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of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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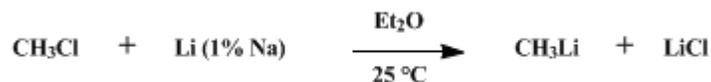
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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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PREPARATION OF LOW-HALIDE METHYLLITHIUM

[Lithium, methyl-]



Submitted by Michael J. Lusch, William V. Phillips, Ronald F. Sieloff, Glenn S. Nomura, and Herbert O. House¹.

Checked by Gregory S. Bisacchi and Robert V. Stevens.

1. Procedure

Caution! The fine lithium dispersion used in this preparation, once washed to remove the mineral oil coating, will ignite spontaneously if exposed to air. Also, the methyl chloride and ether used are very volatile and highly flammable. The entire preparation, including the disposal of any residual lithium, should be performed in an efficient hood with a safety shield in front of the apparatus. A suitable dry-powder fire extinguisher should be kept at hand to extinguish any fires resulting from the accidental spillage of the washed lithium dispersion or of the methyllithium solution.

A dry, 1-L, three-necked, round-bottomed flask equipped with a large Teflon-covered magnetic stirring bar, a thermometer, and a dry ice condenser (Note 1) is flushed with argon (Note 2), then capped with a serum stopper, and subsequently maintained under a positive pressure of argon (Note 2). A 30% dispersion of lithium metal (in mineral oil) containing 1% sodium (13.9 g, 2.00 g-atom of lithium) (Note 3) is rapidly weighed and transferred to the flask.

The lithium is washed three times by transferring approximately 150-mL portions of anhydrous ethyl ether (Note 4) into the flask through the serum stopper by forced siphon through a stainless-steel cannula, stirring the resulting suspension of lithium briefly, allowing the lithium to rise to the surface, and finally withdrawing the major part of the underlying ether by forced siphon through a cannula. Anhydrous ethyl ether (500 mL) is added to the resultant oil-free lithium. Methyl chloride gas (bp -24°C , $d_{-24^\circ\text{C}}^{25^\circ\text{C}}$ 0.99 g/mL) from a compressed gas cylinder is passed through a flask containing Linde 4A molecular sieves and into a dry, 100-mL Pyrex graduated cylinder equipped with a 24/40 standard taper joint attached to a Claisen adapter and dry ice condenser, and cooled to -24°C with a bath of dry ice-acetone (Figure 1). When 52.7 mL (52.5 g, 1.04 mol) of liquid methyl chloride has been collected, the adapter and condenser are removed, several boiling chips are added to the cold (-24°C) graduated cylinder, and the cylinder is stoppered with a rubber septum which is inserted a stainless-steel cannula. The other end of this cannula is inserted through the rubber septum of the flask so that its tip is just above the liquid surface of the reaction flask. Dry ice-acetone is then added to the condenser attached to the reaction flask. Vigorous stirring of the ethereal lithium dispersion is begun and the methyl chloride is added over approximately a 1.5-hr period. The rate at which methyl chloride is distilled into the reaction vessel is controlled by slight cooling or warming of the graduated cylinder that contains the liquid methyl chloride. During addition, the initial grey suspension changes to a brown to purple suspension; by the end of the addition, little, if any, lithium metal should be seen floating on the surface of the ether solution when stirring is interrupted. After the addition of methyl chloride is complete, the reaction mixture is stirred at 25°C for an additional 0.5–1 hr and then allowed to stand overnight or longer (Note 5) at 25°C under a static argon atmosphere, whereupon the precipitated lithium chloride settles to the bottom of the flask. The dry ice condenser and thermometer are removed from the flask and replaced with rubber septa. The supernatant methyllithium solution is transferred by forced siphon using a large-gauge cannula through a glass wool pad (Note 6) into a receiving flask previously flushed with an inert gas (Figure 2). The receiving flask, which contains the filtrate, a pale-yellow solution of methyllithium, is removed (Note 7) and stored in a refrigerator for 12–24 hr during which time an additional small quantity of lithium chloride separates as fine crystals. The resulting supernatant solution is transferred with a stainless-steel cannula and a slight positive pressure of argon or nitrogen into one or more suitable oven-dried, nitrogen-filled storage bottles capped with rubber

septa. Two 1-mL aliquots of the solution are removed with a hypodermic syringe for a modified Gilman titration (Note 8) and a 5-mL aliquot is removed with a hypodermic syringe to determine the halide concentration (Note 9). The solution contains 1.40–1.77 M methyl lithium accompanied by 0.07–0.09 M lithium chloride corresponding to a 70–89% yield of methyl lithium. If this solution is protected from oxygen and moisture, it may be stored at 0–25°C for several months (and remain active).

Figure 1. Condensing the methyl chloride.

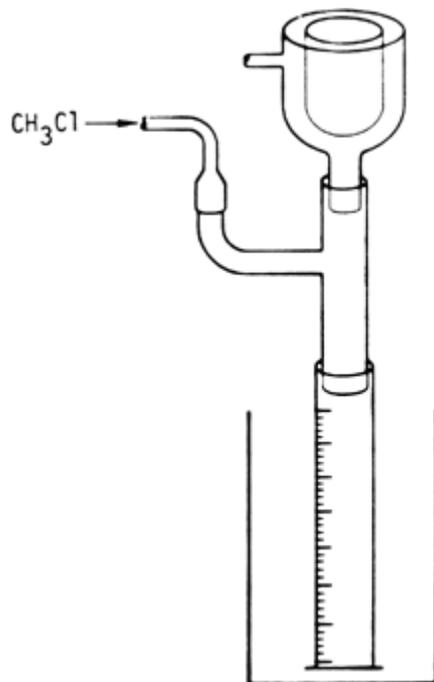
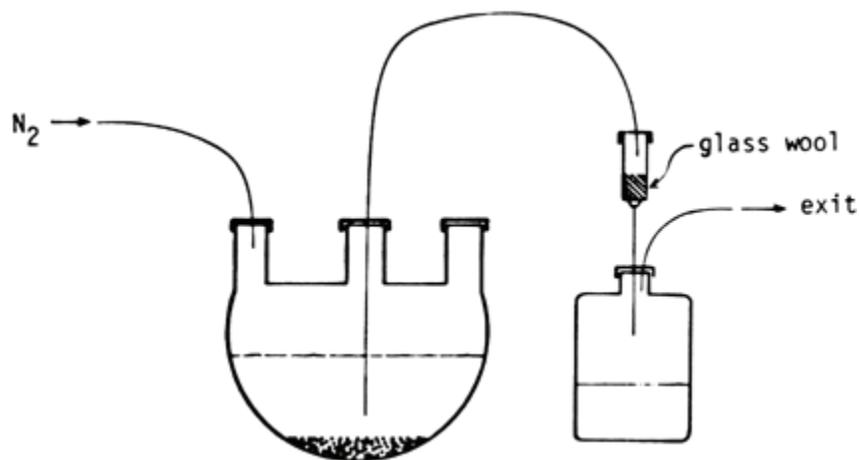


Figure 2. Decanting the methyl lithium solution.



2. Notes

1. The dry ice condenser used with the apparatus should have sufficient condensing capacity to prevent the loss of significant amounts of methyl chloride; a condenser 38 cm long and 3.8 cm in diameter was suitable.

Since finely divided lithium floats on the surface of the solvent and will be in contact with the atmosphere in the reaction vessel, an argon atmosphere, rather than a nitrogen atmosphere, should be used to avoid formation of the insoluble reddish-brown lithium nitride.

2. A slight positive pressure of argon was maintained in the vessel throughout the reaction by using an

argon line connected to both a bubbler containing Nujol and the inlet on the dry ice condenser.

3. A dispersion in mineral oil of 30% (by weight) of lithium containing 1% by weight of sodium is marketed by Alfa Products, Morton Thiokol, Inc. This oilcoated dispersion may be exposed to the air during transfer and weighing and is conveniently transferred from its container by pouring through a wide-mouth funnel. Small quantities of the dispersion that adhere to the apparatus may be disposed of by rinsing in a stream of warm water to lower the viscosity of the oil and allow the suspended lithium to react with water at a controlled rate. To dispose of large quantities of this dispersion (or any quantity of lithium powder no longer coated with oil), the material should be suspended in anhydrous ether under an argon atmosphere and *tert*-butyl alcohol should be added dropwise to the suspension until all of the lithium metal has been consumed. Since hydrogen is liberated during these disposal procedures, they should be performed in an efficient hood.

4. Anhydrous ethyl ether was distilled from lithium aluminum hydride immediately before use.

5. Although most of the lithium chloride separates from the ether solution as a finely divided solid during the reaction, additional small quantities of lithium chloride continue to separate for 12–14 hr. After standing overnight, a typical reaction contains a precipitate of finely divided brownish-pink solid below a clear, pale-yellow solution.

6. A convenient filter was constructed by packing glass wool, previously dried in an oven, into a 20-mL Luer-Lok syringe barrel fitted with a 15-gauge needle. The syringe barrel was capped with a serum stopper. A large-diameter cannula (at least 15 gauge) should be used to transfer the methyllithium solution from the flask to the filter since smaller-gauge cannulas are frequently plugged by solid particles.

7. As soon as the receiver containing the methyllithium solution has been removed and stoppered, the residual solids in the reaction flask and the filtration apparatus should be rinsed into another receiver with anhydrous ether under an atmosphere of argon or nitrogen. The ether slurry of solids, which may contain some unchanged lithium metal, should be treated cautiously in a hood with *tert*-butyl alcohol to consume any residual lithium metal before the mixture is discarded.

8. One 1-ml aliquot is added to 1.0 mL of freshly distilled 1,2-dibromoethane (bp 132°C) in an oven-dried flask that contains a static atmosphere of nitrogen or argon. After the resulting solution has been allowed to stand at 25°C for 5 min, it is diluted with 10 mL of water and titrated for base content (residual base) to a phenolphthalein endpoint with standard 0.100 M hydrochloric acid. The second 1-mL aliquot is added cautiously to 10 mL of water and then titrated for base content (total base) to a phenolphthalein endpoint with standard aqueous 0.100 M hydrochloric acid. The methyllithium concentration is the difference between the total base and residual base concentrations.^{2 3} Alternatively, the methyllithium concentration may be determined by titration with a standard solution of *sec*-butyl alcohol employing 2,2'-bipyridyl as an indicator.^{4 5}

9. To determine the concentration of chloride ion,^{6 7} a 5-mL aliquot of the methyl-lithium solution is cautiously added to 25 mL of water and the resulting solution is acidified with concentrated sulfuric acid and then treated with 2–3 mL of ferric ammonium sulfate [Fe(NH₄)(SO₄)₂ · 12 · H₂O] indicator solution and 2–3 mL of benzyl alcohol. The resulting mixture is treated with 10.0 mL of standard aqueous 0.100 M silver nitrate solution and then titrated with standard aqueous 0.100 M potassium thiocyanate solution to a brownish-red endpoint.

3. Discussion

Although ethereal solutions of methyllithium may be prepared by the reaction of lithium wire with either methyl iodide⁸ or methyl bromide⁹ in ether solution, the molar equivalent of lithium iodide or lithium bromide formed in these reactions remains in solution and forms, in part, a complex with the methyllithium.¹⁰ Certain of the ethereal solutions of methyllithium currently marketed by several suppliers including Alfa Products, Morton Thiokol, Inc., Aldrich Chemical Company, and Lithium Corporation of America, Inc., have been prepared from methyl bromide and contain a full molar equivalent of lithium bromide. In several applications such as the use of methyllithium to prepare lithium dimethylcuprate^{11 12} or the use of methyllithium in 1,2-dimethoxyethane to prepare lithium enolates from enol acetates or trimethylsilyl enol ethers,⁵ the presence of this lithium salt interferes with the titration and use of methyllithium. There is also evidence indicating that the stereochemistry observed during addition of methyllithium to carbonyl compounds may be influenced significantly by the presence of a lithium salt in the reaction solution.¹³ For these reasons it is often desirable to use ethereal solutions of methyllithium that do not contain an equivalent amount of lithium iodide or lithium

bromide.

The reaction of lithium with methyl chloride in ether solution produces a solution of methyllithium from which most of the relatively insoluble lithium chloride precipitates. Etheral solutions of "halide-free" methyllithium, containing 2–5 mol % of lithium chloride, were formerly marketed by Foote Mineral Company and by Lithium Corporation of America, Inc., but this product has been discontinued by both companies. Comparable solutions are also marketed by Alfa Products and Aldrich Chemical Company; these solutions have a limited shelf life and older solutions have often deteriorated badly even before the container is opened. Since an ether solution of methyl chloride reacts very slowly with lithium wire used in reactions with methyl bromide or methyl iodide, the present procedure¹⁴ uses a finely divided suspension of lithium metal containing 1% (by weight) of sodium^{10,15} to achieve a rapid reaction with methyl chloride. The finely divided lithium containing 1% sodium is marketed as a 30% (by weight) dispersion in mineral oil and must be washed free of this protective hydrocarbon diluent before use in order to avoid contamination of the final methyllithium reagent with a substantial amount of a mixture of high molecular weight hydrocarbons. Since lithium is less dense than common organic solvents such as diethyl ether or pentane, the washing procedure must be done with special care to avoid starting a fire with the pyrophoric, finely divided lithium.³ Finely divided lithium with somewhat higher or lower percentages of sodium are expected to work equally well.

This preparation is referenced from:

- [Org. Syn. Coll. Vol. 8, 226](#)

References and Notes

1. School of Chemistry, Georgia Institute of Technology, Atlanta, GA 30332.
2. Whitesides, G. M.; Casey, C. P.; Krieger, J. K. *J. Am. Chem. Soc.* **1971**, *93*, 1379;
3. Linstrumello, G.; Krieger, J. K.; Whitesides, G. M. *Org. Synth.* **1976**, *55*, 103. (Lithium wire containing 1% sodium is no longer available commercially.)
4. Watson, S. C.; Eastham, J. F. *J. Organomet. Chem.* **1967**, *9*, 165;
5. Gall, M.; House, H. O. *Org. Synth., Coll. Vol. VI* **1988**, 121;
6. Kolthoff, I. M.; Sandell, E. B. "Textbook of Quantitative Inorganic Analysis," 2nd ed.; Macmillan: New York, 1947; pp. 572–574;
7. Skoog, D. A.; West, D. M. "Fundamentals of Analytical Chemistry," 2nd ed.; Holt, Rinehart, and Winston: New York, 1969; pp. 233–234.
8. Schollkopf, U.; Paust, J.; Patsch, M. R. *Org. Synth., Coll. Vol. V* **1973**, 859.
9. Wittig, G.; Hesse, A. *Org. Synth., Coll. Vol. VI* **1988**, 901.
10. Wakefield, B. J. "The Chemistry of Organolithium Compounds"; Pergamon: New York, 1974; pp. 8–11, 21–25.
11. Eliel, E. L.; Hutchins, R. O.; Knoeber, Sr. M. *Org. Synth., Coll. Vol. VI* **1988**, 442;
12. Muchmore, D. C. *Org. Synth., Coll. VI* **1972**, 762.
13. Ashby, E. C.; Noding, S. A. *J. Org. Chem.* **1979**, *44*, 4371.
14. We are indebted to Dr. W. Novis Smith, formerly with Foote Mineral Company, and now with Stauffer Chemical Company, Dobbs Ferry, New York, for supplying the general preparative procedure that we have adapted to the laboratory-scale preparation described here.
15. Kamienski, C. W.; Esmay, D. L. *J. Org. Chem.* **1960**, *25*, 1807.

Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

H₂O

1,2-dimethoxyethane
trimethylsilyl enol ethers
sulfuric acid (7664-93-9)
hydrochloric acid (7647-01-0)
ether,
ethyl ether,
diethyl ether (60-29-7)
hydrogen (1333-74-0)
silver nitrate (7761-88-8)
oxygen (7782-44-7)
nitrogen (7727-37-9)
methyl chloride (74-87-3)
acetone (67-64-1)
sodium (13966-32-0)
Benzyl alcohol (100-51-6)
1,2-dibromoethane (106-93-4)
methyl bromide (74-83-9)
Methyl iodide (74-88-4)
potassium thiocyanate (333-20-0)
Pentane (109-66-0)
phenolphthalein (77-09-8)
lithium (7439-93-2)
lithium aluminum hydride (16853-85-3)
Methylithium,
Lithium, methyl-,
methyl-lithium (917-54-4)
Lithium chloride (7447-41-8)
argon (7440-37-1)

tert-butyl alcohol (75-65-0)

lithium iodide (10377-51-2)

sec-butyl alcohol (78-92-2)

2,2'-bipyridyl (366-18-7)

lithium dimethylcuprate

lithium bromide (7550-35-8)

lithium nitride (26134-62-3)

ferric ammonium sulfate