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

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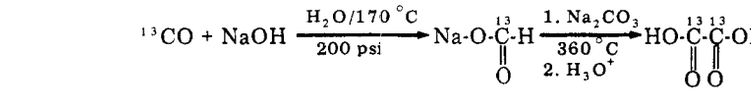
Compounds labeled with stable isotopes such as D, ^{13}C, ^{15}N, or ^{18}O have recently been shown[1,2] to be very useful for the diagnosis of diseased states in man because they lack the potential danger of their radioactive analogues, are not toxic at moderate levels in the body, and are easily identified 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 ex-



periments 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.

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).

Acknowledgments. The author gratefully acknowledges the support of the Cottrell Research Starter Grant, administered by Research Corporation, and the generous gift of the labeled carbon monoxide by Stohler Isotope Chemicals, Inc. The author also is indebted to Dr. Donald Chichester for his help in editing this manuscript.

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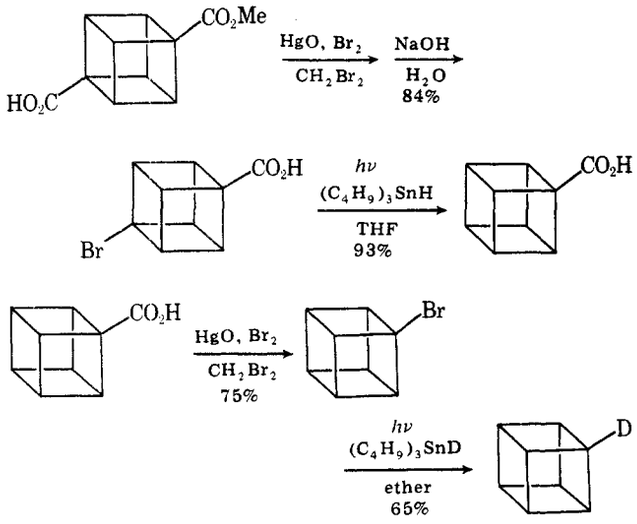
Dissolving metals reduce strained bridgehead halides.[1] The yields in these reactions are generally satisfactory only when

the product is a strong carbon acid.[2] Thus, the poor yield in the reduction of bromohomocubane, 16–34%, by this method is not surprising.[3] Organotin hydrides also reduce alkyl halides to the corresponding hydrocarbons.[4] To illustrate, 1-bromoadamantane is readily converted to adamantane in excellent yield.[1] However, the reduction of more strained halides proceeds less easily. Thus, 1-bromonorborane is reduced to norborane in 10–20% yield.[5] Recently, the reduction of aromatic halogen compounds by tin hydride was reported to be catalyzed by ultraviolet light.[6] The yields were excellent. We have extended this reaction for the reduction of bridgehead bromides. Our results are summarized in Table I.

These results indicate that the photocatalyzed tin hydride reaction provides a convenient method for the reduction of bridgehead bromides. In particular, this method affords an improved route for the preparation of monosubstituted cubanes from cubanedicarboxylic acid.[7,8] The monodeuterio compound was synthesized in this way.



This photochemical process was not as effective with bridgehead chlorides. 1-Chloroadamantane gave only 25% adamantane in 4 h.

Experimental Section[9]

Tri-*n*-butyltin Hydride. Tri-*n*-butyltin hydride [bp 98.5–99 °C (3.5 mm)] was prepared by the method of van der Kerk, Noltes, and Liujten.[10] The corresponding deuterium compound was prepared by the method of Tamborski, Ford, and Soloski in 23% yield.[11]

Reduction of 1-Bromoadamantane. A solution of bromoadamantane (1.075 g, 0.005 mol) and tri-*n*-butyltin hydride (2.0 g, 0.0069 mol) in hexane (50 mL) was irradiated with a low-pressure mercury lamp (15 W, λ_{max} 254 nm, TNN 15/32 quartz lamp) at 0 °C under a nitrogen atmosphere for 2 h. Gas chromatographic analysis indicated 100% conversion of the bromide to adamantane.

Reduction of 1-Chloroadamantane. A solution of 1-chloroadamantane (855 mg, 5 mmol) and tri-*n*-butyltin hydride (2.0 g, 6.9 mmol) in hexane (50 mL) was irradiated as described previously. The reaction was only 20% complete as shown by gas chromatography. The reaction mixture was then further irradiated for 2 h. The reduction to adamantane was then 25% complete. The remaining 75% was unreacted 1-chloroadamantane.

Reduction of 4-Phenyl-1-bromobicyclo[2.2.2]octane. A solution of 4-phenyl-1-bromobicyclo[2.2.2]octane (663 mg, 2.5 mmol) and tri-*n*-butyltin hydride (1 g, 3.45 mmol) in ether (50 mL) was irradiated as described previously. Gas chromatography revealed a quantitative transformation to the hydrocarbon. The solution was evaporated to dryness in vacuo. The residue was chromatographed on acid-washed alumina (100 g, eluent hexane) to yield a colorless solid. Sublimation gave pure 1-phenylbicyclo[2.2.2]octane (4.17 mg, 90%, mp 83–84 °C, lit.[12] 78–80 °C).

Reduction of 1-Bromo-9,10-dihydro-9,10-ethanoanthracene. A solution of the bromide (570 mg, 2 mmol) and tri-*n*-butyltin hydride (725 mg, 2.5 mmol) in ether (50 mL) was irradiated as described previously. Gas chromatography revealed a quantitative transformation to the corresponding hydrocarbon. The solution was evaporated in vacuo and the residue was chromatographed on acid washed alumina (100 g, eluent hexane) to yield a solid residue which was recrystallized from methanol to afford the pure hydrocarbon (390 mg, 95%, mp 205–207 °C, lit.[13] 206–207 °C).

Table I. Reduction of Bridgehead Bromides with Tri-*n*-butyltin Hydride

Registry no.	Compd	Solvent	Time, h	Yield, %
768-90-1	1-Bromoadamantane	Hexane	2	100[a]
714-68-1	4-Phenyl-1-bromobicyclo[2.2.2]octane	Hexane	2	90[b]
62707-85-1	1-Bromo-9,10-dihydro-9,10-ethanoanthracene	Ether	2	95[b]
13474-70-9	1-Bromonorborane	Ether	2	68[b] (85[a])
37794-29-9	4-Bromocubanecarboxylic acid	THF	4	93[b]
59346-69-9	Bromocubane[c]	Ether	6	65[d]

[a] By VPC. [b] Isolated. [c] Reaction with tri-*n*-butyltin deuteride. [d] Isolated after two sublimations.

Reduction of 1-Bromobicyclo[2.2.1]heptane. A solution of the bromide (350 mg, 2 mmol) and tri-*n*-butyltin hydride (725 mg, 2.5 mmol) in ether (50 mL) was irradiated as described previously. Gas chromatography showed that the reaction was 85% complete. The solvent was removed in vacuo and the residue was chromatographed on acid-washed alumina (60 g, eluent benzene) to provide a white solid which was sublimed to yield pure norborane (130 mg, 68%, mp 86–87 °C, lit.[14] 86–87 °C).

4-Bromocubanecarboxylic Acid. 4-Carbomethoxycubanecarboxylic acid (3.6 g, 17.4 mmol) and red mercuric oxide (3.7 g, 17.4 mmol) in dibromomethane (100 mL) were stirred and warmed to 75 °C in a flask protected from light. A solution of bromine (4.8 g, 30 mmol) in dibromomethane (30 mL) was added dropwise. Heating (75 °C) was continued for 2 h, during which time all of the mercuric oxide dissolved. The solvent was removed in vacuo. The residue was triturated several times with hexane. The hexane extract (500 mL) was evaporated to yield crude methyl 4-bromocubanecarboxylate. This crude ester was refluxed in aqueous sodium hydroxide (10%, 60 mL) for 2 h. The solution which resulted washed with chloroform [the residual ester (0.15 g) was extracted] and then acidified carefully with hydrochloric acid. The neutralized solution was extracted with ether. The organic layer was washed with brine, dried over sodium sulfate, decolorized with Norite, and evaporated to dryness to give 4-bromocubanecarboxylic acid which was recrystallized from methylene chloride–carbon tetrachloride to give a pure product (3.3 g, 84%, mp 210 °C dec, lit.[15] 210 °C dec).

Cubanecarboxylic Acid. A solution of 4-bromocubanecarboxylic acid (3.2 g, 14.1 mmol) and tri-*n*-butyltin hydride (5.5 g, 18.9 mmol) in tetrahydrofuran (200 mL) was irradiated as described previously for 4 h. The solvent was then removed in vacuo and the residue was taken up into ether (100 mL). The ethereal solution was extracted with aqueous sodium hydroxide (10%, 150 mL). The base solution was first washed with ether, neutralized with hydrochloric acid, and extracted again with ether. The latter ethereal layer was dried over sodium sulfate, treated with Norite, and filtered. Removal of solvent in vacuo gave cubanecarboxylic acid (1.85 g, 93%, mp 125–126 °C, lit.[8b] 125–126 °C).

Bromocubane. A mixture of cubanecarboxylic acid (888 mg, 6 mmol) and mercuric oxide (1.3 g, 6 mmol) in dibromomethane (20 mL) was warmed to 75 °C in the dark. Bromine (1.2 g, 7.5 mmol) in dibromomethane (5 mL) was added slowly. The mixture was stirred at 75 °C for 2 h. At this time all the mercuric oxide had dissolved and a clear orange solution was obtained. Dibromomethane was removed in vacuo and the residue was extracted with hexane. The hexane solution was passed through a short alumina column (20 g, eluent hexane). The solid obtained by evaporation was recrystallized from petroleum ether (30–60 °C) at −20 °C to give bromocubane (823 mg, 75%, mp 28–29 °C). The parent peaks in the mass spectrum occurred at *m/e* 183.9711, 181.9779. The base peak was at 103.0561. The NMR spectrum ($CDCl_3$) exhibited complex multiplet absorptions at δ 4.27 (m, 3 H) and 4.11 (m, 4 H).

Anal. Calcd for C_8H_7Br: C, 52.46; H, 3.82; Br, 43.72. Found: C, 52.61; H, 3.69; Br, 43.58.

Cubane-*d*. A mixture of bromocubane (823 mg, 4.5 mmol) and

tri-*n*-butyltin deuteride (2.33 g, 8 mmol) in ether (50 mL) was irradiated for 6 h. The solvent was carefully removed in vacuo at room temperature and the residue was distilled at 0.1 mm. The distillate was mixed with silica gel (1 g). This mixture was heated to sublime pure cubane-*d* (306 mg, 65%, mp 131–132 °C in sealed capillary, lit.[8b] 131–132 °C). The IR (KBr) spectrum exhibited absorptions at 3000, 2250, 1220, and 840 cm^{-1}. The low-resolution mass spectrum exhibited peaks at *m/e* 106 (7.5), 105 (65) 104 (100), and 103 (7.4).

Registry No.—Tri-*n*-butyltin hydride, 688-73-3; adamantane, 281-23-2; 1-chloroadamantane, 935-56-8; 1-phenylbicyclo[2.2.2]octane, 23062-62-6; 9,10-dihydro-9,10-ethanoanthracene, 5675-64-9; norborane, 279-23-2; methyl 4-bromocubanecarboxylate, 37794-28-8; cubanecarboxylic acid, 53578-15-7; tri-*n*-butyltin deuteride, 6180-99-0; cubane-*d*, 59346-73-5.

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Reaction of Arylsulfonylalkyl Arenesulfonates with Hydroxide Ion. Nucleophilic Displacement at Sulfonate Sulfur

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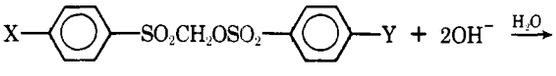
Recent studies have revealed that arylsulfonylmethyl arenesulfonates (1) react with sodium hydroxide in aqueous solution to yield sodium arenesulfinate, formaldehyde, and sodium arenesulfonate.[1] The reaction was thought to proceed



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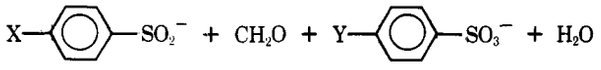


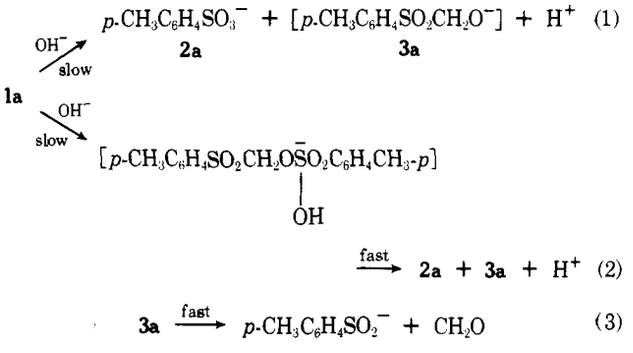
via a specific-base-catalyzed process involving rate-limiting decomposition of the corresponding α-sulfonyl carbanion. This mechanism, which is essentially different from that for the hydrolysis of arylsulfonylmethyl perchlorates[2a] and nitrates,[2b] was based on the following observations: (1) the absence of a measurable reaction with a series of nucleophiles (F^-, I^-, NO_2^-, and N_3^-) in methanol; (2) no enhanced reaction rates in 0.1 N NaOH upon addition of Br^- or F^- in concentrations as high as 0.1 M; (3) the solvent deuterium isotope effect [$k(OD^-)/k(OH^-)$ ca. 1.4]; and (4) fast CH/CD exchange at the α-sulfonyl carbon atom in 0.1 M NaOD in D_2O.

During the course of our investigation of microenvironmental effects on this reaction,[3] we obtained experimental data which cast considerable doubt on the correctness of the proposed mechanism. Therefore, we have investigated the mechanism in more detail and the results led us to propose that the sulfonates 1 preferentially undergo nucleophilic attack on sulfonate sulfur by hydroxide ion rather than hydrolyze via a specific-base-catalyzed process.

Results and Discussion

Reaction with ^{18}O-Enriched Hydroxide Ion. After reaction of 1a (X = Y = CH_3) in 50% (v/v) dioxane–water (at 67 °C) or in 33% (v/v) EtOH–H_2O (at 80 °C) containing 0.1 M NaOH and using ^{18}O-enriched water (1.5 atom % ^{18}O), the sodium *p*-toluenesulfonate formed was isolated as its *S*-benzylisothiouronium salt.[4] Mass spectrometric analysis of this product indicated that ^{18}O was incorporated in the sulfonate anion and the excess isotope abundance was in accord with exclusive S–O bond fission in the ^{18}O-labeled medium. The isotopic tracer did not appear in the starting material which was recovered before completion of the reaction. In a separate experiment it could also be shown[5] that under the same reaction conditions the *p*-toluenesulfonate anion does not exchange ^{16}O for ^{18}O. Therefore, we conclude that the ^{18}O-enriched *p*-toluenesulfonate anion is formed from either a one-step displacement of *p*-$CH_3C_6H_4SO_2CH_2O^-$ (3a) via attack of OH^- at the sulfonate sulfur atom of 1a (eq 1)[6] or via an addition–elimination type mechanism (eq 2) with rate-limiting attack by OH^- as the initial step (Scheme I). The

Scheme I



negative entropy of activation for the reaction ($\Delta S^{\ddagger} = -17$ eu for 1a)[1] is also consistent with a bimolecular rate-determining step. The *p*-tolylsulfonylmethoxide leaving group (3a) is known to decompose very rapidly into *p*-toluenesulfinate anion and formaldehyde (eq 3).[7]

These results clearly show the marked preference for nucleophilic attack at the sulfonate sulfur atom rather than C–O bond cleavage. This unusual situation is most compatible with the steric and field effects of the sulfonyl group[8] in the sulfonates 1 which will strongly hamper nucleophilic displacement at the α-sulfonyl carbon atom.[9]

Substituent Effects. Table I presents second-order rate constants (k_{OH^-}) for the reaction of four sulfonates *p*-$CH_3C_6H_4SO_2CH(R_1)OSO_2R_2$ (1a–d) with sodium hydroxide (0.3–2.0 M) in 33% (v/v) EtOH–H_2O at 47.4 °C and constant ionic strength (μ = 2.0 M). Most noticeable is the pronounced rate decrease by a factor of ca. 3×10^3 upon replacing R_2 = Me (1c) for R_2 = *t*-Bu (1d). Apparently, nucleophilic attack at the sulfonate sulfur atom of 1c is sterically hindered by the bulky