A Convenient Method for [^{14}C]Carbonylation Reactions

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SUMMARY

A simple, efficient method for generation of ^{14}CO from Ba^{14}CO$_3$ has been developed. Reduction of ^{14}CO$_2$ using LiBEt$_3$H gave [^{14}C]formate in good yield which was treated with conc. H$_2$SO$_4$ to effect dehydration to ^{14}CO. Through direct attachment of a reaction vessel containing aryl substrate and Pd(0) catalyst, [^{14}C]carbonylation reactions were performed without the use of a mercury transfer pump. [^{14}C]Carbonylation reactions using ^{14}CO generated in this manner have been shown to proceed in good yield with a variety of substrates.

Key Words: Palladium catalyzed carbonylation, [^{14}C]CO, [^{14}C]formic acid.

INTRODUCTION

Transition metal catalyzed carbonylation reactions have become a standard means of one-carbon homologation using aryl or vinyl halide and triflate substrates.[1] These reactions are performed under mild conditions which are compatible with a wide range of functional groups, permitting efficient access to ketones,[2] carboxylic acids,[3] esters[4] and amides.[5] Application of this methodology to labeled synthesis using [^{14}C]carbon monoxide would be an attractive, general protocol for late-stage radiocarbon introduction into complex organic molecules. Surprisingly, very few examples of [^{14}C]carbonylation have been reported. This can be attributed to a

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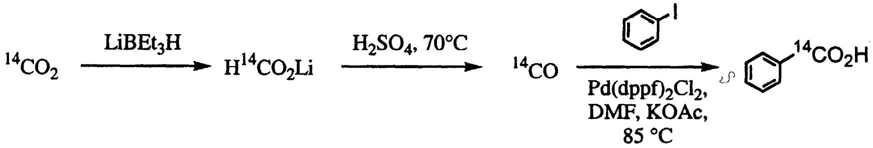
variety of factors which include the non-condensable nature of CO causing cumbersome procedures for its transfer after generation and the instability of the radioactive gas to long-term storage.[6] Additionally, the efficiency of many carbonylation reactions using stoichiometric quantities of ^{14}CO under sub-atmospheric pressure is unclear. Herein, we describe a procedurally convenient, one-pot generation of ^{14}CO from $Ba^{14}CO_3$ and its subsequent direct use in [^{14}C]carbonylation reactions.

RESULTS AND DISCUSSION

The method most often used for generation of ^{14}CO involves reduction of $^{14}CO_2$ gas over a bed of zinc dust at >400 °C.[7] This process requires a high temperature oven containing a column of zinc dust and a Toepler mercury pump for transferring ^{14}CO to the reaction vessel. We initially evaluated this method using the carbonylation of iodobenzene to benzoic acid as a model reaction. While reasonable radiochemical yields of benzoic acid (30-45% using 2 equivalents of $^{14}CO_2$) could be obtained, several practical drawbacks were apparent, including (1) multiple passes of $^{14}CO_2$ through the zinc bed were required for optimal yield of ^{14}CO, making the process labor intensive; (2) using standard size glassware and oven, the process was not effective for conversion of quantities of $^{14}CO_2$ below 1 mmol; (3) the size and complexity of the apparatus make routine reassembling impractical and was, therefore, best suited for use in a dedicated fume hood; (4) mercury contamination and disposal, especially when radioactive, were undesirable.

An alternative carbon monoxide generating reaction is the dehydration of formic acid with conc. sulfuric acid.[8] We found this approach was efficiently initiated from $^{14}CO_2$ by reduction to [^{14}C]formate with $LiBEt_3H$ in *ca.* 80% yield (equation). Treatment of the crude reaction mixture with sulfuric acid followed by heating to 70 °C for 1h provided effective conversion to ^{14}CO.[9] In order to conduct on-line [^{14}C]carbonylation reactions, a flask containing iodobenzene, KOAc, and [1,1-Bis(diphenylphosphino)ferrocene]dichloro-palladium(II) ($Pd(dppf)_2Cl_2$) in DMSO was attached prior to the addition of sulfuric acid. Following completion of the dehydration, the reaction vessel was heated at 85 °C for 15 h to provide [^{14}C]benzoic acid in a 72 % isolated yield.

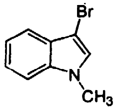
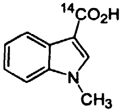
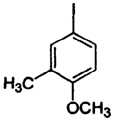
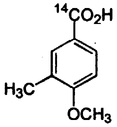
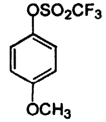
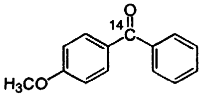


Equation. [^{14}C]Carbonylation reaction of iodobenzene from $^{14}CO_2$.

In an effort to further simplify the procedure, we examined the dehydration of aqueous lithium [^{14}C]formate. Quenching of the $LiBEt_3H$ reaction mixture with water provided a crude solution of lithium [^{14}C]formate in *ca* 80 % yield. Dropwise addition of conc. sulfuric acid as before to this solution produced carbonylation yields of [^{14}C]benzoic acid similar to that of the anhydrous, non-isolation method. In this manner, routine [^{14}C]carbonylation reactions could be performed rapidly by allocation of a crude lithium [^{14}C]formate aqueous stock solution. Extended storage of the stock solution, frozen at –30 °C for 5 months, resulted in no significant decrease in carbonylation yields, indicating good radiochemical stability of the lithium [^{14}C]formate.

The use of these procedures for the [^{14}C]carbonylation of several halides and one triflate to provide a variety of carbonyl containing products was investigated (Table). The reactions were typically performed with *ca* 2 equivalents of $Ba^{14}CO_3$. In the case of iodobenzene, only a slight decrease in yield was observed when the amount of $Ba^{14}CO_3$ was reduced to 1 equivalent (entry 1); however, a more significant effect was observed using bromobenzene (entry 4). The use of 1 equivalent of iodobenzene and 1 equivalent of $Ba^{14}CO_3$ actually represents a slight undercharge of the halide since the conversion of $Ba^{14}CO_3$ to [^{14}C]formic acid was shown to proceed in *ca* 80% yield. Therefore, the 72% yield shown (entry 1) can be more accurately represented as a 90% radiochemical yield based on ^{14}CO. The lower yield of 1-methyl-3-indole[^{14}C]carboxylic acid (entry 5) was most likely a result of the decomposition of 1-methyl-3-bromoindole under the reaction conditions.

Table: Synthesis of C-14 labeled carbonyl compounds *via* carbonylation of various substrates.[a]

Entry	Substrate	Product	Catalyst	Yield[b,c]
1	PhI	$Ph^{14}CO_2H$	$Pd(dppf)_2Cl_2$	72 %[d], 80 %
2	PhI	$Ph^{14}CO_2Me$	$Pd(dppf)_2Cl_2$	71 %
3	PhI	$Ph^{14}CHO$	$Pd(dppf)_2Cl_2$	67 %
4	PhBr	$Ph^{14}CO_2H$	$Pd(PPh_3)_4$	60 %[d], 78 %[e]
5			$Pd(PPh_3)_4$	41 %[e]
6			$Pd(dppf)_2Cl_2$	69 %
7			$Pd(dppf)_2Cl_2$	46 %[e]

[a] all reactions were run with 2 equivalents of $Ba^{14}CO_3$ unless otherwise noted. [b] Yield based upon HPLC purity and radioactivity in the organic extract. [c] Yields reported are based upon aryl substrate. [d] Reaction was run with 1 eq of $Ba^{14}CO_3$. [e] prepared from aqueous [^{14}C]formic acid

In summary, we have developed a protocol for conducting routine Pd-catalyzed [^{14}C]carbonylation reactions starting from $^{14}CO_2$. This procedure uses an apparatus which is easy to assemble and is much less cumbersome to operate than those of the previously reported methods. Of particular note, the sequence can be implemented without intermediate isolation or further localization of the ^{14}CO; a feature which should also be advantageous for the production of short lived ^{11}CO for PET ligand synthesis.[10] Additional applications of this [^{14}C]carbonylation process are under investigation and will be the subject of future publications.

EXPERIMENTAL

General: Anhydrous solvents were obtained from Aldrich and were dried over 4 Å molecular sieves for at least 24 h prior to use. Pd(dppf)$_2$Cl$_2$ was obtained from Aldrich, and Pd(PPh$_3$)$_4$ was obtained from Alpha. Analytical HPLC was performed using a Shimadzu HPLC system with LC-10ATVP pumps, SPD-10AVP UV detector, CTO-10ASVP column oven heated to 40 °C, a SCL-10A controller and a Packard Radiomatic™ 150TR flow monitor. ^{1}H and ^{13}C NMR spectra were recorded on a Varian U-400 spectrometer. The reaction products were identified by HPLC comparison with the commercially available material unless otherwise noted using either method A (20 to 60 % MeCN-0.1 % trifluoacetic acid over 30 min), method B (30 to 70 % MeCN-0.1 % trifluoacetic acid over 30 min), or method C (53 % MeCN-0.1 % trifluoroacetic acid for 30 min). All HPLC analyses were conducted on a Zorbax SB C-8 column heated to 40 °C and concluded with a 10 min wash of 100 % MeCN.

General procedure for one-pot carbonylation reactions: [^{14}C]Benzoic acid from Iodobenzene and ^{14}CO$_2$:

The apparatus consisted of a three-necked flask connected to a vacuum manifold, a stopcock with a rubber septum, and a 90° bent adapter (see figure). The bent adapter was connected to a one-necked flask which contained the carbonylation solution (the Pd complex, aryl halide, nucleophile, proton scavenger, and solvent).

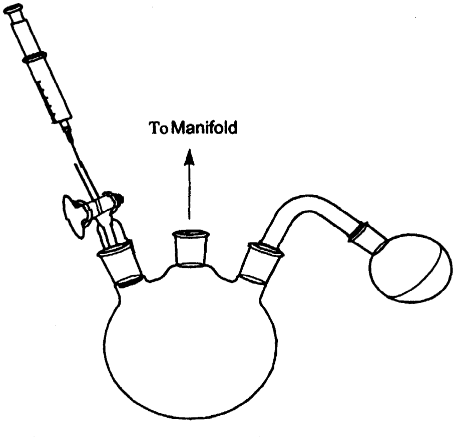


Figure. Depiction of the apparatus used in the one-pot carbonylation procedure.

The three-necked flask and the round bottom flask were charged with $LiBEt_3H$ (0.8 mL of 1 M solution in THF, 0.8 mmol) and with $Pd(dppf)_2Cl_2$ (5 mg, 0.0066 mmol), KOAc (50 mg, 0.51 mmol), iodobenzene (69 mg, 0.34 mmol) and DMSO (3 mL) respectively, and both flasks were cooled in liquid nitrogen and evacuated to 0.01 mm Hg. $^{14}CO_2$ (*ca* 18 mCi) was generated from $Ba^{14}CO_3$ (67 mg, 0.34 mmol, 18 mCi, 54 mCi/mmol) and $PbCl_2$ (669 mg, 2.4 mmol) by heating for *ca* 5 min with a Bunsen burner.[11] The THF solution was warmed to 0 °C and stirred for 2 h followed by slow dropwise addition of H_2SO_4 (21 mL) through the stopcock and septum.[12] The stopcock was closed, and the acidic solution contained within the three-necked flask was stirred at 70 °C for 1 h. The DMSO solution in the one-necked flask was then stirred for 15 h at 85 °C after which the vacuum was released. The solution was diluted with EtOAc (10 mL) and 1 M HCl (5 mL). The organic layer was removed and was then extracted with a saturated aqueous solution of $NaHCO_3$ (2 X 5 mL). The aqueous extract was acidified to a pH of 2 (determined by pH paper) with 1 M HCl and was extracted with EtOAc (3 X 5 mL) to give 13 mCi of $Ph^{14}CO_2H$ (72 %). HPLC analysis (method A) of the product showed the radiochemical purity to be 93 %. ^1H NMR (400 MHz, $CDCl_3$) δ 8.14 (dd, 2H, *J*=8.2, 1.2 Hz), 7.63 (tt, 1H, *J*=7.4, 1.3 Hz), 7.49 (t, 2H, *J*=7.8 Hz).

Methyl [^{14}C]benzoate: The general one-pot procedure was followed using $LiBEt_3H$ (3 mL of 1M solution in THF, 3.0 mmol), $Ba^{14}CO_3$ (390 mg, 1.98 mmol, 2.5 mCi, 1.26 mCi/mmol), $PbCl_2$ (3.63 g, 13.1 mmol), H_2SO_4 (20 mL), $Pd(dppf)_2Cl_2$ (8 mg, 0.011 mmol), MeOH (200 μL, 32 mmol), $N\textit{i}Pr_2Et$ (300 μL, 129 mmol), iodobenzene (212 mg, 1.0 mmol) and DMSO (1 mL) to afford 0.94 mCi (71 %) of a brown oil. The oil had an 83 % radiochemical purity by HPLC analysis (method A) and was identical to unlabeled methyl benzoate by ^1H and ^{13}C NMR. ^1H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, 2H, *J*=7.1 Hz), 7.55 (m, 1H), 7.44 (m, 2H), 3.92 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 132.9, 130.2, 129.6, 128.3, 52.1.

3-methoxy-4-methyl-[C]benzoic acid: The one-pot carbonylation procedure was followed using $LiBEt_3H$ (1 mL of a 1M solution in THF, 1.0 mmol), $Ba^{14}CO_3$ (70 mg, 0.35 mmol, 19 mCi, 53 mCi/mmol), $PbCl_2$ (774 mg, 2.78 mmol), H_2SO_4 (15 mL), $Pd(dppf)_2Cl_2$ (6 mg, 0.007 mmol), KOAc (51 mg, 0.59 mmol), 4-iodo-2-methoxytoluene (35 mg, 0.14 mmol) and DMSO (1 mL) to give 6.1 mCi (0.12 mmol, 84 % purity, 69 %) of 3-methoxy-4-methyl-[^{14}C]benzoic acid. The product was characterized by HPLC (method A) and ^{1}H NMR analysis. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (dd, 1H, *J*=7.7,1.4 Hz), 7.52 (d, 1H, *J*=1.4 Hz), 7.22 (d, 1H, *J*=7.7 Hz), 3.90 (s, 3H), 2.29 (s, 3H)

[^{14}C]benzaldehyde: The one-pot carbonylation procedure was followed using $LiBEt_3H$ (0.5 mL of a 1 M solution in THF, 0.5 mmol), $Ba^{14}CO_3$ (67 mg, 0.34 mmol, 18 mCi, 53 mCi/mmol), $PbCl_2$ (702 mg, 2.78 mmol) H_2SO_4 (20 mL), $Pd(dppf)_2Cl_2$ (20 mg, 0.027 mmol), iodobenzene (52 mg, 0.26 mmol) and THF (1 mL). The reaction flask – a two necked flask in this case - was heated at 50 °C for 6 h as a solution of Bu_3SnH (215 mg, 0.74 mmol) in THF (6 mL) was added *via* syringe pump over a period of 6 h through a septum according to the procedure of Stille.[13] Heating was continued for 12 h. The reaction mixture was diluted with EtOAc (10 mL) and was then washed with 1M HCl (2 X 5 mL) and saturated aqueous solutions of $NaHCO_3$ (2 X 5 mL) and NaCl (5 mL). The organic layer was dried ($MgSO_4$) and filtered to give 9.3 mCi which was 99 % pure by HPLC (method A).

Lithium [^{14}C]Formate from $^{14}CO_2$: A three-necked flask containing $LiBEt_3H$ (1.5 mL of a 1 M solution in THF, 1.5 mmol) was cooled in liquid nitrogen and was evacuated to 0.01 mm Hg. $^{14}CO_2$ was generated from $Ba^{14}CO_3$ (104 mg, 0.52 mmol, 28 mCi, 53 mCi/mmol) and $PbCl_2$ (689 mg, 2.5 mmol) and was condensed into the three-necked flask. The reaction mixture was warmed to 0 °C and was stirred vigorously for 2 h at 0 °C and 2 h at rt. The reaction was halted by the addition of water (2 mL), and the aqueous solution was determined to contain 22 mCi (79%) by liquid scintillation counting.

General procedure for carbonylation from [^{14}C]formic acid: [^{14}C]$PhCO_2H$ from Bromobenzene and $H^{14}CO_2H$

A three necked flask containing an aqueous solution of $H^{14}CO_2Li$ (180 µL, 1 mCi, 53 mCi/mmol, 0.019 mmol) and HCO_2H (50 mg, 1.08 mmol) was connected to a vacuum adapter, a stopcock attached to a septum, and a round bottom flask containing bromobenzene (84 mg, 0.53 mmol), KOAc (61 mg, 0.61 mmol), $Pd(PPh_3)_4$ (20 mg, 0.017 mmol) and DMSO (2 mL) *via* a 90° bent adapter. The flask was evacuated to 0.01 mm Hg, and concentrated H_2SO_4 (12 mL) was added dropwise through the stopcock and septum. The stopcock was closed, and the aqueous solution was heated for 1 h at 70 °C. The other round bottom-flask was heated for 15 h at 70 °C after which the vacuum was released. The DMSO solution was cooled to rt, diluted with CH_2Cl_2 (10 mL), and was acidified with 0.1 % HCl (10 mL). The layers were separated, and the organic layer was washed with 0.1 % HCl (10 mL) and determined to contain 380 µCi (78 %) by liquid scintillation counting. The product was pure by HPLC analysis (method A).

[^{14}C]3-Indolecarboxylic acid from [^{14}C]formic acid: The general procedure for carbonylations from formic acid was followed using $H^{14}CO_2Li$ (3.9 mCi, 0.073 mmol, 53 mCi/mmol) in water (700 µL), H_2SO_4 (15 mL), $Pd(PPh_3)_4$ (18 mg, 0.016 mmol), KOAc (30 mg, 0.34 mmol), of 3-bromoindole[14] (40 mg, 0.18 mmol) and DMF (1 mL) to give 1.6 mCi (0.030 mmol, 92 % purity, 41 %) of [^{14}C]3-indolecarboxaldehyde. The product was characterized by HPLC (method A) and ^{1}H NMR. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (m, 1H), 7. 85 (s, 1H) 7.35 (m, 3H).

[^{14}C]*p*-Methoxybenzophenone: The general procedure for carbonylations from formic acid was followed using $H^{14}CO_2Li$ (1 mCi, 1.1 mmol, 0.9 mCi/mmol) in water (200 µL), H_2SO_4 (15 mL), $PhSnMe_3$ (251 mg, 1.04 mmol), *p*-methoxyphenyl trifluoromethylsulfonate[15] (178 mg, 0.74 mmol), $Pd(dppf)_2Cl_2$ (7 mg, 0.01 mmol), LiCl (70 mg, 1.7 mmol), powdered 4 Å sieves (39 mg), and DMF (1 mL) provided 900 µCi (64 % purity by HPLC analysis using method B) of a brown oil. Purification by flash column chromatography (10:1 Hexane:EtOAc) gave 305 µCi

(68 mg, 46 %) of [^{14}C]*p*-methoxybenzophenone which was characterized by ^{1}H and ^{13}C NMR and HPLC (method C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81(d, 2H, *J*=8.9 Hz), 7.74(d, 2H, *J*=7.1 Hz), 7.54(m, 1H), 7.45(m, 2H), 6.94 (d, 2H, *J*=8.9 Hz), 3.86(s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.4, 163.1, 138.2, 132.4, 131.8, 130.0, 129.6, 128.1, 113.4, 55.4.

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