An Improved Synthesis of 4-Ethylsulfonyl-1-naphthalenesulfonamide

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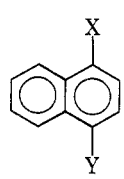
4-Ethylsulfonyl-1-naphthalenesulfonamide (**1**, ENS) has been reported[1] to promote experimental bladder carcinogenesis. ENS has previously been synthesized from 4-amino-1-naphthalenesulfonic acid in an unspecified yield by Brimelow and Vasey.[2] Turner and Dean[3] have reported that the method of Brimelow and Vasey gives low chemical yields and have described their own synthesis of ENS starting from 4-nitro-1-naphthylamine. In our hands, the method of Turner and Dean, which introduces both sulfur functions by diazonium salt reactions, has given an overall yield on the order of 10%. We report here a convenient high-yield, five-step synthesis of ENS which we believe to be superior to both other methods.

Conversion of commercially available 1-naphthalenethiol (**2**) to the ethylthioether **3** was accomplished by standard procedures.[4] Sulfonation of **3** using 1 equiv of chlorosulfonic acid gave the sulfonic acid **4** which was isolated as the sodium salt **5**. The acid chloride **6** was prepared from **5** according to the method of Bosshard et al.[5] Direct conversion of **3** to **6** by using 2 equiv of chlorosulfonic acid was attempted, but a dark-colored, heterogeneous product was obtained and the one-step conversion was deemed unsuitable. Treatment of **6** with ammonia gave the thioether sulfonamide **7** which was converted to ENS by peroxide oxidation. The ir spectrum of ENS synthesized by these reactions was identical with that of ENS prepared by the method of Turner and Dean.[3] This serves to establish that the sulfonation of **3** took place in the 4 position, since their starting material and products were known to have 1,4-substituent orientation. The overall conversion of **2** to **1** was typically 50–60%. Both **7** and ENS exhibited two different crystalline modifications: mp 128 or 141 °C for **7** and mp 184 or 198 °C for ENS. In both cases, crystallization from alcohol produced the higher melting forms in instances where the previously unreported lower melting forms were obtained as crude reaction products.



1, X = SO_2NH_2; Y = SO_2Et
2, X = H; Y = SH
3, X = H; Y = SEt
4, X = SO_3H; Y = SEt
5, X = SO_3Na; Y = SEt
6, X = SO_2Cl; Y = SEt
7, X = SO_2NH_2; Y = SEt

Experimental Section

General. Melting points and boiling points are uncorrected. Anhydrous solvents were prepared by drying over molecular sieve. Infrared spectra were recorded on a Perkin-Elmer Model 710 spectrophotometer. Reactions were monitored and product purity checked by thin layer chromatography on precoated silica gel 60 F-254 plates (EM Laboratories) using toluene–ethyl acetate (1:1 v/v) as a developing solvent. The compounds and their approximate R_f values follow: **1** (0.47), **3** (0.91), **6** (0.91), **7** (0.64).

1-Ethylthionaphthalene (3). A mixture of **2** (26.44 g, 0.165 mol) and NaOH solution (2.5 N, 138 ml) was cooled in an ice bath. Diethyl sulfate (30.4 g, 0.197 mol) was added, and the mixture was stirred for 20 min. The ice bath was removed, and the mixture was refluxed for 1 h. A pale-yellow oil separated upon cooling. The reaction mixture was extracted with ether, and the organic layer was separated, washed with water, and dried over anhydrous $MgSO_4$. After the ether was removed (steam bath), the residue was fractionated through a 6-cm column packed with glass helices to give **3** as a colorless liquid (28.2 g, 91%), bp 98–105 °C (0.2 Torr) [reported[6] 175–176 °C (25 Torr)].

Sodium 4-Ethylthio-1-naphthalenesulfonate (5). A solution of **3** (14.1 g, 75 mmol) in anhydrous $CHCl_3$ (75 ml) was placed in a flask equipped with a magnetic stirrer, addition funnel, condenser, and drying tube and was cooled in an ice bath. A solution of chlorosulfonic acid (8.74 g, 75 mmol) in anhydrous $CHCl_3$ (150 ml) was added dropwise over a period of 1.5 h. A colorless solid began to precipitate from the reaction mixture after ca. two-thirds of the chlorosulfonic acid had been added. (In another reaction, this solid was filtered to give **4** as a colorless powder, mp 81–83 °C). After stirring for 0.5 h, the ice bath was removed, and stirring was continued for 1 h. Evaporation of the $CHCl_3$ under reduced pressure gave a colorless semisolid which was partitioned between ether (50 ml) and water (150 ml). The aqueous layer was separated, warmed to expel residual ether, and made basic by the addition of 50% NaOH solution (8 g), during which time a colorless precipitate formed. Saturated NaCl solution (100 ml) was added and the mixture cooled. The precipitate was filtered and washed sparingly with cold water to give **5** (18.4 g, 82%) as a colorless solid containing one-half of a water of hydration: ir (KBr) 3400 (OH), 1200 ($ArSO_3Na$), and 1070 cm^{-1} ($ArSO_3Na$).

Anal. Calcd for $C_{12}H_{11}S_2O_3Na \cdot \frac{1}{2}H_2O$: C, 48.15; H 4.00; Na, 7.68. Found: C, 48.38; H, 4.18; Na, 7.64.

4-Ethylthio-1-naphthalenesulfonyl Chloride (6). A mixture of **5** (2.90 g, 9.7 mmol) and anhydrous DMF (4 ml) was placed in a flask equipped with a magnetic stirrer, condenser, and drying tube and was cooled in an ice bath. Thionyl chloride (1.10 ml, 15 mmol) was added, and after 5 min the ice bath was removed and the mixture allowed to warm to room temperature. Stirring was continued for 2.5 h. Evaporation of the DMF under reduced pressure gave a yellow oil which was extracted with warm benzene (3 × 40 ml). After centrifugation to remove precipitated salt, the organic extracts were combined, washed with water (2 × 15 ml), and dried over anhydrous $MgSO_4$. Evaporation of the benzene under reduced pressure gave **6** (2.73 g, 98%, mp 78–80 °C) as a yellow solid which was sufficiently pure for the next reaction. Crystallization from acetonitrile gave **6** as yellow needles: mp 80–81 °C; ir (KBr) 1365 ($ArSO_2Cl$), 1195, 1165 ($ArSO_2Cl$), and 1145 cm^{-1}.

Anal. Calcd for $C_{12}H_{11}S_2O_2Cl$: C, 50.26; H, 3.87, Found: C, 50.29; H, 4.00.

4-Ethylthio-1-naphthalenesulfonamide (7). A solution of **6** (1.43 g, 5 mmol) in anhydrous acetonitrile (20 ml) was placed in a flask equipped with a magnetic stirrer, gas inlet, and balloon and was cooled in an ice bath. Anhydrous ammonia was added through the gas inlet. A precipitate developed immediately in the reaction mixture. The mixture was stirred for 1 h with periodic additions of ammonia sufficient to keep the balloon slightly inflated. Water was added, and the acetonitrile was evaporated in a stream of air. Filtration of the precipitated solid gave **7** as colorless needles (1.25 g, 93%), mp 141–142 °C (reported[2] 141–142 °C). The material was sufficiently pure for conversion to ENS: ir (KBr) 3380 (NH), 3270 (NH), 1305 ($ArSO_2NH_2$), 1145 cm^{-1} ($ArSO_2NH_2$).

4-Ethylsulfonyl-1-naphthalenesulfonamide (1). A mixture of **7** (1.34 g, 5 mmol), HOAc (7.5 ml), and 30% H_2O_2 (5 ml, 37 mmol) was heated to 90 °C for 1 h. Water (75 ml) was added to the hot, pale-yellow solution, and the product separated as fine crystals. The mixture was cooled in ice, filtered, and washed with water to give **1** as colorless needles (1.37 g, 91%): mp 198–199 °C (reported[2,3] 198 °C); ir (KBr) 3345 (NH), 3250 (NH), 1335 ($ArSO_2R$), 1310 ($ArSO_2NH_2$), 1280, 1190, 1165 ($ArSO_2R$), 1145 ($ArSO_2NH_2$), and 1125 cm^{-1}.

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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.

References and Notes

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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]

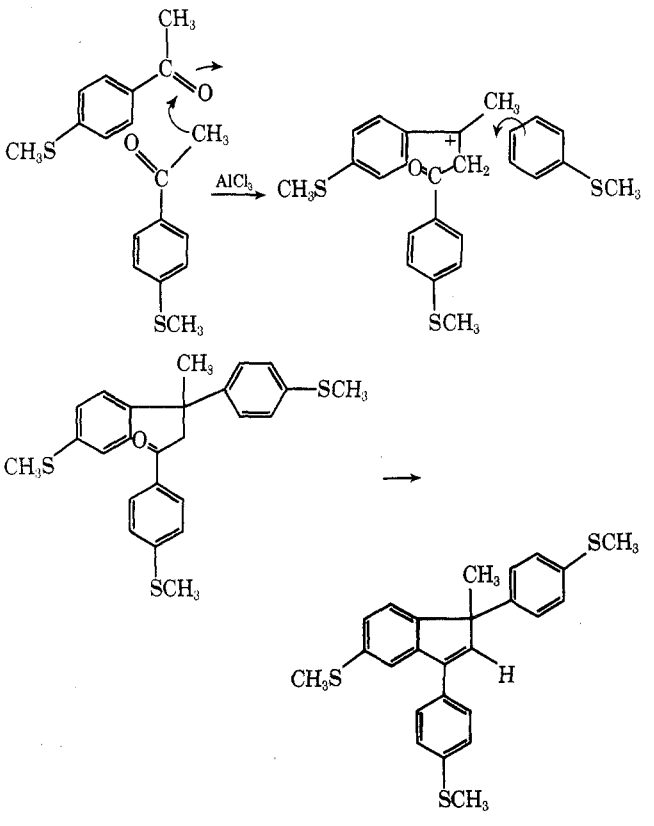
Table I. Acetylation[a] of Thioanisole at 22–24°C

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.

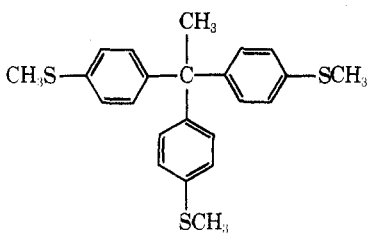
Two by-products of unusual structure were noted, especially in reactions which contained a large excess of uncomplexed thioanisole. The first one, fluorescent, was assigned the indene structure, **1**, on the basis of a variety of spectral analyses and chemical plausibility. It probably arose by some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



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