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# Carbon-14 labeled methyl 2-chloro-2-oxoacetate: a convenient carbon-14 labeled oxalyl chloride equivalent

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**Oxalyl chloride is a versatile two-carbon building block for synthesizing organic molecules. Carbon-14 labeled oxalyl chloride should be a useful reagent for labeling many of these compounds. Unfortunately, its preparation suffers from low radiochemical yield and problems with stability, isolation and analysis. Because of these issues, the reagent is not a convenient or practical carbon-14 label source. Synthetically, methyl 2-chloro-2-oxoacetate reacts as an oxalyl chloride equivalent. This report describes a reliable and efficient two-step synthesis of carbon-14 labeled methyl 2-chloro-2-oxoacetate ([$^{14}$C]-1) from readily available carbon-14 labeled dimethyl oxalate ([$^{14}$C]-2). The labeled oxalate was first treated with aqueous base to give the mono-potassium salt of 2-methoxy-2-oxoacetate ([$^{14}$C]-3), which was then reacted with oxalyl chloride to give [$^{14}$C]-1 as a solution in dichloromethane. The overall radiochemical yield for this process was essentially quantitative, and [$^{14}$C]-1 was found to be stable and easy to use in further synthetic manipulations.**

**Keywords:** carbon-14 synthesis; oxalyl chloride; methyl 2-chloro-2-oxoacetate; ethyl 2-chloro-2-oxoacetate; dichloropyrazinones

## Introduction

Oxalyl chloride is a useful two-carbon building block for organic syntheses. There are numerous molecules of pharmaceutical interest that can be prepared from oxalyl chloride, including those possessing 1,2-diketone functionality.[1–13] Labeling these compounds with carbon-14 should be efficiently accomplished from carbon-14 labeled oxalyl chloride. Unfortunately, the literature descriptions for the preparation of carbon-14 labeled oxalyl chloride are difficult to repeat and low yielding.[14–16] Additionally, it should be noted that carbon-14 labeled oxalyl chloride is unstable at high specific activity and hard to assay for purity, diminishing its synthetic utility. Given these difficulties, there is a need for a carbon-14 labeled oxalyl chloride equivalent that is stable and easy to prepare in consistently high yield.

Methyl and ethyl 2-chloro-2-oxoacetate have been used as two-carbon building blocks much like oxalyl chloride.[17–21] However, a search of the literature did not reveal any synthetic preparations of carbon-14 labeled methyl or ethyl 2-chloro-2-oxoacetate, although the syntheses of unlabeled methyl and ethyl 2-chloro-2-oxoacetate are known.[17,22,23] With the appropriate modifications, these literature procedures were adapted for the preparation of carbon-14 labeled methyl 2-chloro-2-oxoacetate, **[$^{14}$C]-1** (Figure 1).

## Results and discussion

The literature preparation of ethyl 2-chloro-2-oxoacetate involves the reaction of diethyl oxalate in aqueous base to give potassium 2-ethoxy-2-oxoacetate.[17] The potassium salt was isolated in high yield, and then reacted with phosphorous oxychloride as part of an *in situ* generation of ethyl 2-chloro-2-oxoacetate for subsequent reaction. Adapting this procedure for a radiolabeled synthesis required the use of relatively inexpensive and commercially available carbon-14 labeled dimethyl oxalate (Scheme 1). Carbon-14 labeled dimethyl oxalate was treated with one equivalent of aqueous potassium hydrogen carbonate. This gave the mono potassium salt **[$^{14}$C]-3**, which was isolated in quantitative radiochemical yield. Treatment of **[$^{14}$C]-3** with oxalyl chloride gave the desired product **[$^{14}$C]-1**, as a solution in dichloromethane. A small aliquot from the **[$^{14}$C]-1** solution was treated with methanol to reform carbon-14 labeled dimethyl oxalate. This aliquot was analyzed by HPLC to ensure complete conversion of **[$^{14}$C]-3** and assess the purity of the **[$^{14}$C]-1** solution. The radiochemical purity of the aliquot was determined to be 99% and the radiochemical yield for the two-step conversion was estimated to be quantitative.

The synthetic utility of carbon-14 labeled methyl 2-chloro-2-oxoacetate (**[$^{14}$C]-1**) and carbon-14 labeled ethyl 2-chloro-2-oxoacetate as a carbon-14 labeled oxalyl chloride equivalent has been demonstrated on several occasions in our lab.[24]

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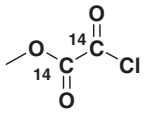
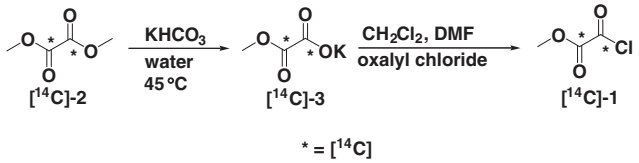



[$^{14}$C]-1

**Figure 1.** Carbon-14 labeled methyl 2-chloro-2-oxoacetate ([$^{14}$C]-1).




**Scheme 1.** Synthesis of carbon-14 labeled methyl 2-chloro-2-oxoacetate ([$^{14}$C]-1).

One example showing the synthesis of a carbon-14 labeled dichloropyrazinone ([$^{14}$C]-7) is highlighted in Scheme 2.

The literature describes a one-pot synthesis of dichloropyrazinones from oxalyl chloride and substituted aminoacetonitriles.[1–4] The yields reported are moderate, 44–76%, when 5 equivalents of oxalyl chloride are used.[1,4] This method is prohibitive from a label efficiency standpoint, when trying to use oxalyl chloride as the label source. To overcome this limitation the procedure was modified for use with labeled reagents, 1 equivalent of carbon-13 labeled oxalyl chloride was allowed to react with the aminoacetonitrile (**4**) and then a second equivalent of unlabeled oxalyl chloride was added. This gave the desired carbon-13 labeled dichloropyrazinone (**7**) in an 80% yield with no dilution of the label. When this same procedure was attempted with high specific activity carbon-14 labeled oxalyl chloride (25 mCi/mmol), the desired product [$^{14}$C]-7 was only obtained in a 5% radiochemical yield. It is worth noting that this procedure gave [$^{14}$C]-7 in a 59% yield when low specific activity carbon-14 labeled oxalyl chloride (1 mCi/mmol) was used.

The difficulties encountered when attempting to synthesize dichloropyrazinone [$^{14}$C]-7 from carbon-14 labeled oxalyl chloride were overcome when carbon-14 labeled methyl 2-chloro-2-oxoacetate ([$^{14}$C]-1) was used as the label source. Carbon-14 labeled methyl 2-chloro-2-oxoacetate ([$^{14}$C]-1) was reacted with the aminoacetonitrile **4** as shown in Scheme 2. The ester [$^{14}$C]-5 was hydrolyzed with base to the corresponding carboxylic acid [$^{14}$C]-6. The crude acid [$^{14}$C]-6 was treated with unlabeled oxalyl chloride to give the desired dichloropyrazinone [$^{14}$C]-7. Overall, the three-step synthesis produced the desired dichloropyrazinone [$^{14}$C]-7 in a 61% radiochemical yield, similar to the one-pot approach and it used only one equivalent of the labeled reagent.

## Experimental procedure

### Materials and methods

All the experimental procedures were optimized using unlabeled material. Reactions were run under an inert atmosphere of argon and stirred magnetically unless otherwise noted. Reactions were monitored by HPLC and TLC and comparisons were made to authentic materials when possible. All reagents and solvents were ACS grade or better and used without further purification. Carbon-14 labeled dimethyl oxalate was obtained from ViTrax Company.

### Instruments

Solvent removal under vacuum was accomplished using a Buchi R-124 rotary evaporator. Proton NMR spectra were recorded on a 400 MHz Bruker Avance spectrometer. TLC analyses (EMD 60 $F_{254}$ silica gel coated plates) were performed as described and using UV (254 nm) and radiochemical detection (QC-Scan, Bioscan Model B-QC). Specific activities were determined by gravimetric analysis using liquid scintillation counting (Wallac Model 1409).

### HPLC

HPLC analyses were performed on a Varian instrument equipped with two PrepStar pumps (Model SD-218, 25 mL pump heads), a ProStar PDA detector (model 330, for analytical UV detection), a ProStar UV-1 detector (model 320, for semipreparative UV detection) and an IN/US β-ram detector (model 3B, for radiochemical purity measurements). The following analytical method (method A) was used for all in process and final product purity analyses.

*HPLC Method A:*

Column: YMC-Pack Pro C18, 3.0 μm (4.6 × 150 mm$^2$); Mobile Phase A: Water with 0.05% trifluoroacetic acid; Mobile Phase B: Acetonitrile with 0.05% trifluoroacetic acid; Conditions: 0% B, 0–5 min; 0–100% B, 5–20 min; 100% B, 20–25 min; 100–0% B, 25–30 min; Flow rate: 1 mL/min; Injection size: 20 μL; Detection: UV at 215 nm and radiochemical (β-ram).

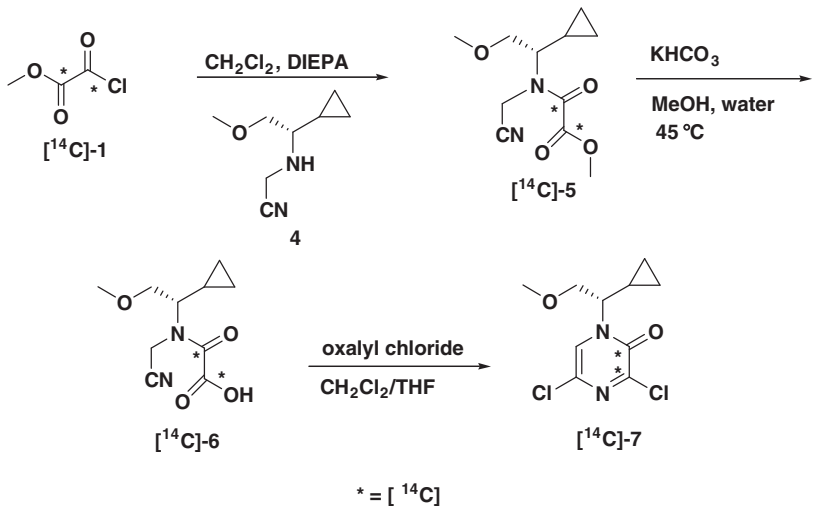
### Experimental

*[$^{14}$C]-Potassium 2-methoxy-2-oxoacetate ([$^{14}$C]-3)*

Unlabeled dimethyl oxalate (0.397 g, 3.36 mmol), carbon-14 labeled dimethyl oxalate ([$^{14}$C]-2, 0.404 g, 3.36 mmol, 150 mCi from ViTrax) (total dimethyl oxalate (hot+cold) (0.794 g, 6.72 mmol)), water (2.9 mL) and potassium hydrogen carbonate (0.67 g, 6.72 mmol) were added to a 10 mL flask.[17] The suspension was heated at 45°C for 16 h. The white suspension slowly turned into a clear solution. The reaction was monitored by HPLC (method A) and judged to be complete. The clear solution was partially concentrated (to about 1 mL) under reduced pressure and then diluted with acetone (8 mL). A white precipitate formed. The suspension was stirred at room temperature for 1 h. The solid was isolated by filtration, washed with acetone (2 mL) and vacuum dried for 19 h to give 0.925 g (97% chemical yield) of carbon-14 labeled potassium 2-methoxy-2-oxoacetate ([$^{14}$C]-3). The product was analyzed by: HPLC, method A, the material was not observed by UV, β-Ram detector 99.1% pure, RT 3.0 min; $^1$H NMR (400 MHz, DMSO-$d_6$) δ ppm 3.47 (s, 3 H). The specific activity was measured and determined to be 162.90 μCi/mg, 23.16 mCi/mmol, total activity 150.8 mCi (100% radiochemical yield).

*[$^{14}$C]-Methyl 2-chloro-2-oxoacetate ([$^{14}$C]-1)*

Unlabeled potassium 2-methoxy-2-oxoacetate (0.142 g, 1.00 mmol), carbon-14 labeled potassium 2-methoxy-2-oxoacetate ([$^{14}$C]-3,




**Scheme 2.** Use of carbon-14 labeled methyl 2-chloro-2-oxoacetate (**[$^{14}$C]-1**) as an oxalyl chloride equivalent.

0.142 g, 1.00 mmol, 162.90 μCi/mg, 23.16 mCi) (total potassium 2-methoxy-2-oxoacetate (hot+cold) (0.284 g, 2.00 mmol)) and dichloromethane (2.9 mL) were added to a round-bottomed flask.[17] Oxalyl chloride (0.19 mL, 2.20 mmol) was then added dropwise (Caution! Gas was evolved.). The addition was slow enough to maintain a gentle bubbling of gas from the solution. Finally, DMF (0.015 mL, 0.200 mmol) was added dropwise. Once again the addition was slow enough to maintain a gentle bubbling of gas from the solution. The reaction was stirred for 2 h at room temperature under argon. During that time the white suspension turned into a cloudy yellow solution. A small aliquot was quenched with methanol, allowed to stand for 5 min and monitored by HPLC. The reaction was determined to be complete by looking for the formation of dimethyl oxalate (**[$^{14}$C]-2**, HPLC method A, the material was not observed by UV, β-Ram detector 98.9% pure, RT 11.3 min) and the disappearance of potassium 2-methoxy-2-oxoacetate (**[$^{14}$C]-3**, HPLC method A, the material was not observed by UV, β-Ram detector, RT 3.0 min). Based on the analysis of the methanol aliquot, it was estimated that [$^{14}$C]-methyl 2-chloro-2-oxoacetate (**[$^{14}$C]-1**) was formed in a quantitative yield (assume 2.00 mmol in 2.9 mL of dichloromethane). The solution containing **[$^{14}$C]-1** was used as is in the next reaction.

*[$^{14}$C]-(S)-Methyl 2-((cyanomethyl)(1-cyclopropyl-2-methoxyethyl)amino)-2-oxoacetate (**[$^{14}$C]-5**)*

Dichloromethane (1.8 mL), (*S*)-2-(1-cyclopropyl-2-methoxyethylamino)acetonitrile (**4**, 0.308 g, 2.00 mmol) and *N*,*N*-diisopropylethylamine (0.87 mL, 5.00 mmol) were added to a vial. This mixture was added dropwise to the solution of **[$^{14}$C]-1** (assume 2.00 mmol in 2.9 mL of dichloromethane) prepared above. The brown solution was stirred for 1 h at room temperature under argon. At that time the reaction was monitored by HPLC (method A) and judged to be complete. The brown solution was diluted with water (10 mL). The aqueous solution was extracted with dichloromethane (4 × 10 mL). The organic solutions were combined, concentrated and vacuum dried for 17 h to give 0.551 g of brown oil. The crude oil was purified by column chromatography (silica, 1:1 hexanes/ethyl acetate). The fractions that contained the desired product were combined and concentrated to give 0.406 g (84% yield for the two steps) of [$^{14}$C]-(*S*)-methyl 2-((cyanomethyl)(1-cyclopropyl-2-methoxyethyl)amino)-2-oxoacetate (**[$^{14}$C]-5**) as a slightly yellow oil. The progress of the column purification was monitored by TLC: product $R_f = 0.50$ using 1:1 hexanes/ethyl acetate. The product was analyzed by HPLC, method A, UV detector 215 nm 94.6% pure, RT 16.4 min, β-Ram detector 96.6% pure;$^1$H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 0.34–0.51 (m, 2H), 0.62–0.84 (m, 2H), 1.08–1.34 (m, 1H), 3.07–3.17 (m, 0.75H), 3.35 (s, 3H), 3.56–3.76 (m, 2.25H), 3.84 (s, 2.25H), 3.93 (s, 0.75H), 4.42 (d, $J = 1.76$ Hz, 1.5H), 4.47–4.63 (m, 0.5H). The specific activity was measured and determined to be 46.62 μCi/mg, 11.20 mCi/mmol, total activity 18.91 mCi (82% radiochemical yield for the two steps).

*[$^{14}$C]-(S)-2-((Cyanomethyl)(1-cyclopropyl-2-methoxyethyl)amino)-2-oxoacetic acid (**[$^{14}$C]-6**)*

Methanol (7.0 mL), [$^{14}$C]-(*S*)-methyl 2-((cyanomethyl)(1-cyclopropyl-2-methoxyethyl)amino)-2-oxoacetate (**[$^{14}$C]-5**, 0.406 g, 1.66 mmol, 46.62 μCi/mg, 11.20 mCi/mmol, 18.91 mCi) and aqueous potassium hydrogen carbonate (0.5 M in water, 10.15 mL, 5.06 mmol) were added to a round-bottomed flask. The solution was heated to 45°C and stirred for 18 h under argon. At that time the reaction was monitored by HPLC (method A) and judged to be complete. The yellow solution was partially concentrated under reduced pressure to remove methanol. The pH of the aqueous solution was adjusted to approximately 2 with 1.0 N hydrochloric acid. The aqueous solution was concentrated under reduced pressure and vacuum dried for 5 h. The off-white solid was diluted with dichloromethane (30 mL) and filtered to remove inorganic salts. The dichloromethane solution was concentrated under reduced pressure and the off-white solid that remained was vacuum dried for 3 h to give 0.414 g (assume quantitative yield) of [$^{14}$C]-(*S*)-2-((cyanomethyl)(1-cyclopropyl-2-methoxyethyl)amino)-2-oxoacetic acid (**[$^{14}$C]-6**). The product was analyzed by HPLC, method A, UV detector 215 nm 94.6% pure, RT 13.1 min, β-Ram detector 94.3% pure;$^1$H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 0.31–0.73 (m, 4H), 1.01–1.15 (m, 1H), 3.32 (s, 1H), 3.35 (s, 2H), 3.43–3.80 (m, 3H), 4.34 (s, 1.3H), 4.61 (s, 0.7H).

*[$^{14}$C]-(S)-3,5-Dichloro-1-(1-cyclopropyl-2-methoxyethyl)pyrazin-2(1H)-one (**[$^{14}$C]-7**)*

Dichloromethane (2.4 mL), THF (2.4 mL), [$^{14}$C]-(*S*)-2-((cyanomethyl)(1-cyclopropyl-2-methoxyethyl)amino)-2-oxoacetic acid (**[$^{14}$C]-6**, 0.414 g, 1.80 mmol), oxalyl chloride (0.63 mL, 7.18 mmol)

and DMF (7.0 μL, 0.09 mmol) were added to a round-bottomed flask. Gas was evolved and the solution changed from clear to slightly yellow. After stirring for 30 min at room temperature the reaction was capped to prevent loss of HCl gas and then it was stirred for 22 h at room temperature. At that time the reaction was monitored by HPLC (method A) and judged to be complete. The orange solution was slowly quenched with the dropwise addition of water (20 mL). The aqueous solution was extracted with dichloromethane (4 × 15 mL). The organic solutions were combined and concentrated under reduced pressure. The yellow solid that remained was vacuum dried for 1 h to yield 0.462 g of crude product. The crude material was purified by column chromatography (silica, 3:1 hexanes/ethyl acetate). The fractions that contained the desired product were combined, concentrated and vacuum dried for 2 h to give 0.331 g (69% yield for the two steps) of [$^{14}$C]-(*S*)-3,5-dichloro-1-(1-cyclopropyl-2-methoxyethyl)-pyrazin-2(1H)-one (**[$^{14}$C]-7**) as a white solid. The progress of the column purification was monitored by TLC: product $R_f$ = 0.37 using 3:1 hexanes/ethyl acetate. The product was analyzed by HPLC, method A, UV detector 215 nm 99.1% pure, RT 18.1 min, β-Ram detector 99.2% pure, the material gave one peak when co-injected with an authentic sample of unlabeled 7;$^1$H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 0.25–0.34 (m, 1H), 0.48–0.56 (m, 1H), 0.59–0.68 (m, 1H), 0.75–0.85 (m, 1H), 1.34–1.45 (m, 1H), 3.33 (s, 3H), 3.59–3.66 (m, 1H), 3.69–3.76 (m, 1H), 4.06–4.14 (m, 1H), 7.55 (s, 1H), the spectrum was identical to an authentic sample of unlabeled 7. The specific activity was measured and determined to be 42.19 μCi/mg, 11.10 mCi/mmol, total activity 3.95 mCi (74% radiochemical yield for the two steps).

## Conclusion

The preparation of **[$^{14}$C]-1** required two steps from a common commercial precursor, carbon-14 labeled dimethyl oxalate. The overall radiochemical yield of **[$^{14}$C]-1** was essentially quantitative and the radiochemical purity was 99%. When comparing the synthesis and the use of carbon-14 labeled oxalyl chloride as a two-carbon building block, **[$^{14}$C]-1** has several advantages. Most significantly, **[$^{14}$C]-1** can be consistently prepared with high specific activity, radiochemical yield and radiochemical purity, and is stable over a longer period of time. In addition, the conversion of carbon-14 labeled dimethyl oxalate to **[$^{14}$C]-1** can be accomplished with minimal purification and manipulation, such as vacuum distillation. Synthetically, the multi-step route also increases the usefulness of the carbon-14 labeled oxalyl building block by accommodating nonequivalent substitution of the oxalyl system.

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