Rearrangement Products of α-Salicylidene-γ-thiobutyrolactones

Gerald A. Miller and Ned D. Heindel*

Department of Chemistry, Lehigh University, Bethlehem, Pennsylvania 18015

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A convenient means of condensing various salicylaldehydes with γ-thiobutyrolactone has been found. The condensation, which is accompanied by a rearrangement, yields either a product of Michael-additive cyclization (a 2,3,3a,9b-tetrahydrothieno[3,2-*c*]coumarin) or one of oxidation (the disulfide of a 3-(2-mercaptoethyl)coumarin).

The salicylidene–thiolactone rearrangement has been previously reported for condensations in which *o*-hydroxybenzaldehydes were reacted with thianaphthen-2-one,[1] 5-ethylthiophen-2(3*H*)-one,[2] or 5-arylthiophen-2-(3*H*)-ones.[3] The thiolactones used in those studies reacted readily, a fact which undoubtedly reflects the aromaticities of their respective enol tautomers. No such activating factor exists for γ-thiobutyrolactone, whose condensations have typically involved strong bases in media of low polarity.[4,5] Zimmer devised a Wittig condensation to circumvent this difficulty and enable the synthesis and photorearrangement of α-salicylidene-γ-thiobutyrolactone (Scheme I) to a product presumed to be the (mercaptoethyl)coumarin (**1a**).[6] Our earlier work in thio lactone rearrangements has suggested that mercaptans such as (**1a**) might undergo closure to cyclic sulfides such as **2a**.[1,7] We thus repeated the reported synthesis of **1a** to effect a complete structural characterization of the molecule.

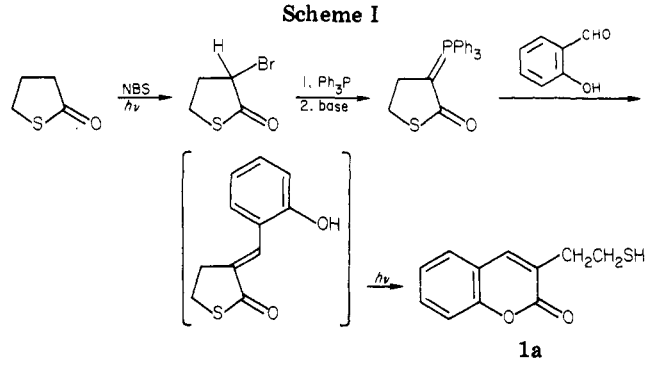
Results and Discussion

α-Bromo-γ-thiobutyrolactone was obtained in 27% yield by an alternative and somewhat more facile synthesis, via the diazotization–bromination of D,L-homocysteine thiolactone (Scheme II), than that reported earlier.[6] We have also modified Zimmer's procedure in that we have isolated and characterized the labile salicylidene thiolactone precursor of **1a**. The published method for the photochemical rearrangement did, indeed, produce the reported 3-(2-mercaptoethyl)coumarin (**1a**). The structure was supported by spectral evidence and nonidentity with the isomeric 2,3,3a,9b-tetrahydrothieno[3,2-*c*]coumarin (**2a**) obtained by the direct base-catalyzed condensation of γ-thiobutyrolactone and salicylaldehyde.

With strong bases in nonpolar solvents the initially formed salicylaldehyde salt precipitates, and while γ-butyrolactone has been condensed under such conditions, we have experienced no success with the more labile thiolactone.[8] However, when sodiosalicylaldehydes were dissolved in Me_2SO it was found possible to condense these materials with γ-thiobutyrolactone (Scheme III) and obtain modest yields of thienocoumarins (**2a–e**), isomeric with the mercaptoethyl compounds of the type reported by Zimmer.[6] It was apparent that the isolation procedure, precipitation of product from the Me_2SO by aqueous acid, allowed recovery of the thienocoumarins as the least soluble components under these conditions. Thin-layer chromatograms of the supernatant revealed a highly complicated reaction mixture from which no other compounds could be readily isolated. The thienocoumarins that were obtained were the analogues of benzo derivatives that we prepared in earlier studies.[7]

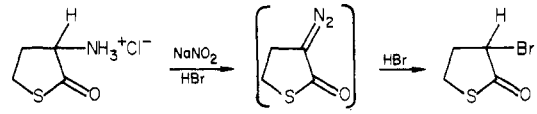
Attempts to improve the yields of **2** were unsuccessful. In fact, heating the reaction mixture generated a significant

Scheme I

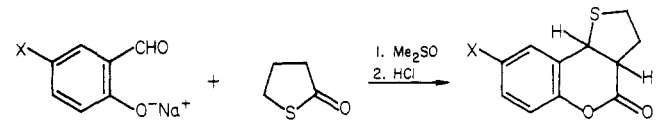


1a

Scheme II



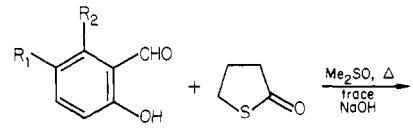
Scheme III

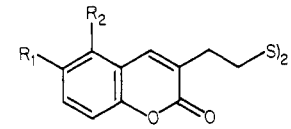


2a, X = H
b, X = Cl
c, X = Br
d, X = CH_3
e, X = CH_3O

2a–e

Scheme IV





3a, R_1 = R_2 = H
b, R_1 = Cl; R_2 = H
c, R_1 = Br; R_2 = H
f, R_1, R_2 = CH=CHCH=CH

(1) R. A. Conley and N. D. Heindel, *J. Org. Chem.*, **40**, 3169 (1975).
(2) N. D. Heindel and J. A. Minatelli, *J. Heterocycl. Chem.*, **13**, 669 (1976).
(3) N. D. Heindel, J. A. Minatelli, and D. Harris, *J. Org. Chem.*, **42**, 1465 (1977).
(4) F. Korte and K. H. Büchel, in "Newer Methods of Preparative Organic Chemistry", Academic Press, New York, 1964, Vol. 3, p 210.
(5) P. Rioult and J. Vialle, *Bull. Soc. Chim. Fr.*, 4477 (1968).
(6) H. Zimmer, F Häupter, S. Kharidia, H. Pauling, R. Gailey, T. Pampalone, T. Purcell, and R. Walter, *Tetrahedron Lett.*, 5435 (1968).
(7) R. A. Conley, Ph.D. Thesis, Lehigh University, 1974; *Diss. Abstr. Int. B*, **35**(11), 5324 (1975).
(8) H. Zimmer and J. Rothe, *J. Org. Chem.*, **24**, 28 (1959).

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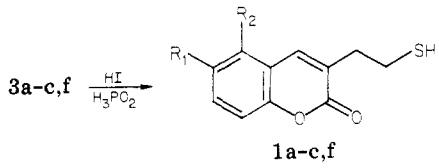
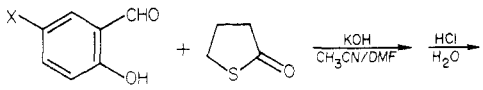
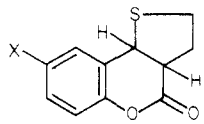
Scheme V



1a-c,f

Scheme VI





2a-c

quantity of disulfide byproduct (**3**); reducing the amount of base present caused these disulfides to be formed as the major products (Scheme IV) . This discovery permitted a new synthetic route to the (mercaptoethyl)coumarins by reduction of these disulfides. In a reversal of the well-known oxidation of mercaptans by iodine,[9] hydroiodic acid containing excess hypophosphorous acid served as a convenient reductant medium. It would appear from previous studies with selenol-promoted reductions of disulfides[10] that the hypophosphorus acid does not in itself directly reduce these disulfides. Under these acidic conditions the free mercaptoethyl compounds resisted cyclization and could be obtained in excellent yields (Scheme V).

Base-catalyzed cyclization of **1a** could be brought about through treatment with either sodium hydroxide in Me_2SO or with triethylamine in chloroform. In addition to the thienocoumarin **2a**, there was also a significant quantity of the disulfide **3a** produced. No **1a** remained unreacted. However, a similar cyclization attempted with **1f** using sodium hydroxide in Me_2SO resulted in recovery of the starting compound with no trace of the corresponding thienocoumarin—presumably a result of a peri-hindrance effect.

In fact, the optimum condition for the synthesis of these thienocoumarins was the direct combination of the salicylaldehydes and thiobutyrolactone in 3:2 acetonitrile/dimethylformamide containing an excess of potassium hydroxide (Scheme VI). The yields obtained were more than double those observed when the sodio salts were employed in Me_2SO (Scheme III).

These applications of the thiolactone rearrangement make several new types of coumarin derivatives available by a simple and direct procedure. Furthermore, the 3-(2-mercaptoethyl)coumarins are stable, isolable compounds unlike 3-(2-mercaptophenyl)coumarins, which tend to spontaneously cyclize to dihydrobenzothienocoumarins.[7]

Experimental Section

Melting points were determined in capillaries in a Thomas-Hoover apparatus or between cover glasses in a Fisher-Johns apparatus and are reported uncorrected. Infrared spectra were obtained in the medium specified on a Perkin-Elmer 283 infrared spectrometer. A Perkin-Elmer Hitachi R20A was utilized to obtain the proton magnetic resonance (^1H NMR) spectra. Chemical shifts are given in parts per million (ppm) downfield from internal tetramethylsilane in the indicated solvents. Combustion analyses were performed by Dr. G. I. Robertson, Florham Park, NJ.

α-Bromo-γ-thiobutyrolactone. A suspension of 30.7 g (0.200 mol) of D,L-homocysteine thiolactone hydrochloride was prepared in 150 mL of 47% hydrobromic acid. The suspension was stirred mechanically in an ice–salt bath while 15.0 g (0.217 mol) of sodium nitrite in 50 mL of chilled water was introduced slowly over 45 min at 5–10 °C. The mixture was stirred for an additional 30 min, allowed to warm to room temperature, and extracted with 3 × 75 mL of benzene. The dried ($MgSO_4$) extracts were evaporated in vacuo and distilled. (CAUTION! In one experiment, unreacted diazo intermediate decomposed explosively on attempted distillation. If crude material contains significant absorption at 2085 cm^{-1}, the reaction is incomplete and no distillation should be attempted.) The product (9.69 g, 27% yield) distilled at 62–65 °C (0.2 mm) (lit.[6] 68 °C at 0.3 mm): IR (CCl_4, matched cells) 1715 cm^{-1}; NMR (CCl_4) δ 2.4–2.8 (m, 2 H, CH_2CH_2S), 3.1–3.8 (m, 2 H, CH_2CH_2S), 4.40 (t, 1 H, CHBr).

α-Salicylidene-γ-thiobutyrolactone. The triphenylphosphonium bromide salt and the triphenylphosphorane ylid derived from it were prepared by Zimmer's method.[6] The ylide (Scheme I; 1.4 g, 4.0 mmol) and 0.50 g (4.0 mmol) of salicylaldehyde in 25 mL of tetrahydrofuran were photolyzed as described for 4 days with a 100-W light bulb (unfrosted) placed within 1 in. of the flask. The contents of the flask were refluxed during this irradiation. Evaporation of the solvent left an oil, which was chromatographed with benzene elutant on a silica gel column (1.5 × 15 cm). A solid fraction was obtained, which when recrystallized from methanol gave 0.30 g (40%) of the title compound: mp 165–166 °C; IR (C_6H_6, matched cells) 1685 cm^{-1}. Anal. Calcd for $C_{11}H_{10}O_2S$: C, 64.06; H, 4.89; S, 15.54. Found: C, 64.26; H, 5.14; S, 15.29.

3-(2-Mercaptoethyl)[1]benzopyran-2-one (1a). When 0.30 g of the Wittig condensation product, α-salicylidene-γ-thiobutyrolactone, was dissolved in 95% ethanol, the orginally recommended solvent,[6] and irradiated with the 100-W lamp for 2 weeks, a nearly quantitative yield of **1a** was obtained. The heat of the lamp was sufficient to effect reflux during this time period. The solid obtained on evaporation of the ethanol, mp 85–87 °C from methanol/water (lit.[6] mp 145 °C), had spectral properties in accord with the assigned structure: IR (KBr disk) 1720 cm^{-1}; NMR ($CDCl_3$) δ 1.41 (t, 1 H, SH), 2.83 and 2.89 (two s, 4 H, CH_2CH_2), 7.1–7.7 (m, 5 H, ArH and ArCH=C). Anal. Calcd for $C_{11}H_{10}O_2S$: C, 64.05; H, 4.89; S, 15.54. Found: C, 63.88; H, 5.03; S, 15.65.

2,3,3a,9b-Tetrahydrothieno[3,2-*c*]coumarins (2a–e). Sodio Salt Procedure. A solution of equimolar amounts, at a concentration of 1 M in Me_2SO solvent, of γ-thiobutyrolactone and the anhydrous sodium salts of 5-X-salicylaldehyde (X = H, Cl, Br, CH_3, and CH_3O for **a–e**, respectively) was sealed and allowed to stand at room temperature overnight. Dilution with a 20-fold excess of water and dropwise acidification with 3 M hydrochloric acid precipitated the crude products, which were recrystallized from ethanol to analytical purity. All products, **2a–e**, displayed complex aliphatic resonances integrating for five protons from δ 1.8 to 3.5 ppm, representing the two methylenes and the single methine flanking the carbonyl. The 9b benzylic hydrogen adjacent to the sulfur was a characteristic doublet of J = 5.5 Hz at 4.63 ± 0.02 ppm in all compounds. In the infrared spectra, prepared in hydrocarbon mull, all products displayed a saturated lactonelike C=O at 1760 ± 10 cm^{-1}.

2a: mp 133–135 °C; 25% yield. Anal. Calcd for $C_{11}H_{10}O_2S$: C, 64.06; H, 4.89; S, 15.54. Found: C, 63.83; H, 5.11; S, 15.72.

2b: 148–150 °C; 7% yield. Anal. Calcd for $C_{11}H_9ClO_2S$: 54.89; H, 3.77; S, 13.32. Found: C, 54.97; H, 3.91; S, 13.20.

2c: 157–159 °C; 10% yield. Anal. Calcd for $C_{11}H_9BrO_2S$: C, 46.33; H, 3.18; S, 11.24. Found: C, 46.12; H, 3.32; S, 11.50.

2d: 144–145 °C; 15% yield. Anal. Calcd for $C_{12}H_{12}O_2S$: C, 65.43; H, 5.49; S, 14.55. Found: C, 65.19; H, 5.65; S, 14.60.

2e: 121–122 °C; 30% yield. Anal. Calcd for $C_{12}H_{12}O_3S$: C, 61.00; H, 5.12; S, 13.57. Found: C, 61.21; H, 5.33; S, 13.74.

Aqueous Base Procedure. Alternatively, a 3:2 mixture of acetonitrile/dimethylformamide containing the 5-X-salicylaldehyde and the thiolactone in equal molar amounts at a concentration of 0.5 M was treated with 5.0 M aqueous sodium hydroxide. Base was added in equimolar amounts to the organic reactants present. The mixture was refluxed overnight, con-

(9) E. E. Reid, "Organic Chemistry of Bivalent Sulfur", Chemical Publishing Co., New York, 1960, Vol 1, p 124.
(10) W. H. H. Günther, *J. Org. Chem.*, 31, 1202 (1966).

centrated to a syrup, diluted with a 20-fold volume of water, and acidified with dilute hydrochloric acid, and the precipitated product was collected by filtration. Recrystallization from methanol gave analytically pure material identical in melting point and spectra with that obtained by the sodio salt method: for **2a**, 51% yield, mp 134–135 °C; for **2b**, 42% yield, mp 147.5–150 °C; for **2c**, 32% yield, mp 157–159 °C.

General Procedure for the Disulfides of 3-(2-Mercaptoethyl)coumarins (3a-f). A solution of 20 mmol of the 5-X-salicylaldehyde (X = H, Cl, or Br) or 2-hydroxy-1-naphthaldehyde, 20 mmol of γ-thiobutyrolactone, 2.0 mmol of pulverized sodium hydroxide, and 7.5 mL of dimethyl sulfoxide was heated for 3 days at 80–85 °C. The mixture was added to 150 mL of water, acidified with 10 mL of concentrated hydrochloric acid, and decanted. The gummy tar that resulted was triturated with hot methanol to yield a crystalline solid, which was recrystallized from 1:1 chloroform/methanol to analytical purity. All compounds scanned as mulls in hydrocarbon media revealed a conjugated coumarin-like C=O at 1707 ± 3 cm^{-1}.

3a: mp 152–154 °C; 43% yield; NMR ($CDCl_3$) δ 3.00 (s, 8 H, two CH_2CH_2), 7.42 (s, 2 H, two ArCH=C), 7.4–7.7 (m, 8 H, two Ar rings). Anal. Calcd for $C_{22}H_{18}O_4S_2$: C, 64.37; H, 4.42; S, 15.62. Found: 64.39; H, 4.65; S, 15.54.

3b: 192–194 °C; 10% yield; NMR (CF_3COOH) δ 3.08 (s, 8 H, two CH_2CH_2), 7.2–7.7 (m, 6 H, two Ar rings), 7.78 (s, 2 H two ArCH=C). Anal. Calcd for $C_{22}H_{16}Cl_2O_4S_2$: C, 55.12; H, 3.36; S, 13.38. Found: C, 54.96; H, 3.43; S, 13.11.

3c: 199–201 °C; 32% yield; NMR (CF_3COOH) δ 3.20 (s, 8 H, two CH_2CH_2), 7.1–8.0 (m, 8 H, overlapping two Ar rings and two ArCH=C). Anal. Calcd for $C_{22}H_{16}Br_2O_4S_2$: C, 46.50; H, 2.84; S, 11.28. Found: C, 46.47; H, 2.90; S, 11.19.

3f: 205–207 °C; 48% yield; NMR (CF_3COOH) δ 3.10 (s, 8 H, two CH_2CH_2), 7.0–8.2 (m, 12 H, two Ar rings), 8.38 (s, 2 H, two ArCH=C); molecular weight by Rast method = 515 ± 7, calcd molecular weight: 510. Anal. Calcd for $C_{30}H_{22}O_4S_2$: C, 70.57; H, 4.34; S, 12.56. Found: C, 70.35; H, 4.39; S, 12.50.

General Procedure for Reduction of Disulfides (3a–c,f) to (Mercaptoethyl)coumarins (1a–c,f). A reductant solution of 7.5 g (30 mmol) of iodine, 7.5 mL of 47% hydroiodic acid, and 10 mL of 50% hypophosphorous acid was prepared and 1 mmol of the disulfide (**3a**, **3b**, **3c**, or **3f**) added to it. The suspension that resulted was stirred at 80 °C until solution occurred, usually 10–20 min, and the solution then was poured into 80–100 mL of cold water. The precipitated solid was filtered, recrystallized from 1:1 methanol/water, and submitted for analysis.

1a: mp 85–87 °C; 86% yield; NMR and IR spectra identical with those reported above.

1b: mp 111–113 °C; 67% yield; NMR ($CDCl_3$) δ 1.39 (t, 1 H, SH), 2.83 and 2.89 (two s, 4 H, CH_2CH_2), 7.3–7.5 (m, 4 H, ArH and ArCH=C); IR (Nujol) 1715 cm^{-1}. Anal. Calcd for $C_{11}H_9ClO_2S$: C, 54.89; H, 3.77; S, 13.32. Found: C, 54.78; H, 3.75; S, 13.01.

1c: mp 104–106 °C; 62% yield; NMR ($CDCl_3$) δ 1.40 (t, 1 H, SH), 2.84 and 2.90 (two s, 4 H, CH_2CH_2), 7.1–7.7 (m, 4 H, ArH and ArCH=C); IR (Nujol) 1720 cm^{-1}. Anal. Calcd for $C_{11}H_9BrO_2S$: C, 46.33; H, 3.18; S, 11.24. Found: C, 46.55; H, 3.47; S, 11.48.

1f: mp 135–138 °C; 68% yield; NMR ($CDCl_3$) δ 1.44 (t, 1 H, SH), 2.90 and 2.98 (two s, 4 H, CH_2CH_2), 7.3–8.4 (m, 7 H, ArH and ArCH=C); IR (Nujol) 1700 cm^{-1}. Anal. Calcd for $C_{15}H_{12}O_2S$: C, 70.29; H, 4.72; S, 12.51. Found: C, 70.01; H, 4.70; S, 12.26.

Cyclization of 1a in Basic Media. A solution of 1.3 mmol of **1a** in either 1 mL of Me_2SO containing 0.05 g of powdered sodium hydroxide or in 2 mL of 1:1 triethylamine/chloroform was degassed with nitrogen, sealed, and agitated at room temperature for 3 h. Thirty milliliters of 1 N sulfuric acid was added to the sodium hydroxide–Me_2SO reaction and the milky suspension was stirred for 12 h to coagulate the product. The triethylamine/chloroform reaction was simply evaporated in vacuo. Subsequent treatment of the crude product was identical. Chromatography (TLC) and spectral examination showed that the starting material had vanished. Preparative thin-layer chromatography on silica gel plates with benzene elutant developed only two spots at R_f 0.19 and 0.65 in approximately a 1:2 ratio. By comparison with the R_f values of standards and by extraction from the scraped bands, the compounds were identified as the disulfide **3a**, mp 150–152 °C, and the thienocoumarin **2a**, mp 133–135 °C. Similar reactions of **1f** returned starting material.

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Registry No. **1a**, 20972-55-8; **1b**, 79043-28-0; **1c**, 79043-29-1; **1f**, 79043-30-4; **2a**, 79043-31-5; **2b**, 79043-32-6; **2c**, 79043-33-7; **2d**, 79043-34-8; **2e**, 79043-35-9; **3a**, 79043-36-0; **3b**, 79043-37-1; **3c**, 79043-38-2; **3f**, 79043-39-3; α-bromo-γ-thiobutyrolactone, 20972-64-9; D,L-homocysteine thiolactone hydrochloride, 6038-19-3; α-salicylidene-γ-thiobutyrolactone, 79043-40-6; α-triphenylphosphorylidene-γ-thiobutyrolactone, 20972-65-0; sodio salicylaldehyde, 3116-83-4; sodio 5-chloro-salicylaldehyde, 66670-52-8; sodio 5-bromo-salicylaldehyde, 66670-53-9; sodio 5-CH_3-salicylaldehyde, 79043-41-7; sodio 5-CH_3O-salicylaldehyde, 79043-42-8; salicylaldehyde, 90-02-8; 5-chloro-salicylaldehyde, 635-93-8; 5-bromo-salicylaldehyde, 1761-61-1; 2-hydroxy-1-naphthaldehyde, 708-06-5.