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Photoinitiated Carbonylation with [^{11}C]Carbon Monoxide Using Amines and Alkyl Iodides

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Photoinitiated radical carbonylation with [^{11}C]carbon monoxide at low concentration was employed in syntheses of carbonyl-^{11}C-labeled amides using alkyl iodides and amines as precursors. Eleven ^{11}C-amides were synthesized in up to 74% decay-corrected radiochemical yields with reaction times of 400 s and with up to 95% conversion of carbon monoxide. Starting with 26.3 GBq of [^{11}C]carbon monoxide, 10.6 GBq of 1-cyclohexane [^{11}C]carbonyl-4-phenyl-piperazine **(15)** was obtained within 35 min from the end of bombardment (33 μA) and with a specific radioactivity of 192 GBq/μmol at the same time point. The influence of solvents was investigated. The described procedure extends the range of accessible labeling methods. The method may also be useful for preparation of ^{13}C- and ^{14}C-substituted compounds.

Introduction

With increasing utilization of positron emission tomography (PET) as a noninvasive molecular imaging technique in medical and biological research and especially as a tool in drug development,[1] there is a growing demand for new tracers and consequently new methods for preparation of radioactive tracers. The labeling of biologically active compounds with ^{11}C imposes the requirement of fast reactions, preferably by one-pot procedures, as dictated by the short half-life of ^{11}C ($t_{1/2}$ = 20.3 min). The submicromolar amounts of labeled substance often put restraints on the reaction conditions, but this may sometimes be turned into an advantage.

Recent technical development for the handling and use of [^{11}C]carbon monoxide has made this compound useful in labeling syntheses. [^{11}C]Carbon monoxide may be obtained in high radiochemical yields from cyclotron-produced [^{11}C]carbon dioxide and used to yield target compounds with high specific radioactivities. A broad range of carbonyl compounds has been labeled using either palladium- or selenium-mediated reactions.[2] The use of transition-metal-mediated reactions is restricted by problems related to the competing β-hydride elimination reaction excluding or at least severely limiting utilization of organo electrophiles having a hydrogen atom in the β-position. We have therefore explored other methods in order to circumvent the problem with β-hydride elimination and to widen the range of structures accessible for labeling.

The extensive and successful studies by Sonoda and Ryu[3] on radical carbonylation of alkyl iodides using carbon monoxide inspired us to adapt this approach to ^{11}C-labeling. To run reactions on the microscale utilizing submicromolar amounts of [^{11}C]carbon monoxide, a special small-scale apparatus was developed. The apparatus consists of a small autoclave equipped with a sapphire window and a mercury lamp with a focusing mirror. This device was used in the present work to establish the principles for photoinduced labeling chemistry employing [^{11}C]carbon monoxide. This project is still in progress both with regard to chemistry research and technical development. The synthetic methods and results using submicromolar quantities of [^{11}C]carbon monoxide differ from those previously described with carbon monoxide at 20−25 atm and will be explained in this paper dealing with ^{11}C-labeled amides.

This paper describes utilization of a fixed reaction time in the labeling synthesis. To achieve the best possible radiochemical yield in a specific labeling synthesis, an important factor is maximal conversion of carbon monoxide, which increases with reaction time. On the other hand, the short lifetime of [^{11}C]carbon should also be taken into account.[4] Considering this and other practical matters related to our experimental setup, a reaction time of 400 s was selected in order to simplify the comparison of experimental results. Generally, the optimal reaction time for each synthesis is determined by taking into account the reaction kinetics, the characteristics of the light source, scale of synthesis, etc.

A stimulus for the work was the objective to synthesize a range of ^{11}C-carbonyl labeled WAY-100365[5] analogues

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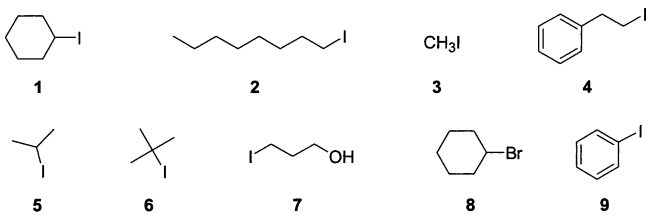

FIGURE 1. Halides used in the study.

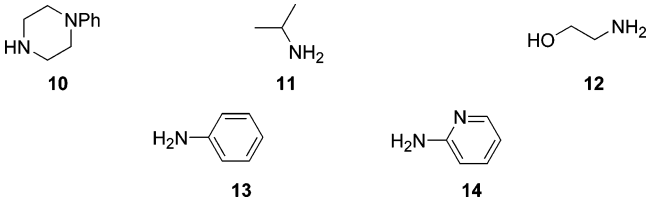

FIGURE 2. Amines used in the study.

for biological screening. The palladium-mediated syntheses worked satisfactorily for labeling of the analogues possessing arylcarboxamide moieties,[6] but there was a need also to include alkylcarboxamides (e.g., cyclohexylcarboxamide as in the case of WAY-100365 itself).

Results and Discussion

The scope and limitation study of radical carbonylation using submicromolar amounts of [^{11}C]carbon monoxide was performed using the alkyl halides (Figure 1) and amines (Figure 2), with the aim of obtaining the labeled amides shown in Table 1.

The reactions were carried out in a 270 μL stainless steel reaction vessel equipped with a sapphire window. The reactor was filled with [^{11}C]carbon monoxide in helium. Then the solution of an alkyl halide together with an amine was transferred to the reactor with a pressure of 35 MPa and the reaction mixture irradiated with focused light from a medium-pressure Hg lamp (400 W) during 400 s. The amount of [^{11}C]carbon monoxide used in these reactions was approximately 10^{-8} mol (10^{-9} L at 35 MPa), corresponding to a partial pressure of 200 Pa. After the synthesis, the crude mixture was evacuated from the reactor into a collection vial. The amount of [^{11}C]carbon monoxide consumed in the reaction was estimated by measurements of radioactivity before and after purge of the gas phase in the collection vial. A sample from the crude reaction mixture was withdrawn for HPLC analysis, and the remaining material was purified by HPLC.

The decay-corrected radiochemical yields of the target compounds were found to depend on the solvent, the nucleophilicity of the amine, and the structure of the organo halide. When low polar solvents (e.g., *n*-hexane and cyclohexane) were used, the conversion of [^{11}C]carbon monoxide did not exceed 5%. It was therefore anticipated that more polar solvents were needed to stabilize the acyl radicals to some extent and facilitate the acylation step, thus pushing the reaction in the direction of the desired path.[7]

The conversion of carbon monoxide to products was indeed favored when the syntheses were carried out in more polar solvents. Thus, the conversion was about 30% with acetone and acetonitrile and about 85% with DMF and DMSO (Table 1, entry 2). However, in the case of DMF and DMSO the amounts of labeled side-products also increased (25−40% estimated by LC) which may be the result of the ability of these solvents to serve as hydrogen donors. When 1-methyl-2-pyrrolidinone (NMP) and 1,3-dimethyl-2-imidazolidinone (DMI) were used as solvents the conversion of carbon monoxide was still high and the purity of the crude product was increased (Table 1, entries 1 and 3).

Attempts to label compounds **17** and **18** using DMSO as solvent resulted in radiochemical yields below 4%. The reason is probably that the nucleophilicity of aniline (**13**) and 2-aminopyridine (**14**) is not sufficient to trap the acyl iodide efficiently. Changing the solvent to NMP resulted in 44% radiochemical yield of amide **17** (Table 1, entry 5) and 2% of **18** (Table 1, entry 6) correspondingly. It is worth mentioning that the amine WAY-100634 showed a reactivity similar to that for **14**.

The reaction of iodo alcohol **7** with [^{11}C]carbon monoxide in the presence of amine **10** led to the prevailent formation of amide **24** over butyrolactone via intramolecular acylation (Table 1, entry 13). This selectivity may serve as evidence for the importance of nucleophilicity in determining the synthesis outcome.

Carboxamidation of iodomethane in NMP and acetonitrile gave only 1% isolated yield of **20** (Table 1, entry 8). The conversion of [^{11}C]carbon monoxide in *n*-hexane increased to 27% (yield 17%), and in THF the conversion and the yield reached 11% and 8%, respectively. In THF, the purity of the crude product determined by HPLC was the best (91%). The highest decay-corrected radiochemical yield was obtained in ethanol (Table 1, entry 9).

When amino alcohol **12** was used, the acylation proceeded almost exclusively on the nitrogen atom (Table 1, entry 10). With 2-iodoethylbenzene **4** the conversion of [^{11}C]carbon monoxide was markedly lower compared to syntheses in which iodides **1** and **2** were used (Table 1, entry 10). The major unlabeled byproduct in the synthesis of **21** was identified as styrene. The elimination pathway leading to isobutene was probably significant also in the synthesis of **23**.

Phenyl iodide gave a rather low decay-corrected radiochemical yield in reaction with amine **10** (Table 1, entry 14). This was probably a result of photodehalogenation[8] of phenyl iodide since the homolysis of aryl iodides is a facile process[9] and decarbonylation of PhCO radical is slow.[7]

Several organobromides were compared with the corresponding iodides in the labeling reactions. Generally, the consumption of [^{11}C]carbon monoxide reached relatively high levels while the purity of the crude product was low with several side-products. For example, the conversion of [^{11}C]carbon monoxide in preparation of **15** from cyclohexyl bromide in DMI was 70% while LC purity of the crude product was only 18%. When cyclohexyl

(5) *N*-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-*N*-2-pyridinyl)-cycloxexanecarboxamide: effective radioligand for imaging of 5-HT1A receptor.

(6) Results to be published elsewhere.

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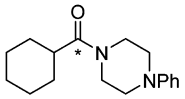
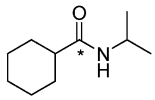
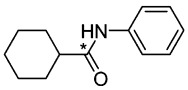
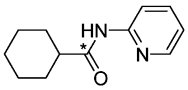
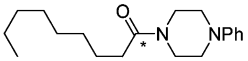
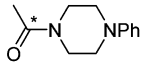
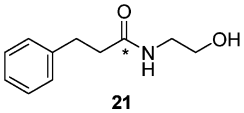
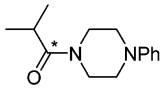
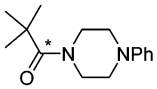
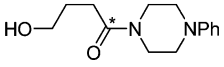
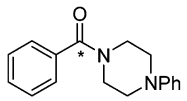
TABLE 1. Trapping Efficiency and Radiochemical Yields of ^{11}C-Labeled Amides (^{11}C Labeling Position Marked with *)

Amide	Entry	Iodide	Amine	Solvent	Conversion of [^{11}C]carbon monoxide (%)[a]	Yield (%)[b]	N[d]
 **15**	1			NMP	81±12	54±15	4
	2	**1**	**10**	DMSO	89±9	42±5	5
	3			DMI	85±4	69±5[c]	3
 **16**	4	**1**	**11**	NMP	89±3	61±8	3
 **17**	5	**1**	**13**	NMP	76±18	44±3	3
 **18**	6	**1**	**14**	NMP	46±11	2±1	3
 **19**	7	**2**	**10**	NMP	64±11	37±9	3
 **20**	8	**3**	**10**	NMP	10±11	1±0	3
	9			ethanol	37±7	27±9	3
 **21**	10	**4**	**12**	NMP	46±13	28±9	3
 **22**	11	**5**	**10**	NMP	85±3	57±1	3
 **23**	12	**6**	**10**	NMP	23±2	17±2	3
 **24**	13	**7**	**10**	NMP	76±2	43±1	3
 **25**	14	**9**	**10**	NMP	10±3	4±1	4

[a] Decay-corrected, the fraction of radioactivity left in the crude product after purge with nitrogen. [b] Radiochemical yield; decay-corrected, calculated from the amount of radioactivity in the crude product before nitrogen purge, and the radioactivity of the LC purified product. [c] Radiochemical yield; decay-corrected, calculated from analytical HPLC. [d] Number of runs.

TABLE 2. Dependence of Conversion and Radiochemical Yield on the Concentration of Reagents[a]

concn of **1** (mM)	concn of **10** (mM)	conversion of [^{11}C]carbon monoxide (%)[b]	LC purity (%)	yield[c] (%)
0	65	12	0	0
1	65	36	5	2
2	65	40	16	6
8	65	36	39	14
15	65	83	63	52
39	65	86	75	64
77	65	91	72	66
77	3	40	5	3
8	7	59	10	6

[a] All reactions were performed in DMSO with a reaction time 400 s. [b] Decay-corrected, the fraction of radioactivity left in the crude product after purge with nitrogen. [c] Radiochemical yield; decay-corrected, calculated from analytical HPLC.

iodide was used, the conversion of [^{11}C]carbon monoxide was 85% and the LC-determined purity was 69%.

In contrast to the corresponding palladium-mediated reaction with [^{11}C]carbon monoxide,[10] the free-radical reactions showed a notable dependence on efficient stirring of the reaction mixture. In our previous works on palladium- and selenium-mediated carbonylations, nearly quantitative conversions of [^{11}C]carbon monoxide in several cases were obtained without stirring.[11] The conversion of [^{11}C]carbon monoxide in the synthesis of **15** increased from 29 ± 4% to 85 ± 7% when stirring was introduced. Likewise, a reduction in pressure from 35 MPa to 10 MPa resulted in a 3-fold decrease of the conversion.

Proper selection of the photoirradiation conditions for generation of radicals was important in optimization of the synthesis. When visible light (a 250 W halogen lamp with UV-stop glass) was used, no labeled product was detected. A negative result was also obtained when the Hg lamp was used with a filter absorbing the 190−420 nm spectral range. The photoirradiation intensity was also important. Lower irradiation intensity gave lower decay-corrected radiochemical yields.

Although the changes of solvent, temperature, stirring, and type of organo halide all had a pronounced effect on the decay-corrected radiochemical yield the basic product pattern remained roughly the same.

The reduction of the amount of reagents used is sometimes desirable in order to facilitate purification and reduce costs. In Table 2, the dependence of the decay-corrected radiochemical yield of compound **15** on this factor is presented. The amounts of side products increased when the concentration of substrates reached a certain threshold.

High specific radioactivity is an important issue in PET studies where amount of tracer should be minimized to keep the biological system unperturbed. Compound **15** was synthesized with a specific radioactivity of 192 GBq/μmol in a 35 min synthesis time after the end of bombardment (33 μAh).

The basic identification of the labeled compounds was performed by comparison of analytical LC retention times for the labeled and reference compounds. The authenticity of the labeled compounds was verified by LC−MS analysis. LC−MS Chromatograms recorded at SIR M + 1 *m/z* for each of the labeled compounds **15**−**25** featured peaks with the same retention time as the chromatogram of the corresponding unlabeled reference substance. All reference compounds were prepared via alternative synthetic routes and characterized via MS and NMR. To collect more solid evidence the synthesis of compound **15** was scaled up. The reaction was performed in the same manner using 866 μL of carbon monoxide of natural isotopic distribution. The amounts of the precursors were correspondingly increased and the reaction time prolonged to 20 min. In this case, [^{11}C]carbon monoxide was used as a tracer to track the target compound. The ^{1}H NMR spectrum of the isolated compound was identical with the spectrum of the reference compound prepared from the appropriate amide and acid chloride.

To verify the labeling position, a ^{13}C-substituted analogue of **22** was synthesized. (^{13}C)Carbon monoxide was added to the [^{11}C]carbon monoxide and the reaction was performed as a standard ^{11}C-labeling except that the amounts of the alkyl iodide and amine were increased and reaction time was extended to 31 min. Calculated from carbon monoxide using radioactivity measurements, the isolated yield of ^{13}C-substituted **22** was 41%. The conversion of (^{13}C)carbon monoxide was 68%. ^{13}C NMR analysis was used to assign the labeling position. The identity of the compound was further confirmed by the ^{1}H NMR spectrum, which showed the characteristic splittings due to ^{1}H−^{13}C coupling.

Conclusions

This work confirms the suitability of radical-mediated carbonylation for the synthesis of labeled amides starting from [^{11}C]carbon monoxide, alkyl iodides, and amines. This method may provide an important complement to the previously described palladium-mediated reactions using [^{11}C]carbon monoxide and allows the preparation of target structures incompatible with Grignard synthesis. The labeled compounds had high specific radioactivities, which is important in PET studies.

This method may also be valuable for synthesis with (^{13}C)carbon monoxide.

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), which was bombarded with 17 MeV protons. [^{11}C]Carbon monoxide was obtained by reduction of [^{11}C]carbon dioxide as described previously.[12] The syntheses with [^{11}C]carbon dioxide were performed with an automated module as part of the system "Synthia 2000". Liquid chromatographic analysis (LC) was

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performed with a gradient pump and a variable-wavelength UV detector in series with a β^+-flow detector. The following mobile phases were used: 25 mM potassium dihydrogenphosphate (A) and acetonitrile/H_2O 50/7 (B). For analytical LC, a C_{18}, 3 μm, 50 × 4.6 mm i.d. column was used at a flow of 2 mL/min. For semipreparative LC, a C_{18}, 4 μm, 250 × 10 mm (i.d.) column was used at a flow of 4 mL/min. An automated synthesis system, Synthia,[13] was used for LC injection and fraction collection. Radioactivity was measured in an ion chamber. A Philips HOK 4/120SE mercury lamp was used as photoirradiation source. In the analysis of the ^{11}C-labeled compounds, unlabeled reference substances were used for comparison in all the 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 TMS via the solvent signals. LC−MS analysis was performed with electrospray ionization.

THF was distilled under nitrogen from sodium/benzophenone. DMSO was purged with helium for 5 min before use. Other solvents were used as supplied without further purification. Compound **7** was synthesized from the corresponding bromide by the Finkelstein reaction. All other starting materials were commercially available.

All reactions were carried out in a high-pressure reactor. The reactor comprises a 270 μL cylindrical cavity in a stainless steel tube. One end of the cavity is sealed and outfitted with two tubes of smaller diameter that serve as filling and evacuation ports. A sapphire window is attached to the opposite end of the cavity. A thermocouple is attached to the outer body of the reactor and serves to control the reaction temperature. An externally driven Teflon-coated magnet bar was used to stir the reaction mixture.

Preparation of ^{11}C-Labeled Amides. A capped vial (1 mL) was flushed with nitrogen and was charged with an amine (50 μmol), triethylamine (100 μmol), and a solvent (500 μL). An organo iodide (50 μmol) was added to the solution roughly 7 min before synthesis. The resulting mixture was pressurized (35 MPa) into the microautoclave (270 μL), precharged with [^{11}C]carbon monoxide in He at ambient temperature. The autoclave was then irradiated with a mercury lamp for 400 s. The crude reaction mixture was then transferred from the autoclave to a capped vial (1 mL) 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 (0.55 to 1 mL) and injected onto the semipreparative LC. Analytical LC and LC−MS were used to assess the identity and radiochemical purity of the collected fraction.

(^{13}C-Carbonyl)-1-isobutanoylpiperazine (22). A capped vial (1 mL) was flushed with nitrogen and charged with 1-phenylpiperazine (165 μmol), triethylamine (180 μmol), and NMP (500 μL). Isopropyl iodide (250 μmol) was added to the solution roughly 7 min before synthesis. The resulting mixture was pressurized (35 MPa) into the microautoclave (270 μL), precharged with [^{11}C]carbon monoxide in He and (^{13}C)carbon monoxide (40 μmol) at ambient temperature. The autoclave was then irradiated with a mercury lamp for 31 min. The crude reaction mixture was then transferred from the autoclave to a capped vial (1 mL) 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 (0.55 mL) and injected onto the semipreparative LC.

General Procedure for Preparation of Amides 15−20, 22, 23, and 25 Used as Reference Compounds. To an ice-cooled solution of an amine (2 mmol) and triethylamine (3 mmol) in dichloromethane (5 mL) was added the acid chloride (2 mmol) dropwise. The reaction mixture was allowed to warm to room temperature and was then stirred for 1 h. Water was added and the mixture extracted with dichloromethane three times. The combined extract was dried over $MgSO_4$, and the solvent was then evaporated under reduced pressure. The crude product was purified with flash chromatography or recrystallized.

1-Cyclohexanecarbonyl-4-phenylpiperazine (15). A colorless oil was obtained after flash chromatography, yield 92%.

***N*-Isopropylcyclohexanecarboxamide (16).** Recrystallization from dichloromethane/pentane gave white crystals, yield 89%.

Cyclohexanecarboxanilide (17). Recrystallization from dichloromethane/pentane gave white crystals, yield 88%.

***N*-2-Pyridylcyclohexanecarboxamide (18).** Purified by flash chromatography and recrystallized from dichloromethane/pentane: pale yellow crystals; yield 52%.

1-Nonanoyl-4-phenylpiperazine (19). Recrystallization from dichloromethane/diethyl ether gave white crystals, yield 81%.

1-Acetyl-4-phenylpiperazine (20). The crude product was purified by column chromatography and recrystallized from dichloromethane/pentane to yield 88% of white crystals.

***N*-(2-Hydroxyethyl)-3-phenylpropionamide (21).** The amino alcohol **12** (15 mmol) was dissolved in dichloromethane (20 mL). The solution was cooled in an ice bath, and a solution of 3-phenylpropionyl chloride (3.4 mmol) in dichloromethane (10 mL) was added dropwise. The reaction mixture was allowed to warm to room temperature and then stirred overnight. The dichloromethane phase was separated, added to water (30 mL) acidified to pH 3 with concentrated hydrochloric acid, and extracted twice with dichloromethane. The combined extract was dried over $MgSO_4$ and evaporated at reduced pressure. Recrystallization from dichloromethane/pentane gave white crystals, yield 81%.

1-Isobutanoyl-4-phenylpiperazine (22). The crude product was purified by column chromatography and recrystallized from diethyl ether/pentane to yield 82% of white crystals.

1-Pivaloyl-4-phenylpiperazine (23). The crude product was purified by column chromatography and recrystallized from diethyl ether/pentane to yield 78% of pale yellow crystals.

1-(4-Hydroxybutanoyl)-4-phenylpiperazine (24). A neat mixture of butyrolactone (1.5 mmol) and 1-phenylpiperazine (1.5 mmol) was heated at 130 °C overnight with stirring. The resulting crude product was cooled to ambient temperature, partitioned between dichloromethane and sodium hydrogen carbonate solution, and extracted thrice with dichloromethane. The combined extract was dried over $MgSO_4$ and evaporated at reduced pressure. The crude product was purified by column chromatography to yield 63% of a colorless oil.

1-Benzoyl-4-phenylpiperazine (25). The crude product was purified by column chromatography and recrystallized from diethyl ether/pentane to yield 85% of white crystals.

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Supporting Information Available: Melting points, ^{1}H and ^{13}C NMR, and MS data for reference compounds **15**−**23**, (carbonyl-^{13}C)**15**, and (carbonyl-^{13}C)**22**. This material is available free of charge via the Internet at http://pubs.acs.org.

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