[CONTRIBUTION FROM THE ROSS CHEMICAL LABORATORY, ALABAMA POLYTECHNIC INSTITUTE]

Some Variations of the Grignard Synthesis of Phosphinic Acids

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Several useful methods are available for the synthesis of phosphinic acids *via* the Grignard reagents. Thus, although the addition of phosphorus oxychloride to a Grignard reagent leads to the formation of a tertiary phosphine oxide

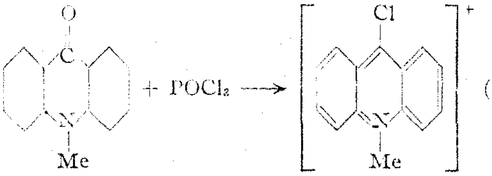
$$3RMgX + POCl_3 = R_3PO + 3MgClX$$

it has been shown that the reversed order of addition employing dilute solutions is capable of limiting the reaction of disubstitution to the extent of about 50%, thus permitting the isolation after conventional hydrolysis, of corresponding yields of phosphinic acids, R_2PO_2H, with relatively small attendant yields of the tertiary phosphine oxides.[1]

Blocking one valence of phosphorus oxychloride by the amide linkage with a secondary amine is another method which has been successfully employed in the past.[2] This method completely eliminates the formation of the tertiary phosphine oxides but adds the complication of the necessary preparation of the corresponding amidodichlorophosphate.

In a search for a simplified synthesis of phosphinic acids *via* the Grignard route, the observation made some years ago by Gleu and Schubert[3] was examined.

These workers noted that the crystalline substance which was formed as the result of mixing N-methylacridone with phosphorus oxychloride yielded diphenylphosphinic acid after treatment with phenylmagnesium bromide, followed by a hydrolytic step. Gleu and Schubert explained their results by postulating an interaction at the carbonyl group, with the formation of the ion-pair: 10-chloro-N-methylacridinium dichlorophosphate, the reaction of which may be shown below.



Without denying the possibility of such an interaction, it appeared, nevertheless, that a quaternary ammonium type compound was also likely to form at the tertiary nitrogen atom as a result of the reaction with the phosphorus oxychloride and that the results obtained by Gleu and Schubert could be explained by a "blocking" of one chlorine of the oxychloride by the formation of such a quaternary compound. Experiments set up on this basis, using pyridine as a readily available amine of the requisite type, appear to have confirmed this point of view. Even under the most unfavorable conditions, *i. e.*, addition of the $POCl_3$–pyridine mixture to the Grignard reagent, the yields of phosphinic acids were fairly good while those of tertiary phosphine oxides were only moderate. The reversed order of addition completely eliminated the tertiary oxide formation and gave satisfactory yields of the phosphinic acids. The scheme which illustrates the reactions used may be shown as

$$POCl_3 + C_5H_5N = C_5H_5N(POCl_2)Cl \xrightarrow[(HOH)]{2RMgX} R_2PO_2H$$

An attempt to carry this principle one step further, by employing two equivalents of pyridine per one mole of phosphorus oxychloride, thus pointing toward the possible synthesis of phosphonic acids, $RPO(OH)_2$, was unsuccessful; only phosphinic acids were isolated, indicating an apparent impossibility of thus "blocking" two chlorine atoms of the oxychloride. It may be added that operations at very low temperatures might lead to success at monosubstitution using pyridine complexes with phosphorus oxychloride. This was not attempted in the present work.

It was found, however, that a minor modification of the previously described blocking procedure, using N,N-diethylamidodichlorophosphate,[2] can lead to a fairly satisfactory synthesis of phosphonic acids. The modification consists of the omission of the refluxing step of the previous procedure. Apparently, the room temperature reaction of the Grignard reagent with the dichloro derivative is definitely a two-step event, with the predominant formation of the monosubstituted product. As a rule, this reaction, which is illustrated below, could hardly compete in the aliphatic series with the convenient syntheses with the esters of phosphorous acid, but it may find application in the aromatic series for the synthesis of definite isomers, which is at best uncertain when the commonly employed Friedel–Crafts method is used.

$$Et_2NPOCl_2 + RMgX = Et_2NPO(R)Cl \xrightarrow{(HOH)} RPO(OH)_2$$

A further exploration of the Grignard reaction revealed that moderate yields of phosphinic acids result from prolonged heating, in the vicinity of 100°, of mixtures of Grignard reagents with the dialkyl esters of phosphonic acids, followed by hydrolysis. Although this reaction may serve as

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[1] Kosolapoff, THIS JOURNAL, **64**, 2982 (1942).

[2] Michaelis and Wegner, *Ber.*, **48**, 316 (1915); Kosolapoff, THIS JOURNAL, **71**, 369 (1949).

[3] Gleu and Schubert, *Ber.*, **73**, 805 (1940).

$$RPO(OR')_2 + R''MgX = RR''PO(OR') \xrightarrow{(HOH)} RR''PO(OH)$$

yet another synthesis of unsymmetric phosphinic acids, the yields are rather low and the long reaction time is unattractive. This reaction may be regarded as an extension of the reaction of Grignard reagents with triethyl phosphite, investigated by Gilman and Robinson.[4]

It may be added that the several syntheses of phosphinic acids reported by the writer have been the result of a search for a rapid and convenient synthesis of these substances, which possess the PO(OH) grouping, without any labile linkages on the remaining valences of phosphorus. Such compounds are vital to the study of the behavior of the PO(OH) group in various reactions. Such a study when performed with labile substances, such as partial esters of phosphoric acid, leads to numerous complications which tend to obscure the true behavior.

Experimental Part

The N,N-diethylamidodichlorophosphate used in this work was prepared from diethylamine and phosphorus oxychloride according to Michaelis' procedure.[5]

The diethyl benzenephosphonate used in this work was obtained by means of the modified Friedel–Crafts reaction from benzene.[6]

Reactions with Pyridine–$POCl_3$ Complex. 1.—To a solution of the Grignard reagent prepared from 137 g. (1 mole) of *n*-butyl bromide and 24 g. of magnesium in 400 ml. of dry ether there was added with vigorous stirring in the course of one hour the mixture resulting from the addition of 77.0 g. (0.5 mole) of phosphorus oxychloride and 40 g. (0.5 mole) of dry pyridine in 200 ml. of dry ether. The addition was regulated so that, without external cooling, the capacity of the reflux condenser was not exceeded. After stirring for two hours, the mixture was allowed to stand overnight, after which the decomposition of the mixture with ice-water (300 g.), followed by extraction of the organic layer with three 300-ml. portions of 5% sodium hydroxide solution and distillation of the organic residue, yielded 31.0 g. (42.5%) (calculated on butyl bromide) of tri-*n*-butylphosphine oxide, a hygroscopic solid, boiling at 185–186° at 18 mm.; its boiling point at atmospheric pressure has been reported as 300°.[7]

The alkaline solution was concentrated under an infrared lamp to approximately 300 ml. and was then acidified with hydrochloric acid. The oil which separated was taken up in 100 ml. of benzene and the extract was evaporated and chilled, when di-*n*-butylphosphinic acid crystallized in stubby needles. After recrystallization from water the product melted at 70–71°, which was in agreement with the earlier preparation[2]; yield 14.5 g. or 16.3% (based on butyl bromide). No detectable amounts of the phosphonic acid were found.

2.—To a solution of 77 g. of phosphorus oxychloride in 250 ml. of dry ether, there was added dropwise with stirring 40 g. of dry pyridine and the resulting mixture was immediately treated dropwise, over the course of fifty minutes, with the Grignard reagent (filtered) prepared as in 1. The mixture was worked up as described in 1. The alkali-washed organic layer yielded less than 1 g. of high-boiling material, from which only a trace of the tertiary phosphine oxide was isolated. The alkaline extract, on the other hand, yielded 42.3 g. (47.5%, based on butyl bromide) of di-*n*-butylphosphinic acid.

3.—The procedure described in 2 was employed in the reaction, which utilized the Grignard reagent from 94 g. (0.57 mole) of *n*-hexyl bromide, 43.0 g. of phosphorus oxychloride (0.285 mole), and 45.0 g. (0.57 mole) of pyridine. Again, only a trace of the tertiary phosphine oxide was detected, while the alkaline extract yielded 27.1 g. (40.5%) of di-*n*-hexylphosphinic acid, which after crystallization from dilute alcohol, melted at 67–68°.

Reaction with N,N-Diethylamidodichlorophosphate.—To the solution of the Grignard reagent prepared from 137 g. (1 mole) of *n*-butyl bromide and 24.3 g. of magnesium in 400 ml. of dry ether there was added over the course of two hours 95.0 g. (0.5 mole) of the amidodichlorophosphate in 100 ml. of ether. The temperature was readily maintained at 5–10° by the use of an ice-water-bath. After continued stirring at this temperature for two hours, the mixture was worked up as described earlier (Kosolapoff, ref. 2). There was obtained 53.2 g. of *n*-butanephosphonic acid (67.0% based on the dichlorophosphate) and less than a gram of the phosphinic acid, which was readily separated by virtue of its relative insolubility in cold water.

Reaction with Diethyl Benzenephosphonate.—Diethyl benzenephosphonate (21.4 g., 0.1 mole) was added in the course of thirty minutes to a solution of phenylmagnesium bromide (from 31.5 g. of bromobenzene and 4.86 g. of magnesium) in 300 ml. of dry ether. After stirring at reflux for one hour, the ether was displaced by dry toluene (150 ml.) and the mixture was stirred for two hours at 85°, followed by six hours at 95°. After decomposition by means of ice and dilute hydrochloric acid, the organic layer was boiled with 300 ml. of concentrated hydrochloric acid with continuous removal of toluene and the residual mixture was refluxed for three hours. The mass which separated on cooling was extracted with dilute ammonium hydroxide and the extract was slowly added to an excess of dilute hydrochloric acid, yielding 7.1 g. (32.5%) of diphenylphosphinic acid, m. p. 192° (from alcohol).

Summary

It has been shown that blocking of one chlorine atom of phosphorus oxychloride may be effectively done by means of pyridine; thus affording a convenient Grignard synthesis of phosphinic acids. The similar results obtained by Gleu and Schubert may be explained by similar quaternization at the tertiary nitrogen atom of N-methylacridone.

Phosphinic acids may be also obtained in poor yields by the reaction of Grignard reagents with dialkyl phosphonates.

Phosphonic acids may be obtained from Grignard reagents and N,N-diethylamidodichlorophosphate at moderately low temperatures.

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(4) Gilman and Robinson, *Rec. trav. chim.*, **48**, 328 (1929).

(5) Michaelis, *Ann.*, **326**, 129 (1903).

(6) Kosolapoff and Huber, THIS JOURNAL, **69**, 2020 (1947).

(7) Davies and Jones, *J. Chem. Soc.*, 33 (1929).