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Late-stage isotopic carbon labeling of pharmaceutically relevant cyclic ureas directly from CO_2

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Dedicated to Dr. Louis Pichat on the occasion of his 92nd birthday

Abstract: A robust, click chemistry inspired procedure for radiolabeling of cyclic ureas was developed. This protocol, suitable for all carbon isotopes (^{11}C, ^{13}C, ^{14}C), is based on the direct functionalization of carbon dioxide: the universal building block for carbon radiolabeling. The strategy is operationally simple, reproducible in different radiochemistry centers, exhibits a remarkably wide substrate scope with short reaction times, and demonstrates superior reactivity compared to previously reported systems. With this procedure, a variety of pharmaceuticals and an unprotected peptide were labeled with high radiochemical efficiency.

Radioisotope labeling has a remarkable impact on our society and particularly on public health: from the collection of precious preclinical absorption, distribution, metabolism, excretion (ADME) and toxicological data, required for drug development and registration with long lived β^- isotopes,[1] to the early diagnosis of disease with non-invasive positron emission tomography (PET) imaging with short lived β^+ radiotracers.[2] Late-stage labeling is the most effective strategy to introduce the radioisotope into the desired organic molecule: allowing its insertion at the last step of the synthesis it provides a beneficial impact on the overall efficiency of the process. Recent developments in late-stage tritium (^3H)[3,4] and fluorine-18 (^{18}F)[5,6] labeling clearly showcased the benefits of such an approach. Carbon is ubiquitously present in nature and it is the overriding choice for isotopic radiolabeling of pharmaceuticals and agrochemicals. Two radioisotopes with diametrically opposite physical properties are commonly used: carbon-14 (β^- emitter, half-life 5730 years) and carbon-11 (β^+ emitter, half-life 20.4 min). Carbon-14 is a favoured isotope in drug development and is often preferred to tritium because of a higher metabolic stability. This natural radioisotope is generated as $Ba[^{14}C]CO_3$, which is further converted to $[^{14}C]CO_2$, the universal precursor of all ^{14}C labeled compounds. Traditionally, $[^{14}C]CO_2$ functionalization requires multi-step approaches and results in the production of long lasting radioactive waste.[7] Carbon-11 would be the most general radioisotope for PET tracers but its narrow half-life makes ^{11}C labeled radiopharmaceuticals extremely challenging to prepare.[8] One major ^{11}C primary precursor produced by cyclotrons is $[^{11}C]CO_2$,[9] an almost chemically inert molecule that is not trivial to introduce directly into complex molecules as pharmaceuticals. Due to such restrictions, the most frequently used method for the introduction of ^{11}C into organic molecules is methylation.[10] $[^{11}C]CO_2$ is transformed into a methylating agent (typically $[^{11}C]CH_3I$ or $[^{11}C]CH_3OTf$) by a series of reactions, which are time and material consuming. Alternatives to methylation are known but seldom applied to pharmaceutically relevant molecules and biomolecules.[11, 12, 13] The development of methodologies capable of converting CO_2 directly into the desired scaffolds, in one single operation, at a late-stage of the synthesis would be highly beneficial for the radiolabeling with carbon isotopes.

Urea is a fundamental functional group in organic chemistry commonly found in pharmaceuticals and dyes (Scheme 1a).[14] Despite its chemical and metabolic stability, no general and efficient labeling protocol has been reported so far. Cyclic ureas have been traditionally labeled using [^{11}C and ^{14}C]-phosgene,[15] a highly toxic radioactive reagent, which can be synthesized only in a rather limited number of laboratories on a routine basis. More recently, a number of methods have been described using carbon monoxide [^{11}C and ^{14}C]CO and metal catalysts or selenium at high pressures (scheme 1b).[11, 16] Alternatives utilizing directly [^{11}C and ^{14}C]CO_2 in presence of 2-tert-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2- diaza phosphorine (BEMP) and $POCl_3$ display limited functional group tolerance.[17]

In this communication, we describe a one-pot operationally simple labeling procedure for the synthesis of cyclic ureas using a sequential Staudinger/Aza-Wittig (SAW) approach directly from [^{11}C and ^{14}C]CO_2. This example of late-stage labeling proved to be broad in scope, highly tolerant towards functional groups, suitable for all isotopes of carbon and effective for the labeling of drugs and an unprotected peptide.

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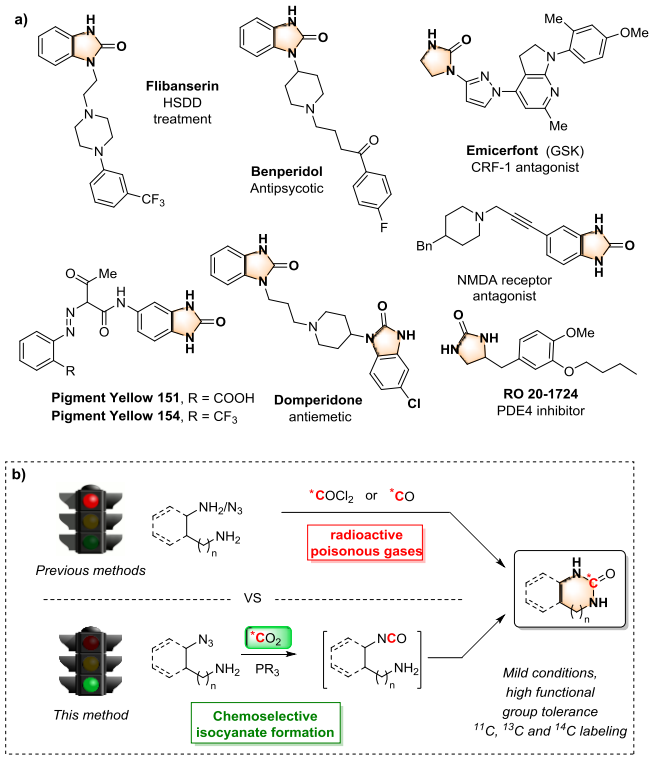
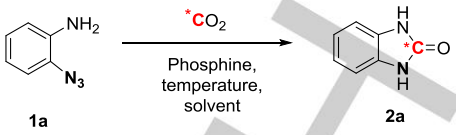


Scheme 1. a) Relevant examples of cyclic ureas; b) synthetic strategies to access radiolabeled ureas.

At the outset, we aimed to develop a general approach to radiolabel cyclic ureas and we reasoned that click chemistry might be a source of inspiration. Azides play a central role in click chemistry and the Staudinger ligation shows high substrate compatibility and is effective even in complex biological media.[18] The *o*-azidoaniline **1a** was identified as an ideal building block. When **1a** was reacted in presence of a phosphine and CO_2 the resulting iminophosphorane undergoes an aza-Wittig reaction to generate an intermediate isocyanate and subsequent intramolecular nucleophile addition delivers the cyclized urea product. Since in radiochemistry CO_2 is the limiting reagent, the optimization of the reaction was performed using a Tritec manifold to precisely deliver stoichiometric amounts of ^{13}C-labeled gas (see SI for details). From preliminary screening experiments, dimethylphenylphosphine (PMe_2Ph) was identified as a superior reducing agent (Table 1 and SI).

Compared to less nucleophilic and more sterically hindered Ph_3P and $MePh_2P$ (Table 1, entry 1-4), PMe_2Ph was highly effective delivering the desired benzoimidazolone ^{13}C-**2a** in only 5 minutes at room temperature (see Table 1, entry 6 and SI for more details). Solvent screening revealed that MeCN and DMF were both suitable for the transformation. Under the optimized reaction conditions in presence of radiolabeled $[^{14}C]CO_2$, **1a** was converted into the labeled urea ^{14}C-**2a** in a remarkable 95% radiochemical yield (RCY). It is worth noting that the transformation required only a stoichiometric amount of $[^{14}C]CO_2$ and a single purification step, thus minimizing the radioactive waste generated and representing a rare example of environmentally sustainable radiolabeling.

Table 1. Optimization of the Staudinger/aza-Wittig with stoichiometric CO_2.



Entry	*CO_2	Phosphine	Temperature	Time	Yield (%)
1	$[^{13}C]CO_2$	PPh_3	65 °C	2h	90
2	$[^{13}C]CO_2$	PPh_3	25 °C	2h	80
3	$[^{13}C]CO_2$	PPh_2Me	25 °C	2h	95
4	$[^{13}C]CO_2$	PPh_2Me	25 °C	1h	84
5	$[^{13}C]CO_2$	$PPhMe_2$	25 °C	1h	95
6	$[^{13}C]CO_2$	$PPhMe_2$	25 °C	5 min	95
7	$[^{14}C]CO_2$	$PPhMe_2$	25 °C	5 min	90[a]
8	$[^{11}C]CO_2$	$PPhMe_2$	25 °C	5 min	79[b]

[a] radiochemical yield; [b] radiochemical conversion. Carbon-13 and -14 experiments were performed in presence of stoichiometric amounts of [^{13}C and $^{14}C]CO_2$; for carbon-11 labeling, precursor **1a** and the phosphine were typically in a 100-fold excess compared to $[^{11}C]CO_2$ (see SI for details).

Encouraged by the exceptionally short time required to reach full conversion, we next looked at its application to ^{11}C-labeling. In stark contrast to ^{14}C, $[^{11}C]CO_2$ is generated using a cyclotron in nanomolar amounts, thus forcing a complete modification of the stoichiometry of the reaction and the use of **1a** and phosphine in large excess compared to $[^{11}C]CO_2$. We were pleased to observe that this protocol was easy to implement and $[^{11}C]$-**2a** was obtained in 79% radiochemical conversion (RCC), without need of CO_2 trapping agents.[19] The radiosynthesis was carried out in automated modules and proved to be compliant with GMP procedures.

We next investigated the substrate scope in the presence of a variety of substituted aromatic *o*-azido anilines, synthesized according to literature procedures (Scheme 2).[20] A whole range of benzoimidazolones **2a-n** were labeled in good to excellent yields both with carbon-13 and carbon-11. Not surprisingly, electron rich anilines proved to be competent substrates for the transformation (**2e-f**). The presence of halogens (**2b-d**) and sterically hindered substituents in *ortho* to the reactive azide (**2i-k**) did not affect the transformation, while electron-withdrawing groups allowed to obtain the product in moderate yields (**2g** and **2h**).

When secondary anilines were used, the desired products **2l-n** were obtained in 52% to 78% yields for carbon-13 and 55% to 62% RCC for carbon-11. The use of simple, reproducible and easy to implement protocols is highly desirable in radiochemistry and particularly for positon emitters, where isotope manipulation is restricted by the use of automated facilities. In this respect, the current technology was successfully implemented in two PET centers, with different automated systems, clearly highlighting the robusteness of this protocol (see SI for details).

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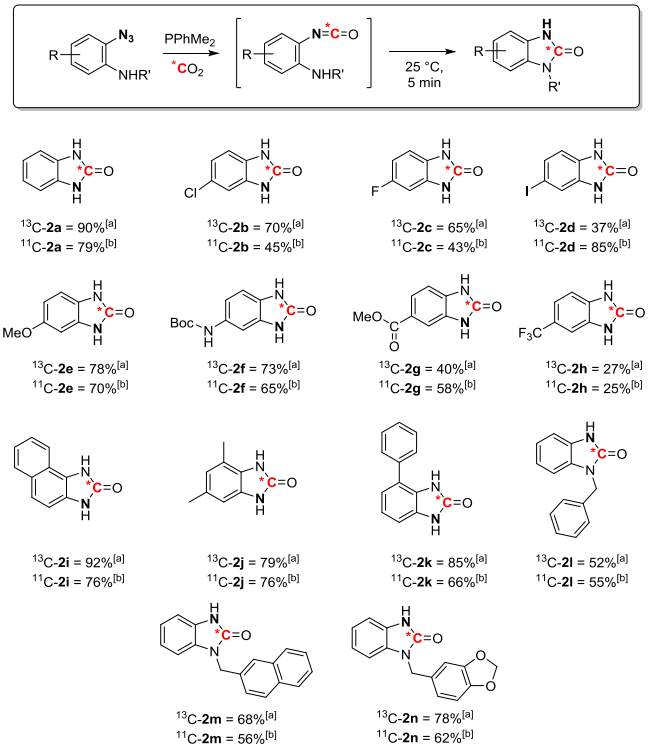
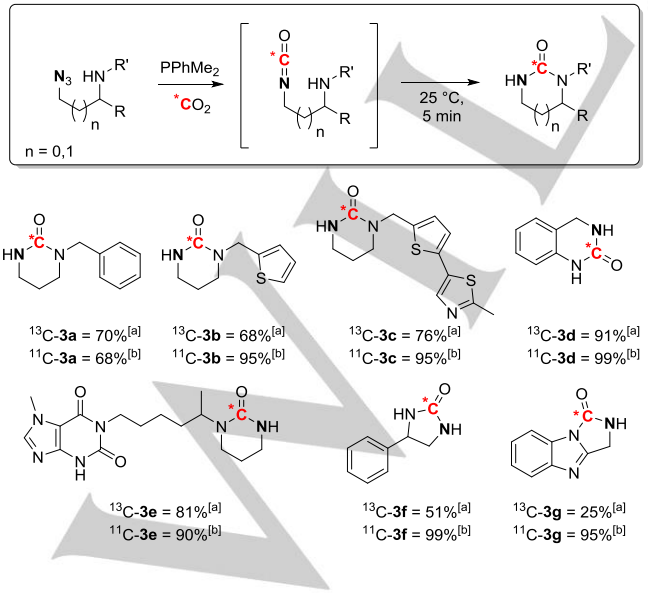


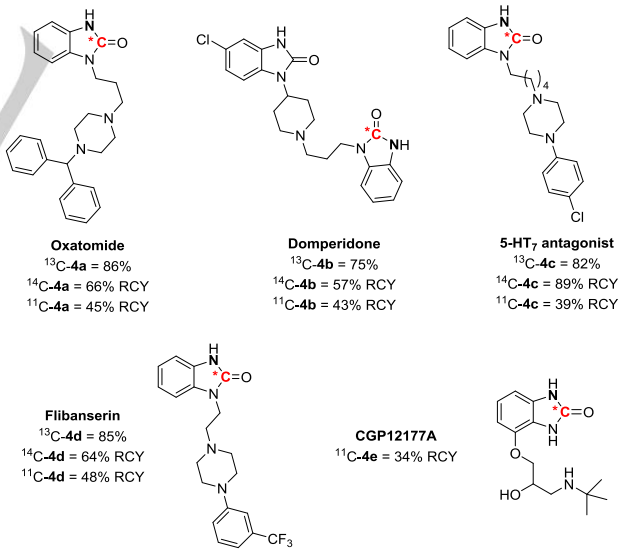
Scheme 2. Late stage labeling of benzoimidazolones with carbon isotopes. The position of the azide on the *o*-azido aniline precursor is highlighted in bold. [a] Isolated yield; [b] radiochemical conversion.

A variety of aliphatic ureas were also succesfully labeled using this procedure. Six membered derivatives **3a-d** were isolated in good to excellent yields. Interestingly, the presence of the guanine ring did not affect the efficiency of the transformation (**3e**). Five membered derivative **3f** was obtained in 51% and 99% with carbon-13 and -11, respectively. Notably, tricyclic urea **3g** was obtained from the corresponding benzimidazole precursor.



Scheme 3. Late stage labeling of aliphatic ureas with carbon isotopes. The position of the azide on the *o*-azido aniline precursor is highlighted in bold. [a] Isolated yield; [b] radiochemical conversion.

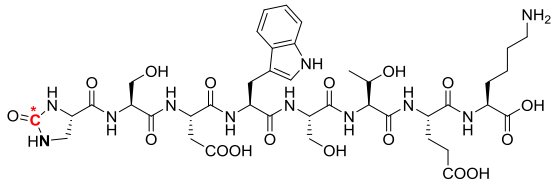
The promising functional group orthogonality of this approach together with the successful implementation to both carbon-13 and carbon-11 prompted the evaluation of the isotopic labeling of pharmaceutically relevant ureas (Scheme 4). Oxatomide, an orally active antihistaminic, was labeled in 86% yield with carbon-13 and 66% radiochemical yield (RCY) with ^{14}C,[21] while ^{11}C-**4a** was obtained ready-to-inject in 45% RCY (molar activity: 75 GBq/μmol) within 30 minutes from the end of bombardment (EOB). Domperidone, a commercially available antiemetic drug, was successfully labeled in 57% RCY from [^{14}C]CO_2 and 43% RCY from [^{11}C]CO_2. The 5-HT_7 antagonist **4c**, whose fluorinated analogue was previously labeled with the short-lived PET isotope fluorine-18,[22] was obtained in 89% and 39% RCY respectively using carbon-14 and carbon-11 isotopes. Flibanserin, a medication approved for the treatment of pre-menopausal women with hypoactive sexual desire disorder (HSDD), was easily labeled in 64% and 48% RCY using carbon-14 and carbon-11 respectively. Finally, CGP12177A, a tracer for β-adrenergic receptor was obtained in 35% isolated RCY and a molar activity of 32 GBq/μmol. In comparison with the previously reported radiosynthesis of ^{11}C-CGP12177A using [^{11}C]phosgene,[23] the SAW approach afforded higher yields and a shorter process without the use of hazardous chemicals. In all cases, the ready-to-inject labeled drugs were isolated in high chemical and radiochemical purities. In addition, the azide precursors were easily synthetized in two linear steps from commercially available anilines.



Scheme 4. Late-stage carbon isotope labeling of pharmaceutically relevant ureas. RCY: radiochemical yield. The position of the azide on the *o*-azido aniline precursor is highlighted in bold.

The use of radiolabeled peptides and proteins as imaging tools for drug development and clinical diagnostics has recently attracted considerable attention.[24] In 2017, two major contributions from Buchwald and Hooker[24b] using H[^{11}C]CN as labeled building block and from Antoni and Skrydstrup[24c] utilizing

[^{11}C]CO were reported. Both methods use efficient metal catalysts for the insertion of the desired tag on series of peptides.



^{14}C-**5** = 43%[a]
^{11}C-**5** = 23%[b]

Scheme 5. Late stage labeling of peptide **5**. The position of the azide on the *o*-azido aniline precursor is highlighted in bold. [a] Isolated yield; [b] radiochemical conversion.

Considering the high efficiency and orthogonality of the SAW sequence, we applied it to a designed peptide sequence bearing the desired azido-amine group and most of the classical reactive moieties displayed by amino acids (alcohols, carboxylic acids, amine, indole). To our delight, we observed a very clean reaction under the optimized reaction conditions affording the radiolabeling of **5** with an encouraging 43% yield from [^{14}C]CO_2 and 23% radiochemical conversion using [^{11}C]CO_2.

In conclusion, we have shown that a late-stage carbon labeling Staudinger aza-Wittig reaction can access functionalized molecules particularly challenging to obtain with conventional procedures. The advantages of the current method are its implementation to all isotopes of carbon (^{11}C, ^{13}C, ^{14}C), a simple and easy to reproduce protocol, a broad substrate scope showcased by the labeling of drug candidates and a preliminary insertion of the carbon tag into an unprotected peptide.

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Keywords: Late stage isotopic labeling • Carbon-11 • Carbon-14 • Heterocycles • Carbon dioxide

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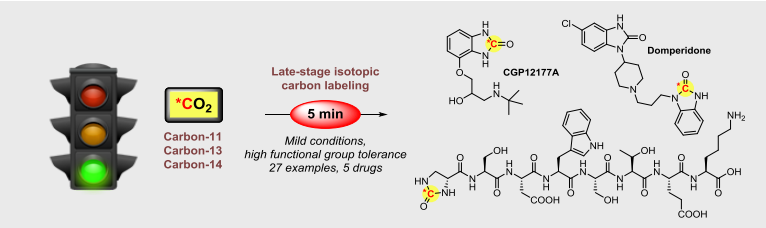

Label with a click: A click chemistry inspired Staudinger / Aza-Wittig approach to carbon labeling was developed. This protocol, suitable for all carbon isotopes (^{11}C, ^{13}C, ^{14}C), is based on the direct functionalization of carbon dioxide, the universal building block for carbon radiolabeling. A variety of pharmaceuticals and an unprotected peptide were labeled with high radiochemical efficiency.

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Late-stage isotopic carbon labeling of pharmaceutically relevant cyclic ureas directly from CO_2