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Synthesis of ^{11}C-labelled *N*,*N*′-diphenylurea and ethyl phenylcarbamate by a rhodium-promoted carbonylation *via* [^{11}C]isocyanatobenzene using phenyl azide and [^{11}C]carbon monoxide

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The reaction with phenyl azide and [^{11}C]carbon monoxide to give *N*,*N*′-diphenyl[^{11}C]urea and ethyl phenyl[^{11}C]carbamate has been studied with the aim of development of a new methodology for carbonylation using [^{11}C]carbon monoxide with high specific radioactivity. The synthesis of ^{11}C-labelled *N*,*N*′-diphenylurea from phenyl azide and [^{11}C]carbon monoxide, with 1,2-bis(diphenylphosphino)ethane-bound Rh(I) complex at 120 °C at a pressure of 35 MPa in the presence of aniline was accomplished in 82% trapping efficiency and 82% conversion yield. This approach was also useful for the synthesis of ethyl phenyl[^{11}C]carbamate with lithium ethoxide as a nucleophilic reagent giving 90% trapping efficiency and 76% conversion yield. These reactions can be considered to proceed *via* a [^{11}C]isocyanate or a [^{11}C]isocyanate-coordinated Rh complex to give the corresponding ^{11}C-products. This protocol provides the chemical basis for the synthesis of [^{11}C]urea and [^{11}C]carbamate derived from [^{11}C]isocyanates.

Introduction

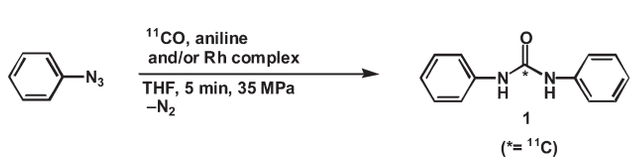
Positron emission tomography (PET) is an expanding non-invasive imaging technique for investigation of *in vivo* biochemistry in research animals but especially allowing early studies in humans.[1] With an increasing number of applications, the technology has met a specific interest in drug development and clinical research. Further advances of labelling chemistry are needed in order to meet the growing demand for labelled potential PET tracers. A key factor of the technique is the synthesis of the labelled molecules. A number of positron emitting radionuclides are available, but from synthetic perspectives the most interesting radionuclides are ^{11}C and ^{18}F with a half-life of 20.4 and 109.8 min, respectively.

The efficient and practical synthetic methodology of the ^{11}C-labelling of carbonyl moieties is important, since molecular structures having carbonyl groups are found in a wide range of bioactive organic compounds. Previously an efficient method of [^{11}C]carbon monoxide production at low concentration and high specific radioactivity was developed[2] allowing a large number of [^{11}C]carbonylations promoted by palladium mediated cross-coupling reactions.[3] These are exemplified in the synthesis of [^{11}C]ketones,[4] [^{11}C]esters,[5] [^{11}C]carboxylic acids,[6] [^{11}C]amides,[2,7] [^{11}C]imides,[8] [^{11}C]ureas,[9] and [^{11}C]carbamoyl compounds.[9] These results have opened an avenue to synthesize a number of pharmaceutically important tracers for applications with PET despite the restrictions in synthetic utility due to time limitations caused by the short half-life. However, harsh conditions such as temperatures of 100–200 °C and use of large amounts of palladium complex have been required to complete the labelling process within a short time (in the range of a few minutes) because of the short half-life. Such conditions sometimes favour side reactions, which give undesired products. In this context, more efficient and milder reaction conditions are preferred for the synthesis of thermo sensitive PET tracers. These requirements have prompted further exploration of new methods for carbonylation using [^{11}C]carbon monoxide, aiming for products with high specific radioactivity.

Aliphatic and aromatic isocyanates are widely used as building blocks for complicated molecules. Isocyanates normally undergo nucleophilic addition with many substrates yielding the product almost quantitatively.[10] [2 + 2], [2 + 3], and [2 + 4] cycloaddition of isocyanate are used to synthesize heterocycles.[10] Actually, many pharmaceutical compounds are produced using isocyanates as intermediates.[10] These attractive characteristics indicate the possibility of synthesizing new [^{11}C]carbonyl functional groups derived from [^{11}C]isocyanate. In this paper, the synthesis of *N*,*N*′-diphenyl[^{11}C]urea[11] **1** and ethyl phenyl[^{11}C]carbamate **2** are shown as model reactions in an explorative study utilizing rhodium-promoted carbonylation reactions.

Results and discussion

To form the [^{11}C]isocyanate under the special conditions required when dealing with short-lived radionuclides, we assumed that the nitrene produced as a reaction intermediate from azide compounds would react with [^{11}C]carbon monoxide in the presence of a transition metal complex, such as a Rh complex, to allow the [^{11}C]isocyanate[12] or a [^{11}C]isocyanate-coordinated Rh complex[13] as a possible intermediate to be used in labelling synthesis. The latter complex would be expected to have a similar reactivity to normal isocyanates. In order to investigate this process, a model reaction[12] for **1** was set up *via* a [^{11}C]isocyanatobenzene starting from phenyl azide (6.6 mg, 55 μmol) kept under the high pressure of 35 MPa by the carrier gas using the micro autoclave technology previously developed (Scheme 1).



1
(*= ^{11}C)

Scheme 1 Model reaction under PET conditions for the development of [^{11}C]urea synthesis.

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Table 1 Synthesis of ^{11}C-labelled *N*,*N*′-diphenylurea by Rh-promoted carbonylation with phenyl azide and [^{11}C]CO

Entry	Rh Complex	Ratio azide : Rh	*T*/°C	[^{11}C]CO trapping efficiency (%)	Conversion yield (%)
1	—	—	190	33	67
2	$[Rh(OCOCH_3)_2]_2$	1 : 0.2	120	30	71
3	$RhCl(PPh_3)_3$	1 : 0.1	120	60	74
4	$RhCl(PPh_3)_3$	1 : 0.01	120	63	89
5	$RhCl(PPh_3)_3$	1 : 0.01	80	70	79
6	$RhCl(PPh_3)_3$	1 : 0.01	60	70	67
7	$[RhCl(cod)]_2$/4P(*o*-tolyl)$_3$	1 : 0.01	80	50	70
8	$[RhCl(cod)]_2$/4PPh_3	1 : 0.01	80	75	70
9	$[RhCl(cod)]_2$/4PPh_3	1 : 0.01	120	80	74
10	$[RhCl(cod)]_2$/4$AsPh_3$	1 : 0.01	120	24	80
11	$[RhCl(cod)]_2$/2dppp	1 : 0.01	120	69	70
12	$[RhCl(cod)]_2$/2dppf	1 : 0.01	120	69	85
13	$[RhCl(cod)]_2$/2dppe	1 : 0.01	120	82	82

Table 2 Synthesis of ^{11}C-labelled ethyl phenylcarbamate by Rh-promoted carbonylation with phenyl azide and [^{11}C]CO

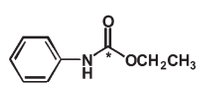
Entry[a]	Rh Complex	Additive	[^{11}C]CO trapping efficiency (%)	Conversion yield (%)
1	$RhCl(PPh_3)_3$	—	27	34
2	$[RhCl(cod)]_2$/2dppe	—	70	25
3	$[RhCl(cod)]_2$/3dppe	—	74	30
4[b]	$[RhCl(cod)]_2$/3dppe	—	70	70
5[c]	$[RhCl(cod)]_2$/3dppe	—	90	0
6	$[RhCl(cod)]_2$/4dppe	—	50	50
7	$[RhCl(cod)]_2$/3dppe	LiBr	81	40
8	$[RhCl(cod)]_2$/3dppe	$LiBF_4$	40	79
9	$[RhCl(cod)]_2$/3dppe	EtOLi	90	76
10	$[RhCl(cod)]_2$/3dppe	EtONa	90	54
11	$[RhCl(cod)]_2$/3dppe	EtOK	94	60

[a] The reactions were conducted at 120 °C. [b] The reaction temperature was 150 °C. [c] Stepwise procedure was used.

Carbonylation reactions using [^{11}C]carbon monoxide at low concentrations are discussed by using two parameters, one indicating the efficiency of trapping in the reaction medium ([^{11}C]CO-trapping efficiency) and the second showing the product yield based on the trapped [^{11}C]carbon monoxide (conversion yield), which can be mentioned as radiochemical yield. At the beginning of the study, a step-wise procedure was used in the synthesis of [^{11}C]isocyanatobenzene from [^{11}C]carbon monoxide and phenyl azide in a high-pressurized autoclave, followed by dilution of the resulting mixture in aniline. To confirm the production of [^{11}C]isocyanatobenzene in the first step, products were directly subjected to analysis using reversed phase HPLC. Unexpectedly, the desired [^{11}C]isocyanatobenzene or its precursor, a [^{11}C]isocyanate Rh complex, may decompose under the acidic conditions of the mobile phase (ammonium formate solution, pH = 3.5) and the radiochemical yield could not be determined.

In order to analyze the ^{11}C-labelled products correctly, a one-pot synthesis of **1** was conducted by adding aniline together with the other reagents in the autoclave. Initially, we observed that the reaction proceeds without a transition metal complex on heating for 5 min at 190 °C under 35 MPa giving a [^{11}C]CO-trapping efficiency of 33% and the desired **1** in 67% conversion yield (Table 1, entry 1), which agreed with previous published work.[14] To increase the trapping efficiency of [^{11}C]carbon monoxide and decrease the reaction temperature, the character of the Rh complex which would allow the coordination of [^{11}C]carbon monoxide and control the reactivity of nitrene was explored. Modulating the amount of Rh complex, the catalytic use of Rh complex relative to the azide compound was found to be necessary. The large or stoichiometric use, which agree with ordinary "PET" conditions, would involve the formation of a stable [^{11}C]CO-coordinated Rh complex and did not give any ^{11}C-labelled product. If the amount of $RhCl(PPh_3)_3$ was decreased to 0.01 eq. to phenyl azide, then the [^{11}C]CO-trapping efficiency and the conversion yield of **1** were further enhanced to 63% and 89%, respectively (entry 4). Interestingly, the reaction with this system also proceeded at 60 °C, giving a [^{11}C]CO-trapping efficiency of 70% and the conversion yield of 67% (entry 6). After extensive studies, the best solution was obtained by the use of a coordinatively unsaturated Rh(I) complex formed *in situ* by mixing $[RhCl(cod)]_2$ (cod = 1,5-cyclooctadiene) and two eq. of 1,2-bis(diphenylphosphino)ethane (dppe). The reaction with this promoter system in THF for 5 min at 120 °C under 35 MPa gave **1** in 82% [^{11}C]CO-trapping efficiency and 82% conversion yield (entry 13). Triphenylphosphine,1,3-bis(diphenylphosphino)-propane (dppp), and 1,1′-bis(diphenylphosphino)ferrocene (dppf) were fairly effective ligands for this reaction (entries 8, 9, 11, and 12). In addition, the use of an excess of phosphine ligands by considering the associative mechanism of Rh chemistry was totally ineffective. Specific radioactivity for **1** was determined to be 516 GBq per μmol.

This procedure was applied to the synthesis of ^{11}C-labelled carbamates choosing ethyl phenyl[^{11}C]carbamate **2** as the model.



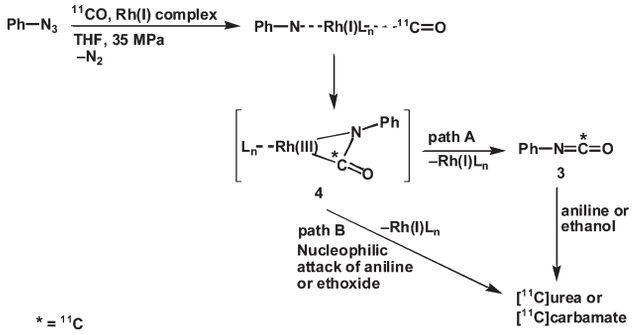
2

The same procedure was used by changing aniline to ethanol as the nucleophilic reagent. This reaction using $[RhCl(cod)]_2$ and two eq. of dppe at 120 °C gave the desired **2** in 70% [^{11}C]CO-trapping efficiency and 25% conversion yield (Table 2, entry 2).

The result could be explained by the weaker nucleophilic power of ethanol compared to aniline. However, slight improvements in [^{11}C]CO-trapping efficiency and conversion yield were observed when using 3 eq. of dppe to $[RhCl(cod)]_2$ and/or in the presence of LiBr (entries 3 and 7). Unfortunately, it was difficult to further increase the conversion yield under these conditions. An increase of temperature to 150 °C improved the conversion yield (70%) for a similar trapping efficiency (entry 4).

If the one-pot operation used in entry 3 of Table 2 was changed to the step-wise procedure with ethanol, which is the same procedure as described in the previous *N*,*N*′-diphenyl[^{11}C]urea synthesis, the reaction did not give the desired ethyl phenyl[^{11}C]carbamate at all (entry 5). We considered that

the formation of [^{11}C]isocyanatobenzene **3** did not proceed efficiently under these conditions (Scheme 2), a reason may be that the isocyanate group usually undergoes nucleophilic attack by ethanol at the high temperature of 120 °C to allow the carbamate formation.[15]



Scheme 2 Supposed reaction pathway.

This might indicate that the [^{11}C]isocyanate-coordinated Rh complex provisionally formulated as **4** is an intermediate, still remaining in the reaction mixture and probably requires the presence of a stronger nucleophile to give the urea and the carbamate. This would be a reason that the nucleophilicity of aniline was sufficient in the previous urea synthesis, but ethanol was not as good nucleophile to produce the carbamate.

When the alkali metal ethoxides were used to enhance the reactivity with this intermediate, the [^{11}C]CO-trapping efficiency and the conversion yield were increased up to 94% and 76%, respectively (entries 9–11). Among these ethoxides, lithium ethoxide was the most efficient to give the optimized yield (entry 9).

In general PET tracer synthesis applying [^{11}C]carbon monoxide, both regarding [^{11}C]CO-trapping efficiency and conversion yield are needed to be more than 70% in order to get sufficient amounts of radioactivity for the preparation of ^{11}C-tracers. In this respect, the results described in this paper meet the demands for PET tracer synthesis.

Conclusion

We have succeeded in developing synthetic methods to prepare *N*,*N*′-diphenyl[^{11}C]urea **1** and ethyl phenyl[^{11}C]carbamate **2** using phenyl azide and [^{11}C]carbon monoxide at low concentrations. The reactions studied here are model reactions but are a step towards the labelling of pharmaceutically important compounds. In this context, this new procedure provides the chemical basis for the synthesis of [^{11}C]urea and [^{11}C]carbamate, and may also be useful in the development of novel PET tracers. Considering the chemistry of isocyanates,[10] this method will be applied to the synthesis of [^{11}C]amide, [^{11}C]isonitrile, and ^{11}C-labelled heterocyclic compounds. This approach will be further explored in future studies.

Experimental

General

[^{11}C]Carbon dioxide production was performed using a Scanditronix MC-17 cyclotron at Uppsala Imanet. The ^{14}N(p,α)^{11}C reaction was performed in a target gas containing nitrogen (AGA, Nitrogen 6.0) and 0.1% oxygen (AGA, Oxygen 4.8), which was bombarded with 17 MeV protons. [^{11}C]Carbon monoxide was produced by reduction of the [^{11}C]carbon dioxide formed in the target. The latter was trapped on a column (Porapac Q) at −196 °C and released by heating and reduced during its passage through a zinc-filled tube at 400 °C. HPLC analysis was performed with a Beckman 126-gradient pump and a Beckman 166 variable wavelength UV-detector in series with a β$^+$-flow detector. The analytical column was a Beckman Ultrasphere ODS C_{18} (250 × 4.6 mm id).

Product analysis

N,*N*′-Diphenyl[^{11}C]urea: mobile phase 0.05 M ammonium formate pH 3.5 and acetonitrile (50 : 50 v/v), flow rate 2.0 mL min^{-1}, detection 254 nm, retention time 5.4–5.7 min.

Ethyl phenyl[^{11}C]carbamate: mobile phase 0.05 M ammonium formiate pH 3.5 and acetonitrile (60 : 40 v/v), flow rate 2.0 mL min^{-1}, detection 254 nm, retention time 6.3–6.6 min

Synthesis of *N*,*N*′-diphenyl[^{11}C]urea 1 (Table 1, entry 13)

In a capped vial (1 mL) containing a solution of phenyl azide (6.6 mg, 55 μmol) in dry THF (300 μL), was added $[RhCl(cod)]_2$ (0.27 mg, 0.55 μmol), and 1,2-bis(diphenylphosphino)ethane (0.44 mg, 1.1 μmol) and the vial was shaken until the solution was homogeneous. After addition of aniline (10 μL, 110 μmol), the resulting mixture was transferred to the micro-autoclave, which was pre-charged with [^{11}C]CO. The autoclave (250 μL) was heated at 120 °C for 5 min under 35 MPa and the crude product was transferred to a reduced pressure vial. The radioactivity was measured before and after the vial was flushed with N_2 (the [^{11}C]CO-trapping efficiency of 82% was determined based on these values). A small amount of crude product was collected and analyzed by reversed phase HPLC. Yield of product: 82%. The product was identified by HPLC with an added authentic reference compound.

Synthesis of ethyl phenyl[^{11}C]carbamate 2 (Table 2, entry 9)

In a capped vial (1 mL) containing a solution of phenyl azide (6.6 mg, 55 μmol) in dry THF (300 μL), was added $[RhCl(cod)]_2$ (0.27 mg, 0.55 μmol), and 1,2-bis(diphenylphosphino)ethane (0.66 mg, 1.65 μmol), and was placed on a shaker until the solution was homogeneous. After addition of a solution of lithium ethoxide (1.0 M, 50 μL, 50 μmol), the resulting mixture was transferred to the micro-autoclave, which was pre-charged with [^{11}C]CO. The micro-autoclave (250 μL) was heated at 120 °C for 5 min under 35 MPa and the crude product was transferred to a reduced pressure vial. The radioactivity was measured before and after the vial was flushed with N_2 (the [^{11}C]CO-trapping efficiency of 90% was determined based on these values). A small amount of crude product was collected and analyzed by the reversed phase HPLC. Yield of product: 76%. The product was identified by HPLC with an added authentic reference compound.

In addition, the reaction using ethanol (20 μL) at 150 °C gave the [^{11}C]CO-trapping efficiency of 70% and the HPLC analytical yield of 70% (Table 2, entry 4).

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