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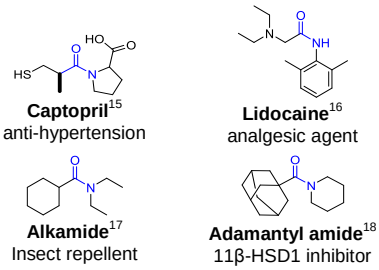
Low-Pressure Radical ^{11}C-Aminocarbonylation of Alkyl Iodides *via* Thermal Initiation

Shiao Y. Chow[a], Luke R. Odell*[a] and Jonas Eriksson*[a]

Abstract: A radical ^{11}C-aminocarbonylation protocol was developed with excellent substrate compatibility to access ^{11}C-labelled amides from alkyl iodides, including 11β-HSD1 inhibitor [*carbonyl*-^{11}C]adamantan-1-yl(piperidin-1-yl)methanone. This protocol serves as a complementary extension of palladium-mediated ^{11}C-aminocarbonylation, which is limited to the preparation of ^{11}C-labelled compounds lacking beta-hydrogens. Use of AIBN as radical initiator and a low-pressure xenon [^{11}C]CO-delivery unit represents a simple and convenient alternative to previous radical ^{11}C-carbonylation methodologies burdened with the need for a proprietary high pressure reactor connected to a light source.

Introduction

Positron Emission Tomography (PET) is a molecular imaging modality with diverse use in biomedical research and clinical diagnostics including monitoring of disease progression.[1] In recent years, a growing number of ^{11}C-labelled compounds derived from [^{11}C]CO have been prepared for preclinical imaging[2–11] based on well-established carbonylative transformations, and [^{11}C]phenytoin has advanced to clinical studies as a P-glycoprotein PET tracer.[12] In addition to its synthetic versatility, incorporation of [^{11}C]CO in radiotracers has a relatively low risk of isotopical dilution due to the low abundance of CO in air, often resulting in very high specific activity suitable for study of low density targets (e.g. receptor systems). Conventionally, [^{11}C]CO is produced readily from cyclotron supplied [^{11}C]CO_2 *via* metal-mediated heterogeneous reduction using heated zinc (400 °C)[13] or molybdenum (850 °C).[14] Due to the short half-life of the ^{11}C radionuclide ($T_{1/2}$ = 20.4 min)[1], efficient reduction of [^{11}C]CO_2 to [^{11}C]CO and transfer of [^{11}C]CO to the reaction vessel is critical to produce useful amounts of product in the subsequent carbonylation reaction.



Captopril[15] anti-hypertension

Lidocaine[16] analgesic agent

Alkamide[17] Insect repellent

Adamantyl amide[18] 11β-HSD1 inhibitor

Figure 1. Bioactive alkyl amides

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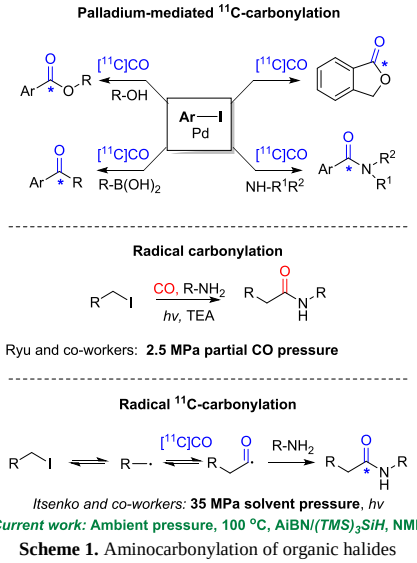
http://www.ilk.uu.se/research/ofk_en/

In syntheses involving ^{11}C-labelled precursors, small reaction vessels are optimal to achieve high reagent concentrations and thereby sustain fast reaction kinetics without requiring large amounts of reagents that may increase cost and compromise the purification process. However, the low solubility of [^{11}C]CO in most solvents[19], coupled with degassing action and venting of the vessel headspace by poorly soluble transfer gas (e.g. helium) render efficient transfer of [^{11}C]CO to small volume reaction vessels difficult, thus hampering its use in production of ^{11}C-labelled compounds. To counteract this, a highly-pressurized small autoclave was developed, in which efficient use of [^{11}C]CO in labelling synthesis was achieved.[20–22] Subsequently, retention of [^{11}C]CO in reaction mixture has been accomplished using less technically challenging approaches, such as chemical fixation of [^{11}C]CO (i.e. copper complexes,[23,24] BH_3.THF,[25] and highly reactive catalytic transition metal complexes,[26,27]), ex-situ conversion[28,29] of [^{11}C]CO_2 to [^{11}C]CO, and more advanced techniques like microfluidics.[30–32] An efficient method of confining [^{11}C]CO at ambient pressure in standard disposable reaction vials using xenon as transfer gas without the need for chemical fixation agents or high reaction pressure was reported by Eriksson and co-workers.[33] The method employed highly soluble xenon as transfer gas to bubble [^{11}C]CO into an organic solvent in a septum equipped vial without significant pressure increase. Importantly, no venting was required to complete [^{11}C]CO transfer, hence minimizing losses prior to the chemical transformation. The utility of this method was exemplified by ^{11}C-labelling of amides, ureas, and esters at ambient pressure. Recently, two reports were published using the same [^{11}C]CO transfer protocol.[2,34] This robust method enables efficient use of [^{11}C]CO in radiosynthesis of PET tracers. Importantly, the use of disposable glass reaction vials allows convenient reaction mixture preparation and eliminates carry over issues associated with the high pressure autoclave system, thus simplifying implementation into a clinical GMP-setting.

Amides[2,5–9,22,26,35–38] are the most common class of compounds explored in palladium mediated ^{11}C-carbonylation. (Scheme 1) Other structures that have been obtained directly from [^{11}C]CO using palladium are aldehydes,[26,39] carboxylic acids,[10,26,40] esters,[4,26,41,42] hydrazides[40], imides[43], ketones[26,44], thioesters[45] and ureas[24]. There are also a few examples of compounds obtained from multi-step synthesis starting with ^{11}C-carbonylation, e.g. ^{11}C-labelled hydroxamic acid[46] from esters, and alkyl iodides[11,39] from aldehydes/carboxylic acids via olefin carbonylation. However, palladium carbonylation is restricted to organic halides lacking beta-hydrogen, e.g. methyl, aryl, benzyl and alkenyl iodides.[47,48] This limitation could potentially be overcome by the recent ^{11}C-carbonylative cross-coupling of alkyl iodides containing beta-hydrogen and amines using air sensitive $Ni(COD)_2$ with bathophenanthroline as supporting ligand.[49] Prior to this development, Itsenko and co-workers employed a radical ^{11}C-carbonylation of alkyl iodides for the preparation of alkyl amides[35], esters[50,51] and carboxylic acids[52] *via* (1) an initial

photochemical radical homolysis of organoiodides to generate alkyl radicals induced by UV irradiation followed by (2) subsequent atom transfer carbonylation. The syntheses were performed using a highly-pressurized (35 MPa) and patent-protected autoclave. To the best of our knowledge, no further studies on the preparation of ^{11}C-labelled alkyl carbonyls have been reported. Ryu and co-workers have disclosed a metal-free aminocarbonylation of alkyl halides using 2,2'-azobis(2-methylpropionitrile) (AiBN) as radical initiator to generate isotopically unmodified alkyl amides in elevated CO atmosphere (2.0-2.5 MPa).[53] In their works, radical reductive dehalogenation of the alkyl iodides was induced *via* a radical chain process using a radical initiator and $(TMS)_3SiH$ as a radical mediator.



Scheme 1. Aminocarbonylation of organic halides

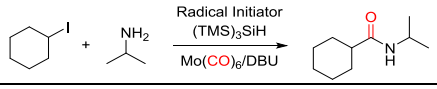
The resulting alkyl radicals underwent addition with CO in the presence of amine nucleophiles to furnish alkyl amides. Encouraged by these findings, we sought to explore the applicability of a thermally-initiated radical reductive dehalogenation approach coupled with a low-pressure [^{11}C]CO delivery system to prepare ^{11}C-labelled alkyl amides, an important class of bioactive compounds and reaction intermediates.[54,55]

Herein, we report the development of low-pressure radical ^{11}C-aminocarbonylation of unactivated alkyl iodides containing beta-hydrogens, employing an improved xenon-based [^{11}C]CO-delivery unit.[33] The carbonylative transformation proceeds *via* radical dehalogenation of alkyl iodides induced by a radical initiator and mediator to form alkyl radicals followed by a subsequent ^{11}C-aminocarbonylation through atom transfer of [^{11}C]CO and subsequent nucleophilic attack by an amine nucleophile to produce ^{11}C-labelled alkyl amides.

Results and Discussion

We initiated our studies by conducting a short aminocarbonylation condition screening study with CO (isotopically unmodified) to map out reaction parameters as a starting point for the corresponding ^{11}C-aminocarbonylation reaction (Table 1). Cyclohexyliodide and isopropylamine were used as model substrates using a previously reported two-chamber vial system,[56,57] and the conversion was monitored by ^{1}H NMR. Cyclohexyl iodide, isopropylamine, AiBN, $(TMS)_3SiH$ and triethylamine were added in chamber 1 in THF (3 mL) and $Mo(CO)_6$ was added to chamber 2 as the *ex situ* solid CO source. The internal pressure of the reaction was measured at 0.23 MPa. The initial attempts were met with limited success, as conversion to the desired amide was poor and formation of the aldehyde side product derived from quenching of acyl radical by $(TMS)_3SiH$ was observed (^{1}H-NMR). A solvent survey (THF, MeOH, DMF, NMP) was carried out in order to stabilize either the alkyl radical (stabilized by non-polar solvent) or acyl radical (solvated by polar solvent), and THF was found to provide the best reaction selectivity without formation of the aldehyde side product. AiBN ($T_{1/2}$ = 1h at 82°C) was replaced with a more efficient initiator 1,1'-azobis(cyclohexanecarbonitrile) (ACCN) ($T_{1/2}$ = 10h at 85°C) with a longer half-life, and a 5-fold improvement in conversion was obtained. Increasingly the amount of ACCN (one-step or portion-wise) was beneficial returning slightly increased yields of 16-19%. However, the yield was lower compared to the general results presented by Ryu *et al* (different compounds), which could be explained by the significantly lower CO partial pressure applied in the current work (0.23 MPa vs 2-2.5 MPa).[53]

Table 1: Optimization of reaction parameters of radical aminocarbonylation of cyclohexyl iodide using isotopically unmodified CO



Entry	Radical Initiator	Solvent	NMR yield
1	AiBN (25 mol-%)	THF	2.9%
2[a]	AiBN (25 mol-%)	THF	-
3	AiBN (25 mol-%)	MeOH	1.3%
4	AiBN (25 mol-%)	DMF	1.1%
5	AiBN (25 mol-%)	NMP	1.0%
6	ACCN (25 mol-%)	THF	15%
7	ACCN (50 mol-%)	THF	16%
8[b]	ACCN (25 + 25 mol-%)	THF	19%

Reaction condition: Chamber 1: Cyclohexyl iodide (0.3 mmol), Isopropylamine (0.3 mmol), TEA (0.6 mmol), $(TMS)_3SiH$ (0.06 mmol), radical initiator (25-50 mol-%), solvent (3 mL). Chamber 2: $Mo(CO)_6$ (0.6 mmol), DBU (1.8 mmol), THF (3 mL). [a]No $(TMS)_3SiH$ added. [b]Second portion of ACCN added after 1h.

In general, the conversion of alkyl iodide to amide using CO was moderate. However, as [^{11}C]CO is used at substoichiometric amount (low nmol amounts) and serves as the limiting reactant in ^{11}C-carbonylation, we believed that the diminutive amount of [^{11}C]CO introduced would be rapidly consumed despite the low conversion observed in initial mapping studies using CO. Thus, we proceeded to explore an ^{11}CO-aminocarbonylation protocol using the model substrates. The reaction mixture (500 µL in THF) was introduced to a 1 mL capped vial and a semi-automated unit was used to reduce [^{11}C]CO_2 and transfer the [^{11}C]CO formed into the vial in xenon gas. (Figure 2) The unit was improved and simplified compared to the previously reported design,[20] with a single valve to direct the process gases without additional gas purification. The [^{11}C]CO_2 (1.1 µAh irradiation) was utilized efficiently and a total of 82% (decay corrected) of radioactivity was recovered in the reaction vial as

[^{11}C]CO (3.5 GBq, non-decay corrected). The loss of activity was primarily due

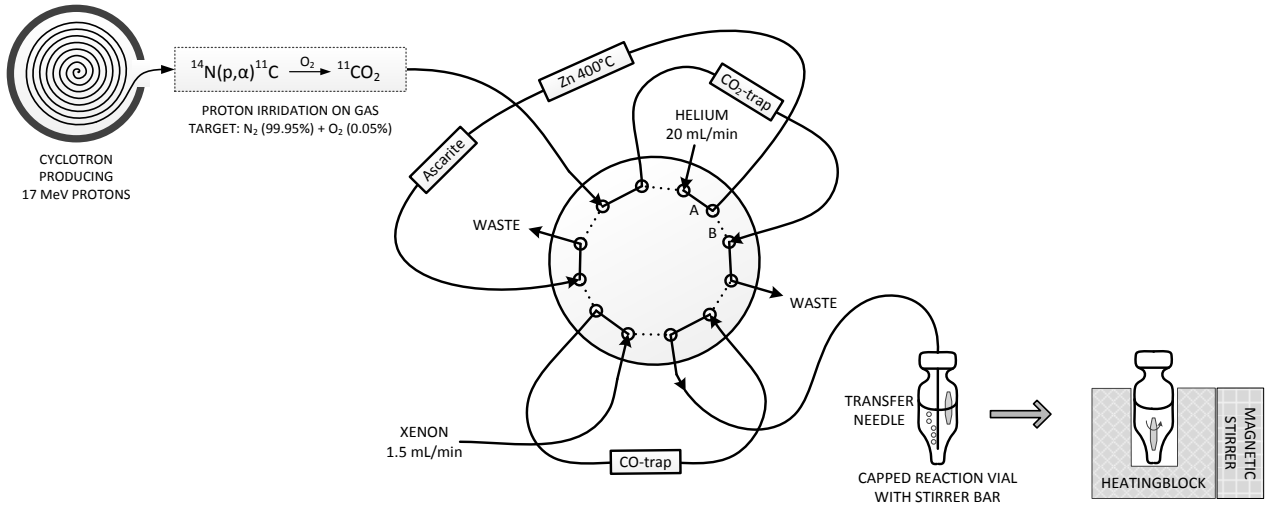
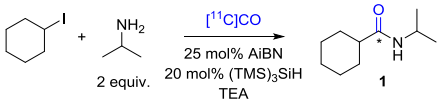


Figure 2. Schematic view of the process to produce and deliver [^{11}C]CO for the ^{11}C-aminocarbonylation. A single 12-port/2-position injection valve was used to direct the gases during the collection of [^{11}C]CO_2, on-line reduction over zinc, concentration of [^{11}C]CO and transfer to the reaction vial. The CO_2-trap and CO-trap which concentrated [^{11}C]CO_2 and [^{11}C]CO contained silica gel and were cooled with liquid nitrogen to trap the radioactive gases and heated to release them. The valve was toggled between position A and B in the following order: 1) A: [^{11}C]CO_2 transfer from the cyclotron to the CO_2-trap. 2) B: On-line reduction to [^{11}C]CO, removal of residual [^{11}C]CO_2 on Ascarite and transfer in helium to the CO-trap. 3) A: [^{11}C]CO transfer in xenon from the CO-trap to the reaction vial. After the process the needle penetrating the septum of the reaction vial was removed.

to absorption of [^{11}C]CO_2 onto the zinc reductant. Typically, the total time required for the collection of [^{11}C]CO_2 and delivery of [^{11}C]CO to the reaction vial was 3 min. Upon introduction of [^{11}C]CO, the vial was heated at 100 °C with vigorous stirring for 5 min. Unfortunately, the reaction was sluggish with poor [^{11}C]CO conversion and reaction selectivity, returning only a trace amount of the ^{11}C-labelled amide (**1)** (Table 2).

Table 2: Optimization of reaction parameters of radical ^{11}C-aminocarbonylation of cyclohexyliodide



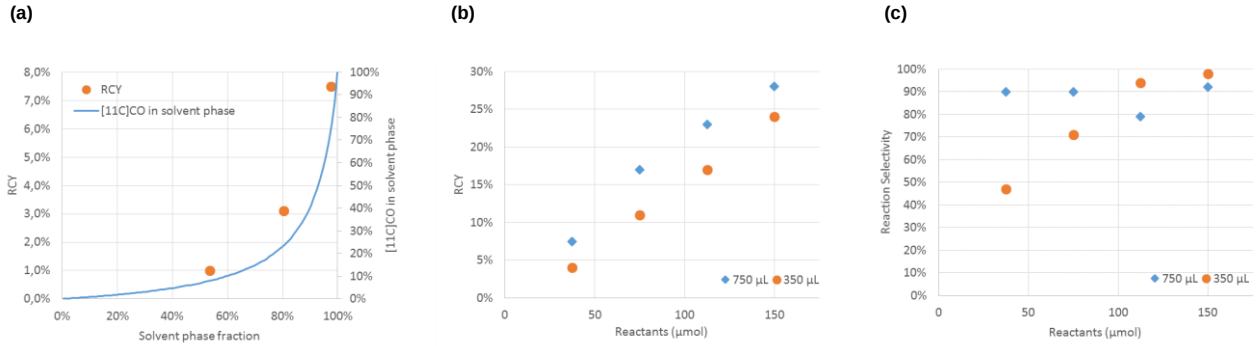
Entry	Iodide mM	AiBN mol-%	Solvent	V_s	Conv.[a]	RS[b]	RCY[c]
1	50	25	THF	500	6%	10%	0.6%
2	50	25	NMP	500	3.4%	28%	1.0%
3	50	25	NMP	750	3.5%	88%	3.1%
4	50	25	NMP	950	9%	90%	7.5%
5	50	25	NMP	750	6.5%	69%	4.5%
6	100	25	NMP	750	19%	90%	17%
7	100	100	NMP	750	24%	88%	21%
8	150	25	NMP	750	29%	79%	23%
9	200	25	NMP	750	30%	92%	28%
10	100	25	NMP	350	9%	47%	4%
11	200	25	NMP	350	16%	71%	11%
12	300	25	NMP	350	18%	94%	17%
13	400	25	NMP	350	24%	98%	24%

Reaction condition: Upon xenon-delivery of [^{11}C]CO, the reaction was heated at 100 °C and stirred vigorously for 5 min. [a]Percentage of [^{11}C]CO converted to non-volatile compounds. [b]Reaction selectivity determined from percentage of desired amide product in the crude reaction mixture assessed by analytical *rp*-HPLC. [c]Decay-corrected radiochemical yield for non-isolated product calculated from the [^{11}C]CO conversion and the reaction selectivity.

The reaction selectivity was improved when the solvent was changed to NMP, however the overall [^{11}C]CO conversion remained unsatisfactory. We postulated that low [^{11}C]CO concentration in the solvent phase, due to poor solvent solubility, may have contributed to the inadequate conversion to the ^{11}C-amide. This contradicts typical Pd- or Rh-mediated reactions which performed efficiently using similar concentrations of [^{11}C]CO in low-pressure systems.[33] The higher efficiency of metal-mediated systems may be explained by either the increase of [^{11}C]CO concentration in solvent phase *via* reversible coordination of [^{11}C]CO to the metal centers, or simply by significantly higher concentration of CO-activating organo-metal complexes compared to the concentration of alkyl radicals formed under the current reaction conditions. Previously reported successful radical ^{11}C-aminocarbonylation initiated by UV-light irradiation did not use transition metals. However, high pressure (35-40 MPa) was employed to transfer reagent solution into the specialized autoclave containing [^{11}C]CO in helium gas (0.4 MPa) resulting in a depleted gas phase.[35] This observation led us to investigate if the ratio of gas phase versus solvent phase could have an effect on the radiochemical yield. To this end, we proceeded with manipulating the ratio of solvent and gas phase in the reaction vial. The gas phase was reduced or nearly eliminated, while the reagent concentrations was kept unchanged (Table 2, entry 2-4; Figure 3a-b). A correlation between increased solvent phase fraction and increased radiochemical yields (RCY) was observed and both conversion of [^{11}C]CO and reaction selectivity were improved. Equations were derived from (*i*) and (ii) to calculate the fraction [^{11}C]CO residing in the solvent phase (*iii*) and the relative concentrations (*iv*) at the different solvent and gas phase ratios. (Figure 3a,

Table 3). The Ostwald solubility constant (L) is defined as the ratio between the concentration of gas molecules in the solvent and in the gas phase at equilibrium.

Figure 3. Influence of solvent phase fraction and reactant concentrations on the radiochemical yield and reaction selectivity



(a) The radiochemical yield improved with increased solvent phase fraction. Concentrations of non-volatile reagents were kept unchanged. The solid line represents the theoretically calculated fraction [^{11}C]CO residing in the solvent phase, equation (iii). **(b)** The radiochemical yield increased with increased concentrations of the alkyl iodide and amine (1:1). A solvent volume of 750 µL (80.4% solvent phase) gave higher yield than 350 µL (37.5% solvent phase). **(c)** The reaction selectivity increased with increased reactant concentrations at low solvent volume (350 µL).

$$L = \frac{C_s}{C_g} \qquad (i)$$

$$n = (C_s \times V_s) + (C_g \times V_g) \qquad (ii)$$

Combining (i) and (ii) gave

$$Fraction\ [^{11}C]CO\ residing\ in\ solvent\ phase = \frac{n_s}{n} = \frac{V_s}{V_s + \frac{V_g}{L}} \qquad (iii)$$

$$Concentration\ [^{11}C]CO\ in\ solvent\ phase = \frac{n_s}{V_s} = \frac{n}{V_s + \frac{V_g}{L}} \qquad (iv)$$

L = Ostwald solubility constant, C_s = [^{11}C]CO concentration in solvent phase, C_g = [^{11}C]CO concentration in gas phase, V_s = volume of solvent phase, V_g = volume of gas phase, n_s = amount of [^{11}C]CO in the solvent, n = total amount of [^{11}C]CO

It was concluded that the increase in radiochemical yield with reduction of gas phase, potentially, could be explained by the exponentially increased fraction [^{11}C]CO residing in the solvent phase (Figure 3a) or the corresponding increase in solvent phase [^{11}C]CO concentration (Table 3), calculated using equation (iii) and (iv), respectively.

Table 3: Calculated solvent phase [^{11}C]CO concentration, solvent phase fraction and radiochemical yield

Entry	V_S (µL)	V_g (µL)	$\frac{V_S}{V_S + V_g}$	C_S[a]	RCY
-	50	883	5.4%	1.0x	ND
-	250	683	26.8%	1.3x	ND
2	500	433	53.6%	3.2x	1.0%
3	750	183	80.4%	6.3x	3.1%
4	910	23	97.5%	9.7x	7.5%

[a]The amount of [^{11}C]CO was not known hence concentration of [^{11}C]CO in the solvent (C_S) is presented as multiples calculated using equation (*iv*) and L_{CO} in NMP = 0.075.[58] ND = Not Determined.

For practical reasons, the total solvent volume of 750 µL was used for further optimizations focused on the influence of radical initiator and the amine and alkyl iodide concentrations. The more efficient ACCN was used *in lieu* of AiBN however no significant improvement in the radiochemical yield was observed. Due to the much shorter reaction time (5 min) compared to the aminocarbonylation with isotopically unmodified CO (20 h), the advantage of ACCN having a longer half-life was less important and not beneficial in this case. Next, the concentration of reactants was increased (50, 100, 150, and 200 mM, entry 4, 6, 8-9) in a bid to promote [^{11}C]CO-consumption by the alkyl radicals. Interestingly, a direct correlation between radiochemical yield and the amount of reactants used was observed (Figure 3b). The need for a higher concentration of reactants suggests radical generation may be the rate-limiting step, resulting in the low [^{11}C]CO conversion in the subsequent ^{11}C-aminocarbonylation step. Increasing the amount of AiBN (up to 1 equiv.) however did not improve the RCY significantly due to possible early termination of the radical chain reaction. (Entry 7) To further investigate the effect of using higher concentration of reactants, the same amount of reactants was maintained albeit in smaller reaction volume (350 µL) to avoid excessive use of reactants (Entry 10-13). Similarly, the radiochemical yield improved with higher reactant concentrations and interestingly, increasing the reactant concentrations had a more pronounced effect on reaction selectivity using smaller reaction volume (Figure 3b-c).

Table 4: Screening of reaction parameters

Parameter	Reaction Condition	[^{11}C]CO conv.[a]	RS[b]	RCY[c]
Standard (Entry 12)	300 s Stirring 100 °C	24%	98%	24%
Reaction Time	180 s	28%	87%	24%
	420 s	32%	87%	28%
Agitation Method	Shaking	27%	95%	26%
	None	11%	86%	9%
Temperature	80 °C	24%	92%	22%
	120 °C	26%	74%	19%

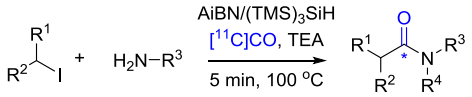
Reaction conditions: Cyclohexyl iodide (400 mM), isopropylamine (1 equiv), TEA (2 equiv), AiBN (25 mol-%), $(TMS)_3SiH$ (20 mol-%), NMP (375 µL). [a]Percentage of [^{11}C]CO converted to non-volatile compounds. [b]Reaction selectivity determined from percentage of desired amide product in the crude reaction mixture assessed by analytical *rp*-HPLC. [c]Decay-corrected radiochemical yield for non-isolated product calculated from the [^{11}C]CO conversion and the reaction selectivity.

The same reaction conditions as in Entry 13 were chosen to probe the optimal reaction time, agitation method and reaction

temperature (Table 4). No significant difference in yields was observed using 3, 5 or 7 min reaction times. Higher reaction temperature was employed to increase reaction rate and improve the solubility of [^{11}C]CO in the solvent, however this resulted only in decreased yield and purity due to side product formation. Vigorous agitation of the reaction mixture was found to be crucial, in which similar radiochemical yield was maintained using mechanical shaker, while a drastic decrease in yield was observed in the absence of agitation. For economical, practical and ease of handling reasons, entry 13 remained the optimal reaction condition.

With the optimized reaction conditions in hand, the full scope of the radical ^{11}C-aminocarbonylation reactions was explored with cyclohexyl iodide and amines, including primary, secondary and aryl amines.

Table 5. Reaction scope of radical ^{11}C-carbonylation of alkyl iodides



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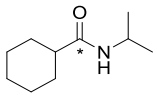
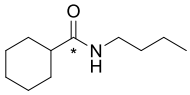
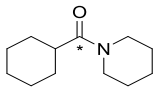
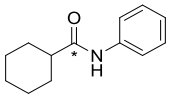
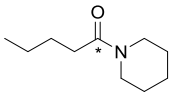
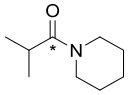
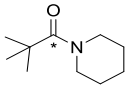
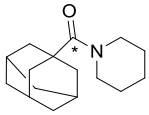
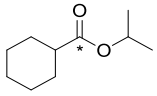
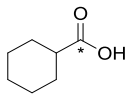
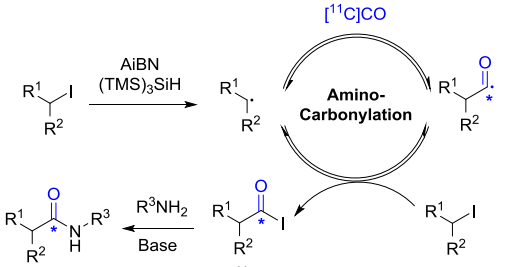
Entry	Product	Conv.[a] (%)	Isolated RCY[b] (%)	n
1		32	25±1.4	2
2		32	24±1.4	2
3		36	24±1.4	2
4		30	20±0.4	4
5		18	9±0	2
6		24	18±0.7	2
7		2	-	2
8	 11β-HSD1 inhibitor	37	18±2.8	2
9		27	11±0.8	2
10		28	-	1

Reaction conditions: Iodide (400 mM), nucleophile (1 equiv), TEA (2 equiv), AiBN (25 mol-%), $(TMS)_3SiH$ (20 mol-%), and NMP (375 µL). Radiochemical purity was >99% for all entries. [a]Percentage of [^{11}C]CO converted to non-volatile compounds. [b]Decay-corrected radiochemical yield for product purified by semi preparative *rp*-HPLC, based on [^{11}C]CO transferred to the reaction vial.

Primary amines and secondary alkyl amines performed well as substrates returning the ^{11}C-labelled amides (**1-3**) in good yields, while a slightly lower yield was observed for aniline product (**4**) due to decreased nucleophilicity. The specific activity of (**4**) was 101±13 GBq/µmol (n=2) at end of synthesis (after purification), the compound was obtained with 1.32±0.04 GBq and >99% radiochemical purity. The total synthesis time was 25 min from end of radionuclide production to isolated product.

The reaction scope was further explored with selected iodides. Isopropyl iodide underwent a smooth reaction with piperidine to afford the ^{11}C-amide product (**6**). A lower yield was observed for (**5**) due to the slow and challenging reductive dehalogenation of *n*-butyl iodide forming instable alkyl radicals typical for primary alkyl iodides. Interestingly, only trace amount of [^{11}C]CO conversion was observed in sterically hindered *tert*-butyl iodide (**7**) while the more strained adamantyl iodide reacted efficiently to give the desired amide (**8**) in 18% yield. In the former case, it is likely that the combination of high radical stability coupled with a slow carbonylation reaction rate[59] led to poor [^{11}C]CO-conversion. Notably, (**8**) was reported as a highly potent and selective 11β-HSD1 inhibitor[18], highlighting the potential utility of our method developed herein to produce biologically-active PET tracers. Lastly, isopropanol and water were exploited as nucleophiles to produce the corresponding alkyl ester (**9**) and carboxylic acid (**10**) derivatives. The use of isopropanol returned moderate yield and only trace amounts of product were observed in the use of water, possibly due to lower nucleophilicity than the corresponding amines.



Scheme 2: Possible mechanism of ^{11}C-aminocarbonylation of alkyl iodides

A possible mechanism for the radical ^{11}C-aminocarbonylation of alkyl iodides is depicted in Scheme 2. We believe that the radical ^{11}C-carbonylative transformation developed herein involves an initial radical dehalogenation of alkyl halides to form alkyl radicals followed by aminocarbonylation in the presence of [^{11}C]CO and amine nucleophiles to furnish the desired alkyl amides. In the initial radical chain reactions, the radical initiator AiBN undergoes thermally-induced decomposition and subsequent H-abstraction[60] a of $(TMS)_3SiH$ gives $(TMS)_3Si\cdot$,

which in turn, mediates the reductive dehalogenation of the alkyl iodide substrate. The formed alkyl radical undergoes addition to [^{11}C]CO to form an acyl radical,[61] which could be either quenched by the starting alkyl iodide to form an acyl iodide, or further oxidized to furnish an acylium ion.[62] In the final ionic step, the acyl iodide or acylium ion is trapped by the amine nucleophile to afford the desired ^{11}C-labeled alkyl amide.

Conclusions

In conclusion, we have developed a low-pressure and versatile radical ^{11}C-aminocarbonylation protocol for the synthesis of ^{11}C-labeled alkyl amides. We showed herein that our ^{11}C-carbonylative transformation provides good substrate accessibility and represents a simple and convenient method to afford productive amounts of ^{11}C-labelled amides. Furthermore, the use of an alcohol nucleophile led to formation of the corresponding radiolabeled ester.

Experimental Section

CHEMISTRY

General Information

All reagents were purchased at high commercial quality and used without further purification. Yields refer to isolated, homogenous and spectroscopically pure material, unless otherwise stated. Reaction outcome was determined using EI-MS. Crude reaction mixtures were purified by silica gel chromatography (E. Merck silica gel, particle size 0.043–0.063 mm). Thin layer chromatography was carried out using E. Merck silica plates (60F-254) with UV light (254 nm) and/or iodine vapour as the visualization agent. Blue light-emitting diodes (12 V, 2 W, λ = 465 nm) were used for irradiation of reaction mixtures. ^{1}H NMR spectra of reference compounds were recorded at 400 MHz and ^{13}C{^{1}H} NMR spectra at 100 MHz. The chemical shifts for ^{1}H NMR and ^{13}C{^{1}H} NMR spectra were referenced to tetramethylsilane *via* residual solvent signals (^{1}H, $CDCl_3$ at 7.26 ppm; ^{13}C, $CDCl_3$ at 77.16 ppm). Low resolution GC/MS analyses were performed with a CP-SIL 8 CB low bleed (30 m × 0.25 mm) capillary column using a 70−300 °C temperature gradient and electron impact ionization at 70 eV. Accurate mass values were determined on a mass spectrometer equipped with an electron-impact ion source and TOF detector.

Synthesis of Reference Compounds

Method A[57]**:** To the CO releasing chamber (C_{co}) of a H-tube was added $Mo(CO)_6$ (0.6 mmol) and MeCN (3.0 mL). The reaction chamber (C_{rxn}) was charged with alkyl iodide (0.3 mmol), amine (0.6 mmol), *fac*-Ir(ppy)$_3$ (2 mol-%), Hantzsch ester (0.15 mmol), tributylamine (0.6 mmol) and MeCN (3.0 mL). The chambers were capped and subjected to a 5 minute N_2 flush, after which DBU (1.8 mmol) was added to C_{co}. The assembly was placed in a Dry-Syn heating block with Cco on a heating plate at 70 °C and C_{rxn} outside of the heating block ($T_{measured}$ = 25 °C). C_{rxn} was then subjected to visible light radiation using blue LED strips for 20 h. The crude reaction mixture was then dry loaded with silica gel directly and purified using standard column chromatography (2.5:2.5:95 EtOAc:HCOOH:Hexane).

Method B: Amine or alcohol (8.0 mmol) was dissolved in DCM (5 mL) in the presence of triethylamine (1 equiv) and cooled to 0 °C. Acid chloride (1 equiv) was added dropwise and the reaction was allowed to return to room temperature and left stirring overnight. The reaction mixture was filtered, washed with chilled DCM, and the solvent was removed in vacuo.

***N*-isopropylcyclohexanecarboxa**mi**de**[35] **(1) (CAS 6335-52-0)** Prepared using method A. Spectral data were in agreement with literature values. White solid (39 mg, 78%) ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.19 (s, 1H), 4.07 (dt, *J* = 8.0, 6.6 Hz, 1H), 2.00 (tt, *J* = 11.7, 3.5 Hz, 1H), 1.89–1.72 (m, 4H), 1.74–1.52 (m, 1H), 1.48–1.35 (m, 2H), 1.31–1.18 (m, 3H), 1.13 (d, *J* = 6.6 Hz, 6H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 175.4, 45.8, 41.1, 29.9, 25.9, 23.0. EI-MS: *m/z* 169.2.

***N*-butylcyclohexanecarboxamide**[63] **(2) (CAS 128037-34-3)** Prepared using method A. Spectral data were in agreement with literature values. White solid (39 mg, 71%), R_f = 0.12 (10% EtOAc in *n*-pentane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.38 (s, 1H), 3.45–3.12 (m, 2H), 2.04 (tt, *J* = 11.8, 3.5 Hz, 1H), 1.90–1.75 (m, 4H), 1.70 – 1.62 (m, 1H), 1.52–1.15 (m, 10H), 0.92 (t, *J* = 7.3 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 176.3, 45.7, 39.3, 31.9, 29.9, 25.9, 20.2, 13.9. EI-MS: *m/z* 183.2.

***N*-cyclohexylcyclohexanecarboxamide**[64] **(3) (CAS 7474-36-4)** Prepared using method A. Spectral data were in agreement with literature values. White solid (57 mg, 90%) ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.25 (s, 1H), 3.87–3.34 (m, 1H), 2.01 (dd, *J* = 11.4, 3.1 Hz, 1H), 1.95–1.52 (m, 12H), 1.48–1.03 (m, 8H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 175.6, 48.2, 45.7, 33.3, 29.8, 25.9, 25.7, 25.0. EI-MS: *m/z* 209.1.

***N*-phenylcyclohexanecarboxamide**[65] **(4) (CAS 2719-26-8)** Prepared using method A. Spectral data were in agreement with literature values. White solid (36 mg, 59%) ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58–7.45 (m, 2H), 7.36–7.28 (m, 2H), 7.15–7.04 (m, 2H), 2.22 (ddt, *J* = 11.7, 7.1, 3.5 Hz, 1H), 1.96 (dd, *J* = 13.0, 3.6 Hz, 2H), 1.89–1.78 (m, 2H), 1.76–1.66 (m, 1H), 1.62–1.47 (m, 2H), 1.39–1.22 (m, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 174.2, 138.0, 128.9, 124.0, 119.6, 46.5, 29.6, 25.6. EI-MS: *m/z* 203.1.

1-(piperidin-1-yl)pentan-1-one[66] **(5) (CAS 18494-52-5)** Prepared using method B. Spectral data were in agreement with literature values. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.46 (s, 4H), 2.36 – 2.27 (m, 2H), 1.67 – 1.49 (m, 4H), 1.40 – 1.29 (m, 2H), 0.92 (t, *J* = 7.3 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 171.4, 45.7, 42.8, 32.9, 27.5, 27.4, 25.9, 24.4, 22.4, 13.7.

2-methyl-1-(piperidin-1-yl)propan-1-one[67] **(6) (CAS 17201-04-6)** Prepared using method B. Spectral data were in agreement with literature values^{1}H NMR (400 MHz, $CDCl_3$) δ 3.49 (t, *J* = 5.5 Hz, 4H), 2.84 – 2.74 (m, 1H), 1.68 – 1.57 (m, 2H), 1.59 – 1.48 (m, 4H), 1.13 – 1.08 (m, 6H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 175.7, 45.1, 30.5, 26.7, 25.1, 19.9. EI-MS: *m/z* 155.3

2,2-dimethyl-1-(piperidin-1-yl)propan-1-one[68] **(7) (CAS 55581-65-2)** Prepared using method A. Spectral data were in agreement with literature values. White solid (9 mg, 17%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.74–3.41 (m, 4H), 1.69–1.59 (m, 2H), 1.58–1.50 (m, 4H), 1.27 (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 176.1, 46.2, 38.7, 28.4, 26.1, 24.7. EI-MS: *m/z* 169.1.

Adamantan-1-yl(piperidin-1-yl)methanone[67] **(8) (CAS 22508-49-2)** Prepared using method A. Spectral data were in agreement with literature values. White solid (56 mg, 72%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.81–3.41 (m, 4H), 2.04–2.01 (m, 2H), 2.01–1.97 (m, 6H), 1.75–1.68 (m, 6H), 1.66–1.59 (m, 3H), 1.57–1.46 (m, 4H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 175.5, 46.4, 41.7, 39.1, 36.7, 28.6, 26.3, 24.8. EI-MS: *m/z* 247.2.

Isopropyl cyclohexanecarboxylate (9) (CAS 6553-80-6) Prepared using method B. Spectral data were in agreement with literature values. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.98 (pd, J = 6.2, 1.0 Hz, 1H), 2.29 – 2.16 (m, 1H), 1.96 – 1.55 (m, 5H), 1.48 – 1.35 (m, 2H), 1.32 – 1.23 (m, 3H), 1.21 (s, 3H), 1.20 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 175.87, 67.16, 43.52, 29.12, 25.92, 25.58, 21.94. EI-MS: *m/z* 170.2

Cyclohexanoic acid (10) (CAS 98-89-5) Commercially purchased. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.33 (tt, *J* = 11.2, 3.6 Hz, 1H), 1.98 – 1.88 (m, 2H), 1.81 – 1.58 (m, 3H), 1.52 – 1.38 (m, 2H), 1.36 – 1.14 (m, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 182.8, 43.3, 29.2, 26.1, 25.8. EI-MS: *m/z* 128.2

RADIOCHEMISTRY

General Information

All reagents were purchased at high commercial quality and used without further purification. Transfer gas helium 6.0 and target gas nitrogen/0.05% oxygen mixture for ^{11}C-radionuclide production were purchased from AGA (Sweden). Xenon 99.995% was purchased from Fluka (USA). Disposable reaction vials (crimp neck, conical 0.9 mL were purchased from VWR (Sweden) and capping septum (1.5 mm, 11 mm aluminium crimp cap, silicone/PTFE seal) was purchased from Scantec Nordic (Sweden). All presented radiochemical yields are decay corrected. Purification was performed by semi-preparative high performance liquid chromatography (VWR LaPrep) equipped with pump (LP-1200), UV detector (Detector 40D), radiodetector (Flow-Count PMT, Bioscan), auto-sampler (TPS, built in-house) and a column (Phenomenex Kinetex 5µm C18 100 Å 150x10.0 mm). Eluents: A = water 0.1% TFA; B = acetonitrile; isocratic elution; 5.0 mL/min. Product elution was monitored using both UV detector (214 nm) and radiodetector. The radiochemical purity and identities of the labelled products were assessed by analytical HPLC (VWR LaChrom Elite) equipped with an auto-sampler (L-2200), pump (L-2130), diode array detector (L-2450), radiodetector (Flow-Count PMT, Bioscan) and a column (Chromolith Performance RP-18e, 100x4.6 mm). Eluents: A = water; B = acetonitrile; 0-10 min 5-95% B; 4 mL/min.

Standard Radical ^{11}C-Aminocarbonylation Protocol

Amine (400 mM), TEA (800 mM equiv), AiBN (25 mol-%), $(TMS)_3SiH$ (20 mol-%) were added into an oven-dried 1 mL capped disposable glass vial equipped with a magnetic stirrer bar. The mixture was dissolved in NMP (375 µL) and purged with nitrogen for 2 min. Alkyl iodide (400 mM) was added to the mixture 5 min prior to the introduction of [^{11}C]CO. [^{11}C]CO_2 was obtained by the ^{14}N(p,α)^{11}C nuclear reaction using 17 MeV protons (MC-17 cyclotron, Scanditronix). Typically 1 µAh irradiations were made. [^{11}C]CO_2 was transferred in a stream of helium to the ^{11}CO-delivery unit and concentrated at the CO_2-trap. The [^{11}C]CO_2 was released and transferred in helium gas (20 mL/min) through a column containing heated zinc and reduced to [^{11}C]CO. Unreacted [^{11}C]CO_2 was subsequently removed by a column containing Ascarite while the [^{11}C]CO was transferred to and concentrated at the CO-trap. The carrier gas was changed to xenon (1.5 mL/min), and [^{11}C]CO was released and transferred to the capped reaction vial. A radioactivity measurement (A_0) was carried out to determine total amount of [^{11}C]CO introduced (3.1 +/- 0.8 GBq). The reaction mixture was stirred vigorously in a heating block at 100 °C with an adjacent magnetic stirrer for 5 min. A radioactivity measurement (A_1) was taken to confirm that no [^{11}C]CO leaked from the vial during the reaction. The crude reaction mixture was transferred by cannula to a 1.5 mL transfer vial followed by a 2:3 acetonitrile:water mixture (1 mL) to rinse the reaction vial. The water component was added to improve chromatography by reducing the elution strength from the solvent used in the reaction. The resulting solution was purged to remove unreacted [^{11}C]CO and potential labelled volatiles. A radioactivity measurement ($A_{converted}$) was carried out on the transfer vial to measure the amount of [^{11}C]CO converted to non-volatile products in the radical carbonylation reaction. Purification was performed by semi-preparative high performance liquid chromatography. Column effluent was monitored using both UV detector (214 nm) and radiodetector. The radioactivity of the collected fraction containing the product (A_P) was then measured. The isolated radiochemical yields were calculated based on [^{11}C]CO transferred to the reaction vial (A_0), activity in the collected fraction (A_P) and RCP. A_0 and A_P were decay corrected to the same time point before calculation:

$$\text{Isolated RCY} = \frac{A_P}{A_0} \text{ x RCP}$$

The radiochemical purity (RCP), concentration and identities of the labelled products were assessed by analytical HPLC. The identity of the radioactive compound was determined *via* co-injection with an isotopically unmodified reference compound. The concentration was assessed by calibration curve based on reference compound solutions with known concentrations. Specific activity (GBq/µmol) was calculated from the activity (A_P) at end of synthesis (after purification), concentration and volume of the collected fraction.

Design and Function of [^{11}C]CO Dispensing Unit

A unit for converting [^{11}C]CO_2 to [^{11}C]CO and confining it in a reaction vial with reagent solution was built in-house. (Figure 2) Helium (20 mL/min) and xenon (1.5 mL/min) were used as carrier gases and the gas flow was regulated by mass flow controllers to maintain constant flow rate. A single 2-position/12 port injection valve (Valco 25.EDC12UWE, Vici) was used to direct the stream of ^{11}C-labeled gas.

1. The valve was switched to connect the gas stream from the cyclotron to the CO_2-trap. Incoming [^{11}C]CO_2 was concentrated at the silica gel trap (100-120 mesh, 50 mg, Alltech) submerged in liquid nitrogen (–196 °C) in a Dewar flask maneuvered using a pneumatic cylinder (Festo).
2. The valve was switched to connect the helium gas stream to the CO- and CO_2-traps and the reductor column, a quartz tube containing zinc granules (14–50 mesh, Merck) heated at 400 °C. The CO-trap was submerged into liquid nitrogen (–196 °C). (Note: Cooling the CO-trap when still connected to the xenon stream was not possible as xenon froze and clogged the CO-trap.) The release of [^{11}C]CO_2 was induced *via* removal of the Dewar flask and subsequent heating using cable heater (100 W, 062BC020AX, Watlow). The released [^{11}C]CO_2 passed through the reductor zinc column to form reduced [^{11}C]CO, and subsequent passage through a Ascarite II column (~20-30 mesh, 0.2 g, Aldrich) removed any incidental trace of [^{11}C]CO_2. [^{11}C]CO was concentrated at the cooled CO-trap (–196 °C) containing anhydrous silica gel (100-120 mesh, 1 mg, Alltech).
3. The valve was switched to connect the CO-trap to the xenon gas stream and the transfer needle. The transfer needle, controlled by a pneumatic cylinder (SMC), was lowered to pierce the septum of the reaction vial and rest in the reaction solution. A magnet was positioned externally to avoid the needle from hitting the stirrer bar. The release of [^{11}C]CO was induced *via* removal of cooling and application of heating using cable heater (88 W, 062BC016AX, Watlow). The released [^{11}C]CO was delivered to the reaction vial in the xenon gas stream bubbled through the reaction solvent. Once the quantitative transfer of [^{11}C]CO was completed, the transfer needle was removed. The high solubility of the xenon transfer gas in organic solvents circumvented significant pressure increase and the transferred [^{11}C]CO remained in the vial since no vent needle was used.

The xenon flow (1.5 ml/min) was turned on (Valco valve, Vici) when incoming [^{11}C]CO_2 was collected at the CO_2-trap, and was turned off after [^{11}C]CO was delivered to the reaction vial. The transfer process took 3

min and only minute amounts of xenon gas was consumed. The configuration of the 12-port valve allows helium to pass through the zinc reductor column, and xenon to pass through the needle at all times regardless of the position of the valve. This prevents incidental oxidation of the zinc reductant by atmospheric oxygen and the needle was purged free from air. By design all flow paths were open at all times reducing pressure build-up and the risk of leakages. In addition, the dispensing unit, operated using solely carrier and transfer gas, eliminates the need for cleaning in between use as well as clogging issues seen commonly in the transfer of reagent solutions using small diameter tubing. The tubing to the CO_2-trap (1/16" o.d., 0.75 mm i.d.) and all other tubing (1/16" o.d., 0.5 mm i.d.) were stainless steel except the PEEK tubing connected to the moving transfer needle. Monitoring of radioactive gas transfer at each step was carried out using activity detectors (pin diodes) positioned at CO_2-trap, CO-trap and the reaction vial.

[*carbonyl*-^{11}C]*N*-isopropylcyclohexanecarboxamide (1)
Prepared following the general procedure. *Run 1:* Starting from 2.97 GBq, 0.34 GBq isolated 21 min post-EOB (decay-corrected RCY 24%). *Run 2:* Starting from 3.44 GBq, 0.42 GBq isolated 23 min post-EOB (decay-corrected RCY 26%). R_t = 3.13 min (Reference: 3.08 min). RCP >99%.

[*carbonyl*-^{11}C]*N*-butylcyclohexanecarboxamide (2)
Prepared following the general procedure. *Run 1:* Starting from 3.33 GBq, 0.39 GBq isolated 21 min post-EOB (decay-corrected RCY 25%). *Run 2:* Starting from 4.0 GBq, 0.53GBq isolated 18 min post-EOB (decay-corrected RCY 25%). R_t = 3.99 min (Reference: 3.91 min). RCP >99%.

[*carbonyl*-^{11}C]*N*-cyclohexylcyclohexanecarboxamide (3)
Prepared following the general procedure. *Run 1:* Starting from 2.59 GBq, 0.34 GBq isolated 18 min post-EOB (decay-corrected RCY 25%). *Run 2:* Starting from 0.87 GBq, 0.11 GBq isolated 18 min post-EOB (decay-corrected RCY 23%). R_t = 4.48 min (Reference: 4.37 min). RCP >99%.

[*carbonyl*-^{11}C]*N*-phenylcyclohexanecarboxamide (4)
Prepared following the general procedure. *Run 1:* Starting from 4.62 GBq, 0.44 GBq isolated 22 min post-EOB (decay-corrected RCY 20%). *Run 2:* Starting from 2.81 GBq, 0.28 GBq isolated 20 min post-EOB (decay-corrected RCY 20%). R_t = 4.56 min (Reference: 4.52 min). Run 3 and 4 specific activity assessment: 101±13 GBq/µmol at end of synthesis and 1.32±0.04 GBq product. RCP >99%.

[*carbonyl*-^{11}C]1-(piperidin-1-yl)pentan-1-one (5)
Prepared following the general procedure. *Run 1:* Starting from 2.73 GBq, 0.12 GBq isolated 18 min post-EOB (decay-corrected RCY 9%). *Run 2:* Starting from 0.72 GBq, 0.034 GBq isolated 17 min post-EOB (decay-corrected RCY 9%). R_t = 3.68 min (Reference: 3.59 min). RCP >99%.

[*carbonyl*-^{11}C]2-methyl-1-(piperidin-1-yl)-propan-1-one (6)
Prepared following the general procedure. *Run 1:* Starting from 2.31 GBq, 0.24 GBq isolated 17 min post-EOB (decay-corrected RCY 18%). *Run 2:* Starting from 3.33 GBq, 0.30 GBq isolated 19 min post-EOB (decay-corrected RCY 17%). R_t = 2.87 min (Reference: 2.81 min). RCP >99%.

[*carbonyl*-^{11}C]Adamantan-1-yl(piperidin-1-yl)methanone (8)
Prepared following the general procedure. *Run 1:* Starting from 2.38 GBq, 0.30 GBq isolated 23 min post-EOB (decay-corrected RCY 18%). *Run 2:* Starting from 4.52 GBq, 0.23 GBq isolated 34 min post-EOB (decay-corrected RCY 24%). R_t = 6.04 min (Reference: 5.96 min). RCP >99%.

[*carbonyl*-^{11}C]Isopropyl cyclohexanecarboxylate (9)
Prepared following the general procedure. *Run 1:* Starting from 4.02 GBq, 0.15 GBq isolated 25 min post-EOB (decay-corrected RCY 11%). *Run 2:* Starting from 2.94 GBq, 0.17 GBq isolated 25 min post-EOB (decay-corrected RCY 14%). R_t = 4.23 min (Reference: 4.17 min). RCP >99%.

Acknowledgements

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Keywords: Radical carbonylation • 11C • Carbon monoxide • Xenon • Radical initiator • Reductive dehalogenation

(1) Schubiger, P. A.; Lehmann, L.; Friebe, M.; Yang, D. J. *J. Nucl. Med.* **2007**, *48* (10), 1750.
(2) van der Wildt, B.; Wilhelmus, M. M. M.; Bijkerk, J.; Haveman, L. Y. F.; Kooijman, E. J. M.; Schuit, R. C.; Bol, J. G. J. M.; Jongenelen, C. A. M.; Lammertsma, A. A.; Drukarch, B.; Windhorst, A. D. *Nucl. Med. Biol.* **2016**, *43* (4), 232.
(3) Verbeek, J.; Eriksson, J.; Syvanen, S.; Labots, M.; de Lange, E. C. M.; Voskuyl, R. A.; Mooijer, M. P. J.; Rongen, M.; Lammertsma, A. A.; Windhorst, A. D. *EJNMMI Res.* **2012**, *2* (1), 36.
(4) Lu, S.; Hong, J.; Itoh, T.; Fujita, M.; Inoue, O.; Innis, R. B.; Pike, V. W. *J. Label. Compd. Radiopharm.* **2010**, *53* (8), 548.
(5) Hong, J.; Lu, S.; Xu, R.; Liow, J.-S.; Woock, A. E.; Jenko, K. J.; Gladding, R. L.; Zoghbi, S. S.; Innis, R. B.; Pike, V. W. *Nucl. Med. Biol.* *42* (12), 967.
(6) Rahman, O.; Takano, A.; Amini, N.; Dahl, K.; Kanegawa, N.; Långström, B.; Farde, L.; Halldin, C. *Nucl. Med. Biol.* **2015**, *42* (11), 893.
(7) Bergman, S.; Estrada, S.; Hall, H.; Rahman, R.; Blomgren, A.; Larhed, M.; Svedberg, M.; Thibblin, A.; Wångsell, F.; Antoni, G. *J. Label. Compd. Radiopharm.* **2014**, *57* (8), 525.
(8) Nordeman, P.; Estrada, S.; Odell, L. R.; Larhed, M.; Antoni, G. *Nucl. Med. Biol.* **2014**, *41* (6), 536.
(9) Åberg, O.; Stevens, M.; Lindh, J.; Wallinder, C.; Hall, H.; Monazzam, A.; Larhed, M.; Långström, B. *J. Label. Compd. Radiopharm.* **2010**, *53* (10), 616.
(10) Åberg, O.; Lindhe, Ö.; Hall, H.; Hellman, P.; Kihlberg, T.; Långström, B. *J. Label. Compd. Radiopharm.* **2009**, *52* (8), 295.
(11) Syvänen, S.; Eriksson, J.; Genchel, T.; Lindhe, Ö.; Antoni, G.; Långström, B. *BMC Med. Imaging* **2007**, *7*:6.
(12) Mansor, S.; Boellaard, R.; Froklage, F. E.; Bakker, E. D. M.; Yaqub, M.; Voskuyl, R. A.; Schwarte, L. A.; Verbeek, J.; Windhorst, A. D.; Lammertsma, A. *J. Nucl. Med.* **2015**, *56* (9), 1372.
(13) Welch, M. J.; Ter-Pogossian, M. M. *Radiat. Res.* **1968**, *36* (3), 580.
(14) Zeisler, S. K.; Nader, M.; Theobald, A.; Oberdorfer, F. *Appl. Radiat. Isot.* **1997**, *48* (8), 1091.
(15) Smith, C.; Vane, J. *FASEB J.* **2003**, *17* (8), 788.
(16) Holmdahl, M. *Acta Anaesthesiol Sc Suppl* **1998**, *13*, 8.
(17) Gaudin, J.-M.; Lander, T.; Nikolaenko, O. *Chem. Biodivers.* **2008**, *5* (4), 617.
(18) Webster, S. P.; Ward, P.; Binnie, M.; Craigie, E.; McConnell, K. M. M.; Sooy, K.; Vinter, A.; Seckl, J. R.; Walker, B. R. *Bioorg. Med. Chem. Lett.* **2007**, *17* (10), 2838.
(19) Purwanto; Deshpande, R. M.; Chaudhari, R. V.; Delmas, H. *J. Chem. Eng. Data* **1996**, *41* (6), 1414.
(20) Kihlberg, T.; Langstrom, B.; Ferm, T.; Eriksson, J. *Methods and apparatus for production and use of [11c] carbon monoxide in labeling synthesis*; ; WO2006008603.
(21) Hostetler, E. D.; Burns, H. D. *Nucl. Med. Biol.* **2002**, *29* (8), 845.
(22) Kihlberg, T.; Långström, B. *J. Org. Chem.* **1999**, *64* (25), 9201.
(23) Kealey, S.; Miller, P. W.; Long, N. J.; Plisson, C.; Martarello, L.; Gee, A. D. *Chem. Commun.* **2009**, *25*, 3696.
(24) Kealey, S.; Husbands, S. M.; Bennacef, I.; Gee, A. D.; Passchier, J. *J. Label. Compd. Radiopharm.* **2014**, *57* (4), 202.
(25) Audrain, H.; Martarello, L.; Gee, A.; Bender, D. *Chem. Commun.* **2004**, *5*, 558.
(26) Dahl, K.; Schou, M.; Amini, N.; Halldin, C. *Eur. J. Org. Chem.* **2013**, *7*, 1228.

(27) Dahl, K.; Schou, M.; Rahman, O.; Halldin, C. *Eur. J. Org. Chem.* **2014**, *2*, 307.
(28) Nordeman, P.; Friis, S. D.; Andersen, T. L.; Audrain, H.; Larhed, M.; Skrydstrup, T.; Antoni, G. *Chem. Eur. J.* **2015**, *21* (49), 17601.
(29) Taddei, C.; Bongarzone, S.; Haji Dheere, A. K.; Gee, A. D. *Chem. Commun.* **2015**, *51* (59), 11795.
(30) Miller, P. W.; Long, N. J.; de Mello, A. J.; Vilar, R.; Audrain, H.; Bender, D.; Passchier, J.; Gee, A. *Angew. Chem. Int. Ed.* **2007**, *46* (16), 2875.
(31) Kealey, S.; Plisson, C.; Collier, T. L.; Long, N. J.; Husbands, S. M.; Martarello, L.; Gee, A. D. *Org. Biomol. Chem.* **2011**, *9* (9), 3313.
(32) Dahl, K.; Schou, M.; Ulin, J.; Sjoberg, C.-O.; Farde, L.; Halldin, C. *RSC Adv* **2015**, *5* (108), 88886.
(33) Eriksson, J.; van den Hoek, J.; Windhorst, A. D. *J. Label. Compd. Radiopharm.* **2012**, *55* (6), 223.
(34) Stevens, M. Y.; Chow, S. Y.; Estrada, S.; Eriksson, J.; Apslund, J.; Orlova, A.; Mitran, M.; Antoni, G.; Larhed, M.; Åberg, O.; Odell, L. R. *ChemOPEN*. DOI: 10.1002/open.201600091.
(35) Itsenko, O.; Kihlberg, T.; Långström, B. *J. Org. Chem.* **2004**, *69* (13), 4356.
(36) Eriksson, J.; Åberg, O.; Långström, B. *Eur. J. Org. Chem.* **2007**, *3*, 455.
(37) Åberg, O.; Långström, B. *J. Label. Compd. Radiopharm.* **2012**, *55* (14), 477.
(38) Donohue, S. R.; Halldin, C.; Schou, M.; Hong, J.; Phebus, L.; Chernet, E.; Hitchcock, S. A.; Gardinier, K. M.; Ruley, K. M.; Krushinski, J. H.; Schaus, J.; Pike, V. W. *J. Label. Compd. Radiopharm.* **2008**, *51* (3), 146.
(39) Eriksson, J.; Antoni, G.; Långström, B. *J. Label. Compd. Radiopharm.* **2006**, *49* (12), 1105.
(40) Karimi, F.; Långstrom, B. *J. Chem. Soc. Perkin Trans. 1* **2002**, 2111-2115.
(41) Takashima-Hirano, M.; Ishii, H.; Suzuki, M. *ACS Med. Chem. Lett.* **2012**, *3* (10), 804.
(42) Ishii, H.; Minegishi, K.; Nagatsu, K.; Zhang, M.-R. *Tetrahedron* **2015**, *71* (10), 1588.
(43) Karimi, F.; Kihlberg, T.; Långstrom, B. *J. Chem. Soc. Perkin Trans 1* **2001**, *13*, 1528.
(44) Karimi, F.; Barletta, J.; Långstrom, B. *Eur. J. Org. Chem.* **2005**, *11*, 2374.
(45) Dahl, K.; Itsenko, O.; Rahman, O.; Ulin, J.; Sjoberg, C.-O.; Sandblom, P.; Larsson, L.; Schou, M.; Halldin, C. *J. Label. Compd. Radiopharm.* **2015**, *58* (5), 220.
(46) Lu, S.; Zhang, Y.; Kalin, J. H.; Cai, L.; Kozikowski, A. P.; Pike, V. W. *J. Label. Compd. Radiopharm.* **2016**, *59* (1), 9.
(47) Wu, L.; Fang, X.; Liu, Q.; Jackstell, R.; Beller, M.; Wu, X. F. *ACS Catal.* **2014**, *4*, 2977.
(48) Wu, X.; Zhao, Y.; Ge, H. *J. Am. Chem. Soc.* **2015**, *137*, 4924.
(49) Rahman, O.; Långström, B.; Halldin, C. *ChemistrySelect* **2016**, *1* (10), 2498.
(50) Itsenko, O.; Långström, B. *Org. Lett.* **2005**, *7* (21), 4661.
(51) Itsenko, O.; Kihlberg, T.; Långström, B. *Eur. J. Org. Chem.* **2005**, *17*, 3830.
(52) Itsenko, O.; Kihlberg, T.; Långstrom, B. *Nat Protoc.* **2006**, *1* (2), 798.
(53) Ryu, I.; Nagahara, K.; Kambe, N.; Sonoda, N.; Kreimerman, S.; Komatsu, M. *Chem. Commun.* **1998**, *18*, 1953.
(54) Montalbetti, C.; Facque, V. *Tetrahedron 61*, 10827.
(55) Greenberg, A.; Breneman, C.; Liebman, J. *The Amide Linkage: Structural Significance in Chemistry, Biochemistry, and Material Science*; Wiley-interscience, 2003.
(56) Chow, S. Y.; Stevens, M. Y.; Odell, L. R. *J. Org. Chem.* **2016**, *81* (7), 2681.
(57) Chow, S. Y.; Stevens, M. Y.; Åkerbladh, L.; Bergman, S.; Odell, L. R. *Chem. Eur. J.* **2016**, *22* (27), 9155.
(58) Burr, B.; Lyddon, L. *87th Annu. Conv. Gas Process. Assoc.* **2008**, *1*, 100.
(59) Litwinienko, G.; Beckwith, L.; Ingold, K. *Chem. Soc. Rev.* **2011**, *40* (5), 2157.
(60) Chatgilialoglu, C.; Timokhin, V. I. In *Encyclopedia of Radicals in Chemistry, Biology and Materials*; John Wiley & Sons, Ltd, 2012.
(61) Sumino, S; Fusano, A.; Fukuyama, T.; Ryu, I. *Acc. Chem. Res.* **2014**, *47* (5), 1563.
(62) Amos, R. I. J.; Gourlay, B. S.; Yates, B. F.; Schiesser, C. H.; Lewis, T. W.; Smith, J. A. *Org. Biomol. Chem.* **2013**, *11*, 170.
(63) Whittaker, A. M.; Dong, V. M. *Angew. Chem. Int. Ed. Engl.* **2015**, *54* (4), 1312.
(64) Do, H.; Bachman, S.; Bissember, A.; Peters, J.; Fu, G. *J. Am. Chem. Soc.* **2014**, *136* (5), 2162.
(65) McCallum, T.; Barriault, L. *J. Org. Chem.* **2015**, *80* (5), 2874.
(66) Li, W.; Wu, X. *Chem. Eur. J.* **2015**, *21* (20), 7374.
(67) Akhrem, I. S.; Avetisyan, D. V; Afanas'eva, L.; Vitt, S. V; Petrovskii, P. V; Orlinkov, A. *Tetrahedron Lett.* **2008**, *49* (8), 1399.
(68) Xie, W.; Zhao, M.; Cui, C. *Organometallics* **2013**, *32* (24), 7440.

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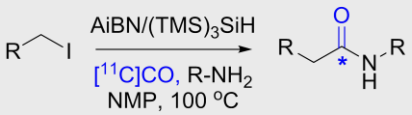

Low-pressure, radical ^{11}C-aminocarbonylation, alkyl amides

Radical Carbonylation

Shiao Y. Chow, Luke R. Odell, Jonas Eriksson**

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Low-Pressure Radical ^{11}C-Aminocarbonylation of Alkyl Iodides via Thermal Initiation

TOC text

A practical and efficient protocol for the preparation of ^{11}C-labelled alkyl amides using a low-pressure xenon system is presented. This methodology, based on thermally initiated radical carbonylation, provides a valuable complement to the transition metal mediated reaction manifold as it allows the use of non-activated β-hydride containing substrates.