# Carbon-11 carboxylation of terminal alkynes with [ 11 C]CO 2

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# Carbon-11 carboxylation of terminal alkynes with [$^{11}$C]$CO_2$

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A copper-catalysed radiosynthesis of carbon-11 radiolabelled carboxylic acids was developed by reacting terminal alkynes and cyclotron-produced carbon-11 carbon dioxide ([$^{11}$C]$CO_2$) in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). A small library of $^{11}$C-labelled propiolic acid derivatives were obtained with a total synthesis time of 15 min from end of bombardment (EOB) with a (non-isolated) radiochemical yield ranging from 7% to 28%.

**KEYWORDS**

[$^{11}$C]$CO_2$, [$^{11}$C]propiolic acid, alkynes, carbon-11, catalysed carboxylation

## 1 | INTRODUCTION

Carbon-11 is a short-lived radionuclide ($t_{1/2}$ = 20.4 min) commonly used to radiolabel molecular probes for use in *in vivo* positron emission tomography (PET) imaging.[1,2] Radiopharmaceuticals labelled with carbon-11 are chemically and biologically indistinguishable from their isotopically stable carbon-12 counterparts.[3–6] Carbon-11 is generally produced using a cyclotron by the $^{14}$N(p, α)$^{11}$C nuclear reaction in the form of [$^{11}$C]$CO_2$ or [$^{11}$C]$CH_4$. Carbon dioxide ([$^{11}$C]$CO_2$) can be directly incorporated into a variety of biologically relevant molecules, forming products such as [*carbonyl*-$^{11}$C]carboxylic acids, [*carbonyl*-$^{11}$C]amides, and [*carbonyl*-$^{11}$C]carbammate.[7–10]

Among [*carbonyl*-$^{11}$C]carboxylic acids, $^{11}$C-labelled propiolic acid derivatives have gained interest because this synthon is present in bioactive molecules such as flavones and coumarins and are amenable to further reactions to produce: (a) propargyl alcohols via a selective reduction of the carboxylic group,[11] (b) alkene or alkane carboxylic acids via a selective reduction of the alkyne function,[12,13] and (c) aliphatic alcohols *via* a reduction of both alkyne and carboxylic groups.[11,13] Given the importance of $^{11}$C-labelled propiolic acid derivatives, several strategies have been applied to carboxylate terminal alkynes with [$^{11}$C]$CO_2$ starting from Grignard reagents,[14] boronic esters[15] and trimethylsilyl derivatives.[16,17] Grignard reagents are highly reactive species limiting their application to simple substrates as they are incompatible with many functional groups. In addition, reactivity with atmospheric $CO_2$ and moisture sensitivity potentially leads to lower molar activities and yields of $^{11}$C-radiotracers unless used with great care.[2,18] Boronic esters have greater stability to atmospheric $CO_2$ and moisture but require the use of functionalised terminal alkynes with an ester. The recently developed approach

using trimethylsilyl terminal alkynes requires as well as the C–H bond functionalisation of terminal alkynes for the construction of C(sp)–Si bonds. Both methods need a two-step process for the preparation of the starting material as functionalised terminal alkynes are not widely commercially available, which may reduce their applicability.[16,17] Thus, we were motivated to explore an alternative $^{11}$C-carboxylation strategy to produce $^{11}$C-labelled propiolic acid derivatives starting from ready-to-use unfunctionalised terminal alkynes.

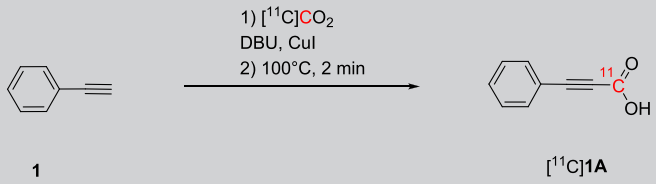
Carboxylation of unfunctionalised terminal alkynes using nonradioactive $CO_2$ has been developed via an in situ metal insertion into the C–H bond of terminal alkynes.[19–27] The alkynyl–metal intermediate is prepared by reacting a terminal alkyne, in the presence of a base (e.g. TBD, TMEDA, DBU), with a catalyst (e.g. AgI, $AgBF_4$, Ag- and Cu-*N*-heterocyclic carbenes, CuI, ferrocene-based bis-phosphine ligand, $Ni(cod)_2$, and $Mo_2(OtBu)_6$). The carboxylation of alkynyl–metal species is obtained using nonradioactive $CO_2$ under mild reaction conditions (25°C to 50°C) leading to propiolic acids with good yields (64% to 99%).[19–27]

To develop a $^{11}$C-carboxylation of terminal alkynes using cyclotron-produced $[^{11}C]CO_2$, we have investigated an efficient and solvent-free method developed by Li *et al*. that describes the carboxylation of phenylacetylene (**1**, 2 mmol, 1 eq.) using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 2 eq.), copper(I)-iodide (CuI, 0.02 eq.), and $CO_2$ (8 MPa) at 50°C for 12 h that lead to phenylpropiolic acid (**1A**) with high yields (92%; Scheme 1 in Table 1).[20] This strategy is not directly translatable to carbon-11 radiochemistry because of the short synthesis times required for carbon-11 radiolabelling (<20 min) and ultra-low $[^{11}C]CO_2$ concentrations used. Here, we report a modification of this solvent-free strategy to obtain $^{11}$C-labelled propiolic acid derivatives (Scheme 1 in Table 1) from unfunctionalized terminal alkynes in short synthesis times (<20 min) using $[^{11}C]CO_2$ obtained directly from a cyclotron. Subsequently, we have studied the influence of solvent on the reaction by adding acetonitrile (MeCN) to the reaction mixture with the aim to extend the method to solid alkyne precursors and to reduce the amount of terminal alkyne required.

## 2 | EXPERIMENTAL

Cyclotron-produced $[^{11}C]CO_2$ was bubbled directly from the target into a reaction vial containing **1**, DBU, CuI without solvent (solvent-free method) or with MeCN (solvent-added method) at 0°C. The outlet gas line of the vial was connected to an Ascarite® cartridge (sodium hydroxide coated silica to trap any gaseous $[^{11}C]CO_2$ not retained by the reaction mixture). After the delivery of $[^{11}C]CO_2$ (1.75 min from end of bombardment), the temperature was increased to 30°C, 50°C, 80°C, and 100°C for 2 and 10 min (Table S1) and the reaction was subsequently cooled at 20°C and quenched with a solution of formic acid (HCOOH) 10% in MeCN. The amount of radioactivity in the Ascarite® and vial was measured to

**TABLE 1** Reaction conditions and optimisation to synthesise $[^{11}C]$**1A** in solvent-free condition




**1** $[^{11}C]$**1A**

| Entry[a] | DBU (eq.) | CuI (eq.) | Flushing (min) | TE (%) | RCP of $[^{11}C]$1A (%) | RCY of $[^{11}C]$1A (%) |
|---|---|---|---|---|---|---|
| 1[b] | 0.1 | 0.02 | 7 | 13, 15 | 94, 96 | 12, 14 |
| 2 | 0.1 | 0.02 | 3 | 15 ± 3 | 94 ± 2 | 14 ± 4 |
| 3 | 0.1 | 0.01 | 3 | 14 ± 1 | 95 ± 5 | 13 ± 3 |
| 4 | 0.01 | 0.01 | 3 | 1 ± 0.5 | 100 ± 0 | 1 ± 0.5 |
| 5 | 0.5 | 0.01 | 3 | 28 ± 5 | 75 ± 8 | 21 ± 1 |
| 6[b] | 1 | 0.04 | 3 | 36 ± 4 | 60 ± 1 | 20, 24 |

[a]$[^{11}C]CO_2$ bubbled into a vial containing phenylacetylene (1.0 eq., 2 mmol), DBU (0.01–1 eq.), and CuI (0.01–0.04 eq.) at 0°C. Then the temperature was increased to 100°C for 2 min followed by a quench using a 10% HCOOH in MeCN solution (700 μl) at 0°C. The system was flushed by helium for 3 (entries 2–6) and 7 (entry 1) minutes at 20°C. $n = 3$.

[b]$n = 2$.

determine the trapping efficiency (TE*, see endnotes), and an aliquot of the crude mixture analysed by analytical radio-HPLC to determine the (nonisolated) radiochemical purity (RCP*, see endnotes ) of the product carbon-11 radiolabelled phenylpropiolic acid ([$^{11}$C]**1A**; Scheme 1 in Table 1).

## 3 | RESULTS AND DISCUSSION

The solvent-free $^{11}$C-carboxylation of terminal alkynes using [$^{11}$C]$CO_2$, applying the same conditions reported by Li et al.[20] (**1** [1 eq., 2 mmol], DBU [2 eq.], and CuI [0.02 eq.]), did not give the desired product ([$^{11}$C]**1A**) although the majority of the [$^{11}$C]$CO_2$ was trapped by the reaction mixture solution (93%) (see the Supporting Information). We hypothesised that the high concentration of DBU would facilitate the trapping of [$^{11}$C]$CO_2$ and hamper the formation of [$^{11}$C]**1A**. Indeed, by decreasing the equivalents of DBU from 2 to 0.1 eq., [$^{11}$C]**1A** was obtained with a RCY of 34% and high TE (84%) after a 2-minute reaction at 100°C. The radio-HPLC chromatographic analysis revealed the presence of [$^{11}$C]**1A** ($t_R$ = 6:17 min) and unreacted [$^{11}$C]$CO_2$. To eliminate the unreacted [$^{11}$C]$CO_2$ from the reaction mixture we applied a helium flush (1.4 ml/min for 3 min) after an acidic quench. The helium flush reduced the TE from 84% to 13% and the RCY from 34% to 13% but increased the RCP from 46% to 95% ($n$ = 2) (see the Supporting Information) confirming the presence of unreacted [$^{11}$C]$CO_2$. Increasing the time of helium flush from 3 to 7 min led to similar TE (14% and 15%; Table 1, entries 1 and 2); therefore, a flushing time of 3 min was used in all subsequent experiments (Table 1, entries 1–3). With the aim to increase both the RCY and TE, we studied the influence of DBU, **1**, and CuI concentrations on RCYs (entries 3–6, Table 1).

Decreasing the amount of CuI from 0.02 to 0.01 eq. did not affect either the RCY (14% vs. 13%; Table 1**,** entry 2 vs. entry 3) or the TE. Instead, decreasing the amount of DBU from 0.1 to 0.01 eq. dramatically decreased the TE to 1% (Table 1, entry 3 vs. entry 4). Increasing the concentration of DBU from 0.1 to 0.5 eq., the TE improved from 14% to 28% and the RCY increased from 13% to 21% (Table 1**,** entry 3 vs. entry 5). A concomitant increase of the amount of DBU to 1 eq. and CuI to 0.04 eq. slightly enhanced the TE from 28% to 36% but did not really vary the RCY (Table 1**,** entry 5 vs. entry 6).[28]

Our next aim was to reduce further the content of **1** from 2 to 0.2 mmol (22 µl); 200 µl of MeCN was added to ensure sufficient [$^{11}$C]$CO_2$ trapping.

Performing the reaction in MeCN with 0.2 mmol of **1**, [$^{11}$C]**1A** was obtained with high RCY of 28% (100°C, 2 min; Table 2, entry 1). To investigate the catalytic role of copper(I), we performed the experiment in the absence of CuI producing [$^{11}$C]**1A** in poor yields (RCY = 4%; Table 2**,** entry 2), and the TE decreased dramatically from 35% to 6%. This is in agreement with the results reported by Li *et al.*,[20] where the yield of carboxylation of terminal

**TABLE 2** Reaction conditions and optimisation to synthesise [$^{11}$C]**1A** using MeCN as solvent

| Entry[a] | CuI (eq.) | Temperature (°C) | Reaction time (min) | TE (%) | RCP of [$^{11}$C]1A (%)[b] | RCY of [$^{11}$C]1A (%)[b] |
|---|---|---|---|---|---|---|
| 1[b] | 0.1 | 100 | 2 | 35 ± 3 | 81 ± 7 | 28 ± 4[b] |
| 2 | - | 100 | 2 | 6 ± 1 | 67 ± 2 | 4 ± 0.5 |
| 3[c] | 0.1 | 100 | 2 | 3 ± 2 | 0 | 0 |
| 4[d] | 0.1 | 100 | 2 | 81 | 12 | 9[d] |
| 5 | 0.1 | 80 | 2 | 13 ± 4 | 70 ± 20 | 8 ± 3 |
| 6 | 0.1 | 120 | 2 | 6 | 56 | 4[d] |
| 7[e] | 0.1 | 35 | 2 | 9 ± 1 | 0 | 0[c] |
| 8 | 0.1 | 100 | 1 | 8 ± 3 | 80 ± 5 | 7 ± 2 |
| 9 | 0.1 | 100 | 3 | 8 ± 2 | 62 ± 6 | 5 ± 2 |
| 10[f] | 0.1 | 100 | 5 | 2, 3 | 27, 53 | 0.5, 1.5 |

[a][$^{11}$C]$CO_2$ was trapped in a solution of phenylacetylene (1 eq., 200 µmol), DBU (1 eq.), and CuI (0.1 eq.) in MeCN (200 µl) stirred at 0°C. This solution was then heated (35°C to 100°C) for 2–5 min. The temperature was decreased to 0°C for quenching with a 10% HCOOH in MeCN solution (700 µl). Helium was flushed through the quenched solution for 3 min at 20°C.
[b]$n$ = 4.
[c]20 µmol of **1**.
[d]DBU has been replaced by BEMP.
[e]$n$ = 1.
[f]$n$ = 2.

alkynes was reduced from 72% to 41% by eliminating the CuI from the reaction mixture.

Diluting all the reagents by a factor of 10 did not yield any [$^{11}$C]**1A** (Table 2, entry 3), and we can estimate that the lower limit will be between 200 and 20 µmol of precursor. The need for 200 µmol (22 µl) of precursor dissolved in 200 µl of MeCN might be a limitation for the use of a poorly soluble starting material. For comparison, the amount of precursor used here (200 µmol) and in other approaches to obtain $^{11}$C-labelled propiolic acid derivatives (60–250 µmol) are in a similar range.[14–17] Moreover, when the DBU ($pK_a$ = 14.2; Table 2, entry 1) was replaced with a stronger base (eq. BEMP $pK_a$ = 27.6; Table 2, entry 4), the RCY of the reaction dramatically decreased to 9%. Varying the reaction temperature from 100°C to 80°C or 120°C, RCYs decreased to 8% and 4%, respectively (Table 2, entries 5 and 6).

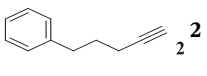
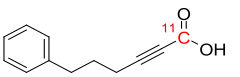
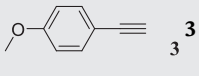
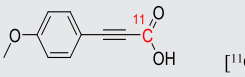
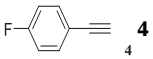
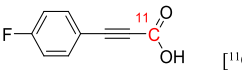
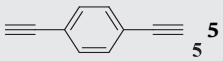
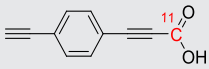
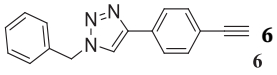
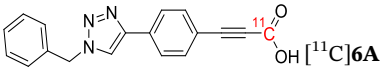
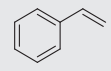
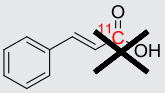
Decreasing further the temperature to 35°C, no product was observed (Table 2, entry 7). Keeping the temperature at 100°C and varying the reaction time from 2 to 1 or 5 min gave an RCY of 7% and 1%, respectively (Table 2, entry 1 vs. entries 8–10). The study on the reaction time (1–5 min; Figure S10) shows that the highest TE value is reached at 2 min. A reaction time of less than 2 min might not be enough to obtain [$^{11}$C]**1A** with a negative impact on TE, whereas a 5-min reaction might have a negative impact on TE possibly due to the low stability of [$^{11}$C]$CO_2$-DBU adduct at higher temperature, facilitating the movement of radioactivity from the reaction mixture to the Ascarite trap.

The direct $^{11}$C-carboxylation of **1** using the conditions reported in entry 1, Table 2, gave a molar activity of 1.37 GBq/µmol at EOB starting from a maximum radioactivity of 300 MBq (see endnotes).†

Despite the optimisation effort to increase the RCY of [$^{11}$C]**1A**, our current method leads to slightly better RCYs than those obtained via Grignard reagents ([$^{11}$C]-2-octynoic acid, RCY 10%)[14] but lower than using trimethylsilyl derivatives ([$^{11}$C]3-phenylpropiolic acid, RCY 97%)[16] and boronic esters ([$^{11}$C]19A, RCY 70%).[15] However, following this $^{11}$C-carboxylation strategy, $^{11}$C-labelled propiolic acid derivatives could be obtained from ready-to-use unfunctionalised terminal alkynes.

Next, the optimised $^{11}$C-carboxylation conditions were applied to a ready-to-use unfunctionalised terminal alkyne bearing an aliphatic chain and a para-substituted phenyl ring with either an electron-donating (**3**) or an electron withdrawing group (**4**) (Table 3). Compounds

**TABLE 3** Radiolabelling aromatic and aliphatic [$^{11}$C]propiolic acid with [$^{11}$C]$CO_2$

| Entry[a] | Precursor | [$^{11}$C]propiolic acid derivatives | TE (%) | RCP (%) | RCY (%) |
|---|---|---|---|---|---|
| 1 |  |  [$^{11}$C]**2A** | 11 ± 3 | 65 ± 5 | 7 ± 2 |
| 2 |  |  [$^{11}$C]**3A** | 11 ± 2 | 76 ± 4 | 8 ± 3 |
| 3 |  |  [$^{11}$C]**4A** | 13 ± 7 | 61 ± 10 | 7 ± 3 |
| 4 |  |  [$^{11}$C]**5A** | 20 ± 2 | 67 ± 3 | 14 ± 1 |
| 5 |  |  [$^{11}$C]**6A** | 12 ± 4 | 71 ± 11 | 9 ± 3 |
| 6[b] |  |  [$^{11}$C]**7A** | 9 | 0 | 0 |

[a]Reaction conditions: [$^{11}$C]$CO_2$, terminal alkynes **2a**–**7a** (0.2 mmol, 1 eq.), DBU (1 eq.), and CuI (0.1 eq.) in MeCN (200 µl) at 0°C; then, solution heated at 100°C for 2 min. Quenched at 0°C with a 10% HCOOH in MeCN solution (700 µl). Helium flushed the vial for 3 min at 20°C. $n$ = 9.
[b]$n$ = 1.

[$^{11}$C]**2A**–**4A** were obtained with good RCYs of 7% to 8%. We observed lower TE in entries 1–3, probably due to the lack of conjugation between the alkynyl and phenyl groups (entry 1) or inductive effect of the ring substituents (entries 2 and 3) affecting the formation of C–$^{11}$C bond formation with a negative impact on TE. Compound [$^{11}$C]**3A** is a common motif found in a family of compounds targeting the free fatty acid receptor 1 (FFAR1), an attractive target for the treatment of type 2 diabetes mellitus.[29] $^{11}$C-labelled propiolic acid derivatives binding FFAR1 might be obtained with this strategy using the corresponding synthetically accessible terminal alkynes as a precursor. The application of this method to radiolabel such molecules might reveal new insights on PET imaging in metabolic diseases. Using terminal alkenes **5** and **6**, the corresponding $^{11}$C-carboxylic acids ([$^{11}$C]**5A** and [$^{11}$C]**6A**) were obtained with a RCY of 14% and 9%, respectively.

The substitution of the alkyne with an alkene (**7**) did not lead to the formation of the corresponding $^{11}$C-carboxylic acid [$^{11}$C]**7A** (Table 3).

## 4 | CONCLUSION

In summary, we have developed a carbon-11 carboxylation reaction that uses [$^{11}$C]$CO_2$ and monosubstituted terminal alkynes to directly obtain $^{11}$C-labelled propiolic acid derivatives. Using the solvent-added approach, (i) [$^{11}$C]**1A** was produced with slightly lower RCY (28% [Table 2**,** entry 1] vs. 13% [Table 1**,** entry 3]) but with a TE 2.5-fold higher than the solvent-free approach and (ii) the amount of starting material **1** needed to perform the radiosynthesis is 10 times lower. The solvent-free strategy has been applied directly to carboxylate aromatic or aliphatic terminal alkynes, which opens the prospect for direct $^{11}$C-carboxylation avoiding the use of functionalised terminal alkynes.

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## CONFLICT OF INTEREST

There are no conflicts to declare.

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## ENDNOTES

* Radiochemical purity (RCP) of the product in the crude has been determined by analytical radio-HPLC. Trapping efficiency (TE) was calculated as the percentage of activity in the reaction vial compared with total activity delivered (reaction vial + Ascarite trap). Radiochemical yield (RCY) was calculated by multiplying TE and RCP.

† This work describes a method development study using short, low current, cyclotron irradiations where obtaining high $A_m$ were not the focus. However, the associated carrier content of compound **1A** was in the range of 26 nmol in 1 ml. Assuming that the stable $^{12}$C carrier content would be in the same range for a standard clinical [$^{11}$C]$CO_2$ production, it is estimated that molar activities of 137 GBq/μmol would be obtained at EOB.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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