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THE REACTION OF PHENYLAMIDOCHELOROPHOSPHATES WITH ARYL GRIGNARD REAGENTS

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The Reaction of Phenylamidochlorophosphates  
with Aryl Grignard Reagents

D. C. Morrison

May 9, 1951

Berkeley, California

THE REACTION OF PHENYLAMIDOCHELOROPHOSPHATES  
WITH ARYL GRIGNARD REAGENTS (1).

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This reaction was studied as a possible approach to the synthesis of aromatic phosphonic acids,  $\text{ArPO}(\text{OH})_2$  from phosphorus oxychloride as starting material. The object of these preparations was to obtain the phosphonic acids in radioactive form from phosphorus oxychloride containing  $\text{P}^{32}$ (2). It was then

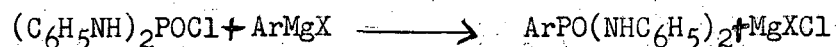
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(2). Axelrod, J. Biol. Chem. 176 295 (1948).

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desired to observe the distribution of these compounds in rats, especially in animals bearing tumors in the hope that some localization in the latter would occur.

Using the dianilido chlorophosphate as an intermediate, and reaction with arylmagnesium bromides, mediocre yields of aryl phosphonic dianilides were obtained apparently according to the equation:



An analogous reaction, the action of aryl Grignards on monoanilido chlorophosphate,  $C_6H_5NHPOCl_2$ , forms very little of the desired product formed by Cl replacement, the phosphinic monoanilides  $Ar_2PONHC_6H_5$ . These reactions are analogous to the phosphinic acid preparations of Michaelis and Wegner (3) and

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(3). Michaelis and Wegner, Ber., 48 316 (1915).

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of Kosolapoff (4) where piperidine and diethylamine respectively, were used to

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(4). Kosolapoff, This Journal, 71 369 (1949).

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block one reactive chlorine atom in the oxychloride.

The secondary dianilido chlorophosphate reacts more satisfactorily with the reagent but in some cases yields are poor. An overall yield of 40% of benzenephosphonic acid dianilide (based on  $POCl_3$ ) in the two-step process was obtained with the phenyl derivative. A considerable excess of Grignard reagent is necessary for success of the reaction. Proper treatment of the product gives a crystalline precipitate of the phosphonic dianilide. This could be hydrolyzed by refluxing with concentrated hydrochloric acid to the free phosphonic acid.

These same phosphonic acid dianilides were usually found among the products from the reaction of monoanilido chlorophosphate with the Grignard reagent. They are believed to result by disproportionation of the monoanilide-chloride forming the dianilido chlorophosphate and subsequent reaction with the arylmagnesium halides. Another interpretation of their formation could be the withdrawal of hydrogen chloride from the monoanilido chlorophosphate

forming the dimeric  $(C_6H_5NPOCl)_2$  followed by reaction with the Grignard reagent. The mixtures of phosphonic dianilide and phosphinic monoanilide are very difficult to separate and only the diphenyl phosphinic acid anilide was obtained in pure condition. However, after hydrolysis with hydrochloric acid, the mixture of phosphonic and phosphinic acids can be more readily separated.

As a control experiment, the interaction of phenylmagnesium bromide with phosphoric acid trianilide was studied, but 85% of the latter was recovered unchanged after several hours of refluxing in ether solution.

Preliminary work showed that aromatic phosphonic acids in the form of their diphenyl esters were formed to a moderate extent by the rapid reaction of the arylmagnesium halides with diphenyl chlorophosphate,  $(C_6H_5O)_2POCl$ . The phenyl and p-tolyl acids were obtained by dropping the Grignard reagent into the ethereal chloro-ester with vigorous stirring in an ice bath, during two to five minutes. The product was poured at once into a large excess of ice and hydrochloric acid. Prolonged alkaline hydrolysis of the product afforded a mixture from which the phosphonic acids could be isolated.

#### EXPERIMENTAL

The dianilido chlorophosphate was obtained by the method of Cook et al (5).

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(5). H. G. Cook, J. D. Ilett, B. C. Saunders, G. J. Stacey, H. G. Watson, I. G. E. Wilding, and S. J. Woodcock. J. Chem. Sec. 2921 (1949).

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It was found, however, that if the ether solution of reactants is dilute enough, most of the product remains in solution and after filtration can be added directly to the Grignard solution.

Preparation of Benzenephosphonic Acid Dianilide.- The following preparation of benzenephosphonic dianilide illustrates the method used for

the phosphonic dianilides.

The reaction product from 18.2 ml. (0.2 moles) of aniline and 9.2 ml. (0.1 mole) phosphorus oxychloride in 400 ml. anhydrous ether, after fourteen hours in the cold, was filtered and the filter residue washed with ether. The combined filtrates were added dropwise at room temperature to phenylmagnesium bromide from 30 ml. (0.285 moles) of bromobenzene and excess magnesium. A white transient precipitate forms during this addition but always dissolves if sufficient Grignard reagent is used. The solution was then refluxed for 1.5 hours, cooled and hydrolyzed by ice and hydrochloric acid. The ether layer (usually containing some suspended product) was washed with sodium hydroxide solution and with water. It was diluted with 250 ml. more ether and left in an ice bath for several hours. The collected and washed product weighed 5.1 g. The filtrate gave 1.1 g. in two crops on further processing. The brown resinous residues, though no crystalline anilide can be obtained from them, will furnish some phosphonic acid on hydrolysis with hydrochloric acid. An exactly similar run employing 20 ml. (0.191 moles) instead of 30 ml. of bromobenzene gave a total yield of 3.8 g. of phosphonic dianilide.

Other preparations of aryl phosphonic dianilides were similar and likewise gave uncrystallizable residues, hydrolysis of which gave additional amounts of the desired aromatic phosphonic acid.

An alternative method of reaction consists of adding the powdered dianilido chlorophosphate in portions to the Grignard solution at room temperature and then refluxing and processing as before. Yields by this process were inferior to those obtained by the first process. Results are given in the Table using the first method. The yield of *o*-tolyl phosphonic dianilide (based on dianilidochlorophosphate) by the second method was 36.7%.



No report of p-anisyl phosphonic dianilide was found in the literature. The compound was recrystallized from acetone-ether.

Anal.: Calcd for  $C_{19}H_{19}N_2PO_2$ : C, 67.45; H, 5.62. Found: C, 67.48; H, 5.85.

Hydrolysis of p-Tolyl Phosphonic Dianilide.- This is given as representative of the hydrolysis reactions. A mixture of 0.73 g. of the dianilide and 50 ml. of concentrated hydrochloric acid was refluxed for one hour and then left overnight on the steam bath. The dry residue was repeatedly ground and extracted with boiling ether. Filtration and evaporation of the combined extracts left 0.348 of p-tolyl phosphonic acid. Yield 89.5%. This was recrystallized from ether-benzene or benzene alone. m. p. 187.5-188.5°C. Lit 189°C. (6).

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(6). Michaelis and Panek, Ber., 13 653 (1880).

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Preparation of Diphenyl Phosphinic Anilide.- The monoanilido chlorophosphate used in this experiment was produced by the method of Caven (7).

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(7) R. M. Caven, J. Chem. Soc., 81 1362 (1902).

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The monoanilido chlorophosphate in powdered form (2.5 g., 0.012 moles) was added gradually to the phenylmagnesium bromide from 8.5 ml. (0.081 moles) of bromobenzene and 1.8 g. (0.075 moles) of magnesium. This solution was refluxed  $1\frac{1}{4}$  hours and then cooled and hydrolyzed. The washed ether layer was concentrated for crystallization. Yield 0.32 of impure material m. p. 199-206°C. After four recrystallizations from benzene this had m. p. 231-233°C. Much intractable residue was left. No simple anilides of diaryl phosphinic acids appear to be described in the literature, though some diaryl thiophosphinic anilides are known.

Anal.: Calcd for  $C_{18}H_{16}PON$ : C, 73.72; H, 5.46. Found C, 73.31; H, 5.67.

Hydrolysis of Diphenyl Phosphinic Anilide.- This anilide was hydrolyzed by concentrated hydrochloric acid similarly to the phosphonic dianilide. The diphenyl phosphinic acid formed was recrystallized from water. m. p. 191-192°C. With other aryl Grignards and the monoanilide chlorophosphate only mixtures were obtained. Some phosphinic acids could be obtained from these by concentrated hydrochloric acid hydrolysis. The phosphonic and phosphinic acids were best separated by taking advantage of the greater water solubility of the former or the greater benzene solubility of the latter.

With the appearance of the article by G. M. Kosolapoff (8) describing a method for phosphonic acids utilizing diethylamine chlorophosphate  $(C_2H_5)_2MPOCl_2$ ,

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(8). G. M. Kosolapoff, This Journal, 72 5508 (1950).

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a few runs of this process were tried using phenylmagnesium bromide. This method appears to give results comparable to the present method.

TABLE I

Phosphonic Dianilides  $ArPO(NHC_6H_5)_2$ 

<u>Ar radical</u>	<u>m. p. °C</u> <u>Lit.<sup>a</sup></u>	<u>m. p. °C</u> <u>Uncer. found.</u>	<u>Yield/POCl<sub>3</sub></u> <u>%</u>
Phenyl	211	211.5	40.3
o-Tolyl	234	230.5	-
p-Tolyl	209	207.5-208.5	21.7
p-Anisyl	-	210	18.1

<sup>a</sup>Michaelis, Ann., 293 193 (1896).

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