Synthesis of *ortho*-Substituted Arylacetic Esters and Related Compounds by Means of Sommelet–Hauser Rearrangement of Sulfur Ylides

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The rearrangement of a series of dimethylsulfonium α-substituted benzylides, *e.g.*, 8, in ethanol has been examined. The ylides 8a,b generated *in situ* by treatment of the sulfonium salts 7a,b with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in ethanol at room temperature, afforded the *o*-(methylthiomethyl)phenylacetic esters 10a,b as a result of the Sommelet–Hauser rearrangement of the tautomeric ylides 9a,b. By contrast, the ylide 14 possessing a furan ring was stable at room temperature, but, on heating in ethanol, gave the rearranged product 15. The ylide 22 stabilized by an acetyl group provided three rearranged products, 23, 24, and 25, in boiling ethanol. Treatment of the sulfonium salts 30a,b with DBU at room temperature afforded the corresponding rearranged products 31a,b. The sulfonium salt 34a prepared from 33a, on treatment with sodium ethoxide, gave the rearranged product 36a, which was then *S*-methylated and treated with DBU to give the 1,2,3-trisubstituted benzene 37a. This method was applied to the synthesis of the fenoprofen analog 39 from 39 from 33b,c.

Keywords Sommelet–Hauser rearrangement; sulfur ylide; arylacetic ester; Friedel–Crafts reaction; α-chlorosulfide; sulfonium salt; tautomerization; Favorskii rearrangement; [2,3] sigmatropic rearrangement; desulfurization

The Sommelet–Hauser rearrangement of benzylsulfonium methylides and related species has been widely used as a selective method for the *ortho* substitution of aromatic substrates.[1] Robert and his co-workers[2] reported that the crystalline stable ylide **2**, prepared from the *gem*-dicyano epoxide **1** and dimethyl sulfide in 3 steps (see Chart 1), on heating in methanol, gave the *ortho*-substituted arylacetic ester **4**. Formation of **4** can be rationalized in terms of the Sommelet–Hauser rearrangement of the tautomeric ylide **3** formed from **2** under the reaction conditions. The ylide **2** was stable in an aprotic solvent such as tetrahydrofuran (THF) even under reflux, indicating that the tautomerization between **2** and **3** occurred only in a protic solvent such as methanol. We have now investigated this rearrangement in more detail by variation of the aromatic ring and the stabilizing group of the ylide **2**. The present paper describes the results of our work in this area, including a new preparation of the requisite ylides and their rearrangement to give various *ortho*-substituted arylacetic esters and related compounds.

We began our investigation by examining the rearrangement of the sulfur ylide **8a**. The ylide **8a** was prepared as follows. Treatment of the Friedel–Crafts reaction product **6a**[3] derived from benzene and α-chlorosulfide **5**, with a stoichiometric amount of silver tetrafluoroborate ($AgBF_4$) in a large excess of methyl iodide at room temperature gave the sulfonium salt **7a**, which was then treated with sodium hydride in THF to give the ylide **8a** quantitatively.

In contrast to the ylide **2**, which requires refluxing conditions for the rearrangement, the ylide **8a** was found to undergo the rearrangement even at room temperature in ethanol to give ethyl 2-(methylthiomethyl)phenylacetate (**10a**) quantitatively. This result indicates that the tautomerization between **8a** and the reactive ylide **9a** readily occurred at room temperature. The relatively high stability

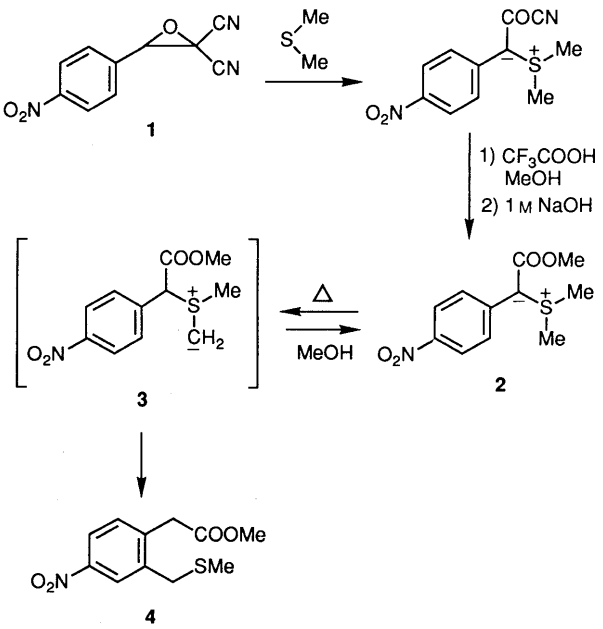

Chart 1

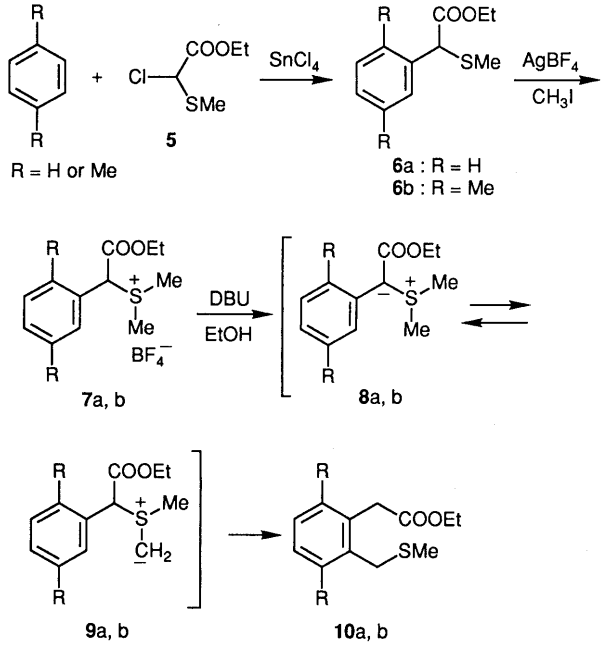

Chart 2

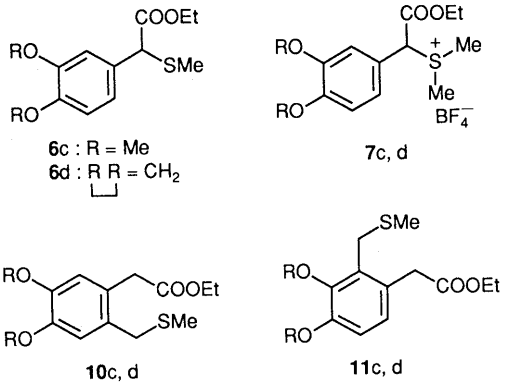

Chart 3

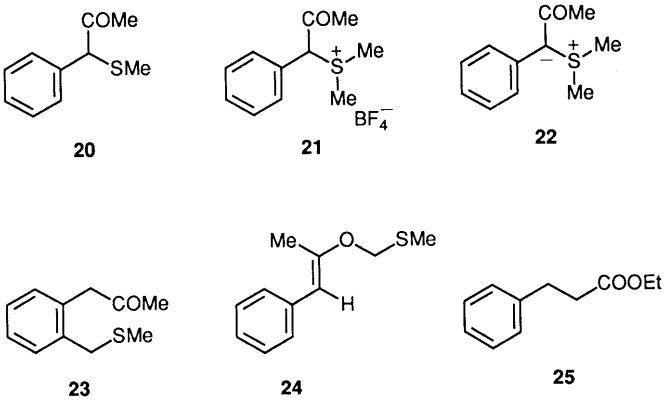

Chart 5

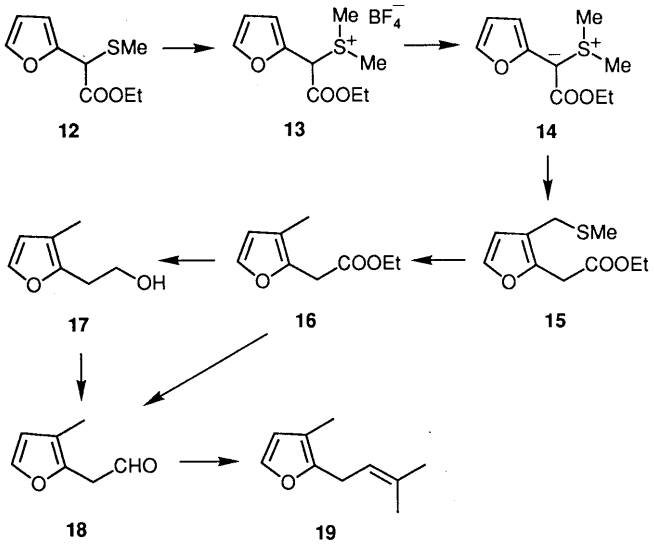

Chart 4

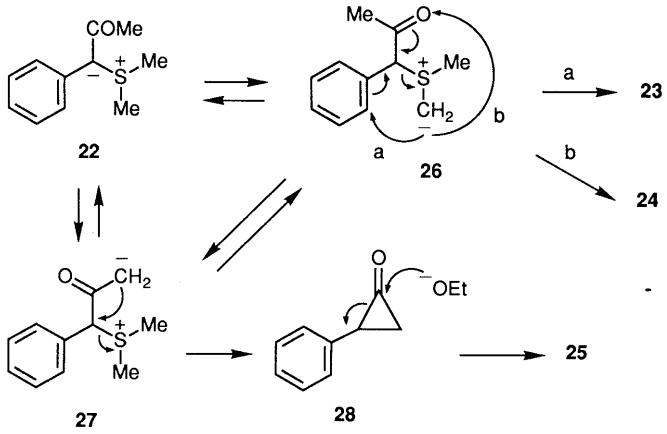

Chart 6

of the reported ylide **2** might be ascribed to the presence of an electron-withdrawing *p*-nitro group on the aromatic ring.

The rearranged product **10a** was obtained more conveniently by treatment of the sulfonium salt **7a** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in ethanol at room temperature in 98% yield. The use of triethylamine in place of DBU afforded a 70% yield of the product **10a**. Similar treatment of the sulfonium salt **7b** with DBU gave **10b** in 82% yield.

S-Methylation of **6c** followed by treatment of the resultant sulfonium salt **7c** with DBU afforded the 2,4,5- and 2,3,4-trisubstituted arylacetic esters **10c** and **11c** in 41 and 14% yields (based on **6c**), respectively. The structures of **10c** and **11c** were confirmed by ^{1}H-nuclear magnetic resonance (^{1}H-NMR) spectroscopy (see Experimental). The sulfonium salt **7d** gave an inseparable mixture of the rearranged products **10d** and **11d** (*ca.* 4 : 1).

The transformation of the furan derivative **13** into the rearranged product **15** was somewhat troublesome. Thus, treatment of **13** with DBU in ethanol at room temperature or under refluxing conditions gave a complex mixture of products. However, when the ylide **14** isolated from **13** was heated in ethanol, the expected rearranged product **15** was obtained in 67% yield (based on **12**). Direct heating of the salt **13** in boiling ethanol in the presence of sodium ethoxide again provided an unsatisfactory result.

We next examined transformation of the product **15** into the aldehyde **18**, which has been shown to be convertible into rose furan (**19**) *via* the Wittig reaction with isopropylidenetriphenylphosphorane.[4] Desulfurization of **15** with tributyltin hydride in the presence of azobisisobutyronitrile (AIBN) in boiling benzene afforded, in 83% yield, the ester **16**, which was then reduced with lithium aluminum hydride to give the alcohol **17** in 85% yield. The ester **16** and the alcohol **17** were subjected to reduction with diisobutylaluminum hydride (DIBAH) and to oxidation with Collins' reagent, respectively. The ^{1}H-NMR spectra of both reaction mixtures clearly showed the presence of the desired aldehyde **18**, but all attempts to purify the product by conventional means were unsuccessful.

The acetyl-stabilized ylide **22**, prepared from the sulfide **20**, was stable at room temperature. However, when the sulfonium salt **21** was heated in boiling ethanol in the presence of DBU, three rearranged products **23**, **24**, and **25** were obtained in 22, 8, and 14% yields (based on **20**), respectively. The *E*-configuration of **24** was determined by comparison of the chemical shift (δ 4.49) of the olefinic proton with those of (*E*)- (δ 4.50) and (*Z*)- (δ 5.23) 2-methoxy-1-propenylbenzenes.[5]

Formation of **23** and **24** can be explained in terms of the common intermediate **26** generated by tautomerization of the ylide **22**. The attack of the anionic center of **26** on the *ortho*-position of the aromatic ring gives the normal Sommelet–Hauser rearrangement product **23** (path a). On the other hand, when carbanion of **26** attacks the carbonyl

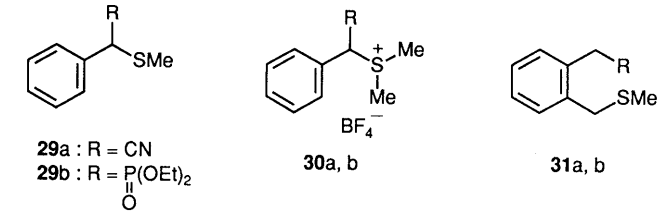

Chart 7

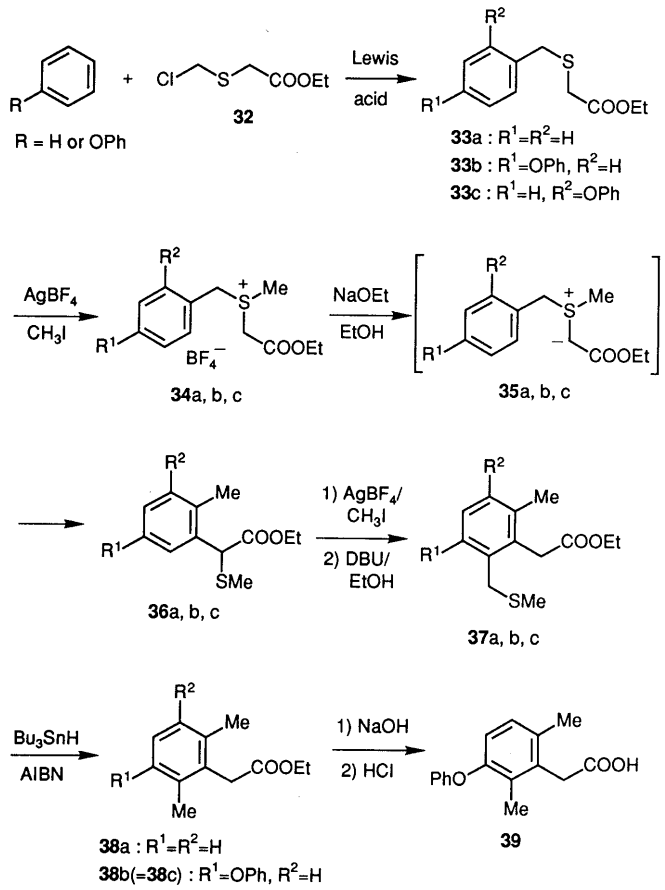

Chart 8

oxygen in a [2,3] sigmatropic manner (path b), the vinyl ether **24** might result.[6] Formation of **25** is of particular interest. This reaction might proceed *via* the Favorskii-type rearrangement of the third tautomer **27**, in which dimethyl sulfide acts as a leaving group, to give the cyclopropanone **28**, as shown in Chart 6.

Treatment of the sulfonium salts **30a** (R=CN) and **30b** [R=P(O)(OEt)$_2$] with DBU in ethanol gave the expected rearranged products **31a** and **31b** at room temperature in 62 and 93% yields, respectively.

Finally, we examined the reaction of the sulfonium salts **34** which were prepared by the Friedel–Crafts reaction of arenes with the α-chlorosulfide **32**[7] followed by *S*-methylation of the resultant products **33**. When **34a** was treated with a stoichiometric amount of sodium ethoxide in ethanol at room temperature, the rearrangement product **36a** was obtained in 60% yield. The use of DBU in place of NaOEt afforded a complex mixture of products containing **36a**. The formation of **36a** from **34a** can be easily rationalized in terms of the Sommelet–Hauser rearrangement of the initially formed stabilized ylide **35a**.

The product **36a** was next subjected to the same rearrangement as described above for **6**, giving the ester **37a** in 76% yield. Desulfurization of **37a** with Bu_3SnH–AIBN afforded the 2,6-dimethylphenylacetic ester **38a** in 60% yield.

The Friedel–Crafts reaction of diphenyl ether with **32** gave an inseparable mixture of the *p*- and *o*-substituted products **33b** and **33c** in a ratio of *ca.* 4:1 and 68% total yield. This mixture was then subjected to a similar sequence of reactions to that described for the preparation of **38a** from **33a** to give the sole product **38b** (=**38c**). A subsequent alkaline hydrolysis of **38b** gave the phenylacetic acid **39**. The carboxylic acid **39** thus obtained can be regarded as an analog of a potent anti-inflammatory agent fenoprofen, but showed no remarkable activity when examined by the carrageenin-induced rat paw edema method.

Experimental

Melting points are uncorrected. Infrared (IR) spectra were recorded with a JASCO A-1 spectrophotometer. ^{1}H-NMR spectra were determined with a JEOL JNM-PMX 60 (60 MHz) or a Varian XL-300 (300 MHz) spectrometer using tetramethylsilane as an internal standard. High-resolution mass spectra (MS) were obtained with a Hitachi M-80 instrument at 20 eV. Column chromatography was performed under pressure on Silica gel 60 PF_{254} (Merck).

[Ethoxycarbonyl(phenyl)methyl]dimethylsulfonium Tetrafluoroborate (7a): A Typical Procedure for the Preparation of Sulfonium Salts Silver tetrafluoroborate (90%) (344 mg, 1.5 mmol) was added in one portion to a stirred solution of **6a**[3] (300 mg, 1.4 mmol) in methyl iodide (10 ml) at room temperature and stirring was continued for 2 h, during which time the sulfonium salt **7a** and silver iodide separated out. The supernatant was removed by decantation, the residue was extracted thoroughly with dichloromethane, and the extract was concentrated *in vacuo* to give the curde sulfonium salt **7a** (487 mg, >100%) as an oil. ^{1}H-NMR ($CDCl_3$, 60 MHz) δ: 1.24 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 2.67 (3H, s, SMe), 3.09 (3H, s, SMe), 4.31 (2H, q, J=7 Hz, $C\underline{H}_2CH_3$), 5.73 (1H, s, CH), 7.48 (5H, s, aromatic protons). This salt was used immediately in the next stage.

Ethyl 2-(Methylthiomethyl)phenylacetate (10a) Method A: A solution of the above salt **7a** (487 mg) in dry THF (2 ml) was added to a suspension of sodium hydride (60% dispersion in mineral oil) (75 mg, 1.9 mmol) in dry THF (8 ml) at −78 °C and the mixture was stirred at the same temperature for 1.5 h. The precipitated salts were removed by filtration and the filtrate was concentrated *in vacuo* to give the crude ylide **8a** (383 mg, >100%) as an oil. ^{1}H-NMR ($CDCl_3$, 60 MHz) δ: 1.26 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 2.87 (6H, s, SMe_2), 4.20 (2H, q, J=7 Hz, $C\underline{H}_2CH_3$), 6.7—7.5 (5H, m, aromatic protons). This ylide **8a** was dissolved in dry ethanol (5 ml) and the solution was allowed to stand at room temperature for 1 h. The solvent was evaporated off and the residue was chromatographed on silica gel (benzene) to give **10a** (312 mg, 99% based on **6a**) as an oil. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1735. ^{1}H-NMR ($CDCl_3$, 60 MHz) δ: 1.24 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 1.99 (3H, s, SMe), 3.73 (2H, s, $ArCH_2$), 3.77 (2H, s, $ArCH_2$), 4.15 (2H, q, J=7 Hz, $C\underline{H}_2CH_3$), 7.22 (4H, s, aromatic protons). *Anal.* Calcd for $C_{12}H_{16}O_2S$: C, 64.26; H, 7.19. Found: C, 64.44; H, 7.24.

Method B: DBU (380 mg, 2.5 mmol) was added to a solution of the crude sulfonium salt **7a** (594 mg), prepared from **6a** (325 mg, 1.55 mmol), in dry ethanol (10 ml) and the mixture was stirred at room temperature for 1 h. After removal of the solvent, dichloromethane (20 ml) was added to the residue and the whole was washed with water, then dried over $MgSO_4$. The solvent was evaporated off and the residue was chromatographed on silica gel (benzene) to give **10a** (340 mg, 98% based on **6a**).

Ethyl 3,6-Dimethyl-1-(methylthiomethyl)phenylacetate (10b) According to a procedure similar to that described for the preparation of **10a** (method B), the sulfonium salt **7b** (207 mg), prepared from **6b**[3] (150 mg, 0.63 mmol) and MeI–$AgBF_4$, was treated with DBU (111 mg, 0.73 mmol) in ethanol to give **10b** (126 mg, 79% based on **6b**), mp 47—48 °C (from hexane). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1730. ^{1}H-NMR ($CDCl_3$, 60 MHz) δ: 1.23 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 2.12 (3H, s, SMe), 2.27 (3H, s, ArMe), 2.38 (3H, s, ArMe), 3.80 (2H, s, $ArCH_2$), 3.83 (2H, s, $ArCH_2$), 4.12 (2H, q, J=7 Hz, $C\underline{H}_2CH_3$), 6.93 (2H, s, aromatic protons). *Anal.* Calcd for $C_{14}H_{20}O_2S$: C, 66.63; H,

7.99. Found: C, 66.46; H, 8.12.

Ethyl 3,4-Dimethoxyphenyl(methylthio)acetate (6c) $SnCl_4$ (0.49 ml, 4.2 mmol) was added to a solution of **5** (700 mg, 4.2 mmol) and veratrole (580 mg, 4.2 mmol) in dichloromethane (20 ml) at 0 °C and the mixture was stirred at room temperature for 1 h. The reaction was quenched by the addition of water (10 ml) and the mixture was extracted with dichloromethane. The solvent was evaporated off and the residue was chromatographed on silica gel (hexane–ethyl acetate, 4 : 1) to give **6c** (1.0 g, 93%) as an oil. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1735. ^{1}H-NMR ($CDCl_3$, 60 MHz) δ: 1.25 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 2.07 (3H, s, SMe), 3.83 (3H, s, OMe), 3.86 (3H, s, OMe), 4.18 (2H, q, J=7 Hz, $C\underline{H}_2CH_3$), 4.45 (1H, s, SCH), 6.7—7.2 (3H, m, aromatic protons). *Anal.* Calcd for $C_{12}H_{18}O_4S$: C, 57.76; H, 6.71. Found: C, 58.03; H, 6.91.

Ethyl 1,3-Benzodioxol-5-yl(methylthio)acetate (6d) According to a procedure similar to that described for the preparation of **6c**, except for the use of $TiCl_4$ instead of $SnCl_4$, 1,3-benzodioxole (500 mg, 4.1 mmol) was allowed to react with **5** (691 mg, 4.1 mmol) to give **6d** (799 mg, 80%) as an oil. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1735. ^{1}H-NMR ($CDCl_3$, 60 MHz) δ: 1.26 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 2.03 (3H, s, SMe), 4.15 (2H, q, J=7 Hz, $C\underline{H}_2CH_3$), 4.37 (1H, s, SCH), 5.88 (2H, s, OCH_2O), 6.7—7.1 (3H, m, aromatic protons). *Anal.* Calcd for $C_{12}H_{14}OS$: C, 56.71; H, 5.55. Found: C, 56.78, H, 5.68.

Ethyl 4,5-Dimethoxy-2-(methylthiomethyl)phenylacetate (10c) and Ethyl 3,4-Dimethoxy-2-(methylthiomethyl)phenylacetate (11c) Using a procedure similar to that described for the preparation of **10a** (method B), the sulfonium salt **7c** (177 mg), prepared from **6c** (131 mg, 0.51 mmol) and MeI–$AgBF_4$, was treated with DBU (87 mg, 0.57 mmol) in ethanol and the reaction mixture was chromatographed on silica gel (hexane–ethyl acetate, 10 : 1). The first eluate gave **11c** (20 mg, 14% based on **6c**) as an oil. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1735. ^{1}H-NMR ($CDCl_3$, 60 MHz) δ: 1.24 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 2.07 (3H, s, SMe), 3.72 (2H, s, $ArCH_2$), 3.84 (8H, s, OMe×2 and $ArCH_2$), 4.14 (2H, q, J=7 Hz, $C\underline{H}_2CH_3$), 6.77, 6.95 (1H each, AB q, J=8 Hz, aromatic protons). Exact MS m/z: Calcd for $C_{14}H_{20}O_4S$: 284.1080. Found: 284.1077.

The second eluate gave **10c** (60 mg, 41% based on **6c**), mp 32—33 °C (from light petroleum). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1735. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.26 (3H, t, J=7.2 Hz, $CH_2C\underline{H}_3$), 2.03 (3H, s, SMe), 3.70 (2H, s, $ArCH_2$), 3.71 (2H, s, $ArCH_2$), 3.87 (3H, s, OMe), 3.88 (3H, s, OMe), 4.15 (2H, q, J=7.2 Hz, $C\underline{H}_2CH_3$), 6.77 (1H, s, aromatic proton), 6.80 (1H, s, aromatic proton). *Anal.* Calcd for $C_{14}H_{20}O_4S$: C, 59.13; H, 7.09. Found: C, 59.11; H, 7.09.

Ethyl 6-Methylthiomethyl-1,3-benzodioxol-5-ylacetate (10d) and Ethyl 4-Methylthiomethyl-1,3-benzodioxol-5-ylacetate (11d) Using a procedure similar to that described for the preparation of **10a** (method B), the sulfonium salt **7d** (186 mg), prepared from **6d** (150 mg, 0.59 mmol), was treated with DBU (121 mg, 0.79 mmol) to give a mixture of **10d** and **11d** (118 mg, 75% based on **6d**) as an oil. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1735. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.25 (3H, t, J=7.2 Hz, $CH_2C\underline{H}_3$), 2.02 (12/5H, s, SMe for **10d**), 2.06 (3/5H, s, SMe for **11d**), 3.658 (8/5H, s, $ArCH_2$ for **10d**), 3.664 (8/5H, s, $ArCH_2$ for **10d**), 3.70 (2/5H, s, $ArCH_2$ for **11d**), 3.75 (2/5H, s, $ArCH_2$ for **11d**), 4.14 (2H, q, J=7.2 Hz, $C\underline{H}_2CH_3$), 5.93 (8/5H, s, OCH_2O for **10d**), 5.95 (2/5H, s, OCH_2O for **11d**), 6.68, 6.72 (1/5H each, AB q, J=7.9 Hz, aromatic protons for **11d**), 6.73 (4/5H, s, aromatic proton for **10d**), 6.75 (4/5H, s, aromatic proton for **10d**). *Anal.* Calcd for $C_{13}H_{16}O_4S$: C, 58.19; H, 6.01. Found: C, 57.72; H, 6.07.

Ethyl (3-Methylthiomethyl-2-furyl)acetate (15) A solution of sodium ethoxide (48 mg, 0.71 mmol) in ethanol (10 ml) was added to a solution of the sulfonium salt **13** (233 mg, 0.71 mmol), prepared from **12**[3] (146 mg, 0.73 mmol) and MeI–$AgBF_4$, in ethanol (5 ml) at 0 °C and the mixture was stirred at room temperature for 10 min. After removal of the solvent, chloroform was added to the residue, the precipitated salts were filtered off, and the filtrate was concentrated *in vacuo* to give the crude ylide **14** (156 mg) as an oil. ^{1}H-NMR ($CDCl_3$, 60 MHz) δ: 1.24 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 2.74 (6H, s, SMe_2), 4.11 (2H, q, J=7 Hz, $C\underline{H}_2CH_3$), 6.0—6.4 (2H, m, H-3 and H-4), 7.25 (1H, d, J=2 Hz, H-5). The ylide **14** thus obtained was dissolved in ethanol (10 ml) and the solution was heated under reflux for 3 h. The solvent was evaporated off and the residue was chromatographed on silica gel (benzene) to give **15** (105 mg, 67% based on **12**) as an oil. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1735. ^{1}H-NMR ($CDCl_3$, 60 MHz) δ: 1.25 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 2.00 (3H, s, SMe), 3.47 (2H, s, $ArCH_2$), 3.63 (2H, s, $ArCH_2$), 4.15 (2H, q, J=7 Hz, $C\underline{H}_2CH_3$), 6.33 (1H, d, J=2 Hz, H-4), 7.27 (1H, d, J=2 Hz, H-5). Exact MS m/z: Calcd for $C_{10}H_{14}O_3S$: 214.0662. Found: 214.0639.

Ethyl (3-Methyl-2-furyl)acetate (16) A mixture of Bu_3SnH (0.28 ml, 1.06 mmol) and AIBN (18 mg, 0.11 mmol) in benzene (10 ml) was added dropwide to a solution of **15** (161 mg, 0.75 mmol) in boiling benzene (8 ml) over a period of 3 h and the mixture was further heated under reflux for 3 h. After removal of the solvent, ethyl ether (10 ml) and a solution of potassium fluoride (500 mg) in water (5 ml) were added to the residue and the mixture was stirred at room temperature overnight. The organic layer was separated, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was chromatographed on silica gel (benzene) to give **16** (104 mg, 83%) as an oil. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1740. ^{1}H-NMR ($CDCl_3$, 60 MHz) δ: 1.23 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 1.97 (3H, s, ArMe), 3.55 (2H, s, $ArCH_2$), 4.13 (2H, q, J=7 Hz, $C\underline{H}_2CH_3$), 6.16 (1H, d, J=2 Hz, H-4), 7.19 (1H, d, J=2 Hz, H-5). Exact MS m/z: Calcd for $C_9H_{12}O_3$: 168.0785. Found: 168.0758.

2-(3-Methyl-2-furyl)ethanol (17) A solution of **16** (90 mg, 0.54 mmol) in dry ethyl ether (5 ml) was added to a suspension of $LiAlH_4$ (42 mg, 1.1 mmol) in dry ethyl ether (5 ml) at 0 °C and the mixture was stirred at room temperature for 2 h. Usual work-up gave **17** (57 mg, 84%) as an oil. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3600, 3420. ^{1}H-NMR ($CDCl_3$, 60 MHz) δ: 1.98 (3H, s, ArMe), 2.10 (1H, br s, OH), 2.80 (2H, t, J=6.5 Hz, $ArCH_2$), 3.80 (2H, br t, J=6.5 Hz, $C\underline{H}_2OH$), 6.14 (1H, d, J=2 Hz, H-4), 7.20 (1H, d, J=2 Hz, H-5). Exact MS m/z: Calcd for $C_7H_{10}O_2$: 126.0680. Found: 126.0680.

Attempted Synthesis of (3-Methyl-2-furyl)acetaldehyde (18) Method A: A 1 M solution of DIBAH in hexane (0.48 ml, 0.48 mmol) was added to a solution of the ester **16** (53 mg, 0.32 mmol) in dry toluene (3 ml) at −78 °C and the mixture was stirred at the same temperature for 1.5 h. A saturated ammonium chloride solution was added to the reaction mixture and the whole was extracted with ethyl ether. The extract was dried over $MgSO_4$ and the solvent was evaporated off to give the crude aldehyde **18** (15 mg). ^{1}H-NMR ($CDCl_3$, 60 MHz) δ: 1.98 (3H, s, ArMe), 3.65 (2H, d, J=2 Hz, $ArCH_2$), 6.25 (1H, d, J=2 Hz, H-4), 7.30 (1H, d, J=2 Hz, H-5), 9.66 (1H, t, J=2 Hz, CHO).

Method B: A solution of the alcohol **17** (85 mg, 0.66 mmol) in dry dichloromethane (1 ml) was added dropwise to a solution of Collins' reagent, prepared from CrO_3 (400 mg, 4 mmol) and pyridine (632 mg, 8 mmol), in dry dichloromethane (15 ml) at room temperature and the mixture was stirred at the same temperature for 15 min. The resultant precipitates were removed by decantation and the organic layer was washed with 1% hydrochloric acid, then dried over $MgSO_4$. The solvent was evaporated off to give the crude aldehyde **18** (58 mg). Attempts to purify the aldehyde **18** by either distillation or chromatography on silica gel were unsuccessful.

Dimethylsulfonium Acetyl(phenyl)methylide (22) A solution of the crude sulfonium salt **21** (218 mg), prepared from **20**[8] (146 mg, 0.81 mmol) and MeI–$AgBF_4$, in ethanol (10 ml) was added to a solution of sodium ethoxide (52 mg, 0.77 mmol) in ethanol (10 ml) and the mixture was stirred at room temperature for 1 h. The solvent was evaporated off, chloroform (10 ml) was added to the residue, and the precipitated salt was filtered off. The filtrate was dried over $MgSO_4$ and concentrated *in vacuo* to give the crystalline ylide **22** (122 mg, 78% based on **20**). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1510. ^{1}H-NMR ($CDCl_3$, 60 MHz) δ: 1.87 (3H, s, COMe), 2.70 (6H, s, SMe_2), 7.0—7.5 (5H, m, aromatic protons). An attempted recrystallization from hexane resulted in partial decomposition of **22**.

2-(Methylthiomethyl)phenylacetone (23), [2-(Methylthiomethoxy)prop-1-enyl]benzene (24), and Ethyl 3-Phenylpropionate (25) DBU (181 mg, 1.2 mmol) was added to a solution of the crude sulfonium salt **21** (224 mg), prepared from **20** (150 mg, 0.83 mmol) and MeI–$AgBF_4$, in dry ethanol (10 ml) and the mixture was heated under reflux for 3 h. After usual work-up, the reaction mixture was chromatographed on silica gel (hexane–ethyl acetate, 60 : 1). The first eluate gave **24** (13 mg, 8% based on **20**) as an oil. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1660. ^{1}H-NMR ($CDCl_3$, 60 MHz) δ: 2.06 (3H, d, J=1.5 Hz, C=CMe), 2.13 (3H, s, SMe), 5.00 (2H, s, OCH_2S), 5.51 (1H, br s, C=CH), 7.1—7.7 (5H, m, aromatic protons). Exact MS m/z: Calcd for $C_{11}H_{14}OS$: 194.0763. Found: 194.0757.

The second eluate gave **25** (20 mg, 14% based on **20**) as an oil. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1730. ^{1}H-NMR ($CDCl_3$, 60 MHz) δ: 1.20 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 2.4—3.2 (4H, m, $ArCH_2CH_2$), 4.10 (2H, q, J=7 Hz, $C\underline{H}_2CH_3$), 7.20 (5H, s, aromatic protons). These spectral data were identical with those of an authentic sample purchased from Aldrich Chemical Company, Inc.

The third eluate gave **23** (35 mg, 22% based on **20**) as an oil. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1720. ^{1}H-NMR ($CDCl_3$, 60 MHz) δ: 1.98 (3H, s, SMe), 2.16 (3H, s, COMe), 3.63 (2H, s, $ArCH_2$), 3.85 (2H, s, $ArCH_2$), 7.21 (4H, s, aromatic protons). Exact MS m/z: Calcd for $C_{11}H_{14}OS$: 194.0763. Found: 194.0757.

2-(Methylthiomethyl)phenylacetonitrile (31a) DBU (111 mg, 0.73 mmol) was added to a solution of the sulfonium salt **30a** (120 mg, 0.45 mmol), prepared from **29a**[8] and MeI–$AgBF_4$, in ethanol (5 ml) and the mixture was stirred at room temperature for 3 h. Usual work-up gave **31a** (49 mg, 62%) as an oil. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 2250. ^{1}H-NMR ($CDCl_3$,

60 MHz) δ: 1.95 (3H, s, SMe), 3.65 (2H, s, $ArCH_2$), 3.86 (2H, s, $ArCH_2$), 7.1—7.5 (4H, m, aromatic protons). *Anal.* Calcd for $C_{10}H_{11}NS$: C, 67.76; H, 6.25; N, 7.90. Found: C, 67.70; H, 6.27; H, 7.75.

Diethyl 2-(Methylthiomethyl)phenylmethylphosphonate (31b) DBU (100 mg, 0.66 mmol) was added to a solution of the sulfonium salt **30b** (228 mg, 0.55 mmol), prepared from **29b**[9] and MeI–$AgBF_4$, in ethanol (5 ml) and the mixture was stirred at room temperature for 2 h. Usual work-up gave **31b** (147 mg, 93%) as an oil. ^{1}H-NMR ($CDCl_3$, 60 MHz) δ:1.23 (6H, t, J=7 Hz, $CH_2C\underline{H}_3\times2$), 2.00 (3H, s, SMe), 3.35 (2H, d, J_{PH}=22 Hz, PCH_2), 3.87 (2H, s, SCH_2), 4.00 (4H, dq, J_{PH}=7 Hz, J_{HH}=7 Hz, $C\underline{H}_2CH_3\times2$), 7.18 (4H, s, aromatic protons). *Anal.* Calcd for $C_{13}H_{21}O_3PS$: C, 54.15; H, 7.34. Found: C, 53.83; H, 7.02.

Ethyl 2-Methylphenyl(methylthio)acetate (36a) Using a procedure similar to that described for the preparation of **7a**, the sulfide **33a**[7] (200 mg, 0.95 mmol) was treated with $AgBF_4$ (206 mg, 0.95 mmol) in methyl iodide (5 ml). Excess methyl iodide was removed by decantation, the residue was extracted with acetonitrile (instead of dichloromethane for **7a**), and the solvent was evaporated off to give the sulfonium salt **34a** (285 mg, 97%) as an oil. The salt **34a** thus obtained was dissolved in ethanol (5 ml) and the whole was added to a solution of sodium ethoxide (63 mg, 0.93 mmol) in ethanol (5 ml) at 0 °C. After stirring of the mixture at room temperature for 40 min, the solvent was removed by evaporation. Chloroform was added to the residue and the precipitated salts were filtered off. The filtrate was concentrated *in vacuo* and the residue was chromatographed on silica gel (benzene–ethyl acetate, 30 : 1) to give **36a** (127 mg, 60%) as an oil. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1740. ^{1}H-NMR ($CDCl_3$, 60 MHz) δ: 1.25 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 2.10 (3H, s, SMe), 2.40 (3H, s, ArMe), 4.20 (2H, q, J=7 Hz, $C\underline{H}_2CH_3$), 4.73 (1H, s, CH), 7.1—7.7 (4H, m, aromatic protons). Exact MS *m/z*: Calcd for $C_{12}H_{16}O_2S$: 224.0869. Found: 224.0842.

Ethyl 2-Methyl-6-(methylthiomethyl)phenylacetate (37a) According to a procedure similar to that described for the preparation of **34a**, the sulfide **36a** (127 mg, 0.57 mmol) was *S*-methylated and the resultant sulfonium salt was heated in boiling ethanol (10 ml) containing DBU (87 mg, 0.57 mmol) for 2 h. Usual work-up gave **37a** (102 mg, 76%) as an oil. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1735. ^{1}H-NMR ($CDCl_3$, 60 MHz) 1.25 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 2.00 (3H, s, SMe), 2.33 (3H, s, ArMe), 3.75 (2H, s, $ArCH_2$), 3.85 (2H, s, $ArCH_2$), 4.15 (2H, q, J=7 Hz, $C\underline{H}_2CH_3$), 7.07 (3H, s, aromatic protons). Exact MS *m/z*: Calcd for $C_{13}H_{18}O_2S$: 238.1026. Found: 238.1036.

Ethyl 2,6-Dimethylphenylacetate (38a) Using a procedure similar to that described for the preparation of **16**, the sulfide **37a** (101 mg, 0.42 mmol) was treated with Bu_3SnH (0.14 ml, 0.504 mmol) and AIBN (6.6 mg, 0.05 mmol). Usual work-up gave **38a** (49 mg, 60%) as an oil. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1735. ^{1}H-NMR ($CDCl_3$, 60 MHz) 1.23 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 2.33 (6H, s, ArMe×2), 3.67 (2H, s, $ArCH_2$), 4.14 (2H, q, J=7 Hz, $C\underline{H}_2CH_3$), 7.05 (3H, s, aromatic protons). Exact MS *m/z*: Calcd for $C_{12}H_{16}O_2$: 192.1149. Found: 192.1151.

Ethyl (4-Phenoxyphenylmethylthio)acetate (33b) and Ethyl (2-Phenoxyphenylmethylthio)acetate (33c) $TiCl_4$ (0.9 g, 4.74 mmol) was added to a solution of **32**[7] (0.8 g, 4.74 mmol) and diphenyl ether (1.2 g, 7.12 mmol) in dichloromethane (40 ml) at 0 °C and the mixture was stirred at room temperature for 18 h. Work-up as described for the preparation of **6c** gave a *ca.* 4 : 1 mixture of **33b** and **33c** (978 mg, 68%) as an oil. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1730. ^{1}H-NMR ($CDCl_3$, 60 MHz) δ: 1.28 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$ for **33b,c**), 3.07 (8/5H, s, SCH_2CO for **33b**), 3.16 (2/5H, s, SCH_2CO for **33c**), 3.81 (8/5H, s, $ArCH_2$ for **33b**), 3.88 (2/5H, s, $ArCH_2$ for **33c**), 4.16 (2H, q, J=7 Hz, $C\underline{H}_2CH_3$ for **33b,c**), 6.8—7.5 (9H, m, aromatic protons for **33b,c**). *Anal.* Calcd for $C_{17}H_{18}O_3S$: C, 67.52; H, 6.00. Found: C, 67.96; H, 6.41.

Ethyl 2-Methyl-5-phenoxyphenyl(methylthio)acetate (36b) and Ethyl 2-Methyl-3-phenoxyphenyl(methylthio)acetate (36c) A solution of sodium ethoxide (59 mg, 0.87 mmol) in ethanol (5 ml) was added to a solution of the mixture of sulfonium salts **34b,c** (350 mg, 0.87 mmol), prepared from **33b,c** and MeI–$AgBF_4$, in ethanol (5 ml) at 0 °C and the mixture was stirred at room temperature for 30 min. Usual work-up gave a mixture of **36b,c** (167 mg, 52%) as an oil. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1740. ^{1}H-NMR ($CDCl_3$, 60 MHz) δ: 1.20 (12/5H, t, J=7 Hz, $CH_2C\underline{H}_3$ for **36b**), 1.23 (3/5H, t, J=7 Hz, $CH_2C\underline{H}_3$ for **36c**), 2.07 (12/5H, s, SMe for **36b**), 2.12 (3/5H, s, SMe for **36c**), 2.27 (3/5H, s, ArMe for **36c**), 2.37 (12/5H, s, ArMe for **36b**), 4.15 (8/5H, q, J=7 Hz, $C\underline{H}_2CH_3$ for **36b**), 4.18 (2/5H, q, J=7 Hz, $C\underline{H}_2CH_3$ for **36c**), 4.66 (4/5H, s, CH for **36b**), 4.77 (1/5H, s, CH for **36c**), 6.7—7.5 (8H, m, aromatic protons for **36b,c**). Exact MS *m/z*: Calcd for $C_{18}H_{20}O_3S$: 216.1131. Found: 216.1117.

Ethyl 6-Methyl-2-methylthiomethyl-3-phenoxyphenylacetate (37b) and Ethyl 2-Methyl-6-methylthiomethyl-3-phenoxyphenylacetate (37c) $AgBF_4$ (90%) (285 mg, 1.32 mmol) was added to a solution of **36,c** (417 mg, 1.32 mmol) in methyl iodide (15 ml) at 0 °C and the mixture was stirred at room temperature for 3 h, during which time only silver iodide separated out. The precipitates were filtered off and the filtrate was concentrated *in vacuo* to give the corresponding sulfonium salt quantitatively. The salt thus obtained was dissolved in ethanol (30 ml) and the mixture was heated under reflux for 2 h in the presence of DBU (200 mg, 1.32 mmol). Usual work-up gave a mixture of **37b,c** (216 mg, 60% based on **36b**, c) as an oil. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1730. ^{1}H-NMR ($CDCl_3$, 60 MHz) δ: 1.23 (3/5H, t, J=7 Hz, $CH_2C\underline{H}_3$ for **37c**), 1.26 (12/5H, t, J=7 Hz, $CH_2C\underline{H}_3$ for **37b**), 2.03 (3/5H, s, SMe for **37c**), 2.07 (12/5H, s, SMe for **37b**), 2.20 (3/5H, s, ArMe for **37c**), 2.30 (12/5H, s, ArMe for **37b**), 3.73 (2/5H, s, $ArCH_2$ for **37c**), 3.83 (8/5H, s, one of $ArCH_2$ for **37b**), 3.87 (2H, s, $ArCH_2$ for **37b,c**), 4.13 (2/5H, q, J=7 Hz, OCH_2 for **37c**), 4.16 (8/5H, q, J=7 Hz, OCH_2 for **37b**), 6.7—7.6 (7H, m, aromatic protons for **37b,c**). Exact MS *m/z*: Calcd for $C_{19}H_{22}O_3S$: 330.1288. Found: 330.1264.

Ethyl 2,6-Dimethyl-3-phenoxyphenylacetate (38b) Using a procedure similar to that described for the preparation of **16**, the mixtue of **37b,c** (86 mg, 0.26 mmol) was treated with Bu_3SnH–AIBN. Usual work-up gave **38b** (70 mg, 95%) as an oil. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1735. ^{1}H-NMR ($CDCl_3$, 60 MHz) δ: 1.24 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 2.20 (3H, s, ArMe), 2.33 (3H, s, ArMe), 3.73 (2H, s, $ArCH_2$), 4.16 (2H, q, J=7 Hz, $C\underline{H}_2CH_3$), 6.7—7.5 (7H, m, aromatic protons). Exact MS *m/z*: Calcd for $C_{18}H_{20}O_3$: 284.1411. Found: 284.1422.

2,6-Dimethyl-3-phenoxyphenylacetic Acid (39) A mixture of **38b** (232 mg, 0.82 mmol) and sodium hydroxide (98 mg, 2.45 mmol) in ethanol (1.5 ml) and water (4 ml) was heated under reflux for 1.5 h. After removal of ethanol, the aqueous layer was acidified to pH 1 with concetrated hydrochloric acid and extracted with ethyl ether. The solvent was evaporated off to give **39** (209 mg, 100%), mp 120—121 °C (from hexane–ethyl acetate). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 2300—3400, 1075. ^{1}H-NMR ($CDCl_3$, 60 MHz) δ: 2.20 (3H, s, ArMe), 2.31 (3H, s, ArMe), 3.75 (2H, s, $ArCH_2$), 6.7—7.5 (7H, m, aromatic protons), 9.2—9.8 (1H, br, COOH). *Anal.* Calcd for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29. Found: C, 74.94, H, 6.27.

References and Notes

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