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DOI: 10.1039/D0CC05031H

COMMUNICATION

Carbon Isotope Labeling of Carbamates by Late-Stage [^{11}C], [^{13}C] and [^{14}C] Carbon Dioxide Incorporation

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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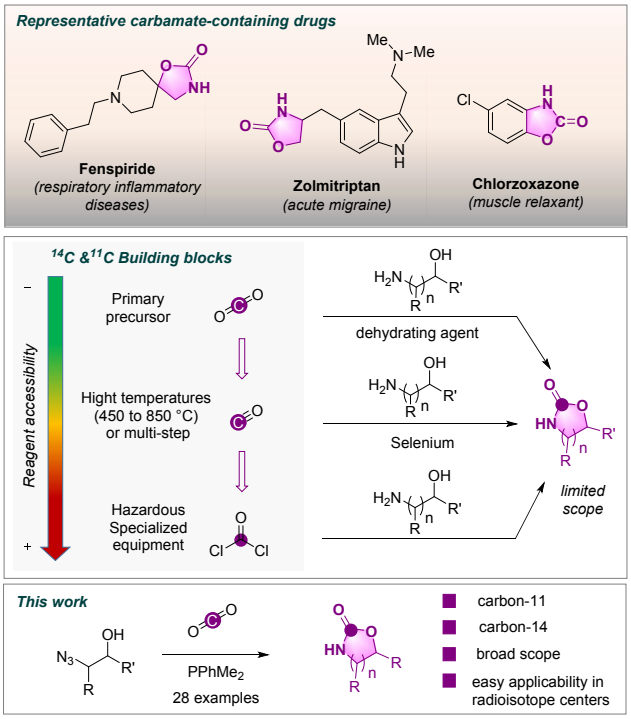
A general procedure for the late-stage [^{11}C], [^{13}C] and [^{14}C]carbon isotope labeling of cyclic carbamates is reported. This protocol allows the incorporation of carbon dioxide, the primary source of carbon-14 and carbon-11 radioisotopes, in a direct, cost-effective and sustainable manner. This method was applied to a variety of carbamates, including pharmaceuticals. A disconnection / reconnection strategy, involving ring opening / isotopic closure, was also implemented.

Introduction

Radiolabeling with carbon isotopes is an attractive strategy in human/veterinary drug development, as well as in plant protecting agent research.[1] The two relevant radioactive isotopes of carbon display antipodean physical properties, which usually require *ad hoc* strategies for their insertion into organic structures. Carbon-14 (^{14}C) is a long-lived β^- emitter relevant in the determination of (pre)clinical drug metabolism and biodistribution.[2] ^{14}C radio-synthesis remains challenging due to the limited number of available row materials, prohibitive costs and generation of long lasting waste ($t_{1/2}$ 5730 years).[3] On the other hand, carbon-11 (^{11}C) is a short-lived positron emitter (β^+), whose implication in positron emission tomography (PET) can hardly be overstated. Challenges related to the 20.4 minutes half-life and the limited amounts of isotope generated by a cyclotron dramatically affect the chemical space tackled in PET centers.[4] In such a dichotomy, the two isotopes share the same primary chemical source: carbon dioxide ([^{14}C]CO_2 and [^{11}C]CO_2). Given the complementarity of their applications, drug discovery would highly benefit from general procedures easily transmutable to both ^{11}C and ^{14}C radioisotopes. Unfortunately, recent developments in late-stage carbon isotope labeling are specific and unsuitable for application to both radioisotopes, either due to practical and/or safety related issues.[5,6] Carbamates are a fundamental functional group, largely found in biologically active compounds and marketed pharmaceuticals (Scheme 1, top).[7] In particular, cyclic carbamates are generally metabolically stable and the carbonyl moiety represents a suitable position for labeling.[8] Due to its high reactivity, the use of [^{14}C] and [^{11}C]phosgene has been investigated, but shortcomings related to safety and the requirement for specialized apparatus have largely limited its utilization (Scheme 1, bottom).[9] In 2002, Långström reported a selenium-mediated carbamoylation reaction in presence of [^{11}C]carbon monoxide.[10] The procedure was applied to simple carbamate derivatives, and later on one drug (Zolmitriptan).[11,12] Methods that utilize [^{11}C]CO_2 and [^{14}C]CO_2 are appealing, but their application was mainly focused on linear carbamates.[13]



Scheme 1. Top: Relevant examples of cyclic carbamates containing pharmaceuticals; middle: synthetic strategies for cyclic carbamate radiosyntesis; bottom: Staudinger / aza-Wittig approach.

Vasdev and co-workers labeled cyclic carbamate [^{11}C]SL25.1188 using BEMP as fixating base in presence of $POCl_3$ as dehydrating reagent.[14] In 2019, Horkka *et al.* reported a procedure where the dehydration step was performed under Mitsunobu conditions, and labeled one cyclic carbamate, benzoxazol-2-one.[15] Very recently, Jakobsson *et al*. reported the synthesis of [^{11}C]carbonyl difluoride.[16] While this reagent has a similar reactivity to phosgene, it is generated from [^{11}C]CO,[17] a secondary precursor obtained from [^{11}C]CO_2 with technically challenging and time-consuming conditions which are unpractical to implement in most PET centers. The current state of the art highlights the need for general procedures that would prove effective on elaborate molecules. Here, we report on a late-stage

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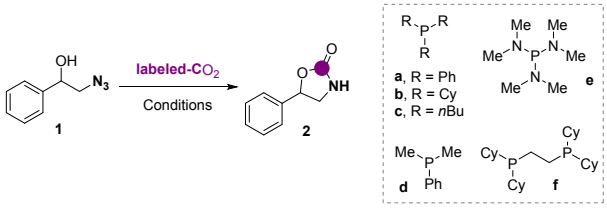
labeling of cyclic carbamates that utilized CO_2 as isotope source. This procedure is suitable to ^{13}C, ^{11}C and ^{14}C, on a variety of substrates including pharmaceuticals.

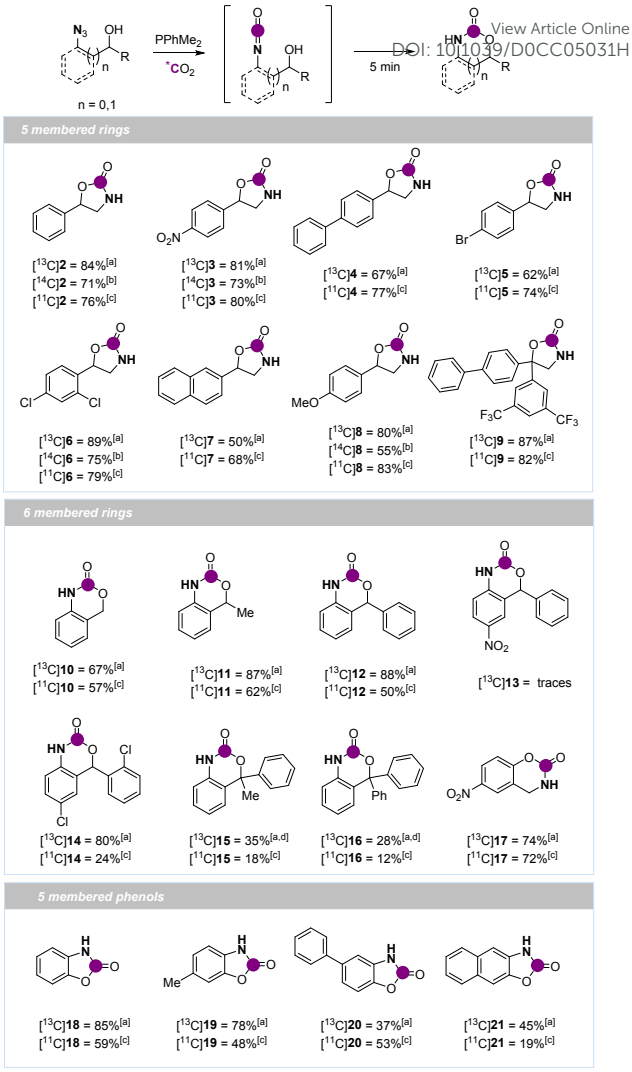
Our recent results on the late-stage labeling of cyclic ureas[18] encouraged us to investigate a Staudinger aza-Wittig approach (SAW) for the ^{14}C- and ^{11}C-labeling of cyclic carbamates, directly from CO_2. Reaction optimization was conducted at room temperature in 5 minutes on model substrate **1**, using stoichiometric $[^{13}C]CO_2$, as ^{14}C-surrogate, and its precise addition was monitored utilizing a RC Tritec manifold.



Entry	*CO_2	Phosphine	Temperature	Time	Yield (%)
1	$[^{13}C]CO_2$	**a**	25 °C	5 min	63
2	$[^{13}C]CO_2$	**b**	25 °C	5 min	46
3	$[^{13}C]CO_2$	**c**	25 °C	5 min	62
4	$[^{13}C]CO_2$	**d**	25 °C	5 min	84
5	$[^{13}C]CO_2$	**e**	25 °C	5 min	0
6	$[^{13}C]CO_2$	**f**	25 °C	5 min	0
7	$[^{14}C]CO_2$	**d**	25 °C	5 min	71[a]
8	$[^{11}C]CO_2$	**d**	70 °C	5 min	76[b]

Table 1. Optimization of the Staudinger aza-Wittig procedure [a] radiochemical yield; [b] decay-corrected radiochemical conversion. Carbon-13 and -14 experiments were performed in 0.7 mL DMF on a 0.1 mmol scale, in presence of stoichiometric amounts of $[^{13}C$ and $^{14}C]CO_2$; for carbon-11 labeling, precursor **1** and the phosphine were typically in a 100-fold excess compared to $[^{11}C]CO_2$.[20]

As expected, the nature of the phosphine had a major impact on the transformation. While the use of triphenylphosphine (**a**) allowed the formation of **[^{13}C]2** in 63% isolated yield, with electron-rich tricyclohexylphosphine (**b**) the yield dropped to 46%. When tri-*n*-butylphosphine (**c**) was utilized, carbamate **[^{13}C]2** was isolated in 62% yield. The best result was obtained with dimethylphenylphosphine (**d**) which provided the corresponding [^{13}C]carbamate with 84% isolated yield. The use of (**e**), reminder of the core structure of commonly used iminophosphoranes trapping agents such as BEMP, was unproductive. While the phosphazide is formed rapidly from (**e**), the subsequent nitrogen release required harsh conditions, as reported by Lyapkalo and co-workers.[19] Finally, the use of bidentate phosphine (**f**) did not provide the desired product.[20] Without further optimization, the procedure was applied to ^{14}C. Pleasingly, **[^{14}C]2** was isolated in 71% RCY directly from $[^{14}C]CO_2$. Compared to previous methods, this procedure is cost-effective and drastically minimizes the generation of radioactive waste. Based on the short reaction time required, application to ^{11}C-labeling seemed feasible. Despite the diametrically different environment and the CO_2 stoichiometry, **[^{11}C]2** was labeled in 76% decay-corrected (d.c.) RCC, under slightly different conditions (70 °C). Importantly, the radiosynthesis was carried out in automated modules, according to nuclear safety requirements for PET tracers production.



Scheme 2. Late-stage labeling of cyclic carbamates with carbon isotopes. [a] Yield of the isolated product; [b] radiochemical yield; [c] d.c. radiochemical conversion; [d] reaction temperature, 150 °C.[20]

Next, we explored the scope on a series of substituted azido alcohols (Scheme 2).[21] Aliphatic 5-membered carbamates were labeled with ^{13}C to provide **[^{13}C]3** to **[^{13}C]9** in 50 to 89% yield. The electronic nature of substituents on the aromatic ring did not affect the reaction outcome and also a sterically hindered quaternary alcohol precursor delivered **9** in 87% yield. Selected substrates were labeled with radiocarbon, to provide **[^{14}C]2**, **3**, **6** and **8** in 55 to 75% RCY, under otherwise identical reaction conditions. Pleasingly, ^{11}C labeling proceeded smoothly in all tested substrates in 68 to 83% d.c. RCC. Next, we looked at the labeling of six membered ring carbamates. The presence of a methyl or phenyl substituent in *alpha* position to the hydroxyl did not affect its reactivity and 2-benzoxazinones **10**-**12** could be efficiently labeled with ^{13}C and ^{11}C isotopes. These derivatives would be quite challenging to label with current methods using CO_2, because of the poor nucleophilicity of anilines.[13] On the other hand, from tertiary alcohol precursors, derivatives **15** and **16** were delivered with a significant drop in the yields and required higher reaction temperature (Scheme 2). In addition, when a strong electron-withdrawing *p*-NO_2 substituent was present on the aromatic azide, only traces amounts of **[^{13}C]13** were recovered. The increased electrophilicity of the isocyanate

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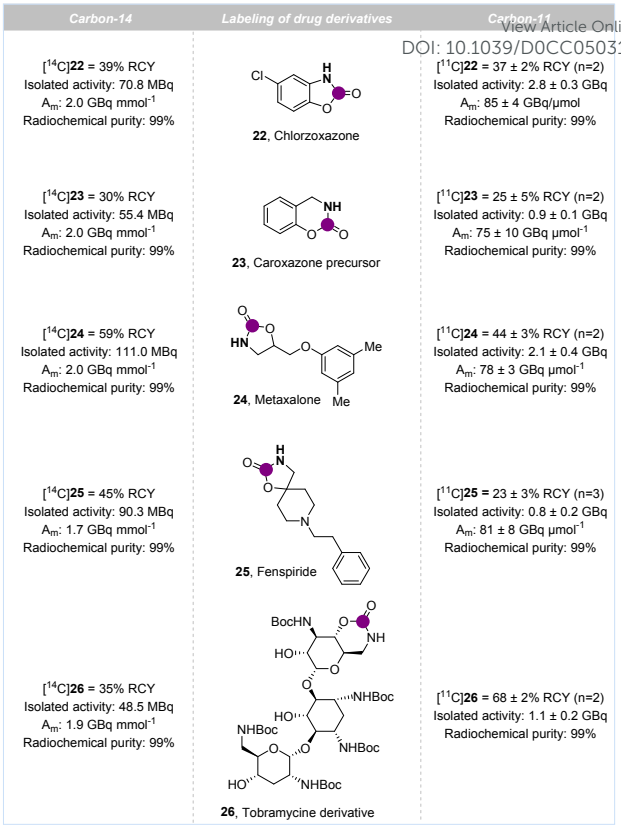
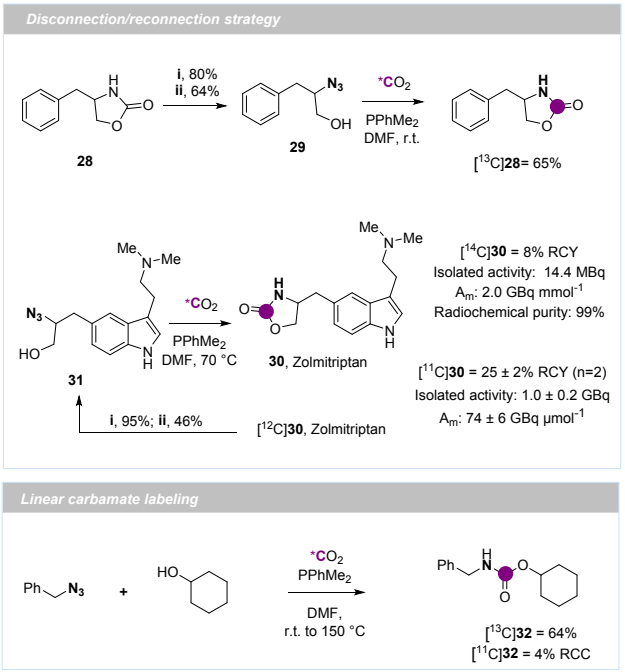
intermediate, which presumably undergoes fast hydrolysis under the reaction conditions, was detrimental to the process. Interestingly, also regioisomeric carbamate **17** could be labeled both with ^{11}C and ^{13}C from the corresponding benzylic azide precursor. In this case, the presence of a nitro group in *para* position to the alcohol was well tolerated: **[^{13}C]17** and **[^{11}C]17** were obtained in 74% and 72% d.c. RCC, respectively. Benzoxazol-2-ones are widely present in pharmaceuticals and their late-stage labeling is a worthwhile endeavour.[22] After some optimization, benzoxazol-2-ones **18**-**21** could be labeled with ^{13}C, in presence of 2 equiv. of DIPEA. Interestingly, the use of CO_2 fixating agents such as DBU, DABCO, DBN and TBD was detrimental to the reaction outcome and did not provide formation of the desired product.[20] On the other hand, when the reaction on model substrate **18** was performed in the absence of DIPEA, the isolated yield dropped to 64%.[20] For short-lived ^{11}C, the optimal conditions were in absence of additive; gentle heating at 70 °C was required and **[^{11}C]18**-**21** were obtained in 19 to 59% RCC. With these results in hand, we next turned our attention to the labeling of pharmaceutically relevant derivatives (Scheme 3). Chlorzoxazone, a FDA approved drug displaying muscle relaxant properties,[23] was labeled from the corresponding azidoalcohol precursor under standard conditions to isolate **[^{14}C]22** in 39% RCY and high molar activity (A_m) 2.0 GBq mmol^{-1}. The short-lived isotopomer, ready-to-inject **[^{11}C]22** was isolated after HPLC purification and formulation in 37 ± 2% d.c. RCY and d.c. A_m of 85 ± 4 GBq/µmol. Caroxazone precursor **23** was labeled in 30% RCY from [^{14}C]CO_2 and 25 ± 5% RCY from [^{11}C]CO_2. Metaxalone, an aliphatic five-membered carbamate with muscle relaxant properties, was obtained in 59% RCY and 44 ± 3% d.c. RCY with carbon-14 and carbon-11, respectively. Next, we focused on Fenspiride, an anti-inflammatory drug, which was recently labeled with tritium.[24] The required *beta*-azido alcohol precursor was obtained in a three-step sequence, including an alkylation, a Corey-Chaykovsky epoxidation and a regioselective ring opening azidation from commercially available materials.[20] This substrate underwent ^{14}C-labeling in 45% RCY and ^{11}C-labeling in 23 ± 3% d.c. RCY. The procedure was also applied for the ^{14}C and ^{11}C labeling of N-Boc protected Tobramycine derivative **26**,[25] on a non-pharmacophoric position, according to previous SAR studies.[26] The SAW approach allowed to isolate the carbamates **[^{14}C]26** and **[^{11}C]26** in 35% and 68 ± 2% d.c. RCY, respectively. In all cases, consistent high A_m and radiochemical purities for both radioisotopes were obtained. The concept of isotope exchange has been largely exploited for hydrogen,[27] but only recently introduced for carbon and, to our knowledge, strictly limited to carboxylic acids.[5] In order to accelerate the access to labeled carbamates and limit the synthesis of precursors, we envisioned a disconnection/reconnection strategy (DRS).[9a] The DRS was first validated on model compound **28**. After carbamate cleavage under strong basic conditions, the corresponding *beta*-amino alcohol underwent a diazo-transfer reaction to obtain the azido alcohol **29** and further converted into **[^{13}C]28** in 65% yield. With this procedure in hand, we next looked to Zolmitriptan, a compound in use for the treatment of acute migraine, commercialized by AstraZeneca. From commercially available unlabeled Zolmitriptan, the azido alcohol **31** was obtained in 46% yield, over two steps. Subsequent SAW reaction allowed to obtain **[^{14}C]30** in moderated 8% RCY, nonetheless with a high A_m of 2 GBq mmol^{-1}. Carbon-11 labeled Zolmitriptan was also synthesized in 25 ± 2% RCY and A_m 74 ± 6 GBq/µmol. Compared to the previous ^{11}C-labeling performed using [^{11}C]CO and selenium,[10,28] this procedure has the advantage to use a more readily accessible carbon-11 source (*i.e.* [^{11}C]CO_2) and avoid the manipulation of selenium derivatives.



Scheme 3. Late-stage radiolabeling of pharmaceutically relevant carbamates. RCY: radiochemical yield; A_m : molar activity. For carbon-11, RCY and A_m are decay-corrected.



Scheme 4. Top: disconnection/reconnection strategy labeling of carbamates with carbon dioxide. Conditions: i) KOH, EtOH/H_2O (4:1), 100 °C, ii) TfN_3, DCM, $CuSO_4$,$5H_2O$, K_2CO_3, MeOH, overnight, r.t. (see SI for details). Bottom: labeling of linear carbamates.

Additionally, the DRS was also successfully performed on Fenspiride.[20] Finally, we looked to extend the methodology to linear carbamates. Although metabolically more labile and generally used as prodrugs, linear carbamates have been labeled with ^{11}C with more

or less success and usually under harsh conditions. For a first proof of concept, we selected substrate **32** that proved highly challenging with previous methods.[13c,29] After some optimization of the intermolecular reaction, **[^{13}C]32** was labeled in 64% yield, after heating the mixture for 15 min at 150 °C. For the application to ^{11}C, the product was observed only in 4% d.c. RCC. This result clearly highlights the challenges related to the inherent physical and technical differences between carbon isotopes. Thought preliminary, this work shows the possibility to reach challenging linear carbamate systems. To conclude, a general methodology for the radiolabeling of cyclic aliphatic and aromatic carbamates has been developed. The reaction takes place with controlled amounts of CO_2, the first available building block for ^{14}C and ^{11}C radioisotopes, resulting in a late-stage carbon isotope labeling of carbamate-containing drugs and analogues. A disconnection/reconnection strategy was successfully implemented thus simplifying the synthesis of precursor and accelerating the whole labeling process. Finally, a proof of concept was obtained with a more challenging linear carbamate.

Acknowledgments

This project received funding from the European Union's Horizon 2020 research and innovation program under the Marie Sklodowska-Curie (g. a. N°675071) and CEA. The authors thank D.-A. Buisson, A. Goudet, S. Lebrequier and E. Marcon for the excellent analytical support and Dr. B. Kuhnast for helpful discussion.

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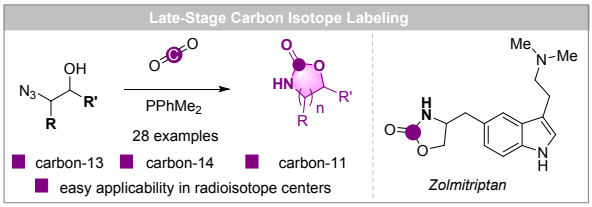

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A general procedure which allows to label cyclic carbamates with all carbon isotopes (^{11}C, ^{13}C, ^{14}C) has been developed. This mild protocol valorizes carbon dioxide, the universal building block for radiolabeling. A series of pharmaceuticals were obtained in high radiochemical yield and purity and a disconnection/reconnection strategy was implemented.