

Preparation of Organolithium Reagents

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An improved procedure for the preparation of methyl-, ethyl-, isopropyl-, *n*-amyl-, and phenyllithium is presented. Advantages of the procedure are due chiefly to the use of lithium sand and an apparatus of special design which allows all operations to be carried out in an inert atmosphere of 98% helium. The general assembly and details of construction of the apparatus are shown.

SINCE the observation by Ziegler and Colonius (10) that organolithium reagents could be prepared directly from the organo halide and lithium, and the many refinements and extensions of this method of preparation by Gilman *et al.* (6-8), these reagents have become much more available and useful to the organic chemist. However, for synthetic work, their preparation on a larger scale than that given by the above authors is usually desirable.

The apparatus and methods given in the literature (1, 2, 6), when applied on a 0.5- to 1.0-mole basis, were tedious and in some cases unsatisfactory. Hence, a modified method was developed, using the apparatus and procedure given below, which uniformly gave good yields of organolithium reagents, in some cases better than those previously reported (7, 8).

product by filtration through the stirrer shaft, described below, prevented losses from exposure of the very reactive organolithium reagent to the air.

Helium (98%), rather than nitrogen, was used as the inert atmosphere for the reaction in order to prevent nitride formation with the finely divided lithium (6). Because of its low price, helium makes an economical inert atmosphere for this type of work.

As shown in Table I, highly successful results were obtained in the preparation of methyl-, ethyl-, isopropyl-, *n*-amyl-, and phenyllithium. However, when the same method was applied to the preparation of benzyl lithium from benzyl chloride in ether, it failed to give any organolithium reagent. As observed by Ziegler and Dersch (11), the products were bibenzyl plus a small amount of unreacted benzyl chloride.

Table I. Yields of Organolithium Reagents

RX Compound	Solvent	Yield RLi, %
CH ₃ I ^a	Et ₂ O	95
C ₂ H ₅ Br ^b	Petroleum ether	92
Is-C ₃ H ₇ Cl ^c	Petroleum ether	88
<i>n</i> -C ₅ H ₁₁ Cl ^d	Petroleum ether	90
C ₆ H ₅ Br ^b	Et ₂ O	98

R = alkyl or aryl radical.

^a Merck, purified by treating with Hg.

^b Merck, reagent, redistilled.

^c Eastman, pure, used directly.

^d Paragon, pure, purified by washing with concentrated sulfuric acid, drying over calcium chloride, and fractionating. The fraction boiling between 105° and 107° was used.

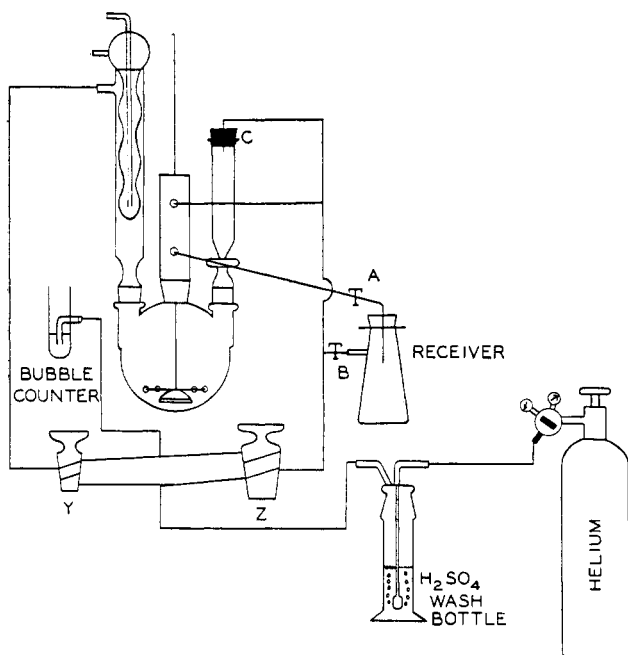


Figure 1. Assembly of Apparatus

The advantages of this method are due chiefly to the use of lithium sand (3, 4, 9) and a simple filtration device which allows all operations to be conducted in an inert atmosphere. Because coating of the lithium in large-scale runs became pronounced and in some cases had a deleterious effect, it was found advantageous to use finely divided lithium. The methods for comminuting lithium ordinarily used—i.e., cutting into small pieces (8) or rasping (6, 7)—proved impractical with the 10-gram (or more) portions of lithium used. Lithium sand, however, prepared by melting lithium in liquid petrolatum and cooling with stirring, was very satisfactory. The method of collecting the reaction

Calculation of the yield of organolithium reagent was based on simple acid titration of an aliquot after decomposition with water. Although this method is known to give high results in some cases (5) due to the cleaving action of certain organolithium compounds on ether, the error is negligible with methyl- and phenyllithium because of their comparative stability in ether (7, 8). These were the only two reagents prepared in ether. The others were prepared in petroleum ether where high results from acid titration are not encountered.

APPARATUS

The general assembly of the apparatus is pictured in Figure 1.

It is essentially a hollow-shaft stirrer carrying a sintered-glass filter at the bottom with a chamber sealed about the upper part of the stirrer shaft, so that gas or liquid may be introduced or withdrawn from the shaft. The stopcocks are so arranged that the helium may bubble through the solution or exert a pressure on its surface. Inasmuch as a pressure of several pounds of helium is used, it is necessary to clamp all parts securely. During the preparation of the organolithium compound, stopcocks Y and Z remain in the position shown, thus causing the helium to bubble through the solution. To effect filtration, Y and Z are reversed and the helium pressure forces the solution through the stirrer shaft and into the receiver. All solutions are introduced into the dropping funnel by removing stopper C. When receivers are changed, pinchclamps A and B are closed, and any type of receiver may be used in place of the filter flask by merely providing the necessary inlet and outlet connections.

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The first apparatus designed is illustrated in Figure 2. The details of construction are obvious and require no special comment.

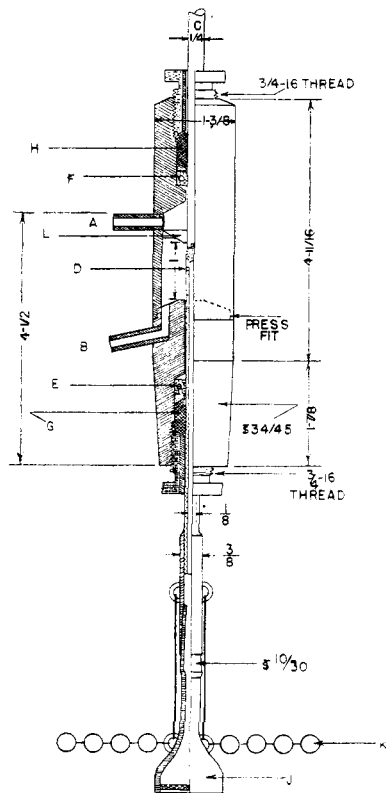


Figure 2. Diagram of Apparatus

- A. Helium tube
- B. Filtrate outlet tube
- C. Stirrer shaft
- D. 2 holes, $\frac{1}{16}$ inch diameter
- E, F. Nice No. 402-2 ball bearings $\frac{1}{4} \times \frac{11}{16}$ inch
- G, H. Graphite-lead-asbestos packing
- J. Ace filter tube 8610, 25-mm. diameter and porosity A (Ace Glass Co., Vineland, N. J.)
- K. Hirschberg type stirrer of 18-gage Chromel wire
- L. Baffle

Stainless steel was used except for the ball bearings, which are of high-chrome carburized steel, and the stirrer shaft, which is brass. The packing nuts are also bushed with brass. The packing is a lead-asbestos-graphite type. Ball bearings are essential under the conditions of unfavorable lubrication encountered. It is necessary to disassemble the apparatus after use to clean and lubricate the ball bearings. The weight of the unit is sufficient to hold it tight in the standard-taper joint against 0.1 atmosphere pressure differential. The modification of the glass filter tube (J, Figure 2) by sealing on a male $10/30$ joint and two glass loops requires no special comment.

The use of packing is always somewhat objectionable. The apparatus was later modified and a lower seal of the type illustrated in Figure 3 was used. Although this is more difficult to construct, it constituted a considerable improvement. The exposed ball bearing is also much easier to clean.

The authors constructed an all-glass apparatus in which the sealing action was effected by very small clearance between the stirrer shaft and its bearing. This method was satisfactory for a few runs, but because of lack of lubrication, the wear was very rapid and excessive leakage soon developed. Rubber seals are rapidly destroyed by solvent action.

PROCEDURE

The apparatus (Figure 1) was swept out with a stream of helium which was continued at a moderate rate throughout the

preparation. Liquid petrolatum (200 ml.), previously heated to 250° with lithium, and 10.4 grams (1.5 grams atoms) of clean lithium were then added to the three-necked flask and heated until the lithium was melted, after which the solution was allowed to cool to room temperature with rapid stirring. The liquid petrolatum was then filtered from the finely divided lithium by reversing the flow of helium and was collected in a 500-ml. filter flask for re-use in subsequent preparations. Occasional plugging of the sintered-glass filter was relieved by reversing the helium flow to backwash the filter. The lithium was washed with 100 ml. of the solvent to be used in the preparation (either absolute ether or dry, unsaturate-free Skellysolve A, boiling point 28° to 38° C.) which was also removed by filtration and collected in a 500-ml. filter flask.

To the washed, finely divided lithium were now added 50 ml. of solvent and, with rapid stirring, several milliliters of the alkyl (or aryl) halide in order to initiate the reaction. The remainder of the 0.5 mole of halide, dissolved in 300 ml. of solvent, was added over the course of 1.5 hours, and the dropping funnel was rinsed with 50 ml. of solvent after the addition was completed. Stirring was continued another hour and, by reversing the helium flow, the reaction mixture was then filtered from excess lithium and lithium halide and collected in a narrow-mouthed 500-ml. graduated cylinder which served as receiver in place of the filter flask. The residue was stirred with 100 ml. of fresh solvent which also was filtered into the receiver, bringing the total volume of filtrate to about 500 ml.

After thorough mixing, the solution was allowed to stand for several hours in the tightly stoppered receiver to permit the insoluble material that passed through the filter to settle. To determine the yield of organolithium reagent, two 5-ml. portions were removed and decomposed with water, and the lithium hydroxide formed (equivalent to the organolithium compound present) was titrated with standard hydrochloric acid. In most cases, the organolithium reagent solution was slightly less than 1 N. The yields are given in Table I.

The procedure had to be modified slightly in the case of ethyllithium because of its limited solubility in petroleum ether. One half the quantities of lithium and ethyl bromide were used, 300 ml. of petroleum ether were added before the reaction mixture was filtered, and both the petroleum ether reaction mixture and wash portion were filtered hot. This resulted in a solution that was 0.29 N at room temperature (27° C.). On cooling, it deposited crystals of ethyllithium which burst into a vivid violet flame when exposed to the air. Phenyllithium was prepared with 2.8 grams of lithium, 15.7 grams of phenyl bromide, and 60 ml. of ethyl ether.

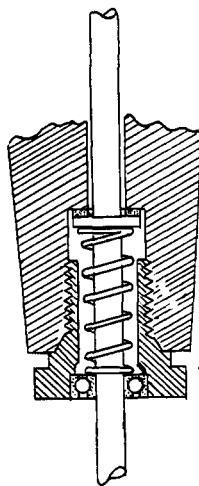


Figure 3. Seal

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