RADICAL LACTONIZATIONS AT ANOMALOUSLY HIGH CONCENTRATIONS

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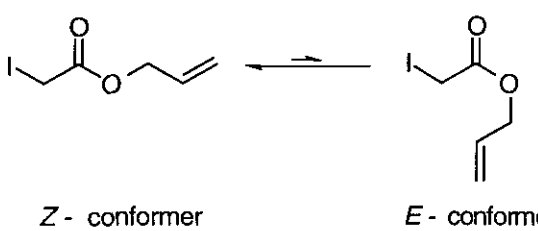
Abstract - Photolyses of phenylseleno and iodo derivatives of allyl and propargyl malonate esters led to formation of phenylseleno and iodobutyrolactones, respectively, in synthetically useful yields. In contrast to allyl iodoacetate, which undergoes intermolecular cyclo-oligomerization at high concentration, malonate esters cyclize cleanly at concentrations as high as 0.78 M.

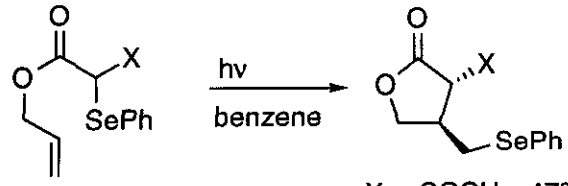
The hexenyl radical cyclization has long been one of the most generally useful radical carbon-carbon bond-forming reactions.[1] The analogous radical cyclization of allyl iodoacetate, leading to a butyrolactone, does not proceed in synthetically useful yields, except under the most stringent of experimental conditions.[2] The attempted reductive cyclization of allyl iodoacetate under tin hydride conditions has been reported to yield only allyl acetate.[2] The attempted cyclization under standard atom-transfer conditions generated the desired butyrolactone in poor yield, in addition to isolable quantities of cyclic dimer and trimer lactones.[2] This effect is predominately due to the high energy of the *E* ester rotamer required for cyclization relative to the lower energy *Z* ester rotamer (Eq. 1), as well as the high barrier to rotation around the CO-O bond exhibited by esters. For methyl formate and methyl acetate, the *E* rotamers have been shown experimentally to be 4.8 and 8.5 kcal/mol higher in energy than the corresponding *Z* rotamers, respectively, with a 10-15 kcal/mol barrier to rotation.[3] These values have also been obtained by high-level *ab initio* calculations.[4] Thus, there is a very low population of the higher energy conformer which is topologically required in order for cyclization to occur. Curran[2] has shown that a 41% yield of the butyrolactone arising from cyclization of allyl iodoacetate can only be obtained at low concentrations (≤ 0.03M), minimizing the intermolecular addition reactions leading to the undesired cyclic dimer and trimer lactones, and elevated temperature (80 °C), maximizing the population of the higher energy *E* conformer.



(Eq. 1)

Z - conformer *E* - conformer

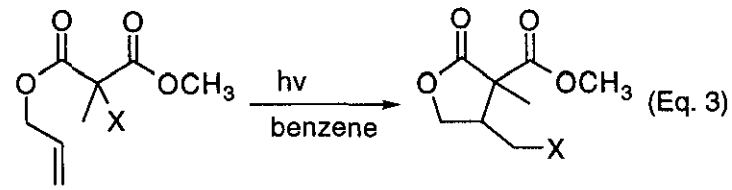
Several years ago, in an initial communication, we reported the first examples of hexenyl radical cyclizations proceeding with transfer of a phenylseleno substituent.[5] Among the more noteworthy examples in this communication were two examples of β-dicarbonyl compounds which underwent cyclization at relatively high concentration (0.5 M in benzene) to generate butyrolactones (Eq. 2). Metal-promoted oxidative radical cyclizations[6] and atom-transfer cyclizations[7] of similar compounds have also been reported. In this paper, in addition to providing further examples of this potentially useful lactonization procedure, we will examine more closely the relationship between concentration and isolated yield of butyrolactone and possible reasons for the surprising ease with which these β-dicarbonyl compounds undergo cyclization.



(Eq. 2)

X = $COCH_3$, 47%
X = $CO_2CH_2CH_3$, 41%

Cyclization precursors (**1a**) and (**1b**) were prepared from the corresponding diesters upon deprotonation with NaH, followed by PhSeCl,[8] I_2, or *N*-iodosuccinimide.[9] The photolytic cyclization of **1a** was attempted at a series of concentrations in order to assess the degree to which high concentrations proved deleterious to the formation of simple butyrolactone products (Eq. 3). Table I summarizes the results of this study. Yields are reported for the isolated diastereomeric mixtures obtained after workup and chromatography. Somewhat surprisingly, synthetically useful yields of cyclized products were obtained at concentrations as high as 0.78 M, with yields improving further at lower concentrations. At the highest concentration employed, 1.0 M, none of the desired cyclized butyrolactone was obtained, but small amounts of a white precipitate was observed. This uncharacterized by-product may have been the result of a cyclo-oligomerization process analogous to that previously observed in reactions of allyl iodoacetate.[2] We also examined the cyclization of the corresponding iodo compound (**1b**) under standard iodine-transfer conditions ($Bu_3SnSnBu_3$, hv, benzene), and observed that the reaction also proceeded in synthetically useful yield at a far higher concentration (0.5 M) than that employed in the aforementioned cyclization of allyl iodoacetate.[2]



(Eq. 3)

1a X = SePh
1b X = I

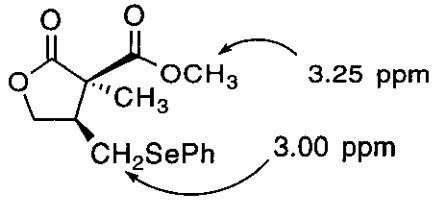
2a X = SePh
2b X = I

Table I.

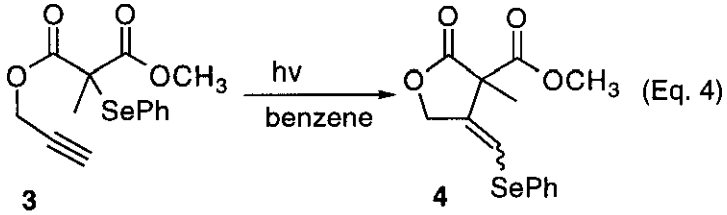
Precursor	Initial Conc. (M)	Isolated Yield (2)	*trans/cis* Ratio
1a	0.18	79%	----
1a	0.50	74%	3.5:1
1a	0.78	55%	----
1a	1.0	0%	----
1b	0.50	51%	5.3:1

Previously, we observed that only the stereoisomer with the exocyclic ketone or ester *trans* to the phenylselenomethylene group was obtained.[5] It was unclear, however, whether the high degree of stereoselectivity observed was associated with the kinetics of radical ring closure, or was the result of subsequent epimerization arising from the acidity of the proton located between the two carbonyl substitutents. Diester (**1a**), in which the labile proton was replaced with a methyl substituent, proved to be a better model compound for assessing the stereoselectivity of the actual radical cyclization. Photolysis of **1a** led to formation of **2a** as a 3.5:1 mixture of stereoisomers. When the methyl ester singlet at 3.25 ppm (C_6D_6) in the isolated major isomer was irradiated, a 10% positive NOE was observed in the signal at 3.00 ppm, which we had assigned to one of the methylene protons in phenylselenomethylene unit. (Figure 1.) No NOE was observed in the signal at 3.02 ppm upon irradiation of the corresponding methyl singlet at 3.75 ppm in the minor product. From this, we determined that the major product was that in which the methyl ester was *cis* to the phenylselenomethylene group. Thus, we conclude that the high degree of *trans* stereoselectivity which we had previously observed was not inherent to the actual radical cyclization, but was the result of epimerization occurring after cyclization, during either the workup or chromatography.

Figure I.



We were also interested in the cyclization reactions of the corresponding propargyl ester, given that we had previously achieved some success in the intermolecular addition of phenylselenomalonates to alkynes.[8] Photolysis of propargyl malonate derivative (**3**) led to butyrolactone (**4**) in 42% yield as a 1.5:1 mixture of alkene stereoisomers in which both products were the result of *5-exo* cyclization. (Eq. 4)



3 **4** (Eq. 4)

The source of the enhanced cyclization ability of these malonate ester radicals was quite puzzling. From this comparable results obtained in the cyclizations of both phenylseleno and iodomalonates, we concluded that the success of the radical cyclization reactions which we were observing was due to properties inherent to the dicarbonyl radical systems being studied, as opposed to the reaction kinetics unique to phenylselenide transfer radical addition. The reasons for this enhanced cyclization ability in malonate radicals are still unclear, and will be the subject of further study.

EXPERIMENTAL SECTION

General. Melting points were obtained on a Hoover-Thomas melting point apparatus and are uncorrected. Infrared spectra were obtained on a Perkin-Elmer 1600 FT-IR. NMR spectra were obtained in $CDCl_3$ on a General Electric GN-300 Omega spectrometer. Gas chromatographic analyses and mass spectroscopy (GC/MS) were carried out on a Hewlett-Packard 5890 gas chromatograph with a 25-m HP-1 methyl silicone capillary column interfaced to a Hewlett Packard 5970 mass selective detector (EI, 70 eV). Elemental Analyses were performed by Atlantic Microlab of Norcross, GA. Photolyses were carried out in screw-cap Pyrex test tubes held 10-15 cm from a 150-W medium pressure Hanovia lamp. Rigorous control of reaction temperature was not attempted during photolyses, but reactions typically warmed to 30-40 °C. All photolysis samples were deoxygenated with bubbling Ar for 15 min prior to irradiation. Benzene and THF were freshly distilled from K/benzophenone under Ar. Reagent-grade hexane and ethyl acetate were distilled prior to use. Medium pressure liquid chromatography (MPLC) and flash chromatography were carried out on Merck grade 9385 230-400 mesh silica gel. Yields are reported for isolated products which were pure by NMR and TLC, except where noted.

Allyl Methyl 2-Methyl-2-(phenylseleno)propanedioate (1a). A 1.00 g (5.8 mmol) portion of allyl methyl 2-methylpropanedioate was dissolved in 40 mL of THF under Ar and cooled to 0 °C. A 0.28 g (7.0 mmol) portion of NaH (60% by weight in mineral oil) was added slowly. After evolution of H_2 had ceased, PhSeCl (1.34 g, 7.0 mmol) was added and the mixture was stirred for 4 h, gradually warming to rt. Ether (100 mL) was added, the resulting mixture was washed with 100 mL of 5% Na_2CO_3. The organic layer was dried over anhydrous $MgSO_4$, filtered, and solvents were removed by rotary evaporation. The product was purified by MPLC (5% ethyl acetate, 95% hexane, v:v) to give 0.95 g (50%) of **1a** as a clear, colorless oil. ^{1}H NMR δ 1.69 (s, 3H), 3.72 (s, 3H), 4.64 (dt , J = 5.50, 1.41 Hz, 2H) 5.21 (ddd, J = 10.47, 2.99, 1.34 Hz, 1H), 5.31 (ddd, J = 17.21, 3.05, 1.41 Hz), 5.86 (m, 1H), 7.30 (m, 2H), 7.40 (m, 1H), 7.60 (m, 2H); ^{13}C NMR δ 23.3, 53.8, 67.2, 119.3, 127.1, 129.6, 130.5, 132.1, 138.9, 170.2, 170.9; IR (neat) 1737 cm^{-1}; MS m/z 328 (M^+). Anal. Calcd for $C_{14}H_{16}O_4Se$: C, 51.39; H, 4.93. Found: C, 51.03; H, 4.81.

Allyl Methyl 2-Methyl-2-iodopropanedioate (1b). A 0.51 g (3.0 mmol) portion of methyl allyl 2-methylpropandioate was dissolved in 20 mL of THF under Ar and cooled to 0 °C. A 0.15 g (3.6 mmol) portion of NaH (60% by wt in mineral oil) was added slowly. In a separate flask, a 0.72 g (3.2 mmol) portion of *N*-iodosuccinimide was dissolved in 5 mL of THF and cooled to -78 °C. The solution of allyl methyl 2-methylpropandioate was added slowly by cannula into the solution of *N*-iodosuccinimide. After 30 min, the solution was allowed to warm to rt. Ether (30 mL) was added, the solution was filtered, and

solvents were removed on a rotary evaporator. The crude mixture was purified by column chromatography on basic alumina (hexane, followed by diethyl ether) to yield 0.46 g (53%) of **1b**, as a clear, colorless oil. ^{1}H NMR δ 2.26 (s, 3H), 3.78 (s, 3H), 4.67 (m, 2H), 5.2-5.4 (m, 2H), 5.8-6.0 (m, 1H); ^{13}C NMR δ 29.6, 33.9, 54.0, 67.7, 119.0, 130.9, 168.6, 169.4; IR (neat) 1732 cm^{-1}; MS m/z 298 (M^+), 171 (M^+ - I).

2-Methoxycarbonyl-2-methyl-3-(phenylselenomethyl)butanolide (2a). A 0.17 g (0.50 mmol) portion of **1a** was dissolved in 1 mL of benzene and photolyzed for 27 h. Flash chromatography (80% hexane, 20% EtOAc, v:v) yielded 71 mg (62%) of the *cis* cyclized isomer (higher R_f) and 20 mg (17%) of the *trans* cyclized isomer (lower R_f). *Cis* isomer, white crystals: ^{1}H NMR δ 1.43 (s, 3H), 2.57 (m, 2H), 3.10 (m, 1H), 3.77 (s, 3H), 4.02 (t, J = 9.25 Hz, 1H), 4.49 (dd, J = 9.25, 7.57 Hz, 1H), 7.2-7.5 (m, 5H); ^{1}H NMR (C_6D_6) δ 1.47 (s, 3H), 2.30 (m, 1H), 2.42 (m, 1H), 3.00 (m, 1H), 3.25 (s, 3H), 3.93 (t, J=9.7 Hz, 1H), 4.26 (t, J=8.3 Hz, 1H), 7.53 (m, 3H), 7.71 (m, 2H); ^{13}C NMR δ 19.1, 24.6, 47.4, 52.9, 54.2, 70.9, 128.0, 128.3, 129.5, 133.4, 168.9, 175.5; IR (KBr) 1785, 1737 cm^{-1} MS m/z 328 (M^+), 171 (M^+ -SePh), 157 ($SePh^+$); mp 57-58 °C. Anal. Calcd for $C_{14}H_{16}O_4Se$: C, 51.39; H, 4.93. Found: C, 51.35; H, 4.96. *Trans* isomer, clear, colorless oil: ^{1}H NMR δ 1.43 (s, 3H), 2.75 (dd, J = 12.20, 10.26 Hz, 1H), 3.02 (dd, J = 12.20, 5.38 Hz, 1H), 3.28 (m, 1H), 3.75 (s, 3H), 3.96 (t, J = 8.79 Hz, 1H), 4.52 (dd, J = 8.79, 6.84 Hz, 1H), 7.30 (m, 3H), 7.48 (m, 2H); ^{13}C NMR δ 13.8, 24.4, 43.6, 53.1, 53.4, 70.4, 127.8, 128.4, 129.4, 133.2, 170.4, 175.2; IR (neat) 1782, 1738 cm^{-1}; MS m/z 328 (M^+), 171 (M^+ -SePh), 157 ($SePh^+$). Anal. Calcd for $C_{14}H_{16}O_4Se$: C, 51.39; H, 4.93. Found: C, 51.19; H, 4.96.

3-Iodomethyl-2-methoxycarbonyl-2-methylbutanolide (2b). A 450 mg (1.5 mmol) portion of **1b** and 89 mg (0.15 mmol) of $Bu_3SnSnBu_3$were dissolved in 3 mL of benzene. The solution was photolyzed for 1.5 h. Solvents were removed by rotary evaporation, the crude reaction mixture was suspended in 5 mL of acetonitrile, and 0.5 g of KF dihydrate was added. The reaction mixture was stirred overnight under Ar. Solvents wre removed by rotary evaporation, and the crude reaction mixture was filtered through a 2 cm pad of Florisil with ether. Solvents were removed by rotary evaporation, and the resulting oil was purified by flash chromatography (20% EtOAc, 80% hexane, v:v) to give 228 mg (51%) of **2b**, which was shown to be a 5.3:1 ratio of stereoisomers by GC/MS. MPLC (15% EtOAc, 85% hexane, v:v) allowed for separation of the mixture into its stereoisomeric components. Major isomer (higher R_f), white crystals: ^{1}H NMR δ 1.51 (s, 3H), 2.80 (m, 2H), 3.26 (dd, J = 3.42, 8.79 Hz, 1H), 3.77 (s, 3H), 4.00 (dd, J = 9.28, 10.26 Hz, 1H), 4.55 (dd, J = 7.32, 9.28 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ –2.2, 19.3, 49.4, 53.0, 54.9, 71.9, 168.3, 175.1. IR (KBr) 1782, 1741 cm^{-1}; MS m/z 267, 171 (M^+ - I); mp 69.5 - 70.5 °C. Minor isomer (lower R_f), clear, colorless oil: ^{1}H NMR δ 1.43 (s, 3H), 3.06 (t, J = 10.01 Hz, 1H), 3.20 (dd, J = 5.70, 10.01 Hz, 1H), 3.47 (m, 1H), 3.82 (s, 3H), 3.98 (dd, J = 8.30, 9.28

Hz, 1H), 4.59 (dd, J = 7.32, 9.28 Hz, 1H); ^{13}C NMR δ −1.5, 13.6, 45.8, 53.4, 54.0, 71.3, 170.0, 174.8; IR (neat) 1782, 1735 cm^{-1}; MS m/z 298 (M^+) 267, 171 (M^+ -I).

Methyl Propargyl 2-Methyl-2-(phenylseleno)propandioate (3). A 1.00 g (5.9 mmol) portion of methyl propargyl 2-methylpropanedioate was dissolved in dry THF (25 mL) under Ar and cooled to 0 °C. A 0.28 g (7.1 mmol) portion of NaH (60% by wt in mineral oil) was added slowly. After evolution of H_2 had ceased, PhSeCl (1.36 g, 7.1 mmol) was added and the mixture was stirred for 16 h, gradually warming to rt. Ether (50 mL) was added, and the resulting mixture was washed with two 25 mL portions of 5% Na_2CO_3. The organic layer was dried over anhydrous $MgSO_4$, filtered, and solvents were removed by rotary evaporation. The product was purified by flash chromatrography (10% EtOAc, 90% hexane, v:v) to give 1.60 g (86%) of **3** as a clear, colorless oil. ^{1}H NMR δ 1.64 (s, 3H), 2.54 (t, J = 2.0 Hz, 1H), 3.67 (s, 3H), 4.66 (d, J = 2.0 Hz, 2H), 7.25 (m, 3H), 7.60 (m, 2H); ^{13}C NMR δ 22.2, 52.4, 53.0, 53.2, 75.4, 76.7, 126.0; 128.7; 129.7, 138.1, 168.9, 169.8; IR (neat) 2130, 1734 cm^{-1}. Anal. Calcd for $C_{14}H_{16}O_4Se$: C, 51.70; H, 4.34. Found, C, 51.68; H, 4.37.

2-Methoxycarbonyl-2-methyl-3-(phenylselenomethylene)butanolide (4). A 325 mg (1.00 mmol) portion of **3** was dissolved in 2 mL of benzene. The solution was photolyzed for 16 h. Solvents were removed by rotary evaporation, and the resulting oil was purified by MPLC (10% EtOAc, 90% hexane, v:v) to give 79 mg (24%) of a higher R_f cyclized isomer and 59 mg (18%) of a lower R_f cyclized isomer, both of which were clear, colorless oils. Higher R_f product: ^{1}H NMR δ 1.63 (s, 3H) 3.77 (s, 3H), 4.84 (dd, J = 2.93, 13.67 Hz, 1H), 4.93 (dd, J = 2.44, 13.67 Hz, 1H), 6.69 (t, J = 2.44 Hz, 1H), 7.35 (m, 3H), 7.45 (m, 2H); ^{13}C NMR δ 19.5, 53.5, 54.4, 70.4, 117.0, 128.0, 129.1, 129.6, 132.2, 138.4, 168.4, 174.5; IR (neat) 1786, 1741 cm^{-1}; MS m/z 326 (M^+), 169 (M^+-SePh). Anal. Calcd for $C_{14}H_{16}O_4Se$: C, 51.70; H, 4.34. Found, C, 51.59; H, 4.34. Lower R_f product: ^{1}H NMR δ 1.78 (s, 3H), 3.79, (s, 3H), 4.87, (dd, J = 1.95, 12.7 Hz, 1H), 4.96, (dd, J = 1.95, 13.18 Hz, 1H), 6.61, (t, J = 1.46 Hz, 1H), 7.32 (m, 3H), 7.47 (m, 2H); ^{13}C NMR δ 18.0, 53.4, 54.2, 71.3, 117.5, 127.9, 129.5, 129.9, 132.4, 136.5, 167.8, 174.8; IR (neat) 1781, 1740 cm^{-1}; MS m/z 326 (M^+), 169 (M^+-SePh). Anal. Calcd for $C_{14}H_{16}O_4Se$: C, 51.70; H, 4.34. Found: C, 52.07; H, 4.43.

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