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Working with Hazardous Chemicals

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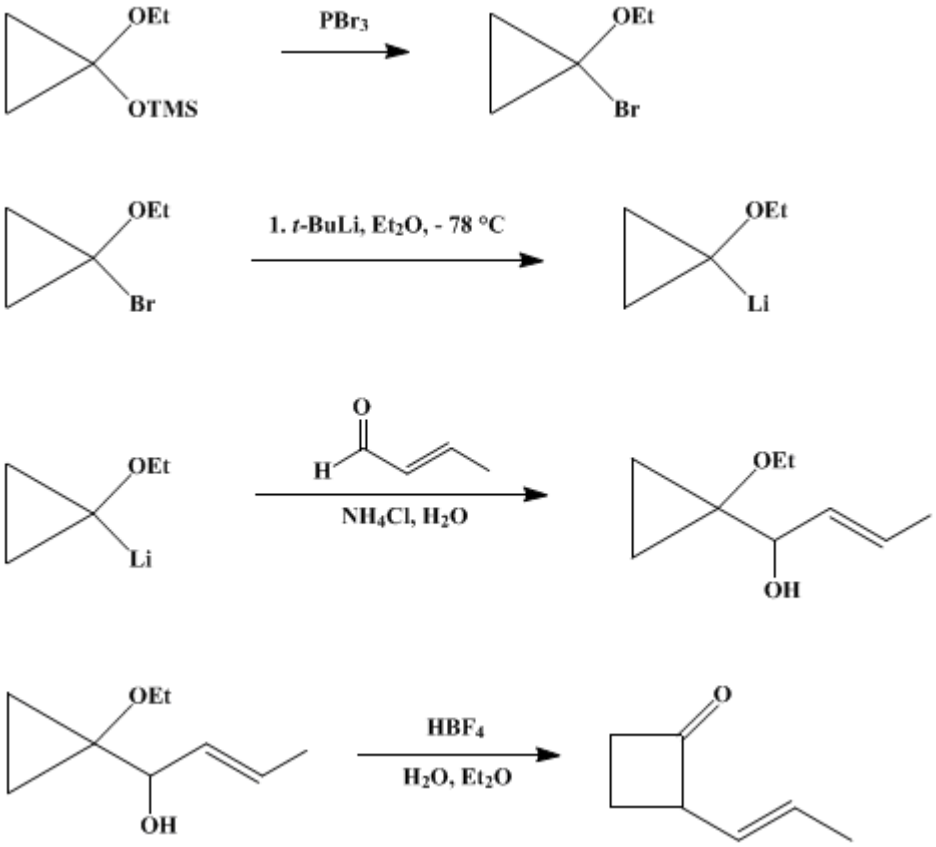
SYNTHESIS OF CYCLOBUTANONES VIA 1-BROMO-1-ETHOXYCYCLOPROPANE: (*E*)-2-(1-PROPENYL)CYCLOBUTANONE

[Cyclobutanone, 2-(1-propenyl)-, (*E*)-]



Submitted by Scott A. Miller and Robert C. Gadwood[1].
Checked by Jeffrey A. McKinney and Leo A. Paquette.

1. Procedure

Caution! tert-Butylithium is extremely pyrophoric and must not be allowed to come into contact with the atmosphere. This reagent should only be handled by individuals trained in its proper and safe use. It is recommended that transfers be carried out by using a 20-mL or smaller glass syringe filled to no more than 2/3 capacity, or by cannula. For a discussion of procedures for handling air-sensitive reagents, see Aldrich Technical Bulletin AL-134. [Note added August 2009].

A. *1-Bromo-1-ethoxycyclopropane.*[2] A 500-mL, round-bottomed flask equipped with a magnetic stirring bar and a calcium sulfate drying tube is charged with 84.1 g (0.483 mol) of 1-ethoxy-1-trimethylsiloxycyclopropane.[3] Phosphorus tribromide (35.6 mL, 103 g, 0.379 mol) (Note 1) is added at room temperature with brisk stirring, followed by a catalytic amount (0.5 ml) of 48% aqueous hydrobromic acid (Note 2). The resulting clear, pale-yellow solution is stirred for 6 hr (Note 3). After the stirring bar is removed, the reaction mixture is distilled by Kugelrohr apparatus at aspirator vacuum (10 mm) from 25 to 70°C to afford crude 1-bromo-1-ethoxycyclopropane (Note 4) and (Note 5). The crude product is dissolved in 300 mL of pentane in a 1-L Erlenmeyer flask and the resulting solution is chilled to −20°C in a dry ice–ethanol: water (30 : 70) bath. While the temperature of the solution is maintained below 25°C, 300 mL of saturated, aqueous sodium carbonate is carefully added (Note 6). The layers are carefully shaken and separated, and the aqueous phase is extracted with 100-mL of pentane. The organic layer is dried over magnesium sulfate, filtered, and most of the pentane is removed by distillation through a 15-cm Vigreux column at atmospheric pressure. The residue is transferred to a smaller distillation flask and distilled through the same column under aspirator vacuum to afford 47.0–57.6 g (59–72%) of

1-bromo-1-ethoxycyclopropane as a colorless liquid (bp 35–43°C, 10 mm) (Note 7) and (Note 8).

Caution! Because of the relatively large amount of pyrophoric tert-butyllithium involved, the following preparation should be performed in a hood behind a safety shield.

B. *(E)-1-Ethoxy-1-(1-hydroxy-2-butenyl)cyclopropane.* A 1-L, three-necked flask is equipped with a gas inlet adapter, a septum, a 250-mL graduated addition funnel capped with a septum, and a magnetic stirring bar (Note 9). The flask is charged with 500 mL of anhydrous diethyl ether (Note 10) and cooled to −78°C under a nitrogen atmosphere. The addition funnel is charged with 177 mL (19.2 g, 0.30 mol) of *tert*-butyllithium (Note 11), transferred from the reagent bottle via a stainless-steel cannula under positive nitrogen pressure. The *tert*-butyllithium is added dropwise to the stirred diethyl ether over approximately 20 min while the cooling bath is maintained at −78°C. After the addition is complete, 26.4 g (0.16 mol) of freshly prepared 1-bromo-1-ethoxycyclopropane is added to the reaction over about 5 min by syringe. The resulting cloudy, colorless, or light-yellow reaction mixture is stirred for 20–25 min, and a solution of 7.0 g (0.10 mol) of crotonaldehyde (Note 12) in 50 mL of anhydrous diethyl ether (chilled to −78°C) is added via a stainless-steel cannula under positive nitrogen pressure. The reaction mixture is stirred at −78°C for an additional 10 min, warmed to 0°C in an ice bath, and carefully quenched with 100 mL of saturated, aqueous ammonium chloride. The layers are shaken and separated and the aqueous phase is extracted with 100 mL of diethyl ether. The combined organic layers are dried over magnesium sulfate and filtered. After the crude adduct is concentrated on a rotary evaporator, it is filtered through a 10-cm pad of silica gel (Note 13) in a sintered-glass funnel with 10% ethyl acetate in hexane. After concentrating again on a rotary evaporator, the crude adduct is obtained as a pale-yellow oil (14.2–15.6 g) (Note 14). This material is not further purified, but is used directly in the next reaction.

C. *(E)-2-(1-Propenyl)cyclobutanone.* To a 1-L, round-bottomed flask equipped with a magnetic stirring bar is added 15.3 g (0.098 mol) of (*E*)-1-ethoxy-1-(1-hydroxy-2-butenyl)cyclopropane, 500 mL of reagent-grade diethyl ether, and 6.6 mL (4.3 g, 0.049 mol) of 48% aqueous fluoboric acid (Note 15). After the reaction mixture is stirred for 15 min at room temperature, it is quenched with 60 mL (0.06 mol) of 1 *M* aqueous sodium carbonate. The layers are carefully shaken and separated, and the organic phase is washed with three 125-mL portions of water (Note 16). The combined aqueous layers are extracted with 100 mL of diethyl ether and the organic phase is dried over magnesium sulfate and filtered. The filtrate is concentrated on a rotary evaporator without external heating and the residue is distilled through a 10-cm Vigreux column under aspirator vacuum. The product, 7.2–8.3 g (66–75% yield from crotonaldehyde), is obtained as a colorless oil, bp 61–65°C (10 mm) (Note 17).

2. Notes

1. Phosphorus tribromide was obtained from the Aldrich Chemical Company, Inc. and used without further purification.

2. The addition of a catalytic amount of hydrobromic acid was frequently found to be necessary to initiate the reaction, especially if the phosphorus tribromide is of high purity. On addition of the hydrobromic acid, the reaction warms noticeably.

3. The course of the reaction is most conveniently followed by ^{1}H NMR analysis of a drop of the reaction mixture in carbon tetrachloride. The downfield quartet of the starting ketal (3.52 ppm) is replaced by a clean quartet at 3.62 ppm from the product. The checkers have found by this technique that reaction is complete in much less than 6 hr.

4. The crude product thus obtained also contains bromotrimethylsilane and hydrobromic acid.

5. *Caution! After distillation the Kugelrohr apparatus should first be cooled and then carefully vented to an atmosphere of nitrogen since traces of elemental phosphorus may be present in the pot residue and may ignite if exposed to air while still hot.*

6. This step neutralizes the hydrobromic acid and bromotrimethylsilane present in the product. Therefore, addition of the aqueous sodium carbonate solution is exothermic and causes vigorous carbon dioxide evolution. Cooling at this stage helps prevent hydrolysis of the product.

7. A low-boiling, silicon-containing fraction is also collected below 37°C (28 mm). The presence of a singlet at 0.10 ppm in the ^{1}H NMR of the product indicates contamination by this low-boiling fraction. Small amounts of this impurity do not seem to interfere in subsequent reactions of the 1-bromo-1-ethoxycyclopropane.

8. 1-Bromo-1-ethoxycyclopropane is relatively unstable at room temperature, but can be stored for several months at −20°C with only slight decomposition. Spectral data for 1-bromo-1-ethoxycyclopropane are as follows: IR (neat) cm^{-1}: 3100 (w), 2985 (s), 2935 (m), 2885 (m), 1445 (m), 1300 (s), 1160 (s), 1060 (s), 795 (s); ^{1}H NMR (CCl_4) δ: 1.17 (m, 7 H), 3.53 (q, 2 H, J = 8); MS (15 eV), *m/e* 164/166 (M^+), 136/138 (base), 85, 57.

9. The glassware was dried in an oven overnight at 110°C and assembled while hot under nitrogen flow.

10. Diethyl ether was dried by distillation from sodium metal/benzophenone.

11. *Caution! tert-Butyllithium is extremely pyrophoric and should be handled on a large scale only by*

experienced personnel. *tert*-Butyllithium was obtained from the Aldrich Chemical Company, Inc. as a 1.7 *M* solution in pentane. In general, this material was used as received without titration.

12. Crotonaldehyde was obtained from The Matheson Company, Inc., and is also available (≥99% grade) from the Aldrich Chemical Company, Inc.

13. Merck Silica Gel 60 (230–400 mesh) was obtained from the Aldrich Chemical Company, Inc. Filtration through silica gel removes residual inorganic salts (mostly lithium chloride), which may interfere in the subsequent rearrangement step.

14. Spectral data for (*E*)-1-ethoxy-1-(hydroxy-2-butenyl)cyclopropane are as follows: ^{1}H NMR ($CDCl_3$) δ: 0.68 (m, 4 H), 1.12 (t, 3 H, *J* = 6), 1.64 (d, 3 H, *J* = 5), 2.46 (s, 1 H), 3.54 (m, 2 H), 4.15 (d, 1 H, *J* = 6), 5.52 (m, 2 H). Occasionally, a minor impurity is formed as a result of the addition of *tert*-butyllithium to crotonaldehyde (singlet at 0.89 ppm in the ^{1}H NMR). This side reaction occurs because of the presence of unreacted *tert*-butyllithium and is best avoided by using the indicated ratio of *tert*-butyllithium to 1-bromo-1-ethoxycyclopropane. The checkers were unable to remove this impurity by fractional distillation.

15. Fluoboric acid was obtained as a 48 wt% aqueous solution from the Aldrich Chemical Company, Inc. On the basis of its density, this solution was calculated to be approximately 7.4 *M* in HBF_4. The checkers used 5.4 mL (0.049 mol) of 60% fluoboric acid.

16. Washing with water helps to remove the ethanol generated in the course of the rearrangement. For higher-boiling cyclobutanones, where the ethanol can easily be removed during distillation, this step is unnecessary.

17. Spectral data for (*E*)-2-(1-propenyl)cyclobutanone are as follows: IR (CCl_4) cm^{-1}: 2960 (s), 1780 (s), 1660 (w), 1450 (m); ^{1}H NMR (CCl_4) δ: 1.62 (m, 3 H), 2.17 (m, 2 H), 2.88 (m, 2 H), 3.73 (m, 1 H), 5.37 (m, 2 H). The product was contaminated by an alcoholic impurity to the extent of 6–11%.

3. Discussion

Cyclobutanones have attained a position of considerable synthetic importance in recent years. In addition to being important synthetic targets themselves, they serve as useful precursors of five-,[4] six-,[5] and eight-membered[6] rings, as well as of a variety of highly functionalized acyclic fragments.[7,8]

In general, cyclobutanones are synthesized by either ketene cycloadditions or by ring expansions of cyclopropyl precursors. For the synthesis of simple α-substituted monocyclic cyclobutanones, the latter method is usually employed, and a variety of approaches have been used to prepare the required cyclopropyl intermediates.

Vinylcyclopropanols have been prepared by the addition of alkenyl Grignard reagents to a variety of cyclopropanone equivalents.[9] On treatment with acid, the vinylcyclopropanols rearrange to α-substituted cyclobutanones. Alternatively, a variety of α-heteroatom-substituted cyclopropyllithium reagents have been developed. These react with aldehydes and ketones to afford cyclopropylcarbinols that also rearrange to cyclobutanones under acid catalysis.[8,10,11] Finally, vinylcyclopropanols and cyclopropylcarbinols have been prepared by the cyclopropanation of enol silyl ethers and allylic alcohols.[12]

There are several advantages to the procedure described here for the synthesis of α-substituted cyclobutanones. The preparation of 1-bromo-1-ethoxycyclopropane is convenient and can be accomplished in good overall yield in only two steps from commercially available ethyl 3-chloropropionate. Metalation of 1-bromo-1-ethoxycyclopropane is rapid and reproducible on a large scale, and (1-ethoxy)cyclopropyllithium adds cleanly to a wide variety of ketones and aldehydes. Finally, rearrangement of the cyclopropylcarbinol adducts occurs smoothly and in high yield.

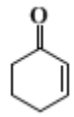
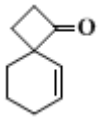
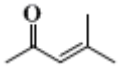
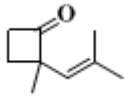
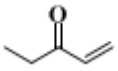
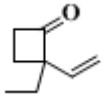
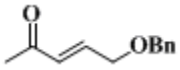
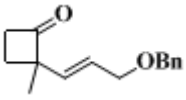
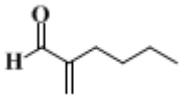
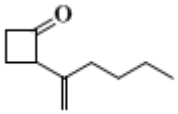
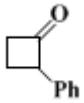
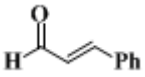
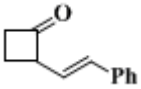
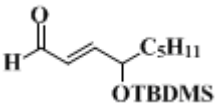
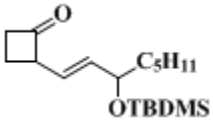
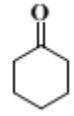
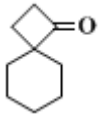
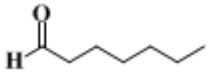
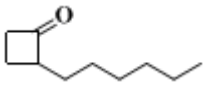
The preparation of 1-bromo-1-ethoxycyclopropane is based on a literature report of the synthesis of 1-bromo-1-methoxycyclopropane from 1-methoxy-1-trimethylsiloxycyclopropane using phosphorus tribromide in pyridine.[13] In our hands, reaction of 1-ethoxy-1-trimethylsiloxycyclopropane under these conditions afforded none of the bromide.

The title cyclobutanone has been prepared previously by the addition of (1-phenylthio)cyclopropyllithium to crotonaldehyde followed by rearrangement with anhydrous stannic chloride in methylene chloride.[11] However, in our experience, the procedure described here is much more convenient and reproducible on a large scale.

As shown in Table I, a wide variety of α-substituted cyclobutanones have been prepared by the general method described here.[14] The time required for rearrangement of the intermediate cyclopropylcarbinols varies from less than 5 min for entry 2 to 48 hr for entry 10. With most enones and enals, only 1,2-addition is observed, but in two cases (entries 3 and 4), a significant amount of the 1,4-adduct was also produced. The increased 1,4-addition seen in entry 3 apparently occurs because of steric factors, whereas that seen in entry 4 presumably occurs because of chelation of the organolithium to the

benzyl ether oxygen.

TABLE I
CYCLOBUTANONE SYNTHESIS VIA 1-BROMO-1-ETHOXYCYCLOPROPANE

Entry	Ketone/aldehyde	Cyclobutanone	Yield(%)
1			97
2			86
3			40
4			30
5			65
6			71
7			79
8			74
9			81
10			81

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14. Entries 2, 9, and 10 of Table I have been reported previously.[2] Entry 1 was carried out by Amy J. DeWinter. Entry 3 was carried out by Scott A. Miller. Entry 4 was carried out by Mark R. Rubino. Entries 5–8 were carried out by Ishwar M. Mallick.

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

silica gel

fluoboric acid

ethanol (64-17-5)

ethyl acetate (141-78-6)

diethyl ether (60-29-7)

ammonium chloride (12125-02-9)

HYDROBROMIC ACID (10035-10-6)

sodium carbonate (497-19-8)

PHOSPHORUS (7723-14-0)

phosphorus tribromide (7789-60-8)

carbon tetrachloride (56-23-5)

nitrogen (7727-37-9)

carbon dioxide (124-38-9)

pyridine (110-86-1)

Benzophenone (119-61-9)

sodium (13966-32-0)

Pentane (109-66-0)

methylene chloride (75-09-2)

stannic chloride (7646-78-8)

magnesium sulfate (7487-88-9)

hexane (110-54-3)

crotonaldehyde (123-73-9)

Lithium chloride (7447-41-8)

ethyl 3-chloropropionate (623-71-2)

Cyclobutanone (1191-95-3)

cyclopropylcarbinol (2516-33-8)

1-ethoxy-1-trimethylsiloxycyclopropane (27374-25-0)

tert-Butyllithium (594-19-4)

1-Bromo-1-ethoxycyclopropane (95631-62-2)

bromotrimethylsilane (2857-97-8)

(1-ethoxy)cyclopropyllithium

1-bromo-1-methoxycyclopropane

1-methoxy-1-trimethylsiloxycyclopropane

(1-phenylthio)cyclopropyllithium

benzyl ether oxygen

(E)-2-(1-Propenyl)cyclobutanone,
Cyclobutanone, 2-(1-propenyl)-, (E)- (63049-06-9)

(E)-1-Ethoxy-1-(1-hydroxy-2-butenyl)cyclopropane (130719-17-4)

(E)-1-ethoxy-1-(hydroxy-2-butenyl)cyclopropane