give *four* bands, all of them weak. Phenolphthalein in alcohol gives only *two* bands corresponding closely to two of the more prominent bands found in phenol-tetrachlorophthalein and in *o*-cresol-tetrachlorophthalein.

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THE MECHANISM OF THE REACTION OF ISOCYANATES AND ISOTHIOCYANATES WITH THE GRIGNARD REAGENT

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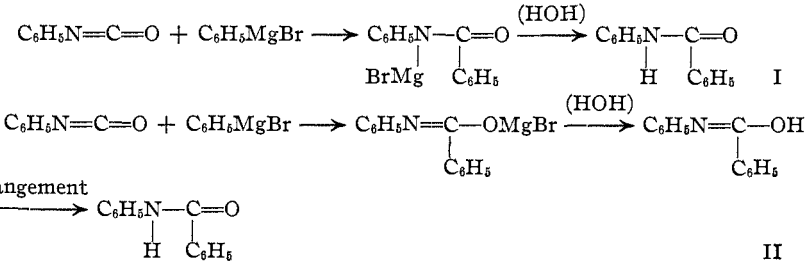
In connection with a series of studies concerned with the mechanism of reaction between the Grignard reagent and compounds having more than one reactive group, it has been shown[1] that with ketenes addition takes place at the carbonyl group and not at the ethylenic linkage. Because of the marked similarity in chemical behavior between ketenes and isocyanates, attention was directed at that time to the desirability of determining the mode of addition of the Grignard reagent to isocyanates, particularly because this class of compounds has two reactive groups (—N=C= and =C=O) which can add the Grignard reagent.

The reactions of ketenes, isocyanates and isothiocyanates with the Grignard reagent have several points in common. First, a liberal excess of the Grignard reagent gives, with each of the types mentioned, one compound. Second, this compound (obviously different in each case) involves the addition of but one molecule of the Grignard reagent. Third, the product formed by hydrolysis in each case throws no light on the mechanism of reaction.

For example, in the formation of benzanilide from phenyl isocyanate and phenylmagnesium bromide the Grignard reagent may have added to the —N=C= linkage (I) or to the carbonyl group (II).



Blaise[2] has shown that when isocyanates react with RMgX compounds

[1] Gilman and Heckert, THIS JOURNAL, **42**, 1010 (1920). Later it was shown that ethylmagnesium iodide does not add to several typical ethylenic hydrocarbons under varying conditions [Gilman and Crawford, THIS JOURNAL, **45**, 554 (1923)].

[2] Blaise, *Compt. rend.*, **132**, 40 (1901).

the products formed are anilides. Without experimental proof he interprets the reaction as one involving primary addition to the carbonyl group. However, as already indicated, the formation of anilides can be explained satisfactorily by either mode of addition.

A standard method for the solution of such a problem is to treat the addition compound, prior to hydrolysis, with some so-called reliable reagent which will replace the —MgBr group by another, in order to give a compound that lends itself to ready identification. The success which attended the use of benzoyl chloride in determining the mechanism of reaction between diphenyl ketene and phenylmagnesium bromide naturally suggested the same compound for this work. Several experiments under varying conditions showed this reagent to be quite unsatisfactory when used in the isocyanate reaction, for the product always obtained (in practically quantitative yields) was that which results on direct hydrolysis—benzanilide.

This prompted a study of other compounds such as diphenyl bromomethane, triphenyl chloromethane, methyl iodide, *p*-nitrobenzyl bromide, ethyl iodide and allyl bromide. A comprehensive series of experiments in which temperature, pressure, solvents and time of heating were varied gave no indication of the replacement of the —MgBr group by another. The chief product and very often the sole product after hydrolysis, which concluded each experiment, was benzanilide.

The next reagent tried was diethyl sulfate. To ascertain its reliability for determining structure, an extensive study was made of its reactions with organomagnesium halides.[3] It was shown with all compounds investigated that the —MgBr group attached to carbon, nitrogen or oxygen was replaced by an ethyl group, but the yields obtained when the —MgBr was attached to oxygen were markedly inferior to those when the same group was attached to carbon or nitrogen.

However, when the addition compound of phenyl isocyanate and phenylmagnesium bromide was treated with diethyl sulfate the only product obtained was benzanilide. In one experiment the yield was practically quantitative, 97.5% when based on phenyl isocyanate. A special examination of all solutions failed to reveal the presence of either of the two possible products of hydrolysis, ethyl aniline or ethyl benzoate. Likewise, the chief product with dimethyl sulfate was benzanilide.

It is probable that no reaction took place with diethyl sulfate. The possibility that diethyl sulfate replaced the —MgBr group attached to oxygen to give N-phenylbenziminoethyl ester, and that this compound on subsequent hydrolysis by aqueous hydrochloric acid gave ethyl chloride and benzanilide is remote. It is known that *aqueous* mineral acids will hydrolyze such imino ethers or esters to the corresponding amine and

[3] Gilman and Hoyle, THIS JOURNAL, **44**, 2621 (1922).

ester.[4] Admittedly, the compound under consideration can be converted into ethyl chloride and benzanilide, but only when *dry* hydrogen chloride is used and the resulting hydrochloride heated at 60°.[5]

There is good reason to believe that addition does not occur at the —N=C group, the —MgBr going to nitrogen. When the addition compound of benzalaniline and phenylmagnesium bromide was treated with diethyl sulfate, a 90.5% yield of N-ethyl-N-phenyl-benzohydrylamine was obtained. This reaction was intentionally selected in the diethyl sulfate work[3] because it involved the replacement by an ethyl group of the —MgBr attached to nitrogen in a compound which has much in common with one of the possible addition compounds (I) of phenyl isocyanate and phenylmagnesium bromide: each contains a nitrogen atom to which are attached the —MgBr group, a phenyl group, and a carbon holding a phenyl group.

There is, on the other hand, some ground for the belief that the —MgBr group could be attached to oxygen and yet suffer no appreciable replacement. In this connection attention has already been directed to the poor yields in the diethyl sulfate work[3] with —OMgBr compounds. Furthermore, related reagents, the halogenalkyl esters of sulfonic acids, replace the —MgBr attached to oxygen with great difficulty and to a very small extent.[6] Other studies in progress in this Laboratory verify the comparatively decided sluggishness of the —OMgBr group in replacement reactions.[7]

At best, such proof of the mechanism of reaction is essentially negative. It was believed that a more positive proof could be obtained by a study of the analogous sulfur compound, phenyl isothiocyanate, inasmuch as some earlier work[8] showed that an —MgBr group attached to sulfur would suffer replacement by a methyl group when treated with dimethyl sulfate. A few preliminary experiments showed this reaction to be quite general. Diethyl sulfate will replace by an ethyl group the —MgBr group which is attached to sulfur in an aliphatic or aromatic compound.

Accordingly, the addition compound of phenyl isothiocyanate and phenylmagnesium bromide was treated with dimethyl and with diethyl sulfates. In each case a smooth reaction took place and S-methyl-thiobenzanilide and S-ethyl-thiobenzanilide were formed, respectively. These appeared to be the chief products, and hydrolysis of the small quantities of intractable oils gave no methyl or ethyl aniline, products which should be formed had addition occurred at the —N=C linkage, the —MgBr going to nitrogen.

[4] Landers, *J. Chem. Soc.*, **83**, 320, 766 (1903). Also, Chapman, *ibid.*, **121**, 1676 (1922).

[5] Lossen, *Ann.*, **265**, 142 (1891).

[6] Gilman and Beaber, THIS JOURNAL, **45**, 839 (1923).

[7] In particular, the reaction between cupric chloride and organomagnesium halides.

[8] Taboury, *Ann. chim. phys.*, **15**, 33 (1908).

There can be little doubt, therefore, concerning the mechanism of addition of the Grignard reagent to isothiocyanates: namely, that addition takes place at the C=S linkage.[9] Because of the marked similarity in properties of isocyanates and isothiocyanates, it is highly probable that addition with isocyanates involves the C=O linkage, according to Scheme (II).

Experimental Part

Ethylation of *p*-Thiocresol.—An ethereal solution of 0.2 moles of *p*-thiocresol was dropped slowly into a cold, well-stirred solution containing approximately 0.3 moles of ethylmagnesium bromide. 0.3 Mole of diethyl sulfate was added to the reaction mixture, and on working up the product in the customary manner a practically quantitative yield of ethyl *p*-tolyl sulfide was obtained. The identification of the sulfide was completed by oxidizing a part to the known ethyl *p*-tolyl sulfone.

Under corresponding conditions (in ether solution and at room temperature) it is possible to ethylate *p*-thiocresol directly without the intermediate formation of the corresponding organomagnesium halide. The yield of sulfide, however, is about 60% and most of the unreacted *p*-thiocresol can be recovered. The use of an alkaline solution would undoubtedly improve the yield materially.

Ethylation of Benzylmercaptan.—Benzylmercaptan was ethylated in a manner strictly analogous to that described above. Here a mixture of compounds was obtained. A portion of the fraction boiling near 215° was identified as ethylbenzyl sulfide by conversion into the corresponding sulfone. No investigation was made of the other fractions.

Reaction of the Addition Compound of Phenyl Isothiocyanate and Phenylmagnesium Bromide with Dimethyl Sulfate and with Diethyl Sulfate.—0.3 Mole of phenyl isothiocyanate dissolved in ether was slowly added to a cool, well-stirred ether solution containing 0.4 mole of phenylmagnesium bromide. After warming the resulting mixture for 2 hours, 0.5 mole of dimethyl sulfate in ether was slowly added. The contents of the flask thickened quite appreciably and became deep red. May[10] in a study of the tautomerism of thio-anilides observed a like color when dimethyl sulfate was added to thiobenzanilide dissolved in neutral media.

Subsequent to a 2-hour period of refluxing, the reaction products were hydrolyzed by pouring into iced hydrochloric acid. The resulting reddish ether layer became light yellow when washed with water. When most of the ether had evaporated spontaneously, the solution was completely filled with long, slightly yellow needles melting[11] at 62°. A single washing with alcohol removed the yellow color and gave 49.2 g. of a compound melting at 63°. This compound was identified as S-methyl-thiobenzanilide by a mixed melting point determination with some of the same compound synthesized after the manner described by May.[10] The yield based on phenyl isothiocyanate is 67%.

An examination of the aqueous solution and of the products of acid hydrolysis obtained from the small quantity of apparently intractable oil contained in the ether

[9] Sachs and Loevy [*Ber.*, **36**, 585 (1903)] in a study of the reaction between isothiocyanates and the Grignard reagent obtained thio-anilides, and without experimental proof interpreted the reaction as one involving addition to the thiocarbonyl group. At that time it was believed that the Grignard reagent would not add to an —N=C group, as in benzalaniline.

[10] May, *J. Chem. Soc.*, **103**, 2272 (1913).

[11] The temperatures recorded in this work are uncorrected.

solution showed methyl aniline to be absent. This indicates that the —MgBr group did not add to nitrogen.

In one experiment when diethyl sulfate was used instead of dimethyl sulfate, the ether was replaced by dry xylene and the reaction mixture refluxed for three hours. After hydrolyzing, and then washing the ether solution with water, a reddish oil was obtained which could not be induced to crystallize. Accordingly, it was distilled in a vacuum and the major part came over at 194° (16 mm.)

This oil resisted hydrolysis by hot concentrated potassium hydroxide. However, it was readily hydrolyzed when refluxed with about 20% hydrochloric acid, giving aniline and ethyl thiolbenzoate. The ethyl thiolbenzoate in turn was identified by the products resulting from alkaline hydrolysis, namely, benzoic acid and ethyl mercaptan.

Accordingly, the oil boiling at 194° (16 mm.) must be S-ethyl-thiobenzanilide. The yield was 60%; n^{28}, 1.6110; d_4^{28}, 1.084.

Analysis.[12] Calc. for $C_{15}H_{15}NS$: S, 13.27. Found: 13.11.

An examination of the several solutions failed to reveal any ethyl aniline.

Summary

It has been proved that the Grignard reagent adds to the thiocarbonyl group in isothiocyanates. By experiment and by analogy it is virtually certain that the Grignard reagent also adds to the carbonyl group in isocyanates.

AMES, IOWA

[CONTRIBUTION FROM THE DEPARTMENTS OF PHARMACOLOGY AND OF TROPICAL MEDICINE, HARVARD MEDICAL SCHOOL]

N,N'-DIMETHYLENESULFUROUS ACID-3,3'-DIAMINO-4,4'-DIHYDROXY-AZOBENZENE: A NITROGEN COMPOUND ANALOGOUS TO SULFARSPHENAMINE[1]

BY WALTER G. CHRISTIANSEN

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Since nitrogen is in the same group of the periodic table as arsenic and antimony, and many classes of physiologically active substances are organic nitrogen compounds, it seemed desirable to examine an azo dye closely related to arsphenamine and to compare its trypanocidal power with that of an arseno compound. If the nitrogen atom in certain physiologically active substances be replaced successively by phosphorus, arsenic and antimony, the products still retain the same type of activity when injected into animals but the activity per unit weight of material decreases as the atomic weight of the element replacing the nitrogen atom increases.[2] It seemed possible, therefore, that since arsphenamine and its antimony

[12] Analysis made by Mr. N. J. Beaber.

[1] This is a continuation of a study of arsphenamine which was made under a grant from the United States Interdepartmental Social Hygiene Board to the Harvard Medical School and which was under the general direction of Doctor Reid Hunt.

[2] Unpublished results of Doctors Reid Hunt and R. R. Renshaw.