existence of abnormal compounds on the basis of absorption experiments only.

2.   The existence of a dihydrochloride of methylaniline has been shown by means of a thermal diagram of the system.

3.   An explanation of the absorption of hydrogen chloride by the normal ammonium salts with and without the formation of stoichiometric compounds has been advanced.

4.   An attempt has been made to bring all molecular compounds of higher orders into one general system.

MINNEAPOLIS, MINNESOTA

AN IMPROVED PROCEDURE FOR THE PREPARATION OF ORGANOLITHIUM COMPOUNDS

BY HENRY GILMAN, E. A. ZOELLNER AND W. M. SELBY

Introduction

The chief and outstanding chemical difference between organometallic compounds containing alkali metals and those prepared from alkaline earth metals is the general tendency of the former to add to some ethylenic linkages and the absence of such addition with organometallic compounds like the Grignard reagent.   There are, of course, occasional differences in a series of organolithium compounds, for example, just as there are differences between RMgX compounds.   It is reasonable to expect that, in general, the mechanisms of reaction of these two groups of organometallic compounds with a given reactant would be similar and, in many cases, identical.   However, the literature contains numerous cases where the mechanism proposed with organoalkali compounds does not agree with that established with organomagnesium compounds.   It was in connection with such studies, as they concern terminal cumulated unsaturated linkages and allylic systems, that we needed phenyl-lithium in quantity.

Organolithium compounds were first prepared by Schlenk and Holtz[1] by the reaction of lithium with an R_2Hg compound in accordance with this general reaction, which has recently been shown to be reversible[2]

$$R_2Hg + Li \longrightarrow 2RLi + Hg \tag{I}$$
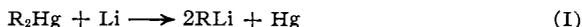
The technique in this operation was subsequently improved and excellent

[1] Schlenk and Holtz, Ber., 50, 272 (1917).   See, also, Groll, THIS JOURNAL, 52, 2998 (1930).

[2] Ziegler and Colonius, Ann., 479, 135 (1930).   For other studies on the reaction between RX compounds and lithium, see Spencer and Price, J. Chem. Soc., 97, 385 (1910), and Wittig and Leo, Ber., 64, 2395, 2405 (1930).

yields of alkyl-lithium compounds were obtained more conveniently.[3] More recently, the elegant studies by Ziegler and Colonius[2] have shown that it is possible to prepare many organolithium compounds by the direct interaction of lithium with an RX compound in ether or benzene, the latter solvent being preferred with alkyl-lithium compounds because they react much more rapidly with ether than do aryl-lithium compounds.

$$RX + 2Li \longrightarrow RLi + LiX \qquad \text{(II)}$$
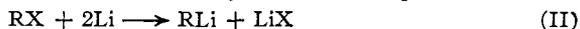
An essential and long-practiced difference in manipulation of organoalkali compounds and compounds like Grignard reagents lies in the use of glass-sealed containers of various modifications for the preparation and subsequent reactions of the organoalkali compounds. The purpose of the sealed containers is to exclude rigidly the deleterious effects of the atmosphere and moisture. However, because RMgX compounds are also sensitive to moisture, oxygen and carbon dioxide and yet can be prepared and manipulated very satisfactorily with a minimum of refinements to diminish the destructive action of moist atmosphere, it occurred to us that a corresponding simpler technique might be used with organoalkali compounds like phenyl-lithium, etc.

This finds support in experiment. Phenyl-lithium, for example, can be prepared very readily and in excellent yields from lithium and bromobenzene in ether. The general manipulation is that used in the preparation of Grignard reagents. Actually, the 95% yield of phenyl-lithium, obtained about as rapidly as the usual 95% yield of phenylmagnesium bromide, is 15–25% in excess of that reported recently.[2] The yields were determined by the acid-titration method of analysis used in studies on organomagnesium compounds. As a check on this analytical procedure, the phenyllithium was treated with an equivalent of benzophenone and the yield of triphenylcarbinol obtained in this manner was essentially that expected. For this reason, it was considered unnecessary to use also the n-butyl bromide–dibenzylmercury indirect method of analysis.[2]

The yield of phenyl-lithium from iodobenzene, lithium and ether was 80%. The yield of phenylmagnesium iodide prepared under corresponding conditions is 85.6%. There is then a resemblance in the effect of various phenyl halides on the yields of phenyl-lithium, and of phenylmagnesium bromide and phenylmagnesium iodide. However, this correlation breaks down apparently when the yields are compared in corresponding experiments where the phenyl halide is added very rapidly to the metal in ether. When bromobenzene is added rapidly to magnesium in ether the yield is 89.8%, or a drop of 4.9% from that obtained under "normal" conditions. With phenyl-lithium prepared by the rapid addition of bromobenzene the drop in yield is of the same order, namely, 3.9%. But with phenyl-

[3] Hager with Marvel, THIS JOURNAL, **48**, 2689 (1926). The latest paper by Marvel and co-workers with organolithium compounds is *ibid.*, **52**, 376 (1930).

lithium prepared by the rapid addition of iodobenzene, there is no drop in yield, whereas the rapid addition of iodobenzene to magnesium in ether gives a 71.8% yield of phenylmagnesium iodide, or a drop of 13.8%.

It might have been predicted that the rapid addition of n-butyl chloride to lithium would not decrease the yield, because the 91.9% yield of n-butylmagnesium chloride obtained under so-called normal conditions is not decreased by a rapid addition of the halide. This prediction is supported by experiment, and there is no essential drop in yield with the rapid addition of n-butyl chloride to lithium in ether. The reaction between lithium and n-butyl chloride in benzene is slow,[2] and under our conditions the yield of n-butyl-lithium after six hours is 70%. However, the formation of n-butyl-lithium in ether is more rapid and yields of 75–80% are readily obtained. No study was made of the optimal conditions for the preparation of n-butyl-lithium since our prime need was phenyl-lithium.

The practical significance of the observation that there is no appreciable drop in yields in the preparation of phenyl-lithium and n-butyl-lithium lies in the fact that these organolithium compounds can be prepared conveniently without regard to the rate of addition of halide. If analogies between organometallic compounds prepared from alkali metals and alkaline earth metals have any significance, then it is probable that the yields of other organolithium compounds will vary with the rate of addition.[4] This is based on published studies on the preparation of such Grignard reagents as allylmagnesium bromide, *tert.*-butylmagnesium chloride, cinnamylmagnesium chloride, etc.

The advantages of manipulating organolithium compounds in either open containers, or with a slow stream of nitrogen in essentially open containers, provided with the conventional mercury-sealed stirrers, will undoubtedly apply with other organoalkali compounds. A case in point is the addition of sodium to benzophenone-anil and the subsequent carbonation of the di-sodium compound, $(C_6H_5)_2C(Na)N(Na)C_6H_5$, to give ultimately diphenylanilinoacetic acid, $(C_6H_5)_2C(NHC_6H_5)COOH$, in practically quantitative yields.[5] It is significant that carbon dioxide, one of the atmospheric constituents that has a deleterious effect on reactive organometallic compounds, reacts with phenyl-lithium to give a very poor yield[2] of benzoic acid. This is in striking contrast with RMgX compounds which generally give very high yields of carboxylic acids.[6] Oxygen with phenyl-

[4] Another important factor is the excess of lithium used. An excess of lithium has no effect[2] on the yields of organolithium compounds mentioned in this paper. An excess of magnesium is very helpful in obtaining high yields of RMgX compounds like allylmagnesium bromide, etc.

[5] Studies by Mr. R. H. Kirby. The original reaction was carried out by Schlenk and Michael, *Ber.*, **47**, 483 (1914).

[6] The only two exceptions in our experience are with the carbonation of allylmagnesium bromide and β-styrylmagnesium bromide.

lithium, as with phenylmagnesium halides, induces chemiluminescence. In these incidental studies the color test for reactive organometallic compounds has been found to be highly useful to determine whether an organolithium compound was formed, and when it was used up in a given reaction. In reactions with ketones, it appears that any unused lithium might act as an indicator by developing distinctive colors (possibly those of ketyls) when the ketone is used up in its reaction with the organolithium compound. For example, in a preparation of triphenylcarbinol from benzophenone and phenyl-lithium, when the phenyl-lithium was used up (as indicated by a negative color test), a violet color developed near some small pieces of unused lithium which had not been removed. Characteristic colors were also observed when the ether solution of n-butyl-lithium was treated with α-naphthyl isocyanate in the preparation of n-valero-α-naphthalide as a derivative.

Experimental Part

The apparatus and general procedure were those used in related studies on organomagnesium compounds. Some modifications, concerned largely with the cutting of lithium, used in the small quantitative studies are unnecessary in the preparation of phenyl-lithium and n-butyl-lithium in large quantities. A few details of the small-sized quantitative experiments are given because they serve to correlate the present procedure with that of organomagnesium halides, and because they may prove of assistance to others in not only determining optimal conditions for some organolithium compounds which cannot now be prepared satisfactorily, but also in determining the relative labilities of halogens in RX compounds toward various metals.

The small quantitative studies were all carried out in a nitrogen atmosphere for two reasons. First, organolithium compounds undergo ready reaction with oxygen. Second, the purity of RX compounds appears to have a greater influence on initiating reaction with lithium than with magnesium. In larger runs it may be unnecessary to use a nitrogen atmosphere with most aryl halides. Such an atmosphere is necessary with a slow reacting compound like chlorobenzene and with the alkyl halides, in order to reduce appreciable decomposition due to the diffusion of atmospheric oxygen.

The metal was cut by means of a chisel and hammer into pieces measuring about 7 × 7 mm. in cross section and 30 mm. in length. These were shaped into prisms of about the above-mentioned dimensions by means of pliers having smooth-faced jaws, and this operation apparently served to press out most of the kerosene under which the original metal was kept. Incidentally, the lithium prisms were shaped fairly uniformly to ensure an approximately constant thin oxide layer. These prisms were readily scraped and cut so that they weighed 0.76 g. (1.1 atoms), the quantity used in the 0.05 mole experiments, allowing a 10% excess. They were then kept, for a few minutes prior to use, under dry ether in an inverted test-tube arrangement provided with a small hole near its upper end to permit escape of any entrapped air. The ether level was over this orifice in the test-tube, and a handle made it convenient to remove the tube from the Erlenmeyer flask in which it was contained.

The simplified, analytical reaction flask used in organomagnesium studies was heated in an oven at 110°, and swept out with pure, dry nitrogen which was admitted through the side neck. After adding 15 cc. of ether, the prism of lithium was cut transversely (by means of a scissors) into about thirty pieces which were allowed to drop into the flask through the main neck, from which issued a stream of nitrogen.

The flask was then attached to the mercury-sealed stirrer (fitting the main neck) and dropping funnel which entered the main neck through a second boring in the rubber stopper holding the stirrer, and a spiral condenser (fitting the side neck).   The top of the spiral condenser and the top of the dropping funnel were connected by tubes provided with pinchcocks which made it possible to admit nitrogen through the condenser or (and) through the dropping funnel.   The nitrogen now left the system through a U-tube having a 2–3 mm. head of mercury pressure.   This gage permitted the subsequent operations with a minimum actual flow of nitrogen, and very little loss of ether.[7]

Then 40 drops of the halide was added to the lithium and ether.   Gentle warming by means of a micro-burner was sufficient to induce prompt reaction.   Reaction having set in, the remainder of the halide in 15 cc. of ether was added either over a period of thirty to thirty-five minutes in a so-called normal run or all at once in those experiments concerned with the effect of rapid addition on the yield.   Stirring was used throughout the preparation.

When the preparation was completed, the flask containing nitrogen was detached from the rest of the apparatus, stoppered and allowed to stand for thirty minutes, at the end of which time any precipitate settled.   The visible unused lithium was readily removed by long-handled tweezers, and aliquots were taken for analysis.[8]   As in related quantitative studies with organomagnesium compounds, each of the experiments was checked at least twice and the degree of accuracy for aliquots from a given preparation is that obtained with Grignard reagents.

Miscellaneous Observations

Size of Lithium.—When the 0.76 g. prism of lithium was cut lengthwise into two pieces, the yield of phenyl-lithium from bromobenzene was 93.1%.   In this experiment, the apparent reaction continued for fifty to fifty-five minutes; whereas under standard conditions with smaller pieces of lithium the apparent reaction continued for ten to twenty minutes.   The mixture was then refluxed for an additional forty-five minutes. For practical purposes it is, therefore, unnecessary to cut the lithium into small pieces if the slightly greater time required for completion of the reaction is of secondary consequence.

Tarnishing of Lithium.—In one experiment with lithium and bromobenzene, the 30–33 pieces of metal (totaling 0.76 g.) were exposed to moist air for one minute, which was sufficient to coat them entirely with a black film.   Reaction set in at once, probably because the sharp-winged small stirrer removed some of the oxide, as was evidenced by the clean, silvery patches on the metal after stirring for a few minutes.   The yield of phenyl-lithium was 86.8%.   It is possible that an adequate excess of tarnished metal may prevent a decrease in yield.   When one piece (0.76 g.) of tarnished lithium was used, the yield was 88.6%, and about five minutes of stirring with the application of heat was required for the starting of reaction.   Stirring was obviously less effective with the single piece of lithium in the small flask.

Time of Reaction.—In every case it appears desirable to apply heat and to use stirring in initiating reaction.   With Grignard reagents it is generally better not to use stirring until after the reaction has commenced.   The time of apparent reaction, after all of the halide had been added very rapidly (in so-called drop runs) to the lithium in ether, varies with the RX compound and is probably a measure of the labiltiy of the halogen toward a given metal.   With iodobenzene this time is ten to fifteen minutes;

[7] In large-sized runs, particularly with slow acting RX compounds, it may be sufficient to use a trap to exclude the atmosphere subsequent to sweeping out the apparatus with nitrogen.

[8] During these operations, nitrogen was admitted through the side neck.

with bromobenzene, thirty-five to forty minutes; and with *n*-butyl chloride, forty to forty-five minutes. The corresponding times when these halides are added separately to magnesium in ether are: ten to fifteen minutes; ten to fifteen minutes; and forty-five to fifty minutes, respectively.

When the apparent reaction is ended, refluxing with stirring should be continued for forty-five minutes. There is no improvement in yield of phenyl-lithium from bromobenzene when this period of refluxing exceeds thirty minutes; and with a fifteen minute period of refluxing the yield was 92%.

Yields of Some Other Aryl-lithium Compounds.—Under corresponding conditions the following yields were determined from RBr compounds, the number in parentheses being the percentage yield when the RBr compound was added rapidly to the lithium: *o*-tolyl-lithium, 93.3 (85.6); *m*-tolyl-lithium, 86.4 (80.0); *p*-tolyl-lithium, 94.9 (95); *o*-anisyl-lithium, 85 (85); *p*-anisyl-lithium, 66.1 (65.3); *α*-naphthyl-lithium, 79 (80); and *β*-naphthyl-lithium 75.3 (47.8).

n-Butyl-litihum.—The time of apparent reaction when all of the *n*-butyl chloride is added to the lithium in ether is forty to forty-five minutes. Gentle refluxing is continued for about two hours, and the yield is 75–80%. In one experiment when the time of refluxing was one-half hour the yield was 67%. When twelve instead of the customary six molecular equivalents of ether were used the yield was 68%. As previously mentioned, the reaction in benzene is much slower than in ether. Because the very high yields of *n*-butyl-lithium in benzene were obtained in twenty-four hours,[2] it may be desirable to prepare *n*-butyl-lithium in benzene in sealed containers; however, effective stirring would probably reduce the time required for complete reaction. The *n*-butyl-lithium was characterized by the preparation of *n*-valero-*α*-naphthalide from *α*-naphthyl isocyanate in accordance with the general directions suggested for this reaction in the preparation of derivatives of reactive organometallic compounds. The preparation of *n*-butyl-lithium in ether can be simplified by adding the freshly cut lithium to all of the halide in ether and thereby dispensing with the use of a dropping funnel.

Summary

Directions are given for the preparation of aryl-lithiums and *n*-butyl-lithium, from lithium and the corresponding halides. Excellent yields are readily obtainable under conditions essentially like those used with the related Grignard reagents.

Attention is directed to some simplifications in procedure which make it possible to prepare and to manipulate some organoalkali compounds in readily available apparatus and without the use of glass sealed containers.

AMES, IOWA