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Synthesis of [^{11}C]/[^{13}C]Acrylamides by Palladium-Mediated Carbonylation

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Two methods are presented for the synthesis of acrylamides labelled with ^{11}C (β^+, $t_{1/2}$ = 20.4 min) and ^{13}C in the carbonyl position. In the first method, [1-^{11}C]acrylic acid is synthesised from [^{11}C]carbon monoxide by palladium-mediated hydroxycarbonylation of acetylene. The labelled carboxylic acid is converted into the acyl chloride and subsequently treated with amine to yield *N*-benzyl[*carbonyl*-^{11}C]acrylamide. The second method utilizes [^{11}C]carbon monoxide in a palladium-mediated carbonylative cross-coupling of vinyl halides and amines. A higher radiochemical yield is achieved with the latter method and the amount of amine needed is decreased to 1/20. The ^{11}C-labelled acrylamides were isolated in up to 81 % decay-corrected radiochemical yield. Starting from 10 ± 0.5 GBq of [^{11}C]carbon monoxide, *N*-benzyl[*carbonyl*-^{11}C]acrylamide was obtained in 4 min with a specific radioactivity of 330 ± 4 GBq μmol^{-1}. Co-labelling with ^{11}C and ^{13}C enabled confirmation of the labelled position by ^{13}C NMR spectroscopy.

Introduction

Transition-metal-catalysed carbonylation has been shown to be useful in the synthesis of carbonyl compounds by incorporation of carbon monoxide.[1] This approach has successfully been adopted in labelling reactions with very low concentrations of [^{11}C]carbon monoxide.[2] However, previously reported syntheses of ^{11}C-labelled amides using [^{11}C]carbon monoxide have not included acrylamides.[3] Compounds labelled with ^{11}C, a β^+-emitting radionuclide with a half-life of 20.4 min, are used as radiotracers in molecular imaging in vivo by positron emission tomography (PET). In labelling of PET tracers attention is usually given to improving the radiochemical yield, radiochemical purity and specific radioactivity [here defined as radioactivity per unit mol of a substance (Bq mol^{-1})]. There are a few central questions in carbonylation with [^{11}C]carbon monoxide that differ from the general scheme of transition-metal-catalysed carbonylation. For instance, the reaction time must be short due to the rapid decay of the radioactive material.[4] Consequently, the rate of product formation needs to be high enough that the radiochemical yield is not compromised. Labelling reactions are optimised with regards to the conversion yield of [^{11}C]carbon monoxide and all other reagents are used in large excess. This means that stoichiometric rather than strictly catalytic reaction conditions apply. The small quantities of [^{11}C]carbon monoxide used in the reactions, approximately 25 nmol, also have an impact on its physical handling. To achieve a high conversion yield of [^{11}C]carbon monoxide, a special technique has been developed to overcome the difficulties associated with its low solubility in most solvents.[5]

The acrylamide functionality is found in several biomedically interesting compounds and may also be used in further chemical modifications, for example Michael additions.[6] In this article the feasibility of using acetylene and [^{11}C]carbon monoxide in palladium-mediated carbonylation to synthesise *N*-benzyl[*carbonyl*-^{11}C]acrylamide is explored. In a second approach, vinyl halides are utilized as substrates for aminocarbonylation to synthesise acrylamides labelled with ^{11}C and ^{13}C. A method to synthesise isotopically unmodified acrylamides on a gram scale is also presented. The isotopically unmodified acrylamides are used as reference material for the characterisation of the labelled amides.

Results and Discussion

Previous methods to synthesise *N*-substituted [*carbonyl*-^{11}C]acrylamides have utilized [^{11}C]carbon dioxide and a Grignard reagent to obtain [1-^{11}C]acrylic acid (**1**). The labelled acid was then converted into the acyl chloride and subsequently treated with an amine to yield the labelled acrylamide derivative. The specific radioactivity was moderate, however, at 200–500 MBq μmol^{-1} decay-corrected to EOB (end of bombardment, end of radionuclide production), probably due to isotopic dilution originating from atmospheric carbon dioxide reacting with the Grignard reagent.[7] Mishani et al. have reported the synthesis of an acrylamide derivative with a specific radioactivity of 55 GBq μmol^{-1} at EOB starting with 37 GBq.[8] To circumvent the moderate specific radioactivity associated with the use of [^{11}C]carbon dioxide, we have explored the possibility

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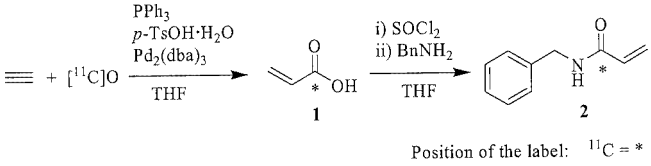
of synthesising ^{11}C-labelled acrylamides from [^{11}C]carbon monoxide.

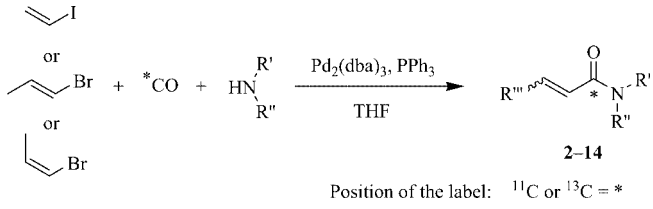
Acetylene was used in the first approach to synthesise *N*-benzyl[*carbonyl*-^{11}C]acrylamide (**2**). Carbonylative coupling of aniline derivatives with acetylenes has been reported to occur under acidic conditions.[9] However, due to the basicity of benzylamine we were not able to perform the reaction in a one-pot fashion by mixing benzylamine and acid – *p*-toluenesulfonic acid or methanesulfonic acid – without precipitation of the corresponding salt. Instead, the synthesis was performed in three steps, as shown in Scheme 1.



Scheme 1. Formation of *N*-benzyl[*carbonyl*-^{11}C]acrylamide by hydroxycarbonylation of acetylene.

A palladium complex was generated in THF by treatment of tris(dibenzylideneacetone)dipalladium [$Pd_2(dba)_3$] with triphenylphosphane and *p*-toluenesulfonic acid monohydrate (*p*TsOH·H_2O).[10] Hydroxycarbonylation of acetylene using [^{11}C]carbon monoxide and the palladium complex gave [1-^{11}C]acrylic acid (**1**), which was converted into the acyl chloride by treatment with thionyl chloride. Benzylamine (82 μmol) was then added to obtain *N*-benzyl[*carbonyl*-^{11}C]acrylamide (**2**) in 51 ± 4% decay-corrected analytical radiochemical yield (n = 2) based on [^{11}C]carbon monoxide. The amine was used in a threefold excess relative to thionyl chloride. Attempts to decrease the amount of amine resulted in lower radiochemical yield.

A second approach to synthesise ^{11}C-labelled acrylamides from vinyl halides and amines was explored according to Scheme 2.



Scheme 2. One-pot synthesis of [*carbonyl*-^{11}C]acrylamides from [^{11}C]carbon monoxide.

A zero-valent (triphenylphosphane)palladium complex was generated from [$Pd_2(dba)_3$] and triphenylphosphane in THF.[10a] The addition of vinyl iodide was followed by a colour change of the solution, which indicates that the oxidative addition occurs instantly at room temperature. Amine was then added and the reaction solution was transferred to a micro-autoclave containing [^{11}C]carbon monoxide. The reagents were kept in the micro-autoclave at 110 °C for 4 min. The excess of palladium complex in relation to [^{11}C]-carbon monoxide was assumed to prevent the possibility of repetitive turns in the catalytic cycle. Consequently, no base was added since amine is present in a large excess and the acid is formed in very low concentrations. A significantly higher radiochemical yield of *N*-benzyl[*carbonyl*-^{11}C]acrylamide (**2**) was achieved with this method than with the first approach using acetylene. At the same time, the amine concentration was decreased to 1/20.

The amines used in the aminocarbonylation to give the acrylamides in Figure 1 range from activated and deactivated anilines to highly nucleophilic amines. The nucleophilicity of the amines corresponds well with the outcome of the reactions. The steric hindrance of the *ortho* substituents lowers the yield compared to *m*- and *p*-substituted anilines, as illustrated in the synthesis of the mono- and disubstituted *N*-(methylphenyl)acrylamides **5a**–**c** (see Table 1). For all entries the amount of amine needed was 4.3 μmol, except for the weakly deactivated and sterically hindered *o*-chloroaniline, which gave **6a** in only moderate yield with

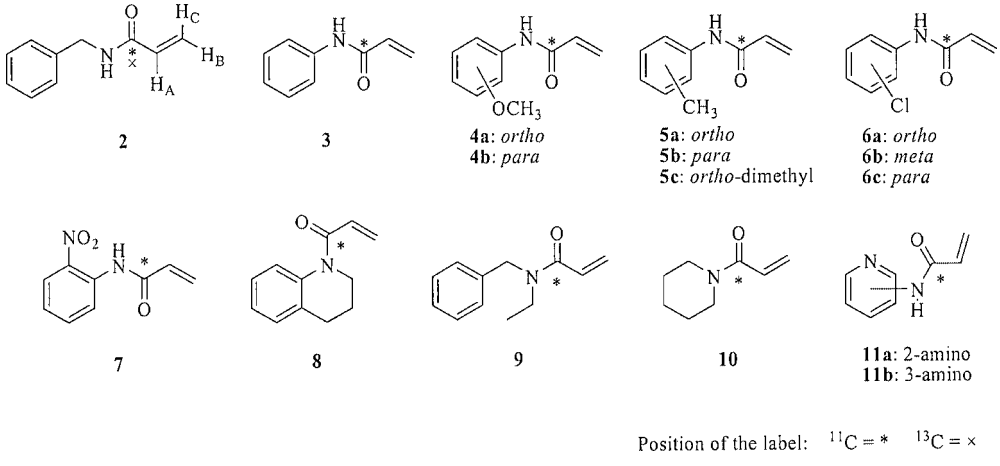


Figure 1. Products obtained from the aminocarbonylation of vinyl iodide.

Table 1. Synthesis of [*carbonyl*-^{11}C]acrylamides by aminocarbonylation of vinyl iodide.

Product	Nucleophile	Amount [μmol]	*T* [°C]	Conversion of [^{11}C]O [%][a,b]	Analytical RCY [%][b,c]	Isolated RCY [%][b,d,e]
2	benzylamine	4.3	110	94 ± 2 (7)	87 ± 9 (5)	81 ± 3 (4)
3	aniline	4.3	110	91 ± 5 (2)	84 ± 6 (2)	74 ± 6 (2)
4a	2-methoxyaniline	4.3	110	–	–	71 ± 4 (2)
4b	4-methoxyaniline	4.3	110	95 ± 2 (2)	86 ± 3 (2)	72 ± 2 (2)
5a	2-methylaniline	4.3	110	94 ± 2 (2)	81 ± 2 (2)	65 ± 4 (2)
5b	4-methylaniline	4.3	110	94 ± 1 (2)	89 ± 1 (2)	72 ± 2 (2)
5c	2,6-dimethylaniline	4.3	110	92 ± 1 (3)	62 ± 4 (3)	52 ± 2 (2)
6a	2-chloroaniline	4.3	110	81	21	–
6a	2-chloroaniline	4.3	145	90	26	19
6a	2-chloroaniline	19	145	85 ± 1 (2)	58 ± 4 (2)	51 ± 1 (2)
6b	3-chloroaniline	4.3	110	95 ± 1 (3)	79 ± 6 (3)	63 ± 1 (3)
6c	4-chloroaniline	4.3	25	88	55	49
6c	4-chloroaniline	4.3	110	96 ± 3 (3)	82 ± 2 (3)	73 ± 1 (2)
7	2-nitroaniline	4.3	110	90	0	0
7	2-nitroaniline	22	150	81	0	0
8	1,2,3,4-tetrahydroquinoline	5.3	110	94 ± 3 (2)	77 ± 5 (2)	66 ± 4 (2)
9	*N*,*N*-benzylethylamine	4.3	110	92 ± 1 (2)	83 ± 1 (2)	75 ± 1 (2)
10	piperidine	4.3	110	90 ± 1 (2)	86 ± 1 (2)	76 ± 1 (2)
11a	2-aminopyridine	4.3	110	86 ± 4 (3)	48 ± 3 (3)	46 ± 2 (2)
11b	3-aminopyridine	4.3	110	94 ± 1 (3)	74 ± 1 (3)	70 ± 1 (2)

[a] Decay-corrected conversion yield of [^{11}C]carbon monoxide to non-volatile products remaining in the reaction mixture after removal of solvent. [b] The number in parentheses is the number of experiments. [c] Decay-corrected analytical radiochemical yield (RCY) determined from the conversion yield and the radiochemical purity assessed by analytical HPLC. [d] Decay-corrected radiochemical yield (RCY) based on the initial amount of radioactivity at the start of the synthesis and the radioactivity of the isolated product. The radioactivity was measured after the reaction mixture had been transferred from the micro-autoclave to an evacuated 1-mL vial. The radioactive residues left in the micro-autoclave were estimated to be less than 1%, hence the amount of initial radioactivity could be determined. [e] Radiochemical purity was >97% in all experiments.

19 μmol. It is worth noting that the reaction of *p*-chloroaniline proceeded even at room temperature, although the radiochemical yield was lower. The aminocarbonylation of *o*-nitroaniline did not give the desired product even when the temperature and concentration of the nucleophile were increased. The reaction with 2-aminopyridine gave a significantly lower yield than the less deactivated 3-aminopyridine in the synthesis of **11a** and **11b**, respectively. [1-^{11}C]Acrylic acid (**1**) was also formed when less reactive amines were used due to the presence of small amounts of water.

(*E*)- and (*Z*)-bromopropene (Figure 2) were also tested as substrates in the aminocarbonylation reaction. The same reaction time and temperature was used as for vinyl iodide. The formation of products **12**–**14** proceeded with retention of configuration of the C=C double bond.[11] With benzylamine as nucleophile, both (*E*)- and (*Z*)-bromopropene gave products in good yields, as shown in Table 2. The less activated 3-chloroaniline led to **14a** (*E*) and **14b** (*Z*) in lower yields. However, **14a** (*E*) was obtained in a significantly higher yield than **14b** (*Z*).

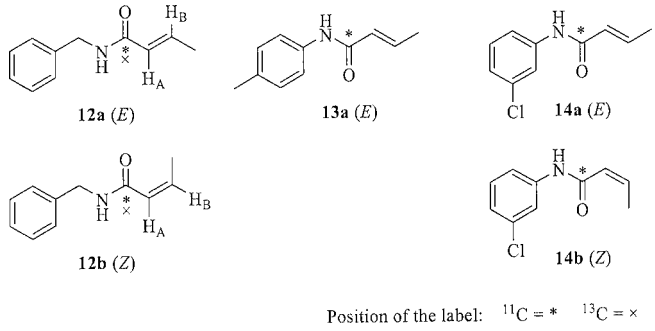


Figure 2. Products obtained by aminocarbonylation of (*Z*)- and (*E*)-bromopropene.

Table 2. Synthesis of [*carbonyl*-^{11}C]acrylamides by aminocarbonylation of (*E*)- and (*Z*)-bromopropene.

Product	Vinyl halide	Nucleophile	Amount [μmol]	*T* [°C]	Conversion of [^{11}C]O[a] [%]	Analytical RCY[a] [%]	Isolated RCY[a] [%]
12a (*E*)		Benzylamine	4.3	110	82±5 (2)	76±5 (2)	72±5 (2)
12b (*Z*)		Benzylamine	4.3	110	84±2 (2)	73±1 (2)	67±1 (2)
13a (*E*)		4-Methylaniline	4.3	110	88±3 (2)	81±4 (2)	67±3 (2)
14a (*E*)		3-Chloroaniline	4.3	110	85±4 (2)	56±6 (2)	41±5 (2)
14b (*Z*)		3-Chloroaniline	4.3	110	76±1 (2)	18±2 (2)	16±2 (2)

[a] For explanations see Table 1.

Compounds **2** and **12a**,**b** were co-labelled with ^{11}C and ^{13}C using the same method as for the ^{11}C labelling. However, when adding [^{13}C]carbon monoxide the amount of carbon monoxide was increased from approximately 25 nmol to 44 μmol. Consequently, the reaction time was prolonged and the amounts of vinyl halide and benzylamine were also increased. The co-labelling enabled confirmation of the labelled position by ^{13}C NMR spectroscopy. Compound **14b** was synthesised from the less basic 3-chloroaniline using carrier-added [^{11}C]carbon monoxide. Triethylamine was needed to obtain enough product for the characterisation by ^{1}H NMR spectroscopy. The introduction of base reduced the number of radiolabelled products to a single product. The compound was also analysed by LC-MS.

High specific radioactivity of the labelled compound is desirable in PET applications to avoid perturbation or saturation of the biological system under study. When assessing the specific radioactivity, cyclotron bombardments of 10 μAh were made, which resulted in 10 ± 0.5 GBq of [^{11}C]-carbon monoxide (n = 2). After 20 min, *N*-benzyl[*carbonyl*-^{11}C]acrylamide (**2**) was isolated with a radioactivity of 4.2 ± 0.3 GBq. The amount of product was 22 ± 1 nmol and the specific radioactivity was 330 ± 4 GBq μmol^{-1} at the end of the synthesis.

Conclusions

[1-^{11}C]Acrylic acid has been synthesised from [^{11}C]carbon monoxide and acetylene by a palladium-mediated hydroxycarbonylation under acidic conditions. The labelled carboxylic acid was converted into its acyl chloride, and subsequent treatment with amine yielded *N*-benzyl[*carbonyl*-^{11}C]acrylamide. A relatively high concentration of amine was needed, however. Significant improvements were achieved when the [*carbonyl*-^{11}C]acrylamides were synthesised by a palladium(0)-mediated aminocarbonylation of vinyl iodides. Aminocarbonylation of (*E*)- and (*Z*)-bromopropene proceeded with retention of the configuration of the C=C double bond. The one-pot synthesis gave products with high radiochemical yields and high specific radioactivity and offered short reaction times, mild conditions and advantages with regards to automation.

Experimental Section

General: ^{11}C was prepared by the $^{14}N(p,\alpha)^{11}C$ nuclear reaction using 17 MeV protons produced by a Scanditronix MC-17 Cyclotron at Uppsala Imanet AB and obtained as [^{11}C]carbon dioxide. The target gas used was nitrogen (AGA Nitrogen 6.0) containing 0.05% oxygen (AGA Oxygen 4.8). The carbonylation reactions were carried out in a 200-μL Teflon-coated micro-autoclave using a previously described technique.[12]

[^{11}C]Carbon dioxide (approximately 25 nmol) was transferred in a stream of nitrogen gas from the cyclotron to a CO_2 trap containing Alltech silica gel 100/120 at –196 °C (Figure 3). The trap was then flushed with helium gas at 20 mL min^{-1} for 1 min before it was warmed up and the [^{11}C]carbon dioxide was transferred in the gas stream through a quartz tube heated at 400 °C containing zinc granules (Merck 14–50 mesh). [^{11}C]Carbon dioxide was reduced to [^{11}C]carbon monoxide in the quartz tube. Any remaining trace of [^{11}C]carbon dioxide was subsequently removed by a column containing Ascarite. [^{11}C]Carbon monoxide was transferred to a CO trap, where it was trapped on Alltech 100/120 silica gel (1 mg) at –196 °C. Valve V3 connecting the CO trap to the micro-autoclave

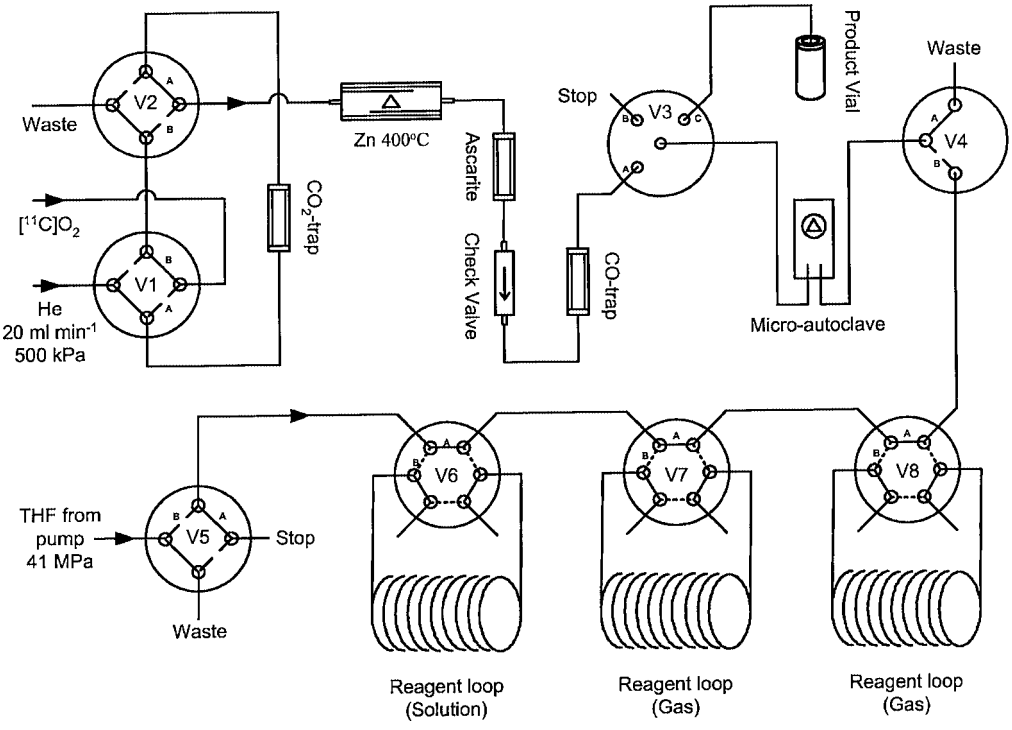


Figure 3. Experimental setup used in the carbonylation reactions.

was then switched to stop, giving rise to a pressure build-up of approximately 400–500 kPa due to the helium carrier gas. Valve V4 was switched to connect the micro-autoclave to the injection valves. The CO trap was heated to release the [^{11}C]carbon monoxide from the silica. [^{11}C]Carbon monoxide was transferred to the micro-autoclave by the pressure difference over the valve upon switching valve V3 to the CO trap. After the transfer, valve V3 was switched to stop. The reagents were then transferred from the reagent loops to the 200-μL micro-autoclave by the pressure of THF pumped at 41 MPa. After 4 min reaction time, the mixture was transferred from the micro-autoclave to the product vial by switching valve V3.

All solvents were reagent grade and distilled prior to use; THF was freshly distilled from sodium/benzophenone under nitrogen. All chemicals were purchased from Aldrich/Fluka, Cambridge Isotope Laboratories Inc. or Fluorochem and used as received. The identities of the ^{11}C-labelled compounds were determined by analytical HPLC using authentic samples as references. Analytical HPLC was performed with a Beckman system, equipped with a Beckman 126 pump, a Beckman 166 UV detector in series with a Bioscan β^+-flow count detector and a Beckman Ultrasphere ODS dp 5-μm column (250 × 4.6 mm). A Gilson 231 XL was used as auto injector. Purification by semi-preparative HPLC was performed with a similar Beckman system equipped with a Beckman Ultrasphere ODS dp 5-μm column (250 × 10 mm). Mobile phase: A) 0.05 M ammonium formate, pH = 3.5; B) acetonitrile. The specific radioactivity of compound **2** was assessed using a Waters Quattro Premier triple quadrupole mass spectrometer with electrospray ionisation, operating in positive mode.

TLC was performed on pre-coated Merck silica gel plates ($60F_{254}$) visualised with UV light. ^{1}H and ^{13}C NMR spectra were recorded with a Varian 400 or 500 MHz spectrometer and chemical shifts are given in ppm (δ) using $CHCl_3$ or DMSO as internal standard. LC-MS analyses of reference compounds were performed with a Gilson reverse-phase HPLC apparatus equipped with a Finnigan ESI mass spectrometer (MeCN/H_2O and 0.1% formic acid). IR spectra were recorded with a Perkin–Elmer Spectrum 100 FT/IR spectrometer as neat compounds.

Synthesis of *N*-Benzyl[*carbonyl*-^{11}C]acrylamide (2) by Carbonylation of Acetylene: [$Pd_2(dba)_3$] (0.70 mg, 1.2 μmol) and PPh_3 (2.7 mg, 10 μmol, 8.6 equiv.) were placed in a 0.8-mL vial equipped with a rubber septum; THF (600 μL) was added, the resulting solution was degassed with argon and 200 μL of the solution was loaded into an injection loop. A second loop (700 μL) was loaded with acetylene (1 atm); THF was pumped through the two loops and the reagents were transferred into a 200-μL Teflon-coated stainless-steel micro-autoclave containing [^{11}C]carbon monoxide. The reagents were kept in the micro-autoclave at 110 °C for 4 min. The reaction mixture was then transferred into a 1-mL septum-equipped evacuated glass vial and the radioactivity was measured. The vial was purged with a stream of nitrogen and the radioactivity was measured again. Thionyl chloride was added to the vial and heated for 1 min, then benzylamine was added and the reaction mixture was kept at room temperature for 1 min before removal of THF at 80 °C for 1–2 min in a stream of nitrogen. The crude product was redissolved in acetonitrile/water and analysed by analytical HPLC.

Synthesis of [*carbonyl*-^{11}C]Acrylamides 2–14 by Carbonylation of Vinyl Halides: [$Pd_2(dba)_3$] (0.70 mg, 1.2 μmol) and PPh_3 (2.7 mg, 10 μmol, 8.6 equiv.) were placed in a 0.8-mL vial equipped with a rubber septum; THF (600 μL) was added and the resulting solution was degassed with argon. Vinyl halide (0.5 μL, 6 μmol) was then added. When bromopropene was used, the oxidative addition to the palladium complex was not visually apparent, hence the vial containing the reaction mixture was preheated at 80 °C for 5 min. Amine was added and 200 μL of the mixture was loaded into an injection loop; THF was pumped through the loop and the reagents were transferred into a 200-μL Teflon-coated stainless-steel micro-autoclave containing [^{11}C]carbon monoxide. The reagents were kept in the micro-autoclave at 110 °C for 4 min. The reaction mixture was then transferred to a 1-mL septum-equipped evacuated glass vial and the radioactivity was measured. The vial was heated at 80 °C for 1–2 min during the removal of THF under a stream of nitrogen gas and the radioactivity was measured again. The crude product was redissolved in acetonitrile/water and purified by semi-preparative HPLC. The radioactivity of the purified product was measured. Analytical HPLC was used to assess the identity and radiochemical purity.

Co-Labelling of Acrylamides at the Carbonyl Position by Carbonylation of Vinyl Halides with [^{11}C]- and [^{13}C]Carbon Monoxide: Complete ^{13}C NMR spectra were obtained for compounds **2** and **12a**. These showed splitting of the signal of the carbon atom adjacent to the carbonyl carbon atom. The ^{1}H NMR spectra matched the spectra of the prepared reference compounds but with additional $^2J_{C,H}$, $^3J_{C,H}$ and $^4J_{C,H}$ couplings.

***N*-Benzyl[*carbonyl*-^{11}C,^{13}C]acrylamide (2):** The synthesis was performed as for the [*carbonyl*-^{11}C]acrylamides with the following modifications. Vinyl halide (23 μL, 0.26 mmol) and benzylamine (47 μL, 0.43 mmol) were used. A second loop (450 μL) was loaded with [^{13}C]carbon monoxide (approx. 3.4 atm, 62 μmol) and the reagents were kept in the micro-autoclave at 110 °C for 20 min. The isolated product was allowed to decay and the solvent was removed under reduced pressure. The resulting solid was extracted with dichloromethane and washed with water and brine. The organic phase was removed under reduced pressure to give the product as a white solid (5.4 mg, 53% based on carbon monoxide). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.37–7.26 (m, 5 H, Ar-*H*), 6.32 (ddd, $^2J_{H,H}$ = 1.5, $^3J_{C,H}$ = 7.0, $^3J_{H,H}$ = 17.0 Hz, 1 H, CH_BH_C), 6.11 (ddd, $^2J_{C,H}$ = 5.1, $^3J_{H,H}$ = 10.3, 17.0 Hz, 1 H, CH_A), 5.86 (br. s, 1 H, N-*H*), 5.67 (m, $^2J_{H,H}$ = 1.5, $^3J_{H,H}$ = 10.3, $^3J_{C,H}$ = 12.7 Hz, 1 H, CH_BH_C), 4.53 (m, 2 H, CH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 165.5 (major peak), 138.1, 130.8 (d, $^1J_{C,C}$ = 63.5 Hz), 128.9, 128.1, 127.8, 127.0, 43.9 ppm. LC-MS ESI+ for $^{12}C_9{}^{13}C_1H_{11}NO$ [M + H]: *m*/*z* = 163.

(2*E*)-*N*-Benzyl[*carbonyl*-^{11}C,^{13}C]but-2-enamide (12a): Yield: 12 mg (quantitative based on carbon monoxide). ^{1}H NMR (400 MHz $CDCl_3$, 25 °C): δ = 7.36–7.26 (m, 5 H, Ar-*H*), 6.88 (ddq, $^3J_{C,H}$ = 7.3, $^3J_{H,H}$ = 6.8, 15.2 Hz, 1 H, CH_B), 5.81 (ddq, $^4J_{H,H}$ = 1.7, $^2J_{C,H}$ = 5.0, $^3J_{H,H}$ = 15.2 Hz, 1 H, CH_A), 5.65 (br. s, 1 H, N-*H*), 4.51 (m, 1 H, CH_2), 1.86 (ddd, $^4J_{C,H}$ = 1.0, $^4J_{H,H}$ = 1.7, $^3J_{H,H}$ = 6.8 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 165.9 (major peak), 140.6, 138.4, 128.9, 128.0, 127.7, 124.9 (d, $^1J_{C,C}$ = 64.8 Hz), 43.8, 17.9 ppm. LC-MS ESI+ for $^{12}C_{10}{}^{13}C_1H_{13}NO$ [M + H]: *m*/*z* = 177.

(2*Z*)-*N*-Benzyl[*carbonyl*-^{11}C,^{13}C]but-2-enamide (12b): Yield: 1 mg (9% based on carbon monoxide). ^{1}H NMR (400 MHz $CDCl_3$, 25 °C): δ = 7.38–7.26 (m, 5 H, Ar-*H*), 6.16 (ddq, $^3J_{H,H}$ = 7.3, 11.3, $^3J_{C,H}$ = 13.0 Hz, 1 H, CH_B), 5.74 (ddq, $^4J_{H,H}$ = 1.8, $^2J_{C,H}$ = 4.6, $^3J_{H,H}$ = 11.4 Hz, 1 H, CH_A), 5.72 (br. s, 1 H, N-*H*), 4.51 (m, 2 H, CH_2), 2.18 (ddd, $^4J_{C,H}$ = 1.3, $^4J_{H,H}$ = 1.8, $^3J_{H,H}$ = 7.2 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 166.6 ppm. LC-MS ESI+ for $^{12}C_{10}{}^{13}C_1H_{13}NO$ [M + H]: *m*/*z* = 177.

Synthesis of (2*Z*)-*N*-(3-Chlorophenyl)[*carbonyl*-^{11}C]but-2-enamide (14b) by Carbonylation of (*Z*)-Bromopropene with Carrier-Added [^{11}C]Carbon Monoxide: The synthesis was performed as for the

[*carbonyl*-^{11}C]acrylamides with the following modifications. 3-Chloroaniline (45 μL, 0.43 mmol) was used instead of benzylamine. Triethylamine (40 μL, 0.27 mmol) was added to the reaction mixture. A second loop (700 μL) was loaded with carbon monoxide (4 atm). Yield: 0.5 mg (2% based on carbon monoxide) ^{1}H NMR (500 MHz $CDCl_3$, 25 °C): δ = 7.71 (m, 1 H, Ar-*H*), 7.36 (m, 1 H, Ar-*H*), 7.24 (m, 1 H, Ar-*H*), 7.08 (m, 2 H, Ar-*H* and N-*H*), 6.29 (dq, $^3J_{H,H}$ = 7.7, 11.4 Hz, 1 H, CH_B), 5.83 (dq, $^4J_{H,H}$ = 1.8, $^3J_{H,H}$ = 11.4 Hz, 1 H, CH_A), 2.21 (dd, $^4J_{H,H}$ = 1.8, 7.7 Hz, CH_3) ppm. LC-MS ESI+ for $C_{10}H_{10}ClNO$ [M + H]: *m*/*z* = 196.

Determination of Specific Radioactivity: The synthesis of *N*-benzyl-[*carbonyl*-^{11}C]acrylamide (**2**) was performed as described above by carbonylation of vinyl iodide. Starting from 10 ± 0.5 GBq of [^{11}C]-carbon monoxide, 4.2 ± 0.3 GBq of product was isolated after 20 min. The volume of the product solution was measured. A series of four calibration standards (15.9, 6.38, 1.27 and 0.319 μM) was prepared from *N*-benzylacrylamide (**2**) and acetonitrile/water. A mass spectrometer with electrospray ionisation operating in positive mode and a tandem mass detector were used for quantification with *m*/*z* = 162 as the precursor ion and *m*/*z* = 90 as the fragment ion. Injection volume: 50 μL; Genesis C18 column; eluent: 20% acetonitrile, H_2O (0.1% formic acid); flow: 0.3 mL min^{-1}. From the preliminary results obtained from the calibration curve, a standard addition series with four standards was prepared and analysed using the same conditions as above. The concentration of the analyte corresponded to a total amount of 22 ± 1 nmol of product and a specific radioactivity of 330 ± 4 GBq μmol^{-1} (*n* = 2) at the end of the synthesis.

Synthesis of Reference Compounds

***N*-(2-Methoxyphenyl)acrylamide (Method A):**[13] A solution of 2-methoxyaniline (1.00 g, 8.12 mmol) and potassium carbonate (1.12 g, 8.12 mmol) in acetone (2.5 mL) and water (2.5 mL) was cooled in an ice bath to below 5 °C. Acroyl chloride (0.740 g, 8.12 mmol) was added dropwise to the solution with vigorous stirring in 10 min. The reaction mixture was warmed to room temperature, stirred overnight and then concentrated to approximately half the volume. The precipitate was collected by filtration, washed with water and dried in vacuo to give the acrylamide as brownish crystals (1.38 g, 96%). M.p. 69–70 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.47 (m, 1 H, Ar-*H*), 7.91 (br. s, 1 H, N-*H*), 7.06 (m, 1 H, Ar-*H*), 6.98 (m, 1 H, Ar-*H*), 6.88 (m, 1 H, Ar-*H*), 6.41 (dd, $^2J_{H,H}$ = 1.5, $^3J_{H,H}$ = 16.9 Hz, 1 H, CH_BH_C), 6.29 (dd, $^3J_{H,H}$ = 10.0, 16.9 Hz, 1 H, CH_A), 5.75 (dd, $^2J_{H,H}$ = 1.5, $^3J_{H,H}$ = 10.0 Hz, 1 H, CH_BH_C), 3.89 (s, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz $CDCl_3$, 25 °C): δ = 163.4, 148.0, 131.7, 127.6, 127.4, 124.0, 121.2, 120.0, 109.9, 55.8 ppm. LC-MS ESI+ for C_9H_9NO [M + H]: *m*/*z* = 178. IR: $\tilde{\nu}_{max}$ = 3226, 1940, 1658, 1525, 1455, 1226, 1020, 742 cm^{-1}.

***N*-Phenylacrylamide:**[14] Method A. Yield: 61% as white crystals. M.p. 104–106 °C. LC-MS ESI+ for C_9H_9NO [M + H]: *m*/*z* = 148.

***N*-(4-Methoxyphenyl)acrylamide:**[15] Method A. Yield >99% as a beige solid. M.p. 97–98 °C. LC-MS ESI+ C_9H_9NO for [M + H]: *m*/*z* = 178. IR: $\tilde{\nu}_{max}$ = 3311, 1660, 1509, 1173, 970, 825 cm^{-1}.

***N*-(2-Methylphenyl)acrylamide:**[16] Method A. Yield: 93% as white crystals. M.p. 109–110 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.83 (m, 1 H, Ar-*H*), 7.28 (br. s, 1 H, N-*H*), 7.23–7.01 (m, 4 H, Ar-*H*), 6.41 (d, unresolved dd, $^3J_{H,H}$ = 16.7 Hz, 1 H, CH_BH_C), 6.30 (dd, $^3J_{H,H}$ = 10.0, 16.7 Hz, 1 H, CH_A), 5.75 (dd, $^2J_{H,H}$ = 1.2, $^3J_{H,H}$ = 10.0 Hz, 1 H, CH_BH_C), 2.25 (s, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 163.8, 135.5, 131.3, 130.6, 129.4, 127.7, 126.9, 125.5, 123.4, 17.9 ppm. LC-MS ESI+ for $C_{10}H_{11}NO$ [M + H]: *m*/*z* = 162. IR: $\tilde{\nu}_{max}$ = 3201, 1930, 1654, 1533, 1252, 747 cm^{-1}.

***N*-(4-Methylphenyl)acrylamide:**[14] Method A. Yield: 91% as white crystals. M.p. 141–142 °C. LC-MS ESI+ for $C_{10}H_{11}NO$ [M + H]: *m*/*z* = 162. IR: $\tilde{\nu}_{max}$ = 3259, 3073, 1896, 1660, 1605, 1543, 1410, 1331, 1251, 947, 812 cm^{-1}.

***N*-(2,6-Dimethylphenyl)acrylamide:**[16] Method A. Yield: 82% as white crystals. M.p. 144–145 °C. LC-MS ESI+ for $C_{11}H_{13}NO$ [M + H]: *m*/*z* = 176.

***N*-(2-Chlorophenyl)acrylamide:**[17] Method A. Yield: >99% as white crystals. M.p. 100–102 °C. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 163.5, 134.6, 131.2, 129.1, 128.4, 127.9, 125.0, 123.0, 121.8 ppm. LC-MS ESI+ for C_9H_8ClNO [M + H]: *m*/*z* 182. IR: $\tilde{\nu}_{max}$ = 3391, 3190, 1934, 1655, 1527, 1477, 1246, 747 cm^{-1}.

***N*-(3-Chlorophenyl)acrylamide:**[18] Method A. Yield: >99% as an off-white powder. M.p. 109–110. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.89 (br. s, 1 H, N-*H*), 7.72 (m, 1 H, Ar-*H*), 7.44 (m, 1 H, Ar-*H*), 7.25 (m, 1 H, Ar-*H*), 7.10 (m, 1 H, Ar-*H*), 6.44 (dd, $^2J_{H,H}$ = 1.3, $^3J_{H,H}$ = 16.8 Hz, 1 H, CH_BH_C), 6.29 (dd, $^3J_{H,H}$ = 10.1, 16.8 Hz, 1 H, CH_A), 5.79 (dd, $^2J_{H,H}$ = 1.3, $^3J_{H,H}$ = 10.1 Hz, 1 H, CH_BH_B) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 164.0, 139.0, 134.7, 130.9, 130.1, 128.5, 134.7, 120.4, 118.2 ppm. LC-MS ESI+ for C_9H_8ClNO [M + H]: *m*/*z* 182. IR: $\tilde{\nu}_{max}$ = 3265, 3073, 1663, 1589, 1537, 1424, 1250, 776 cm^{-1}.

***N*-(4-Chlorophenyl)acrylamide:**[14] Method A. Yield: 91% as a white powder. M.p. 185 °C. LC-MS ESI+ for C_9H_8ClNO [M + H]: *m*/*z* = 182.

***N*-Benzylacrylamide:**[14] Method A. Yield: 87% as a white solid. M.p. 68–69 °C. LC-MS ESI+ for $C_{10}H_{11}NO$ [M + H]: *m*/*z* = 162.

***N*-Benzyl-*N*-ethylacrylamide:** Method A. Yield: 95% as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.31–7.15 (m, 5 H, Ar-*H*), 6.65–6.44 (2 × dd, $^3J_{H,H}$ = 10.3, 16.9 Hz, 1 H, CH_A), 6.44–6.30 (2 × dd, $^2J_{H,H}$ = 2.2, $^3J_{H,H}$ = 16.9 Hz, 1 H, CH_BH_C), 5.64 (2 × dd, $^2J_{H,H}$ = 2.2, $^3J_{H,H}$ = 10.3 Hz, 1 H, CH_BH_C), 4.59 (2 × br. s, 2 H, CH_2), 3.36 (2 × q, $^3J_{H,H}$ = 6.9 Hz, 2 H, CH_2CH$_3$), 1.11 (2 × t, $^3J_{H,H}$ = 6.9 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 166.5, 166.2, 137.8, 137.2, 128.9, 128.6, 128.4, 128.2, 128.11, 128.06, 127.6, 127.3, 126.4, 50.7, 48.6, 41.8, 41.4, 14.3, 12.73 ppm. LC-MS ESI+ for $C_{12}H_{15}NO$ [M + H]: *m*/*z* = 190. IR: $\tilde{\nu}_{max}$ = 2975, 1644, 1429, 1244, 977, 730, 697 cm^{-1}.

1-Acryloyl-1,2,3,4-tetrahydroquinoline:[19] Method A. Yield: 86% as a yellow oil. An analytical sample was prepared by crystallisation from EtOAc/pentane to give a pink gum. ^{1}H NMR (500 MHz $CDCl_3$, 25 °C): δ = 7.16–7.04 (m, 4 H, Ar-*H*), 6.51 (dd, $^3J_{H,H}$ = 10.0, 16.8 Hz, 1 H, CH_A), 6.42 (dd, $^2J_{H,H}$ = 2.2, $^3J_{H,H}$ = 16.8 Hz, 1 H, CH_BH_C), 5.63 (dd, $^2J_{H,H}$ = 2.2, $^3J_{H,H}$ = 10.0 Hz, 1 H, CH_BH_C), 3.84 (m, 2 H, NHCH_2), 2.70 (m, 2 H, Ar-CH_2), 1.95 (m, 2 H, CH_2) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 165.6, 138.3, 133.2, 130.0, 128.4, 127.4, 126.1, 125.2, 124.9, 43.2, 27.0, 24.0 ppm. LC-MS ESI+ for $C_{12}H_{13}NO$ [2 M + H]: *m*/*z* = 375. IR: $\tilde{\nu}_{max}$ = 2940, 1919, 1645, 1489, 1404, 752 cm^{-1}.

1-Acryloylpiperidine:[14] Method A. Yield: 78% as a colourless oil. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 165.2, 128.1, 126.9, 46.9, 43.0, 26.6, 25.5, 25.5 ppm. LC-MS ESI+ for $C_8H_{13}NO$ [M + H]: *m*/*z* = 140. IR: $\tilde{\nu}_{max}$ = 2935, 2855, 1643, 1433, 1248 cm^{-1}.

(2*E*)-*N*-Benzylbut-2-enamide:[20] Method A. Yield: 95% as a white powder. M.p. 112–114 °C. IR: $\tilde{\nu}_{max}$ = 3263, 3080, 1669, 1625, 1554, 1232, 966, 735, 671 cm^{-1}.

(2*E*)-*N*-(4-Methylphenyl)but-2-enamide:[21] Method A. Yield: 93% as a white solid. M.p. 127–128 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.45 (br. s, 1 H, N-*H*), 7.43 (AA′XX′, 2 H, Ar-*H*), 7.11 (AA′XX′, 2 H, Ar-*H*), 6.96 (dq, $^3J_{H,H}$ = 6.8, 15.1 Hz, 1 H, CH_B),

5.95 (dq, $^4J_{H,H}$ = 1.7, $^3J_{H,H}$ = 15.1 Hz, 1 H, CH_A), 2.31 (s, 3 H, Ar-CH_3), 1.88 (dd, $^4J_{H,H}$ = 1.7, $^3J_{H,H}$ = 6.8 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 164.1, 141.3, 135.6, 133.9, 129.6, 125.6, 120.1, 21.0, 18.0 ppm. LC-MS ESI+ for $C_{11}H_{13}NO$ [M + H]: *m*/*z* = 175.

(2*E*)-*N*-(3-Chlorophenyl)but-2-enamide:[22] Method A. Yield: 80% as an off white solid. M.p. 93–94 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.68 (m, 1 H, Ar-*H*), 7.40 (m, 1 H, Ar-*H*), 7.30 (br. s, 1 H, N-*H*), 7.23 (m, 1 H, Ar-*H*), 7.07 (m, 1 H, Ar-*H*), 7.00 (dq, $^3J_{H,H}$ = 7.0, 15.1 Hz, 1 H, CH_B), 5.94 (dq, $^4J_{H,H}$ = 1.8, $^3J_{H,H}$ = 15.1 Hz, 1 H, CH_A), 1.91 (dd, $^4J_{H,H}$ = 1.8, $^3J_{H,H}$ = 7.0 Hz, 3 H, CH_3) ppm. LC-MS ESI+ for $C_{10}H_{10}ClNO$ [M + H]: *m*/*z* = 196. IR: $\tilde{\nu}_{max}$ = 3268, 1673, 1643, 1589, 1535, 1410, 762 cm^{-1}.

***N*-(Pyridin-2-yl)acrylamide (Method B):**[23] Acroyl chloride (0.97 g, 10.6 mmol) was added dropwise to a cold solution (–78 °C) of 2-aminopyridine (1.00 g, 10.6 mmol) in dichloromethane (100 mL) and triethylamine (1.5 mL, 10.6 mmol) in 10 min. The reaction mixture was slowly warmed to 0 °C over 3 h. The reaction mixture was then concentrated to a solid residue, which was purified by flash chromatography, eluting with 40% ethyl acetate in pentane, to give the title compound as white crystals (1.10 g, 70%). M.p. 71 °C. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 9.30 (br. s, 1 H, N-*H*), 8.34 (m, 1 H, Ar-*H*), 8.28 (m, 1 H, Ar-*H*), 7.38 (m, 1 H, Ar-*H*), 7.06 (m, 1 H, Ar-*H*), 6.48 (dd, $^2J_{H,H}$ = 1.3, $^3J_{H,H}$ = 16.9 Hz, 1 H, CH_C), 6.30 (dd, $^3J_{H,H}$ = 10.2, 16.9 Hz, 1 H, CH_A), 5.79 (dd, $^2J_{H,H}$ = 1.3, $^3J_{H,H}$ = 10.2 Hz, 1 H, CH_B) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 164.0, 151.8, 147.6, 138.8, 131.1, 128.7, 120.0, 114.9 ppm. LC-MS ESI+ $C_8H_8N_2O$ for [M + H]: *m*/*z* = 149. IR: $\tilde{\nu}_{max}$ = 2988, 1925, 1682, 1578, 1439, 1317, 1198, 783 cm^{-1}.

***N*-(Pyridin-3-yl)acrylamide:**[24] Method B. Yield: 38% as yellow crystals. M.p. 118–121 °C. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 164.4, 144.7, 140.7, 135.5, 130.7, 128.9, 128.1, 124.2 ppm. LC-MS ESI+ $C_8H_8N_2O$ for [M + H]: *m*/*z* = 149. IR: $\tilde{\nu}_{max}$ = 2913, 1906, 1687, 1553, 1418, 1270, 791, 703 cm^{-1}.

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