

A Novel Synthesis of Allenic Lactones by Use of the [2,3]Sigmatropic Rearrangement of Cyclic Propargylsulfonium Ylides

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(Received March 3, 1992)

The [2,3]sigmatropic rearrangement of the cyclic propargylsulfonium ylides generated from ethyl 5-phenylthio-3-pentynyl and ethyl 6-phenylthio-4-hexynyl diazomalonates provided the novel allenic lactones, 2-ethoxycarbonyl-2-phenylthio-3-vinylidene-5-pentanolide and 6-hexanolide, respectively.

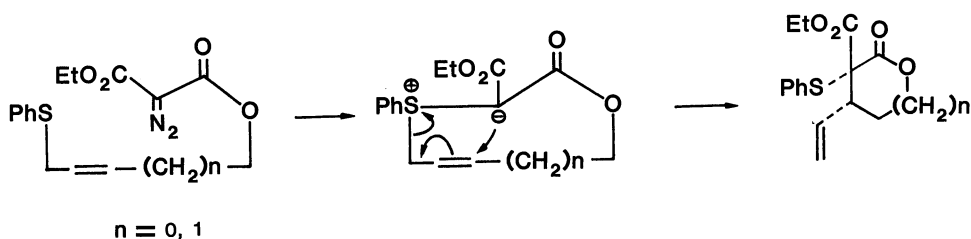
We have been studying the utility of the [2,3]sigmatropic rearrangement of cyclic allylsulfonium ylides directed toward the one-step preparation of lactonic compounds, and have reported that the acyclic Z-olefins possessing an allyl sulfide and a diazomalonyl group give the β -vinyl five- and six-membered lactones in a stereoselective fashion by the [2,3]sigmatropic rearrangement of the medium-sized cyclic sulfonium ylides (Scheme 1).¹⁾ This methodology has been extended to the one-step synthesis of γ,δ -unsaturated seven-membered,²⁾ bridged,³⁾ and spiro-fused lactones,⁴⁾ and to a new spiro annulation reaction.⁵⁾

The above findings aroused our interest in the reactivity of the diazomalonate possessing an acetylene unit in place of the Z-olefin; an acyclic compound having both a diazomalonyl and propargyl sulfide functions at the terminal positions would give an allenic lactone, provided that the formation of the cyclic propargylsulfonium ylide followed by the [2,3]sigmatropic rearrangement is possible (Scheme 2). To our knowledge, little are known not only about the sigmatropic rearrangement of the cyclic propargylsulfonium ylides,⁶⁾ but also about

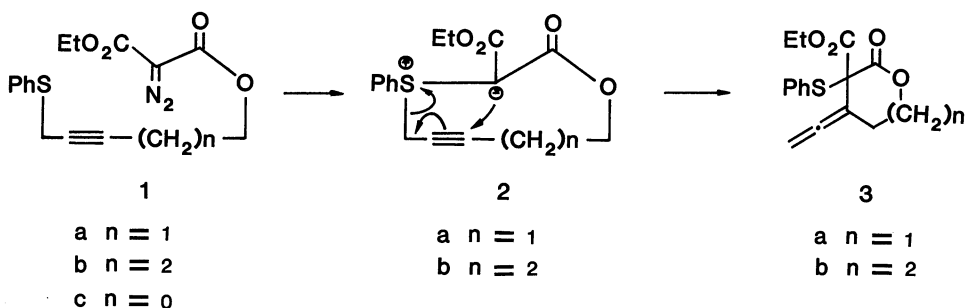
the general synthesis of allenic lactones. Herein is reported the preparation of the required acetylenic diazomalonates as well as their rhodium-catalyzed [2,3]-sigmatropic rearrangements.

Results and Discussion

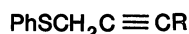
In the present case starting with the acetylenic diazomalonates, it is suggested by an examination of Dreiding models that the formation of the cyclic sulfonium ylides followed by their [2,3]sigmatropic rearrangements would occur when their ring sizes are nine- and ten-membered (2, $n=1,2$). Therefore, our synthesis began with the preparation of the acetylenic alcohols, 5-phenylthio-3-pentyn-1-ol (**5**) and 6-phenylthio-4-hexyn-1-ol (**6**), from the common starting material, phenyl propargyl sulfide (**4**).¹⁾ Condensation of the lithium acetylide derived from **4** with ethylene oxide in the presence of diethyl ether–boron trifluoride (1/1)⁷⁾ afforded **5** in a good yield, while alkylation with 3-(*t*-butyldimethylsiloxy)propyl chloride,⁸⁾ followed by desilylation provided **6** in 40% overall yield. In



Scheme 1.



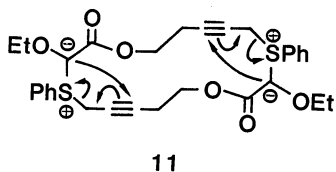
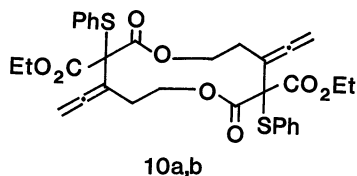
Scheme 2.



- 4 R = H
 5 R = CH₂CH₂OH
 6 R = CH₂CH₂CH₂OH
 7 R = CH₂OH
 8 R = CH₂CH₂OCOCH₂CO₂Et
 9 R = CH₂OCOCH₂CO₂Et

addition, to examine the limitation for the formation of the cyclic propargylsulfonium ylide in terms of the ring size, 4-phenylthio-2-butyne-1-ol (7) was prepared by condensation of the above lithium salt with formaldehyde. The preparation of the acetylenic diazomalonates was next carried out using the three alcohols obtained above. Esterification of the alcohols 5 and 7 with ethyl hydrogen malonate, followed by diazotization of the resulting malonates 8 and 9 with toluenesulfonyl azide gave the diazomalonates 1a and 1c, respectively, in acceptable overall yields. On the other hand, the direct diazomalonoylation of 6 with ethyl hydrogen diazomalonate⁹⁾ in the presence of diethyl azodicarboxylate and triphenylphosphine provided the desired diazomalonate 1b in 70% yield.

Reaction of the diazomalonate 1a with 0.01 molar amount of rhodium(II) acetate in refluxing benzene (1.0%, w/v) gave two kinds of isolable products; the allenic six-membered lactone 3a [ν 1960 (C=C=C) and 1750 cm⁻¹ (C=O); δ =4.90 (2H, brs, C=C=CH₂)] and a diastereomeric mixture of bislactones 10a,b, which were separable by chromatography on silica gel, in 16 and 13% yields, respectively, along with intractable polar compounds. When the concentration of the reaction solution decreased to 0.2% (w/v), the yield of 3a increased to 29%, whereas that of 10 decreased to 6%.



Similarly, the diazomalonate 1b was treated with rhodium(II) acetate under the 0.2% (w/v) concentration to give the seven-membered lactone 3b [ν 1955 (C=C=C) and 1750 cm⁻¹ (C=O); δ =4.85 (2H, brs, C=C=CH₂)] in

24% yield as the sole isolable product. In this case, the formation of bislactones, predictable from the aforementioned reaction of 1a, was not detected.

Although the yields of the allenic lactones are unexpectedly low, it was proved that treatment of the acetylenic diazomalonates 1a and 1b with rhodium(II) acetate affords the allenic lactones 3a and 3b by the [2,3]sigmatropic rearrangements of a nine-membered propargylsulfonium ylide 2a and a ten-membered one 2b, respectively. The low yields of 3a and 3b can be rationalized by the presumption that carbene insertion reactions compete to produce a mixture of the intractable products. The formation of the bislactones 10a,b is accounted for by the bimolecular bis-ylides formation followed by the double [2,3]sigmatropic rearrangement as depicted in 11.

Finally, the diazomalonate 1c was subjected to the rhodium-catalyzed rearrangement under the similar reaction conditions used for the above reactions, giving a mixture of polar products in which no allenic lactones were detectable. This results indicated that the formation of the eight-membered sulfonium ylide (2, $n=0$) including an acetylene unit is structurally inaccessible, as predicted by the examination of Dreiding models.

Experimental

IR spectra were obtained with a JASCO A-3 infrared spectrometer. ¹H NMR spectra were recorded on a JEOL FX90Q spectrometer with tetramethylsilane as an internal standard. All reactions were carried out under dry N₂ or Ar atmosphere. Extracts obtained on aqueous workup were washed successively with water and brine, and dried over Na₂SO₄, unless otherwise stated. Column chromatography was performed by using silica gel (Merck, Kieselgel 60, 70–230 mesh), and Kieselgel GF₂₅₄ was employed for preparative thin-layer chromatography (TLC) as an absorbent. Solvents used for elution are shown in parentheses.

5-Phenylthio-3-pentyn-1-ol (5). To a stirred solution of phenyl propargyl sulfide (4)¹¹⁾ (740 mg, 5.0 mmol) in THF (7 ml) at -78°C was added dropwise a 1.55 M solution (1 M=1 mol dm⁻³) of butyllithium in hexane (3.2 ml, 5.0 mmol). After being stirred for 30 min, ethylene oxide (0.37 ml, 7.5 mmol) and diethyl ether–boron trifluoride (1/1) (710 mg, 5.0 mmol) were added successively, and stirring was continued for an additional 15 min. The reaction was quenched by addition of aqueous NH₄Cl and the product was extracted with CH₂Cl₂. Evaporation of the solvent left an oil which was chromatographed on silica gel (hexane–AcOEt, 3:2) to give 5 (612 mg, 64%) as an oil. IR (CHCl₃) 3600, 3450, 1590 cm⁻¹; ¹H NMR (CDCl₃) δ =0.84 (1H, brs, OH), 2.3–2.5 (2H, m), 3.5–3.8 (4H, m), 7.2–7.6 (5H, m).

Found: C, 68.80; H, 6.32; S, 17.00%. Calcd for C₁₁H₁₂OS; C, 68.71; H, 6.29; S, 16.67%.

6-Phenylthio-3-hexyn-1-ol (6). According to the procedure for preparation of 5, a 1.55 M solution of butyllithium in hexane (3.5 ml, 5.5 mmol) was added to a solution of 4 (741 mg, 5.0 mmol) in THF (7 ml) at -78°C and the resulting solution was stirred at this temperature for 30 min, then at -30°C for 30 min, and recooled to -78°C. To this solution, a solution of

3-(*t*-butyldimethylsiloxy)propyl chloride⁸⁾ (1.25 g, 6.0 mmol) and hexamethylphosphoric triamide (HMPA) (986 mg, 5.5 mmol) in THF (5 ml) was added and stirring was continued for an additional 30 min. The reaction was quenched by addition of aqueous NH₄Cl and the product was extracted with ether. Removal of the solvent gave 6-(*t*-butyldimethylsiloxy)-1-phenylthio-2-hexyne (2.0 g) as an oil; ¹H NMR (CDCl₃) δ=0.02 (6H, s), 0.83 (9H, s), 1.83–2.05 (4H, m), 3.5–3.8 (4H, m), 7.2–7.5 (5H, m).

To a stirred solution of the above oil in THF (10 ml) was added a 1.1 M solution of tetrabutylammonium fluoride in THF (6.8 ml, 7.5 mmol), and the resulting solution was stirred at room temperature overnight. Water was added and the product was extracted with CH₂Cl₂. Removal of the solvent gave **6** (351 mg, 40%) as an oil. IR (CHCl₃) 3350, 1585 cm⁻¹; ¹H NMR (CDCl₃) δ=1.62 (1H, brs, OH), 1.6–2.4 (4H, m), 3.5–3.9 (4H, m), 7.1–7.5 (5H, m).

The oil **6** was immediately used for the next malonate synthesis (vide infra) because of instability on standing at room temperature.

4-Phenylthio-2-butyne-1-ol (7). According to the procedure described for preparation of **5**, a 1.55 M solution of butyllithium in hexane (3.2 ml, 5.0 mmol) was added to a solution of **4** (740 mg, 5.0 mmol) in THF (7.0 ml) with stirring at –78 °C. Gaseous formaldehyde generated by heating paraformaldehyde at 160–170 °C was passed through the well-stirred mixture by means of a stream of dry N₂ over 20 min. The reaction was quenched by addition of aqueous NH₄Cl and the product was extracted with ether. Removal of the solvent left an oil which was chromatographed on silica gel (hexane–AcOEt, 1 : 1) to give **7** (625 mg, 70%) as an oil. IR (CHCl₃) 3630, 3450, 1590 cm⁻¹; ¹H NMR (CDCl₃) δ=1.90 (1H, brs, OH), 3.64 (2H, t, *J*=1.8 Hz), 4.20 (2H, t, *J*=1.8 Hz), 7.2–7.5 (5H, m).

Found: C, 67.37; H, 5.71; S, 18.31%. Calcd for C₁₀H₁₀OS: C, 67.38; H, 5.66; S, 17.99%.

Ethyl 5-Phenylthio-3-pentynyl Malonate (8). A solution of **5** (463 mg, 2.41 mmol), ethyl hydrogen malonate (1.04 g, 7.89 mmol), 4-dimethylaminopyridine (DMAP) (32 mg, 0.26 mmol), and dicyclohexylcarbodiimide (DCC) (1.36 g, 6.58 mmol) in CH₂Cl₂ (5 ml) was stirred at room temperature for 2 h, and the reaction was quenched by addition of aqueous NH₄Cl. The precipitate thereby formed was filtered off through a short Celite column and the filtrate was washed with brine. Evaporation of the solvent followed by purification of a residue by chromatography on silica gel (hexane–AcOEt, 3 : 1) gave **8** (551 mg, 75%) as an oil. IR (CHCl₃) 1760, 1740, 1590 cm⁻¹; ¹H NMR (CDCl₃) δ=1.30 (3H, t, *J*=7.2 Hz), 2.4–2.7 (2H, m), 3.36 (2H, s), 3.62 (2H, t, *J*=1.8 Hz), 4.0–4.4 (4H, m), 7.2–7.6 (5H, m).

Found: C, 62.92; H, 5.93; S, 10.48%. Calcd for C₁₆H₁₈O₄S: C, 62.72; H, 5.92; S, 10.46%.

Ethyl 4-Phenylthio-2-butyryl Malonate (9). According to the procedure for preparation of **8**, a solution of **7**, (353 mg, 1.98 mmol) in CH₂Cl₂ (12 ml) was treated with ethyl hydrogen malonate (785 mg, 5.94 mmol) under the presence of DMAP (24 mg, 0.20 mmol) and DCC (1.02 g, 4.95 mmol), giving **9** (444 mg, 77%) as an oil. IR (CHCl₃) 1760, 1735, 1670, 1590 cm⁻¹; ¹H NMR (CDCl₃) δ=1.28 (3H, t, *J*=7.2 Hz), 3.38 (2H, s), 3.64 (2H, t, *J*=1.8 Hz), 4.22 (2H, q, *J*=7.2 Hz), 4.72 (2H, t, *J*=1.8 Hz), 7.2–7.6 (5H, m).

Found: C, 61.70; H, 5.51; S, 11.02%. Calcd for C₁₅H₁₆O₄S: C, 61.62; H, 5.52; S, 10.97%.

Ethyl 5-Phenylthio-3-pentynyl Diazomalonate (1a). A solution of **8** (551 mg, 1.80 mmol), *p*-toluenesulfonyl azide (562 mg, 2.85 mmol), and triethylamine (769 mg, 7.60 mmol) in acetonitrile (10 ml) was warmed with stirring at 45 °C for 2 d. After cooling to room temperature, the resulting mixture was poured into water, and extracted with ether. The combined extracts were washed successively with aqueous Na₂CO₃, water, aqueous HCl, water, and brine and dried. Evaporation left an oil which was chromatographed on silica gel (hexane–AcOEt, 3 : 1) to give **1a** (397 mg, 66%) as an oil. IR (CHCl₃) 2150, 1750, 1730, 1690 cm⁻¹; ¹H NMR (CDCl₃) δ=1.32 (3H, t, *J*=7.2 Hz), 2.4–2.7 (2H, m), 3.60 (2H, t, *J*=1.8 Hz), 4.25 (2H, t, *J*=1.8 Hz), 4.32 (2H, q, *J*=7.2 Hz), 7.2–7.6 (5H, m).

Found: C, 58.01; H, 4.88; N, 8.46; S, 9.63%. Calcd for C₁₆H₁₆N₂O₄S: C, 57.82; H, 4.85; N, 8.43; S, 9.65%.

Ethyl 4-Phenylthio-2-butyryl Diazomalonate (1c). According to the procedure described for preparation of **1a**, a solution of **9** (444 mg, 1.52 mmol) in acetonitrile (9 ml) was treated with *p*-toluenesulfonyl azide (45 mg, 2.28 mmol) and triethylamine (615 mg, 6.08 mmol), giving **1c** (366 mg, 76%) as an oil. IR (CHCl₃) 2170, 1760, 1735, 1590 cm⁻¹; ¹H NMR (CDCl₃) δ=1.30 (3H, t, *J*=7.2 Hz), 3.62 (2H, t, *J*=1.8 Hz), 4.30 (2H, q, *J*=7.2 Hz), 4.80 (2H, t, *J*=1.8 Hz), 7.2–7.6 (5H, m).

Found: C, 56.60; H, 4.50; N, 8.83; S, 10.15%. Calcd for C₁₅H₁₄N₂O₄S: C, 56.59; H, 4.43; N, 8.80; S, 10.07%.

Ethyl 6-Phenylthio-3-hexynyl Diazomalonate (1b). To a stirred solution of **6** (55 mg, 0.26 mmol), triphenylphosphine (205 mg, 0.78 mmol), and ethyl hydrogen diazomalonate⁹⁾ (136 mg, 0.78 mmol) in THF (5 ml) was added at room temperature diethyl azodicarboxylate (136 mg, 0.78 mmol) and the resulting mixture was stirred for 15 h. The mixture was diluted with water and extracted with CH₂Cl₂. Evaporation followed by purification of a residual oil with chromatography on silica gel (hexane–AcOEt, 5 : 1) gave **1b** (63 mg, 70%) as an oil. IR (CHCl₃) 2150, 1755, 1730, 1690 cm⁻¹; ¹H NMR (CDCl₃) δ=1.30 (3H, t, *J*=7.2 Hz), 1.8–2.5 (4H, m), 4.1–4.5 (4H, m), 4.86 (2H, t, *J*=1.8 Hz), 7.2–7.5 (5H, m).

Found: C, 58.90; H, 5.28; N, 8.16; S, 9.22%. Calcd for C₁₇H₁₈N₂O₄S: C, 58.94; H, 5.23; N, 8.06; S, 9.26%.

2-Ethoxycarbonyl-2-phenylthio-3-vinylidene-5-pentanolid (3a) and Bis lactone (10a,b). A solution of **1a** (100 mg, 0.30 mmol) and rhodium(II) acetate (1.3 mg 3.0×10⁻³ mmol) in benzene (50 ml) was heated at 80 °C for 30 min, and cooled to room temperature. The solvent was mostly removed under reduced pressure and the residual oil was purified by preparative medium-pressure LC (Kusano Kagaku KHLC-201-32 system fitted with 2.5×10 cm column packed with silica gel) using a mixed solvent, hexane–AcOEt (3 : 1), to give **3a** (26.3 mg, 29%) and a mixture of diastereomeric bis lactones **10** (5.3 mg, 6%).

3a: An oil; IR (CHCl₃) 1960, 1750 cm⁻¹; ¹H NMR (CDCl₃) δ=1.26 (3H, t, *J*=7.2 Hz), 2.4–2.8 (2H, m), 4.0–4.8 (2H, m), 4.8–5.0 (2H, m), 7.2–7.7 (5H, m).

Found: *m/z* 304.3700. Calcd for C₁₆H₁₆O₄S: *M*, 304.3698.

The mixture of diastereomeric bis lactones **10** was separated by preparative thin-layer chromatography (hexane–ether, 10 : 1, three times development) to give two isomers, **10a** and **10b**. Their stereostructures are not determined.

10a: An oil; IR (CHCl₃) 1960, 1735 cm⁻¹; ¹H NMR (CDCl₃) δ=1.10 (6H, t, *J*=7.2 Hz), 2.4–2.6 (4H, m), 3.8–4.3 (6H, m), 4.5–4.9 (2H, m), 5.0–5.2 (4H, m), 7.1–7.7 (10H, m).

Found: *m/z* 608.7400. Calcd for C₃₂H₃₂O₈S₂: *M*, 608.7403.

10b; An oil; IR (CHCl₃) 1960, 1735 cm⁻¹; ¹H NMR (CDCl₃) δ=1.08 (6H, t, *J*=7.2 Hz), 2.4—2.6 (4H, m), 3.8—4.3 (6H, m), 4.4—4.8 (2H, m), 5.16 (4H, t, *J*=1.8 Hz), 7.2—7.7 (10H, m).

Found: *m/z* 608.7402. Calcd for C₃₂H₃₂O₈S₂: *M*, 608.7403.

2-Ethoxycarbonyl-2-phenylthio-3-vinylidene-6-hexanolide (3b). According to the procedure described for preparation of **3a**, treatment of **1b** (221 mg, 0.64 mmol) with rhodium(II) acetate (2.8 mg, 6.4×10⁻³ mmol) in benzene (110 ml) gave **3b** (49 mg, 24%) as an oil. IR (CHCl₃) 1955, 1750, 1725 cm⁻¹; ¹H NMR (CDCl₃) δ=1.22 (3H, t, *J*=7.2 Hz), 1.8—2.4 (2H, m), 2.4—2.7 (2H, m), 4.0—4.7 (4H, m), 4.7—5.2 (2H, m), 7.2—7.8 (5H, m).

Found: C, 64.25; H, 5.81; S, 10.12%. Calcd for C₁₇H₁₈O₄S: C, 64.13; H, 5.70; S, 10.07%.

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- 9) This reagent was prepared from partial hydrolysis of diethyl diazomalonate with aqueous potassium hydroxide followed by libeation of the acid ester from the resulting potassium hydrogen diazomalonate with aqueous hydrochloric acid in 77% overall yield. Details will be published in due course.