Bull. Chem. Soc. Jpn., **65**, 2471—2474 (1992)

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)

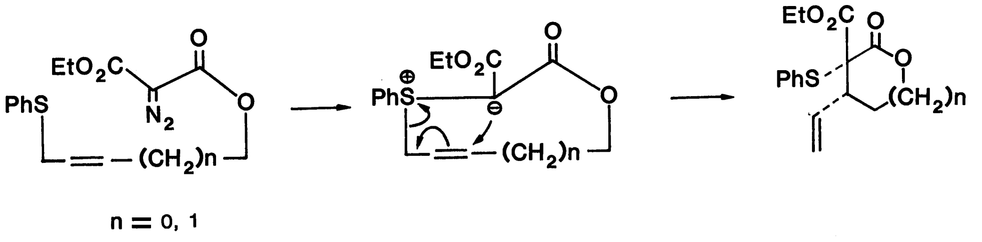
The [2,3]sigmatropic rearrangement of the cyclic propargylsulfonium ylides generated from ethyl 5-phenylthio-3-pentynyl and ethyl 6-phenylthio-4-hexynyl diazomalonates provided the novel allenic lactones, 2-ethoxycarbonyl-2-phenylthio-3-vinylidene-5-pentanolide and 6-hexanolide, respectively.

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)

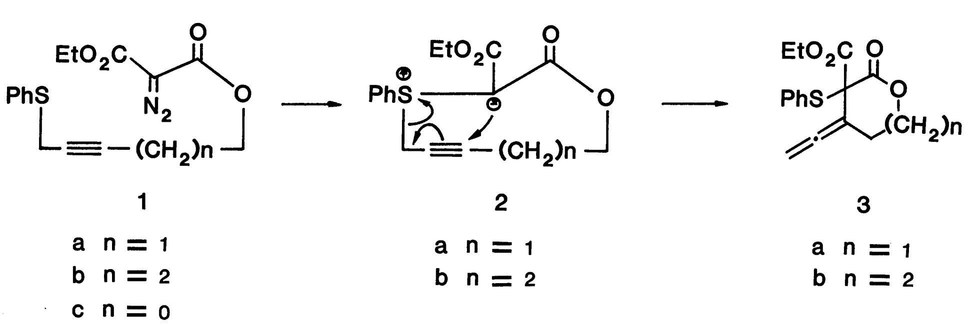
The above findings aroused our interest in the reactivity of the diazomalonate possessing an acetylene unit in place of the *Z*-olefin; an acyclic compound having both a diazomalonyl and propargyl sulfide functions at the terminal positions would give an allenic lactone, provided that the formation of 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-phenythio-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.



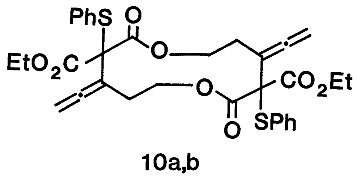
Scheme 2.

$PhSCH_2C{\equiv}CR$

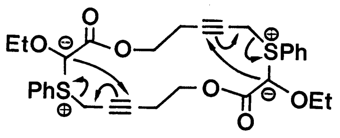
4 $R = H$
5 $R = CH_2CH_2OH$
6 $R = CH_2CH_2CH_2OH$
7 $R = CH_2OH$
8 $R = CH_2CH_2OCOCH_2CO_2Et$
9 $R = CH_2OCOCH_2CO_2Et$

addition, to examine the limitation for the formation of the cyclic propargylsulfonium ylide in terms of the ring size, 4-phenylthio-2-butyn-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 diazomalonylation of **6** with ethyl hydrogen diazomalonate[9] 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=CH$_2$)] 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%.



10a,b



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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=CH$_2$)] 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. ^{1}H NMR spectra were recorded on a JEOL FX90Q spectrometer with tetramethylsilane as an internal standard. All reactions were carried out under dry N$_2$ or Ar atmosphere. Extracts obtained on aqueous workup were washed successively with water and brine, and dried over Na_2SO_4, unless otherwise stated. Column chromatography was performed by using silica gel (Merck, Kieselgel 60, 70—230 mesh), and Kieselgel GF$_{254}$ 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**)[1] (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 NH_4Cl and the product was extracted with CH_2Cl_2. 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 ($CHCl_3$) 3600, 3450, 1590 cm^{-1}; ^{1}H NMR ($CDCl_3$) 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 $C_{11}H_{12}OS$; 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 chloride[8] (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 NH_4Cl 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 ($CDCl_3$) 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 CH_2Cl_2. Removal of the solvent gave **6** (351 mg, 40%) as an oil. IR ($CHCl_3$) 3350, 1585 cm^{-1}; ^1H NMR ($CDCl_3$) 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-butyn-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 N_2 over 20 min. The reaction was quenched by addition of aqueous NH_4Cl 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 ($CHCl_3$) 3630, 3450, 1590 cm^{-1}; ^1H NMR ($CDCl_3$) 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 $C_{10}H_{10}OS$: 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), etyl 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 CH_2Cl_2 (5 ml) was stirred at room temperature for 2 h, and the reaction was quenched by addition of aqueous NH_4Cl. 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 ($CHCl_3$) 1760, 1740, 1590 cm^{-1}; ^1H NMR ($CDCl_3$) 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 $C_{16}H_{18}O_4S$: C, 62.72; H, 5.92; S, 10.46%.

Ethyl 4-Phenylthio-2-butynyl Malonate (9). According to the procedure for preparation of **8**, a solution of **7**, (353 mg, 1.98 mmol) in CH_2Cl_2 (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 ($CHCl_3$) 1760, 1735, 1670, 1590 cm^{-1}; ^1H NMR ($CDCl_3$) 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 $C_{15}H_{16}O_4S$: 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 Na_2CO_3, 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 ($CHCl_3$) 2150, 1750, 1730, 1690 cm^{-1}; ^1H NMR ($CDCl_3$) 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 $C_{16}H_{16}N_2O_4S$: C, 57.82; H, 4.85; N, 8.43; S, 9.65%.

Ethyl 4-Phenylthio-2-butynyl 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 ($CHCl_3$) 2170, 1760, 1735, 1590 cm^{-1}; ^1H NMR ($CDCl_3$) 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 $C_{15}H_{14}N_2O_4S$: 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 diazomalonate[9] (136 mg, 0.78 mmol) in THF (5 ml) was added at room termerature 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 CH_2Cl_2. 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 ($CHCl_3$) 2150, 1755, 1730, 1690 cm^{-1}; ^1H NMR ($CDCl_3$) 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 $C_{17}H_{18}N_2O_2S$: C, 58.94; H, 5.23; N, 8.06; S. 9.26%.

2-Ethoxycarbonyl-2-phenylthio-3-vinylidene-5-pentanolide (3a) and Bislactone (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 bislactones **10** (5.3 mg, 6%).

3a: An oil; IR ($CHCl_3$) 1960, 1750 cm^{-1}; ^1H NMR ($CDCl_3$) 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 $C_{16}H_{16}O_4S$: M, 304.3698.

The mixture of diastereomeric bislactones **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 ($CHCl_3$) 1960, 1735 cm^{-1}; ^1H NMR ($CDCl_3$) 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. Cacld for $C_{32}H_{32}O_8S_2$: M, 608.7403.

10b; An oil; IR ($CHCl_3$) 1960, 1735 cm^{-1}; ^{1}H NMR ($CDCl_3$) 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 $C_{32}H_{32}O_8S_2$: 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 ($CHCl_3$) 1955, 1750, 1725 cm^{-1}; ^{1}H NMR ($CDCl_3$) 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 $C_{17}H_{18}O_4S$: 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.