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DIRECT SYNTHESIS OF DIALLYL SULFIDES FROM ALLYL ALCOHOLS AND HEXAMETHYLDISILATHIANE

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Abstract: Diallyl sulfides were obtained in 60–90% yields by reaction of various allyl alcohols (1.0 equiv) with hexamethyldisilathiane (~0.55 equiv) in CH_2Cl_2 at room temperature in the presence of $BF_3{\cdot}OEt_2$ (0.8–1.1 equiv).

INTRODUCTION

Diallyl sulfides have practical synthetic applications to the sulfur vulcanization of rubber.[1,2] Some diallyl sulfides, such as dicyclohexenyl sulfide, dicyclopentenyl sulfide, bis(1,4-butadienyl) sulfide, and diethynyl sulfide, are of value as solvents and raw materials in industry.[3] They have also been used as starting materials for organic reactions.[4–6] Wattenberg et al.[7] reported that some diallyl sulfides isolated from garlic and onions exhibit

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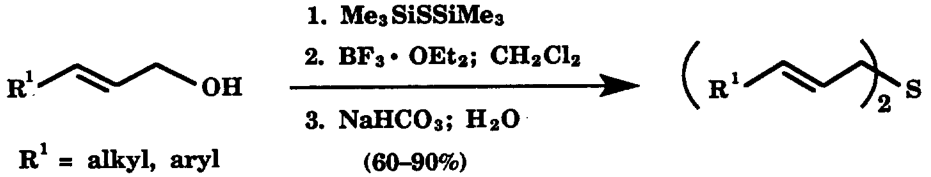
inhibitory effects on benzo[α]pyrene-induced neoplasis of the forestomach. These sulfides can increase glutathione S-transferase activity in the forestomach tumors.

Various methods are available for the preparation of diallyl sulfides; most of which require two steps or more.[3,8–13] We herein report a new and efficient method for the synthesis of diallyl sulfides directly from allyl alcohols, readily available starting materials.

RESULTS AND DISCUSSION

In the presence of $BF_3 \cdot OEt_2$, we treated an allyl alcohol with ~0.55 equiv of hexamethyldisilathiane in CH_2Cl_2 at 0 °C (Scheme 1). After aqueous workup, the corresponding diallyl sulfide was isolated in 60–90% yields. In these reactions, two molecules of an allyl alcohol were coupled with one molecule of hexamethyldisilathiane to give one molecule of a diallyl sulfide. This newly developed procedure was applicable to alkyl- (e.g., **1**, **3**, **5**, **7**, **9**, and **13**) and arakyl-substituted (e.g., **11**) allyl alcohols (see Table 1).

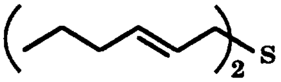
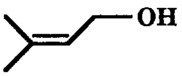
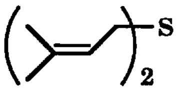
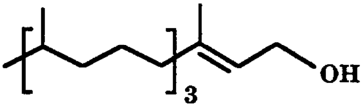
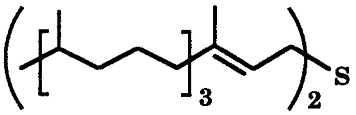
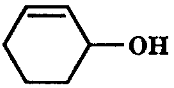
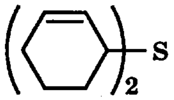
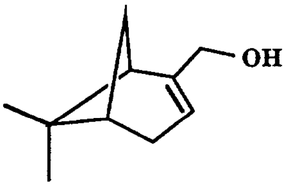
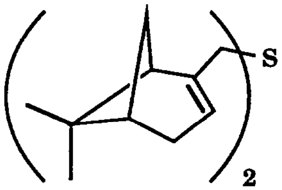
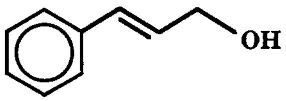
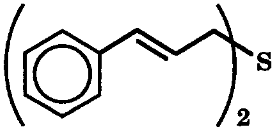
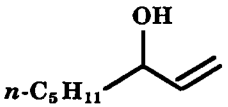
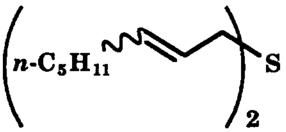
Scheme 1



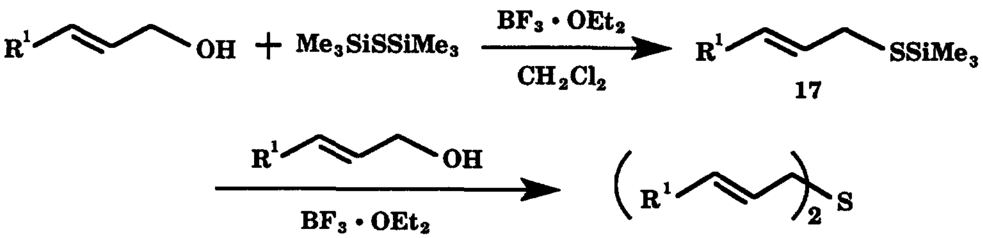
An allyl alcohol can be converted to a thiol by use of one equivalent of hexamethyldisilathiane and $BF_3 \cdot OEt_2$.[14] We found that conversion of an allyl alcohol to the desired diallyl sulfide can be accomplished by using 0.55 equiv of hexamethyldisilathiane; a plausible mechanism for this conversion is dipicted in Scheme 2. Initially, an allyl alcohol was converted to a trimethylsilylated allyl sulfide (**17**). Trimethylsilyl sulfides are known to be active towards allyl alcohols in the presence of $BF_3 \cdot OEt_2$;[14] thus **17** reacted with the second equivalent of allyl alcohol in situ to afford a diallyl sulfide.

By use of an allyl alcohol bearing a terminal C–C double bond (e.g., **13**) as the starting material, a mixture of diallyl alcohols were obtained in 63% overall yield, which included *cis,cis*-, *cis,trans*-, and *trans,trans*-diallyl sulfides in a ratio of 1:2:1. The reactions proceeded by an S_N2' mechanism.[14]

Table 1. Synthesis of Diallyl Sulfides from Allyl Alcohols and Hexamethyldisilathiane in the Presence of $BF_3 \cdot OEt_2$

Allyl Alcohol	Diallyl Sulfide	Yield (%)
 1	 2	75
 3	 4	60
 5	 6	87
 7	 8	90
 9	 10	65
 11	 12	70
 13	 *cis,cis* : *cis,trans* : *trans,trans* 14 15 16 = 1 : 2 : 1	63

Scheme 2



EXPERIMENTAL SECTION

General Procedure. All reactions were carried out in oven-dried glassware (120 °C) under an atmosphere of nitrogen. Hexanes and EtOAc from Tilley Chemical Co. and CH_2Cl_2 from J. T. Baker Chemical Co. were dried and distilled from CaH_2. $BF_3{\cdot}OEt_2$ from Aldrich Chemical Co. was distilled from CaH_2 under reduced pressure. The following compounds and reagents were purchased from Aldrich Chemical Co.: cinnamyl alcohol, 2-cyclohexen-1-ol, *trans*-2-hexen-1-ol, 3-methyl-2-buten-1-ol, (1*R*)-(–)-myrtenol, 1-octen-3-ol, and phytol. Hexamethyldisilathiane from Fluka Chemical Co. was stored in serum capped bottles under argon over molecular sieves 4A. Analytical thin-layer chromatography (TLC) analyses were performed on precoated plates (silica gel GHLF), purchased from Analtech Inc. Gas chromatography analyses were carried out on a Hewlett–Packard 5794 instrument equipped with a 12.5-m cross-linked methyl silicone gum capillary column (0.2-mm i.d.); the injector temperature was set up at 260 °C. Purification by gravity column chromatography was performed with EM Reagents Silica Gel 60 (particle size 0.063–0.200 mm, 70–230 mesh ASTM). Separations by radial thin-layer chromatography were performed on a model 7924T Chromatotron from Harrison Research. The plates with 1-mm thickness were coated with EM Reagents Silica Gel 60 PF_{254} containing gypsum. Separation by high pressure liquid chromatography was carried out by use of a Hewlett–Packard 1050 instrument. Infrared spectra were measured on a Perkin–Elmer 1600 Series FT-IR. Proton NMR spectra were obtained on a Varian CFT-20 (80 MHz) or a Brüker AC 200 spectrometer by use of chloroform-*d* as solvent and tetramethylsilane as an internal standard. High-resolution mass spectra were obtained by means of a VG Analytical 70-S mass spectrometer.

Standard Procedure for the Preparation of Diallyl Sulfides. To a stirring CH_2Cl_2 solution containing an allyl alcohol (0.10–0.30 g, 1.0 equiv) and hexamethyldisilathiane (0.55 equiv) was added $BF_3{\cdot}OEt_2$ (0.8–1.1 equiv) at 0 °C. After being stirred under an atmosphere of nitrogen at room temperature for 24 h, the reaction mixture was diluted by addition of Et_2O (50 mL). This diluted mixture was then washed with saturated aqueous $NaHCO_3$ (2 × 10 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine solution (20 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated to give a yellow oil. The resultant liquid was purified by chromatography to give the desired diallyl sulfide.

Di(*trans*-2-hexenyl) Sulfide (**2**). The standard procedure was followed by use of *trans*-2-hexen-1-ol (**1**, 99 mg, 0.99 mmol, 1.0 equiv), hexamethyldisilathiane (97 mg, 0.54 mmol, 0.55 equiv), $BF_3{\cdot}OEt_2$ (154 mg, 1.08 mmol, 1.1 equiv), and CH_2Cl_2 (10.0 mL). After purification by use of a Chromatotron (1-mm plate, EtOAc/hexanes = 1:19), di(*trans*-2-hexenyl) sulfide **2** (147 mg, 75%) was obtained as a yellow oil; GC (column temperature program: initial temperature 90 °C, duration 2.00 min; increment rate 15 °C/min; final temperature 250 °C) t_R 11.55 min; TLC R_f 0.49 (hexanes as eluant); ^1H NMR (80 MHz, $CDCl_3$): $\delta = 0.88$ (t, $J = 5.6$ Hz, 6 H, 2 × CH_3), 1.2–1.5 (m, 4 H, 2 × $MeCH_2$), 1.8–2.2 (br s, 4 H, 2 × $=CCH_2$), 3.03 (d, $J = 5.1$ Hz, 4 H, 2 × SCH_2), 5.20–5.50 (m, 4 H, 4 × =CH); IR (neat): $\nu = 2942, 2919, 2848, 1454, 1372, 955, 908$ cm^{-1}; HRMS for $C_{12}H_{22}S$ calcd 198.1437, found 198.1441.

Diprenyl Sulfide (**4**). The standard procedure was followed by use of 3-methyl-2-buten-1-ol (**3**, 150 mg, 1.74 mmol, 1.0 equiv), hexamethyldisilathiane (171 mg, 0.96 mmol, 0.55 equiv), $BF_3{\cdot}OEt_2$ (198 mg, 1.39 mmol, 0.80 equiv), and CH_2Cl_2 (15.0 mL). After purification by use of a Chromatotron (1-mm plate, hexanes as eluant), diprenyl sulfide **4** (177 mg, 60%) was obtained as a yellow oil; GC (column temperature program: initial temperature 90 °C, duration 2.00 min; increment rate 15 °C/min; final temperature 250 °C) t_R 4.55 min; TLC R_f 0.29 (hexanes as eluant); ^1H NMR (80 MHz, $CDCl_3$): $\delta = 1.72$ (s, 6 H, 2 × CH_3), 1.73 (s, 6 H, 2 × CH_3), 3.32 (d, $J = 6.3$ Hz, 4 H, 2 × SCH_2), 5.21–5.36 (m, 2 H, 2 × =CH); IR (neat): $\nu = 3020, 2950, 2900, 1650, 1430, 1365, 1220, 1020, 995, 835$ cm^{-1}; HRMS for $C_{10}H_{18}S$ calcd 170.2120, found 170.2123.

Diphytyl Sulfide (**6**). The standard procedure was followed by use of phytol (**5**, 292 mg, 0.98 mmol, 1.0 equiv), hexamethyldisilathiane (97 mg, 0.54 mmol, 0.55 equiv), $BF_3 \cdot OEt_2$ (154 mg, 1.08 mmol, 1.1 equiv), and CH_2Cl_2 (10.0 mL). After purification by use of a Chromatotron (1-mm plate, EtOAc/hexanes = 1:19), diphytyl sulfide **6** (508 mg, 87%) was obtained as a yellow oil; GC (column temperature program: initial temperature 90 °C, duration 2.00 min; increment rate 15 °C/min; final temperature 250 °C) t_R 11.55 min; TLC R_f 0.70 (hexanes as eluant); ^1H NMR (80 MHz, $CDCl_3$): $\delta = 1.09–2.13$ (m, 72 H, $10 \times CH_3 + 18 \times CH_2 + 6 \times CH$), 3.05 (d, $J = 4.9$ Hz, 4 H, $2 \times SCH_2$), 5.13–5.35 (m, 2 H, $2 \times {=}CH$); IR (neat): $\nu = 3000, 2780, 1690, 1485, 1400, 1250, 1180, 765$ cm^{-1}; HRMS for $C_{40}H_{78}S$ calcd 590.5824, found 590.5829.

Di(2-cyclohexenyl) Sulfide (**8**). The standard procedure was followed by use of 2-cyclohexen-1-ol (**7**, 97 mg, 0.99 mmol, 1.0 equiv), hexamethyldisilathiane (97 mg, 0.54 mmol, 0.55 equiv), $BF_3 \cdot OEt_2$ (155 mg, 1.09 mmol, 1.1 equiv), and CH_2Cl_2 (10.0 mL). After purification by use of a Chromatotron (1-mm plate, EtOAc/hexanes = 1:19), di(2-cyclohexenyl) sulfide **8** (173 mg, 90%) was obtained as a yellow oil; GC (column temperature program: initial temperature 90 °C, duration 2.00 min; increment rate 15 °C/min; final temperature 250 °C) t_R 7.50 min; TLC R_f 0.54 (EtOAc/hexanes = 1:19); ^1H NMR (80 MHz, $CDCl_3$): $\delta = 1.45–2.20$ (m, 12 H, $6 \times CH_2$), 3.31–3.48 (br, 2 H, $2 \times SCH$), 5.54–5.72 (m, 4 H, $4 \times {=}CH$); IR (neat): $\nu = 3030, 2930, 1645, 1440, 1351, 995, 921, 870, 830, 788, 742, 731$ cm^{-1}; HRMS for $C_{12}H_{18}S$ calcd 194.1129, found 194.1131. The spectroscopic data of this compound are consistent with those reported.[3,9,10,15]

Dimyrtenyl Sulfide (**10**). The standard procedure was followed by use of (1*R*)-(–)-myrtenol (**9**, 150 mg, 0.99 mmol, 1.0 equiv), hexamethyldisilathiane (97 mg, 0.54 mmol, 0.55 equiv), $BF_3 \cdot OEt_2$ (154 mg, 1.08 mmol, 1.1 equiv), and CH_2Cl_2 (10.0 mL). The reaction mixture was stirred at room temperature for 24 h. After purification by use of a Chromatotron (1-mm plate, EtOAc/hexanes = 1:19), dimyrtenyl sulfide **10** (194 mg, 65%) was obtained as a yellow oil; GC (column temperature program: initial temperature 90 °C, duration 2.00 min; increment rate 15 °C/min; final temperature 250 °C) t_R 11.55 min; TLC R_f 0.58 (EtOAc/hexanes = 1:19); ^1H NMR (80 MHz, $CDCl_3$): $\delta = 0.80$ (s, 6 H, $2 \times CH_3$), 1.10–1.31 (m, 6 H, $2 \times CH_2CH$), 1.29 (s, 6 H, $2 \times CH_3$), 2.20–2.25 (m, 6 H, $2 \times CHC{=}CCH_2$), 3.34 (br s, 4 H, $2 \times SCH_2$), 5.25–5.41 (br m, 2 H, $2 \times {=}CH$); IR (neat): $\nu = 2950, 2860, 1630, 1450, 1443, 1370, 1350, 1210, 875$ cm^{-1}; HRMS for $C_{20}H_{30}S$ calcd 302.2399, found 302.2403.