Organic Syntheses

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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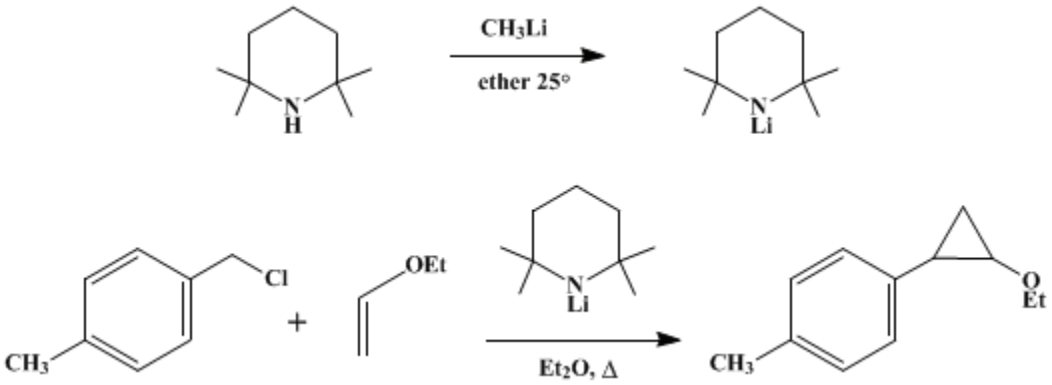
CARBENE GENERATION BY α-ELIMINATION WITH LITHIUM 2,2,6,6-TETRAMETHYLPIPERIDIDE: 1-ETHOXY-2-*p*-TOLYLCYCLOPROPANE

[Benzene, 1-(2-ethoxycyclopropyl)-4-methyl]



Submitted by Charles M. Dougherty[1] and Roy A. Olofson[2].
Checked by Mark W. Johnson and Robert M. Coates.

1. Procedure

Caution! Benzene has been identified as a carcinogen; OSHA has issued emergency standards on its use. All procedures involving benzene should be carried out in a well-ventilated hood, and glove protection is required.

A 250-ml., three-necked, round-bottomed flask equipped with a 50-ml. pressure-equalizing dropping funnel capped by a rubber septum, an efficient reflux condenser connected to a nitrogen inlet, and a magnetic stirrer (Note 1) is charged with 7.02 g. (0.0500 mole) of α-chloro-*p*-xylene (Note 2) and 45.6 g. (0.633 mole) of ethyl vinyl ether (Note 3). A solution of 7.06 g. (0.0501 mole) of 2,2,6,6-tetramethylpiperidine (Note 4) in 15 ml. of dry diethyl ether is injected through the septum into the dropping funnel. Lithium 2,2,6,6-tetramethylpiperidide is generated *in situ* by injecting 46.5 ml. (0.0502 mole) of a 1.08 *M* solution of methyllithium in ether (Note 5) through the septum over a 5–10-minute period (Note 6) and (Note 7). After another 10 minutes, the contents are added dropwise to the vigorously stirred solution in the flask at a rate that maintains a gentle reflux. When the *ca.* 2-hour addition period is complete, the white slurry is stirred overnight at room temperature (Note 8). Water (10 ml.) is added dropwise to the stirred suspension, and the contents of the flask are poured into a separatory funnel containing 100 ml. of ether and 100 ml. of water. The aqueous layer is separated and extracted with two 100-ml. portions of ether. The combined ether solutions are washed successively with 10% aqueous citric acid (Note 9), 5% aqueous sodium hydrogen carbonate, and water, dried with anhydrous calcium chloride, filtered and evaporated with a rotary evaporator. The residual liquid is distilled at reduced pressure, affording 6.6–7.0 g. (75–80%) of 1-ethoxy-2-*p*-tolylcyclopropane, b.p. 116–118° (10 mm.), 95–96° (3.2 mm.) (Note 10).

2. Notes

1. The glassware is dried in an oven at approximately 125° and assembled while still warm. The nitrogen inlet, which consists of a T-tube assembly connected to an oil bubbler, is attached, and the apparatus is allowed to cool while being swept with a stream of dry nitrogen. The septum is placed on top of the dropping funnel, and the nitrogen flow adjusted to maintain a slight positive pressure of nitrogen within the apparatus during the reaction.

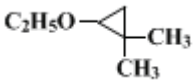
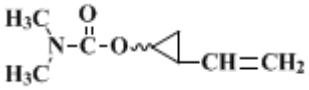
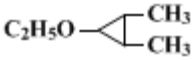
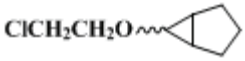
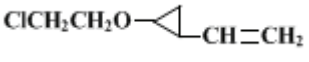
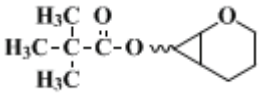
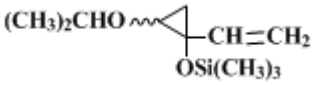
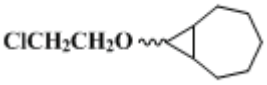
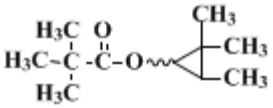
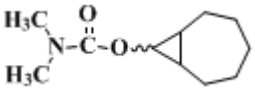
2. α-Chloro-*p*-xylene was obtained from Aldrich Chemical Company, Inc., and purified by distillation under reduced pressure.
3. Ethyl vinyl ether was supplied by Aldrich Chemical Company, Inc., and distilled from sodium. If simple alkenes are used in place of ethyl vinyl ether, the submitters find that the yields of cyclopropanes are improved by dilution of the olefin with one or two volumes of ethyl ether.
4. 2,2,6,6-Tetramethylpiperidine, furnished by Aldrich Chemical Company, Inc., Fluka A G, and ICN Life Sciences Group, is sometimes contaminated with traces of water, hydrazine, and/or 2,2,6,6-tetramethyl-4-piperidone. These impurities may be removed by drying with sodium hydroxide or potassium hydroxide pellets, filtering, and distilling at atmospheric pressure, b.p. 153–154°. The purified amine can be stored indefinitely under a nitrogen atmosphere.
5. Methyllithium in ethyl ether from Ventron Corporation was used. Directions for the preparation of ethereal methyllithium from methyl bromide are also available [see *Org. Synth.*, **Coll. Vol. 6**, 901 (1988).] The checkers standardized the solution immediately before use by diluting a 2.5-ml. aliquot with 10 ml. of benzene and titrating with a 1 *M* solution of 2-butanol in xylene according to the procedure of Watson and Eastham[3] [see *Org. Synth.*, **Coll. Vol. 6**, 121 (1988)], with 1,10-phenanthroline as indicator. The submitters report that the yield of arylcyclopropane is lower if a commercially available solution of *n*-butyllithium in hydrocarbon solvents is used.
6. The methane generated is vented by passage through the oil bubbler.
7. Since the reaction between methyllithium and 2,2,6,6-tetramethylpiperidine is relatively slow at lower temperatures, lithium 2,2,6,6-tetramethylpiperidide is best prepared at room temperature. The reagent may, however, be used over a wide range of temperatures.
8. Approximately the same yields are obtained if the product is isolated after 2–3 hours.
9. The use of aqueous citric acid avoids the formation of insoluble gelatinous precipitates, which result when hydrochloric acid is employed. Sulfuric acid is a suitable alternative to citric acid but must be used in substantial excess to prevent precipitation 2,2,6,6-Tetramethylpiperidine may be recovered from the citric acid extract by making the aqueous solution basic and extracting with ether.
10. The product, a mixture of *cis*- and *trans*-isomers in the ratio of about 2:1, has the following spectral properties: IR (liquid film) cm^{-1} (strong): 1510, 1440, 1370, 1340, 1120, 1080; ^1H NMR (CCl_4), δ (multiplicity, number of protons, assignment): 0.63–1.3 (m, 5H, cyclopropyl CH_2 and OCH_2CH_3), 1.4–2.0 (m, 1H, cyclopropyl C*H*), 2.23 (s, 1H, *trans*-aromatic CH_3), 2.28 (s, *ca.* 2H, *cis*-aromatic CH_3), 2.8–3.7 (m, 3H, $CHOCH_2CH_3$), 6.7–7.2 (m, 4H, C_6H_4). The following specific absorptions in the ^1H NMR spectrum may be used to estimate the ratio of the two isomers, δ (multiplicity, coupling constant *J* in Hz., number of protons, assignment); *cis*-isomer: 0.92 (t, *J* = 7, 3H, OCH_2CH_3), 7.02 (center of *AA'BB'* m, 4H, C_6H_4); *trans*-isomer: 1.14 (t, *J* = 7, 3H, OCH_2CH_3), 6.88 (center of *AA'BB'* m, 4H, C_6H_4).

3. Discussion

This procedure describes the generation of the strong, nonnucleophilic amide base, lithium 2,2,6,6-tetramethylpiperidide, which is used in the regioselective abstraction of a proton from a very weak carbon acid containing other sites reactive toward nucleophilic attack.[4,5] In contrast, most other strong bases undergo preferential alkylation with benzyl halides. 1-Ethoxy-2-*p*-tolylcyclopropane is one of over a dozen aryl cyclopropanes, cyclopropenes, and cyclopropanone ketals that have been prepared by this method[5] (Table I). An analog, 1-methoxy-2-phenylcyclopropane, has been obtained in 8% yield from the reaction of methyllithium with dichloromethyl methyl ether in styrene.[6] The alkene is present in large excess, as is commonly the case for reactions involving short-lived carbene intermediates. In the present procedure ethyl vinyl ether serves as both solvent and reactant. For best results with alkenes lacking alkoxy substituents, approximately two volumes of ether or tetrahydrofuran should be used as diluent. Alkoxy,[7,8] acyloxy,[9] alkenyl,[5,10,11] trialkylsilyl,[10] and trialkylstannyl[10] carbenes have been generated and trapped *in situ* with alkenes and alkynes by this method, affording a variety of substituted cyclopropanes.

TABLE I
PREPARATION OF CYCLOPROPANES FROM ALKYL HALIDES, ALKENES, AND LITHIUM 2,2,6,6-TETRAMETHYLPIPERIDIDE

Product	Yield (%)	Product	Yield (%)

	66[7]		21[9]
	66[7]		64[8]
	74[8]		39[9]
	46[7]		62[8]
	35[9]		20 (24)[9]

Lithium 2,2,6,6-tetramethylpiperidide has also been used to advantage in a number of other types of reactions. This base reacts with aryl halides[5,10,12,13] (and, less cleanly, with aryl sulfonates[14]), giving benzynes, which have been trapped with thiolates,[5] acetylides,[5,14] enolates,[10,13,14] and conjugated dienes.[10,12,14] Replacement of halogen by hydrogen, a major reaction observed between other dialkylamide bases and aryl halides, does not occur with lithium 2,2,6,6-tetramethylpiperidide.[5] While alkyl benzoates undergo selective deprotonation at the *ortho*-position upon treatment with this amide base,[15] methyl thiobenzoate and *N,N*-dimethylbenzamide are metallated at the methyl group, forming dipole-stabilized carbanions.[16] The organolithium intermediates produced condense with the remaining ester or amide, affording various aryl ketones. Lithiation of dibromomethane[17] and at the α-position of isocyanides[18] with lithium 2,2,6,6-tetramethylpiperidide produces an organolithium intermediate reactive toward carbonyl compounds. In the synthesis of enol carbonates from ketone enolates and chloroformates, this base is the only one to accomplish the reaction in high yield.[19] Lithium 2,2,6,6-tetramethylpiperidide has been shown to be the base of choice for irreversible ketone enolate formation[20] and has been used to discriminate sterically between two potential enolate sites to yield alkylation products with extremely high regioselectivity.[21] The enolate anions of esters[5,22] and dianions of β-keto esters[23] and propiolic acid[24] have been formed by reaction with lithium 2,2,6,6-tetramethylpiperidide. It is a superior base for metallation of selenides,[25] selenoacetals, and selenoketals.[26] Other reactions in which this hindered base has proved effective include the conversion of an epoxide to an enolate anion,[27] the generation of certain α-lithioörganoboranes,[28] the preparation of the highly strained tetracyclo(4.2.0.0^{2,4}.0^{3,5})oct-7-ene from the appropriate tosylhydrazone,[29] and the insertion of magnesium into bacteriopheophytin α.[30] In many of these reactions, other bases, including less hindered amide bases such as lithium diisopropylamide, gave either lower yields or different products entirely.

References and Notes

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

Lithium 2,2,6,6-tetramethylpiperidide

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

ether,
ethyl ether,
diethyl ether (60-29-7)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

citric acid (77-92-9)

sodium hydrogen carbonate (144-55-8)

magnesium (7439-95-4)

nitrogen (7727-37-9)

methane (7782-42-5)

potassium hydroxide (1310-58-3)

sodium (13966-32-0)

methyl bromide (74-83-9)

xylene (106-42-3)

hydrazine (302-01-2)

dibromomethane (74-95-3)

styrene (100-42-5)

n-butyllithium (109-72-8)

Tetrahydrofuran (109-99-9)

Methyllithium (917-54-4)

ethyl vinyl ether (109-92-2)

Dichloromethyl methyl ether (4885-02-3)

2-Butanol (78-92-2)

lithium diisopropylamide (4111-54-0)

1,10-phenanthroline (66-71-7)

Benzene, 1-(2-ethoxycyclopropyl)-4-methyl,
1-Ethoxy-2-p-tolylcyclopropane

2,2,6,6-tetramethylpiperidine (768-66-1)

2,2,6,6-tetramethyl-4-piperidone (826-36-8)

1-methoxy-2-phenylcyclopropane

methyl thiobenzoate

propiolic acid (471-25-0)

tetracyclo(4.2.0.$0^{2,4}$.$0^{3,5}$)oct-7-ene

α-chloro-p-xylene (104-82-5)

N,N-dimethylbenzamide (611-74-5)