Synthesis of Aliphatic [*carbonyl*-^{11}C]Esters Using [^{11}C]Carbon Monoxide

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Aliphatic esters were labelled with a short-lived radionuclide, ^{11}C with $t_{½}$ = 20.3 min, at the carbonyl position using [^{11}C]carbon monoxide via rapid (6 min) photoinduced radical-mediated carbonylation reactions. The esters were prepared from primary, secondary, and tertiary alkyl iodides, and various alcohols, including *tert*-butyl alcohol and phenol. The use of strong bases was necessary to achieve good radiochemical yields in short reaction times. Isolated decay-corrected radiochemical yields were in the range of 40–68 %. For example, methyl hydrogen dodecanoate was labelled at the ester carbonyl in 61 % isolated decay-corrected radiochemical yield with a specific radioactivity of 158 GBq/μmol within approximately 25 min of the production of [^{11}C]carbon monoxide. Two (^{13}C)substituted esters were synthesised using this method to verify the labelling position.

Introduction

Positron emission tomography (PET) has been recognised as a powerful tracer imaging technique. Apart from its established use in life science research and as a diagnostic tool in medicine,[1] there is growing interest in exploiting its potential in drug development.[2–5] The tracers for PET are compounds labelled with short-lived positron-emitting radionuclides, such as ^{11}C, ^{18}F, and ^{15}O. Among these, ^{11}C has a unique position because of the synthetic diversity of carbon chemistry. Carbon is present in virtually all bioactive compounds, and labelling does not modify its chemical properties. The short half-life of ^{11}C (20.3 min) and its high radioactivity have a major impact on the design of the labelling synthesis, making time an important parameter.[6] Radiation safety requires that synthetic procedures be highly automated. Consequently, the development of reliable methods for the preparation of radiolabelled tracers may play an important role in the successful application of PET in biomedical research.

Several methods have been employed for synthesising [*carbonyl*-^{11}C]esters. Accelerator target produced [^{11}C]carbon dioxide is a simple labelling precursor used for this purpose. The esters of the formula R[^{11}C]O$_2$R′, having an alkyl moiety R, were previously synthesised in multi-step reactions, via either [*carbonyl*-^{11}C]acylhalides[7] or [*carbonyl*-^{11}C]ketenes[8] as the acylating agents, and starting from the appropriate Grignard reagents and [^{11}C]carbon dioxide. [^{11}C]Carbon monoxide, which may be prepared by the reduction of [^{11}C]carbon dioxide,[9] has found increasing use in PET labelling chemistry with the development of techniques for handling submicromolar quantities of [^{11}C]carbon monoxide.[10] Transition metal-mediated carbonylation has also been used to prepare [*carbonyl*-^{11}C]esters.[11,12] This approach, however, is limited mainly to compounds in which R is methyl or an aryl moiety, due to the competing β-elimination, which is generally pertinent to the transition metal-mediated reactions.[13]

The concept of using free radical-ionic reactions for the preparation of carbonyl compounds from alkyl iodides and carbon monoxide[14,15] has become a valuable complement to transition metal carbonylations. The interest in applying radical carbonylation in the ^{11}C labelling was related to the β-elimination, and the method was considered to offer potential for widening the range of accessible labelled compounds. This approach was recently introduced to the preparation of ^{11}C-labelled amides and carboxylic acids.[16,17]

This study examines the application of free radical-mediated reactions in the synthesis of aliphatic [*carbonyl*-^{11}C] esters from various alcohols, alkyl iodides, and [^{11}C]carbon monoxide.

Results and Discussion

Several alkyl iodides (Figure 1) and alcohols (Figure 2) were used to investigate the scope and limitations of free radical-mediated [^{11}C]labelling (Scheme 1).

On average, 10^{-8}–10^{-9} mol of [^{11}C]carbon monoxide, in a ratio 1:100 000 to the carrier gas (He), was used in the syntheses. From the value of the total pressure in the reactor (35–40 MPa), the partial pressure of [^{11}C]carbon monoxide was estimated to be approximately 200–500 Pa. The concentration of alkyl iodides was typically 0.2 mM. The concen-

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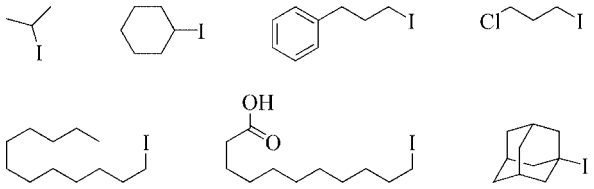


Figure 1. Iodides used in the labelling of [*carbonyl*-^{11}C]esters.

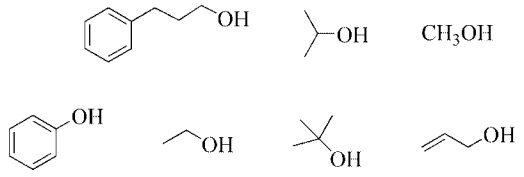


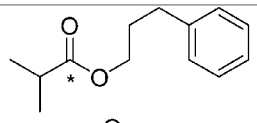
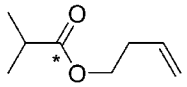
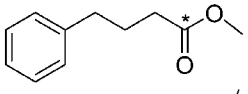
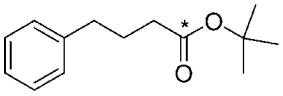
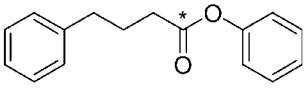
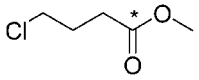
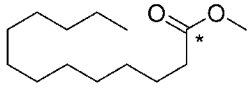
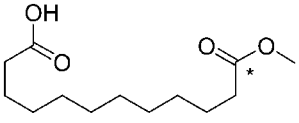
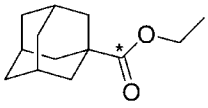
Figure 2. Alcohols used in the labelling of [*carbonyl*-^{11}C]esters.

$$RI + [^{11}C]O + R'OH \xrightarrow[\text{base}]{h\nu} R[^{11}C]O_2R'$$

Scheme 1.

tration of higher molecular weight iodides, iodododecane and 1-iodoadamantane, was 0.1 mM. Simple alcohols may be used as solvents in essentially microscale ^{11}C-labelling syntheses. On the other hand, the possibility of performing a labelling reaction using an equivalent amount of an alcohol as a reagent in an inert solvent was investigated. This may be of interest in cases in which the alcohol is either a solid or a high molecular weight complex compound. The reactions were run for 6 min at 35 °C. All specified radiochemical yields are corrected for radioactive decay.

Table 1. Radiochemical yields for ^{11}C-labelled esters.

Entry	Labelled compound[a]	Solvent	Additive [mmol]	Convn. of ^{11}CO[b] [%]	Purity[c] [%]	Yield[d] [%]	Isolated[e] [%]	N[f]
1		THF	LiHMDS (0.1)	84 ± 1	94 ± 3	79 ± 3	67 ± 1	3
2		THF/allyl alcohol (4:1)	BuLi (0.07)	67 ± 5	79 ± 2	53 ± 5	43 ± 6	3
3		MeOH	–	1–73	81–96	1–64	up to 40	10
4		THF	BuLi (0.1)	80 ± 2	73 ± 2	58 ± 3	42 ± 3	4
5a		THF/H_2O (4:1)	KOH (0.1)	89	56	50	38	1
5b		THF	BuLi (0.1)	73 ± 4	85 ± 3	63 ± 5	51 ± 3	3
6a		THF/H_2O (4:1)	KOH (0.05)	78 ± 11	80 ± 4	62 ± 6	56 ± 4	2
6b		THF/CH_3OH (5:2)	BuLi (0.07)	82 ± 5	79 ± 3	65 ± 3	56 ± 3	3
7		THF/CH_3OH (5:1)	LiHMDS (0.02)	75 ± 4	86 ± 1	65 ± 4	50 ± 1	3
8		CH_3OH	KOH (0.1)	86 ± 3	80 ± 6	68 ± 5	60±3	3
9		THF/C_2H_5OH (4:1)	LiHMDS (0.05)	84±1	93 ± 3	78 ± 2	53 ± 3	3

[a] The position of ^{11}C is denoted by an asterisk. [b] Conversion: percent fraction of reacted [^{11}C]carbon monoxide. [c] Purity: percent fraction of the ester product in the crude reaction mixture, determined by HPLC. [d] Decay-corrected radiochemical yield determined by HPLC: "conversion" multiplied by "purity" and divided by 100. [e] Isolated decay-corrected radiochemical yield of the purified product. [f] Number of runs.

Previously, a similar reaction, but using amines as nucleophiles, was investigated.[16] Carbonylation with amines could be performed using alcohols as solvents, but without the evident formation of [^{11}C]esters as by-products, thus indicating that the reactivity of alcohols was insufficient for achieving good radiochemical yields in a short reaction time.[18] Indeed, when the labelling of esters was attempted using pure alcohols as solvents, the radiochemical yields of [^{11}C]esters from unfunctionalised iodoalkanes did not exceed 5%. The addition of bases was reported to be crucial to the success of this synthesis with isotopically unmodified carbon monoxide.[19] However, none of the amines that were employed (triethylamine, pyridine, DMAP, or DBU) improved the yields under the ^{11}C-labelling conditions, in which [^{11}C]carbon monoxide is in a limited supply compared to the other reactants. The design of the synthetic equipment was such that it was difficult to use inorganic bases of low solubility, such as potassium carbonate, in the appropriate reaction medium; however, the addition of 0.02–0.1 mmol of potassium hydroxide, which is sufficiently soluble in lower alcohols, significantly improved the radiochemical yields (Table 1, entries 5a, 6a, and 8). Apparently, the presence of small amounts of alkoxides is critical under these conditions, to shift the overall equilibrium radical carbonylation process[20] towards product formation. Another strong base, lithium hexamethyldisilylamide (LiHMDS), was also useful (Table 1, entries 1, 7, and 9). Acylation of *tert*-butyl alcohol was more challenging. With the use of LiHMDS and other bases the repeatability of the radiochemical yield was low. Improved results were achieved using *n*-butyllithium (Table 1, entry 4). The corresponding [^{11}C]acids were occasionally observed as labelled by-products, probably due to small amounts of water present in solvents or reagents.

The labelling of a phenol ester was considered to be difficult because of the more complex reactivity of phenols[21] than of aliphatic alcohols. Phenols, apart from being photoactive themselves, have the potential to inhibit free radical reactions owing to their relatively low H–O bond dissociation energies. Phenol is also an ambident nucleophile reacting either with oxygen or carbon. Finally, the product, a phenol ester, is photo-labile and undergoes photo-Fries rearrangement,[22] as was confirmed by an independent experiment. Indeed, the ^{11}C-labelling reactions lead to the formation of several [^{11}C]products, the ratio of which varied but did not clearly correlate with either the reaction conditions or the purity of reagents. In this case, the use of *n*-butyllithium was advantageous, as it allowed the reaction to produce stable results (Table 1, entry 5b). Phenol ester was also prepared in a good yield using aqueous THF solution (Table 1, entry 5a).

With 1-iodo-3-phenylpropane the conversion of [^{11}C]carbon monoxide was, in some cases, higher than 40% even without the addition of a base (Table 1, entry 3). Though the conversion rate *varied* more with the use of 1-iodo-3-phenylpropane than with the use of other alkyl iodides, the conversion of [^{11}C]carbon monoxide was distinctly higher than when simple alkyl iodides were used.

The labelled product in a crude reaction mixture was identified using HPLC by comparison with the retention time of the reference: an identical, isotopically unmodified, compound. The molecular masses of the labelled compounds were then verified using LC–MS analysis.

The position of the ^{11}C label was confirmed using NMR spectroscopy. Two ^{13}C-substituted compounds, (^{13}C)methyl 4-phenylbutanoate and (^{13}C)3-phenylpropyl 2-methylpropanoate, were prepared on the same equipment in scaled-up reactions by adding (^{13}C)carbon monoxide. The identity of the compounds was confirmed by the ^{1}H NMR spectra, which showed splitting due to the ^{1}H–^{13}C couplings. Strong carbonyl signals in the ^{13}C NMR spectra appeared at the same chemical shift as did the reference, isotopically unmodified compounds.

Conclusions

Various alcohols, including *tert*-butyl alcohol and phenol were used in the labelling of aliphatic [*carbonyl*-^{11}C]esters via radical-mediated carbonylation, together with alkyl iodides and [^{11}C]carbon monoxide. High, up to 68%, decay-corrected radiochemical yields were obtained in 6-min-long reactions. This approach offers several advantages over syntheses based on the Grignard reaction, in terms of the number of steps and the scope of the functional groups that may be present in the substrates. As a one-pot, three-component coupling procedure, it is adaptable for fast tracer screening by simply replacing either the iodides or alcohols; as a result, it is thought to be useful for the synthesis of PET tracers. After appropriate modifications this method should also be applicable to the synthesis using (^{13}C) and (^{14}C) carbon monoxide.

Experimental Section

The labelling reactions were carried out in a 270-μL stainless steel autoclave equipped with an optical window to allow the irradiation of the reaction mixture by a xenon lamp. [^{11}C]Carbon dioxide was produced with 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 the reduction of [^{11}C]carbon dioxide, and handled as described previously.[10] Liquid chromatography analysis was performed using 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 labelled products. Radioactivity was measured in an ion chamber (Veenstra Instrumenten BV, VDC-202). In the analysis of the ^{11}C-labelled compounds, the retention times of isotopically unchanged reference substances were used in identifying the labelled products. NMR spectra were recorded on a Varian Unity-400 spectrometer in $CDCl_3$ at 400 MHz for ^{1}H and at 100 MHz for ^{13}C, at 25 °C. Chemical shifts were referenced to either the solvent signal (δ = 77 ppm) or the residual solvent proton signal (δ =7.26 ppm). LC–MS analysis was performed on Waters Quattro Premier micro mass

coupled with a Waters Alliance LC instrument using electrospray ionisation in the ESI– mode for methyl hydrogen dodecanoate and the ESI+ mode for all other compounds. THF was distilled under nitrogen from sodium/benzophenone.

11-Iodoundecanoic acid was prepared according to the published procedure[24] from the corresponding bromide; other alkyl iodides and alcohols were purchased and used as supplied without purification if signs of decomposition were not obvious. The alcohols were anhydrous grade and kept over 4-Å molecular sieves.

Preparation of [*carbonyl*-^{11}C]Esters. General Procedure: An alcohol (200 μmol) or phenol (100 μmol) and an appropriate base (Table 1) were placed in a capped vial (1 mL, flushed beforehand with nitrogen to remove air) and dissolved in THF (500 μL). In some cases the alcohol was used as a solvent or co-solvent together with THF (Table 1). An iodide (100 μmol) was added to the solution approximately 7 min before the start of the synthesis. The resulting mixture was pressurised (over 40 MPa) in the autoclave containing [^{11}C] carbon monoxide (10^{-8}–10^{-9} mol) in helium. The mixture was irradiated with the light of an Xe lamp (280–400 nm) for 6 min at 35 °C with stirring. The crude reaction mixture was then transferred from the autoclave to a capped vial, held under reduced pressure. After measurement of the radioactivity, the vial was purged with nitrogen and the radioactivity was measured again. The crude product was diluted with acetonitrile or methanol (0.6 mL) and injected on the semi-preparative LC for purification. Analytical LC and LC–MS were used to assess the identity and radiochemical purity of the collected fractions. The radiochemical purity of the purified labelled esters was over 97% in all syntheses.

(^{13}C)3-Phenylpropyl 2-Methylpropanoate: 3-Phenyl-1-propanol (120 μL, 1.35 mmol) was dissolved in THF (320 μL) in a capped vial (1 mL, flushed beforehand with nitrogen to remove air). The solution of *n*-butyllithium in THF (2.5 M, 65 μL, 160 μmol) was carefully added to the resulting solution. Isopropyl iodide (320 μmol) was added approximately 7 min before the radiolabelling reaction. The autoclave was filled first with [^{11}C]carbon monoxide (10^{-8}–10^{-9} mol) in helium and then with (^{13}C)carbon monoxide (approximately 40 μmol). After that, the solution of the iodide and alcohol was transferred to the autoclave and the reaction mixture pressurised to approximately 40 MPa. The reaction mixture was irradiated (Xe lamp, 280–400 nm) for 1 h with stirring. During this time the temperature rose from 35 °C to 55 °C. The crude reaction mixture was then transferred from the autoclave to a capped vial, held under reduced pressure. The crude product was diluted with acetonitrile (0.6 mL) and purified by the semi-preparative LC. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.33–7.24 (m, 2 H), 7.22–7.15 (m, 3 H), 4.09 (dt, $J_{H,C}$ = 2.9 Hz, 2 H), 2.69 (m, 2 H), 2.55 (ds, $J_{H,C}$ = 7.0 Hz, 1 H), 1.96 (m, 2 H), 1.18 (dd, $J_{H,C}$ = 4.9 Hz, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 177.2 (strongest, carbonyl), 141.3, 128.43, 128.39, 126.0, 63.5 (d, $J_{C,C}$ = 2.7 Hz), 34.0 (d, $J_{C,C}$ = 57.0 Hz), 32.2, 30.3 (d, $J_{C,C}$ = 2.2 Hz), 19.0.

(^{13}C)Methyl 4-Phenylbutanoate was prepared in the same way from 1-iodo-3-phenylpropane (370 μmol) without a base. The reaction was run in methanol for 1 h. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.37–7.24 (m, 2 H), 7.22–7.15 (m, 3 H), 3.66 (d, $J_{H,C}$ = 3.9 Hz, 3 H), 2.65 (m, 2 H), 2.33 (m, $J_{H,C}$ = 7.4 Hz, 2 H), 1.97 (m, $J_{H,C}$ = 4.4 Hz, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 173.9 (carbonyl).

Reference Compounds: Ethyl adamantane-1-carboxylate and methyl 4-chlorobutanoate were purchased, other compounds were synthesised using known methods. The NMR spectroscopic data were in accordance with published data. 3-Phenylpropyl 2-methylpropanoate[25] and allyl 2-methylpropanoate[26] were prepared according to the method presented in ref.[27], methyl 4-phenylbutanoate[28] and methyl tridecanoate[29] according to ref.[30], *tert*-butyl 4-phenylbutanoate[28] according to ref.[31], phenyl 4-phenylbutanoate[28] according to ref.[32], and methyl hydrogen dodecanoate[33] according to the method described in ref.[34]

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