The Chemistry of Sulfonyl Isothiocyanates. I[1]

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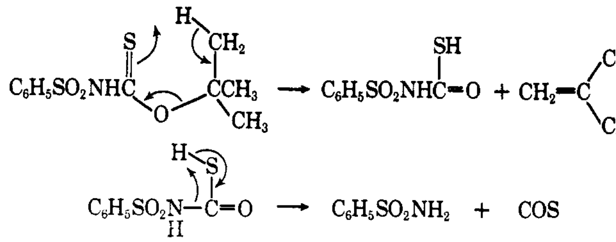
Benzenesulfonyl isothiocyanate (I) reacted with ethanol and 2-propanol to give, respectively, ethylbenzenesulfonylthiourethan (III) and isopropylbenzenesulfonylthiourethan (IV). The reaction of I with 2-methyl-2-propanol gave benzenesulfonamide. 2-Chloroethanol and I afforded an oil from which two cyclic compounds, $C_9H_9NO_3S_2$ (V) and $C_9H_9NO_4S$ (VI), were obtained. 2-Chloroaniline and I gave N-(2-chlorophenyl)-N′-(benzenesulfonyl)thiourea (VII) and the compound $C_{19}H_{15}N_3O_2SCl_2$ (VIII). Similarly, 2-chloro-4-nitroaniline gave N-(2-chloro-4-nitrophenyl)-N′-(benzenesulfonyl)thiourea (IX). Glycine and I produced N-(benzenesulfonyl)-N′-(acetic acid)thiourea (X), which cyclized to the five-membered-ring compound $C_9H_8N_2O_3S_2$ (XI). Thiourea reacted with 1 mole of I to give the expected addition product XII. The addition of an ether solution of I to methylmagnesium iodide gave N-(benzenesulfonyl)thioacetamide (XIII), while the addition of I to phenylmagnesium bromide afforded N-(triphenylmethyl)benzenesulfonamide (XV) and benzenesulfonamide. On the other hand, addition of phenylmagnesium bromide to I gave the 1:1 addition product, N-(benzenesulfonyl)thiobenzamide (XIV).

Organic isothiocyanates of the general formula RNCS have been known for more than a century and their reactions thoroughly investigated.[2,3] On the other hand, organic sulfonyl isothiocyanates had not been prepared until recently when Dickore and Kuehle[4] reported the preparation of a number of them by treating sulfonyliminodithiocarbonic acid salts ($RSO_2N{=}C(SM)_2$) with phosgene, thionyl chloride, or a phosphorus halide. In our laboratory the effect of the sulfonyl group on the isocyanate group has received a great deal of attention in recent years.[5,6,7] Sulfonyl isocyanates react facilely with many reagents which either fail or slowly react with ordinary isocyanates. Therefore, it was of interest to us to explore the reactions of the now available sulfonyl isothiocyanates and to compare the reactions with those of ordinary isothiocyanates.

Alcohols have been reported to react very slowly with isothiocyanates in the cold.[8] Benzenesulfonyl isothiocyanate (I) reacted exothermally with ethanol to give a 79.9% yield of ethyl benzenesulfonyl thiourethan (III). The infrared spectrum of III showed many absorption bands in the 1000–1600-cm^{-1} range. Two bands which consistently appeared in all the compounds which we tentatively assign structures of thiourethan, thiourea, or thioamide, were the bands at about 1380 and 1290 cm^{-1}. The band at 1380 cm^{-1} is very close to the 1408-cm^{-1} absorption band in the spectrum of thiourea. Compound III showed nmr absorption at τ 0.8 which was typical for the —SO_2-NHC(=S)— group.

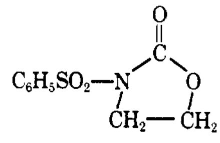
Similarly, 2-propanol reacted with I to give isopropylbenzenesulfonylthiourethan (IV) in 92.0% yield. The reaction of I with 2-methyl-2-propanol, however, was more complex. While no thiourethan was obtained, the main product was benzenesulfonamide. The reaction may be postulated as going through the thiourethan and then decomposing as shown in eq 1.



(1)

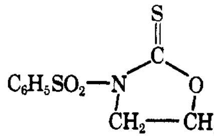
When the reaction was carried out in a stoppered flask, gas pressure built up in the flask.

The reaction of I with 2-chloroethanol produced an oil. Heating the oil with pyridine gave a substance which appeared from elementary analyses, ir, and nmr to be V. In another attempt, a small yield of a cyclic



V

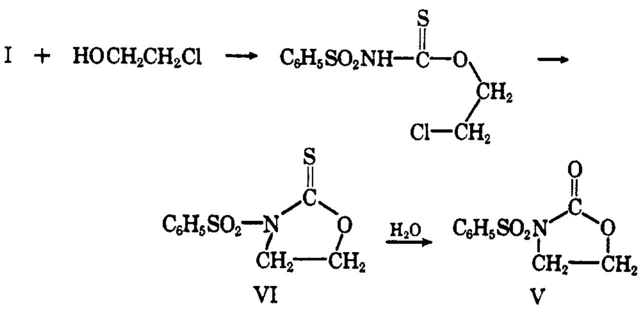
compound, VI, was obtained without the pyridine



VI

treatment. Since V was obtained after the reaction mixture came into contact with water, it may be postulated that VI was a precursor of V (Scheme I). Although V was not obtained in high purity, it is inter-

Scheme I



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[1] Presented in part at the 153rd National Meeting of the American Chemical Society, Miami Beach, Fla., April 1967.

[2] "Methoden der Organichen Chemie," Houben-Weyl, Vol. IX, George Thieme Verlag, Stuttgart, 1955.

[3] N. Kharasch, Ed., "Organic Sulfur Compounds," Vol. I, Pergamon Press Inc., New York, N. Y., 1961, pp 326–338.

[4] K. Dickore and E. Kuehle, German Patent 1,183,492 (Dec 17, 1964); *Chem. Abstr.*, **62**, 7691 (1965).

[5] J. W. McFarland and J. B. Howard, *J. Org. Chem.*, **30**, 957 (1965).

[6] J. W. McFarland and W. A. Burkhardt, *ibid.*, **31**, 1903 (1966).

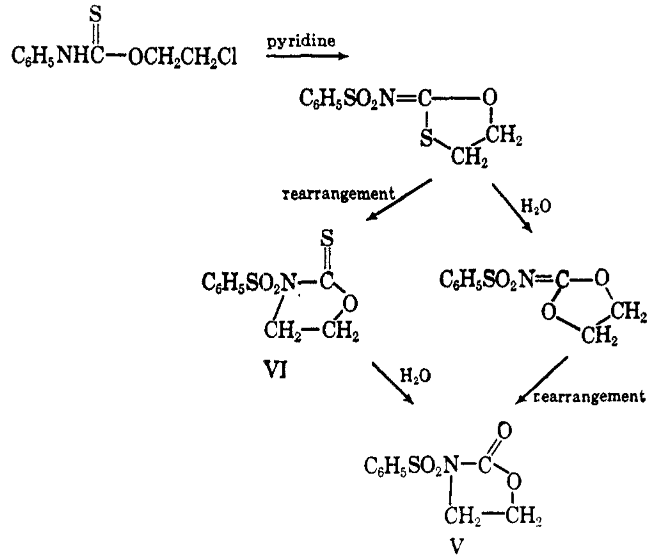
[7] J. W. McFarland, D. Lenz, and D. J. Grosse, *ibid.*, **31**, 3798 (1966).

[8] A. Dadieu, *Ber.*, **64B**, 358 (1931).

esting that a double carbonyl peak was present in the ir spectrum at 1770 and 1685 cm^{-1}.

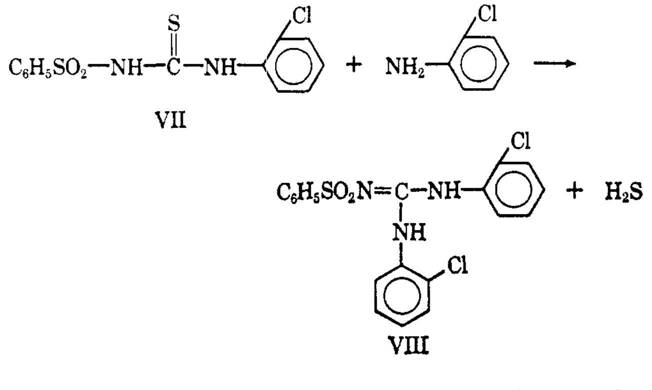
It has been suggested by a referee that the reaction could possibly have also taken the path shown in Scheme II. It is possible that the 1695-cm^{-1} band in the spectrum of V could be due to the C=N bond of one of the above structures, but due to the fact that it occurs at a higher frequency than most C=N bands, it is more likely a carbonyl impurity.

SCHEME II



2-Chloroaniline reacted in a normal fashion with I to afford 96.2% of N-(2-chlorophenyl)-N′-(benzenesulfonyl)thiourea (VII) when a 1:1 ratio of reagents was employed. When more than 2 moles of 2-chloroaniline was used the yield of thiourea was lower and a second product (VIII) was obtained, representing the reaction of 2 moles of amine and 1 mole of isothiocyanate. (See Scheme III.)

SCHEME III

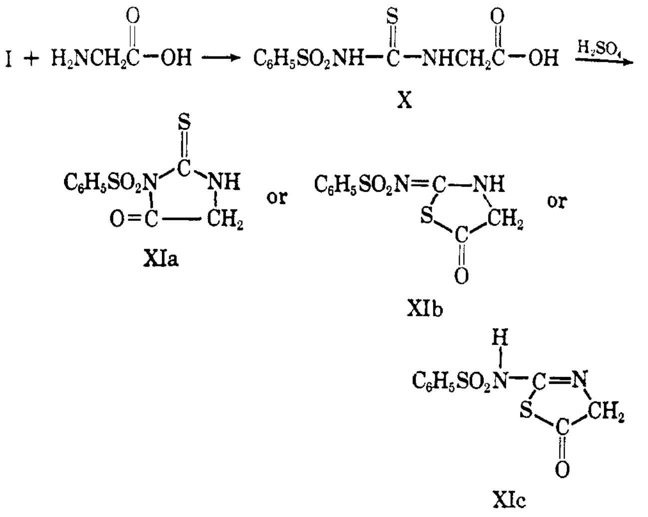


In a similar manner 2-chloro-4-nitroaniline and I gave an 80.6% yield of N-(2-chloro-4-nitrophenyl)-N′-(benzenesulfonyl)thiourea (IX).

The amino group of glycine added to I to give N-(benzenesulfonyl)-N′-(acetic acid)thiourea (X) in 85.3% yield. In aqueous solution X behaves as a strong acid. Titration with dilute sodium hydroxide showed 2 titratable hydrogens (actual value obtained was 1.93).

Treatment of X with concentrated sulfuric acid in methanol split out water to give the five-membered ring compound (XI). Inasmuch as both X and XI showed infrared absorptions at 1380 and 1290 cm^{-1}, it is highly possible that they contain thiocarbonyl groups and, therefore, structure XIa is favored over XIb or XIc. (See Scheme IV.)

SCHEME IV



One mole of I reacted with thiourea to give the expected product XII from the addition of one of the amino groups to a molecule of isothiocyanate.

Finally, the reaction of I with Grignard reagents was investigated. The latter reagents and ordinary isothiocyanates have been shown to give thioamides.[9-11] When I was added to methylmagnesium iodide the expected addition product, N-(benzenesulfonyl)thioacetamide (XIII), was obtained upon hydrolysis of the intermediate in 71.0% yield.

When I was added to phenylmagnesium bromide, a high melting (243–245°) solid (XV) was obtained, but none of the expected 1:1 addition product. The other products were benzenesulfonamide and unidentified oils which contained the isothiocyanate group. Compound XV was shown by melting point, mixture melting point, infrared, and elementary analyses to be N-(triphenylmethyl)benzenesulfonamide. It was obtained in 27.3 and 50.0% yields, respectively, when the ratio of isothiocyanate to Grignard reagent was 1:1 and 1:3. Its presence in the mixture of products may be rationalized by the sequences of reactions given in Scheme V. The odor of hydrogen sulfide was very much in evidence during hydrolysis.

The 1:1 addition product, N-(benzenesulfonyl)thiobenzamide (XIV), was obtained in 72.8% yield, however, when phenylmagnesium bromide was added to an ether solution of I at 0°.

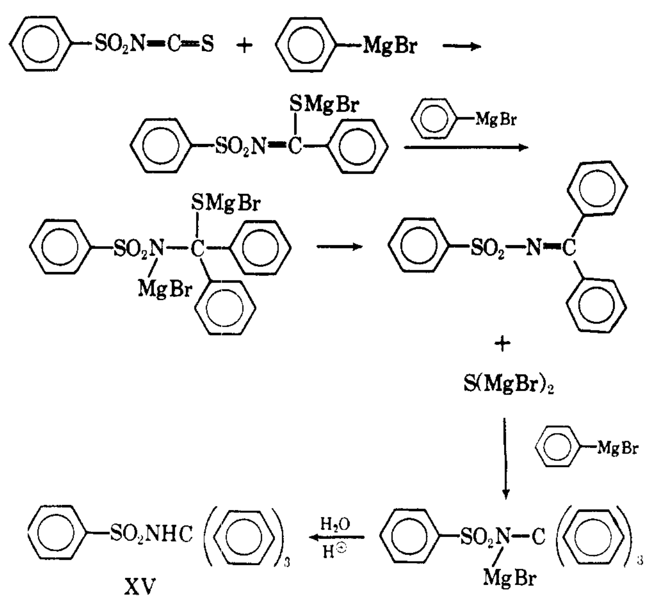
All of the infrared spectral work was done on KBr pellets. As already pointed out, the C=S assignments are highly tentative and it may be that some of the other bands between 1000–1600 cm^{-1} are connected in some way with either the C=S vibrations or the C—N or C—O groups of thioureas, thioamides, or thiourethans. Considerably more work is necessary before precise assignments can be made.

(9) R. Adams, H. B. Bramlet, and F. H. Tendick, *J. Am. Chem. Soc.*, **42**, 2369 (1920).

(10) D. E. Worrall, *ibid.*, **44**, 2971 (1925).

(11) F. F. Blicke and H. Zinnes, *ibid.*, **77**, 4849 (1955).

Scheme V



Experimental Section

Benzenesulfonyl Isothiocyanate (I).—Benzenesulfonyl isothiocyanate (I) was prepared by a modification of the procedure of Dickore and Kuehle.[4] Into a 1-l. three-necked flask fitted with stirrer and reflux condenser were placed 156.0 g (1.0 mole) of benzenesulfonamide, 126.0 g (2.25 moles) of KOH, and 400 ml of CS_2. The resulting slurry was stirred vigorously and heated under reflux for 6 hr. The CS_2 was decanted from the cooled mixture and the red-orange solid triturated twice with 100 ml of acetone and then with 100 ml of ethanol. The solid (209 g) was dried under vacuum and added along with 300 ml of dry benzene to a 1-l. three-necked flask fitted with stirrer, dropping funnel, and reflux condenser. The flask was cooled in ice and 125 ml thionyl chloride was added dropwise with stirring during 1 hr. The yellow mixture was stirred for 2 hr at room temperature and filtered. The solvent was removed from the filtrate under reduced pressure. The residue was distilled giving 76.6 g (38.5%) of I, bp 103–105° (0.5 mm).

After long periods of standing some of the liquid isothiocyanate solidified. The solid, II, was collected by filtration and recrystallized from $CHCl_3$, mp 118–120°.

Anal. Calcd for $(C_7H_5NO_2S_2)_n$: C, 42.25; H, 2.51; N, 7.03; S, 32.15. Found: C, 42.43; H, 2.79; N, 6.93; S, 32.02.

The infrared spectrum of II showed strong bands at 1900, 1600, and 1560 cm^{-1}.

Ethyl Benzenesulfonyl Thiourethan (III).—Ethanol (5 ml) and 1.49 g (0.0075 mole) of I were mixed in a 25-ml erlenmeyer flask. After 15 min, the excess ethanol was evaporated on a steam bath leaving an oil which solidified upon cooling. Recrystallization from CCl_4–petroleum ether (bp 60–70°) gave 1.47 g (79.9%) of a white solid, mp 87–88°.

Anal. Calcd for $C_9H_{11}NO_3S_2$: C, 44.10; H, 4.48; N, 5.70; S, 26.10. Found: C, 43.88; H, 4.56; N, 5.82; S, 25.53.

The infrared spectrum of III showed bands at 3080 (N–H), 1380 and 1290 (possibly due to C=S), and 1360 and 1170 cm^{-1} (SO_2). The nmr spectrum confirmed the structure for III, having a 3 H triplet at τ 8.78, a 2 H quadruplet at 5.57, a 3 H multiplet at 2.37, a 2 H multiplet at 2.0, and a 1 H broad band (N–H) at 0.8.

Isopropyl Benzenesulfonyl Thiourethan (IV).—The reaction of 1.67 g (0.0084 mole) of I and 4 ml of 2-propanol was exothermic and gave after removal of excess alcohol an oil which slowly solidified, weight 2.0 g (92.0 %), mp 75–79°. Recrystallization from benzene–petroleum ether afforded platelets with constant mp 78–79°.

Anal. Calcd for $C_{10}H_{13}NO_3S_2$: C, 46.33; H, 5.02. Found: 46.58; H, 5.06.

Infrared absorption bands were noted at 3150, 1380, 1290, 1360, and 1165 cm^{-1}.

Reaction of I with 2-Methyl-2-propanol.—A mixture of 1.74 g (0.0087 mole) of I and 4 ml of 2-methyl-2-propanol at room temperature gave a very slightly exothermic reaction. After 1 hr precipitation of a white solid began. The mixture was allowed to stand for a total of 5 hr and then was diluted with 15 ml of petroleum ether. The precipitate was collected and amounted to 0.75 g (55.0%), mp 152–155°, with authentic benzenesulfonamide mmp 152–154°. The infrared spectra of the two substances were also identical.

Reaction of I with 2-Chloroethanol.—Ten milliliters of 2-chloroethanol and 7.99 g (0.04 mole) I were allowed to react. A thick oil was obtained which did not crystallize. The oil was heated under reflux for 2 hr with 20 ml of toluene and 15 ml of pyridine. A dark oil separated and 30 ml of water was added which dissolved the oil. The two layers were separated and when the organic layer was cooled in ice, 2.11 g of white solid, V, separated, mp 130–135°. An additional 1.66 g of V was obtained by removing the toluene solvent under reduced pressure, mp 130–135° (previous softening). Several attempts at purification by recrystallization did not sharpen the melting point.

Anal. Calcd for $C_9H_9NO_4S$: C, 47.58; H, 3.96; N, 6.17; S, 14.10. Found: C, 47.30; H, 4.42; N, 6.45; S, 17.09.

The infrared spectrum showed strong bands at 1770 and 1695 cm^{-1} and no N–H absorption.

The nmr spectrum indicated that the substance is approximately 70% V, accompanied by other compounds. It is presently believed that the impurity is partly VI, since the latter has been isolated as shown below.

In a second experiment 6.64 g (0.0333 mole) of I and 7.88 g (0.097 mole) of 2-chloroethanol were mixed in 8 ml of dry ether and allowed to stand at room temperature overnight. The oil which remained after removal of solvent and excess alcohol under reduced pressure weighed 10.7 g. Trituration with 1:1 ether–petroleum ether gave 1.0 g (12.4%) of solid VI, mp 83–86°. Recrystallization from benzene–petroleum ether gave VI with mp 86–88°.

Anal. Calcd for $C_9H_9NO_3S_2$: C, 44.44; H, 3.70; S, 26.34. Found: C, 44.71; H, 3.81; S, 26.68.

The infrared spectrum showed bands at 1390 and 1288 cm^{-1}, but no N–H band. The nmr spectrum showed triplets (2 H) at τ 5.43 and 6.55 (J = 14 cps), a multiplet (2 H) at 2.1, and a multiplet (3 H) at 2.46.

Evaporation of the solvent from the original product afforded an oil which was triturated with petroleum ether. The insoluble solid amounted to 1.70 g (32.5%), mp 153–155°, with benzenesulfonamide mmp 153–155°.

Removal of the petroleum ether solvent gave an unidentified oil with infrared absorption at 3620, 3300, 1755, and 1700 cm^{-1}.

N-(2-Chlorophenyl)-N′-(benzenesulfonyl)thiourea (VII).—A solution of 1.79 g (0.014 mole) of 2-chloroaniline in 25 ml of CCl_4 was added to a solution of 3.18 g (0.016 mole) of I in 25 ml of CCl_4 in a 125-ml erlenmeyer flask. Upon mixing the reagents a white precipitate appeared and was collected by filtration, weight 4.4 g (96.2%), mp 152–153°. Recrystallization from $CHCl_3$–petroleum ether did not change the melting point.

Anal. Calcd for $C_{13}H_{11}N_2O_2S_2Cl$: C, 47.80; H, 3.45; N, 8.57; S, 19.60. Found: C, 47.78; H, 3.65; N, 8.70; S, 19.45.

Infrared bands appeared at 3280, 3050, 1380, 1280, 1370 and 1140 cm^{-1}. The nmr spectrum confirmed the assigned structure.

In another experiment 8.04 g (0.04 mole) of I and 12.1 g (0.095 mole) of 2-chloroaniline were mixed without solvent. The reaction mixture became hot and a solid precipitated, 8.01 g (61.3%), mp 140–144°. Recrystallization from $CHCl_3$–petroleum ether gave VII with constant mp 152–153°.

Dilution of the filtrate with petroleum ether gave an oil which soon solidified to produce 2.0 g (11.9%) of material with mp 118–120°. Recrystallization from ethanol gave compound VIII with mp 119–120°.

Anal. Calcd for $C_{19}H_{15}N_3O_2SCl_2$: C, 54.30; H, 3.57; N, 10.00; S, 7.62; Cl, 16.90. Found: C, 54.69; H, 4.21; N, 9.98; S, 7.54; Cl. 17.00.

The following infrared absorption bands were assigned as indicated: 3360 and 3250 (N–H); 1610 (N=C); 740 (C–Cl); 1360 and 1130 cm^{-1} (SO_2). There were no absorption bands at 1380 and 1280 cm^{-1}.

N-(2-Chloro-4-nitrophenyl)-N′-(benzenesulfonyl)thiourea (IX).—A solution of 3.34 g (0.0168 mole) of I and 2.19 g (0.0127 mole) of 2-chloro-4-nitroaniline in 8 ml of dry toluene contained in a stoppered 25-ml erlenmeyer flask was heated in a 100° oil bath for 6 hr. The yellow precipitate was collected by filtration and recrystallized from toluene, 3.80 g (80.6%), mp 147.5–149°.

Anal. Calcd for $C_{13}H_{10}N_3O_4S_2Cl$: C, 42.00; H, 2.68. Found: C, 41.75; H, 2.97.

The infrared spectrum showed among other absorption bands those at 3260, 3120, 1550, 1445, 1380, 1290, 1345, and 1145 cm^{-1}.

N-(Benzenesulfonyl)-N'-(acetic acid)thiourea (X).—A mixture of 5.45 g (0.027 mole) of I, 2.02 g (0.027 mole) of glycine, and 75 ml of dry CCl_4 was heated under reflux for 18 hr and allowed to cool to room temperature. The precipitate was collected by filtration. Washing the precipitate on the filter with acetone dissolved the product and left the unreacted glycine on the filter. The acetone solution was evaporated to about 10 ml and diluted with petroleum ether. The resulting precipitate was collected and amounted to 6.31 g (95.3%), mp 125–128° dec. Recrystallization from water gave X with mp 144–145°.

Anal. Calcd for $C_9H_{10}N_2O_4S_2$: C, 39.45; H, 3.65; N, 10.25; S, 23.35. Found: C, 39.58; H, 3.73; N, 10.62; S, 23.64.

Infrared and nmr analyses confirmed the structure for X. The product is a strong acid in aqueous solution, and titration with standard base showed the number of titratable hydrogens to be 1.93.

Dehydration of X to Cyclic Structure XI.—N-(Benzenesulfonyl)-N'-(acetic acid)thiourea (X, 2.0 g, 0.0073 mole) was mixed with 10 ml of methanol and 12 ml of concentrated H_2SO_4 and allowed to stand for 2 hr. The solution was poured into ice water, and the resulting precipitate was collected by filtration and recrystallized from toluene. The product XI amounted to 1.0 g (53.5%), mp 181–183°.

Anal. Calcd for $C_9H_8N_2O_3S_2$: C, 42.22; H, 3.13; S, 25.00. Found: C, 42.34; H, 3.39; S, 25.00.

The infrared spectrum showed absorption bands at 3320, 1718, 1382, 1284, 1350, and 1145 cm^{-1}.

Reaction of I with Thiourea.—A mixture of 7.0 g (0.035 mole) of I, 1.21 g (0.0159 mole) of thiourea, and 20 ml of dry toluene was placed in a stoppered 50-ml erlenmeyer flask and heated in a 100° oil bath for 24 hr. The precipitate was collected by suction filtration and washed with toluene. After boiling in ethanol, the insoluble solid amounted to 3.31 g (75.7%), mp 240–242° dec. Recrystallization from a mixture of dimethyl sulfoxide and toluene gave product XII with mp 242–243° dec.

Anal. Calcd for $C_8H_9N_3O_2S_3$: C, 34.90; H, 3.27; N, 15.26; S, 34.90. Found: C, 35.67; H, 2.77; N, 15.44; S, 35.09.

N-(Benzenesulfonyl)thioacetamide (XIII).—A solution of 3.80 g (0.019 mole) of I in 50 ml of anhydrous ether was added dropwise and under N_2 to a solution of 0.021 mole of methylmagnesium iodide in 100 ml of anhydrous ether at 0° during 20 min. The mixture was stirred at room temperature for 1 hr, cooled back to 0°, and hydrolyzed with 100 ml of cold 1 *N* HCl. The ether layer was separated, washed with cold water, and dried over $CaCl_2$. Evaporation of the ether gave 2.9 g (71.0%) of solid, mp 140–145°. Recrystallization from toluene–petroleum ether gave XIII with mp 145–146°.

Anal. Calcd for $C_8H_9NO_2S_2$: C, 44.65; H, 4.19; N, 6.52; S, 29.77. Found: C, 44.98; H, 4.42; N, 6.63; S, 29.63.

Infrared absorption bands appeared at 3200, 1383, 1282, 1340, and 1150 cm^{-1}.

N-(Benzenesulfonyl)thiobenzamide (XIV).—Phenylmagnesium bromide prepared from 0.80 g (0.033 mole g-atom) of magnesium and 5.50 g (0.035 mole) of bromobenzene in 30 ml of dry ether was added dropwise under N_2 with stirring at 0° during 20 min to a solution of 5.97 g (0.030 mole) of I in 30 ml of dry ether. The mixture was stirred an additional 4.5 hr at 0° and then hydrolyzed with 100 ml of cold 0.5 *N* HCl. Work-up as above gave a yellow semisolid (7.3 g) which was triturated twice with 25-ml portions of petroleum ether. The insoluble material was 6.04 g (72.8%) of an orange solid, mp 108–120°. Recrystallization from benzene–petroleum ether gave XIV with mp 118–120°.)

Anal. Calcd for $C_{13}H_{11}NO_2S_2$: C, 56.32; H, 3.97; N, 5.06. Found: C, 55.81; H, 4.15; N, 5.34.

In a second experiment a solution of 5.97 g (0.03 mole) of I in 30 ml of dry ether was added at 0° to a solution of the Grignard reagent prepared from 0.80 g (0.033 g-atom) of Mg and 5.50 g (0.035 mole) of bromobenzene in 30 ml of dry ether during 20 min. The mixture was stirred an additional 30 min at 0° and 3.5 hr at room temperature. Upon hydrolysis, a solid, XV, precipitated and was collected, 1.10 g (27.3%), mp 220–225°. Recrystallization from benzene gave constant mp 243–245°, with authentic N-(triphenylmethyl)benzenesulfonamide[7] mmp 243–245°. Infrared spectra of the two compounds were similar.

Anal. Calcd for $C_{25}H_{21}NO_2S$: C, 75.19; H, 5.26; N, 3.51. Found: C, 75.84; H, 5.49; N, 3.74.

Work-up of the original ether layer gave a mixture of solid and oil which was triturated with 1:1 benzene–petroleum ether to give 1.0 g (21.2%) of benzenesulfonamide, mp 152–154°, with an authentic sample mmp 152–154°. The residue was a red oil which absorbed strongly at 1900 cm^{-1} (NCS).

A third experiment in which 5.97 g (0.03 mole) of I in 30 ml of ether was added to a solution prepared from 15.07 g (0.096 mole) of bromobenzene and 2.24 g (0.092 g-atom) of Mg in 60 ml of ether produced 6.0 g (50%) of XV, mp 185–195°. Recrystallization from benzene gave product with mp 243–245°.

Registry No.—I, 1424-53-9; III, 14627-83-9; IV, 13068-44-5; V, 14627-86-1; VI, 14627-86-2; VII, 14627-87-3; VIII, 14627-88-4; IX, 14633-58-0; X, 14633-59-1; XI, 14746-01-1; XII, 14633-60-0; XIII, 14633-61-5; XIV, 10520-98-6; XV, 860-71-9.

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