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A New Method for the Synthesis of 2-Substituted 2-Buten-4-olide *via* α-Substituted β-Phenylthio-γ-butyrolactone

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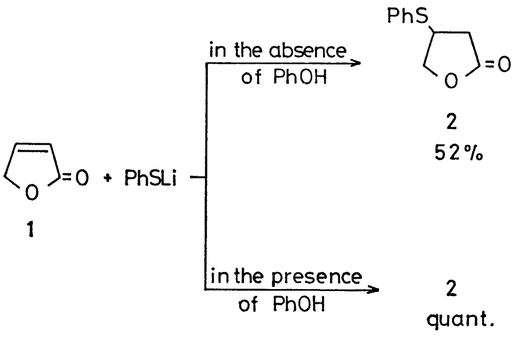
The addition reaction of lithium benzenethiolate to 2-buten-4-olide in the presence of aldehydes and ketones afforded α-substituted β-phenylthio-γ-butyrolactones (**4a**—**f**). The dehydrosulfenylation of **4a**—**d** proceeded smoothly to give 2-substituted 2-buten-4-olide by the reflux of α-substituted β-phenylsulfinyl-γ-butyrolactone, which was prepared by the oxidation of **4a**—**d**, in the presence of triethylamine.

A number of methods for the preparation of 2- or 3-buten-4-olides[1a—d] exist because of the interest in the synthesis of natural products. In a previous paper, a covenient method for the preparation of 3-substituted 2-buten-4-olide using α,α-bis(phenylthio)-γ-butyrolactone was reported which was readily prepared by the reaction of γ-butyrolactone with *N*-phenylthiophthalimide.[2]

In the present study, the introduction of substituent groups to the α-position of 2-buten-4-olide (**1**) was investigated by the reaction of the lithium salt of β-phenylthio-γ-butyrolactone (**2**) with aldehydes and ketones and subsequent dehydrosulfenylation.

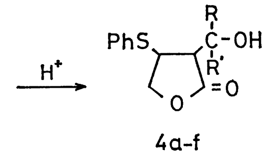
Results and Discussion

*Synthesis of α-Substituted β-Phenylthio-γ-butyrolactones (**4a**—**f**).* The Michael addition reaction of lithium benzenethiolate to **1** afforded **2**. However, when lithium benzenethiolate was allowed to react with **1** in THF at −50 °C and the reaction mixture quenched with 10% hydrochloric acid, **2** was obtained in only 52% yield because of the addition reaction of the resulting lithium salt of **2** to unreacted **1** to yield the lactone derivative (**3**). Therefore, in order to avoid the undesired addition reaction, the reaction was conducted in the presence of phenol, which neutralized the resulting lithium salt of **2** to give **2** quantitatively.



The alkylation of **2** with alkyl halides (methyl iodide, benzyl bromide, butyl bromide) in the presence of lithium diisopropylamide was examined, but this attempt was unsuccessful due to the formation of alkyl phenyl sulfide. This shows that the α-anion of **2** decomposes to the benzenethiolate anion and **1**.

The synthesis of α-substituted β-phenylthio-γ-butyrolactones was established by the reaction of the α-anion of **2** with aldehydes and ketones as electrophiles. The reaction of **2** with benzaldehyde in the presence of lithium diisopropylamide in THF at −50 °C for 2 h afforded α-(1-hydroxybenzyl)-β-phenylthio-γ-butyrolactone (**4a**) in 52% yield. Furthermore, it was found that the yield of **4a** was increased to 92% when a mixture of benzaldehyde and **1** was added to a solution of lithium benzenethiolate in THF at −50 °C. This reaction involves two different addition reactions, *i.e.*, the α-anion of **2** generated by the addition of lithium benzenethiolate to **1** underwent subsequent addition to benzaldehyde to give **4a**.



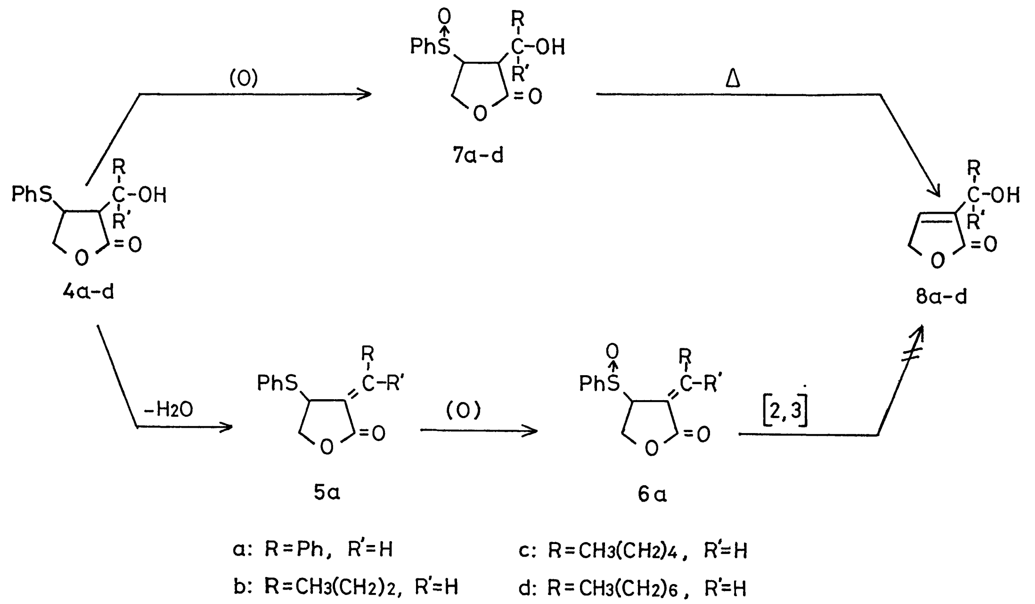
4a-f

a: R=Ph, R'=H
b: R=CH3(CH2)2, R'=H
c: R=CH3(CH2)4 R'=H
d: R=CH3(CH2)6, R'=H
e: R=Ph, R'=CH3
f: R=R'=C2H5

Scheme 1.

In a similar manner, the reactions with other aldehydes and ketones were investigated and these results are given in Table 1. As shown in Table 1, the reaction with acetophenone or 3-pentanone gave unsatisfactory results compared with the other aldehydes.

Dehydrosulfenylation. Dehydrosulfenylation[3] of **4a**—**d** to **8a**—**d** was achieved by elimination of the sulfinyl group of the α-substituted β-phenylsulfinyl-γ-butyrolactones (**7a**—**d**) prepared by the oxidation of **4a**—**d**. Oxidation of **4a** to α-(1-hydroxybenzyl)-β-phenylsulfinyl-γ-butyrolactone (**7a**) with *m*-chloroperbenzoic acid was conducted in dichloromethane at 0 °C for 1 h. Subsequent elimination of the sulfinyl group of **7a** without further purification in refluxing THF for 3 h in the presence of one equivalent of triethylamine afforded 2-(1-hydroxybenzyl)-2-buten-4-olide (**8a**) in 75% yield. Substitution of lead acetate as the eliminating agent in refluxing methanol gave **8a** in 60% yield. The results of dehydrosulfenylation of **4a**—**d** to **8a**—**d** are summarized in Table 2. For **8b**, **8c**, and **8d**, where the reaction time was longer than 1.5 h in the



Scheme 2.

TABLE 1. THE REACTION OF **1** WITH ALDEHYDES AND KETONES

Entry	Aldehyde or ketone	Temp °C	Time h	Product	Yield[a] %
1	Benzaldehyde[b]	−50	2	**4a**	92
2	Butanal[b]	−50	1.5	**4b**	61
3	Hexanal[b]	−50	1.5	**4c**	73
4	Octanal[b]	−50	1.5	**4d**	56
5	Acetophenone[c]	−50 −40	1 1	**4e**	17
6	3-Pentanone[c]	−40 −30	1 1	**4f**	7

a) The yields are based on **1**. b) For entry 1, 2, 3, and 4, 1.5 equiv of aldehyde was used. c) For entry 5 and 6, 2 equiv of ketone was used.

TABLE 2. FORMATION OF **8a**—**d**

Entry	Oxidation[a]		Thermolysis[b]		
	Sulfenyl lactone	Sulfinyl lactone	Time h	Product	Yield[c] %
1	**4a**	**7a**	3	**8a**	65
2	**4b**	**7b**	1.5	**8b**	84
3	**4c**	**7c**	1.5	**8c**	58
4	**4d**	**7d**	1.5	**8d**	69

a) Oxidation was conducted in dichloromethane at 0 °C and the oxidation products were used for the subsequent thermolysis without further purification. b) Thermolysis was conducted in refluxing THF in the presence of triethelamine. c) Yields are calculated from sulfenyl lactones **4a**—**d**.

thermolysis step, dehydration products were obtained.

In addition, a second method of dehydrosulfenylation, which involves [2,3] sigmatropic rearrangement of allyl sulfoxide (**6a**),[4] was attempted. The conversion of **4a** to **6a** was conducted as follows. Compound **4a** was treated with one equivalent of sulfuric acid in refluxing benzene with azeotropic removal of water to give α-benzylidene-β-phenylthio-γ-butyrolactone (**5a**) (90% yield). Oxidation of **5a** with *m*-chloroperbenzoic acid in dichloromethane afforded **6a** quantitatively. Several reaction conditions for the [2,3] sigmatropic rearrangement were examined, however, but the desired **8a** could not be obtained, the starting material **6a** being recovered in almost cases. The use of trimethylphosphite as the thiophile gave the reduction product, **5a**.

Thus a convenient method for the preparation of **8a**—**d** was established. Several reports exist of the introduction of substituent groups on the α-position of α,β-unsaturated ketones and esters.[5] In the reaction studied here the α-anion of **2** serves as an α-anion of **1**. The advantages of this method are (1) the starting materials are inexpensive and readily available; (2) there is no need to isolate the intermediate **2** and (3) the generation of the α-anion of **2** is performed by a week base, lithium benzenethiolate.

Experimental

Preparation of β-Phenylthio-γ-butyrolactone (2). To a solution of benzenethiol (1.10 g, 0.01 mol) in THF (10 ml) was added dropwise a hexane solution of butyllithium (15%, 6.3 ml, 0.01 mol) at −50 °C under nitrogen and the mixture stirred for 15 min. A THF (8 ml) solution of 2-buten-4-olide (**1**)[6] (0.84 g, 0.01 mol) and phenol (0.94 g, 0.01 mol) was added to this mixture over 10 min, and the mixture stirred for 1 h at −50 °C. The reaction mixture was warmed to room temperature and washed with 10% sodium carbonate to remove the phenol and extracted with three 30 ml portions of ether and dried over sodium sulfate. After removal of the solvent, the residual oil was chromatographed on silica gel using benzene as an eluting agent to yield 1.90 g (98%) of **2**: mp 51—52 °C (recrystallized from 2-propanol). IR 1770 cm^{-1}. NMR (CDCl$_3$) δ 6.98—7.27 (5H, m), 3.70—4.50 (3H, m), 2.06—3.00 (2H, m). MS 194 (M$^+$). Found: C, 61.55; H, 5.15; S, 16.46%. Calcd for $C_{10}H_{10}O_2S$: C, 61.83; H, 5.19; S, 16.50%.

α-(1-Hydroxybenzyl)-β-phenylthio-γ-butyrolactone (4a).

To a THF (8 ml) solution of benzenethiol (550 mg, 5 mmol) was added butyllithium (in hexane, 15%, 3.2 ml, 5 mmol) at −50 °C and the mixture stirred for 15 min. To this solution was added dropwise over 15 min a mixture of **1** (420 mg, 5 mmol) and benzaldehyde (795 mg, 7.5 mmol) in THF (10 ml) and the reaction mixture stirred for 1.5 h at −50 °C. The reaction mixture was poured with stirring into cold saturated ammonium chloride solution and extracted with three 30 ml portions of ether and the extracts dried over anhydrous sodium sulfate. After removal of the solvent, the residual oil was chromatographed on silica gel using benzene as an eluting agent to give 1344 mg (92%) of **4a**. Further purification of **4a** was conducted by recrystallization from 2-propanol: mp 127—127.5 °C. IR 3420, 1758 cm^{-1}. NMR (DMSO-d_6) δ 6.83—7.20 (10H, m), 6.02 (1H, d), 4.00—4.85 (3H, m), 3.30 (1H, s), 2.45 (1H, br). MS 300 (M$^+$). Found: C, 67.84; H, 5.37; S, 10.65%. Calcd for $C_{17}H_{16}O_3S$: C, 67.99; H, 5.37; S, 10.67%.

In a similar manner, α-(1-hydroxybutyl)-β-phenylthio-γ-butyrolactone (**4b**), α-(1-hydroxyhexyl)-β-phenylthio-γ-butyrolactone (**4c**), α-(1-hydroxyoctyl)-β-phenylthio-γ-butyrolactone (**4d**), α-(1-hydroxy-1-phenylethyl)-β-phenylthio-γ-butyrolactone (**4e**), and α-(1-ethyl-1-hydroxypropyl)-β-phenylthio-γ-butyrolactone (**4f**) were obtained in 61%, 73%, 56%, 17%, and 7% yields respectively. The reaction temperature and time for each aldehyde or ketone are as follows: −50 °C for 1.5 h for butanal, hexanal, and octanal; −50 °C for 1 h, −40 °C for 1 h for acetophenone; −40 °C for 1 h, −30 °C for 1 h for 3-pentanone. **4b**: IR 3450, 1758 cm^{-1}. NMR (CDCl$_3$) δ 7.20—7.60 (5H, m), 3.37—4.70 (4H, m) 2.42—2.85 (2H, m), 1.30—1.80 (4H, m), 0.93 (3H, t). MS 266 (M$^+$). **4c**: IR 3450, 1760 cm^{-1}. NMR (CDCl$_3$) δ 7.10—7.38 (5H, m), 3.70—4.68 (4H, m), 3.15 (1H, s) 2.52 (1H, t), 1.30 (8H, br), 0.88 (3H, t). MS 294 (M$^+$). **4d**: IR 3450, 1770 cm^{-1}. NMR (CDCl$_3$) δ 7.10—7.38 (5H, m), 3.72—4.68 (4H, m), 3.41 (1H, s), 2.52 (1H, t), 1.25 (12H, br), 0.88 (3H, t). MS 322 (M$^+$). **4e**: IR 3490, 1770 cm^{-1}. NMR (DMSO-d_6) δ 6.90—7.20 (10H, m), 4.50 (1H, s), 2.93—3.75 (3H, m), 2.38 (1H, d), 1.63 (3H, s). MS 314 (M$^+$). **4f**: IR 3500, 1775 cm^{-1}. NMR (CDCl$_3$) δ 7.35—7.65 (5H, m), 3.92—4.40 (2H, m), 2.20—3.35 (3H, m), 1.22—1.82 (4H, m), 0.83 (6H, dt). MS 280 (M$^+$).

*Preparation of α-Benzyliden-β-phenylthio-γ-butyrolactone (**5a**).* A solution of **4a** (3.00 g, 0.01 mol) in benzene (50 ml) in the presence of one equivalent of *p*-toluenesulfonic acid or concd sulfuric acid was heated under reflux for 8 h using a water separator. The reaction mixture was cooled to room temperature, washed with 10% sodium carbonate solution, extracted with THF–CHCl$_3$ (1:1), and dried. Removal of the solvent under reduced pressure and recrystallization from 2-propanol gave 2.54 g (90%) of **5a**: mp 218—219 °C. IR 1760 cm^{-1}. NMR (DMSO-d_6) δ 6.20—7.20 (11H, m), 3.50—4.65 (3H, m). MS 282 (M$^+$). Found: C, 72.27; H, 5.00; S, 11.35%. Calcd for $C_{17}H_{14}O_2S$: C, 72.53; H, 4.94; S, 11.40%.

*Preparation of α-Benzyliden-β-phenylsulfinyl-γ-butyrolactone (**6a**).* To a solution of **5a** (564 mg, 2 mmol) in dichloromethane (20 ml) was added dropwise a dichloromethane (15 ml) solution of *m*-chloroperbenzoic acid (414 mg, 2.4 mmol) at 0 °C. The reaction mixture was stirred for 1 h. The reaction mixture was washed with 10% sodium hydrogencarbonate, extracted with dichloromethane and dried over anhydrous sodium sulfate. Evaporation of the solvent gave an oil of **6a** and treatment with ether provided crystals of **6a** (578 mg, 97%): mp 169 °C (dec). IR 1780 cm^{-1}. NMR (DMSO-d_6) δ 6.80—7.60 (11H, m), 3.60—4.65 (3H, m). MS 298 (M$^+$). Found: C, 68.87; H, 4.92; S, 10.77%. Calcd for $C_{17}H_{14}O_3S$: C, 68.44; H, 4.73; S, 10.75%.

*General Procedure for Oxidation of **4a—d**.* To a solution of the β-phenylthio lactone derivative in dichloromethane (15 ml, for 1 g of the lactone) was added dropwise a dichloromethane solution of *m*-chloroperbenzoic acid (1.2 equiv) at 0 °C. The reaction mixture was stirred for 1 h at 0 °C, washed with 10% aqueous sodium hydrogencarbonate and dried. Evaporation of the solvent under reduced pressure gave the β-phenylsulfinyl derivative in quantitative yield. The products thus obtained, **7a—d** were used for subsequent thermolysis without further purification.

*General Procedure for Thermolysis of β-Phenylsulfinyl-γ-butyrolactones (**7a—d**).* A solution of the β-phenylsulfinyl-γ-butyrolactone derivative in THF (20 ml for 1 g of the lactone) in the presence of one equivalent of triethylamine was heated under reflux for 1.5—3 h. After removal of the solvent under reduced pressure the residue was chromatographed on silica gel using benzene–ether (3:1) as an eluent to give the 2-substituted 2-buten-4-olide.

Analytical and spectral results are as follows:

*2-(1-Hydroxybenzyl)-2-buten-4-olide (**8a**).* 75%. IR 3425, 1740 cm^{-1}. NMR (CDCl$_3$) δ 6.95—7.25 (6H, m), 5.40 (1H, s) 4.65 (2H, t), 3.37 (1H, br). MS 190 (M$^+$). Found: C, 69.97; H, 5.38%. Calcd for $C_{11}H_{10}O_3$: C, 69.46; H, 5.30%.

*2-(1-Hydroxybutyl)-2-buten-4-olide (**8b**).* 84%. IR 3425, 1730 cm^{-1}. NMR (CDCl$_3$) δ 7.18—7.30 (1H, m), 4.76 (2H, t), 4.42 (1H, br), 4.10 (1H, s), 1.08—1.98 (4H, m), 0.90 (3H, t). MS 138 (M−18). The spectral data of the dehydration product, 2-(1-butenyl)-2-buten-4-olide, of **8b** was shown since the elemental analysis of **8b** gave unsatisfactory results. IR 1745 cm^{-1}. NMR (CCl$_4$) δ 5.92—7.22 (3H, m), 4.80 (2H, s) 2.15 (2H, q), 1.08 (3H, t). MS 138 (M$^+$).

*2-(1-Hydroxyhexyl)-2-buten-4-olide (**8c**).* 58%. IR 3425, 1735 cm^{-1}. NMR (CDCl$_3$) δ 7.31—7.35 (1H, m), 4.80 (2H, t), 4.45 (1H, br), 3.55 (1H, br), 1.33 (8H, brs), 0.90 (3H, t). MS 166 (M−18). Found: C, 64.90; H, 9.04%. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75%.

*2-(1-Hydroxyoctyl)-2-buten-4-olide (**8d**).* 69%. IR 3425, 1750 cm^{-1}. NMR (CDCl$_3$) δ 7.10—7.25 (1H, m), 4.80 (2H, t), 4.38 (1H, br), 3.10 (1H, br), 1.30 (12H, brs), 0.90 (3H, t). MS 194 (M−18). Due to the difficulty in the further purification of **8d**, elemental analysis was achieved by dehydration product, 2-(1-octenyl)-2-buten-4-olide, of **8d** as follow. Found: C, 74.04; H, 9.31%. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34% [IR 1750 cm^{-1}. NMR (CCl$_4$) δ 5.90—7.23 (3H, m), 4.76 (2H, s), 1.35 (10H, brs), 0.90 (3H, t). MS 194 (M$^+$).]

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