[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY, MASSACHUSETTS AGRICULTURAL COLLEGE]

THE PREPARATION OF COMPOUNDS OF THE TYPE OF MALACHITE GREEN AND OF PHENOLPHTHALEIN BY MEANS OF THE GRIGNARD REACTION[1]

BY JOSEPH S. CHAMBERLAIN AND MALCOLM F. DULL[2]

RECEIVED JULY 30, 1928 PUBLISHED NOVEMBER 6, 1928

Malachite Green Type

Baeyer and Villiger[3] used the Grignard reaction for preparing *p*-aminotriphenylcarbinol from *p*-aminobenzoic acid methyl ester and phenylmagnesium bromide and also from *p*-aminobenzophenone and the same Grignard reagent. At the same time they prepared numerous related compounds, including the dye Malachite Green, which resulted from the reaction between phenylmagnesium bromide and Michler's ketone, 4,4-tetramethyldiaminobenzophenone. Votocek and Matejka[4] prepared alkoxy derivatives of Malachite Green by the reaction between Michler's ketone and magnesium compounds of ring-halogenated phenol ethers and also from the esters of anisic acid by reaction with the Grignard reagent made from *p*-bromodimethylaniline. Gilman and Schulze[5] made use of the formation of colored products from Michler's ketone as a qualitative test for Grignard reagents.

Thus the preparation of Malachite Green itself by the Grignard reaction is well established, and also the formation of the Grignard reagent from *p*-bromodimethylaniline. However, the preparation of the latter seems to have been difficult and uncertain for Baeyer and Villiger[3] were unable to obtain it in their efforts to make methyl violet. Sachs and Ehrlich[6] successfully prepared the Grignard reagent from *p*-bromodimethylaniline by activating the magnesium with ethyl bromide and Baeyer[7] prepared Grignard reagents from *o*-, *m*- and *p*-iododimethylaniline by activating the magnesium with iodine. Hurd and Webb[8] prepared and used the Grignard reagent from *p*-bromodimethylaniline in making *p*-dimethylaminophenylmethylcarbinol. The formation of magnesium compounds with halogen derivatives of other tertiary amines was also studied by F. and L. Sachs.[9]

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[1] In memory of Ira Remsen.

[2] The results presented in this paper represent a part of the material contained in the thesis presented by Mr. Dull to the Graduate School of the Massachusetts Agricultural College, June, 1928, for the degree of Master of Science.

[3] Baeyer and Villiger, *Ber.*, **36**, 2794 (1903).

[4] Votocek and Matejka, *Ber.*, **46**, 1755 (1913).

[5] Gilman and Schulze, THIS JOURNAL, **47**, 2002 (1925).

[6] Sachs and Ehrlich, *Ber.*, **36**, 4296 (1903).

[7] Baeyer, *Ber.*, **36**, 2759 (1903).

[8] Hurd and Webb, THIS JOURNAL, **49**, 546 (1927).

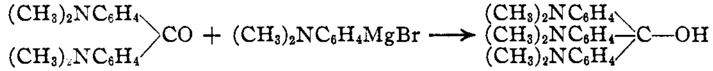
[9] Sachs and Sachs, *Ber.*, **37**, 3088 (1904).

The first part of the present investigation concerns the preparation of the Grignard reagent from *p*-bromodimethylaniline, by Sachs and Ehrlich's or Baeyer's method of activating the magnesium, and the reaction of this reagent with Michler's ketone, resulting in the formation of methyl violet, and also the preparation of the Grignard reagent from *p*-bromobenzoic acid and its reaction with Michler's ketone to the formation of chrome green.

Experimental

As a preliminary experiment Malachite Green was prepared in the same manner in which Baeyer and Villiger made it by the reaction of phenylmagnesium bromide on Michler's ketone. The carbinol was obtained in good yield, purified and analyzed. It was also converted into its salts. All of the results identified the product as Malachite Green, thus corroborating the work of Baeyer and Villiger.

Methyl Violet.—This compound, being the hexamethyltriaminotriphenylcarbinol, if possible of preparation by the Grignard reaction as attempted by Baeyer and Villiger, should result from Michler's ketone by reaction of the Grignard reagent obtained from *p*-bromodimethylaniline.



$$\left.\begin{matrix}(CH_3)_2NC_6H_4\\(CH_3)_2NC_6H_4\end{matrix}\right\rangle CO + (CH_3)_2NC_6H_4MgBr \longrightarrow \left.\begin{matrix}(CH_3)_2NC_6H_4\\(CH_3)_2NC_6H_4\\(CH_3)_2NC_6H_4\end{matrix}\right\rangle C{-}OH$$

Michler's ketone Grignard reagent Methyl violet (carbinol)

The *p*-bromodimethylaniline was prepared and identified, and from it the Grignard reagent was obtained by the following procedure, activating the magnesium by Sachs and Ehrlich's method.

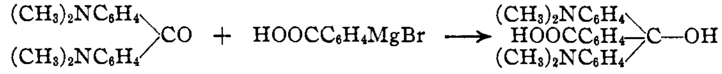
One and three-tenths grams of magnesium turnings was placed in a 150cc. flask and an ethereal solution of 8 g. of ethyl bromide added. The ether used in all cases was specially prepared for use in making Grignard reagents by drying over phosphorus pentoxide, and during reactions was protected from outside moisture by tubes of calcium chloride. The ethyl bromide used was specially purified also.

The flask containing the mixture of magnesium and ethyl bromide was then connected with a reflux condenser carrying a calcium chloride tube at the top. A crystal of iodine was now added to the contents of the flask. After the reaction had continued for three or four minutes, the bulk of the liquid was rapidly decanted and an ethereal solution of 12.5 g. of *p*-bromodimethylaniline added in its place. The new mixture was then warmed gently on the steam-bath and in a very short time a vigorous reaction began. When the magnesium had all dissolved the contents of the flask were cooled and 15 g. of Michler's ketone was added through the condenser tube. The flask was then again warmed for an hour. The ether layer in the flask became deep red in color and a gummy solid was deposited. After cooling, the ether layer was decanted and evaporated. A gummy, almost black mass separated which, in water, yielded an intense violet color. This product was hydrolyzed by boiling with water and after drying yielded 9.0 g. The ether-insoluble product that remained in the flask proved to be unchanged Michler's ketone and amounted to 7.0 g. A part of the product obtained from the ether solution was converted into the chloride salt, and also into the double salt of zinc chloride, yielding characteristic products with brilliant turkey bronze coloration. Its water solution gave a deep violet color. The original carbinol was then purified by recrystallization from alcohol and analyzed with the following results.

Anal. Calcd. for $C_{25}H_{31}N_3O$: C, 77.07; H, 8.03; N, 10.79; O, 4.11. Found: C, 77.06; H, 7.65; N, 10.36; O (by diff.) 4.93.

There seems to be no doubt, therefore, that a reactive Grignard reagent may be prepared from *p*-bromodimethylaniline and that with Michler's ketone it yields methyl violet.

Chrome Green.—This dye, being the *p*-carboxy derivative of Malachite Green, should result by the Grignard reaction from Michler's ketone and the Grignard reagent obtained from *p*-bromobenzoic acid.



$$\begin{matrix}\mathrm{(CH_3)_2NC_6H_4}\\ \mathrm{(CH_3)_2NC_6H_4}\end{matrix}\!>\mathrm{CO} + \mathrm{HOOCC_6H_4MgBr} \longrightarrow \begin{matrix}\mathrm{(CH_3)_2NC_6H_4}\\ \mathrm{HOOCC_6H_4}\\ \mathrm{(CH_3)_2NC_6H_4}\end{matrix}\!>\mathrm{C{-}OH}$$

Michler's ketone

Grignard reagent from *p*-bromobenzoic acid

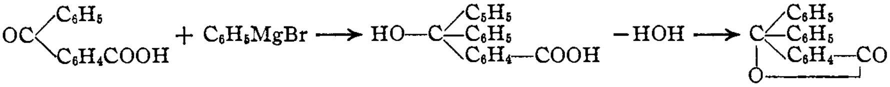
Chrome green (carbinol)

The preparation of the Grignard reagent from *p*-bromobenzoic acid was unsatisfactory, though various methods of activating the magnesium were tried. It was found, however, that on the addition of Michler's ketone a noticeable sea-green color was produced. The ether solution contained enough of this color product to dye wool mordanted with potassium dichromate (a property of chrome green dye) a permanent sea-green color. It was not possible, however, to obtain a sufficient quantity of this compound to afford identification other than the qualitative one just mentioned.

Phenolphthalein Type

To study the Grignard reaction for the preparation of compounds of the type of phenolphthalein, it was decided to attempt the preparation of phthalophenone (diphenylphthalide) from *o*-benzoylbenzoic acid.

According to Beilstein [4th ed., Vol. VII, p. 828] the reaction of phenylmagnesium bromide upon esters of this ketone acid results in the formation of *o*-dibenzoylbenzene. This product is obtained by the reaction of one molecule of the Grignard reagent with the carboxyl carbonyl of the ester. If, however, the phenylmagnesium halide should react with the ketone carbonyl, then phthalophenone should result by the loss of water from the *o*-carboxytriphenylcarbinol, which would be the direct product of the Grignard reaction.



$$\mathrm{OC}\!<\!\begin{matrix}\mathrm{C_6H_5}\\ \mathrm{C_6H_4COOH}\end{matrix} + \mathrm{C_6H_5MgBr} \longrightarrow \mathrm{HO{-}C}\!<\!\begin{matrix}\mathrm{C_6H_5}\\ \mathrm{C_6H_5}\\ \mathrm{C_6H_4{-}COOH}\end{matrix} - \mathrm{HOH} \longrightarrow \mathrm{C}\!<\!\begin{matrix}\mathrm{C_6H_5}\\ \mathrm{C_6H_5}\\ \mathrm{C_6H_4{-}CO}\end{matrix}\ (\mathrm{C{-}O{-}CO})$$

o-Benzoylbenzoic acid

o-Carboxytriphenylcarbinol

Phthalophenone

Ostersetzer[10] studied this reaction but was unable to obtain phthalophenone as "only an oily reaction product" resulted. He did, however, ob-

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[10] Ostersetzer, *Monatsh.*, **34**, 795 (1913).

tain methylphenylphthalide, analogous to phthalophenone (diphenylphthalide) by using methylmagnesium iodide instead of phenylmagnesium iodide.

Experimental

A preliminary attempt to effect a reaction between *o*-benzoylbenzoic acid itself and one molecule of phenylmagnesium bromide resulted in failure, practically all of the acid being recovered unchanged. The direct product formed was unquestionably the magnesium salt or the magnesium halide double salt of the acid.

The procedure was then modified by using double molecular quantities of the Grignard reagent. Five and four-tenths grams of magnesium turnings was placed in a one-liter flask, to which was then added 200 cc. of dry ether and 40 g. of bromobenzene. The reaction was started in the usual manner. After it had ceased and the contents of the flask had cooled, an ethereal solution of 20 g. of *o*-benzoylbenzoic acid was added slowly and with constant shaking. The flask was connected with a reflux condenser and heated for about thirty-six hours. It was then cooled and the ether solution filtered off with suction. After being washed several times with dry ether, the residue was dried over sulfuric acid in a vacuum. When the last traces of ether had been removed, the solid product was treated with about 200 cc. of water containing about 20 cc. of sulfuric acid and kept cool under running water. A rather vigorous reaction took place with the formation of a solid mass of yellow, gummy material. This was treated four times with boiling water in order to remove any traces of unchanged benzoylbenzoic acid. After drying, it was extracted with petroleum ether to remove any bromobenzene. It was then recrystallized three times from hot alcohol.

The compound thus obtained was difficultly soluble in cold alcohol but easily in hot, from which it crystallized in leaflets melting at 115°. This is the melting point of phthalophenone while that of dibenzoylbenzene is 145°. It was soluble in ether, benzene, acetone, concentrated sulfuric acid and hot alcoholic alkali, from which latter solution it was reprecipitated by diluting with water and acidifying. It was insoluble in water, petroleum ether, aqueous alkali and concentrated hydrochloric acid. After several careful tests no oxime could be obtained on treating the substance with hydroxylamine, thus indicating that it was not a ketone.

An analysis was made for carbon and hydrogen and the molecular weight was determined by the freezing-point method using benzene as the solvent. The results obtained are as follows.

Anal. Calcd. for $C_{20}H_{14}O_2$: C, 83.89; H, 4.93; O, 11.18; mol. wt., 286.2. Found: C, 83.99; H, 5.14; O (by diff.) 10.87; mol. wt., 277.5.

As dibenzoylbenzene and phthalophenone are isomers, the above molecular weight determination and analysis would apply equally well to either. The properties, however, as given above do not agree with those given for dibenzoylbenzene, but are those of phthalophenone. It seems reasonable to conclude, therefore, that the product obtained was phthalophenone.

Summary

Grignard reagents were prepared from *p*-bromodimethylaniline and (qualitatively) from *p*-bromobenzoic acid. These reagents yielded with Michler's ketone dyes of the Malachite Green type, namely, methyl violet and chrome green.

The Grignard reagent, phenylmagnesium bromide, reacts with *o*-benzoylbenzoic acid in the proportion of two molecules to one, with the formation of phthalophenone and not dibenzoylbenzene.

AMHERST, MASSACHUSETTS

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

PSEUDO BASES AND THEIR SALTS IN THE ISOXAZOLE SERIES. SECOND PAPER[1]

BY E. P. KOHLER AND N. K. RICHTMYER

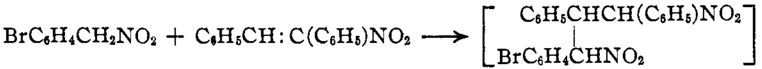
RECEIVED AUGUST 2, 1928 PUBLISHED NOVEMBER 6, 1928

In the first paper[2] it was shown that when the salts that are obtained by methylating triphenyl isoxazole are treated with bases they undergo a series of transformations which can be represented by the sequence

$$\text{Salt} \rightleftharpoons \text{base} \rightleftharpoons \text{pseudo base} \longrightarrow \text{anhydro compound}$$

Owing to the instability of the base and the pseudo base it was possible to isolate only the first and last members of this series, and it was impossible to establish the structure of the pseudo base, the anhydro compound and their derivatives because all of these substances contain three groups which are the same. We have now found that some of these difficulties can be avoided by alkylating with ethyl instead of with methyl sulfate and that most of the others can be overcome by substituting bromophenyl for one of the phenyl groups.

The change from methylation to ethylation presented no complications but the preparation of a substance which differs from triphenyl isoxazole only in having a substituent in one of the phenyl groups proved to be exceedingly troublesome. No isoxazoles of this type are known and no intermediates are available for making them by any of the methods employed in the preparation of triphenyl isoxazole. Since all methods which hold any promise of success are equally likely to give a mixture of isomers we decided to undertake the preparation of the *p*-bromo compounds by way of the isoxazoline oxides.[3] To this end we condensed *p*-bromophenyl nitromethane with nitrostilbene. It was to be expected that this condensation would give a mixture of two isoxazoline oxides



$$BrC_6H_4CH_2NO_2 + C_6H_5CH{:}C(C_6H_5)NO_2 \longrightarrow \left[\begin{array}{l} C_6H_5CHCH(C_6H_5)NO_2 \\ \quad | \\ BrC_6H_4CHNO_2 \end{array}\right]$$

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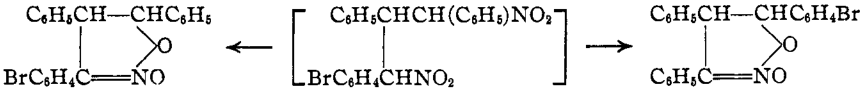

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[1] In memory of Ira Remsen.

[2] Kohler and Blatt, THIS JOURNAL, **50**, 1217 (1928).

[3] Kohler and Barrett, *ibid.*, **46**, 2105 (1924).