Carboxylation of Alkyl Iodides with [^{11}C] and (^{13}C)Carbon Monoxide: Using Sulfoxides as Oxygen Nucleophiles

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Abstract: ^{11}C-Labeled carboxylic acids were prepared from alkyl iodides and [^{11}C]carbon monoxide by irradiation by UV light in anhydrous DMSO solutions in the presence of triethylamine. Sulfoxides other than DMSO can be used and may be used in stoichiometric amounts using inert solvents.

Key words: sulfoxides, radical reactions, carbonylations, carboxylic acid, photochemistry

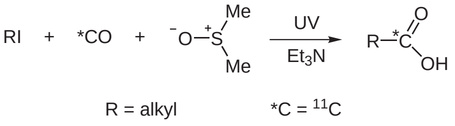
Biologically active organic compounds labeled with stable and radioactive carbon isotopes have found broad application as tracers in biochemical studies. In particular, compounds labeled with short-lived ^{11}C ($\tau_{1/2}$ = 20.3 min)[1] are used in positron emission tomography (PET), a nuclear medicine technique for molecular imaging in vivo.[2] The increasing use of PET in clinical practice,[3] drug development,[4] and biomedical research has stimulated the development of new labeling strategies.[5] ^{11}C is produced using particle accelerators and is available in a few simple chemical forms.[6] Furthermore, the short half-life of ^{11}C seriously restricts the scope of the synthetic methods applicable to ^{11}C-labeling.[7]

The carboxylic functional group is frequently found in bioactive molecules and may be conveniently labeled via the carboxylation of a Grignard reagent using cyclotron-produced [^{11}C]carbon dioxide.[8] The labeling of functionalized acids, however, may become difficult due to the reactivity of Grignard reagents. An alternative approach is radical carbonylation[9] of organoiodides using [^{11}C]carbon monoxide as a labeling precursor.[10]

The radical carbonylation reaction is based on the favorable combination of several radicals and a final ionic step.[9b] The formation of an acyl iodide intermediate in a sequence of radical steps is considered as reversible and endothermic.[9b] The trapping of the acyl iodide with a nucleophile, resulting in the formation of a stable product in the ionic step, serves as the driving force for the reaction. Less reactive nucleophiles lead to longer reaction times with unlabeled carbon monoxide[9b] and decrease the radiochemical yields in reactions with [^{11}C]carbon monoxide,[10b] due to competing radioactive decay. The radiochemical yields in the labeling of acids using water as a nucleophile may be improved by using hydroxide anion. However, the strong base promotes side reactions, like elimination and nucleophilic substitution. It is often the case that these side reactions are not problematic in ^{11}C-synthesis, because other reactants are used in a large excess to [^{11}C]carbon monoxide.[11] More demanding are the larger-scale applications, e.g. with (^{13}C)carbon monoxide, which is more practical to use in stoichiometric amounts with respect to other reactants.

Here we report that DMSO and other sulfoxides may be advantageously used as nucleophiles in radical carbonylation for the synthesis of ^{11}C- and ^{13}C-labeled carboxylic acids. The method benefits from the orthogonal reactivity of sulfoxides towards alkyl and acyl halides thereby avoiding the side reactions caused by strong bases. The high reactivity of DMSO and other sulfoxides toward acid halides is known: sulfoxides operate as oxygen nucleophiles to produce acids.[12]

^{11}C-Labeled carboxylic acids were prepared from alkyl iodides and [^{11}C]carbon monoxide by irradiation with UV light in anhydrous DMSO solutions in the presence of triethylamine (Scheme 1). The reaction proceeds rapidly at ambient temperature (30–35 °C) providing high conversion of [^{11}C]carbon monoxide and high radiochemical yields in a short reaction time (6 min; Table 1). The addition of triethylamine was essential; however, the exact role of triethylamine is not yet clear.[13] Neither water as a source of hydroxyl group nor the use of strong bases was required.



Scheme 1

The reactivity of DMSO in radical carbonylation is higher than that of alcohols or water but less than the reactivity of alkyl amines. In fact, DMSO has been used as a solvent for carrying out carbonylation employing [^{11}C]carbon monoxide with amine nucleophiles.[10a] The analysis of the data confirmed that in the former case the reactions gave [^{11}C]acids as byproducts, with the yields dependent on the reactivity of the amines. With alcohol nucleophiles the [^{11}C]acids were the major products (over 80%). Hence

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Table 1 Yields of Labeled Acids

Entry	Product	Sulfoxide/Solvent	Conversion CO[a,d] (%)	Purity[b,d] (%)	Yield[c,d] (%)
1	[1-^{11}C]4-Phenylbutyric acid	DMSO	84	74	62±4
2		Dibutylsulfoxide, (1.0 mmol)/THF	67	70	47±7
3		Dibutylsulfoxide, (0.1 mmol)/THF	76	35	27[e]
4	[1-^{11}C]Cyclohexane carboxylic acid	DMSO	79	85	67±3
5		DMSO–THF (9:1)	76	86	65±3
6	[1-^{11}C]Heptadecanoic acid	DMSO–THF (1:1)	81	76	64±3
7	[1-^{11}C]2,2-Dimethylpropionic acid	DMSO	2	60	ca. 1
8	[1-^{11}C]2-Propylpentanoic acid	DMSO	84	89	75±1
9	[1-^{11}C]4-(4-Hydroxyphenyl) butyric acid	DMSO	79	49	39±4

[a] Conversion: based on reacted [^{11}C]carbon monoxide.
[b] Radiochemical purity of the product.
[c] Decay-corrected radiochemical yield determined by HPLC.
[d] Average over 2–4 runs.
[e] Single run.

DMSO may be placed between amines and alcohols in ranking the reactivity of the nucleophiles in radical carbonylation.

Radiochemical yields in radical carbonylation increase with the polarity of the solvent;[10a] thus the high polarity of DMSO makes it a superior reaction media. On the other hand, the solubility of long-chain alkyl iodides in this solvent is poor. In such cases THF may be used as a co-solvent (Table 1, entries 5 and 6). Other sulfoxides have the same reactivity pattern and may also be used, for example, dibutyl sulfoxide (Table 1, entry 2). DMSO may be preferred, because it can be easily separated from the radiolabeled product using reversed-phase preparative HPLC.

Owing to the high reactivity of sulfoxides this method was useful with iodide substrates that gave poor results using the previously described approach, for example, [1-^{11}C]4-(4-hydroxyphenyl)butyric acid was obtained from 4-(3-iodopropyl)phenol in 39% yield (Table 1, entry 9). Previously, using aqueous basic conditions no product could be detected. The labeling of pivalic acid gave a low yield (Table 1, entry 7).

The orthogonal reactivity of sulfoxides in nucleophilic substitution reactions at *sp*^{3}- and *sp*^{2}-carbons makes it possible to transfer this method to a synthesis using ^{13}C-substituted and isotopically unmodified carbon monoxide. In one reaction (^{13}C)carbon monoxide was used together with [^{11}C]carbon monoxide, which resulted in the synthesis of (^{13}C)4-phenylbutyric acid in 25% yield.[14]

Sulfoxides and triethylamine are highly hygroscopic compounds. Though anhydrous reagents were employed in the syntheses, the presence of small amounts of water could not be excluded. Water may potentially be the nucleophilic reactant; however, the following observations point to the conclusion that the source of carboxyl oxygen in the products is the sulfoxide: (a) the addition of methanol as a competing nucleophile does not give a rise to labeled methyl ester; (b) the yields of acids using water–organic solvent (other than DMSO) in the presence of triethylamine were much lower; and (c) DMSO and less polar sulfoxides may be used as reagents in an inert solvent (Table 1, entries 2, 3 and 5).

To summarize, the free radical carboxylation of alkyl iodides using carbon monoxide and sulfoxides as oxygen nucleophiles is a simple procedure for the preparation of ^{11}C-labeled and ^{13}C-substituted compounds under mild conditions.

All reactions were performed in a 270 μL stainless steel batch-type reactor fitted with a sapphire window.[15] The photoirradiation from a xenon lamp (L8253, Hamamatsu Photonics) was supplied into the reactor through the window using a light guide.

Typical Procedure

Et$_3$N (25 μL, 0.18 mmol) and alkyl iodide (0.1 mmol) were dissolved in DMSO or DMSO–organic solvent (450 μL) and transferred into an autoclave charged with [^{11}C]carbon monoxide. Then the contents of the reactor was pressurized to ca. 40 MPa and irradiated with the xenon lamp using an optical filter in the range 280–400 nm. After 6 min the reactor was discharged into a collection vial and purified using LC.

The labeled compounds were identified in the reaction mixture using HPLC and were referenced to identical isotopically unmodified compounds. Furthermore, the products were characterized using LCMS. The labeling position was confirmed via NMR spectroscopy of the (^{13}C)4-phenylbutyric acid, obtained using a mixture of (^{13}C)- and [^{11}C]carbon monoxide.

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