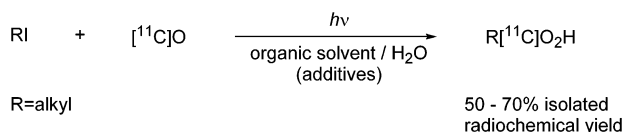# Radical-Mediated Carboxylation of Alkyl Iodides with [¹¹C]Carbon Monoxide in Solvent Mixtures

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RI　　+　　[¹¹C]O　→ (hν, organic solvent / H₂O (additives))　→　R[¹¹C]O₂H

R=alkyl

50 - 70% isolated radiochemical yield

[*carboxyl*-¹¹C]Carboxylic acids were prepared from alkyl iodides via photoinitiated radical reactions using 10^{-8} mol of [¹¹C]carbon monoxide in binary and ternary homogeneous solvent mixtures. Short- (isobutyric), medium-, and long-chain saturated fatty acids (heptadecanoic) were labeled with isolated decay-corrected radiochemical yields ranging from 55% to 70% in 5−7-min reactions. The conversion of [¹¹C]carbon monoxide to products reached 80−90%. To obtain good yields in the reactions performed in water−acetonitrile and water−THF mixtures, the addition of tetrabutylammonium hydroxide or potassium hydroxide was essential. The carboxylation was efficient for primary and secondary alkyl iodides. The carboxylation of tertiary iodides was feasible for 1-iodoadamantane but not for *tert*-butyl iodide. The dependence of the radiochemical yields on reaction time, photoirradiation conditions, and organic and inorganic additives was studied. The method provides a one-step route to [*carboxyl*-¹¹C]carboxylic acids; traditional methods, in contrast, would require several steps. For example, using the devised reaction conditions, 3.19 GBq of purified [1-¹¹C]1,10-decanedicarboxylic acid (specific radioactivity 188 GBq/μmol) was obtained within 35 min of the end of 10 μAh bombardment. (1-¹³C)4-Phenylbutyric acid was synthesized using (¹³C)-carbon monoxide for identifying the labeling position with ¹H and ¹³C NMR.

Introduction

Biologically active compounds labeled with ¹¹C are extensively used as tracers in positron emission tomography (PET), a noninvasive molecular imaging technique that has been recognized as an important tool in medical and pharmaceutical applications.[1] Carboxylic functionality is found in many bioactive compounds, so it is a potential position for labeling with a short-lived, positron-emitting radionuclide ¹¹C (half-life 20.3 min).

At present, [*carboxyl*-¹¹C]carboxylic acids are commonly prepared using [¹¹C]carbon dioxide or hydrogen [¹¹C]-cyanide,[2,3] by carbonation of Grignard reagents[4] or hydrolysis of intermediate nitriles,[5] respectively. Aromatic [*carboxyl*-¹¹C] acids may also be synthesized from [¹¹C]-carbon monoxide and aryl or benzyl halides (or triflates) in palladium-mediated reactions.[6] The last method, unlike the first two, is a versatile one-step procedure; however, it has limited value for the labeling of aliphatic acids due to competing β-elimination from alkyl halides.

This paper presents a convenient one-pot method, based on free-radical carbonylation with [¹¹C]carbon monoxide, for the labeling of aliphatic carboxylic acids. Though in general the methodology for synthesizing carboxylic acid derivatives by free-radical carbonylation
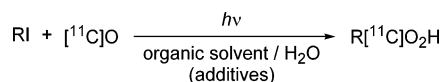
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(1) *Principles of Nuclear Medicine*, 2nd ed.; Wagner, H. N. J., Szabo, Z., Buchanan, J. W., Eds.; W. B. Saunders Co.: Philadelphia, PA, 1995.

(2) Antoni, G.; Kihlberg, T.; Långström, B. In *Handbook of Radiopharmaceuticals*: *Radiochemistry and Applications*; Welch, M. J., Redvanly, C. S., Eds.; John Wiley & Sons Ltd.: Chichester, UK, 2003; pp 141−194.

(3) Kihlberg, T.; Antoni, G.; Långström, B. In *Handbook of Nuclear Chemistry*; Vértez, A., Nagy, S., Klencsár, Z., Eds.; Kluwer Academic Publishers: Amsterdam, The Netherlands, 2003; Vol. 4, pp 119−165.

(4) Kawashima, H.; Yajima, K.; Kuge, Y.; Hashimoto, N.; Miyake, Y. *J. Label. Compd. Radiopharm.* **1997**, *39*, 181−193. Yajima, K.; Kawashima, H.; Hashimoto, N.; Miyake, Y. *J. Phys. Chem.* **1996**, 14936−14940.

(5) Antoni, G.; Långström, B. *J. Label. Compd. Radiopharm.* **1989**, *27*, 571−576. Takahashi, T.; Ido, T.; Hatano, K.; Iwata, R.; Nakanishi, H. *Appl. Radiat. Isot.* **1990**, 649−654. More references to the preparation of [¹¹C]acids may be found in: Iwata, R. *Reference Book for PET Radiopharmaceuticals*; http://kakuyaku.cyric.tohoku.ac.jp/public/Reference%20Book%202004c%20for%20web.pdf (accessed Nov 2004).

(6) Karimi, F.; Långström, B. *J. Chem. Soc.*, *Perkin Trans. 1* **2002**, 2256−2259.

SCHEME 1[a]

$$RI + [^{11}C]O \xrightarrow[\text{organic solvent / H}_2\text{O}]{h\nu} R[^{11}C]O_2H$$
$$\text{(additives)}$$

[a] Typically, the initial concentration of iodide in a solvent mixture was 0.2 mM. The partial pressure of [¹¹C]carbon monoxide in the reactor during the reaction was in the region of 200-800 Pa due to dilution with a carrier gas. The total pressure in the reactor was 40 MPa. The amount of reacted [¹¹C]carbon monoxide is referred to in the text as "the conversion of [¹¹C]carbon monoxide". The percent ratio of the expected labeled product to the total amount of radioactivity in the crude product was determined by analytical HPLC, and is referred to as "the radiochemical purity of the crude product" or, in the tables, simply as "purity". All yields set forth in this paper are decay-corrected radiochemical yields. The "yields determined by HPLC" were calculated as the product of "the conversion of [¹¹C]carbon monoxide" and "the purity of the crude product" divided by 100.

of alkyl iodides has been comprehensively developed,[7,8] the synthesis of carboxylic acids has evoked little interest.

The preparative procedures for labeling with ¹¹C must meet several requirements, and these were taken into account in the current study. The synthetic procedures and workup are subject to time constraints[9] associated with the short lifetime of the radionuclide. Synthesis with [¹¹C]carbon monoxide is necessarily microscale,[10] owing to the method of production of the radioactive carbon, with a consequent influence on reaction kinetics.[11] Other important issues, especially in PET tracer applications, are specific radioactivity and ease of purification of the labeled product.

Results and Discussion

Preparing carboxylic acids from alkyl iodides (Scheme 1) is challenged by the requirement to bring together lipophilic reactants and water in the reaction medium.

Formation of carboxylic acids was observed[12] when radical carbonylation was performed in water using surfactants. The reactions were, however, unselective, and the product (acid, ester, or a mixture of both) apparently depended on the hydrophobicity of the iodide substrate. We used semiautomatic synthetic equipment[13] to carry out reactions with [¹¹C]carbon monoxide, and handling heterogeneous reactant solutions proved to be technically difficult. For this reason, and intending to obtain proper chemical selectivity, we turned to the use of solvent mixtures[14] to overcome the immiscibility issue. The use of the ethanol−water mixture for the carbony-

TABLE 1. Effect of the Organic Component in Mixed Solvents on Radiochemical Yield of [1-¹¹C]4-Phenylbutyric Acid[a,d]
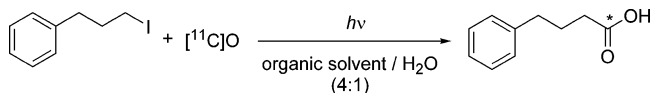
organic solvent	convn of [¹¹C]O (%)	purity (%)[b]	yield (%)[c]	no. of runs
NMP	21 ± 4	92 ± 1	19 ± 3	2
acetonitrile	45 ± 1	76 ± 2	34 ± 1	2
THF	57 ± 2	81 ± 4	49 ± 3	3

[a] Other reaction conditions: 30 °C, photoirradiation 300−400 nm, reaction time 6 min 40 s. [b] Decay-corrected radiochemical yield determined by LC. [c] Decay-corrected radiochemical yield determined by LC. [d] The asterisk marks the label position.

lation of iodooctane has been reported,[12] but the yield of nonanoic acid was low.

The mechanism of radical-mediated carbonylation[7] consists of several steps of both radical and ionic type. In this reaction the acyl iodide, reversibly formed via free radical chain reaction, is trapped by a nucleophile to yield a carboxylic acid derivative. The solvent effects,[7,15,16] as our previous study showed,[17] may be expediently used to tune the reactivity in order to improve the synthesis. According to our observations, the hydroxy group could not efficiently compete with the amino group in radical-mediated labeling reactions. Water therefore was thought to be significantly less reactive than amines toward the acyl iodide, and in order to synthesize acids at good yields it was necessary to compensate for the low reactivity by using high concentrations of water or to increase the strength of the nucleophile, e.g., to use hydroxide anion.

Several water-miscible organic solvents were investigated. *N*-Methyl-2-pyrrolidone, which provided an appropriate medium for analogous reactions with amines leading to labeled amides,[17] did not serve equally well in synthesizing [¹¹C]acids (Table 1). The reactions carried out in acetonitrile−water and THF−water mixtures gave higher yields. Various surfactants were also investigated; however, the chemical selectivity was low, as has been reported.[12] Surfactants also occasionally affected LC separation unfavorably and hampered the purification process, which was undesirable considering the time restrictions.

Water,[18] a nucleophilic reactant in this reaction, is also a cosolvent when taken at high concentrations. Acyl radicals, having a more polar character than parent alkyl radicals and carbon monoxide,[16] should be stabilized in polar media. The reversibility of the addition of alkyl radicals to carbon monoxide[7] implies that with increased solvent polarity the rate of decarbonylation would decrease. Use of a polar reaction medium also increases the rate of the ionic step: the acylation of a nucleophile. Compared to nonpolar solvents, polar solvents, besides their beneficial role, also promote some unwanted side reactions, such as solvolysis of the alkyl iodides, elimina-

(7) Chatgilialoglu, C.; Crich, D.; Komatsu, M.; Ryu, I. *Chem. Rev.* **1999**, 1991−2069.

(8) Ryu, I. *Chem. Soc. Rev.* **2001**, 16−25. Ryu, I.; Miyazato, H.; Kuriyama, H.; Matsu, K.; Tojino, M.; Fukuyama, T.; Minakata, S.; Komatsu, M. *J. Am. Chem. Soc.* **2003**, *125*, 5632−5633.

(9) Långström, B.; Kihlberg, T.; Bergström, M.; Antoni, G.; Bjorkman, M.; Forngren, B. H.; Forngren, T.; Hartvig, P.; Markides, K.; Yngve, U.; Ogren, M. *Acta Chem. Scand.* **1999**, 651−669.

(10) Fowler, J. S.; Wolf, A. P. *Acc. Chem. Res.* **1997**, 181−188.

(11) Långström, B.; Bergson, G. *Radiochem. Radioanal. Lett.* **1980**, 47−54.

(12) Sugiura, M.; Hiroyuki, H.; Kobayashi, S. *Chem. Lett.* **2003**, *32*, 898−899.

(13) Kihlberg, T.; Långström, B. *Method and apparatus for production and use of [¹¹C]carbon monoxide in labeling synthesis;* PCT international application PCT/SE02/01222.

(14) Fialkov, Y. Y.; Chumak V. L. In *Handbook of Solvents*; Wypych, G., Ed.; Chem. Tec. Publishing: Toronto, Canada, 2001; pp 505−564.

(15) Kurnyshova, O. A.; Gristan, N. P.; Tsentalovich, Yu. P. *Phys. Chem. Chem. Phys.* **2001**, 3677−3682.

(16) Zhang, X.; Nau, W. M. *J. Phys. Org. Chem.* **2000**, 634−639.

(17) Itsenko, O.; Kihlberg, T.; Långström, B. *J. Org. Chem.* **2004**, 4356−4360.

(18) Synthetic radical reactions in aqueous solutions are reviewed in: Yorimitsu, H.; Shinokubo, H.; Oshima, K. *Synlett* **2002**, 674−686.

TABLE 2. Decay-Corrected Radiochemical Yields of [1-¹¹C]Acids Obtained under Various Photoirradiation Conditions[a]

	photoirradiation wavelength	
labeled product	300−400 nm	full spectrum
[1-¹¹C]pentanoic acid	7	18
[1-¹¹C]nonanoic acid	2	11
[1-¹¹C]tridecanoic acid	7	16
[1-¹¹C]4-phenylbutyric acid	58	64

[a] Reaction conditions: THF/H$_2$O 4:1, 60 °C, reaction time 5 min.

TABLE 3. Effect of Reaction Conditions and Added Base on Yield of [1-¹¹C]Tridecanoic Acid

reaction conditions[a]	convn of [¹¹C]O (%)	purity (%)	yield (%)[b]
40 °C, *hν* 300−400 nm, 6 min 40 s	4	84	3
60 °C, *hν* 300−400 nm, 5 min	7	92	6
90 °C, *hν* full spectrum, 6 min 40 s	29	97	28
40 °C, *hν* 300−400 nm, 6 min 40 s and TBAOH 0.5 equiv	80	84	67

[a] Temperature, photoirradiation wavelength, reaction time. [b] Decay-corrected radiochemical yield determined by LC.

TABLE 4. Effect of Reaction Conditions on Radiochemical Yield of [1-¹¹C]tridecanoic Acid[a]

reaction conditions	convn of [1-¹¹C]O (%)	purity (%)	yield (%)[b]
60 °C, *hν* full spectrum	80	84	67 (49)
30 °C, *hν* full spectrum	83	84	70 (51)
30 °C, *hν* 300−400 nm	82	91	75 (58)

[a] Reaction conditions: THF/H$_2$O 4:1, reaction time 5 min, TBAOH 0.3 equiv. [b] Decay-corrected radiochemical yield determined by LC; isolated decay-corrected radiochemical yields are shown in parentheses.

tion, and electron-transfer reactions. Water, as a protic solvent, is capable of forming the hydrogen bond to the carbonyl group, thus decreasing the activation energy for decarbonylation[15] and acylation.

The optimization of the synthesis was attempted using 3-phenyliodopropane as a model substrate. Initial experiments showed that the higher the ratio of water to organic solvent in the mixture, the higher the purity of the crude product. On the other hand, the iodides are less soluble in systems of high water content. For 3-phenyliodopropane and more hydrophilic iodides, several water-miscible solvents were suitable (Table 1); however, for more hydrophobic long-chain iodides the miscibility of reactants became a key factor, and the THF−water solvent system was found to be the most convenient.[19] In seeking general reaction conditions for the labeling of carboxylic acids, the effects of temperature, reaction time, photoinitiation parameters, additives, and bases were examined.

The decay-corrected radiochemical yields of [¹¹C]4-phenylbutyric acid were in the 60−70% range in the temperature interval between 35 and 95 °C, dropping to 40% when the temperature decreased to 25 °C. The difference in yield was related only to the conversion of [¹¹C]carbon monoxide, while the purity of the crude product was 85 ± 2% in all the experiments.

Reaction time is an important parameter in the practical preparation of compounds labeled with short-lived radionuclides. Overlong reactions are not productive and result in decreased radiochemical yield and specific radioactivity of the labeled compound. The optimal reaction time for the labeling of [1-¹¹C]-4-phenylbutyric acid was approximately 5−6 min, as determined experimentally[11] from the plot of radiochemical yield (in this case not corrected for radioactive decay) versus time.

Attempts to obtain comparable radiochemical yields in synthesizing acids from several unfunctionalized aliphatic iodoalkanes, employing the same reaction conditions as for 1-iodo-3-phenylpropane, unexpectedly failed. Under pH-neutral conditions, the carbonylation of simple alkyl iodides gave distinctly lower yields than did the carbonylation of 1-iodo-3-phenylpropane (Table 2). Evidently the behavior of 1-iodo-3-phenylpropane differs from that of the alkyl iodides that do not contain phenyl substituent.

A possible reason for this could be differences in the photochemistry of the iodides. To increase the conversion

of [¹¹C]carbon monoxide, several syntheses of tridecanoic [¹¹C]acid were performed at elevated temperatures and using the full spectrum of the UV lamp. Despite increased consumption of alkyl iodides, the yields of the labeled acid were still low (Table 3). The most effective way to improve the yield was to add 0.5 equiv of tetrabutylammonium hydroxide (TBAOH) to the reactant mixture (Table 3).

The optimal amount of TBAOH that provided the highest radiochemical yields of [1-¹¹C]tridecanoic acid was determined to be approximately 0.3−0.4 equiv. Further increase in the amount of TBAOH over 0.6−0.8 equiv led to a decline in the purity of the crude product and an overall decrease in the radiochemical yield. For labeling reactions assisted with TBAOH, radiochemical yields were nearly independent of temperature and photoirradiation wavelength (Table 4).

Apart from TBAOH, several other bases were investigated. Amine bases (triethylamine, *N*-methylmorpholine, and DMAP) did not improve the synthesis (Table 5, entries 1, 2, and 7). Conversion of [¹¹C]carbon monoxide increased at the expense of side reactions, while yields of labeled acids actually decreased. Of several inorganic bases, potassium hydroxide was the one that had a positive effect comparable to that of TBAOH.[20]

Furthermore, it was also observed that yield was not significantly influenced by acidity, even when the acidity of the medium increased, approaching pH 2 (Table 5, entry 6).

The impact of photoirradiation intensity was also investigated. For the series of labeling syntheses of [*carboxyl*-¹¹C]isobutyric acid promoted with TBAOH, yield increased and reached a plateau at approximately half the maximum output of the UV light source and remained constant afterward. The purity of the crude product was 96 ± 2% in all the experiments.
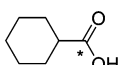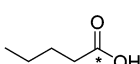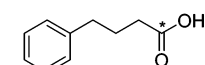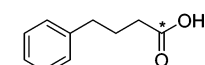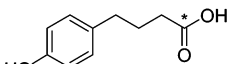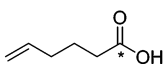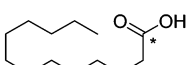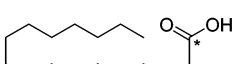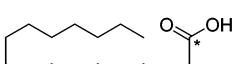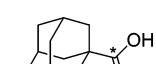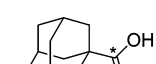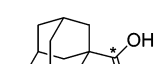
A number of compounds were labeled using the devised reaction conditions (Table 6). Mixed solvents provided suitable reaction media for carrying out the radical-mediated carboxylation of both short- and long-chain primary alkyl iodides (Table 6, entries 3, 8, and 9).

(19) Compared to other organic solvents examined, THF solutions of iodohexadecane, the most lipophilic of the studied substrates, were capable of incorporating the greatest amounts of water. This solvent mixture was also capable of dissolving small amounts of inorganic additives while retaining its homogeneity.

TABLE 5. Effect of Additives on Radiochemical Yield of [1-¹¹C]4-Phenylbutyric Acid[a]

entry	additive, amount (mmol)	organic solvent	convn of [¹¹C]O (%)	purity (%)	yield (%)[b]	N[c]
1	triethylamine, 0.18	THF	76 ± 1	19 ± 1	14 ± 1	2
2	N-methylmorpholine, 0.18	THF	62	46	29	1
3	KOH, 0.05	THF	75 ± 6	85 ± 4	63 ± 5	2
4	TBAOH, 0.05	THF	81 ± 1	83 ± 1	48 ± 2	2
5	KOH, 0.05	ACN	71 ± 1	84 ± 4	61 ± 4	2
6	acetic acid, 0.33	ACN	45 ± 3	90 ± 11	41 ± 2	2
7	DMAP, 0.05	ACN	53 ± 3	58 ± 9	34 ± 11	2
8	TBAF, 0.05	ACN	58 ± 4	23 ± 16	13 ± 8	2

[a] Reaction conditions: organic solvent/H_2O 4:1, 30 °C, photoirradiation 300−400 nm, reaction time 6 min 40 s. [b] Decay-corrected radiochemical yield determined by LC. [c] Number of runs.

TABLE 6. Radiochemical Yields for ¹¹C-Labeled Acids

Entry	Labeled compound[a]	Solvents	Additive (mmol)	[¹¹C]O conv. (%)	Yield[b] (%)	Isolated Yield (%)	N[c]
1		THF/H₂O (4:1)	TBAOH (0.03)	82 ± 2	80 ± 2	70 ± 2	3
2		ACN/H₂O (3:2)	KOH (0.04)	84 ± 1	81 ± 1	67 ± 4	3
3		THF/H₂O (4:1)	TBAOH (0.03)	81 ± 3	74 ± 2	59 ± 7	3
4a		THF/H₂O (4:1)	KOH (0.04)	79	68	51	1
4b		THF/H₂O (4:1)	-	73 ± 5	62 ± 5	-	3
5		THF/H₂O	-	< 0.2	-	-	3
6		various	various	≤ 3	< 1	-	10
7		THF/H₂O (4:1)	TBAOH (0.03)	36	d	-	3
8		THF/H₂O (4:1)	TBAOH (0.03)	82 ± 2	73 ± 2	55 ± 4	4
9a		THF/H₂O (9:1)	TBAOH(0.03)	82	68	52	1
9b		THF/acetone/H₂O (3:1:1)	-	91 ± 4	82 ± 4	65 ± 4	3
10a		THF/H₂O (4:1)	TBAOH (0.13)	84	76	-	1
10b		THF/H₂O (4:1)	-	37	34	-	1
11a		ACN/H₂O (4:1)	KOH (0.1)	81 ± 6	77 ± 5	63 ± 4	3
11b		ACN/H₂O (9:1)	TBAOH (0.2)	94	56	33	1
11c		THF/H₂O (9:1)	TBAOH (0.15)	90	64	55	1

[a] The position of the ¹¹C label is denoted by an asterisk. [b] Decay-corrected radiochemical yield determined by LC. [c] Number of runs. [d] Unseparated peaks.

Secondary alkyl iodides gave slightly higher radiochemical yields than did primary ones (Table 6, entries 1, 2, 3, 8, and 9); however, the carboxylation of *tert*-butyl iodide could not be accomplished (Table 6, entry 6). Though a trace with a retention time matching that of labeled 2,2-dimethylpropionic acid was detected on an analytical HPLC chromatogram, the product could not be isolated for further characterization. On the other

hand, 1-iodoadamantane could be efficiently carboxylated (Table 6, entries 11a−c). This difference may be explained by the dissimilar ability of the two iodides to participate in the side reactions that proceed via carbocation intermediates, such as solvolysis, elimination, and electron transfer.[21] The rigid structure of adamantane precludes the formation of the strained bridgehead cation, whereas the *tert*-butyl cation is easily formed. According to our

observations the amounts of the iodide consumed in the reactions were much higher in the case of *tert*-butyl iodide.

To increase the solubility of iodohexadecane, the most lipophilic of the used iodides, the water fraction in the solvent mixture (THF–water) was reduced from 1/4 to 1/10 (Table 6, entry 9).

[1-^{11}C]1,10-Decanedicarboxylic acid was prepared under basic conditions (Table 6, entry 10). Labeling this compound via Grignard synthesis would require several steps, including the protection of the carboxylic group in the precursor.

The carboxylation of 5-iodo-1-pentene (Table 6, entry 7) gave a complex mixture of labeled products. The carboxylation of 4-(3-iodopropyl)phenol resulted in very low yields (Table 6, entry 5). Interestingly, the addition of phenol or 4-ethylphenol to the reactant mixture in preliminary test experiments had virtually no effect on the synthesis of 4-phenylbutyric [^{11}C]acid from (3-iodopropyl)benzene.

In the end, we found that a ternary THF–acetone–water system may be a better alternative, because similar yields were achieved under nonbasic conditions (Table 6, entries 9a vs 9b). As noted above, irradiation with the full light spectrum of the lamp, and under the same reaction conditions (i.e. using the THF–water system as solvent), led to no effect of comparable magnitude. These observations may indicate that acetone can act as a triplet sensitizer.[22] Should this be so, intersystem crossing in alkyl-substituded benzenes may account for the higher yields of [1-^{11}C]4-phenylbutyric acid than of the saturated [^{11}C]unsubstituted acids. This observation encouraged us to undertake more thorough investigation of the phenomenon.

Radiochemical purity of the labeled compounds after LC purification was in the range of 97–99%.

To verify the labeling position, *carboxyl*-^{13}C-substituted 4-phenylbutyric acid was synthesized using (^{13}C)carbon monoxide together with [^{11}C]carbon monoxide. The reaction was performed as ^{11}C-labeling. The identity of the compound and the labeling position were confirmed by the ^{1}H and ^{13}C NMR experiments.

Specific radioactivity is an important quality of ^{11}C-labeled compounds used as PET tracers. For example, 3.19 GBq of [1-^{11}C]1,10-decanedicarboxylic acid was obtained with specific radioactivity of 188 GBq/μmol within 35 min of the end of 10 μA bombardment.

Conclusions

Photoinitiated free-radical carboxylation of primary, secondary, and in some cases tertiary alkyl iodides with [^{11}C]carbon monoxide has been developed and applied in the rapid synthesis of [1-^{11}C]carboxylic acids. This method offers an alternative synthetic route to [*carboxyl*-^{11}C]-compounds, and therefore may be of value in view of several advantages it offers: i.e., high (50–70%) decay-corrected radiochemical yields of ^{11}C-labeled acids and high (80–90%) conversion of [^{11}C]carbon monoxide were achieved in short (5–7 min) reaction times. Organic solvent–water mixtures provide an equally suitable reaction medium for carboxylating short- and long-chain alkyl iodides. The functional groups that are not compatible with other labeling methods (e.g., Grignard) are tolerated; therefore protection–deprotection may not be required. As a one-step, one-pot procedure, it is suitable for rapid synthesis employing short-lived nuclides. The reaction media is compatible with subsequent purification by means of preparative HPLC. Organic iodides, used as starting materials, do not trap the stable-isotope counterpart of the labeling precursor (carbon monoxide in this case) from the atmosphere during storage, and therefore do not contribute to the isotopic dilution of labeled products. Investigation of the observed reactivity patterns and the effect of acetone is currently in progress.

Experimental Section

[^{11}C]Carbon dioxide production was performed using a Scanditronix MC-17 cyclotron at Uppsala Imanet. The ^{14}N-(p,α)^{11}C reaction was employed in a gas target, containing nitrogen (Nitrogen 6.0) and 0.1% oxygen (Oxygen 4.8), that was bombarded with 17 MeV protons. [^{11}C]Carbon monoxide was obtained by reducing [^{11}C]carbon dioxide as described previously.[13] Liquid chromatographic analysis (LC) was performed with a gradient pump and a variable-wavelength UV detector in series with a β^+-flow detector. An automated synthesis apparatus, Synthia,[23] was used for LC purification of the labeled products. Radioactivity was measured in an ion chamber. A xenon–mercury lamp was used as a photoirradiation source. In analyzing the ^{11}C-labeled compounds, isotopically unchanged reference substances were used for comparison in all LC runs. NMR spectra were recorded at 400 MHz for ^{1}H and at 100 MHz for ^{13}C, at 25 °C. Chemical shifts were referenced to residual protons in solvents (CDCl$_3$: 7.26 ppm; DMSO-d_6: 2.50 ppm) in proton spectra and to solvent signals (CDCl$_3$: 77.00 ppm; DMSO-d_6: 39.52 ppm) in carbon spectra. LC-MS analysis was performed using electrospray ionization (ESI-).

Solvents: THF was distilled under nitrogen from sodium/benzophenone; all other solvents were commercial grade. The solvents were purged with helium before use.

The alkyl iodides were commercially available or otherwise prepared from commercial alkyl bromides via the Finkelstein reaction.

Preparation of [*carboxyl*-^{11}C]Acids. General Procedure. An iodide (100 μmol) was placed in a capped vial (1 mL, flushed beforehand with nitrogen to remove oxygen) and dissolved in THF (400 μL). Water (100 μL) and an optional additive were added to the solution ca. 7 min before the start of synthesis. The resulting mixture was pressurized (over 40 MPa) in a microautoclave (270 μL) that was pre-charged with [^{11}C]carbon monoxide (10^{-8}–10^{-9} mol) mixed with He. The mixture was irradiated with a UV source for 5–7 min while stirring at 35 °C. The crude reaction mixture was then transferred from the autoclave to a capped vial held under reduced pressure. After measuring the radioactivity, the vial was purged with nitrogen and the radioactivity measured again. The crude product was diluted with acetonitrile or methanol (0.6 mL) and injected on the semipreparative LC. Analytical LC and LC-MS were used to assess the identity and radiochemical purity of the collected fraction.

(20) TBAOH was more convenient than KOH due to its higher solubility in mixed solvents. The addition of KOH to mixed solvents often resulted in separation of two liquid phases, formation of stable emulsions, and precipitation of reactants. The emulsions were also suitable for labeling synthesis, though they gave less reproducible results. With short-chain (more hydrophilic) iodides, when more water-rich solvent mixtures could be employed, KOH was used without noticeable complications (Table 6, entry 2).

(21) Kropp, P. J.; Adkins, R. L. *J. Am. Chem. Soc.* **1991**, *113*, 2709–2717.

(22) *Photochemical Key Steps in Organic Synthesis*: *An Experimental Course*; Mattay, J., Griesbeck, A. G., Eds.; VCH: Weinheim, Germany, 1994; p 5.

(1-¹³C)4-Phenylbutyric acid[24] was synthesized from (3-iodopropyl)benzene as described in the general procedure. (¹³C)Carbon monoxide (approximately 0.05 mmol) was added to [¹¹C]carbon monoxide and the reaction was run for 1 h. ¹H NMR (400 MHz, CDCl₃): δ 10.0 (br s, 1H), 7.35−7.18 (m, 5H), 2.70 (m, 2H), 2.41 (m, $^2J_{\mathrm{H^{13}C}}$ = 7.3 Hz, 2H), 2.00 (m, $^3J_{\mathrm{H^{13}C}}$ = 4.4 Hz, 2H). ¹³C NMR (100 MHz, CDCl₃): δ 180.5, 141.2, 128.5, 128.4, 126.0, 34.9 (d, $^2J_{\mathrm{^{13}C^{13}C}}$ = 3.8 Hz), 33.0 (d, $^1J_{\mathrm{^{13}C^{13}C}}$ = 55.5 Hz), 26.2.

4-(4-Hydroxyphenyl)butyric acid[25] was prepared via demethylation of 4-(4-methoxyphenyl)butyric acid by boron tribromide.[26] ¹H NMR (400 MHz, DMSO-d_6): δ 11.96 (br s, 1H), 9.12 (br s, 1H), 6.96 (m, 2H), 6.67 (m, 2H), 2.46 (t, 2H), 2.18 (t, 2H), 1.73 (tt, 2H). ¹³C NMR (100 MHz, DMSO-d_6): δ 174.3, 155.4, 131.5, 129.1, 115.0, 33.6, 33.0, 26.6.

4-(3-Iodopropyl)phenol.[27] 4-(3-Hydroxypropyl)phenol (330 mg) was stirred with hydroiodic acid (47%, 10 mL) at 100 °C overnight. The reaction mixture was allowed to cool and then poured into water (20 mL). The resulting mixture was ex-tracted with ether. The extract was washed successively with concentrated water solutions of Na₂S₂O₃ and Na₂HCO₃. The ethereal solution was dried over MgSO₄ and evaporated at reduced pressure to yield 531 mg (94%) of colorless oil. ¹H NMR (400 MHz, CDCl₃): δ 7.06 (m, 2H), 6.78 (m, 2H), 4.80 (br s, 1H), 3.16 (t, 2H), 2.66 (t, 2H), 2.09 (tt, 2H). ¹³C NMR (100 MHz, CDCl₃): δ 153.8, 132.6, 129.7, 115.3, 35.2, 35.0, 6.4.

11-Iodoundecanoic acid[28] **and 5-iodo-1-pentene**[29] were prepared via the Finkelstein reaction from the corresponding bromides.

Supporting Information Available: The ¹³C NMR spectra of the following compounds, prepared for use as labeling precursors or references: 4-(4-hydroxyphenyl)butyric acid, 4-(3-iodopropyl)-phenol, 5-iodo-1-pentene, and 11-iodoundecanoic acid. This material is available free of charge via the Internet at http://pubs.acs.org.

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(23) Bjurling, P.; Reineck, R.; Westerberg, G.; Gee, A. D.; Sutcliffe, J.; Långström, B. In *Proceedings of the VIth workshop on targetry and target chemistry*; TRIUMF: Vancouver, Canada, 1995; pp 282−284.

(24) Wempe, M. F.; Grunwell, J. R. *J. Org. Chem.* **1995**, 2714−2720.

(25) Defauw, J. M.; Murphy, M. M.; Jagdmann, G. E.; Hu, H.; Lampe, J. W.; Hollinshead, S. P.; Mitchell, T. J.; Crane, H. M.; Heerding, J. M.; Mendoza, J. S.; Davis, J. E.; Darges, J. W.; Hubbard, F. R.; Hall, S. E. *J. Med. Chem.* **1996**, 5215−5227.

(26) McOmie, J. F. W.; Watts, M. L.; West, D. E. *Tetrahedron* **1968**, 2289−2292.

(27) Cheng, C.-S.; Ferber, C.; Bashford, R. I., Jr.; Grillot, G. F. *J. Am. Chem. Soc.* **1951**, *73*, 4081−4084.

(28) Matsuyama, H.; Nakamura, T.; Kamigata, N. *J. Org. Chem.* **1989**, *24*, 5218−5223.

(29) Snider, B. H.; Hawryluk, N. A. *Org. Lett.* **2001**, *3*, 569−572.