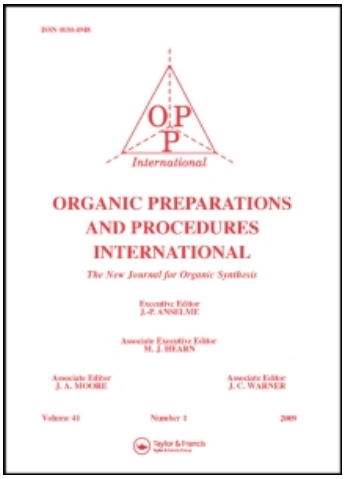


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# AN INEXPENSIVE AND CONVENIENT PREPARATION OF METHOXYMETHYL AND PHENYLTHIOMETHYL ETHERS

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# AN INEXPENSIVE AND CONVENIENT PREPARATION OF METHOXYMETHYL AND PHENYLTHIOMETHYL ETHERS

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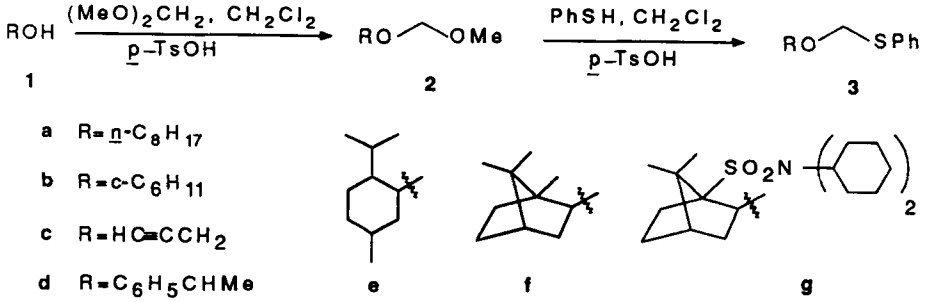
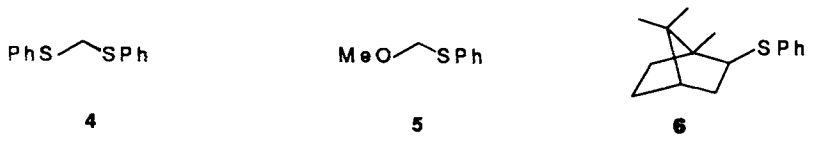
We have found that primary and secondary alcohols can be readily converted into methoxymethyl (MOM) ethers by acid promoted acetal exchange with dimethoxymethane and that a subsequent controlled exchange of the unsymmetrical MOM ethers with thiophenol affords phenylthiomethyl (PTM) ethers in good yields. The procedure works well for acid sensitive alcohols and serves as an inexpensive and convenient method for the large scale preparation of either MOM or PTM ethers despite some limitations.



MOM ethers are useful alcohol protecting groups[1,2] and can play important roles in metallation procedures[3] while PTM ethers serve as acyl anion equivalents[4] and synthetic intermediates.[5] MOM ethers are usually prepared under basic conditions from the alcohol and chloromethyl methyl ether which is a potent carcinogen. Acid-catalyzed procedures frequently afford low yields,[2a-b] although MOM ethers have been prepared from phenols and dimethoxymethane. The procedure has apparently not been extended to simple aliphatic alcohols.[2c]

α-Methoxythioanisole is readily prepared by reaction of thiophenol and methylal with acid catalysis.[4b] Acid promoted exchange reactions have been used to prepare some O,S-acetals and ketals[4-6] while alternative routes to complex O,S-acetals have been described.[7] The reaction of alcohols with α-halosulfides appears to be a facile route to O,S-acetals and works well for primary alcohols which are used as the reaction solvent.[8] Recently MOM ethers have been converted into PTM ethers[5a-b,9a] while methoxyethoxymethyl (MEM) ethers have been converted into isopropyl thiomethyl ethers.[9b] Although the reagents are generally efficient they have limitations for large scale preparations.



In the initial studies, isoborneol (**1f**) was converted into the MOM ether (**2f**) with dimethoxymethane and p-toluenesulfonic acid with azeotropic removal of methanol under conditions described by Yardley.[2c] The time required for consumption of isoborneol was dependent upon the quantity of acid employed and optimal conditions involved 4% of acid/alcohol (wt/wt). MOM ethers were readily prepared from a variety of primary and secondary alcohols (Table 1) generally using 10% acid/alcohol (wt/wt). It is noteworthy that good yields and clean reactions were obtained from isoborneol, menthol, α-phenethyl alcohol, and propargyl alcohol which are prone to rearrangement or dehydration in acidic medium. The allylic alcohols, 2-methyl-3-buten-2-ol and 3-methyl-3-buten-2-ol, afforded rearranged MOM ethers in modest yields. The MOM

ether of hydroxysulfonamide (**1g**) could not be prepared by this procedure which gave only recovered **1g**.

Treatment of 1.0 g of the MOM ether of isoborneol (**2f**) with thiophenol and p-TsOH afforded a mixture of camphene (11%), bis(phenylthio)methane (**4**, 38%), methoxyphenylthiomethane (**5**, 6%), as

TABLE 1. Preparation of MOM and PTM Ethers

| Alcohol | Time (hrs) | MOM (2) (%)[a] | Time (hrs) | PhSH (eqs) | PTM (3) (%)[a] | 4 (% yield)[b] | 5 (% yield)[b] |
|---|---|---|---|---|---|---|---|
| **1a** | 10 | **a** (94) | 7 | 1 | **a** (58) 72 | 17 | 7 |
| **1b** | 10 | **b** (68) | 6 | 1 | **b** (63) 74 | 13 | 9 |
| **1c** | 12 | **c** (62) | 6 | 1 | **c** <5 | (70) | |
| **1d** | 12 | **d** (74) | 12 | 1 | **d** (53)[c] | 14 | 3 |
| | | | 6 | 2 | (60) 60 | 19 | 12 |
| **1e** | 7 | **e** (83) | 7 | 1 | **e** (56) 54 | 27 | 6 |
| **1f** | 12 | **f** (77) | 12 | 1 | **f** (55) 61 | 22 | 8 |
| | | | 6 | 2 | (67) 81 | 13 | 11 |

a) Yields in parenthesis are based upon isolated purified products. b) Yields determined from NMR. c) 1-Phenylthioethylbenzene was also formed (29%).

TABLE 2. Spectroscopic Data for MOM Ethers

| MOM (2) | $^1$H NMR -CH(R)O-[a] (J, Hz) | $^1$H NMR $-OCH_2O-$ (J, Hz) | $^{13}$C NMR $-OCH_3$ | $^{13}$C NMR -CH(R)O-[a] | $^{13}$C NMR $-OCH_2O-$ | MS m/z (intensity)[b] |
|---|---|---|---|---|---|---|
| **a** | 3.51 (6)[c] | 4.61 | 3.35 | 67.8 | 96.4 | 143(21), 113 (5), 45(100) |
| **b** | 3.17-3.59[d] | 4.67 | 3.35 | 74.9 | 94.3 | 144(2), 113(8) 83(13), 45(100) |
| **c** | 4.21 (2)[e] | 4.70 | 3.37 | 79.0 | 94.1 | 100(3), 69(35) 61(19), 45(100) |
| **d** | 4.62 (5)[f] | 4.42 | 3.25 | 73.7 | 94.1 | 166(0.1), 105 (27), 45(100) |
| **e** | 3.08-3.44[d] | 4.57[g] (7) | 3.28 | 77.0 | 95.0 | 200(.1),169(.2) 139(1), 45(100) |
| **f** | 3.18-3.50[d] | 4.47[g] (7) | 3.33 | 84.0 | 95.6 | 167(1), 137 (31), 45(100) |

a) R = alkyl or H. b) Per cent of base peak. c) Triplet. d) Complex multiplet. e) Doublet. f) Quartet. g) Center of AB quartet.

well as the desired PTM ether (**3f**, 45%). Subsequent experimentation showed that the distribution of products was dependent upon the amount of acid used and the reaction time. Optimal conditions required two equivalents of thiophenol and 0.064 g of acid/1.0 g of MOM ether. Under these conditions **3f** was obtained contaminated with 13% of **4**. Attempted purification on silica gel promoted partial decomposition of **3f**. $^1H$ NMR and mass spectral analysis indicated formation of isobornyl phenylthio ether (**6**). This decomposition product was not obtained on chromatography with fluorisil or alumina.

The MOM ether of α-phenethyl alcohol (**2d**) afforded **3d**, **4**, **5**, and 1-phenylthioethylbenzene (29%) upon treatment with 1.0 eq of thiophenol. Utilization of two equivalents of thiophenol afforded a significantly cleaner reaction and higher yield of the PTM ether **3d**. The MOM ethers of n-octanol, cyclohexanol, and menthol could be converted into the PTM ethers uneventfully. The propargyl MOM ether afforded **4** (70%) and gave very low yields of the PTM ether under all reaction conditions.

In summary, the acid promoted acetal exchange procedure can be used to prepare MOM ethers of primary and secondary alcohols that are only moderately prone to acid catalyzed rearrangements or dehydrations. The MOM ethers in turn can be converted into PTM ethers using a similar exchange reaction with thiophenol. The latter reaction is rather sensitive to substrate and reaction conditions but can be controlled to give good yields of PTM ethers generally contaminated with roughly 20% of **4**. Despite these limitations, the methodology should provide a convenient procedure for the large scale preparation of MOM and PTM ethers from a wide range of primary and secondary alcohols.

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## EXPERIMENTAL SECTION

NMR spectra were recorded as $CDCl_3$ solutions on either a JEOL-FX 90Q (unless specified) or IBM-NR-200 AF instrument. Proton NMR chemical shifts are reported as δ values in parts per million (ppm) relative to tetramethylsilane (TMS) as internal standard. The carbon NMR chemical shifts are in ppm downfield from TMS and are referenced with respect to internal $CDCl_3$ (δ 77.0 for center line). Infrared spectra were recorded on a Nicolet 5DX FT IR spectrometer as neat samples unless otherwise noted. Mass spectral measurements were performed on a Hewlett-Packard 5840 gas chromatography / mass spectrometer at 70 eV and mass data are tabulated as m/z and intensity of the base peak. Elemental analysis were determined by Atlanta Microlab Inc., Atlanta, GA.

Methylal, p-toluenesulfonic acid, thiophenol, isoborneol, and propargyl alcohol were purchased from Aldrich and used without purification. Molecular sieves (3Å) were purchased from Fisher Scientific.

**General Procedure A. Preparation of MOM Ethers.**- Methylene chloride (150 mL), alcohol (5.0 g ), dimethoxymethane (4.5 eq), and p-toluenesulfonic acid (4-10%, wt/wt) were added to a 250 mL round bottom flask which was fitted with a soxhlet extractor containing 3Å molecular sieves. The reaction mixture was heated to reflux with stirring until the alcohol had disappeared as evidenced by TLC. The organic phase was washed with saturated aqueous $Na_2CO_3$, water, brine and dried over $MgSO_4$. Products were purified by distillation: **2b** bp. 109-110°/110 mm Hg, **2c** bp. 115°/760 mm Hg, **2e** bp. 78°/2.0 mm Hg, **2f** bp. 68°/7 mm Hg. Crude samples of **2a** and **2d** were ≥ 95% pure by NMR. Chromatography $R_f$ values (silica gel, ethyl acetate/petroleum ether, 4:96, v/v) are: **2a** (0.46), **2b** (0.39), **2c** (0.34) **2d** (0.43), **2e** (0.50) and **2f** (0.69).

**General Procedure B. Preparation of PTM Ethers.**- Methylene chloride (150 mL), MOM ether (1.0 g), thiophenol (1.1 eq.), and p-toluenesulfonic acid (0.1 g) were added to a 250 mL round-bottom flask fitted with a soxhlet extractor containing 3Å molecular sieves. The mixture was heated to reflux until the disappearance of the MOM ether as evidenced by TLC. The organic phase was washed with 15% NaOH, water, brine and dried over $MgSO_4$. Products were purified by column chromatography (silica gel) using ethyl acetate/petroleum ether (4/96, v/v) unless otherwise noted.

Bis(phenylthio)methane (**4**, $R_f$ 0.62) and α-methoxythioanisole (**5**, $R_f$ 0.52) were obtained as by-products.

**[(n-Octyloxy)methylthio]benzene (3a).**- General procedure B was followed to afford **3a** contaminated with **4** ($R_f$ 0.78, benzene) and **5** ($R_f$ 0.44, benzene). Purification by column chromatography ($R_f$ 0.85, benzene) gave pure **3a**. IR 2927 (s), 2858 (s), 1081 (s), 910 (w), 739 (s), 691 (s) $cm^{-1}$; NMR: δ 0.87 (t, J = 8 Hz, 3 H), 0.98-1.74 (m, 12 H), 3.58 (t, J = 6 Hz, 2 H), 4.97 (s, 2 H), 6.87-7.48 (m, 5 H); $^{13}C$ NMR: δ 14.0, 22.6, 26.2, 29.2, 29.3, 31.8, 68.8, 76.2, 126.5, 128.8, 130.2, 136.4; mass spectrum m/z (intensity): 252 (15, $M^+$), 143 (10, $M^+$-SPh), 123 (71, $^+CH_2SPh$), 109 (30, $^+SPh$).

Anal. Calcd for $C_{15}H_{24}OS$: C, 71.42; H, 9.52. Found: C, 71.23; H, 9.50

**[(Cyclohexyloxy)methylthio]benzene (3b).**- General procedure B was followed. Purification by distillation gave pure **3b**: b.p. 117°C, 0.2 mm Hg; IR 2933 (s), 2858 (m), 1067 (s) 739 (m), 691 (m) $cm^{-1}$; NMR: δ 0.98-2.01 (m, 10 H), 3.35-3.56 (m, 1 H), 4.89 (s, 2 H), 6.83-7.39 (m, 5 H); $^{13}C$ NMR: δ 24.0, 25.8, 31.9, 73.1, 75.0, 126.4, 128.8, 130.2, 136.5; mass spectrum m/z (intensity): 222 (62, $M^+$), 123 (24, $^+CH_2SPh$), 113 (45, $M^+$-SPh), 109 (8, $^+SPh$), 83 (44, $M^+$-$OCH_2SPh$).

Anal. Calcd for $C_{13}H_{18}OS$: C, 70.22; H, 8.16. Found: C, 70.22; H, 8.17

**[(α-Methylbenzyloxy)methylthio]benzene (3d).**- General procedure B was followed with the exception that 2.0 eq of thiophenol was used. Purification by medium pressure liquid chromatography (MPLC) ($R_f$ 0.35, silica gel, benzene/petroleum ether, v/v) gave pure **3d**: IR 3063 (w), 3029 (w), 2974 (m), 1074 (s), 1047 (s), 849 (w), 732 (s), 698 (s) $cm^{-1}$; NMR: δ 1.40 (d, J = 6 Hz, 3 H), 4.72 (ABq, $\delta_A$ = 4.92, $\delta_B$ = 4.52, $J_{AB}$ = 12 Hz, 2 H), 4.83 (q, J = 6 Hz, 1 H), 6.83-7.45 (m, 10 H); $^{13}C$ NMR: δ 23.6, 73.0, 74.5, 126.7, 127.8, 128.6, 128.9, 130.2, 136.1, 142.3; mass spectrum m/z

(intensity): 244 (2, $M^+$), 123 (3, $^+CH_2SPh$), 121 (2, $M^+-CH_2SPh$), 105 (100, $M^+-OCH_2SPh$), 77 (7, $Ph^+$).

Anal. Calcd for $C_{15}H_{16}OS$: C, 73.73; H, 6.60. Found: C, 73.80; H, 6.61

**[(5-Methyl-2-(1-methylethyl)cyclohexyloxy)methylthio]benzene (3e)**[9a]. - General procedure B was followed. Purification by flash chromatography (florisil, $R_f$ 0.69 silica gel TLC) gave pure **3e**: IR 2954 (s), 2920 (s), 1061 (s), 739 (s), 694 (m) $cm^{-1}$; NMR: δ 0.68 (d, J = 7 Hz, 3 H), 0.83 (d, J = 7 Hz, 3 H), 0.90 (d, J = 7 Hz, 3 H), 0.58-2.23 (m, 9 H), 3.12-3.52 (m, 1 H), 4.94 (ABq, $\delta_A$ = 5.02, $\delta_B$ = 4.88, $J_{AB}$ = 10 Hz, 2 H), 6.83-7.37 (m, 5 H); $^{13}C$ NMR: δ 15.8, 21.0, 22.2, 23.0, 25.0, 31.3, 34.3, 39.8, 48.2, 72.5, 76.5, 126.0, 128.6, 129.0, 136.6; mass spectrum m/z (intensity): 278 (6, $M^+$), 169 (5, $M^+-SPh$), 154 (23, $M^+-SPh-CH_3$), 109 (27, $PhS^+$).

**[((1,7,7-Trimethyl-[2.2.1.]bicyclohept-2-yl)oxy)methylthio]benzene (3f)**.- General procedure B was followed with the exception that 2.0 eq of thiophenol and 0.064 g of p-TsOH was used. Purification by MPLC (alumina, petroleum ether, $R_f$ 0.69 silica gel TLC) or distillation (b.p. 155-160°C, 0.2 mm Hg) gave pure **3f**: IR 2954 (s), 2878 (s), 1067 (s), 736 (s), 691 (s) $cm^{-1}$; NMR: δ 0.79 (s, 3 H), 0.84 (s, 3 H), 0.95 (s, 3 H), 0.89-1.87 (m, 7 H), 3.64 (t, J = 4 Hz, 1 H), 4.82 (ABq, $\delta_A$ = 4.87, $\delta_B$ = 4.77, $J_{AB}$ = 10 Hz, 2 H), 6.87-7.21 (m, 5 H); $^{13}C$ NMR: δ 11.9, 20.2, 27.3, 34.4, 38.3, 45.1, 46.6, 49.0, 74.2, 84.5, 126.2, 128.7, 129.8, 136.6; mass spectrum m/z (intensity): 276 (4, $M^+$), 137 (100, $M^+-OCH_2SPh$), 123 (12, $^+CH_2SPh$), 109 (17, $^+SPh$).

Anal. Calcd for $C_{17}H_{24}OS$: C, 73.91; H, 8.69. Found: C, 73.89; H, 8.69

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