A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red "Caution Notes" within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior to performing a reaction, a thorough risk assessment should be carried out that includes a review of the potential hazards associated with each chemical and experimental operation on the scale that is planned for the procedure. Guidelines for carrying out a risk assessment and for analyzing the hazards associated with chemicals can be found in Chapter 4 of Prudent Practices.

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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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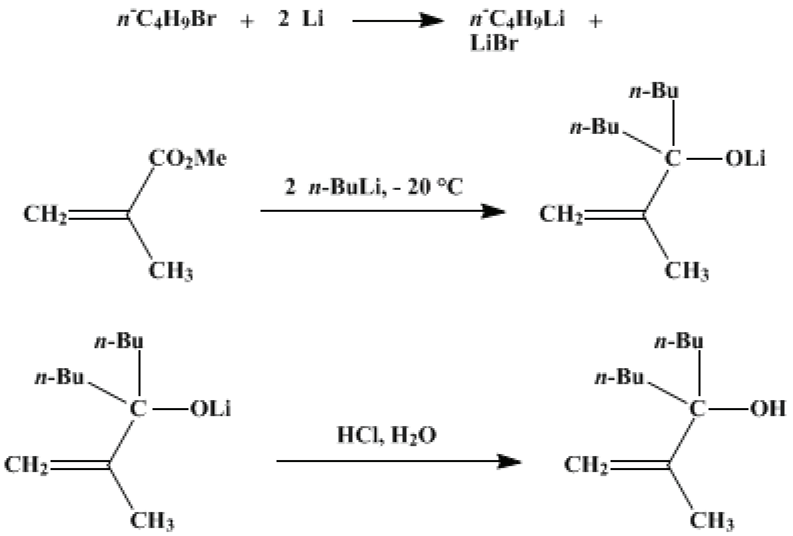
3-BUTYL-2-METHYLHEPT-1-EN-3-OL

[5-Nonanol, 5-(2-propenyl)-]



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1. Procedure

A 2-l., four-necked flask equipped with a sealed, Teflon-paddle stirrer, a mercury thermometer, a gas-inlet tube, and a dropping funnel is charged with 1.2 l. of anhydrous tetrahydrofuran (Note 1) and 50 g. (7.1 g.-atoms) of lithium pieces (Note 2) under an atmosphere of prepurified nitrogen. The stirred mixture is cooled to −20° with an acetone dry-ice bath and a mixture of 100 g. (1.00 mole) of methyl methacrylate (Note 3), and 411 g. (3.00 moles) of *n*-butyl bromide (Note 4) is added dropwise over a period of 3–4 hours. During this addition, an exothermic reaction ensues and is controlled at −20° (Note 5), and on completion of the addition, the vessel is maintained at this temperature, with stirring, for an additional 30 minutes. The contents of the flask are filtered with suction through a 70-mm.-diameter, slit-sieve Buchner funnel, without filter paper, to remove the excess lithium metal. The filtrate is concentrated on a rotary evaporator at aspirator pressure. The residual lithium alcoholate is hydrolyzed by the addition of 1 l. of 10% hydrochloric acid, with ice bath cooling. The liberated alcohol is extracted with two 400-ml. portions of diethyl ether, and the combined ether extracts are washed with two 400-ml. portions of water and dried over 100 g. of anhydrous magnesium sulfate. After suction filtration and removal of the ether on a rotary evaporator at aspirator pressure, the crude alcohol is distilled under reduced pressure through a 40-cm. Vigreux column, yielding 147–158 g. (80–86%) of 3-butyl-2-methyl-1-hepten-3-ol, b.p. 80° (1mm.). The purity of the product, determined by GC analysis, is greater than 99%.

2. Notes

1. Reagent grade (stabilized) tetrahydrofuran was allowed to stand over molecular sieves for 24 hours, refluxed for 2 hours with sodium wire, and finally distilled and used within 48 hours. The checkers found that it was convenient simply to percolate the tetrahydrofuran, after preliminary drying over molecular sieves, through a column of grade I, neutral aluminum oxide, under nitrogen, directly into the reaction flask, until the required volume of solvent was collected.
2. A convenient form of lithium metal can be purchased from Associated Lead Manufacturers Ltd., 14 Gresham Street, London. A typical analysis shows a purity of 99.6%, and it can be obtained as 1.3-cm.-diameter rod coated with petroleum jelly. A comparable form of lithium metal can be purchased from

Ventron Corporation, Chemicals Division, Beverly, Massachusetts. Preparation for use involves weighing, washing with petroleum ether (b.p. 40–60°), and cutting the rod by scissors so that the pieces fall into the reaction vessel. The rod is cut into pieces about 0.5 cm. long that have an average weight of 0.3 g. per piece. Since excess lithium is employed in this reaction, accurate weighing is unnecessary.

3. Reagent grade methyl methacrylate monomer was dried over powdered calcium hydride and freshly distilled before use. The checkers found that identical yields could be obtained when Matheson, Coleman and Bell Chromatoquality methyl methacrylate monomer was used as received with no purification.

4. Reagent grade *n*-butyl bromide (greater than 98% pure) was used after drying over molecular sieves.

5. The reaction is highly exothermic and the submitters have found that isothermal conditions are best maintained by using cooling equipment consisting of a cooling bath seated on a pneumatically operated labjack and controlled by a temperature sensor which is attached to the thermometer dipping into the reaction vessel. This equipment, known as Jack-o-matic, is supplied by Instruments for Research and Industry, Cheltenham, Pennsylvania.

3. Discussion

This method has general applicability in that the carbonyl compound may be an aldehyde, a ketone, or an ester.[2] Similarly, the halide may be chloride, bromide, or iodide, although yields are generally lower with iodides. Alkyl and aryl halides react with equal facility, and the alkyl halide may be primary, secondary, or tertiary. A few examples of the yields obtained with a variety of reagents are given in Table I (the yields quoted are obtained by GC analysis of the reaction mixture using an internal standard).

TABLE I

Carbonyl Compound	Halide	Product	Yield %
Propionaldehyde	Ethyl bromide	3-Pentanol	90
Benzaldehyde	Chlorobenzene	Benzhydrol	100
Di-*n*-butyl ketone	*n*-Butyl bromide	Tri-*n*-butyl carbinol	91
Ethyl formate	*n*-Butyl bromide	5-Nonanol	91
Acrolein	Ethyl bromide	1-Penten-3-ol	90
Butyraldehyde	*sec*-Butyl bromide	3-Methyl-4-heptanol	89

For maximum yield, care must be taken to ensure that the rate of addition of the reagents is not excessive. If this occurs, the alkyllithium is generated in the presence of significant amounts of unchanged alkyl halide, and Wurtz condensation may be favored. The rate of formation of the alkyllithium is proportional to the surface area of the lithium metal; therefore, at a constant rate of addition, an increase in the lithium surface available for reaction will reduce the probability of Wurtz condensation.

Excess alkyl halide is required to compensate for these side reactions; commonly, only a 10–20% excess is used, rather than the 50% quoted in the method above. The yields given in the table are those obtained with 20% excess halide. The submitters have scaled up the reaction by a factor of 40 with no lowering of yield.

The technique is more efficient than the conventional Grignard reaction for three main reasons: (1) it is a one-stage process; (2) the yields are generally higher; and (3) the final product isolation is cleaner and more convenient.

References and Notes

1. Explosives Research and Development Establishment, Ministry of Defense, Waltham Abbey, Essex, U.K.

2. P. J. Pearce, D. H. Richards, and N. F. Scilly, *J. Chem. Soc. D*, 1160 (1970); Brit. Pat. Appl. 61956 (1969).

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

petroleum ether

hydrochloric acid (7647-01-0)

ether,
diethyl ether (60-29-7)

Acrolein (107-02-8)

n-butyl bromide (109-65-9)

Ethyl bromide (74-96-4)

sec-Butyl bromide (78-76-2)

Propionaldehyde (123-38-6)

nitrogen (7727-37-9)

benzaldehyde (100-52-7)

chlorobenzene (108-90-7)

sodium wire (13966-32-0)

butyraldehyde (123-72-8)

ethyl formate (109-94-4)

3-Pentanol (584-02-1)

lithium (7439-93-2)

magnesium sulfate (7487-88-9)

5-Nonanol (623-93-8)

aluminum oxide (1344-28-1)

Tetrahydrofuran (109-99-9)

benzhydrol (91-01-0)

calcium hydride (7789-78-8)

methyl methacrylate (80-62-6)

3-BUTYL-2-METHYLHEPT-1-EN-3-OL,
3-Butyl-2-methyl-1-hepten-3-ol

5-Nonanol, 5-(2-propenyl)- (76071-61-9)

1-Penten-3-ol (616-25-1)

3-Methyl-4-heptanol (1838-73-9)

di-n-butyl ketone (502-56-7)

tri-n-butyl carbinol (597-93-3)