The Chemistry of Sulfonyl Isocyanates. II.[1] Reactions with Grignard Reagents

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Phenylsulfonyl isocyanate (I) reacted with phenyl, ethyl, and isopropyl Grignard reagents. Hydrolysis of the intermediates afforded 1:1 addition products, N-sulfonylamides. Similarly, *p*-tolylsulfonyl isocyanate (VII) reacted with phenyl and methyl Grignard reagents to give upon hydrolysis the 1:1 products. The mode of mixing the reagents at 0° did not affect the product yield, but at ether reflux the yield decreased when Grignard reagent was in excess.

The chemistry of sulfonyl isocyanates has recently been reviewed.[3] Most of the reactions are similar to those of ordinary isocyanates, but the sulfonyl isocyanates are considerably more reactive. Hindered alcohols and phenols react facilely with sulfonyl isocyanates, whereas the reactions with phenyl isocyanate are very slow.[1] The strong electrophilicity of sulfonyl isocyanates has been shown by the formation of 1:1 adducts with tertiary amines.[4]

In our continuing exploration into the chemistry of sulfonyl isocyanates, it was of interest to study the reaction with Grignard reagents. With the increasing availability of the sulfonyl isocyanates this was thought to provide a simple but useful method for obtaining N-sulfonylamides.

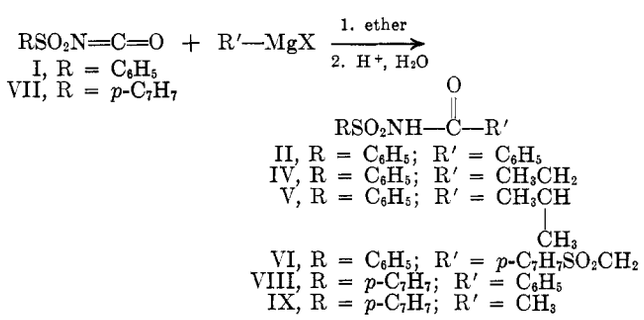
Although unpublished work in our laboratory shows that acyl isocyanates and Grignard reagents give rather complex reactions involving both the isocyanate and carbonyl groups, it was not expected that the sulfonyl group would react with the Grignard reagents. Indeed, there is considerable evidence in the literature that organometallics do not attack the $-SO_2-$ group except under drastic conditions.[5-12]

Phenylsulfonyl isocyanate (I) reacted rapidly with phenylmagnesium bromide at room temperature to give after hydrolysis the expected product, N-(phenylsulfonyl)benzamide (II). If the sulfonyl group is reduced by or reacts in some other way with Grignard reagent, lower yields of II should be obtained when the Grignard reagent is in excess. To test such a possibility, two modes of mixing the reagents were employed. In one case the isocyanate was added slowly to the Grignard reagent (forward addition), and in the other case the Grignard reagent was added to the isocyanate (inverse addition). The yields were 45.0 and 73.2%, respectively, for the forward and inverse additions.

In one reaction in which isocyanate was added to Grignard reagent, 12.5% of benzenesulfonanilide (III) was obtained. How this product was formed is not clear. One possibility which suggests itself is the intermediate formation of a sulfonyl nitrene which reacts with the Grignard reagent.[13,14]

When I was added to ethylmagnesium bromide at room temperature only an oil was obtained, from which 20% of benzenesulfonamide was recovered. When the Grignard reagent was added to I, however, 84.3% of N-(phenylsulfonyl)propionamide (IV) was obtained. Again, it was evident that inverse addition was preferable for obtaining the 1:1 addition product.

I was added to isopropylmagnesium bromide to afford 28.0% of N-(phenylsulfonyl)isobutyramide (V) and 67.9% of benzenesulfonamide. Inverse addition gave a 67.0% yield of V. In this instance reduction of the sulfonyl group, although always a possibility, did not take place because I was recovered as benzenesulfonamide.



Finally, I was added to *p*-tolylsulfonylmethylmagnesium bromide[12] to give N-(phenylsulfonyl)-α-(*p*-tolylsulfonyl)acetamide (VI) in 58.2% yield.

In all the above reactions the reagents were mixed at room temperature and the heat of reaction caused the ether solvent to reflux. Furthermore, the mixtures were usually heated under ether reflux after mixing of reagents. To determine if temperature would affect the course of reaction several reactions were carried out at 0°. At this lower temperature, the reaction between *p*-tolylsulfonyl isocyanate (VII) and phenylmagnesium bromide gave equally good yields of N-(*p*-tolylsulfonyl)-benzamide (VIII) in forward and inverse additions (76.0 and 75.1%, respectively). Furthermore, when VII was added to 2 equiv of phenylmagnesium bromide, the yield was 70.5%.

That the yield of VIII is lowered by the presence of excess Grignard reagent at higher temperatures was further demonstrated by carrying out the reaction of

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VII with phenylmagnesium bromide at the boiling point of ether. Both the forward and inverse additions were accompanied by ether refluxing and after addition the mixtures were heated under reflux for 2.5 hr. From the forward reaction was obtained 37.2% of VIII and from the inverse reaction was obtained 70.8% of VIII.

The addition of VII to methylmagnesium iodide at 0° afforded 88.4% of N-(*p*-tolylsulfonyl)acetamide (IX), showing again that good yields of addition products can be obtained by adding the isocyanate to the Grignard reagent provided that the temperature is low.

Since all possible products were not isolable it is not certain why forward additions at the higher temperatures gave poor yields of 1:1 products. With the excess Grignard reagent the higher temperature could have caused at least two competing reactions to become more important. One of these would be reduction of the $-SO_2-$. No sulfides or mercaptans were isolated but sulfide-like odors were detected in some reaction mixtures. The other reaction could have been the attack of additional Grignard reagent upon the 1:1 product to give complex products. The isolation of a sulfonamide in some instances could have resulted from such complex reactions or from work-up of the reaction mixtures.

Experimental Section

Phenylsulfonyl isocyanate (I) was prepared by the method of Billeter[15] and purified by distillation through a 30-in. spinning-band column. *p*-Tolylsulfonyl isocyanate (VII) was obtained from the Upjohn Co., Carwin Organic Chemicals, and used without further purification.

Reactions of Phenylsulfonyl Isocyanate (I). A. With Phenylmagnesium Bromide. Forward Addition.—Bromobenzene (6.95 g, 0.044 mole) in 25 ml of dry ether was added with stirring under nitrogen to 1.00 g (0.041 g-atom) of magnesium covered with 10 ml of dry ether in a 250-ml, three-necked round-bottomed flask during 20 min. To the Grignard solution was added with stirring a solution of 5.90 g (0.032 mole) of I in 20 ml of ether during 40 min. During addition the mixture turned cherry red and a pink precipitate appeared. The mixture was stirred an additional 2.5 hr at reflux temperature after which the mixture of solid and liquid was yellow.

The reaction mixture was hydrolyzed with 100 ml of cold 1 *N* hydrochloric acid solution. The aqueous layer was washed with two 20-ml portions of ether; the combined yellow organic extracts were washed with three 20-ml portions of water. After drying over magnesium sulfate, the organic extracts were concentrated under reduced pressure. The resulting semisolid was recrystallized from benzene–petroleum ether (30–60°) to give 3.78 g (45.0%) of N-(phenylsulfonyl)benzamide (II), mp 145.5–146°, lit.[16] mp 146–147°. II showed infrared bands at 3320 and 1700 cm^{-1}, and an nmr peak at τ 0.42 corresponding to the N–H, in addition to phenyl hydrogen.

Anal. Calcd for $C_{13}H_{11}NO_3S$: C, 59.77; H, 4.21. Found: C, 59.50; H, 4.45.

The residue from the crystallization was a yellow oil.

In another experiment similar to the one above, the residual oil was dissolved in ether and allowed to stand 2 days. Crystals had formed and were collected and recrystallized from benzene: mp 115–116° (12.5% yield), mmp 115–116° with an authentic sample of benzenesulfonanilide (III). The infrared spectra of the two samples were identical.

Inverse Addition.—The phenylmagnesium bromide was prepared in 35 ml of dry ether from 7.10 g (0.045 mole) of bromobenzene and 1.02 g (0.042 g-atom) of magnesium. The Grignard solution was added with stirring and under nitrogen to a solution of 6.0 g (0.033 mole) of I in 25 ml of ether during 40 min. The orange-yellow mixture of solid and liquid was heated under reflux for 1 hr and then hydrolyzed as above. After removal of solvent the slightly oily solid residue was recrystallized from benzene–petroleum ether to afford 6.27 g (73.2%), mp 144–145.5°. Recrystallization from benzene–petroleum ether gave material with constant mp 145.5–146°. Infrared spectra and mixture melting point showed this product to be identical with the II prepared above.

B. With Ethylmagnesium Bromide. Inverse Addition.—The Grignard reagent was prepared from 3.50 g (0.032 mole) of bromoethane and 0.73 g (0.030 g-atom) of magnesium, in 25 ml of dry ether. The ethylmagnesium bromide solution was added to a solution of 5.00 g (0.027 mole) of I in 25 ml of dry ether with stirring under nitrogen during 45 min at room temperature. The resultant mixture of white solid and almost clear liquid was stirred under nitrogen at room temperature for an additional 3 hr. The mixture was hydrolyzed as was the mixture which gave II. The ether solvent was evaporated to approximately 10 ml and the solid which had precipitated was collected: 4.86 g (84.3%), mp 70–74°. Recrystallization from benzene–petroleum ether gave N-(phenylsulfonyl)propionamide (IV) with constant mp 74–75°. IV absorbed at 3250 and 1720 cm^{-1} in the infrared corresponding to N—H and C=O, respectively. The nmr spectrum showed a 3 H triplet at τ 8.93, a 2 H quadruplet at 7.65, and a 1 H singlet at 0.72, corresponding to methyl, methylene, and N—H groups, in addition to the phenyl hydrogen.

Anal. Calcd for $C_9H_{11}NO_3S$: C, 50.70; H, 5.16. Found: C, 50.66; H, 5.13.

The addition of isocyanate to Grignard reagent gave a mixture from which a 20% yield of benzenesulfonamide was obtained. The remainder was an oil which could not be crystallized.

C. With Isopropylmagnesium Bromide. Forward Addition.—The isopropylmagnesium bromide was prepared from 3.95 g (0.032 mole) of 2-bromopropane and 0.73 g (0.030 g-atom) of magnesium in 25 ml of dry ether. A solution of 5.00 g (0.027 mole) of I in 35 ml of dry ether was added with stirring and under nitrogen during 20 min. The reaction mixture was stirred at room temperature for 2 hr and at reflux temperature for 1 hr. After hydrolysis and work-up, the ether solution was evaporated to approximately 30 ml and cooled at 0°. The white precipitate was collected and amounted to 1.74 g (28.0%), mp 110–128°. Recrystallization from benzene gave N-(phenylsulfonyl)isobutyramide (V) with constant mp 127–128.5°. The infrared spectrum of V exhibited N–H absorption at 3250 and carbonyl absorption at 1715 cm^{-1}. In addition to phenyl hydrogen absorption, the nmr spectrum showed a 6 H doublet at τ 8.90, a 1 H septet at 7.50, and an N–H peak at 0.83.

Anal. Calcd for $C_{10}H_{13}NO_3S$: C, 52.86; H, 5.73. Found: C, 52.94; H, 6.01.

Concentration of the ether solvent from which V was obtained afforded a greasy solid which was recrystallized from benzene: 2.91 g (67.9%), mp 150–153°. The infrared spectrum and mixture melting point showed this substance to be benzenesulfonamide.

Inverse Addition.—The above reaction was repeated with identical amounts of reagents and solvent. The difference was that the Grignard solution was added to the solution of isocyanate during 30 min. The mixture was heated under reflux for 2 hr after the addition of the Grignard reagent. Removal of the ether solvent afforded 4.15 g (67.0%) of white solid, mp 99–124°. Recrystallization from benzene gave material with constant mp 127–128.5°, and identical by infrared and mixture melting point with the V above.

D. With *p*-Tolylsulfonylmethylmagnesium Bromide. Forward Addition.—The *p*-tolylsulfonylmethylmagnesium bromide was prepared[12] from 5.10 g (0.030 mole) of methyl *p*-tolyl sulfone and 0.032 mole of ethylmagnesium bromide in 20 ml of dry ether and 50 ml of dry benzene. To the Grignard mixture was added under nitrogen with stirring at room temperature during 15 min a solution of 5.49 g (0.030 mole) of I in 15 ml of dry benzene. The mixture was stirred at room temperature for 3 hr and hydrolyzed with 75 ml of 1 *N* hydrochloric acid solution. During hydrolysis a white solid precipitated and was collected: 6.16 g (58.2%), mp 200–203°. Recrystallization from acetone–petroleum ether and from benzene gave crystals of N-(phenylsulfonyl)-α-(*p*-tolylsulfonyl)acetamide (VI) with constant mp 208–210°. The infrared spectrum showed peaks at 3250 and 1720 cm^{-1}, indicating N—H and C=O.

Anal. Calcd for $C_{15}H_{15}NS_2O_5$: C, 50.99; H, 4.25; N, 3.97; S, 18.13. Found: C, 51.27; H, 4.44; N, 4.21; S, 18.13.

Evaporation of solvent from the original organic layer gave an oil. Swirling with 20 ml of ether afforded 0.40 g (7.8%

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recovery) of white solid, mp 79–85°. Recrystallization from ethanol–water gave material with mp 84–86°, mmp 84–86° with methyl *p*-tolyl sulfone. The infrared spectrum was also identical with that of methyl *p*-tolyl sulfone.

Reactions of *p*-Tolylsulfonyl Isocyanate (VII). A. With Phenylmagnesium Bromide. Forward Addition.—Phenylmagnesium bromide was prepared from 4.08 g (0.026 mole) of bromobenzene and 0.59 g (0.024 g-atom) of magnesium in 20 ml of dry ether. The solution of Grignard reagent was cooled in ice and to it was added with stirring and under nitrogen a solution of 4.33 g (0.022 mole) of VII in 30 ml of dry ether during 20 min. The mixture of white precipitate and pink solution was stirred at ice temperature for an additional 30 min and then for 4 hr at room temperature.

The mixture was hydrolyzed with 100 ml of 0.5 *N* hydrochloric acid solution. A white precipitate appeared and was filtered off: 1.57 g (26.0%), mp 145–147°. Work-up of the filtrate and final removal of solvent from the organic layer gave 4.23 g of greasy solid. Swirling with benzene and filtering afforded 3.03 g (50.0%) of white solid, mp 144–147°. Since infrared and mixture melting point showed the two samples to be identical, they were combined (total yield 76.0%) and recrystallized from benzene to constant mp 147–148°, lit.[17] mp 147° for N-(*p*-tolylsulfonyl)-benzamide (VIII). Infrared absorption peaks at 3400 and 1715 cm^{-1} indicated N–H and carbonyl. Nmr peaks at τ 7.72 (3 H) and 0.92 (1 H) were evidence for the tolyl methyl group and N–H, respectively, in addition to phenyl hydrogen peaks.

Anal. Calcd for $C_{14}H_{13}NO_3S$: C, 61.09; H, 4.73. Found: C, 61.20; H, 4.69.

A similar reaction was run except that a 1:2 ratio of isocyanate to Grignard reagent was used. The yield of VIII was 70.5%.

A forward additon reaction with a 1:1 isocyanate to Grignard reagent ratio was carried out in which the ether was allowed to reflux during addition and the mixture was heated under reflux for an additional 2.5 hr. The yield of VIII was only 34.1%. The other product was a red oil.

Inverse Addition.—Phenylmagnesium bromide prepared from 4.08 g (0.026 mole) of bromobenzene and 0.59 g (0.024 g-atom) of magnesium in 20 ml of dry ether was added to a solution of 4.33 g (0.022 mole) of VII in 30 ml of dry ether during 20 min at ice temperature. After stirring at 0° for 30 min and at room temperature for 4 hr, the mixture was hydrolyzed with 100 ml of 0.5 *N* hydrochloric acid solution. The oily solid which precipitated was collected and amounted to 6.19 g. Swirling with 50 ml of 1:2 benzene–petroleum ether gave 4.54 g (75.1%) of crystals, mp 140–144°. Recrystallization from benzene gave VIII with constant mp 147–148°, identical by infrared and mixture melting point with the VIII above. Removal of the solvent from the original organic layer gave an intractable yellow oil, with infrared bands at 3600, 3300, 1740, and 1690 cm^{-1}.

An identical reaction was run except that the ether was allowed to reflux during addition and the mixture was subsequently heated under reflux for 2.5 hr. The yield of VIII was 70.8%.

B. With Methylmagnesium Iodide. Forward Addition.—A solution of 4.33 g (0.022 mole) of VII in 30 ml of dry ether was added with stirring under nitrogen during 20 min at 0° to the methylmagnesium iodide prepared from 3.69 g (0.026 mole) of iodomethane and 0.59 g (0.024 g-atom) of magnesium in 20 ml of dry ether. The mixture was stirred at 0° for 30 min and at room temperature for 4 hr. Upon hydrolysis with 50 ml of 1 *N* hydrochloric acid solution a white precipitate formed and was collected: 1.90 g (41.0%), mp 138–139.5°. Recrystallization from benzene–petroleum ether gave N-(*p*-tolylsulfonyl)acetamide (IX) with constant mp 138.5–139°, lit.[18] mp 139°. Strong infrared absorption was observed at 3250 and 1720 cm^{-1}.

Anal. Calcd for $C_9H_{11}NO_3S$: C, 50.70; H, 5.16. Found: C, 50.59; H, 5.10.

Removal of solvent from the original ether layer gave 2.20 g (47.4%) of solid, mp 120–130°. Recrystallization from benzene–petroleum ether gave material with constant mp 138.5–139°, and identical by infrared and mixture melting point with the IX above.

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New Benzomorphan Ring Closure in the Synthesis of 5-Phenylbenzomorphans

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Base-catalyzed, internal N-alkylation of amides of 2-bromo-4-(carboxymethyl)-4-phenyl-1-tetralone is stereospecific and gives 5-phenylbenzomorphan-3,8-diones. These keto lactams have been converted, by reduction *via* 8-hydrazone or by stepwise hydrogenolysis involving 8-chloro intermediates, to 5-phenylbenzomorphan-3-ones, and then by hydride reductions into the corresponding benzomorphans.

Synthesis of quaternary carbon compounds structurally related to morphine is a field of durable interest to many chemists. Of a number of approaches which have been followed, four (Scheme I, A–D) have been particularly successful in duplicating all or part of the morphine structure. (A) The Grewe piperideine → morphinan cyclization[1] has been extended to synthesis of a number of morphinans, isomorphinans and benzomorphans.[2] (B) Reductive closure of 1,2-tetralindione-4-acetonitriles to isomorphinans,[3] key to the first total synthesis of morphine, has been used in synthesis of other isomorphinans.[2,3] (C) Displacement of a suitable leaving group (OAc) β to nitrogen on a chain appended to a 2-aminotetralin system, by a carbanion which becomes the quaternary carbon atom, led to morphinans and a second total synthesis of morphine.[4] (D) Displacement of 2-bromo in a 1- or 3-tetralone system by quaternization of a β-dialkylaminoethyl chain appended at quaternary carbon 4 has also been employed as a route to benzomorphans.[2,5] With this work there are to be grouped other less practical, if scarcely less interesting, attempts to synthesize quaternary carbon analogs and precursors of the morphine

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