Research Article

Journal of Labelled Compounds and Radiopharmaceuticals

Received 24 December 2009, Revised 4 May 2010, Accepted 7 May 2010 Published online 5 August 2010 in Wiley Online Library

(wileyonlinelibrary.com) DOI: 10.1002/jlcr.1803

Synthesis of substituted [^{11}C]ureas and [^{11}C]sulphonylureas by Rh(I)-mediated carbonylation

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The urea moiety is present in many biologically active compounds and thus an attractive target for ^{11}C-labelling. To extend the scope of the rhodium(I)-mediated carbonylative cross-coupling reaction between an azide and an amine and investigate its tolerance for functional groups, we have synthesized eight ureas and two sulphonylureas that were ^{11}C-labelled in the carbonyl position. The decay-corrected analytical radiochemical yields were in the range of 14–96% (from [^{11}C]carbon monoxide). For example: starting from 1.33 GBq [^{11}C]carbon monoxide, 0.237 GBq (66%) of the cytotoxic sulphonylurea [^{11}C]LY-181984 11 was isolated within 60 min from end of bombardment. The mild reaction conditions and generality regarding functional groups of this method make it an attractive alternative to the [^{11}C]phosgene method for the synthesis of ^{11}C-labelled ureas.

Keywords: urea; sulphonylurea; carbonylation; [^{11}C]carbon monoxide; rhodium(I)

Introduction

The urea and sulphonylurea moieties are commonly used in the design of biologically active compounds, including K_{ATP}-channel antagonists,[1] angiotensin II AT_1 antagonists,[2] cytotoxic agents,[3] and CXCR2 chemokine receptor antagonists.[4]

The use of positron emission tomography (PET) in drug development has the potential to speed up the progression of a lead compound toward its first test in man by radiolabelling of the drug.[5] PET is also extensively used as a clinical diagnostic tool. The radionuclide ^{11}C (β^+, $t_{1/2} = 20.4$ min) can be used to label a native compound. Because of the short half-life, ^{11}C should preferably be introduced in a one-pot procedure in the last step in the synthetic route. Therefore robust, general, mild and high-yielding methods that are suitable for automation are highly desirable.

The most commonly used method to synthesize [^{11}C]ureas is the [^{11}C]phosgene method. [^{11}C]Phosgene can be obtained via chlorination of [^{11}C]methane to [^{11}C]Cl_4 and subsequent oxidation over a metal or metal oxide.[6–8] This multistep method is tedious and often gives low specific activity. [^{11}C]Phosgene can also be obtained via chlorination of [^{11}C]carbon monoxide at elevated temperatures over $PtCl_4$,[8] or photolytically using elemental chlorine gas.[9] Several alternative routes to [^{11}C]ureas have been developed, including the selenium-mediated carbonylation, which gives high yields of cyclic ureas and carbamates in very high specific activity. As a consequence of the mechanism of this reaction and the use of very low concentration of [^{11}C]carbon monoxide, this method works best with primary amines.[10] Symmetric ureas have been prepared directly from [^{11}C]carbon dioxide and the corresponding amine.[11] Reactive triphenylphosphine imines and [^{11}C]carbon dioxide gave moderate yields of [^{11}C]ureas when strong nucleophiles were used, and lower yields when the weak nucleophile aniline (110 mM) was used.[12]

It has been shown in large-scale chemistry that rhodium(I)-complexes can catalyse the carbonylative cross-coupling between an azide and a nucleophile, under very mild conditions (1 bar, 25–50°C), to form the corresponding urea, carbamate, or thiocarbamate.[13–17] This reaction has been adapted to small-scale ^{11}C-labelling chemistry using [^{11}C]carbon monoxide in a model reaction to form *N*,*N*′-diphenyl[^{11}C]urea and ethyl phenyl[^{11}C]carbamate.[18] Recently, this method was used to ^{11}C-label a small library of dual VEGFR-2/PDGFR-β inhibitors at the urea position.[19]

We wish to extend the potential use of the rhodium(I)-mediated [^{11}C]urea synthesis by describing its tolerance for a number of common functional groups. The ^{11}C-labelling of the biologically active insulin secretagogue tolbutamide **10** and the cytotoxic agent LY-181984 **11** is also described.

Experimental section

^{11}C was prepared by the ^{14}N(p,α)^{11}C nuclear reaction using 17 MeV proton beam produced by a Scanditronix MC-17 Cyclotron at Uppsala Imanet, GE Healthcare and obtained as [^{11}C]carbon dioxide. The target gas used was nitrogen (AGA Nitrogen 6.0)

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containing 0.05% oxygen (AGA Oxygen 4.8). The carbonylation reactions were carried out in a 200-μl stainless steel micro-autoclave according to a previously described method.[20, 21] THF was freshly distilled over sodium and benzophenone under a nitrogen atmosphere. All other chemicals were purchased from Aldrich/Fluka and used without further purification. The identities of the ^{11}C-labelled compounds were determined by using analytical HPLC using authentic samples as references. Analytical HPLC was performed on a Beckman system, equipped with a Beckman 126 pump, a Beckman 166 UV detector in series with a Bioscan β^+-flow count detector, and a Beckman Ultrasphere ODS dp 5 μ column (250 × 4.6 mm). A Gilson 231 XL was used as the auto-injector. Mobile phase: (A) 50 mM Ammonium formate pH 3.5 and (B) Acetonitrile. Purification with semi-preparative HPLC was performed on a similar Beckman system equipped with a Genesis C18 120 4μ (250 × 10 mm). Mobile phase: (A) 50 mM Ammonium formate pH 3.5 and (B) Acetonitrile. ^{1}H and ^{13}C NMR spectra were recorded on a Varian 400 or 500 MHz spectrometer and chemicals shifts are given in ppm (δ) using $CHCl_3$ (7.26 ppm for ^{1}H, and 77.16 for ^{13}C) or DMSO-d_n (2.50 ppm for ^{1}H, and 39.52 for ^{13}C) as the internal standard. IR spectra were recorded on neat compounds using a Perkin Elmer Spectrum 100 FT/IR spectrometer.

Labelling chemistry

General labelling method exemplified with 1-(4-hydroxyphenyl)-3-phenyl[^{11}C]urea ***2***

To a capped and argon-purged 1.2-ml vial containing cyclooctadiene rhodium(I) chloride dimer, $[RhCl(COD)]_2$ (0.75 mg, 1.5 μmol), was added a solution of triphenylphosphine, PPh_3 (0.82 mg, 3.12 μmol), in THF (1.00 ml). The mixture was shaken vigorously until everything was dissolved. Of the resulting rhodium complex solution, 100 μl was transferred to a capped and argon-purged 0.8-ml vial and phenyl azide (0.95 mg, 8.0 μmol) was added as a solution in THF (100 μl). The reaction mixture was kept in r.t. for approx 10 min before 4-aminophenol (4.35 mg, 40 μmol) was added as a solution in THF (100 μl). The resulting solution was injected on to a 200-μl loop and then transferred to a 200-μl micro-autoclave containing [^{11}C]carbon monoxide (approx. 30 nmol) and helium. The reaction was kept at a constant temperature of 80°C for 5 min before it was ejected into a capped and evacuated 5-ml vial. The micro-autoclave was pressurized once more and ejected into the vial, where the radioactivity was measured. The solvent was removed under a stream of nitrogen in a heating block at 70°C and the radioactivity was measured again. The residue was dissolved in acetonitrile (1 ml) and an aliquot was taken for analysis by using analytical UV-radio-HPLC. Co-injection of an authentic sample was performed to identify the product peak, which was isocratic 40% B for 10 min then 95%B for 15 min at 1 ml min^{-1}, Rt = 8.9 min. The crude product was purified using semi-preparative HPLC in isocratic 40% B, 4 ml min^{-1}, Rt = 9.0 min.

Azides

4-Methyl-benzenesulphonyl azide ***1c***[20]

To an ice-cold solution of *p*-TsCl (2.00 g, 10.5 mmol) was added dropwise an aqueous solution of NaN_3 (0.683 g, 10.5 mmol). The reaction mixture was allowed to warm to r.t. and stirred for 4 h, then extracted with ether and dried over $MgSO_4$. Evaporation of the solvent gave the product (1.736 g, 84%) as a colourless oil. ^{1}H NMR (500 MHz, $CDCl_3$, 25°C) δ: 7.84 (AA'XX, 2H, Ar-*H*), 7.40 (AA'XX', 2H, Ar-*H*), 2.48 (s, 3H, CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25°C): 146.3, 135.6, 130.4, 127.6, 21.9 ppm. IR λ: 2121 (s, azide), 1595 (m), 1366(s), 1158(s), 1084(s), 812(s), 742(s), 655(s) cm^{-1}. Direct inlet EI+ for *m/z*: 155 (azide radical, 93%), 91(100), 65(52).[21]

Reference urea compounds

General procedure

A solution of the aniline (1.68 mmol) in dichloromethane or THF (2.5–5 ml) was added dropwise to an ice-cold solution of phenyl isocyanate (0.200 g, 1.68 mmol) in dichloromethane or THF (2.5–5 ml) under N_2. After 30 min, the reaction mixture was allowed to warm to r.t. and stirred for 2–6 h. After concentration to approximately half volume, the precipitate was collected and recrystallized in an appropriate solvent.

1-(4-Hydroxyphenyl)-3-phenyl-urea ***2***[22]

^{1}H NMR (400 MHz, DMSO-d_6, 25°C) δ: 8.96 (s, 1H), 8.45 (s, 1H), 8.25 (s, 1H), 7.43 (m, 2H, Ar-*H*), 7.25 (m, 1H, Ar-*H*), 7.21 (m, 1H, Ar-*H*), 6.94 (m, 1H, Ar-*H*), 6.69 (m, 1H, Ar-*H*) ppm. ^{13}C NMR (100 MHz, DMSO-d_6, 25°C) δ: 152.7, 152.5, 139.9, 131.0, 128.5, 120.4, 118.0, 115.1 ppm. LC-MS ESI+ *m/z* for $C_{13}H_{12}N_2O_2$ [M+H]: 229, [M+H+MeCN]: 270, [2 × M+H]: 457.

4-(3-Phenyl-ureido)-benzoic acid ***3***

^{1}H NMR (400 MHz, DMSO-d_6, 25°C) δ: 12.5 (br s, 1H), 9.14 (s, 1H), 8.87 (s, 1H), 7.86 (m, 2H), 7.55 (m, 2H), 7.46 (m, 2H), 7.30 (m, 2H), 7.00 (m, 1H) ppm. LC-MS ESI+ *m/z* for $C_{14}H_{12}N_2O_3$ [M+H]: 257, [M+H+MeCN]: 298, [2 × M+H]: 513.

1-(2-Iodo-phenyl)-3-phenyl-urea ***4***[23]

^{1}H NMR (400 MHz, DMSO-d_6, 25°C) δ: 9.35 (s, 1H), 7.85–7.83 (m, 3H), 7.47 (m, 2H), 7.34 (m, 1H), 7.30 (m, 1H), 7.27 (m, 1H), 6.84 (m, 1H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6, 25°C)δ: 152.3, 139.8, 139.5, 138.8, 128.7, 128.4, 124.9, 123.0, 121.9, 118.2, 91.2 ppm. LC-MS ESI+ *m/z* for $C_{13}H_{11}IN_2O$ [M+H]: 339, [M+H+MeCN]: 380, [2 × M+H]: 677.

1-(3-Cyano-phenyl)-3-phenyl-urea ***5***

^{1}H NMR (400 MHz, DMSO-d_6, 25°C) δ: 8.92 (s, 1H), 8.75 (s, 1H), 7.96 (s, 1H), 7.66 (m, 1H), 7.47 (m, 4H), 7.29 (m, 2H), 6.98 (m, 1H) ppm. LC-MS ESI+ *m/z* for $C_{14}H_{11}N_3O$ [M+H]: 238, [M+H+MeCN]: 279, [2 × M+H]: 475.

1-(4-Acetyl-phenyl)-3-phenyl-urea ***6***[24]

^{1}H NMR (400 MHz, DMSO-d_6, 25°C) δ: 9.06 (s, 1H), 8.76 (s, 1H), 7.88 (m, 2H), 7.54 (m, 2H), 7.42 (m, 2H), 7.25 (m, 2H), 6.95 (m, 1H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6, 25°C) δ: 196.3, 152.2, 144.4, 139.3, 130.4, 129.7, 128.9, 122.3, 118.4, 117.1, 23.4 ppm. LC-MS ESI+ *m/z* for $C_{15}H_{14}N_2O_2$ [M+H]: 255, [M+H+MeCN]: 296, [2 × M+H]: 509.

Piperidine-1-carboxylic acid phenyl amide ***7***[25]

^{1}H NMR (400 MHz, DMSO-d_6, 25°C) δ: 8.34 (s, 1H), 7.47 (m, 2H), 7.22 (m, 2H), 6.91 (m, 1H), 3.41 (m, 4H), 1.58 (m, 2H), 1.50 (m, 4H)

ppm. ^{13}C NMR (100 MHz, DMSO-d_6, 25°C) δ: 154.8, 140.7, 158.0, 121.3, 119.5, 44.6, 25.4, 24.0 ppm. LC-MS ESI+ *m/z* for $C_{12}H_{16}N_2O$ [M+H]: 205, [M+H+MeCN]: 246.

Piperazine-1-carboxylic acid phenyl amide ***8***[26]

The addition order was reversed, however, a significant portion of the formed product was the corresponding N^1,N^4-diphenyl-piperazine-1,4-dicarboxamide. LC-MS ESI+ *m/z* for $C_{11}H_{15}N_3O$ [M+H]: 206, [M+H+MeCN]: 247, [2 × M+H]: 410.

1-Butyl-3-phenyl-urea ***9***

^{1}H NMR (400 MHz, DMSO-d_6, 25°C) δ: 8.37 (s, 1H), 7.38 (m, 2H), 7.20 (m, 2H), 6.87 (m, 1H), 6.09 (m, 1H), 3.05 (m 2H), 1.39 (m, 2H), 1.31 (m, 2H), 0.89 (t, J = 7.1 Hz, 3H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6, 25°C) δ: 155.2, 140.6, 128.7, 120.9, 117.6, 38.7, 31.9, 19.6, 13.7 ppm. LC-MS ESI+ *m/z* for $C_{11}H_{16}N_2O$ [M+H]: 193, [M+H+MeCN]: 234, [2 × M+H]: 385.

N-[(4-chlorophenyl)amino]carbonyl-4-methylbenzenesulphonamide ***11***

^{1}H NMR (500 MHz, $CDCl_3$:DMSO-d_6, 25°C) δ: 9.95 (br s, 1H), 8.00 (br s, 1H), 7.65 (m, 2H), 7.06 (m, 4H), 6.93 (m, 2H), 2.17 (s, 3H) ppm. LC-MS ESI+ *m/z* for $C_{14}H_{13}ClN_2O_3S$ [M+H]: 325.

Results and discussion

The lack of a general one-pot procedure for synthesizing differently substituted [^{11}C]ureas from simple starting materials in high specific activity and high yields prompted us to further explore the Rh(I)-mediated carbonylation using [^{11}C]carbon monoxide.[18–19] Because carbon monoxide is less abundant in the air than carbon dioxide, the use of online produced [^{11}C]carbon monoxide as the labelled precursor generally results in labelled products with lower isotopic dilution and higher specific activity. We have previously shown that [^{11}C]ureas synthesized via Rh(I)-mediated carbonylative cross-coupling can be obtained in specific activities in the order of 100–600 GBq · μmol^{-1}.[10, 18–19]

The radioactivity was produced via the ^{14}N(p,α)^{11}C nuclear reaction and was obtained in the target as [^{11}C]carbon dioxide. The radioactivity was concentrated at −196°C, transferred online via a helium flow to the hotcell and concentrated once again on a silica column at −196°C. The helium-carrier-added [^{11}C]carbon dioxide was reduced to [^{11}C]carbon monoxide over zinc at 400°C, concentrated on silica at −196°C, and transferred to a 200-μl micro-autoclave using a previously described technique.[27, 28]

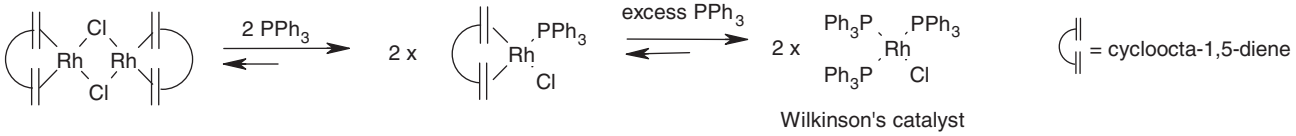
The active rhodium complex was prepared by mixing the cyclooctadiene rhodium(I) chloride dimer $[Rh(cod)Cl]_2$ with triphenylphosphine (Rh:P = 1:1). The actual active complex achieved was not characterized but it is likely that Rh(I)-dimer is split into two Rh(I)(cod)PPh_3Cl on coordination of a triphenylphosphine according to the first step in Scheme 1.[29]

Using an *in situ* formed rhodium–phosphine complex has previously been shown superior to the use of Wilkinson's catalyst.[18] To the rhodium complex was added an azide (**1a-c**) and just before the reaction mixture was injected onto a loop an amine was added. The reaction mixture was transferred to a micro-autoclave pre-charged with [^{11}C]carbon monoxide (8–80 nmol, the variation is due to unwanted isotopic dilution origin from the target gas as well as surface bound CO_2 on the Zn granules used for the online reduction of [^{11}C]O_2) in helium and pressurized with solvent (35 MPa) and kept at 80°C for 5 min.[30] The partial pressure of [^{11}C]carbon monoxide in the gas mixture during the reaction is very low, 8–80 Pa. This is one of the differences between small-scale [^{11}C]carbon monoxide chemistry and large-scale chemistry, where carbon monoxide pressures of 100–1 × 10^5 kPa are common.

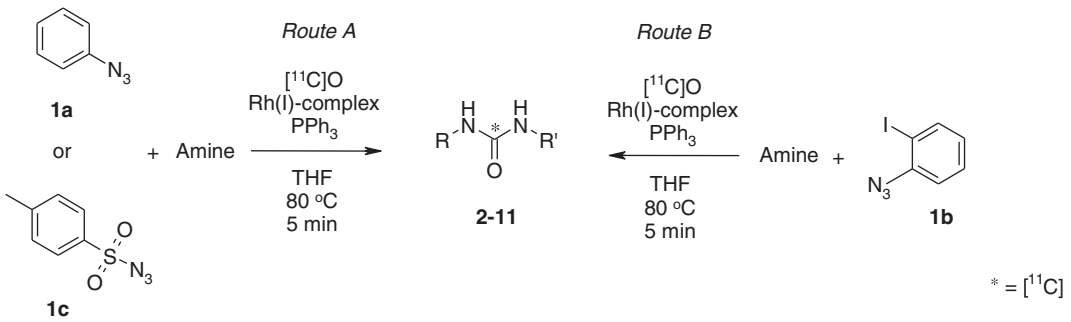
We recently showed that higher radiochemical yields can generally be obtained in this reaction by increasing the concentration of the nucleophile.[19] The standard nucleophile concentration (100 mM) used in this report was chosen to reflect the influence of the substituents rather than to maximize the yields. Three azides and nine amine nucleophiles (Scheme 2) were used to synthesize **10** labelled compounds (Figure 1).

Generally, when phenylazide **1a** (Route A) was used as substrate and strong nucleophiles were used, the reactions were very clean and gave high radiochemical yields of the expected [^{11}C]ureas, while weaker nucleophiles gave lower yields and formation of by-products. Both acidic and basic functional groups were well tolerated in the nucleophiles (Table 1, Entries 1, 2, 7–9). The radiochemical yields roughly correlates with the nuclophilicity of the amines secondary amines > primary amines = activated anilines > deactivated anilines.[31] However, piperidine (Table 1, Entry 7) gave an unexpectedly low yield compared with butylamine (Table 1, Entry 9), possibly due to its very hygroscopic properties.

Aryl iodides are generally good substrates for oxidative addition to transition metal complexes, such as Rh(I), and could potentially lead to unwanted side reactions. Indeed, when 1-azido-2-iodobenzene **1b** (Route B) was used as the substrate and aniline was the nucleophile, two distinct products accounted for over 95% of the converted [^{11}C]carbon monoxide; urea **4** was the minor product of the two (Table 1, Entry 4). When instead azide **1a** (Route A) was used as substrate and 2-iodoaniline was used as nucleophile, low [^{11}C]O-conversion and 36% radiochemical yield was the result. Still, this reaction was cleaner and 70% of the converted [^{11}C]carbon monoxide was converted to the desired urea **4**. Thus, the lower yield is to a high degree a reflection of the low nucleophilicity of the 2-iodoaniline rather than formation of unwanted by-products (Table 1, Entry 3). Thus, an aromatic iodide in the substrate (Table, Entry 4) is more problematic than an iodide in the nucleophile (Table 1, Entry 3), despite that there is five times as much nucleophile present. The nucleophile is always added as the last reagent to the reaction mixture before



Scheme 1. Formation of the active Rh(I)-phosphine complex.



Scheme 2. Rhodium(I)-mediated carbonylative cross-coupling of an azide and an amine to form a [^{11}C]urea.

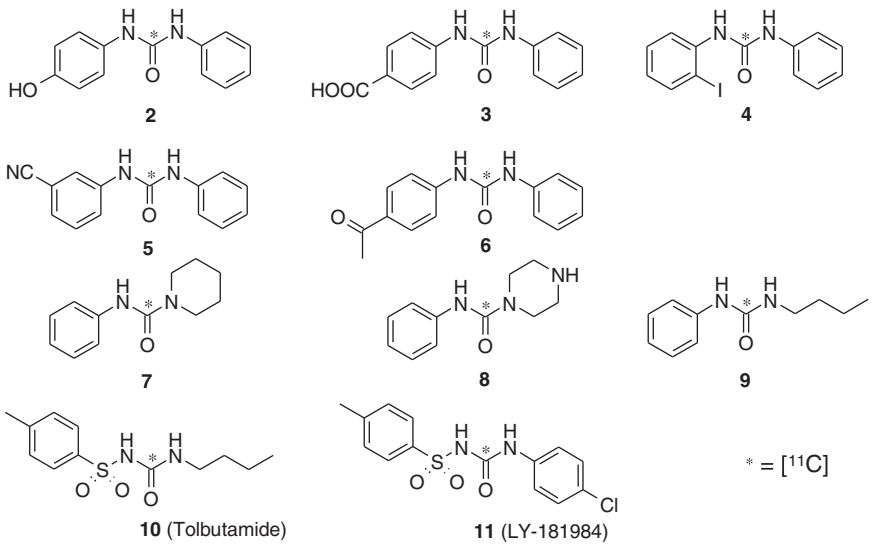


Figure 1. Urea derivatives labelled with ^{11}C at the carbonyl position.

Table 1. Rh(I)-mediated [^{11}C]urea synthesis

Entry	Product	Azide	Amine	[^{11}C]O-conv. (%)[a,b]	Anal. RCY (%)[b,c]
1	**2**	**1a**	4-Hydroxyaniline	89±1 (2)	88±1 (2)
2	**3**	**1a**	4-Carboxyaniline	59±3 (2)	56±4 (2)
3	**4**	**1a**	2-Iodoaniline	52±3 (2)	36±0 (2)
4	**4**	**1b**	Aniline	76±9 (2)	26±13 (2)
5	**5**	**1a**	3-Cyanoaniline	71±7 (4)	24±7 (4)
6	**6**	**1a**	4-Acetoaniline	27±1 (2)	14±1 (2)
7	**7**	**1a**	Piperidine	84±0 (2)	62±2 (2)
8	**8**	**1a**	Piperazine	96±1 (2)	96±1 (2)
9	**9**	**1a**	Butylamine	88±3 (2)	88±3 (2)
10	**10** (Tolbutamide)	**1c**	Butylamine	90±3 (2)	83±1 (2)
11[d]	**11** (LY-181984)	**1c**	4-Chloroaniline	93	79
12[e]	**11** (LY-181984)	**1c**	4-Chloroaniline	92	78

Standard conditions were: helium-carrier-added [^{11}C]carbon monoxide (0.05–0.5 mM) pressurized in a 200-µl micro-autoclave to 35 MPa with a solution of $[Rh(cod)Cl]_2$ (0.40 mM), triphenylphosphine (0.80 mM), a phenylazide (**1a** or **1b)** or *p*-toluenesulphonylazide **1c** (20 mM) and an amine (100 mM) in THF at 80°C for 5 min.

[a]Decay-corrected conversion yield of [^{11}C]carbon monoxide to non-volatile products remaining in the reaction mixture after removal of solvent via a stream of nitrogen at 70°C. When the reaction mixture was transferred from the micro-autoclave to a 5-ml evacuated vial, the radioactivity in the vial was measured. The radioactive residues left in the micro-autoclave were estimated to be less than 1%. Hence, the amount of initial radioactivity of [^{11}C]carbon monoxide could be determined.

[b]The numbers in parentheses indicate the number of experiments.

[c]Anaytical radiochemical yield as the sum of the decay-corrected analytical HPLC radiochromatogram and the decay-corrected conversion of [^{11}C]carbon monoxide.

[d]Amine (370 mM), **1c** (16 mM).

[e]Amine (185 mM), **1c** (16 mM), $[Rh(cod)Cl]_2$ (0.20 mM), triphenylphosphine (0.40 mM).

injection to the micro-autoclave, which suggests that coordination or oxidative addition of the azide to the rhodium(I) complex under these reaction conditions may prevent the oxidative addition of the iodide. The formation of a nitrene complex on loss of molecular nitrogen is also a plausible reaction mechanism.[16]

Meta-cyanoaniline is a weak nucleophile and yielded a very lipophilic byproduct as the major labelled product, whereas the desired urea **5** was produced in only 24% radiochemical yield (Table 1, Entry 5). The deactivated *p*-acetylaniline gave low [^{11}C]O-conversion and resulted in low a yield of urea **6**, probably due to its low nucleophilicity (Table 1, Entry 6). The reaction with the strong nucleophile *n*-butylamine and phenylazide **1a** gave the urea **9** as the only labelled product. The related reaction using *p*-toluenesulphonylazide **1c** as the substrate gave a slightly lower yield of [^{11}C]tolbutamide **10** (Table 1, Entries 9 and 10). The loss of product on purification (compared with the analytical radiochemical yield) were in the range of 10–30% as exemplified by compounds **2** and **11** that were isolated using semi-preparative HPLC in 61 and 68% decay-corrected radiochemical yield, respectively.

Another perspective to consider in selecting which molecular fragment to be the nucleophile or azide except for the reactivity is the potential problems in the final work up, such as using HPLC to separate a high concentration of the nucleophile from a low concentration of the labelled product.

Conclusions

Rh(I)-mediated carbonylations of azides to form [^{11}C]ureas tolerate both acidic and basic substituents. Generally, strong nucleophiles gave higher yields and cleaner reactions. An aromatic iodide in the substrate competes for coordination/oxidative addition to the metal and results in high byproduct formation and low radiochemical yields. An aromatic iodide in the nucleophile interfered less and gave higher yield and a cleaner reaction. Sulphonazides worked well as substrates and the cytotoxic agent [^{11}C]LY-181984 **11** was obtained in useful radiochemical yields. Overall, the robust method utilizing Rh(I)-mediated carbonylative cross-coupling of an azide and an amine to form [^{11}C]ureas is an attractive alternative to established methods, such as the use of [^{11}C]phosgene.

Acknowledgement

This work was conducted in collaboration with Uppsala Imanet, GE Healthcare. Assoc. Prof. Tor Kihlberg and Dr. Tamara Church are gratefully acknowledged for linguistic advice and commenting on the text.

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