compounds that can be prepared from [^{11}C]isocyanates, obtained from the reaction of triphenylphosphinimines with [^{11}C]CO_2.

Experimental

General methods

Unless otherwise stated, all chemical reagents were purchased from Aldrich. Solvents were purified and dried by standard procedures before use. Thin-layer chromatography (TLC) was carried out using aluminum sheets (20 × 20 cm) with silica gel F_{254} from Merck. Spots were visualized under UV (254 nm). ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker AC-200 or a MSL 400 spectrometer. Chemical shifts (δ) were determined relative to the solvent and converted to the tetramethylsilane scale using $\delta = 2.52$ ppm for DMSO-d_6. [^{11}C]Carbon dioxide was produced by the ^{14}N(p,α)^{11}C nuclear reaction using an IBA 18/9 cyclone (dimethylsulfoxide: DMSO; tetrahydrofuran: THF; *N*,*N*-dimethylformamide: DMF).

Synthesis of the reference urea derivatives. General procedure

The appropriate amine (0.26 mmol) was dissolved in 400–600 µl ether. Phenylisocyanate (0.32 mmol) was added and the solution was stirred for 0.5–3 h at room temperature. The formed white precipitate was filtered off, washed with ether and dried. The products were analyzed by two different HPLC systems: A: Kromasil 100 RP C18 column (250 × 4.6 mm; CH_3CN/H_2O 40/60, 1 ml/min), and system B: RP-Select B C8, 5 µm column (150 × 4.6 mm; MeOH/H_2O 45/55, 1 ml/min); both systems with UV = 221 and 254 nm.

1-benzyl-3-phenylurea (4a). Benzylamine (**3a**, 0.26 mmol, 29 µl) and phenylisocyanate (0.32 mmol, 35 µl) were used. Yield 48 mg (0.21 mmol, 82%). ^{1}H NMR (200 MHz, DMSO-d_6) δ 8.58 (bs, 1H, CH_2NH), 7.43–7.18 (m, 9H, *o*- and *m*-arom, NH), 6.90 (t, 1H, $J = 7.20$ Hz, *p*-benzyl), 6.63 (t, 1H, $J = 6.80$ Hz, *p*-phenyl), 4.30 (d, 2H, $J = 5.90$ Hz, CH_2) ppm,

^{13}C NMR (50 MHz, DMSO-d_6) δ 157.8, 141.2, 138.6, 129.3, 128.4, 128.1, 126.8, 120.8, 117.4, 42.5 ppm. Analytically calculated for $C_{14}H_{14}N_2O$: C, 74.31; H, 6.24; N, 12.38. Found: C, 74.25; H, 6.25; N, 12.31. M.p. 174–176°C. System A: retention time of 16.7 min; system B: retention time of 13.6 min.

1,3-diphenylurea (4b). Aniline (**3b**, 0.26 mmol, 24 µl) and phenylisocyanate (0.32 mmol, 35 µl) were used. Yield 38 mg (0.18 mmol, 70%). ^{1}H NMR (200 MHz, DMSO-d_6) δ 8.82–8.58 (bs, 2H, NH), 7.60–7.09 (m, 6H, phenyl), 7.09–6.81 (m, 4H, phenyl) ppm. ^{13}C NMR (50 MHz, DMSO-d_6) δ 152.6, 140.2, 128.6, 121.6, 117.9 ppm. Analytically calculated for $C_{13}H_{12}N_2O$: C, 73.57; H, 5.70; N, 13.20. Found: C, 73.29; H, 5.63; N, 13.03. M.p. 251–253°C. System A: retention time of 21.0 min; system B: retention time of 13.9 min.

1-phenyl-3-propylurea (4c). *n*-Propylamine (**3c**, 0.26 mmol, 22 µl) and phenylisocyanate (0.32 mmol, 35 µl) were used. Yield 42 mg (0.23 mmol, 90%). ^{1}H NMR (200 MHz, DMSO-d_6) δ 8.41 (bs, 1H, NH), 7.51–6.78 (m, 5H, phenyl), 6.19 (bs, 1H, NH), 3.19–2.92 (m, 2H, NHCH_2), 1.62–1.30 (m, 2H, CH_2CH$_3$), 1.06–0.72 (m, 3H, CH$_3$) ppm. ^{13}C NMR (50 MHz, DMSO-d_6) δ 151.3, 134.9, 128.3, 120.5, 117.2, 40.5, 22.6, 10.9 ppm. Analytically calculated for $C_{10}H_{14}N_2O$: C, 67.39; H, 7.92; N, 15.72. Found: C, 67.29; H, 7.83; N, 15.58. M.p. 115–117°C. System A: retention time of 8.4 min; system B: retention time of 6.9 min.

N-[2-(5-methoxy-1H-indol-3-yl)-ethyl]-benzamide (4d). 5-methoxy-tryptamine (**3d**, 0.26 mmol, 50 mg) and phenylisocyanate (0.32 mmol, 35 µl) were used. Yield 60 mg (0.19 mmol, 73%). ^{1}H NMR (200 MHz, DMSO-d_6) δ 10.69 (s, 1H, NH), 8.50 (s, 1H, NH), 7.41–6.73 (8H, arom), 6.19–6.07 (m, 1H, phenyl), 3.74 (s, 3H, CH$_3$), 3.48–3.30 (m, 2H, CH$_2$NH), 2.82 (t, 2H, CH_2CH$_2$NH, $J = 7.41$ Hz) ppm. ^{13}C NMR (50 MHz, DMSO-d_6) δ 159.3, 153.3, 136.66, 132.4, 130.1, 128.7, 122.3, 120.6, 117.4, 111.4, 111.2, 101.9, 97.9, 55.5, 40.7, 24.6 ppm. Analytically calculated for $C_{18}H_{19}N_3O_2$: C, 69.88; H, 6.19; N, 13.58. Found: C, 69.63; H, 6.00; N, 13.32. M.p. 80–82°C. System A: retention time of 8.3 min; system B: retention time of 9.4 min.

Synthesis of ^{11}C-labeled ureas. General procedure

The (dry) silicone septum sealed reaction vial was charged with phenyltriphenylphosphinimine (**1**, 19.6 µmol, 7 mg) and the appropriate amine, dissolved in 600 µl of dry THF, cooled to −60°C and purged with helium. The [^{11}C]CO_2 was transferred to the reaction vial via a helium carrier gas (10 ml/min). The amount of [^{11}C]CO_2 trapped usually was >99% and varied in these experiments between 5 and 7 GBq. After obtaining maximum radioactivity in the vial, the carrier gas was switched off, needles were removed and the vial

was heated at 60°C for 6 min and then cooled to 21°C. The product was analyzed and identified by two different HPLC systems: A: Kromasil 100 RP C18 column (250 × 4.6 mm; CH_3CN/H_2O 40/60, 1 ml/min), and system B: RP-Select B C8, 5 μm column (150 × 4.6 mm; $MeOH/H_2O$ 45/55, 1 ml/min); both systems with UV = 221 and 254 nm and homemade radioactivity detection (Na(I)). The radiochemical yields were determined based on the HPLC chromatograms. In all cases, the retention time of the unreacted $[^{11}C]CO_2$ was 6.2 min (A) or 4.5 min (B).

1-benzyl-3-phenyl-[^{11}C]urea ([^{11}C]4a). Benzylamine (**3a**, 8 μl, 73 μmol) was used. System A: retention time of 16.7 min; system B: retention time of 13.6 min; both corresponding to **4a**, thereby confirming its identity. The overall decay-corrected radiochemical yield was 46 ± 4% ($n = 3$).

1,3-diphenyl-[^{11}C]urea ([^{11}C]4b). Aniline (**3b**, 6 μl, 66 μmol) was used. System A: retention time of 21.0 min; system B: retention time of 13.9 min; both corresponding to **4b**, thereby confirming its identity. The overall decay-corrected radiochemical yield was 8 ± 1% ($n = 3$).

1-phenyl-3-propyl-[^{11}C]urea ([^{11}C]4c). *n*-Propylamine (**3c**, 10 μl, 120 μmol) was used. System A: retention time of 8.4 min; system B: retention time of 6.9 min; both corresponding to **4c**, thereby confirming its identity. The overall decay-corrected radiochemical yield was 49 ± 3% ($n = 3$).

N-[2-(5-methoxy-1H-indol-3-yl)-ethyl]-benz[^{11}C]amide ([^{11}C]4d). 5-Methoxy-tryptamine (**3d**, 2.4 mg, 13 μmol) was used. System A: retention time of 8.3 min; system B: retention time of 9.4 min; both corresponding to **4d**, thereby confirming its identity. The overall decay-corrected radiochemical yield was 45 ± 3% ($n = 3$).

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