

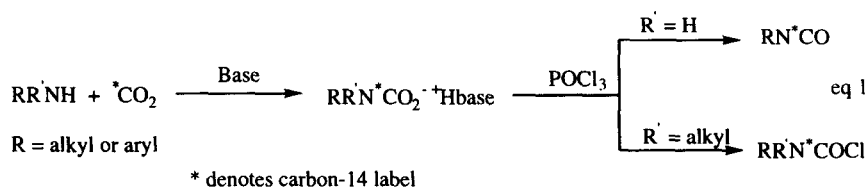
Efficient Utilization of [¹⁴C]Carbon Dioxide as a Phosgene Equivalent for Labeled Synthesis

Dennis C. Dean*, Michael A. Wallace, Tina M. Marks and David G. Melillo

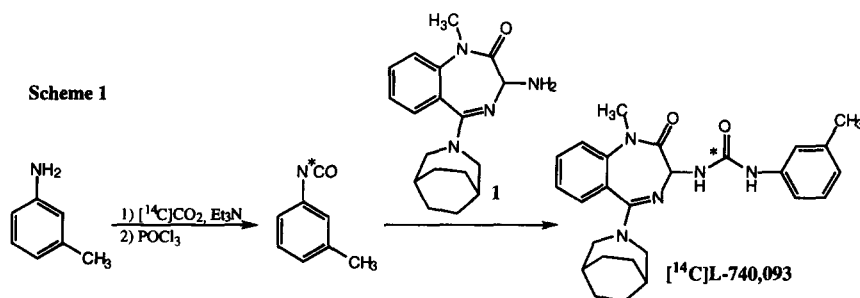
Merck Research Laboratories, P.O. Box 2000, Rahway, NJ 07065

Abstract: Addition of one equivalent [¹⁴C]carbon dioxide to primary or secondary amines in the presence of ternary base, followed by reaction of the resulting [¹⁴C]carbamate salt with phosphorus oxychloride or thionyl chloride, represents a cost effective alternative to labeled phosgene. © 1997, Elsevier Science Ltd. All rights reserved.

The incorporation of isotopic carbon into molecules of biological interest using labeled phosgene permits rapid access to a variety of useful intermediates such as isocyanates, carbamates, and carbamyl chlorides.¹ However, in the case of radioactive [¹⁴C]phosgene, inconvenient preparation², high commercial price³, limited radiochemical stability⁴, and the need to often use a large excess of labeled reagent to minimize amine dimerization combine to detract from its widespread utility. An alternative method which directly employs [¹⁴C]carbon dioxide would eliminate these problems. While several methods have been reported for reacting amines with carbon dioxide to form carbamate salts⁵ which are then converted to ureas or carbamates, these procedures lack both generality and appropriate reaction conditions to function as practical alternatives. A notable exception has recently been described by McGhee and coworkers involving carbamate salt formation by bubbling excess carbon dioxide through a solution of a suitable amine and strong organic base⁶. Dehydration (1° amines)^{6c} or chlorination (2° amines)^{6c} to form isocyanates and carbamyl chlorides, respectively, can then be readily effected using reagents such as phosphorus oxychloride. This methodology appeared potentially useful for isotopic synthesis if labeled carbon dioxide could be introduced and reacted as a limiting reagent. Additionally, it was unclear if more electron deficient amines, such as anilines, could be used in this process. Herein, we report that readily available [¹⁴C]carbon dioxide can be used effectively in this sequence as a general substitute for [¹⁴C]phosgene for reaction with a wide variety of alkyl and aromatic amines (eq. 1).



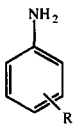
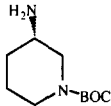

As a first example, we investigated the formation of *m*-tolyl [^{14}C]isocyanate, a key intermediate in the synthesis of labeled CCK_B antagonist L-740,093⁷ (Scheme 1). Addition of one equivalent of [^{14}C]carbon dioxide (generated by fusing barium [^{14}C]carbonate and lead chloride⁸) to a solution of *m*-toluidine and excess triethylamine in dichloromethane at $-78\text{ }^\circ\text{C}$, followed by warming to $-20\text{ }^\circ\text{C}$ and treatment with an equivalent of phosphorous oxychloride, produced *m*-tolyl [^{14}C]isocyanate in 80% yield. Subsequent addition of amine **1** provided [^{14}C]L-740,093 in an overall yield of 70% based on [^{14}C]carbon dioxide. An earlier synthesis of this tracer using [^{14}C]phosgene had proceeded in an overall radiochemical yield of only 25% as a result of extensive dimerization of *m*-toluidine to form symmetrical urea byproduct.



In order to determine the generality of the procedure, and assess the effect of amine basicity on isocyanate formation, a representative panel of primary amines were subjected to the [^{14}C]carbonation/dehydration protocol (Table 1, Entries 1-8). Aniline, *m*-toluidine, and 4-haloanilines (Entries 1-4) all provided good yields of isocyanate using standard conditions. Not surprisingly, anilines substituted with strongly electron withdrawing substituents (Entries 5,6) provided much lower isocyanate yields due to inefficient trapping of carbon dioxide.⁹ In the case of methyl 4-aminobenzoate (Entry 5), this effect could be partially overcome by the use of *N*-dicyclohexyl-*N*',*N*',*N*'',*N*'''-tetramethyl guanidine (CyTMG) and pyridine in place of triethylamine. This base combination has been employed previously to provide additional stabilization of carbamate salts.^{6c} The yield of aliphatic hexyl isocyanate¹⁰ (Entry 7) also benefited from the use of highly polarizable CyTMG base which decreased symmetrical urea formation.

In a similar manner, [^{14}C]carbaryl chlorides could be obtained in useful, albeit low, radiochemical yield (Table 1, Entries 9-11) using CyTMG and one equivalent of [^{14}C]CO₂. The reason for the lower yields of carbaryl chlorides utilizing one equivalent carbon dioxide is not understood at this point.

Table 1. Formation of [^{14}C]isocyanates and carbamyl chlorides using [^{14}C]CO $_2$.

Entry	Amine	Procedure ^a	Isocyanate yield ^b	Entry	Amine	Procedure ^a	Isocyanate yield ^b
							
1	R = H	A	85%	7	CH ₃ (CH ₂) ₅ NH ₂	A B	52% 75%
2	R = 3 - Me	A	80%	8		A	45%
3	R = 4 - Br	A	87%				
4	R = 4 - F	A	85%				
5	R = 4 - CO ₂ Me	A B	10% 35%				
6	R = 4 - NO ₂	A B	0% 0%				
				9	(CH ₃ CH ₂ CH ₂) ₂ NH	B	35%
				10		B	20%
				11	PhNH(CH ₃)	B	23%

^a Procedure A: Reactions were carried out at -20 °C using 1 mmol of amine, 1.1 eq. [^{14}C]CO $_2$ and 5 eq. Et₃N in dichloromethane, followed by addition of 1.05 eq. of POCl₃. Procedure B: Same as Procedure A except 1 eq. of N-cyclohexyl-N',N'',N'''-tetramethylguanidine and 1 eq. of pyridine were used in place of triethylamine and thionyl chloride was used as dehydrating agent. ^b Yields were determined by liquid scintillation counting of crude isocyanate or carbamyl chloride solution for quantitation of total radioactivity in conjunction with HPLC radiochromatographic analysis the isocyanate or of the corresponding N',N'-diethylurea prepared by quenching crude isocyanate into a large excess of diethylamine. Retention times of isocyanates and ureas were established using unlabeled reference.

In conclusion, the use of stoichiometric amounts of labeled carbon dioxide under the McGhee protocol represents a cost effective, convenient alternative to labeled phosgene for the preparation of most isocyanates and carbamyl chlorides. Although illustrated here using [^{14}C]CO $_2$, this process should be of general utility for other radioactive and stable isotopes of carbon and oxygen¹¹ where similar problems with labeled phosgene exist. Additional applications of this methodology for labeled synthesis and further optimization of reaction conditions are under investigation.

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References and Notes

- For recent examples see (a) Haynes, U.J.; Swigor, J.E.; Kaneko, T. *J. Labelled Compd. Radiopharm.* **1990**, 28, 241. (b) Neena, A.; Agawal, V.K.; Satyavan, S.; Srivastava, V.M. *Pharmazie* **1987**, 42, 332. (c) Etzel, W.A.; Berger, S. *J. Labelled Compd. Radiopharm.* **1990**, 28, 977. (d) Mirko, M.; Farrokhzad, S.; Yamamoto, L.; Feindel, W. *J. Nucl. Med.* **1982**, 23, 895. (e) Conway, T.; Diksic, M. *Appl. Radiat. Isot.* **1991**, 42, 441.

2. [^{14}C]Phosgene is typically prepared from [^{14}C]carbon monoxide, obtained by initial reduction of [^{14}C]carbon dioxide, through Toepler pump transfer into a vessel of frozen chlorine gas followed by irradiation with high intensity visible light: see Murry, A.; Williams, D.L. *Organic Synthesis with Isotopes*, Interscience Publishers, New York, pp.585-587, 1958.
3. Americal Radiolabeled Chemicals, Inc. pricing: [^{14}C]phosgene - 1 mCi for \$1000 vs. barium [^{14}C]carbonate - 1 mCi for \$74.
4. Although quantitative stability data for [^{14}C]phosgene has not been determined, we have found the usable shelf-life as a toluene solution or as a gas at high specific activity to be limited to 1-2 months when stored at $-20\text{ }^{\circ}\text{C}$.
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8. Zwiebel, N.; Turkevich, J.; Miller, W.W. *J. Am. Chem. Soc.* **1949**, *71*, 376.
9. Preparation of isocyanates from electron deficient anilines can be accomplished by employing a large excess of phosgene. For the synthesis of p-nitrophenyl isocyanate see Shriner, R.L.; Horne, W.H.; Cox, R.F.B. *Org. Synth., Coll. Vol. II*, 453.
10. **Typical procedure: Preparation of hexyl [^{14}C]isocyanate (Entry 7, procedure B).**
 To a glass tube containing a 14/20 ground glass joint was placed barium [^{14}C]carbonate (84 mg, 0.424 mmol, 4 mCi) and lead(II) chloride (960 mg, 4.24 mmol). The tube was attached to a vacuum manifold to which was also attached a flask containing a mixture of hexylamine (43 mg, 0.424 mmol), N-dicyclohexyl-N',N'',N''',N'''-tetramethyl guanidine (85 mg, 0.424 mmol), and pyridine (33 mg, 0.424 mmol) in 3 mL of toluene. The toluene solution was frozen with liquid nitrogen, the system evacuated to ~ 0.5 torr, and [^{14}C]CO₂ generated by heating the solid mixture with a Bunsen burner for 5 min. The reaction flask was sealed off and allowed to warm to $-20\text{ }^{\circ}\text{C}$ and aged for 30 min. The solution was recooled to $-78\text{ }^{\circ}\text{C}$ and a solution of thionyl chloride (53 mg, 0.445 mmol) in 0.3 mL of toluene was added. The mixture was stirred for 20 min. at $-20\text{ }^{\circ}\text{C}$ and 1 h at room temperature. The toluene solution was found to contain 3.1 mCi (77% recovery) of radioactivity by liquid scintillation counting. HPLC analysis (Zorbax SB-C8 column, linear gradient of 30-100% acetonitrile / 0.1% aqueous phosphoric acid over 25 min, 1 mL/min, UV at 220 nm and Packard 525 flow monitor radioactivity detector) indicated the hexyl [^{14}C]isocyanate had a radiochemical purity of 95% (overall yield = 73%). This solution was used directly in subsequent transformations.
11. For example, unlike, [^{18}O]phosgene is commercially unavailable and very inconvenient to prepare, whereas [^{18}O]CO₂ is readily available.

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