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Photoinitiated Free Radical Carbonylation Enhanced by Photosensitizers

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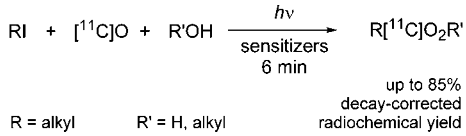
ABSTRACT



$$\mathrm{RI} + [^{11}\mathrm{C}]\mathrm{O} + \mathrm{R'OH} \xrightarrow[\text{sensitizers, 6 min}]{h\nu} \mathrm{R}[^{11}\mathrm{C}]\mathrm{O_2R'}$$

R = alkyl R' = H, alkyl up to 85% decay-corrected radiochemical yield

The enhancing effect of several photosensitizers in photoinitiated radical carbonylation is demonstrated and applied to accelerate the synthesis of compounds labeled with short-lived ^{11}C. With the sensitizers, the synthesis of [*carbonyl*-^{11}C]esters and acids from alkyl iodides, [^{11}C]carbon monoxide, alcohols, and water provided up to 75–85% decay-corrected radiochemical yields in 6-min reactions under mild conditions. Acetone was used as a sensitizer in preparing ^{13}C-substituted 1,10-decanedicarboxylic acid from (^{13}C)carbon monoxide.

The synthesis of ^{11}C-labeled compounds, used as tracers in positron emission tomography (PET),[1] is time constrained,[2] because the half-life of the radionuclide is short—20.3 min. To obtain high yields in a short time the reaction conditions are appropriately designed by exploiting solvent effects, adjusting temperature, taking excess substrates, and using highly reactive reagents. The increasing interest in using [^{11}C] compounds has been a stimulus for developing improved methods for labeling, using a handful of accessible labeling precursors.[3] A representative example is rapidly expanded in the recent years by using [^{11}C]carbon monoxide as a building block in labeling.[4]

The radical-mediated carbonylation[5] has been a subject of our interest as an efficient method for the synthesis of aliphatic carboxylic acids and their derivatives from [^{11}C]carbon monoxide and alkyl iodides.[6] The radiochemical yields showed strong dependence on the properties of the nucleophile: while yields of the reactions with amines were high, those of the reactions with water and alcohols were low. In the latter case increasing the temperature had a minor effect,[6b] and the low reactivity of the oxygen nucleophiles[6b,c] was compensated for by converting them into conjugated bases. While studying the influence of solvents, we noticed that radiochemical yields were significantly enhanced when

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Table 1. Effect of Additives on Radiochemical Yield of Methyl [*carbonyl*-^{11}C]Hexanoate[16]

additive, 0.005 mmol, 280-400 nm	E_S,[a] kJ/mol	E_T,[b] kJ/mol	conversion of ^{11}CO,[c] %	purity,[d] %	yield,[e] %	N[f]
(without optical filter)	–	–	4 ± 1	62 ± 5	3 ± 1	2
–	–	–	3 ± 2	82 ± 3	2 ± 1	3
p-xylene	435[g]	337	5	88	4	1
acetone	372	332	4	94	4	1
xanthone	324	310	55 ± 7	80 ± 3	44 ± 4	3
dibenzofuran	398	293	7 ± 3	84 ± 11	6 ± 3	3
triphenylamine	362	291	27 ± 1	90 ± 1	23 ± 1	3
benzophenone	311	289	68 ± 3	82 ± 4	55 ± 4	3
fluorene	397	284	3 ± 1	89 ± 1	2 ± 1	2
triphenylene	352	280	3 ± 1	82 ± 13	3 ± 1	3
2-acetylnaphthalene	325	249	1	73 ± 8	1	2
biacetyl	267	236	1	72	1	1
benzil	247	227	36 ± 1	70 ± 13	25 ± 5	3
fluorenone	266	211	4	59	2	1

[a] Singlet energy. [b] Triplet energy. [c] Conversion: percent fraction of reacted [^{11}C]carbon monoxide. [d] Purity: percent fraction of the ester product in the crude reaction mixture, determined by HPLC. [e] Decay-corrected radiochemical yield determined by HPLC: "conversion" multiplied by "purity" and divided by 100. [f] Number of runs. [g] Lowest excited-state energy values, ordered by triplet state energies, are taken from ref 17.

reactions were run in acetone, in the absence of bases. This was of possible relevance for the development of milder conditions for the labeling carbonylation. This study was undertaken to examine whether the observed phenomenon is general and how it can be applied.

Acetone[7] was assumed to have a sensitizing[8] effect on the photochemical step, the generation of alkyl radicals by the photolysis of alkyl iodides.[9] Data from the literature suggest that this assumption is reasonable. Despite the facility of C−I bond homolysis, quantum yields for the photolysis of iodoalkanes are less than unity.[10] In solution, the photolysis of alkyl iodides also produces carbocations,[11] rationalized as a result of electron transfer within a solvent-caged radical pair.[12] Carbocations are accountable for the appearance of typical ionic products. The photolysis of alkyl halides is accelerated by many factors, particularly in the presence of aromatic hydrocarbons[13] and aliphatic and aromatic ketones.[14] It has been noticed that photosensitizers may influence the partitioning between the primary products of the photolysis: alkyl radicals and carbocations.[15] Consequently, sensitization may affect the distribution of products between free radical carbonylation and ionic side reactions. Thus, sensitization and quenching studies were attempted.

A simple reaction system was selected for study,[16] with 1-iodopentane taken as a representative unsubstituted iodoalkane (eq 1):

$$C_5H_{11}I + [^{11}C]O + CH_3OH \rightarrow C_5H_{11}[^{11}C]O_2CH_3 \quad (1)$$

The observed enhancement of the radiochemical yields by acetone promoted us to verify whether other ketones[17] exert a similar effect. Benzophenone significantly increased the radiochemical yield over that of an unsensitized reaction (Table 1). The high efficiency of singlet−triplet intersystem crossing in the case of benzophenone[17] points toward the involvement of a triplet exited state.[14a] Xanthone was also effective, but not fluorenone or 2-acetylnaphthalene, which have lower lying triplets. Benzil, the triplet energy of which is relatively low, nonetheless increased the radiochemical yield. Within the range of the ketones studied, the enhancing effect found is in accordance with the hydrogen abstracting ability of ketones in their excited states, or, more precisely, with the properties that give rise to this ability.[8a,b] Xanthone, benzophenone, and benzil abstract hydrogen atoms with rate constants significantly greater than those of 2-actylnaphthalene, biacetyl, and fluorenone.[17] Note, however, that yields

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(9) The influence of photolysis conditions on carbonylation has been noted: the use of Pyrex glass to filter xenon lamp irradiation has been found crucial (ref 5a,b).

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(16) All reactions were run for 6 min at 35 °C. On average 10^{-8}−10^{-9} mol of [^{11}C]carbon monoxide, in a ratio of 1:100 000 to the carrier gas (He), was used in the syntheses. From the value of 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 amount of an organic iodide was 0.1 mmol. All specified radiochemical yields are corrected for radioactive decay. Reaction mixtures were irradiated with a xenon lamp equipped with an optical filter, transmitting in the 280−400 nm range.

(17) Murov, S.; Carmichael, I.; Hug, G. L. *Handbook of Photochemistry*, 2nd ed.; Marcel Dekker: New York, 1993.

are not decreased in the synthesis of **4** (Figure 1, Table 4) from propan-2-ol, an efficient hydrogen donor.

Use of fluorene, dibenzofuran, and triphenylene does not improve yields, although they have excited-state properties comparable to those of the ketones that were effective.

Several tertiary amines have been used before as bases in connection with carbonylation, using [^{11}C]carbon monoxide.[6] Triethylamine, pyridine, and 4-(dimethylamino)pyridine have been found not to be helpful. In contrast, triphenylamine, listed as a photosensitizer,[17] was an amine that showed a favorable effect (Table 1). The mechanism of action must, however, be different from that of triethylamine, because triphenylamine, rather than the alkyl iodide, is the major light-absorbing species. Triethylamine is known to promote the photochemical generation of alkyl radicals from alkyl iodides.[18] The proposed mechanism includes the formation of exiplex, which undergoes photodecomposition to yield a carbon radical and an iodide anion. In a reaction with benzophenone, the addition of triethylamine led to a significant decrease in the radiochemical yield.

The possibility of observing photochemical quenching was examined by using 1,3-cyclohexadiene and biphenyl as quenchers. The quenching was difficult to detect while studying the carbonylation of 1-iodopentane because the yields of unsensitized reactions were low. Therefore a different reaction was studied. Under the same reaction conditions the carbonylation of 1-iodo-3-phenylpropane generally gave higher radiochemical yields than does the carbonylation of simple iodoalkanes,[6b,c] and was of interest for studying the influence of the phenyl substitution in alkyl iodides.

$$\mathrm{Ph(CH_2)_3I + [^{11}C]O + CH_3OH \rightarrow Ph(CH_2)_3[^{11}C]O_2CH_3} \qquad (2)$$

The reactivity of 1-iodo-3-phenylpropane in a THF−methanol system without additives was low (Table 2). For this reason, carbonylation in a THF−water system, which was efficient without the addition of strong bases or sensitizers,[6b] was investigated (eq 3). Adding 1,3-cyclohexadiene indeed decreased the radiochemical yield; however, 1,3-cyclohexadiene turned out to be reactive, increasing the number of radiolabeled products. Biphenyl[19] was then taken as a quencher. The photoirradiation intensity was reduced twice, so that the radiochemical yields of reactions without additives decreased to about 50% of the average yields obtained with full UV source power. Under these conditions, the sensitization with benzophenone and quenching with biphenyl were both apparent (Table 3).

$$\mathrm{Ph(CH_2)_3I + [^{11}C]O + H_2O \rightarrow Ph(CH_2)_3[^{11}C]O_2H} \qquad (3)$$

Table 2. Effect of Additives on the Radiochemical Yield of Methyl [*carbonyl*-^{11}C]-4-Phenylbutanoate

additive, mmol	conv ^{11}CO,^{a} %	purity,^{b} %	yield,^{c} %	N^d
−	4 ± 4	95 ± 2	4 ± 3	3
benzohenone, 0.001	39	88	34	1
benzohenone, 0.005	60 ± 2	89 ± 5	53 ± 1	3
triphenylene, 0.005	3 ± 1	80 ± 2	2 ± 1	3

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

Table 3. Effect of Additives on the Radiochemical Yield of [1-^{11}C]-4-Phenylbutyric Acid

irradiation power, %	additive, mmol	conv ^{11}CO,^{a} %	purity,^{b} %	yield,^{c} %	N^d
100	−	72 ± 3	85 ± 2	62 ± 3	2
50	−	34 ± 1	85 ± 3	28 ± 2	2
50	benzohenone, 0.0035	69 ± 1	79 ± 2	54 ± 1	2
50	biphenyl,^{e} 0.005	5 ± 1	75 ± 4	4 ± 1	2

[a] Conversion: percent fraction of reacted [^{11}C]carbon monoxide. [b] Purity: percent fraction of the acid product in the crude reaction mixture, determined by HPLC. [c] Decay-corrected radiochemical yield determined by HPLC: "conversion" multiplied by "purity" and divided by 100. [d] Number of runs. [e] Lowest excited-state energies: singlet 391 and triplet 274 kJ/mol, ref 17.

The UV spectra of 1-iodo-3-phenylpropane and biphenyl confirmed that under the experimental conditions the iodide absorbed more than 50% of the light. The cause of the significant difference between the reactivity of 1-iodo-3-phenylpropane in the THF−water and the THF−methanol systems without sensitizers (cf. first entries in Tables 2 and 3) is not clear.

If the accepted chain propagation mechanism[5a] is functioning, a conceivable role of sensitizers is increasing the efficiency of the C−I bond homolysis. The assumption that the effect is due to triplet energy transfer is consistent with the data of other researchers (see above). The low quantum yield of the photolysis of alkyl iodides has been explained as a result of in-cage recombination of the radical pair.[10] Energy transfer from the triplet state of ketones should create a triplet radical pair after the C−I bond rupture.[8a,15b] The recombination of the triplet radical pair is spin forbidden,[8a,20] therefore the probability of its dissociation is higher than that of a singlet pair. For the same reason, the efficiency of electron transfer within a triplet radical pair may also be decreased, diminishing the share of ionic side reactions. Thus the overall effect of the sensitization may be by increasing the concentration of the free alkyl radicals.

Using photosensitizers thus allows the attainment of high radiochemical yields in radical carbonylations using weakly reactive oxygen nucleophiles but without using strong bases.

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[19] Biphenyl did not show reactivity or enhancing capabilities in the carbonylation of 1-iodopentane.

[20] Buchachenko, A. L. *Pure Appl. Chem.* **2000**, *72*, 2243−2258.

Several examples of ^{11}C-labeled compounds are shown in Figure 1. Acetone, which was not effective in low concentrations[21] (Table 1), was used as a solvent (Table 4). The use of acetone is advantageous, because it can be readily removed in the purification step, which should be rapid considering the short half-life of ^{11}C. A more efficient sensitizer, benzophenone, is effective in rather low concentrations (Tables 1−4).

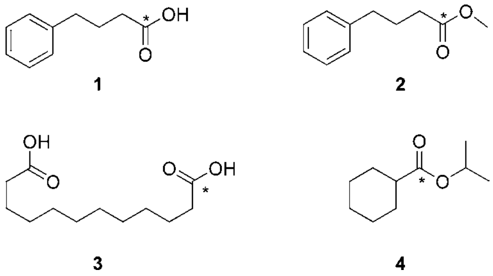

Figure 1. Examples of labeled compounds (* = ^{11}C).

Table 4. Radiochemical Yields of Labeled Compounds

	solvents	additive, mmol	conv ^{11}CO, %	yield,[a] %	N[b]
1	acetone/H_2O (4:1)	−	91 ± 3	73 ± 3	3
2	acetone/CH_3OH (4:1)	−	86 ± 1	85 ± 1	3
3	acetone/H_2O (4:1)	−	86 ± 4	73 ± 5	3
4	THF/IPA[c] (1:1)	Ph_3N, 0.1	47 ± 3	37 ± 3	2
4	THF/IPA (1:1)	Ph_2CO, 0.1	85	71	1
4	acetone/IPA (1:1)	−	85 ± 2	80 ± 3	2

[a] Decay-corrected radiochemical yield determined by LC. [b] Number of runs. [c] Isopropyl alcohol.

An interesting consequence of using benzophenone was the relaxed demands for the purity of reaction solvents. A test experiment with commercial THF, containing radical inhibitor (3,5-di-*tert*-butyl-4-hydroxytoluene) provided a yield comparable to those obtained with degassed and distilled THF.

Preparation of ^{13}C-substituted compounds by radical carbonylation was considered as a reaction in which sensitizers might be used with advantage. In this case, the concentration of (^{13}C)carbon monoxide is usually higher, and longer reaction times would be required. The longer reaction times and the use of strong bases lead to the consumption of alkyl iodides and nucleophiles in direct reaction between them. When using sensitizers instead of bases, side reactions were suppressed. As an illustration, ^{13}C-substituted 1,10-decanedicarboxylic acid was synthesized to verify the labeling position. (^{13}C)Carbon monoxide was added to the [^{11}C]carbon monoxide, and the reaction was performed on the equipment used for ^{11}C-labeling. The amount of alkyl iodide was increased twice to 0.2 mmol and the reaction time was extended to 1 h.[22] The isolated yield of the ^{13}C-substituted acid was 48%, estimated from the radioactivity measurements; the conversion of (^{13}C)carbon monoxide was 68%. The identity of the compound and the labeling position were confirmed by the ^{1}H and ^{13}C NMR experiments.

To summarize, several photosensitizers, mainly ketones, were found to enhance radiochemical yields in photoinitiated radical carbonylations using short-lived [^{11}C]carbon monoxide and alkyl iodides. High yields of [^{11}C]esters and acids were obtained without having to use strong bases, which would be required otherwise. The most efficient sensitizers can be employed in catalytic amounts and do not make purification more complicated. These conditions were useful for preparing ^{13}C-substituted acid and should also be suitable for carbonylations with (^{14}C)carbon monoxide.

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Supporting Information Available: Experimental details and ^{13}C NMR spectrum of (1-^{13}C)1,10-decanedicarboxylic acid. This material is available free of charge via the Internet at http://pubs.acs.org.

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[21] This is perhaps because the photophysical properties of acetone are different from those of benzophenone (see ref 17).

[22] The reaction conditions were not optimized.