



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](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.

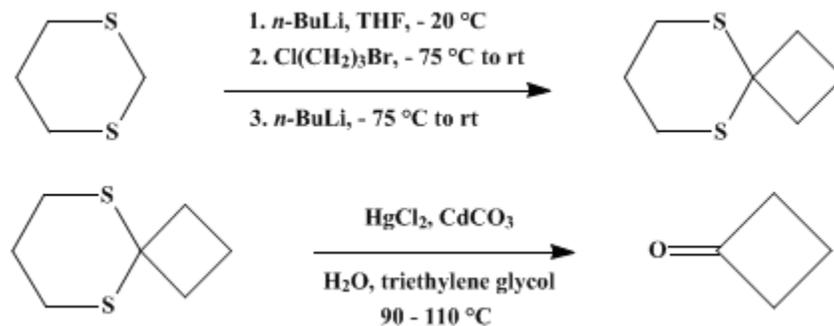
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*These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.*

*Organic Syntheses, Coll. Vol. 6, p.316 (1988); Vol. 51, p.76 (1971).*

## CYCLIC KETONES FROM 1,3-DITHIANE: CYCLOBUTANONE



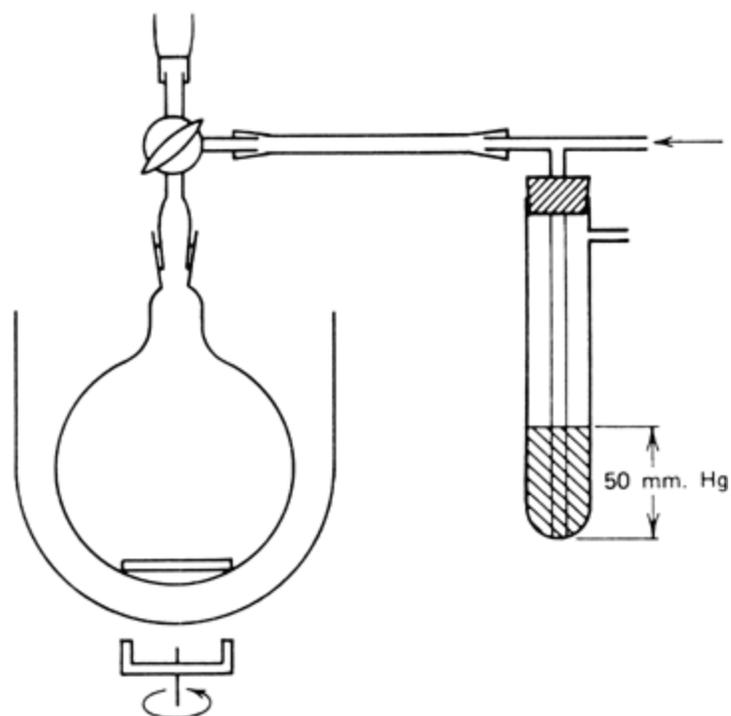
Submitted by D. Seebach<sup>1</sup> and A. K. Beck.

Checked by Jose F. Pazos and Richard E. Benson.

### 1. Procedure

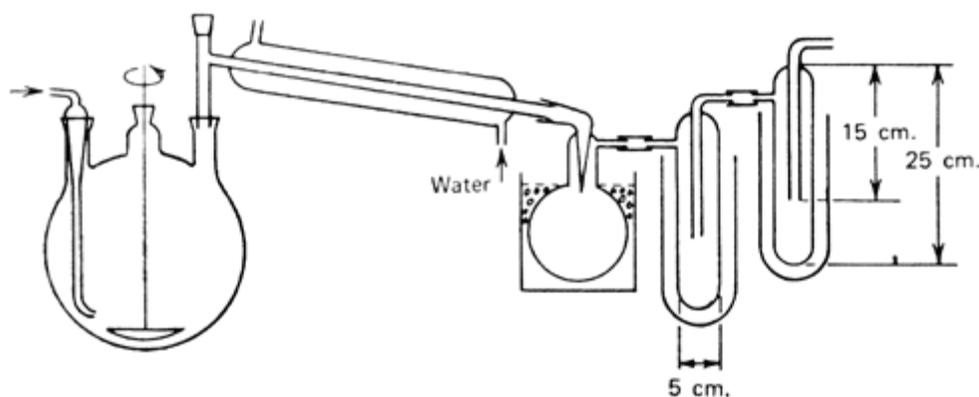
A. *5,9-Dithiaspiro[3.5]nonane*. A dry, 2-l., one-necked, round-bottomed flask containing a magnetic stirring bar (Note 1) is flushed with dry nitrogen (Note 2), and 1.25 l. of dry tetrahydrofuran (Note 3) and 50 g. (0.42 mole) of 1,3-dithiane (Note 4) are added. The flask is quickly equipped with a three-way stopcock bearing a standard tapered joint, a rubber septum, and a nitrogen inlet, as shown in Figure 1 (Note 5). The solution is stirred with an efficient magnetic stirrer and cooled to an external temperature of  $-20^\circ$  with a methanol-dry ice bath. A 3% excess (total of 0.43 mole) of 1.5–2.5 M *n*-butyllithium in *n*-hexane (Note 6) is added through the rubber septum with a syringe. The bath temperature is kept between  $-10^\circ$  and  $-20^\circ$  for 2 hours before the temperature of the bath is reduced to  $-75^\circ$  (Note 7) and 65.5 g. (44.5 ml., 0.417 mole) of 1-bromo-3-chloropropane (Note 8) is added with a syringe over 10 minutes. The temperature of the bath is raised to  $-30^\circ$  over a 2-hour period by gradually replacing the cold methanol with warm methanol. The bath is removed and stirring is continued until the reaction flask is at room temperature (Note 9). The flask is again cooled to  $-75^\circ$  (Note 7) and 0.44 mole of *n*-butyllithium in *n*-hexane (Note 6) is added with a syringe over 10 minutes. After the addition is complete, the temperature of the reaction flask is allowed to rise to room temperature overnight (Note 10). The solvent is removed from the product with a rotary evaporator at  $50^\circ$  and aspirator pressure. Water (300 ml.) and diethyl ether (500 ml.) are added to the product in the flask, the ether layer is separated, and the aqueous layer is washed again with 500 ml. of ether. The organic layers are combined, washed with 200 ml. of water, and dried over 10 g. of anhydrous potassium carbonate. The ether is removed by distillation to yield about 75 g. of crude product. Distillation through a packed column gives 44–57 g. (65–84%) of *5,9-dithiaspiro[3.5]nonane*, b.p.  $65\text{--}75^\circ$  (1 mm.),  $n_D^{20}$  1.5700. This product is of sufficient purity for use in Part B (Note 11).

Figure 1.



B. *Cyclobutanone*. A 2-l., three-necked flask is fitted with an efficient mechanical stirrer and a water-cooled condenser assembled for downward distillation to which is attached a 250-ml. receiver with a side arm. Two cold traps are attached consecutively to the distillation apparatus as shown in Figure 2 (Note 12). The receiver is immersed in an ice-water bath, and the traps are immersed in dry ice and acetone. To the flask is added 45 g. (0.28 mole) of 5,9-dithiaspiro[3.5]nonane, 900 ml. of triethylene glycol, and 150 ml. of water. Stirring is begun, and 163 g. (0.600 mole) of mercury(II) chloride (Note 13) and 51.5 g. (0.300 mole) of cadmium carbonate (Note 13) are added. A nitrogen-inlet tube reaching to the bottom of the flask is inserted into the third neck of the flask, and nitrogen is introduced at approximately 50 ml. per minute. The reaction flask is heated to 90° in an oil bath, and the temperature is slowly increased to 110° over a 2–3 hour period. Water and cyclobutanone are carried into the receivers. The water in the receiving flask is saturated with sodium chloride, and the resulting solution is transferred to a separatory funnel. The flask is rinsed with 25 ml. of dichloromethane, and this solution is used for an initial washing of the aqueous solution. The aqueous solution is shaken three additional times with 25-ml. portions of dichloromethane. The dichloromethane solutions are combined and added to the traps to dissolve cyclobutanone. The resulting solution is transferred to a 250-ml. flask, the traps are rinsed with a small amount of dichloromethane, and the rinse is combined with the original solution. The organic solution is dried over 5 g. of anhydrous sodium sulfate, filtered, and the solvent is removed by distillation through a 20-cm., helix-packed, vacuum-insulated column. The product is transferred to a 25-ml. flask, 5 ml. of mesitylene is added, and the product is distilled through a spinning-band column. The fraction boiling at 95–100° is collected, yielding 12–15.8 g. (60–81%) (Note 14) of cyclobutanone.

Figure 2.

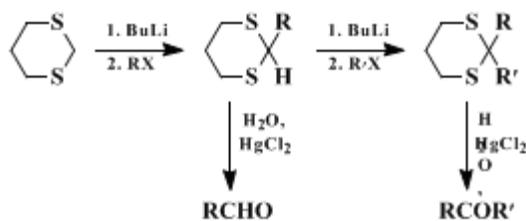


## 2. Notes

1. Efficient stirring is required throughout the reaction.
2. If available, [argon](#) is preferable to [nitrogen](#) because of its higher density.
3. The checkers used reagent grade [tetrahydrofuran](#) (available from Fisher Scientific Company) from a freshly opened bottle. The submitters used [tetrahydrofuran](#) purified by distillation from [lithium aluminum hydride](#). See *Org. Synth., Coll. Vol. 5*, 976 (1973), for warning regarding purification of [tetrahydrofuran](#).
4. [1,3-Dithiane](#) was prepared as described in *Org. Synth., Coll. Vol. 6*, 556 (1988), and sublimed prior to use.
5. During the entire reaction sequence a positive pressure of approximately 50 mm. of [nitrogen](#) is maintained against the atmosphere with a mercury bubbler.
6. The titer of the solution should be determined prior to use. The checkers used product available from Foote Mineral Company.
7. Only a slight excess of dry ice should be added.
8. Available from Eastman Organic Chemicals. The product was distilled prior to use, b.p. 140–142°.
9. Approximately 2 hours is required.
10. The submitters have found that the ring closure reaction is essentially complete by the time the temperature reaches  $-20^{\circ}$ .
11. GC analysis using a column containing 20% silicone DC 200 on Gas Chrom Z at  $160^{\circ}$  showed the product to be 96% pure.
12. The traps are attached in a reverse manner. The diameter of the inner tubing is 1.5 cm.
13. Anhydrous practical grade reagents were used.
14. The IR spectrum (neat) shows strong absorption at  $1775\text{ cm.}^{-1}$ . The purity of the product is greater than 95% as established by GC on a 4-ft. column containing 20% silicone DC 200 on Gas Chrom Z at  $50^{\circ}$ . The  $^1\text{H}$  NMR spectrum ( $\text{CCl}_4$ ) shows a pentet at  $\delta$  1.83 ( $J = 8\text{ Hz.}$ ) and a triplet at 3.01 ( $J = 8\text{ Hz.}$ ) in a ratio 1:2, respectively.

## 3. Discussion

The best large-scale preparation of [cyclobutanone](#) is the reaction of [diazomethane](#) with ketene.<sup>2</sup> It requires a ketene generator and necessitates handling large quantities of the potentially hazardous diazo compound. A more frequently used method for the preparation of [cyclobutanone](#) starts with [pentaerythritol](#), the final step being the oxidative degradation of [methylenecyclobutane](#),<sup>4,3</sup> which can also be prepared from other precursors.<sup>5</sup> A general survey of all methods used to obtain [cyclobutanone](#) has been published.<sup>6,7</sup>



The procedure described here is an example of the use of the dithiane method<sup>8</sup> for the preparation of ketones. The reactions appear to be general, and the yields are satisfactory. The dithiane method can be successfully applied to the synthesis of rings containing up to seven carbon atoms with a slight modification<sup>9,10</sup> of the procedure above. The synthesis of larger rings may require high dilution methods.<sup>9</sup>

Aldehydes and open-chain ketones are also available from dithiane.<sup>9</sup> Carbonyl compounds with high optical activity<sup>9</sup> have been synthesized, including those that undergo facile racemization. An extensive review covering all applications of this reaction up to June 1969 has been authored by one of the submitters.<sup>9</sup> Methods and limitations for the preparation of silyl ketones<sup>11</sup> ( $R_3SiCOR$ ) and germanyl ketones ( $R_3GeCOR$ ) have been described.<sup>12</sup>

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 320
- Org. Syn. Coll. Vol. 6, 324
- Org. Syn. Coll. Vol. 6, 542
- Org. Syn. Coll. Vol. 6, 869
- Org. Syn. Coll. Vol. 7, 114
- Org. Syn. Coll. Vol. 7, 153

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## References and Notes

1. Institut für Organische Chemie der Universität (TH) Karlsruhe, West Germany. [Present address: Laboratorium für Organische Chemie, ETH-Zentrum, CH-8092 Zurich, Switzerland.]
  2. P. Lipp and R. Köster, *Ber. Dtsch. Chem. Ges.*, **64**, 2823 (1931); P. Lipp, J. Buchkremer, and H. Seeles, *Justus Liebigs Ann. Chem.*, **499**, 1 (1932); S. Kaarsemaker and J. Coops, *Recl. Trav. Chim. Pays-Bas*, **70**, 1033 (1951); cf. ref. <sup>3</sup>.
  3. J.-M. Conia, P. Lriverend, and J.-L. Ripoll, *Bull. Soc. Chim. Fr.*, 1803 (1961).
  4. J. D. Roberts and C. W. Sauer, *J. Am. Chem. Soc.*, **71**, 3925 (1949).
  5. J.-M. Conia and J. Gore, *Bull. Soc. Chim. Fr.*, 735 (1963).
  6. J.-M. Conia and J. Gore, *Bull. Soc. Chim. Fr.*, 726 (1963).
  7. D. Seebach, in E. Müller, Ed., "Methoden der Organischen Chemie," (Houben-Weyl), Vol. 4/4, Georg. Thieme Verlag, Stuttgart, 1971.
  8. E. J. Corey and D. Seebach, *Angew. Chem.*, **77**, 1134, 1135 (1965) [*Angew. Chem. Int. Ed. Engl.*, **4**, 1075, 1077 (1965)].
  9. D. Seebach, *Synthesis*, **17**, (1969), and references cited therein.
  10. D. Seebach, N. R. Jones, and E. J. Corey, *J. Org. Chem.*, **33**, 300 (1968).
  11. E. J. Corey, D. Seebach, and R. Freedman, *J. Am. Chem. Soc.*, **89**, 434 (1967).
  12. A. G. Brook, *Adv. Organomet. Chem.*, **7**, 95 (1968).
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potassium carbonate (584-08-7)

    methanol (67-56-1)

        ether,  
        diethyl ether (60-29-7)

sodium chloride (7647-14-5)

sodium sulfate (7757-82-6)

    nitrogen (7727-37-9)

    acetone (67-64-1)

1-bromo-3-chloropropane (109-70-6)

mercury(II) chloride (7487-94-7)

    Mesitylene (108-67-8)

    dichloromethane (75-09-2)

    Pentaerythritol (115-77-5)

    Diazomethane (334-88-3)

        butyllithium,  
        n-butyllithium (109-72-8)

    Tetrahydrofuran (109-99-9)

lithium aluminum hydride (16853-85-3)

    n-hexane (110-54-3)

    argon (7440-37-1)

    triethylene glycol (112-27-6)

    dithiane (505-20-4)

    Cyclobutanone (1191-95-3)

    1,3-Dithiane (505-23-7)

    methylenecyclobutane (1120-56-5)

5,9-dithiaspiro[3.5]nonane (15077-16-4)

    cadmium carbonate (513-78-0)

