Chemistry of 1-(Trimethylsiloxy)-1-methoxy-3-[alkyl(aryl)thio]-1,3-butadienes and the Synthesis of Aryl Sulfides via a Cycloaromatization Reaction

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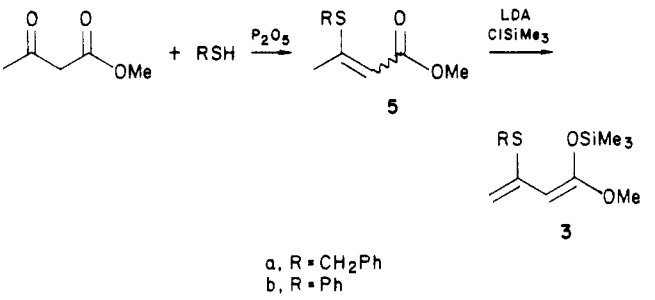
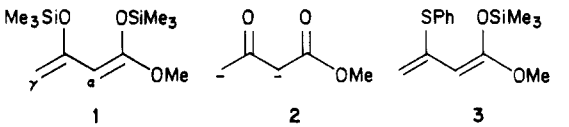
The preparation of 1-(trimethylsiloxy)-1-methoxy-3-[alkyl(aryl)thio]-1,3-butadienes and their Lewis acid catalyzed reactions with a number of carbonyl electrophiles are described.

The last decade has witnessed an explosive development in the chemistry of enol silyl ethers.[1,2] It is now well recognized that enol silyl ethers can be prepared,[1,2] often with good regioselectivity.[3] They undergo reactions that are complementary[4] to those of enolate anions. The equivalence of aldol,[4] Michael,[5] Mannich,[6] Claisen,[7] and Stobbe[8] reactions can be carried out with enol silyl ethers. Furthermore, in the alkylation reactions,[9] they can be alkylated with tertiary alkyl halides,[10,11] whereas enolate anions can be alkylated with primary and secondary alkyl halides. Another important development is the chemistry of dienol silyl ethers.[12] Their use as Diels–Alder dienes have been exploited fully in the synthesis of carbocyclic and heterocyclic compounds.[13-15] 1-Siloxybutadienes undergo reactions selectively at the γ-position,[16] whereas dienolates react at the α-position, illustrating once again the complementary nature of the two types of chemistry. Our own attention[17-19] has focused mainly on the chemistry of bis(enol silyl ethers) such as **1** because they can be considered as the equivalent of the corresponding enolate dianion **2**. Thus **1** undergoes reactions with electrophiles at the γ-position first followed then by reaction at the α-position.[17] Using **1** as a 1,3-dinucleophile, we have developed a cycloaromatization reaction for the regiocontrolled synthesis of phenols[20,21] as well as the synthesis of

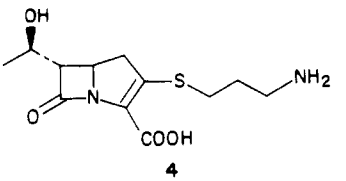
Scheme I



carbocyclic systems.[22] Such an approach has been used for the synthesis of sclerin[23] and Δ^1-tetrahydrocannabinol.[24]



We report here the chemistry of 1-(trimethylsiloxy)-1-methoxy-3-[alkyl(aryl)thio]-1,3-butadienes **3**, the 3-thio analogue of **1**. Several features of **3** are of interest in this study. One may like to know whether the regioselectivity of **3** in its reaction with elecrophiles is influenced by the presence of thio group. The second question relates to the ability of **3** to act as a dinucleophile even though it is only a mono(enol silyl ether). This has a direct bearing on the extension of the cycloaromatization reaction to the synthesis of aryl sulfides, thus making the reaction a more general approach to the construction of aromatic compounds. The role of **3** as a Diels–Alder diene is also of interest in synthesis it will lead to a masked cyclohexa-1,3-dione, where the two carbonyl functions are easily differentiated. Finally, we note that for thienamycin **4** and similar carbapenems, the structure can in principle be constructed by a combination of a monocyclic β-lactam and **3**.[25]



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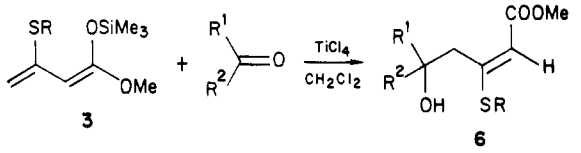
Results and Discussion

Preparation of 1-(Trimethylsiloxy)-1-methoxy-3-[alkyl(aryl)thio]-1,3-butadiene. Methyl 3-thio-(*E*)-2-butenoates **5** can be prepared readily by the literature procedure from diketene.[26] Alternatively, methyl acetoacetate can react with thiols and P_2O_5[27] to give a mixture of (*E*)- and (*Z*)-**5**. Reaction of **5** and lithium diisopropylamide (LDA) in tetrahydrofuran at −78 °C followed by quenching of the anion with chlorotrimethylsilane gave the enol silyl ether **3** in good yield (Scheme I). NOE experiments established the stereochemistry of **3b** to be *Z*. The stereochemistry of **3a** was assigned as *Z* as well in view of the similar chemical shifts of the vinyl protons in their 1_H NMR spectra. On the other hand, the same stereoisomer was obtained even though the starting **5** contains a mixture of *E* and *Z* isomers.

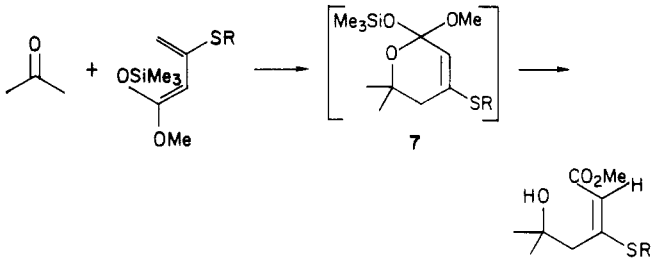
Compound **3** appears to be less sensitive to moisture in air than the corresponding bis(enol ether) **1**. In our hands, **3** can be kept in the freezer (0 °C) without deterioration for up to 4 weeks.

Reactions of 3 with Carbonyl Electrophiles. Compound **3** reacts with a number of carbonyl electrophiles under $TiCl_4$ conditions to give γ-products **6** exclusively in all cases. Regioselectivity in the reaction of dienyl silyl



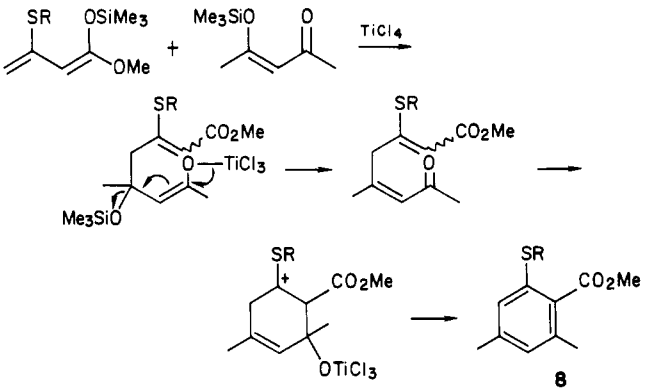
a, R = $PhCH_2$, $R^1 = R^2 = CH_3$
b, R = Ph, $R^1 = R^2 = CH_3$
c, R = $PhCH_2$, $R^1, R^2 = C_5H_{10}$
d, R = Ph, $R^1, R^2 = C_5H_{10}$
e, R = Ph, R^1 = Ph, R^2 = H

ether with electrophiles has been a subject of much recent studies.[16] Our present results indicate that the thio substituent at the 3-position, like the corresponding 3-siloxy substituent, enhances the γ-selectivity. Another interesting observation is the fact the product **6** retains the enethiol ether structure. Furthermore, the stereochemistry of the olefin is predominantly *E*. This raises the possibility that the reaction may have proceeded through a cyclic intermediate **7**. Similar intermediate has been proposed for the reaction between 3-siloxy-1-methoxy-1,3-butadiene and carbonyl compounds under Lewis acid conditions.[15]

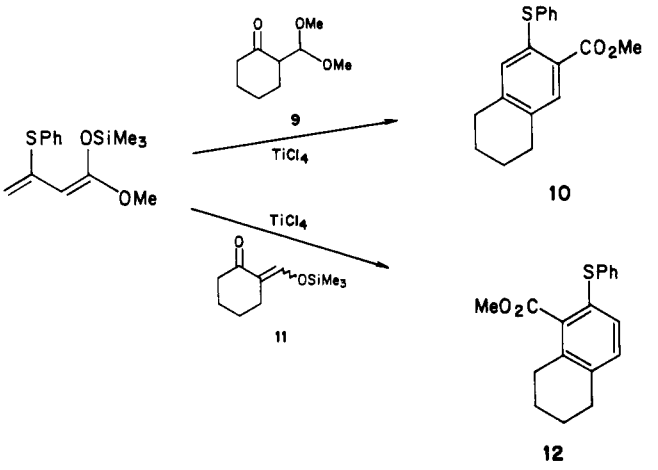


We are less inclined to favor such a cyclic intermediate as the sole pathway under our reaction conditions. This is due to the fact that when benzaldehyde was used as the electrophile, the product **6e** showed a substantial amount of the *Z* isomer. We have shown independently that the *Z* isomer could not have been formed by isomerization of the *E* isomer under the reaction conditions.

Scheme II



Scheme III



Cycloaromatization Reaction for the Synthesis of Aryl Sulfides. Reaction of **3** with 4-(trimethylsiloxy)-pent-3-enone, a 1,3-dicarbonyl equivalent, gave the aromatic compound **8** under $TiCl_4$ conditions. The cycloaromatization must have proceeded by reaction of **3** first at the γ-position followed by an intramolecular condensation at the α-position and then aromatization (Scheme II). The reaction is similar to the cycloaromatization reaction we have previously reported for the synthesis of phenolic compounds.[20,21] The direction of the cycloaromatization reaction can be controlled by using 1,3-dicarbonyl equivalents of different reactivities. Thus **3b** condensed with **11** to give the isomeric aromatic compound **12** (Scheme III) From the structures of **10** and **12**, it is clear that, in the electrophilic component, the relative reactivities are in the following order: The conjugative position is more reactive than the carbonyl functioin which is more reactive than the acetal function.[20]

Arylsulfur compounds are usually prepared by substitution reactions, either nucleophilic or electrophilic, of existing aromatic precursor compounds.[28] Such an approach is often plagued with the problem of regioselection in obtaining the desired substitution pattern. The cycloaromatization process offers the advantage of regiocontrol in the synthesis of arylsulfur compounds. This can be illustrated by the synthesis of the tetracyclic thia lactone **13**. Previous syntheses of this type of compounds often encountered problems of regiochemistry and mixture of isomers were usually obtained.[29] Compound **10**, obtained

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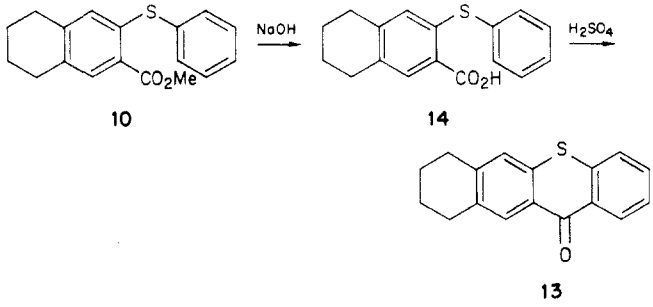
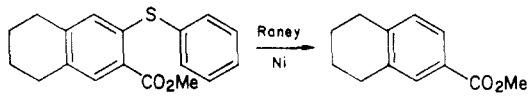
by the cycloaromatization reaction, can only be cyclized in one way. Thus, alkaline hydrolysis of **10** followed by acid cyclization gave **13** as the only product in good yield.



10 14 13

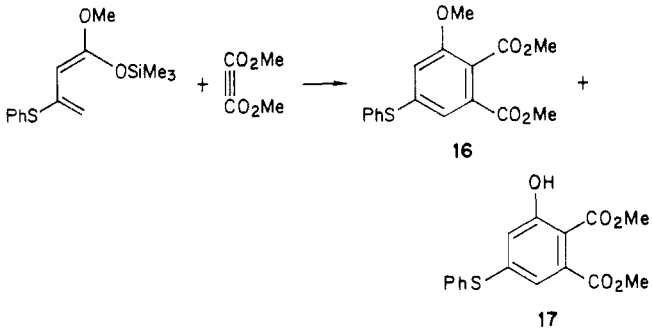
These results complement our previous reported cycloaromatization reactions leading to phenolic[20,21] and anilino[30] compounds. Furthermore, the sulfur moity can be readily removed by hydrogenolysis. For example, when compound **10** was subjected to treatment with Raney nickel, the desulfurized aromatic compound **15** was obtained in good yield. Thus, the present reaction represents an approach to the synthesis of substituted benzoic acids as well.



10 15

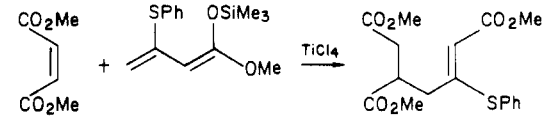
Diels–Alder Reactions. In recent years, the use of heteroatom-substituted butadienes in synthesis has received much attention. Dienes with both sulfur and an oxygen substituents in the 1,2-, 1,4-, and 2,3-substitution patterns[31-34] have been investigated. Compound **3**, with the oxygen and the sulfur substituents in the 1,3-pattern, offers the advantage that the Diels–Alder adduct would be a 1,3-cyclohexanedione with the two carbonyl groups differently masked.

Reaction of **3** with dimethyl acetylenedicarboxylate proceeded readily to give the aromatic compounds **16** and **17** in good yield.



16 17

On the other hand, reaction of **3** with dimethyl maleate did not give any Diels–Alder adduct under thermal conditions. Addition of a Lewis acid, such as aluminum chloride or titanium tetrachloride, gave the Michael adduct **18**. This suggests that compound **3** is not particularly effective as a Diels–Alder diene, and its propensity to undergo Michael addition therefore offers some interesting potential in organic synthesis. We are exploring this aspect of its chemistry.



18

Experimental Section

Melting and boiling points are uncorrected. Infrared spectra were obtained from films on NaCl plates for liquids and from solutions in 0.1-mm cells for solids by using a Perkin-Elmer 297 spectrophotometer. The ^1H NMR spectra were recorded on Varian XL-200, T-60, and T-60A instruments with Me_4Si as internal standard. Mass spectra were obtained on a DuPont 492B machine operating at 70 eV. Column chromatography was performed on silica gel (Merck). Et_3N and *i*-Pr_2NH were dried by distillation from CaH_2; hexane and CH_2Cl_2 from P_2O_5. THF was distilled under nitrogen from sodium–benzophenone directly into the reaction vessel.

(*E*)-3-(Alkylthio)crotonic Acids. The carboxylic acids were prepared according to the reported methods.[26]

(*E*)-3-(Benzylthio)crotonic acid: mp 111 °C (with bubbling); IR ($CHCl_3$) 2980 br, 1670, 1591 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.5 (s, 3 H), 4.1 (s, 2 H), 5.72 (s, 1 H), 7.43 (s, 5 H), 11.33 (br, 1 H); MS, *m/e* (relative intensity) 208 (M^+, 17), 145 (22), 117 (22), 91 (100); exact mass calcd for $C_{11}H_{12}O_2S$ 208.056, obsd 208.054.

Methyl (*E*)-3-(Phenylthio)crotonate (5b). To a well-stirred solution of 10 g (51.6 mmol) of 3-(phenylthio)crotonic acid and 20% aqueous KOH (3.76 g, 67 mmol) was added 6.4 mL of dimethyl sulfate (6.34 mL, 67 mmol) slowly. The stirring was continued for 2 h, and then 100 mL of saturated $NaHCO_3$ solution was added. The mixture was heated at 70 °C for 15 min. The ester was extracted with ether and dried over $MgSO_4$. The solvent was evaporated, and the ester was distilled under vacuum to give **5b**, bp 168 °C (7 mm), in 86% yield: IR (film) 1710, 1610 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.38–7.49 (m, 5 H), 5.21–5.24 (q, 1 H), 3.58 (s, 3 H), 2.42 (d, J = 0.4 Hz, 3 H); MS, *m/e* (relative intensity) 208 (M^+, 76), 177 (76), 149 (100), 134 (51), 109 (57); exact mass calcd for $C_{11}H_{12}O_2S$ 208.056, obsd 208.054.

1-(Trimethylsiloxy)-1-methoxy-3-(phenylthio)-1,3-butadiene (3b). To a solution of 1.7 mL of diisopropylamine (12 mmol) in 30 mL of dry THF under N_2 was added 8.0 mL of 1.5 M *n*-butyllithium in hexane after cooling to 0 °C. The reaction mixture was cooled to −78 °C. A quantity of 2.1 g of **5b** in 10 mL of THF was added and the solution stirred for 20 min. The yellow-colored solution was quenched with 2.0 mL (16 mmol) of chlorotrimethylsilane. The solvent was removed under reduced pressure after a further 20 min, and the residue was washed and filtered with cold, dry hexane. The hexane was removed from the filtrate under reduced pressure to give **3b** in quantitative yield. Compound **3b** can be kept in a stoppered container for up to 4 weeks in the freezer without obvious decomposition but is slowly hydrolyzed to **5b**, when exposed to air: IR (film) 1625, 1580 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.21–7.44 (m, 5 H), 5.52 (s, 1 H), 5.02 (s, 1 H), 4.11 (s, 1 H), 3.47 (s, 3 H), 0.27 (s, 9 H).

1-(Trimethylsiloxy)-1-methoxy-3-(benzylthio)-1,3-butadiene (3a) was prepared as described for **3b** by using compound **5a**. **3a** is not as stable as **3b** and is used immediately in its reactions: IR (film) 1638 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.27 (s, 5 H), 5.28 (s, 1 H), 4.83 (s, 1 H), 4.13 (s, 1 H), 3.92 (s, 2 H), 3.52 (s, 3 H), 0.23 (s, 9 H).

Methyl 5-Hydroxy-5-phenyl-3-(phenylthio)pent-2-enoate (6e). To a well-stirred mixture of **3b** (1.12 g, 4 mmol) and benzaldehyde (0.43 g, 4 mmol) in 20 mL of CH_2Cl_2 under nitrogen at −78 °C was added titanium tetrachloride (0.45 mL, 4 mmol). After 3 h, the dark red mixture was added to aqueous $NaHCO_3$ and extracted with ether. The extract was dried ($MgSO_4$) and evaporated to give an oil, which was column chromatographed (eluant, 20% ethyl acetate–hexane) to give *E* (mp 82–84 °C) and *Z* (viscous oil) isomers of methyl 5-hydroxy-5-phenyl-3-(phenylthio)pent-2-enoate in the ratio of 2:1, respectively, with 68% yield.

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(*E*)-**6e**: IR ($CHCl_3$) 3430 br, 1702, 1595 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.91 (dd, J = 3.4 and 13.7 Hz, 1 H), 3.5 (dd, J = 9.8 and 13.7 Hz, 1 H), 5.39 (s, 1 H), 3.65 (s, 3 H), 4.03 (d, J = 6 Hz), 5.01–5.13 (m, 1 H), 7.21–7.58 (m, 10 H); MS, m/e (relative intensity) 314 (M^+, 2), 282 (36), 208 (89), 176 (84), 149 (100); exact mass calcd for $C_{18}H_{18}O_3S$ 314.098, obsd 314.095.

(*Z*)-**6e**: IR ($CHCl_3$) 3600, 1694, 1578 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.13 (d, J = 2.7 Hz, 1 H), 2.44 (dd, J = 9.4 and 14 Hz, 1 H), 2.66 (dd, J = 3.2 and 14 Hz, 1 H), 3.75 (s, 3 H), 4.59–4.68 (m, 1 H), 5.97 (s, 1 H), 7.17–7.45 (m, 10 H); MS, m/e (relative intensity) 314 (M^+, 4), 208 (64), 176 (34), 149 (69), 28 (100); exact mass calcd for $C_{18}H_{18}O_3S$ 314.098, obsd 314.096.

Methyl 5-Hydroxy-5-methyl-3-(phenylthio)hex-2-enoate (6b). To a well-stirred mixture of **3b** (1.12 g, 4 mmol) and acetone (0.29 mL, 4 mmol) in dry CH_2Cl_2 (20 mL) under nitrogen at −78 °C was added titanium tetrachloride (0.45 mL, 4 mmol). After 5 h, the dark red colored mixture was added to aqueous $NaHCO_3$ and extracted with ether. The extract was dried ($MgSO_4$), and the solvent was evaporated. The crude product was purified by column chromatrography (eluant, 15% ethyl acetate–hexane) to give **6b** (oil) in 71% yield: IR (film) 3455 br, 1682, 1593 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.39 (s, 6 H), 3.06 (s, 2 H), 3.58 (s, 3 H), 3.6–3.72 (br, 1 H), 5.3 (s, 1 H), 7.41–7.53 (m, 5 H); MS, m/e (relative intensity) 266 (M^+, 20), 234 (27), 176 (51), 149 (66), 110 (85), 59 (100); exact mass calcd for $C_{14}H_{18}O_3S$ 266.098, obsd 266.095.

Methyl 5-Hydroxy-5-methyl-3-(benzylthio)hex-2-enoate (6a). The reaction was performed as above with **3a** and acetone. The product, an oil, was purified by column chromatography (eluant, 15% ethyl acetate–hexane) to give methyl 5-hydroxy-5-methyl-3-(benzylthio)pent-2-enoate (mp 65–67 °C) in 58% yield: IR (film) 3450 br, 1706, 1685, 1585 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.32 (s, 6 H), 3.00 (s, 2 H), 3.57 (s, 1 H), 3.67 (s, 3 H), 4.03 (s, 2 H), 5.75 (s, 1 H), 7.3 (s, 5 H); MS, m/e (relative intensity) 280 (M^+, 1), 262 (10), 248 (13), 222 (14), 131 (25), 91 (100).

Methyl 4-(1-Hydroxy-1-cyclohexyl)-3-(phenylthio)but-2-enoate (6d). The reaction was performed as above with **3b** and cyclohexanone. The crude product was purified by column chromatography (eluant, 15% ethyl acetate–hexane) to give **6d** (mp 86–87 °C) in 69% yield: IR ($CHCl_3$) 3440 br, 1678, 1590 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.13–2.13 (m, 10 H), 3.03 (s, 2 H), 3.5 (s, 1 H), 3.57 (s, 3 H), 5.32 (s, 1 H), 7.45 (s, 5 H); MS, m/e (relative intensity) 306 (M^+, 3), 274 (28), 208 (74), 176 (62), 149 (87), 110 (80), 55 (100). When the reaction was allowed to proceed overnight instead of **3h**, 4-(phenylthio)-1-oxaspiro[5.5]undec-3-en-2-one was also obtained in addition to compound **6d**: IR ($CHCl_3$) 1681 cm^{-1}; ^1H NMR ($CDCL_3$) δ 0.83–2.17 (m, 10 H), 2.5 (s, 2 H), 5.3 (s, 1 H), 7.4 (s, 5 H); MS, m/e (relative intensity) 274 (M^+, 5), 149 (22), 109 (43), 85 (55), 43 (100); exact mass calcd for $C_{16}H_{18}O_2S$ 274.103, obsd 274.107.

Methyl 4-(1-Hydroxy-1-cyclohexyl)-3-(benzylthio)but-2-enoate (6c). The reaction was performed as above with **3a** and cyclohexanone. The product was purified by column chromatography (eluant, 15% ethyl acetate–hexane) to give **6c** in 67% yield as an oil: IR (film) 3450 br, 1685, 1584 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.77–2.5 (m, 10 H), 2.97 (s, 2 H), 3.47 (s, 1 H), 3.65 (s, 3 H), 4.00 (s, 2 H), 5.73 (s, 1 H), 7.28 (s, 5 H); MS, m/e (relative intensity) 288 (14), 197 (24), 190 (10), 179 (15), 151 (15), 125 (18), 91 (100).

Methyl 4,6-Dimethyl-2-(phenylthio)benzoate (8). To a well stirred mixture of **3b** (1.12 g, 4 mmol) and 4-(trimethylsiloxy)-pent-3-en-2-one (0.69 g, 4 mmol) in dry CH_2Cl_2 (20 mL) under nitrogen at −78 °C was added titanium tetrachloride (0.45 mL, 4 mmol). The mixture became dark red. After 5 h, the crude reaction mixture was added to aqueous $NaHCO_3$ and extracted with ether. The ether extract was dried ($MgSO_4$), and the solvent was evaporated. The crude product was purified by column chromatography (eluant, 5% ethyl acetate–hexane) to give 8 as a colorless oil (700 mg, 64%): IR (film) 1728, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.17 (s, 3 H), 2.27 (s, 3 H), 3.77 (s, 3 H), 6.83 (s, 2 H), 7.15 (s, 5 H); MS, m/e (relative intensity) 272 (M^+, 91), 241 (96), 239 (100), 208 (76), 177 (95); exact mass calcd for $C_{16}H_{16}O_2S$ 272.087, obsd 272.082.

Methyl 2-(phenylthio)-5,6,7,8-tetrahydronaphthalene-1-carboxylate (12) was prepared from **3b** and **11** as described for **8**. The product was purified by column chromatography (eluant, 10% ethyl acetate–hexane) to give **10** as a yellowish colored oil (630 mg, 53%): IR (film) 1730, 1585 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.5–2.02 (m, 4 H), 2.37–3.0 (m, 4 H), 3.83 (s, 3 H), 7.22 (s, 5 H), 7.04 (d, J = 8.1 Hz, 1 H); MS, m/e (relative intensity) 298 (M^+, 33), 265 (38), 206 (49), 174 (100), 149 (49); exact mass calcd for $C_{18}H_{18}O_2S$ 298.103, obsd 298.103.

Methyl 3-(Phenylthio)-5,6,7,8-tetrahydronaphthalene-2-carboxylate (10b). To trimethyl orthoformate (0.53 g, 5 mmol) in dry CH_2Cl_2 (5 mL) under nitrogen at −78 °C were added $TiCl_4$ (0.56 mL, 5 mmol) and cyclohexanone trimethylsilyl enol ether (0.85 g, 5 mmol). After 2 h at −78 °C a further 0.56 mL of $TiCl_4$ was added, followed by **3b** (1.4 g, 5 mmol) in dry CH_2Cl_2 (5 mL). After a further 3 h at −78 °C and overnight at room temperature, the crude reaction mixture was worked up as for **8**. Column chromatography with 8% ethyl acetate–hexane as eluant gave **10** as light yellowish needles (900 mg, 61%). One recrystallization from hexane gave white, large needles, mp 114–115 °C: IR ($CHCl_3$) 1705 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.5–2.1 (m, 4 H), 2.35–3.0 (m, 4 H), 3.9 (s, 3 H), 6.57 (s, 1 H), 7.4 (s, 5 H), 7.65 (s, 1 H); MS, m/e (relative intensity) 298 (M^+, 100), 267 (43), 221 (25), 239 (18); exact mass calcd for $C_{18}H_{18}O_2S$ 298.103, obsd 298.097.

Methyl 3-(benzylthio)-5,6,7,8-tetrahydronaphthalene-2-carboxylate (10a) was prepared as above by using **3a**. Recrystallization from hexane gave **10a** as white colorless needles, mp 98–99 °C (799 mg, 45%): IR ($CHCl_3$) 1705 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.47–2.03 (m, 4 H), 2.5–3.0 (m, 4 H), 3.88 (s, 3 H), 4.13 (s, 2 H), 7.0 (s, 1 H), 7.13–7.57 (m, 5 H), 7.65 (s, 1 H); MS, m/e (relative intensity) 312 (M^+, 56), 280 (49), 221 (57), 191 (31), 91 (100); exact mass calcd for $C_{19}H_{20}O_2S$ 312.118, obsd 312.118.

Methyl 5,6,7,8-Tetrahydronaphthalene-2-carboxylate (15). A quantity of 300 mg of Raney Ni (ethanol washed) was added to 100 mg of **10b** in 5 mL of absolute ethanol. After 6 h, the catalyst was filtered, and the solvent was evaporated to give **15** as a colorless oil (52 mg, 82%): IR (film) 1725, 1613 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.6–2.13 (m, 4 H), 2.57–3.03 (m, 4 H), 3.92 (s, 3 H), 6.97–7.37 (m, 1 H), 7.63–7.93 (m, 2 H); MS, m/e (relative intensity) (M^+, 49), 159 (74), 131 (100); exact mass calcd for $C_{12}H_{14}O_2$ 190.099, obsd 190.096.

3-(Phenylthio)-5,6,7,8-tetrahydronaphthalene-2-carboxylic Acid (14). A mixture of 596 mg of **10b** in 15 mL of methanol and 10 mL of 20% aqueous KOH was refluxed for 10 h. The solvent was removed under reduced pressure, the residue was dissolved in 5% aqueous KOH, and the aqueous phase was washed with ether. The aqueous phase was neutralized with concentrated HCl and extracted with ether. The ether extracts were dried ($MgSO_4$), and the solvent was removed. The carboxylic acid was recrystallized from methanol to give **14** as colorless prisms, mp 193–194 °C (545 mg, 96%): IR ($CHCl_3$) 1685 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.53–2.03 (m, 4 H), 2.4–3.17 (m, 4 H), 6.57 (s, 1 H), 7.17–7.70 (m, 5 H), 7.85 (s, 1 H); MS, m/e (relative intensity) (M^+, 100), 240 (16), 197 (24), 191 (44), 128 (36); exact mass calcd for $C_{17}H_{16}O_2S$ 284.087, obsd 284.089.

12*H*-7,8,9,10-Tetrahydrobenzo[*b*]thioxanthen-12-one (13). A mixture of 250 mg of **14** in sulfuric acid (3 mL) was stirred under nitrogen for 1.5 h at 100 °C. The cooled mixture was poured onto ice, and the crude product was extracted with chloroform. Unreacted starting material was removed by extraction with 10% sodium carbonate. The chloroform solution was washed with water, dried ($MgSO_4$), and evaporated to dryness. The resultant yellow solid was recrystallized from chloroform–hexane as yellow crystalline needles, mp 186–187 °C (175 mg, 76%): IR ($CHCl_3$) 1630, 1595 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.53–2.13 (m, 4 H), 2.63–3.2 (m, 4 H), 7.2 (s, 1 H), 7.3–7.63 (m, 3 H), 8.27 (s, 1 H), 8.35–8.65 (m, 1 H); MS, m/e (relative intensity) 266 (M^+, 100), 251 (20), 238 (39), 221 (23), 210 (29); exact mass calcd for $C_{17}H_{14}OS$ 266.077, obsd 266.075.

Dimethyl 3-Methoxy-5-(phenylthio)-*o*-phthalate (16). A quantity of 0.49 mL of dimethyl acetylenedicarboxylate was added to a well-stirred solution of 1.12 g of **3b** in mL of benzene at 10 °C and stirring continued for 16 h. The solvent was removed under reduced pressure, and the crude reaction mixture was dissolved in THF. A solution of 5 mL of 5% aqueous HCl was added and stirred for 5 min. The solvent was removed, and the organic phase was extracted with ether. The ether extract was dried (Na_2SO_4), and the solvent was removed. The mixture was submitted to column chromatography (eluant, 30% ethyl acetate–hexane) to give dimethyl 3-methoxy-5-(phenylthio)-*o*-

phthalate, mp 85–87 °C, and dimethyl 3-hydroxy-5-(phenylthio)-o-phthalate, mp 75–77 °C, in 2:1 ratio with 80% yield.

Compound **16**: IR (KBr): 2952, 1740, 1725, 1590 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.73 (s, 3 H), 3.82 (s, 3 H), 3.9 (s, 3 H), 6.93 (d, J = 2 Hz, 1 H), 7.33 (s, 5 H), 7.45 (d, J = 2 Hz, 1 H); MS, m/e (relative intensity) 332 (M^+, 69) 301 (100), 286 (13), 269 (18), 241 (19), 171 (17), 134 (18); exact mass calcd for $C_{17}H_{16}O_5S$ 332.072, obsd 332.067.

Compound **17**: IR (KBr) 2960, 1732, 1670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.8 (s, 3 H), 3.83 (s, 3 H), 6.47 (s, 2 H), 7.38 (m, 5 H), 10.63 (s, 1 H); MS, m/e (relative intensity) 318 (M^+, 5), 252 (29), 208 (33), 177 (30), 149 (49), 134 (34), 28 (100); exact mass calcd for $C_{16}H_{14}O_5S$ 318.055, obsd 318.056.

Dimethyl (Z)-3-(Phenylthio)-5-(methoxycarbonyl)-2-adepate (18). To a well-stirred solution of **3b** (1.12 g, 4 mmol) and dimethyl maleate (0.5 mL, 4 mmol) in 20 mL of CH_2Cl_2 under nitrogen at −78 °C was added titanium tetrachloride (0.45 mL, 4 mmol). After 5 h, the dark red colored mixture was added to aqueous $NaHCO_3$ and extracted with ether. The extract was dried (Na_2SO_4) and evaporated to give an oil, which was column chromatographed (eluant, 25% ethyl acetate–hexane) to give 18 as an oil in 78% yield. The E isomer of 18 was also formed as a minor product, as evidenced by ^1H NMR.

Compound **18**: IR (film) 2950, 1745, 1730, 1705 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.13 (m, 5 H), 5.75 (s, 1 H), 3.63 (s, 3 H), 3.50 (s, 3 H), 3.43 (s, 3 H), 2.03–2.83 (m, 5 H); MS, m/e (relative intensity) 352 (M^+, 27), 320 (25), 289 (24), 261 (38), 183 (50), 28 (100); exact mass calcd for $C_{17}H_{20}O_6S$ 352.098, obsd 352.098.

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Registry No. **3a**, 102736-24-3; **3b**, 102736-25-4; (*E*)-**5a**, 102736-26-5; (*E*)-**5b**, 102736-27-6; **6a**, 102736-28-7; **6b**, 102736-29-8; **6c**, 102736-30-1; **6d**, 102736-31-2; (*E*)-**6e**, 102736-32-3; (*Z*)-**6e**, 102736-33-4; **8** (R = Ph), 102736-34-5; **10a**, 102736-35-6; **10b**, 102736-36-7; **11**, 74590-75-3; **12**, 102736-37-8; **13**, 102736-38-9; **14**, 102736-39-0; **15**, 23194-33-4; **16**, 102736-40-3; **17**, 102736-41-4; (*Z*)-**18**, 102736-42-5; (*E*)-**18**, 102736-43-6; (*E*)-3-(benzylthio)crotonic acid, 67959-54-0; benzaldehyde, 100-52-7; acetone, 67-64-1; cyclohexanone, 108-94-1; 4-(phenylthio)-1-oxaspiro[5.5]undec-3-en-2-one, 102736-44-7; 4-(trimethylsiloxy)-pent-3-en-2-one, 13257-81-3; cyclohexanone trimethylsilyl enol ether, 6651-36-1; dimethyl acetylenedicarboxylate, 762-42-5; dimethyl maleate, 624-48-6.

Nucleophilic Aromatic Substitution with Elimination in a Dinitrosalicylic Lactone or Ester via Meisenheimer Intermediates

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The dinitro lactone **1b** and dinitro ester **2b** derived from salicylic acid undergo S_NAr reactions in the presence of a variety of N-, O-, and S-nucleophiles. Substitution is accompanied by elimination of the β-ethyleneoxy group, the ester group in no case being retained in the product. The dinitro amide **3b** was inert under the same conditions. With amines as nucleophiles, the final products are salicylamides; with aniline, hydroxide, methoxide, and thiophenolate/methanol, salicylates are formed. Thiocyanate effected S_N2 cleavage of the ether in **1b** or **2b**. Meisenheimer intermediates A and B could be isolated and characterized and were shown to be interconvertible. They, in turn, can be transformed to the final S_NAr products with the appropriate nucleophiles.

In the course of exploring the chemistry of salicylate derivatives, the dinitro lactone **1b** was subjected to treatment with aqueous ammonia, with the intention of converting it to the salicylamide **3b**. The unexpected result was formation of "iramine" (**4c**; Table I), a potent anticoccidiosis agent.[2]

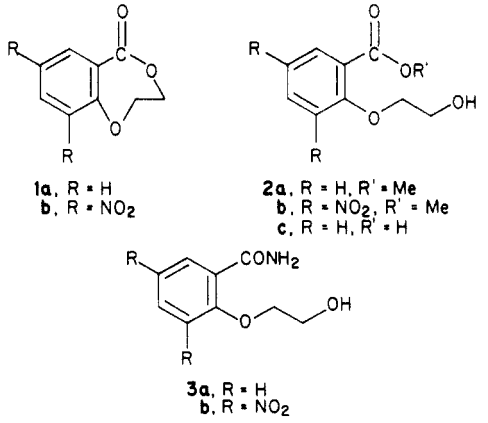
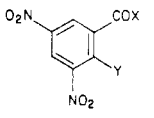


Table I. S_NAr Products from Lactone 1b or Ester 2b with Various Nucleophiles

nucleophile	product	X	Y
	 4		
NaOH	**4a**	OH[a]	OH
PhSH, NaOH	**4b**	OH[a]	SPh
NH_3	**4c**	NH_2	NH_2
NH_2CH_3	**4d**	$NHCH_3$	$NHCH_3$
$NH(CH_3)_2$	**4e**	$N(CH_3)_2$	$N(CH_3)_2$
$PhNH_2$[c]	**4f**	OH[b]	NHPh
CH_3O^-Na	**4g**	OH[a]	OCH_3

[a] Usually first isolated as Na salt. [b] First isolated as anilinium salt. [c] Lactone substrate only.

Because the transformation of **1b** to iramine involves ammonolysis of the lactone as well as nucleophilic displacement of the alkoxy group ortho and para to the nitro substituents, we were interested in determining whether the dual-step behavior was unusual for ammonia as a nucleophile and, further, which step was occurring first. We therefore undertook a systematic study of the behavior of **1b** and related compounds toward a series of nucleophiles (Nu). Among the reagents chosen for study were several N-, O-, and S-nucleophiles known to be effective in S_NAr

(1) Taken in part from: Rothenberger, S. D. Ph.D. Dissertation, University of New Hampshire, 1985.

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