Registry No.—1, 842-00-2; **2**, 529-36-2; **3**, 17539-31-0; **4**, 57559-91-8; **5**, 57559-92-9; **6**, 57559-93-0; **7**, 28177-06-2; chlorosulfonic acid, 7790-94-5.

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Reinvestigation of the Acetylation of Thioanisole. Effect of the Mole Ratio of Aluminum Chloride

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In the chloromethylation of thioanisole with methylal and Lewis acids,[1] it was shown that the ratio of the products, *p*- and *o*-methylthiobenzyl chloride, could be controlled over a wide range by choice of the Lewis acid and the mole ratio in which it was used. The phenomenon was attributed to reaction of thioanisole as its Lewis acid complex.[2] The stronger the complex, the greater the para position specificity.

To my knowledge, this distinctive behavior of the methylthio substituent in electrophilic substutions has not previously been emphasized. An example of a different electrophilic reaction would lend credence to the idea which has, at the least, considerable synthetic value.

I now wish to report that when acetyl chloride is added to a solution of thioanisole and aluminum chloride in 1,2-dichloroethane (EDC), the yield and isomer ratio of the methylthioacetophenones are influenced by the molar ratio of the reactants. Table I gives some idea of the magnitude of the effect. Increasing the ratio of thioanisole from unity to 11:1 drops the yield from near quantitative to 40%. At the same time the ratio of *p*- to *o*-methylthioacetophenone decreases from 500:1 to 6:1. The order of addition was not a factor; mixing in all cases was at −10 to −20°C, and the reaction mixtures were worked up after 20–24 h at room temperature.[3]

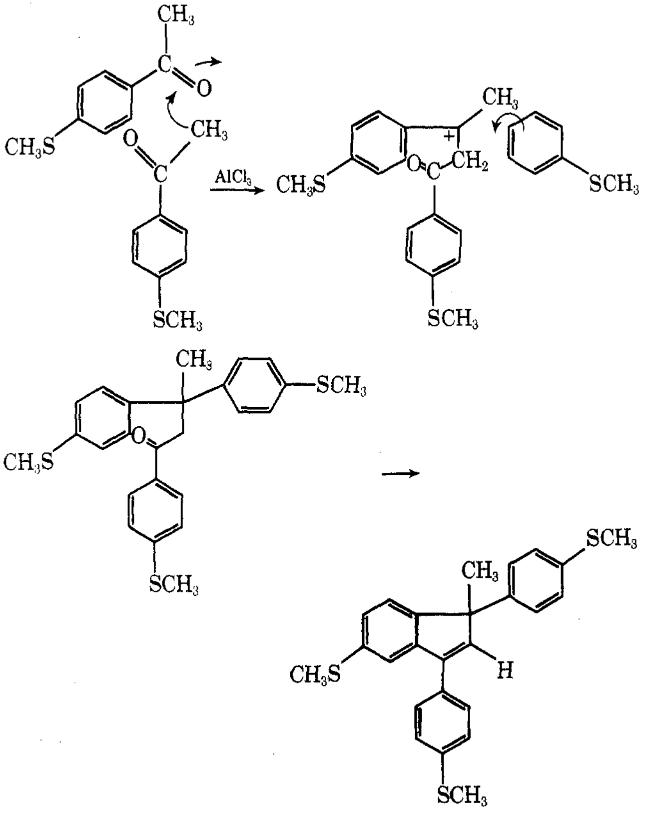
Table I. Acetylation[a] of Thioanisole at 22–24°C

Reaction	Mole ratio thioanisole: $AlCl_3$	Para/ortho ratio[b]	Yield, %[c]
1	1	99.8–0.2	95
2	2	98–2	95
3	5	95–5	80
4	11	86–14	40

[a] Acetyl chloride was equimolar with aluminum chloride. The amount of solvent EDC was changed slightly in order to maintain the same total reaction volume. Reaction 4 was run neat in the excess thioanisole. [b] From GC area percent measurements. No meta isomer was detected with three different GC and two different TLC systems. [c] Computed by GC internal standard method (heptadecane). Includes both isomers.

Reactivity of thioanisole is markedly retarded by excess $AlCl_3$. When 1 equiv of $AlCl_3$ was added for *each* reagent, the yield dropped to 14% without significant by-product formation.[4] When 1 equiv of 1:1 acetyl chloride–$AlCl_3$ complex was added to equimolar thioanisole, benzene, and aluminum chloride in EDC, approximately equal yields[5] of acetophenone and methylthioacetophenone were formed. Had the previously reported[6] K_{rel} thioanisole/benzene value of 7.2×10^3 applied, the benzene would have remained essentially unreacted.

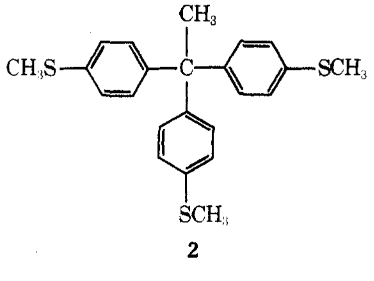
Two by-products of unusual structure were noted, especially in reactions which contained a large excess of uncomplexed thioanisole. The first one, fluorescent, was assigned the indene structure, 1, on the basis of a variety of spectral analyses and chemical plausibility. It probably arose by some variant of the scheme below.



1

In particular, 1 shows in the ^1H NMR ($CDCl_3$) three distinguishable *S*-methyls (δ 2.4), one *C*-methyl (δ 1.7), one vinylic proton (δ 6.4), and a complex pattern of 11 aromatic protons. Uv absorbance [log ε 4.57 (MeOH) at 277 nm] and mass spectrum (M^+ *m/e* 420) are supportive. The positions of *S*-methyl substitution are only presumed to be as shown.

The second compound may be assigned a structure on the basis of its much simpler NMR and molecular ion at *m/e* 396.



2

The aromatic AA′BB′ pattern, single *S*-methyl resonance, and a *C*-methyl signal in the overall ratio of 4:3:1 can fit only the symmetrical **2**. Condensation of *p*-methylthioacetophenone with two molecules of an aromatic seems an unexceptional reaction; however, it does not appear to have been reported.

In summary, the type and extent of sulfur complexation in thioanisole, and presumably analogous compounds, with Lewis acids can markedly affect the rate and product of some electrophilic reactions.

Experimental Section[7]

Materials. Reagents and solvents were used as obtained from commercial suppliers.

Pure ***p*-methylthioacetophenone** was obtained from an acetylation in EDC which was run equimolar in aluminum chloride, acetyl chloride, and thioanisole. The pure material showed mp 82–83°C (heptane) (lit.[8] 79–80°C); NMR (CCl_4) δ 2.45 (s, 6, CH_3), 7.45 (m, 4, aromatic). The two methyl groups were resolved by the addition of a little pyridine. Mass spectrum *m/e* (rel intensity) 166 (M^+, 59), 151 (100), 123 (21), 108 (14).

Pure ***o*-methylthioacetophenone** was formed by reaction of methyllithium with *o*-methylthiobenzoic acid in ether. Crystals from hexane showed mp 44.5–46.5°C (lit.[9] mp 45–47°C). The NMR was as previously described.[9] Mass spectrum *m/e* (rel intensity) 166 (M^+, 33), 151 (100), 127 (7), 108 (10). While this compound was readily separated from its para isomer on the GC column used,[10] resolution by TLC on commercial silica gel plates with hexane–benzene mixtures was unsatisfactory.

Acetylation Experiments. A. Entry 1, Table I. Two milliliters (28.1 mmol) of acetyl chloride was added over 2–3 min to a cold (−10 to −20°C) solution of 28.4 mmol of $AlCl_3$ and 30 mmol of thioanisole in 33 ml of EDC with stirring in a nitrogen atmosphere. The reaction mixture was warmed to and stirred at room temperature for 20–24 h, then quenched onto ice and water and worked up conventionally. The dried ($MgSO_4$) solution was diluted to a standard volume with EDC for quantitation by GC. Experiment 2 used 56 mmol of thioanisole and 30 ml of EDC; 3 used 141 mmol of thioanisole and 20 ml of EDC; and 4 was run with 311 mmol of thioanisole as reactant and solvent. All other aspects of these experiments were identical with 1 above.

B. Excess $AlCl_3$. Reaction was similar to A above, except that the mixture of 60.5 mmol of $AlCl_3$ and 30 mmol of thioanisole in 32 ml of EDC was a slurry at first. After addition of 28.1 mmol of acetyl chloride, substantial solution occurred. Work-up as before gave a product solution which represented a 98:2 para:ortho isomer ratio in 14% overall yield. Thin layer chromatograms of the nonvolatile constituents showed no other appreciable products.

C. To cold (−10 to −20°C) solutions of 28.1 mmol of acetyl chloride and 28.4 mmol of aluminum chloride in 27 and 32 ml of EDC were added 84.5 and 42.2 mmol of thioanisole, respectively. After completion and work-up as in A, the isomer ratios were 98.8:1.2 and 99.5:0.5, respectively.

D. Competitive Acetylation. To 4 g (30 mmol) of aluminum chloride in 18 ml of EDC were added 2.22 g (28.5 mmol) of benzene and 3.49 g (28.1 mmol) of thioanisole below 0°C. The $AlCl_3$ dissolved. A solution of electrophile was prepared by adding 2.21 g (28.2 mmol) of acetyl chloride to a cold (0 to −10°C) stirred slurry of 3.8 g (28.5 mmol) of aluminum chloride in 12 ml of EDC. The latter solution was added to the former below −10°C, and the reaction allowed to continue as with the others. After the same work-up GC determination showed 48.6:51.4 area ratios of *p*-methylthioacetophenone to acetophenone, equivalent to 43:57 molar ratios. The para/ortho ratio of methylthioacetophenones was 96:4.

By-Product Isolation. A reaction similar to entry 4 (Table I) was freed of most of the excess thioanisole by distillation under high vacuum following the normal work-up. The residue was crystallized from hot heptane to give impure methylthioacetophenone and a mother liquor enriched in the impurities. Fractional crystallization of the mother liquor residue first with ether, then ethyl acetate and acetonitrile gave the pure 1,3-diaryl-1-methylindene **1**, mp 145.5–146.5°C, needles from CH_3CN. The NMR is described in the text, as is the uv absorption spectrum. Mass spectrum *m/e* (rel intensity) 420 (M^+, 100), 405 (15), 373 (30), 166 (13), 151 (47), 149 (33).

Anal. Calcd for $C_{25}H_{24}S_3$: C, 71.38; H, 5.97. Found: C, 71.39; H, 5.95.

The other component, **2**, a triarylethane, was obtained from the above ether crystallization almost pure. Recrystallization twice from acetonitrile gave single spot material: mp 142–144°C; NMR ($CDCl_3$) δ 2.13 (s, 3, CCH_3), 2.44 (s, 9, SCH_3), 7.12 (q, 12, aromatic); mass spectrum *m/e* (rel intensity) 396 (M^+, 40), 381 (100), 366 (4.5), 287 (4.8), 273 (8.9), 272 (14), 178 (5.7), 174 (6.7).

Anal. Calcd for $C_{23}H_{24}S_3$: C, 69.65; H, 6.1. Found: C, 69.13; H, 5.79.

A portion of another experiment was chromatographed on preparative layer SiO_2 plates with hexane–benzene to give a fraction consisting almost exclusively of **1** and **2**. Integration of the ^1H NMR spectrum showed 11 and 15% conversions to **1** and **2**, respectively, from acetyl chloride.

Registry No.—**1**, 57559-89-4; **2**, 57559-90-7; *p*-methylthioacetophenone, 1778-09-2; aluminum chloride, 7446-70-0; acetyl chloride, 75-36-5; thioanisole, 100-68-5; *o*-methylthioacetophenone, 1441-97-0; *o*-methylthiobenzoic acid, 3724-10-5.

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(7) Melting points are uncorrected. Elemental analyses are by Mr. J. P. Gilbert and his associates of these laboratories, NMR spectra were obtained with a Jeolco C-60 HL or Hitachi Perkin-Elmer R-24A spectrometer. Mass spectra were obtained with an LKB 9000 spectrometer at 70 eV. For the sake of brevity, only portions of some spectra are reported.

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(10) 10 ft × 0.25 in. 3% Poly A-103 on 100/120 Gas Chrom Q.

Regioselectivity in the Cyclization of β,γ-Epoxy Carbanions. Application to the Total Synthesis of *trans*-Chrysanthemic Acid[1]

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It is generally found that three- and five-membered carbocycles form considerably faster than four-membered rings in intramolecular displacement reactions.[2] A notable exception was recently reported[3] after a study of the regioselectivity in δ-epoxynitrile cyclizations involving S_N2 type transition states. Such systems are unique in that, with equal substitution at both ends of the oxirane ring, cyclobutanes are always formed in preference to cyclopentanes. In view of the fact that previous reactions involving the base-promoted cyclization of the corresponding epoxy esters were generally carried out in protic solvents,[4] a study was undertaken to determine the site of attack in intramolecular alkylations undergone by β,γ- and γ,δ-epoxy carbanions in an aprotic solvent. The results of cyclizations undergone by a few representative β,γ-epoxy carbanions (**7**) are discussed in this note.

In two of the three systems (**5a,b**) examined, formation of a three-membered carbocycle requires substitution at a