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Synthesis of Sodium Formate-^{13}C and Oxalic Acid-$^{13}C_2$

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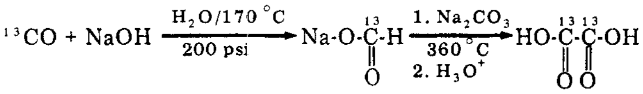
Compounds labeled with stable isotopes such as D, ^{13}C, ^{15}N, or ^{18}O have recently been shown[1,2] to be very useful for the diagnosis of diseased states in man because they lack the potential danger of their radioactive analogues, are not toxic at moderate levels in the body, and are easily identified in labeled molecules by mass spectrometry. Our research program required large amounts of oxalic acid-$^{13}C_2$ (1) for incorporation studies involving compounds of biological interest to be used in the production of $^{13}CO_2$ for breath tests.[3]

A review of the literature concerning suitable laboratory preparations of oxalic acid revealed only two convenient methods for the incorporation of a double $^{13}C_2$ label: (1) the reductive coupling of CO_2 over molten sodium or potassium,[4,5] which proved to be unsuitable because of low yields (10– 17%), and (2) the pyrolysis of sodium formate.[6,7] Preliminary experiments with nonlabeled sodium formate, pyrolyzed to 360 °C, produced only a trace of oxalic acid,[8] and generated considerable amounts of sodium carbonate. However, the yield of oxalic acid was increased substantially by the pyrolysis of sodium formate with a 2-molar equivalence of sodium carbonate. The excess sodium carbonate appeared to keep the desired oxalic acid from deteriorating to carbonate at elevated temperatures.



$$\mathrm{^{13}CO + NaOH \xrightarrow[200\ psi]{H_2O/170\ ^\circ C} Na\text{-}O\text{-}\overset{13}{\underset{\underset{O}{\|}}{C}}\text{-}H \xrightarrow[\substack{360\ ^\circ C\\ 2.\ H_3O^+}]{1.\ Na_2CO_3} HO\text{-}\overset{13}{\underset{\underset{O}{\|}}{C}}\text{-}\overset{13}{\underset{\underset{O}{\|}}{C}}\text{-}OH}$$

2 1

In the first effort to prepare the precursor sodium formate-^{13}C, it was found that a stirred solution of sodium hydroxide under CO at 1 atm showed little uptake of the gas. However, when the CO was charged into a reaction bomb under pressure, over a stirred solution of hot sodium hydroxide, the gas was quantitatively consumed. Reaction with 90% ^{13}CO under these experimental conditions resulted in >99% yield of ^{13}C-labeled sodium formate. Pyrolysis of this sodium formate-^{13}C at 360 °C for 30 min, while intimately mixed with a molar excess of sodium carbonate, resulted in the formation of oxalic acid-$^{13}C_2$ in >90% overall yields.

This synthesis is a convenient, inexpensive, and high-yield procedure for the preparation of a new two-carbon, $^{13}C_2$-labeled molecule. Oxalic acid-$^{13}C_2$ is now readily available as a reactive precursor for labeling experiments with larger molecules.

Experimental Section

Sodium Formate-^{13}C (2). Into a 300-mL Parr pressure bomb were placed 6.0 g (0.15 mol) of sodium hydroxide, 20 mL of water, and a stirring bar. The apparatus was sealed and a tank of 90% ^{13}CO (Stohler Isotope Chemicals, Inc.) attached utilizing minimum dead volume connections. After evacuation of the trapped air, the reaction bomb was charged at 200 psi with 0.15 mol (3.3 L) of 90% ^{13}CO, heated to 170 °C, and stirred for 12 h. During that time the pressure slowly rose to 400 psi and finally dropped to 40 psi. After 12 h the bomb was cooled to reveal only a very slight pressure. The bomb was opened, the solution removed and transferred by pipet, and the water rotary evaporated away to yield 10.2 g (99% yield) of sodium formate-^{13}C: mp 250–252 °C; IR (KBr) 2810 and 2715 ($^{13}HC{=}O$), 1550 and 1365 ($^{13}CO_2Na$), 1317 and 763 cm^{-1}.

Oxalic Acid-$^{13}C_2$ (1). The above 10.2 g (0.15 mol) of sodium formate-^{13}C was intimately ground with 31.8 g (0.30 mol) of Na_2CO_3 and placed in an open-ended glass tube. The tube and contents were pyrolyzed in a pyrolysis oven to 360 °C over a period of 30 min. After cooling, the contents of the tube were transferred to a 500-mL beaker with a minimum amount of water. Concentrated HCl was added to reach a pH 1.0. Crystals of oxalic acid were filtered off (5.1 g) and the mother liquor evaporated to dryness. The residue of sodium chloride and product was sublimed under vacuum ($\approx 7 \times 10^{-2}$ Torr) at 200 °C for 2 h to yield another 1.2 g of pure oxalic acid-$^{13}C_2$.[9] Total yield[10] was 6.3 g (93.3%) of oxalic acid-$^{13}C_2$: mp 99–100 °C dec; IR (KBr) 3425 and 3280 ($^{13}CO_2H$), 1120 and 715 cm^{-1}; mass spectrum *m/e* (rel intensity)[11] 92 (M^+, 0.06), 58 (3), 47 (50), 46 (100), 45 (22), and 30 (21).

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Registry No.—**1**, 62654-02-8; **2**, 23102-86-5; sodium hydroxide, 1310-73-2; ^{13}CO, 1641-69-6.

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(8) Yields were monitored by titrating reaction solutions with 0.001 M $KMnO_4$ until a red color persisted [*Chem. Abstr.*, **9**, 2043 (1915)] and by classical color reactions for oxalic acid [L. H. Chernoff, *J. Am. Chem. Soc.*, **42**, 1784 (1920)] using resorcinol and H_2SO_4.
(9) Sublimation at 105 °C under vacuum for 12 h yielded 1.4 g of oxalic acid on a duplicate run (total yield 6.5 g, 96%). Additional labeled material was separated from the NaCl crystal lattice by dissolving in water, rotary evaporation, and repeating sublimation.
(10) The labeled and nonlabeled oxalic acid gave satisfactory spectroscopic properties (IR and MS) when compared to each other and authentic oxalic acid.
(11) Mass spectral analyses were performed using a 70-eV Du Pont 490-F mass spectrometer. Samples were probe distilled directly into the ion source of the mass spectrometer.

Photoreduction of Bridgehead Halides with Organotin Hydride

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Dissolving metals reduce strained bridgehead halides.[1] The yields in these reactions are generally satisfactory only when