11 C-Labeling: Intracyclic Incorporation of Carbon-11 into Heterocycles

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^{11}C labeling: Intracyclic incorporation of carbon-11 into heterocycles.

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Abstract: Labeling of heterocycles with carbon-11 is generally performed through peripheral functionalizations and more scarcely inside heterocyclic core. Such less common approach usually requires preliminary multi-step synthesis of reactive species. Herein, a cyclization reaction by direct use of cyclotron-produced [^{11}C]CO_2 is described to obtain various heterocycles intracyclically labeled in only 10 minutes.

Introduction

Positron emission tomography (PET) is a non-invasive medical imaging technique used as diagnostic tool in several pathologies.[1] PET is also more and more applied in drug design, allowing in vivo quantitative biodistribution and pharmacokinetic studies.[2] This method requires radiolabeling of molecules with a positron emitting radioisotope.[3] Among the most useful isotopes, fluorine-18 and carbon-11 are preferentially employed. Even if fluorine-18 is preferred due to its superior radioactive half-life (109 min for fluorine-18 vs 20 min for carbone-11), ^{11}C-molecules are still predominantly used for research purposes. Indeed, it is easier to obtain radiolabeled equivalent of existing drugs by “isotopic replacement” of carbon atom.

The main strategy for compounds labeling is generally peripheral introduction of ^{11}C-subtituents.[3a, 4] Radiolabeling inside the molecules core, in particular of heterocyclic structures, has been scarcely described.

Few intracyclic labelings with carbon-11 have been previously performed with various ^{11}C-reagents:[5] [^{11}C]phosgene,[6] [^{11}C]formic acid or derivatives,[7] [^{11}C]formaldehyde,[8] [^{11}C]cyanide,[9] [^{11}C]thiocyanate,[10] [^{11}C]CS_2[11] or [^{11}C]CO.[12] However, all these reagents require their preliminary preparation, often in tedious conditions, which is time consuming. The starting material is generally [^{11}C]CO_2 produced with a cyclotron by ^{14}N(p, α)^{11}C nuclear reaction. Consequently, direct use of cyclotron-produced [^{11}C]CO_2 could be of interest to obtain intracyclic radiolabeled heterocycles. Nevertheless, because of low reactivity of CO_2, this approach has so far been little investigated.

A first approach has been described by an in situ formation of isocyanates.[13] [^{11}C]CO_2 has been trapped by a diamine or an amino-alcohol in a first step, followed by a dehydration in a second step, mediated by $POCl_3$. The resulting isocyanates were then cyclized to provide corresponding imidazolones or oxazolidinones. This method still requires two steps and appears limited in term of substrates scope. More recently, cyclic ureas were synthesized by cyclization of azidoamines with [^{11}C]CO_2, mediated by phosphine.[14] However, this method is limited to urea compounds. Furthermore, heteroaromatic compounds cannot be directly obtained following these strategies.

Results and Discussion

We have previously described direct ^{11}C-methylation of amines through an in situ metal/carbene-mediated reduction of carbon dioxide.[15] During this process, the intermediate formation of formamides has been demonstrated. Consequently, we supposed that a similar strategy applied to diamines could lead to cyclic compounds.

This hypothesis has been evaluated with 1,2-phenylenediamine (**1a**) as starting material to obtain the corresponding benzimidazole (**2a**) (Table 1).

Starting from the described conditions for methylation of amines (entry 1), we were delighted to observe the formation of the expected benzimidazole **2a**, with good radiochemical yields (entry 1). However, in this assay, 10 mg of diamine **1a** have been used. Generally, smaller amounts (ca. 20 µmol) of starting material are engaged in radiolabeling reactions. Unfortunately, by decreasing the diamine **1a** quantity (1.1 mg), to match with a more traditional amount, radiochemical yield also dramatically diminished (entry 2). By using a slight excess of $ZnCl_2$ and **IPr** (1,3-Bis(2,6-diisopropylphenyl)imidazol-2-ylidene), a satisfactory result was reobtained (entry 3). However, an excess of silane appeared to be necessary to observe the expected cyclization (entries 3-4).

Some similar cyclizations have also been described with non-radioactive CO_2.[16] Described conditions did not use any metal catalysts with a reaction time of 24h. Nevertheless, in our case the use of $ZnCl_2$ appeared to be crucial to observe cyclization in a reaction time of only 20 min, more consistent with carbon-11 half-life (entry 5). The metal certainly contributes to accelerate reaction so fitting with the short time imposed by radioactive decay.

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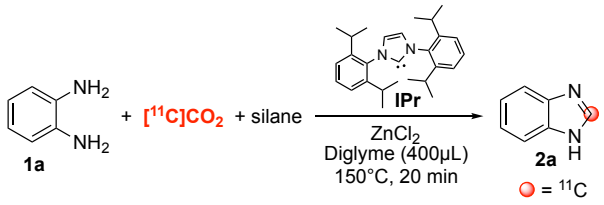
Table 1. Cyclization reaction with **1a** and $[^{11}C]CO_2$.



Entry	**1a** (mg)	$ZnCl_2$ (equiv.)	**IPr** (equiv.)	Silane (equiv.)	**2a**(%)[a]
1	10	0.15	0.15	$PhSiH_3$ (1.00)	68
2	ca. 1.1	0.15	0.15	$PhSiH_3$ (8.50)	27
3	ca. 1.1	1.2	1.2	$PhSiH_3$ (8.50)	52
4	ca. 1.1	1.2	1.2	$PhSiH_3$ (1.60)	-
5	ca. 1.1	-	1.2	$PhSiH_3$ (8.50)	-
6	ca. 1.1	1.2	1.2	PHMS (28.90)	32
7	ca. 1.1	1.2	1.2	Ph_2SiH_2 (11.00)	83
8	ca. 1.1	1.2[b]	1.2	Ph_2SiH_2 (11.00)	-

[a] Radiochemical yields (RCY) were estimated from trapped $[^{11}C]CO_2$ within the reactor and are decay-corrected from end of $[^{11}C]CO_2$ trapping inside reactor. [b] with $FeCl_3$ instead of $ZnCl_2$.

With $PhSiH_3$ as reducing agent, the cyclization reaction is in competition with methylation of amino groups which can proceed in similar conditions.[15] Indeed, some side-products arising from this methylation competitive reaction were also observed. To circumvent this drawback, less reducing silanes have been envisaged. If only low yields were obtained with PMHS (Poly(methylhydrosiloxane)), a higher and very good radiochemical yield was observed with Ph_2SiH_2 (entries 6-7). In this case, no methylation of amines was detected. Finally, $FeCl_3$ has also been envisaged as catalyst but without any success (entry 8).

Even if a reaction time of 20 min is compatible with carbon-11 radiolabeling, shorter durations are generally expected. Consequently, with optimal conditions (entry 7), reaction time was reduced to 10 min. An important decrease of radiochemical yield has been observed (Table 2, entries 1-2). Microwave activation was deleterious for the reaction, as already observed in the previously described radiomethylation reactions (entry 3).[15] Doubling catalysts amounts did not bring significant improvement (entry 4). In contrast, an increase of concentration of precursor **1a**, associated with a decrease of reaction volume, brought positive effects and excellent radiochemical yields were observed (entries 5-7). By switching from 200 µL to 100 µL, no significant improvement was observed. An attempt to reduce reaction time to 5 min led only to a medium result (entry 8). In view of these results, a volume of 200 µL will be generally preferred for further investigations, to avoid potential solubility problems.

Table 2. Effect of reaction time and solvent volume[a]

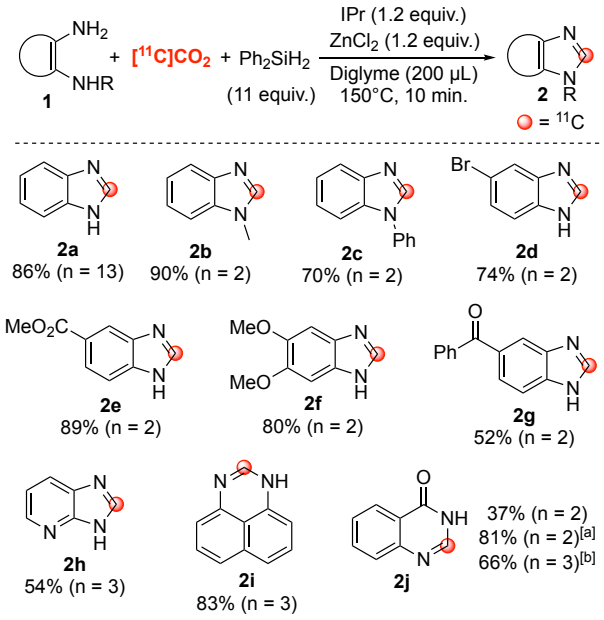
Entry	Reaction time (min)	Diglyme volume (µL)	**2a**(%)[b]
1	20	400	83
2	10	400	25
3	10[c]	400	1
4	10[d]	400	38
5	10	300	66
6	10	200	87
7	10	100	90
8	5	100	48

[a] Conditions: **1a** (1.1-2.2 mg), $ZnCl_2$ (1.2 equiv.), **IPr** (1.2 equiv.), Ph_2SiH_2 (11 equiv.), diglyme, 150°C, 10 min). [b] Radiochemical yields (RCY) were estimated from trapped $[^{11}C]CO_2$ within the reactor and are decay-corrected from end of $[^{11}C]CO_2$ trapping inside reactor. [c] under microwave irradiation (100 W). [d] $ZnCl_2$ (2.4 equiv.), **IPr** (2.4 equiv.).

In these optimal conditions, molar activity of produced benzimidazole **2a** was around 18 GBq/µmol. To study the scope of this radiolabeling, various aromatic diamines were then studied (Scheme 1).

Various benzimidazoles were obtained with, in general, satisfactory to good radiochemical yields. Substitution onto nitrogen atom does not significantly influence the obtained results (**2a**-**c**). Whatever the electronic character (electron withdrawing or donor) of aromatic substituents, similar yields were observed (**2a**-**f**). However, slightly lower yields were observed with **2g** and **2h**, maybe due to a competitive coordination of $ZnCl_2$ catalyst by the carbonyl function (**2g**) or the nitrogen atom of the pyridine core (**2h**). Interestingly, reaction is compatible with functional groups such as ketone (**2g**), ester (**2e**) or bromine (**2d**). In particular, no reduction side-products were detected.

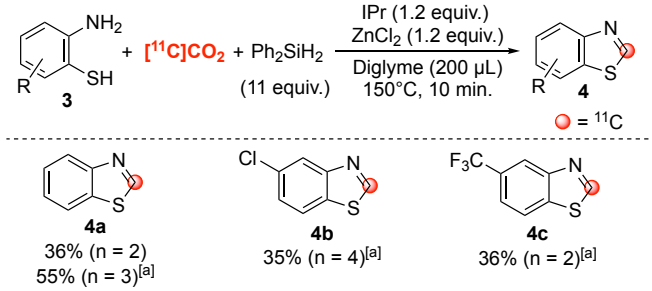
To extend this radiolabeling methodology, 6-membered rings have been also studied. Thus, perimidine **2i** was obtained with similar good yields compared to benzimidazoles. More interestingly, quinazolinone **2j** was also synthesized starting from corresponding 2-aminobenzamide. Because of the weakest nucleophilicity of amide group, the expected cyclic product was formed with only a medium radiochemical yield. However, a good result was achieved by doubling reaction time to 20 min. By decreasing solvent volume to 100 µL, a better yield was also observed in 10 min.



Scheme 1. Cyclizations of aromatic diamines with $[^{11}C]CO_2$. Radiochemical yields are mean values and were estimated from trapped $[^{11}C]CO_2$ within the reactor and are decay-corrected from end of $[^{11}C]CO_2$ trapping inside reactor. [a] reaction time = 20 min. [b] diglyme volume = 100 µL.

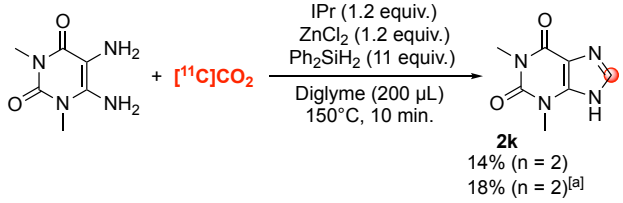
If benzimidazoles represent privileged structure in medicinal chemistry and drugs,[17] benzothiazoles are also important heterocyclic compounds in drug design and pharmaceutical agents.[18] This heterocycle is also used in radiotracers development, as illustrated by β-amyloid radioligand $[^{11}C]$PIB.[19] Consequently, our method was extended to aminobenzenethiols (**3**) to obtain, for the first time, intracyclically ^{11}C-labeled benzothiazoles **4** (Scheme 2).

With optimal conditions used for benzimidazoles, only modest radiochemical yield was observed (**4a**). As demonstrated previously (Scheme 1; **2j**), by decreasing solvent volume (100 µL instead of 200 µL), a better result is obtained. Nevertheless, in general, radiochemical yields remain modest, but suitable for workable radiolabelings.



Scheme 2. Cyclizations of aminobenzenethiols with $[^{11}C]CO_2$. Radiochemical yields are mean values and were estimated from trapped $[^{11}C]CO_2$ within the reactor and are decay-corrected from end of $[^{11}C]CO_2$ trapping inside reactor. [a] diglyme volume = 100 µL.

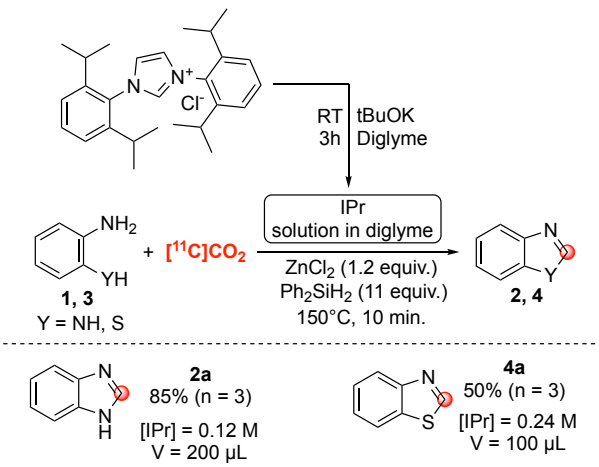
This one-step, late stage, intracyclic labeling has been applied to the first ^{11}C-labeling of theophylline drug[20] (**2k**), with intracyclic incorporation of radioisotope (Scheme 3).



Scheme 3. Intracyclic labelling of theophylline. Radiochemical yields are mean values and were estimated from trapped $[^{11}C]CO_2$ within the reactor and are decay-corrected from end of $[^{11}C]CO_2$ trapping inside reactor. [a] diglyme volume = 100 µL

$[^{11}C]$Theophylline was obtained in a modest radiochemical yield. However, in view of the low reactivity of the starting diamine, the result remains quite satisfactory and demonstrates the usefulness of this method to label elaborated molecules.

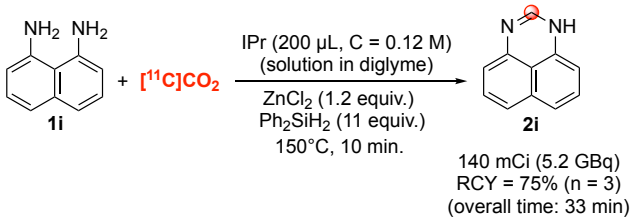
During these previous investigations, some reproducibility issues were observed with a batch of **IPr**. Despite various analyses of the different batches of **IPr**, we have not succeeded to determine the reasons of such issues. Consequently, to try to circumvent such potential drawback, a preliminary preparation of **IPr** solutions in diglyme, just before use, was envisaged (Scheme 4). In comparison to commercial **IPr**, similar results were observed with benzimidazole or benzothiazole. This use of home-made solution of **IPr** constitutes a valuable alternative to potential reproducibility issue and we warmly recommend this simple to implement solution to avoid some disappointments during radiolabelings.



Scheme 4. Cyclization reactions with home-made solution of IPr. Radiochemical yields are mean values and were estimated from trapped $[^{11}C]CO_2$ within the reactor and are decay-corrected from end of $[^{11}C]CO_2$ trapping inside reactor.

Finally, in order to demonstrate the effective productivity of this new radiolabeling approach, a full radiosynthesis, with HPLC

purification, was performed with perimidine **2i** (Scheme 5). Noteworthy, a home-made solution of **IPr** was preferred.



Scheme 5. Production of perimidine **2i**. The RCY value is mean value and was estimated from trapped $[^{11}C]CO_2$ within the reactor and are decay-corrected from end of $[^{11}C]CO_2$ trapping inside reactor.

A good radioactive quantity (140 mCi, 5.2 GBq) of $[^{11}C]$perimidine (**2i**) was produced with a high radiochemical yield (RCY = 75%) and with a good radiochemical and chemical purity. This result is very encouraging and demonstrates the usefulness of this original radiolabeling method to produce radiotracers.

Conclusions

To conclude, cyclization reactions by direct use of cyclotron-produced $[^{11}C]CO_2$ were described to obtain in a late stage and one-pot process, heterocyclic and heteroaromatic compounds intracyclically labeled with carbon-11. This strategy constitutes a proof of concept about direct use of $[^{11}C]CO_2$ in "radiocyclization" reactions and should open the way to new developments concerning radiolabeling of heterocyclic molecules.

Experimental Section

Synthesis of $[^{11}C]$perimidine (2i): 200 µL of freshly prepared **IPr** solution in diglyme (24 µmol, 1.2 eq) was added to a 1 mL vial containing 3.15 mg of 1,8-diaminonaphtalene (20 µmol, 1eq). The resulting solution was sonicated for 2 min and transferred to a 1.1 mL conical vial pre-charged with 3.35 mg of zinc chloride (24.2 µmol, 1.21 eq). After addition of 40 µL of diphenylsilane (0.215 mmol, 11 eq), the vial was sealed and placed into the automated synthesis module 10 min before end of bombardment. When the desired level of radioactivity was reached in cyclotron (nearly 3000 mCi – 111 GBq), reaction with $[^{11}C]CO_2$ proceeded according previous general procedure (see SI). After 10 min of heating at 150°C, the reaction vial was cooled at 20°C for 2.5 minutes. Then, 2 x 100 µL of MeOH were sequentially added to the reaction mixture (30 seconds apart) and after further 20 seconds, the whole content of the reaction vial was loaded into a 3 mL HPLC loop. 700 µL of additional MeOH were used for rinsing the reaction vial and loaded into the HPLC loop before injection on semi-preparative HPLC column (Macherey-Nagel Nucleodur C18 HTec column (10µm, 10 x 250mm). HPLC purification was conducted at 3 mL/min with acetate buffer pH 5.2/MeCN (55/45) as mobile phase. Radioactive and UV monitoring at 254 nm allowed the collection of 346-386 mCi (12.8-14.3 GBq, decay-corrected) of purified 1H-$[^{11}C]$Perimidine **2i**. Retention time was 8 minutes. Radiochemical yields were ranging from 70 to 80% decay-corrected.

Acknowledgements ((optional))

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Keywords: Carbon-11 • Heterocycles • Radiochemistry • Radiolabeling • Positron emission tomography

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