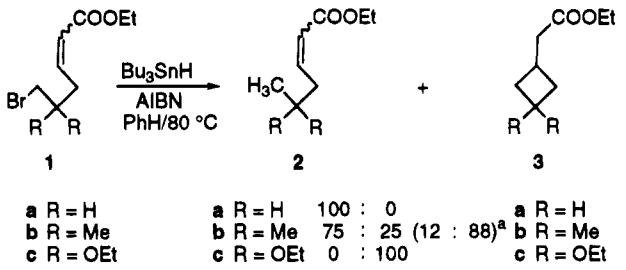
gem-Dialkoxy Effect in Radical Cyclizations To Form Cyclopropane Derivatives: Unusual Oxidation of a Dialkoxyalkyl Radical[1]

Michael E. Jung*,[2] and Mehrak Kiankarimi

Department of Chemistry and Biochemistry, University of California, Los Angeles, California 90024

Received May 2, 1995

Recently we published an example of the synthetic utility of the *gem*-dialkoxy effect for the efficient preparation of strained four-membered rings by radical cyclization.[3] As shown below, under similar conditions cyclization of the ethyl 6-bromo-2-hexenoates **1a–c** gave either the acyclic **2a–c** or cyclic **3a–c** products. The dihydrido substrate **1a** gave only the acyclic product **2a.** *gem*-dimethyl substitution, e.g., **1b**, increased the amount of cyclic product **3b** to 25% of the mixture under normal conditions and to nearly 90% under catalytic conditions. However, the diethoxy substrate **1c** cyclized completely under normal conditions to give only the cyclobutanone ketal **3c**, thus indicating the preparative power of the *gem*-dialkoxy effect.[4] We speculated that this *gem*-dialkoxy effect might also allow for the formation of

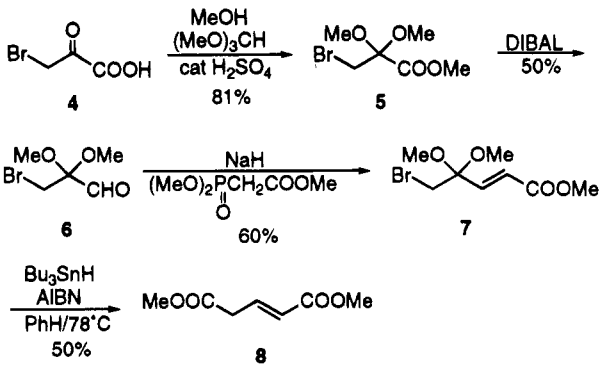


a) Catalytic hydride conditions (syringe pump addition of Bu_3SnH to reaction mixture)

cyclopropanone ketals. We now report the results of radical cyclizations of dialkoxy substituted systems aimed at forming cyclopropanone ketals, which afforded an unexpected product due to oxidation of the intermediate radical.

The substrate for the radical cyclization **7** was prepared as follows. Ketalization and esterification of commercially available bromopyruvic acid **4** afforded **5**.[5] Conversion to the known aldehyde **6**[5] and Horner–Emmons reaction afforded the desired methyl 5-bromo-4,4-dimethoxy-2-pentenoate (**7**). Treatment of this bromoalkene with tributylstannane under normal conditions (AIBN, PhH, 78 °C) afforded not the expected cyclopropane derivative but rather dimethyl glutaconate (**8**) in 50% isolated yield.

The most likely mechanism for this transformation is the following, shown in Scheme 1. Reaction of **7** with tributyltin hydride and AIBN would generate the expected radical **9** which would cyclize to give the cyclopropane **10**. Reduction of either of these species with the



stannane would produce the acyclic and cyclic products, **11** and **12**, respectively. However, the radical **10** can rearrange by β-bond scission to produce the more stable dialkoxyalkyl radical **13**, which on hydride reduction would give the dimethyl acetal **14**. Oxidation of the radical would afford the observed product **8**. Thus this reaction amounts to a substituted vinyl shift of the radical **9** driven by the higher stability of the α,α-dialkoxyalkyl radical **13** vs the β,β-dialkoxyalkyl radical **9**.[6]

There is some evidence for this mechanism. Conducting the reaction under high hydride concentrations (10 equiv of Bu_3SnH) furnished a 51% yield of the dimethyl acetal **14** with none of the diester **8**. Using intermediate amounts of hydride produced mixtures of **8** and **14**. The oxidizing agent is presumably adventitious oxygen in the solvent, although attempts to degas the benzene solution did not greatly diminish the amount of diester **8** formed. We have ruled out one other possibility, namely a radical-chain mechanism in which **13** would abstract bromine from **7** to give **9** and the α-bromo acetal which would lead to **8** with loss of methyl bromide. Since this process would be catalytic in hydride, we ran the reaction using only 10 mol % Bu_3SnH and obtained a 5–10% yield of the diester **8**, thereby showing that the reaction is not catalytic in hydride and thus eliminating that possible mechanism.

In summary we have observed an unusual oxidation of a dialkoxyalkyl radical, produced by a vinyl transfer, to give an ester in good yield.

Experimental Section

General. All temperatures are uncorrected and reactions were carried out under nitrogen with the exclusion of moisture. Benzene and toluene were distilled from CaH_2. Tetrahydrofuran (THF) was distilled from sodium/benzophenone ketyl radical. Chromatography was conducted on 230–400 mesh silica gel (SiO_2), using hexanes and ether as solvents. ^1H NMR spectra were recorded at 400 MHz and ^{13}C at 100 MHz in deuteriochloroform as solvent.

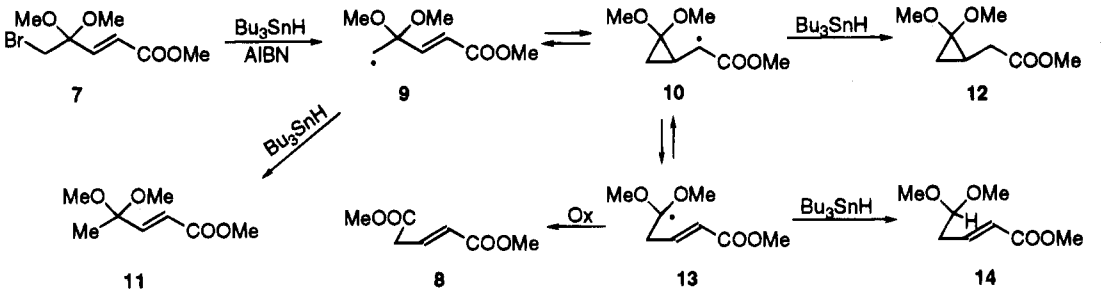
Methyl 3-bromo-2,2-dimethoxypropanoate (5). This ester was prepared from commercially available bromopyruvic acid by an application of the method of Chari and Kozarich and showed identical spectroscopic properties.[5]

3-Bromo-2,2-dimethoxypropanal (6). The bromo ester **5** (1.80 g, 7.93 mmol) was dissolved in anhydrous toluene (20 mL) and cooled to −78 °C . A solution of DIBAL (10.3 mL, 1.0 M in hexane) was added dropwise. Reaction mixture was stirred for 6 h at −78 °C and quenched with 1 N HCl (7 mL) followed by

(1) Presented at the 33rd GECO Conference, Corsica, France, September 1992.
(2) American Chemical Society Arthur C. Cope Scholar, 1995.
(3) Jung, M. E.; Trifunovich, I. D.; Lensen, N. *Tetrahedron Lett.* **1992**, *33*, 6719.
(4) For an earlier example of the *gem*-dialkoxy effect, see: Sternbach, D. D.; Rosanna, D. M.; Onan, K. D. *Tetrahedron Lett.* **1985**, *26*, 591.
(5) Chari, R. V. J.; Kozarich, J. W. *J. Org. Chem.* **1982**, *47*, 2355.
(6) (a) For similar vinyl transfers, see: Beckwith, A. L. J.; Ingold, K. U. In *Rearrangement in Ground and Excited States;* de Mayo, P.; Academic Press: New York, 1980; Vol. 1, p 161. (b) For conceptually similar formyl transfers, see: Jung, M. E.; Choe, S. W. T. *Tetrahedron Lett.* **1993**, *34*, 6247 and references therein.

0022-3263/95/1960-7013$09.00/0

Scheme 1



ether (50 mL). After warming to room temperature, the organic layer was separated and washed with additional 1 N HCl (2 × 7 mL). Upon drying with magnesium sulfate and evaporation, a yellow oil was obtained (0.94 g). The crude product contained a mixture of starting material and the desired aldehyde. The estimated yield of the aldehyde in the mixture is 50%. The NMR data matches that in the literature.[5]

(*E*) Methyl 5-Bromo-4,4-dimethoxy-2-pentenoate (7). Sodium hydride (0.14 g, 5.8 mmol) was placed in dry THF (20 mL) under an atmosphere of nitrogen and cooled in an ice bath. Trimethyl phosphonoacetate (1.1 g, 5.7 mmol) was added dropwise with rapid stirring to the suspension. The resulting white gelatinous mixture was further cooled to −78 °C, and a solution of **6** (0.76 g, 3.8 mmol in 4 mL of dry THF) was syringed in gradually. The reaction flask was allowed to warm up to room temperature. The mixture was stirred at room temperature overnight and quenched with saturated NH_4Cl solution (15 mL). Excess THF was evaporated and the residue was redissolved (H_2O 3 mL, EtOAc 20 mL). The organic layer was separated and washed with one portion of K_2CO_3 and two portions of brine. After drying with $MgSO_4$ and evaporation the residue was chromatographed on silica gel (hexane/ether 3:1). The desired olefinic ester **7** was isolated as a colorless oil (0.577 g, 60%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.66 (d, J = 15.7 Hz, 1H), 6.27 (d, J = 15.7 Hz, 1H), 3.78 (s, 3H), 3.45 (s, 2H), 3.23 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.18, 144.05, 126.17, 99.08, 51.85, 49.60, 32.53; FT-IR cm^{-1} 2951.5 (s), 2835.7 (m), 1732.30 (s), 1668.64 (m), 1164.6 (s), 1122.7 (s); MS (EI) m/z (rel intensity) 253.0 ([M]$^+$, 45), 221.0 (73), 191.0 (62), 173.1 (62), 159.1 (100), 141.1 (72). High resolution EI MS (m/z) 255.0059, calcd for $C_8H_{14}O_4Br^{81}$ 255.0055; 253.0080, calcd for $C_8H_{14}O_4Br^{79}$ 253.0075.

Radical Cyclizations of 7: (*E*)-Dimethyl 2-Pentenedioate (8) and Methyl 5,5-Dimethoxy-2-pentenoate (14).

A. With 1.5 Equiv of Tributylstannane. To a solution of the bromo enoate **7** (100 mg, 0.4 mmol) in degassed benzene (30 mL) were added tributyltin hydride (174 mg, 0.6 mmol) and AIBN (20.4 mg, 0.12 mmol), and the solution was heated at 78 °C until the reaction was complete (TLC). After cooling, excess benzene was evaporated, and the residue was dissolved in a small volume of ether. A concentrated solution of KF in water (10 g/100 mL) was then added, and the mixture was stirred overnight. The resulting white precipitate was filtered and the organic layer was separated. After evaporation of the solvent, the residue was partitioned between pentane and acetonitrile. The acetonitrile layer was dried with $MgSO_4$ and evaporated at reduced pressure. Gradient chromatography on silica gel (hexane/ether 10:1 to 3:1) afforded the diester **8** (32 mg, 50%). The ^{1}H NMR of this compound is identical to the literature spectrum of dimethyl glutaconate.

B. With 10 Equiv of Tributylstannane. Following the above procedure but using excess (10 equiv) of the tin hydride gave the dimethoxy enoate **14** (36 mg, 51%) as a colorless solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.82 (dt, J = 15.7, 7.2 Hz, 1H), 5.83 (dt, J = 15.7, 1.5 Hz, 1H), 4.39 (t, J = 5.6 Hz, 1H), 3.64 (s, 3H), 3.26 (s, 6H), 2.45 (ddd, J = 7.2, 5.6, 1.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.54, 143.40, 123.36, 102.79, 53.01, 51.36, 35.76; FT-IR cm^{-1} 2953.4 (m), 1726.5 (s), 1661.9 (m), 1124.6 (s), 972.2 (m). High resolution EI MS (m/z) 173.0807, calcd for $C_8H_{13}O_4$ (M − H)$^+$ 173.0814.

Acknowledgment. We thank the National Institutes of Health (GM 31349) for generous financial support.

JO9508199