Ortho-Selective Alkylation of Phenols with Symmetric Sulfides and Sulfuryl Chloride

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(Received May 18, 1987)

Synopsis. Sulfuryl chloride has been shown to be useful activator for sulfides in the selective preparation of ortho-alkylated phenols via [2,3]sigmatropic rearrangement. By this process, ortho-alkylated phenols have been prepared with various symmetric sulfides in good yields. The rearrangement products having 3-chloropropyl or 3-methyl-3-butenyl moiety have been converted into 2*H*-1-benzopyran derivatives.

We reported previously ortho-selective alkylation of phenols with sulfoxides and thionyl chloride via a [2,3]sigmatropic rearrangement.[1-3] However, in general, sulfoxides are hygroscopic and accessible by the oxidation of the corresponding sulfides. Therefore, we hoped that phenoxysulfonium salts **3** could be prepared from sulfides,[4] which are easier to handle than sulfoxides. Since the intermediates in the formation of phenoxysulfonium salts **3** with sulfoxides and thionyl chloride seem to be chlorosulfonium salts, we anticipated that the same sulfonium salts could be generated when sulfuryl chloride was used as an activator of sulfides. In this paper, we report a new method of selective ortho-alkylation of phenols using dialkyl sulfides and sulfuryl chloride, and also the facile preparation of 2*H*-1-benzopyrans by the cyclization of the resulting *o*-alkylphenols.

When sulfide was used, the operation of the alkylation of phenol could be simplified compared to the use of sulfoxides. Namely, sulfuryl chloride was added to a mixture of phenol **2** and sulfide **1** in dichloromethane at low temperature, followed by addition of triethylamine and then the reaction mixture was warmed to room temperature before work-up. We found that both the temperature and the period of the reaction of a sulfide with sulfuryl chloride affected the yield of **5**. The yield of *o*-alkylated phenol **5** decreased when the reaction time was prolonged at the same temperature. This tendency is enhanced at higher temperature, because of the thermolability of phenoxysulfonium salts **3**.

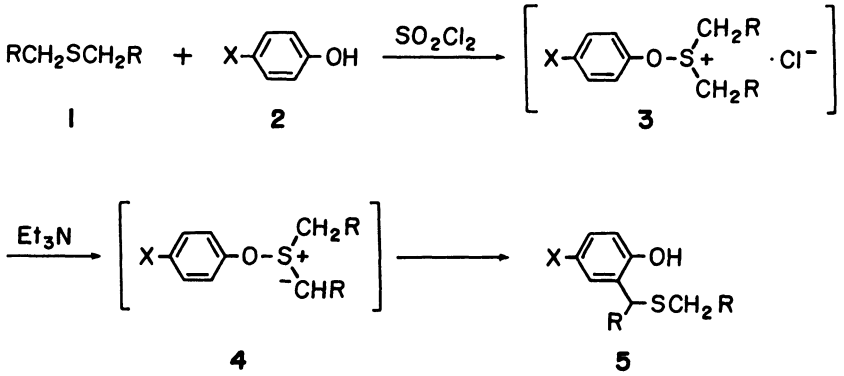
We investigated the alkylation of phenol **2** with various symmetric dialkyl sulfides **1** (Scheme 1). These results are summarized in the Table 1. Reaction of phenol (**2**; X=H) and sulfides **1** afforded the corresponding *o*-alkylated phenols **5** in good yields. Also, we investigated the reaction of para-substituted phenols **2** (X=Me, Cl, Ph, CO_2Et) with bis(2-acetoxyethyl) sulfide (**1**; R=CH_2OAc). In these cases, the expected products **5f—i** were obtained in good yields, except in the case of **5i**.

Next we studied the conversion of the rearrangement products **5j** and **5m** into 2*H*-1-benzopyran derivatives. We reported previously a facile synthesis of coumarin

Table 1. Ortho-Selective Alkylation of Phenols with Symmetric Sulfides and Sulfuryl Chloride

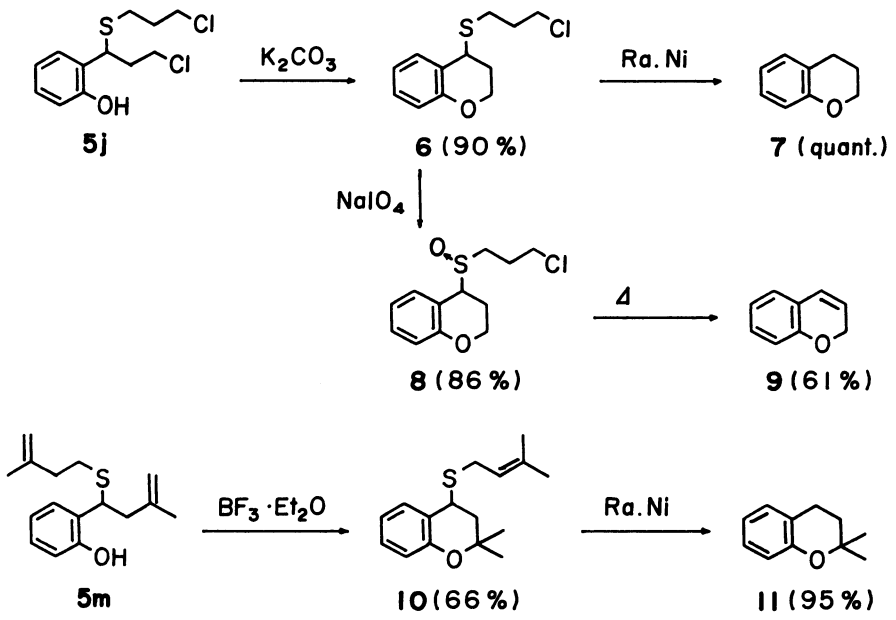
Product	R	X	Yield/%[a]
5a	H	H	72 (78)
5b	Me	H	67 (69)
5c	Ph	H	56 (68)
5d	CH_2CO_2Me	H	70 (80)
5e	CH_2OAc	H	77
5f	CH_2OAc	Me	73
5g	CH_2OAc	Cl	61
5h	CH_2OAc	Ph	76[b]
5i	CH_2OAc	CO_2Et	31[b]
5j	CH_2CH_2Cl	H	83 (61)
5k	CH_2CMe_2Cl	H	67
5l	CH_2CMe_2OAc	H	77
5m	$CH_2CMe{=}CH_2$	H	63

a) Yields from the corresponding sulfoxides are given in parentheses. see Ref. 2. b) Dichloromethane-*N*,*N*-dimethylformamide (10:1) was used as a solvent.



1 2 3 4 5

Scheme 1.



Scheme 2.

from **5d**.[2] Herein, we report the preparation of chromene and chromane derivatives. The results are illustrated in Scheme 2. Thus, the treatment of **5j** with potassium carbonate followed by Raney nickel afforded chromane (**7**). Also, chromene (**9**) was prepared by sodium periodate oxidation of **6**, followed by β-elimination of sulfoxide **8**. Cyclization of **5m** with boron trifluoride etherate gave chromane derivative **10**, which possessed a 3-methyl-2-butenylthio group as the result of migration of carbon-carbon double bond. Then desulfurization of **10** with Raney nickel gave 2,2-dimethylchromane (**11**) in 95% yield. These results demonstrate that the terminally functionalized *o*-alkylphenols **5d**, **5j**, and **5m**, which are readily obtained by the present [2,3]sigmatropic rearrangement, are very useful for the synthesis of 2*H*-1-benzopyran derivatives.

Experimental

Melting points are uncorrected. IR spectra were measured on either a Hitachi 215 or a Hitachi 260-50 spectrometer. ^{1}H NMR spectra were obtained with a JEOL JNM-C-60M or a JEOL FT-90Q with tetramethylsilane as an internal standard. The known compounds were established on the basis of spectroscopic properties of itself and of the description of literature. Column chromatography was normally effected with Wakogel C-200 (Wako Pure Chemical Industries).

General Procedure. Sulfuryl chloride (2.2 ml, 22 mmol) was added dropwise to the mixture of sulfide **1** (22 mmol) and phenol **2** (66 mmol) in dry dichloromethane (200 ml) at −40 °C. After the reaction mixture was stirred for 20 min at −40 °C, triethylamine (20 ml) was added to the reaction mixture at −30 °C. The solution was allowed to warm to room temperature, and it was then poured into dilute hydrochloric acid. The organic layer was separated and the aqueous solution was extracted with ether. The combined organic layers were washed with water and brine, dried ($MgSO_4$), and then evaporated. The residue was chromatographed on a column to give the ortho-alkylated phenol **5**.

The following new compounds were prepared using the above procedure. The other compounds were established on the basis of spectroscopic properties of itself and of the products prepared from phenol and the corresponding sulfoxides.[2]

2-[2-Acetoxy-1-(2-acetoxyethylthio)ethyl]phenol (5e): Yield 77%. IR (neat) 3370, 2940, 1730, 1710, 1240, and 1220 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ=2.03 (6H, s), 2.71 (2H, t, J=6), 4.18 (2H, t, J=6), 4.3—4.7 (3H, m), and 6.7—7.5 (5H, m). Found: C, 56.58; H, 6.03%. Calcd for $C_{14}H_{18}O_5S$: C, 56.36; H, 6.08%.

2-[2-Acetoxy-1-(2-acetoxyethylthio)ethyl]-4-methylphenol (5f): Yield 73%. Mp 64—65 °C. IR (KBr) 3280, 2920, 1730, 1700, 1270, and 1240 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ=2.03 (6H, s), 2.23 (3H, s), 2.68 (2H, t, J=6), 4.15 (2H, t, J=6), 4.42 (3H, s), and 6.5—7.1 (4H, m). Found: C, 57.59; H, 6.43%. Calcd for $C_{15}H_{20}O_5S$: C, 57.68; H, 6.45%.

2-[2-Acetoxy-1-(2-acetoxyethylthio)ethyl]-4-chlorophenol (5g): Yield 61%. Mp 95—96.5 °C. IR (KBr) 3230, 2930, 1730, 1695, 1270, and 1245 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ=2.07 (6H, s), 2.6—2.8 (2H, m), 4.20 (2H, t, J=6), 4.2—4.3 (3H, m), and 6.7—7.3 (4H, m). Found: C, 50.66; H, 5.11%. Calcd for $C_{14}H_{17}ClO_5S$: C, 50.53; H, 5.15%.

2-[2-Acetoxy-1-(2-acetoxyethylthio)ethyl]-4-phenylphenol (5h): Yield 76%. IR (neat) 3400, 2950, 1735, 1710, and 1230 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ=2.05 (6H, s), 2.7—2.9 (2H, m), 4.22 (2H, t, J=6), 4.5—4.7 (3H, m), and 6.8—7.6 (9H, m). Found: C, 64.30; H, 5.90%. Calcd for $C_{20}H_{22}O_5S$: C, 64.15; H, 5.92%.

Ethyl 3-[2-Acetoxy-1-(2-acetoxyethylthio)ethyl]-4-hydroxybenzoate (5i): Yield 31%. IR (neat) 3230, 2970, 1740, 1710, 1270, and 1230 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ=1.39 (3H, t, J=7), 2.06 (6H, s), 2.77 (2H, t, J=7), 4.1—4.7 (7H, m), 6.92 (1H, d, J=8), 7.92 (1H, dd, J=2, 8), 8.04 (1H, d, J=2), and 8.34 (1H, bs). Found: C, 55.54; H, 6.02%. Calcd for $C_{17}H_{22}O_7S$: C, 55.12; H, 5.99%.

2-[3-Chloro-1-(3-chloro-3-methylbutylthio)-3-methylbutyl]phenol (5k): Yield 67%. IR (neat) 3350, 1580, 1490, 1450, 1370, and 1230 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ=1.43, 1.57 (12H, each s), 1.7—2.0 (4H, m), 2.2—2.6 (2H, m), 4.42 (1H, t, J=7), 6.20 (1H, bs), and 6.6—7.3 (4H, m). Found: C, 57.53; H,

7.21%. Calcd for $C_{16}H_{24}Cl_2OS$: C, 57.31; H, 7.21%.

2-[3-Acetoxy-1-(3-acetoxy-3-methylbutylthio)-3-methylbutyl]phenol (5l): Yield 77%. IR (neat) 3300, 2970, 1720, and 1250 cm^{-1}. ^1H NMR ($CDCl_3$) δ=1.32 (6H, s), 1.42, 1.46 (6H, each s), 1.67 (3H, s), 1.88 (3H, s), 2.0—3.2 (6H, m), 4.50 (1H, dd, J=4, 8), 6.7—7.3 (4H, m), and 7.87 (1H, bs). Found: C, 62.50; H, 7.77%. Calcd for $C_{20}H_{30}O_5S$: C, 62.80; H, 7.90%.

2-[3-Methyl-1-(3-methyl-3-butenylthio)-3-butenyl]phenol (5m): Yield 63%. IR (neat) 3320, 3075, 2925, 1645, and 750 cm^{-1}. ^1H NMR ($CDCl_3$) δ=1.60, 1.67 (6H, each s), 2.2—2.4 (4H, m), 2.57 (2H, d, J=8), 4.17 (1H, t, J=8), 4.67 (4H, bs), and 6.6—7.3 (5H, m). Found: C, 73.53; H, 8.44%. Calcd for $C_{16}H_{22}OS$: C, 73.24; H, 8.45%.

4-(3-Chloropropylthio)-3,4-dihydro-2*H*-1-benzopyran (6). Potassium carbonate (2.76 g, 20 mmol) was added to a solution of **5j** (0.51 g, 1.83 mmol) in acetone (30 ml). After the mixture was refluxed for 3 h, it was filtered. The filtrate was concentrated. The residue was chromatographed on a column (benzene) to give **6** (0.40 g, 90%). IR (neat) 1580, 1480, 1260, and 750 cm^{-1}. ^1H NMR (CCl_4) δ=1.8—2.3 (4H, m), 2.57 (2H, t, J=7), 3.55 (2H, t, J=6), 3.95 (1H, t, J=4), 4.1—4.6 (2H, m), and 6.6—7.3 (4H, m). Found: C, 59.07; H, 6.17%. Calcd for $C_{12}H_{15}ClOS$: C, 59.37; H, 6.23%.

3,4-Dihydro-2*H*-1-benzopyran (7). The mixture of **6** (60 mg, 0.25 mmol) and Raney nickel (W4) (ca. 4 g) in ethanol (5 ml) was refluxed for 1 h. After the mixture was filtered, the filtrate was concentrated. The residual oil was chromatographed on a column (5% AcOEt–hexane) to give **7** (33 mg, quant.)

4-(3-Chloropropylsulfinyl)-3,4-dihydro-2*H*-1-benzopyran (8). A solution of sodium periodate (0.396 g, 1.85 mmol) in water (2 ml) was added dropwise to a solution of **6** (0.383 g, 1.58 mmol) in ethanol (6 ml) at 0 °C. The solution was stirred for 24 h at 0 °C. After the precipitate was filtered, the filtrate was poured into water. The aqueous solution was extracted with chloroform. The organic layer was washed with brine, dried ($MgSO_4$), and then evaporated. The residue was chromatographed on a column (13% AcOEt–benzene) to afford **8** (0.354 g, 86%). IR (neat) 3400, 1580, 1485, 1220, and 1030 cm^{-1}. ^1H NMR (CCl_4) δ=1.6—2.5 (4H, m), 2.5—3.0 (2H, m), 3.60 (2H, t, J=7), 3.8—3.9 (1H, m), 4.0—4.4 (2H, m), and 6.7—7.2 (4H, m). Found: C, 55.61; H, 5.83%. Calcd for $C_{12}H_{15}ClO_2S$: C, 55.70; H, 5.84%.

2*H*-1-Benzopyran (9). A solution of **8** (0.20 g, 0.774 mmol) in toluene (100 ml) was refluxed for 3 h and then concentrated. The residual oil was chromatographed on a column (30% benzene–hexane) to give **9** (0.062 g, 61%).

3,4-Dihydro-2,2-dimethyl-4-(3-methyl-2-butenylthio)-2*H*-1-benzopyran (10). Boron trifluoride etherate (0.1 ml, 0.8 mmol) was added to a solution of **5m** (100 mg, 0.8 mmol) in dichloromethane (3 ml) at room temperature under nitrogen atmosphere. After the mixture was stirred for 90 min, it was washed with water. The organic layer was dried and then evaporated. The residual oil was chromatographed on a column (2% AcOEt–hexane) to afford **10** (66 mg, 66%). IR (neat) 2980, 1605, and 760 cm^{-1}. ^1H NMR (CCl_4) δ=1.23, 1.43 (6H, each s), 2.07 (2H, d, J=8.2), 5.20 (1H, t, J=8). Found: C, 73.60; H, 8.53%. Calcd for $C_{16}H_{22}OS$: C, 73.24; H, 8.45%.

3,4-Dihydro-2,2-dimethyl-2*H*-1-benzopyran (11). The mixture of **10** (60 mg, 0.23 mmol) and Raney nickel (W4) (ca. 4 g) in ethanol (5 ml) was refluxed for 1.5 h. After the mixture was filtered, the filtrate was concentrated. The residual oil was chromatographed on a column (5% AcOEt–hexane) to give **11** (35 mg, 95%).

We are indebted to Mr. Shuichi Sato and Mr. Norimichi Iwase for valuable technical help and to Mrs. Hiroko Suesawa for measuring some of the NMR spectra.

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