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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.

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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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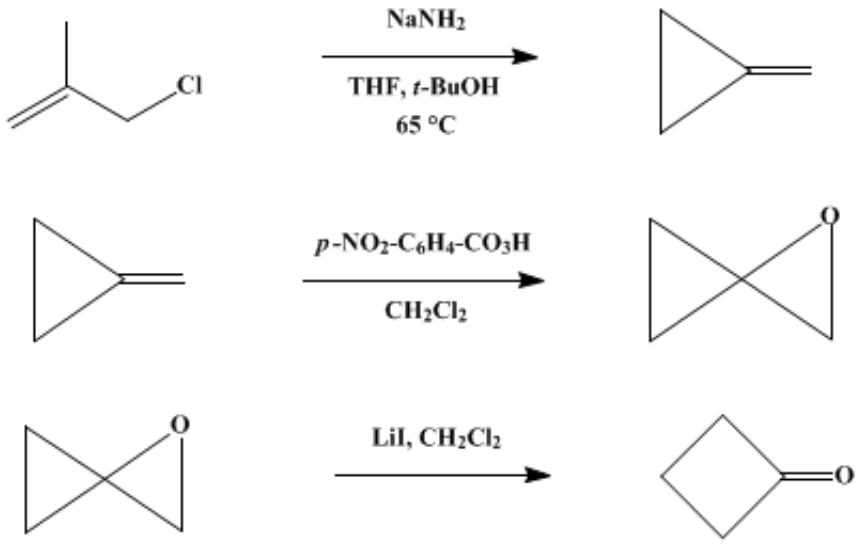
CYCLOBUTANONE FROM METHYLENECYCLOPROPANE *via* OXASPIROPENTANE



Submitted by J. R. Salaun, J. Champion, and J. M. Conia[1].
Checked by Z. Stojanac and Z. Valenta.

1. Procedure

Caution! Reactions and subsequent operations involving peracids and peroxy compounds should be run behind a safety shield. Peroxy compounds should be added to the organic material, never the reverse. For relatively fast reactions, the rate of addition of the peroxy compound should be slow enough so that it reacts rapidly and no significant unreacted excess is allowed to build up. The reaction mixture should be stirred efficiently while the peroxy compound is being added, and cooling should generally be provided since many reactions of peroxy compounds are exothermic. New or unfamiliar reactions, particularly those run at elevated temperatures, should be run first on a small scale. Reaction products should never be recovered from the final reaction mixture by distillation until all residual active oxygen compounds (including unreacted peroxy compounds) have been destroyed. Decomposition of active oxygen compounds may be accomplished by the procedure described in Korach, M.; Nielsen, D. R.; Rideout, W. H. Org. Synth. 1962, 42, 50 (Org. Synth. 1973, Coll. Vol. 5, 414). [Note added January 2011].

Caution! The preparation of methylenecyclopropane must be carried out in an efficient hood because ammonia is evolved. Oxaspiropentanes have been widely used as useful synthetic intermediates and appear to be quite stable; nevertheless, in view of the nature of the compounds, it is recommended that the preparation and handling of oxaspiropentane be carried out behind a safety screen.

A. *Methylenecyclopropane* (Note 1). A dry, 3-l., three-necked, round-bottomed flask with ground-glass fittings is equipped with a sealed stirrer (Note 2) driven by a heavy-duty motor, an efficient condenser fitted with a silica gel drying tube, and a 500-ml., pressure-equalizing dropping funnel connected to a nitrogen inlet. The flask is charged with 450 g. (11.5 moles) of sodium amide (Note 3) and 750 ml. of anhydrous tetrahydrofuran (Note 4), and the dropping funnel with a solution of 283.5 g. (3.831 moles) of anhydrous *tert*-butyl alcohol (Note 5) in 300 ml. of anhydrous tetrahydrofuran While the sodium amide suspension is stirred vigorously under a nitrogen atmosphere, the solution of *tert*-butyl

alcohol is added dropwise at room temperature over 3 hours. The stirred mixture is heated to 45°, with an oil bath, for 2 hours, at which point it may be necessary to add additional tetrahydrofuran (Note 6). The outlet of the condenser is connected with an adapter to a 250-ml. gas washing bottle containing 100 ml. of 5 *N* sulfuric acid, to eliminate evolved ammonia (Note 7). A silica gel drying tube (15 cm. long) joins the gas washing bottle to a 300-ml. cold trap protected from the atmosphere with a calcium chloride drying tube and cooled in a methanol–dry-ice bath maintained at −80° (Note 8). A solution of 228 g. (2.52 moles) of 3-chloro-2-methyl-1-propene (Note 9) in 500 ml. of dry tetrahydrofuran is added to the stirred basic mixture, which is then heated to 65° over a period of approximately 8 hours; a light nitrogen stream is used to carry the methylenecyclopropane into the cold trap. After the addition is complete, the reaction mixture is stirred and heated to 65° for 3 more hours (Note 10). The trap flask contains 58 g. (43%) of methylenecyclopropane (Note 11).

B. *Oxaspiropentane*. A 3-l., three-necked, round-bottomed flask equipped with a sealed stirrer, a thermometer, and an efficient condenser cooled by methanol–dry ice (Note 12) is charged with 450 ml. of dichloromethane and 200 g. (1.09 moles) of 4-nitroperbenzoic acid (Note 13). The mixture is stirred and cooled to −50° by immersion of the flask in a methanol–dry-ice bath before 58 g. (1.1 moles) of methylenecyclopropane is distilled directly into the flask with a gas-inlet tube reaching to the bottom of the flask. The cooling bath is removed so that the temperature gradually rises; at about 0° the exothermic reaction starts. The temperature is maintained below 20° by occasional immersion of the flask in an ice–water bath; the methylenecyclopropane is allowed to reflux slowly (Note 14). After refluxing stops, the mixture is stirred overnight at room temperature. The 4-nitrobenzoic acid is removed by filtration and washed twice with 100-ml. portions of dichloromethane. The combined organic layers, which still contain about 10% of the total amount of 4-nitrobenzoic acid, are distilled at room temperature under reduced pressure (15 mm.) to eliminate the acid completely (Note 15). The distillate is concentrated to *ca*. 200 ml. of dichloromethane by distillation through a 15-cm., helix-packed, vacuum-insulated column, at a maximum oil bath temperature of 60° (Note 16).

C. *Cyclobutanone* (Note 16). The resulting solution of oxaspiropentane (35%) in 200 ml. dichloromethane is added dropwise at room temperature to a magnetically stirred solution containing 5–10 mg. of lithium iodide in 50 ml. of dichloromethane (Note 17), (Note 18), at such a rate as to maintain gentle reflux of the solvent. After the addition, when the reaction mixture returns to room temperature, the transformation into cyclobutanone is complete. The dichloromethane solution is washed with 20 ml. of saturated aqueous sodium thiosulfate and 20 ml. of water, dried over magnesium sulfate, and concentrated by distillation of the solvent through a 15-cm., helix-packed, vacuum-insulated column. The residual liquid consists of cyclobutanone (95%) and 3-buten-2-one and 2-methylpropenal (5%).[2] A final distillation at 760 mm. through a 50-cm., stainless-steel spinning band column yields 41 g. (64% from methylenecyclopropane) of pure cyclobutanone, b.p. 100–101° (Note 19), (Note 20).

2. Notes

1. The procedure described for the synthesis of methylenecyclopropane is patterned after the method reported by Caubere and Coudert.[3] Methylenecyclopropane is also available from the stepwise method described by Köster and co-workers.[4]
2. The checkers used a stirrer for vacuum work (Teflon bearing, Fisher Scientific Company). The submitters used a mercury-sealed stirrer.
3. The submitters used sodium amide (obtained from Fluka A G as small lumps under kerosene) which was washed with anhydrous tetrahydrofuran and ground with a mill. The checkers used freshly opened and recently purchased cans of sodium amide powder (Fisher Scientific Company); older reagent gave unsatisfactory results.
4. Tetrahydrofuran is purified by distillation from lithium aluminium hydride after 48 hours of refluxing over potassium hydroxide (see *Org. Synth.*, **Coll. Vol. 5**, 976 (1973).
5. *tert*-Butyl alcohol was refluxed overnight over calcium hydride and distilled.
6. The checkers obtained a heavy slurry at this stage which became heavier during addition of 3-chloro-2-methyl-1-propene. They found it necessary to dilute with more tetrahydrofuran (about 450 ml. for the scale given in the procedure) before the allyl chloride was added.
7. It is advisable to insert a safety bottle to avoid any run-back of sulfuric acid into the reaction flask. The gas washing bottle must be cooled by immersion in a large water bath (15°); the sulfuric acid

solution is replaced by a fresh 5 *N* solution when neutralized by evolved ammonia (checked by phenolphthalein).
8. Methylenecyclopropane, b.p. 11° (760 mm.), is volatile at room temperature; all adapter fittings must be carefully checked. The checkers recommend the use of two cold traps in series.
9. 3-Chloro-2-methyl-1-propene (methallyl chloride) is available from Fluka A G and Eastman Organic Chemicals. The chloride, b.p. 72° (760 mm.), was distilled before use.
10. In the checkers' hands, at least 24 hours was needed to produce the bulk of methylenecyclopropane; small amounts of the product condenser during an additional 24-hour period.
11. The yield is determined by weighing the cold trap before and after distillation of methylenecyclopropane. Any small amounts of tetrahydrofuran carried into the methylenecyclopropane trap are eliminated in a subsequent distillation. By ^{1}H NMR analysis the checkers found that no tetrahydrofuran reached the cold traps; the spectrum (CD_2Cl_2) shows a triplet at δ 1.00 and a quintuplet at δ 5.35 in the ratio 4:2.
12. *Caution! The yield isolated from this reaction depends on the efficiency of this condenser; the epoxidation is exothermic and methylenecyclopropane is volatile.*
13. The 4-nitroperoxybenzoic acid (technical, 77–85%) may be obtained from the Aldrich Chemical Co., Inc., or Fluka A. G. (or from its U.S. representative, Tridom Chemical Inc.), or may be prepared from 4-nitrobenzoic acid.[5] The oxidation of methylenecyclopropane to oxaspiropentane has been reported to proceed in the same manner, in 48% yield, with the less expensive reagent *m*-chloroperbenzoic acid (MCPBA).[2]
14. Cooling below 0° stops the reaction.
15. A short-path distillation apparatus is used, the distillate (oxaspiropentane plus dichloromethane) being trapped in a receiver placed in a methanol–dry-ice bath cooled to –80°. The checkers found it useful to drive out last traces of product by adding several milliliters of dichloromethane to the residual thick paste and distilling. The ^{1}H NMR spectrum (CD_2Cl_2) shows an octet at δ 0.85 and a singlet at δ 3.00 in the ratio 4:2.
16. If the oil bath temperature reaches 80°, the residue consists of cyclobutanone (75%) and oxaspiropentane (25%). Distillation of this residue at 97–103° (760 mm.) yields cyclobutanone and oxaspiropentane; however, as reported[2] oxaspiropentane can be distilled at low temperature (36°) in vacuum (20 mm) without rearrangement.
17. *Caution! Addition of lithium iodide (catalytic amount) to a dichloromethane solution containing more than 30% oxaspiropentane leads to a very vigorous reaction.*
18. Dichloromethane from the previous distillation is used.
19. The purity of cyclobutanone was checked by GC on a 3.6-m. column containing 20% silicone SE-30 on chromosorb W at 65°. The IR spectrum (neat) shows carbonyl absorption at 1779 cm.$^{-1}$; the ^{1}H NMR spectrum (CCl_4) shows a multiplet at δ 2.00 and a triplet at δ 3.05 in the ratio 1:2.
20. The checkers obtained yields of 61–64% on smaller-scale runs (~ 10 g. of cyclobutanone).

3. Discussion

This method for the preparation of cyclobutanone *via* oxaspiropentane is an adaptation of that reported by Salaün and Conia.[6] Although cyclobutanone has been known now for over 75 years,[7] renewed interest in the potential of this small ring compound has led to several recently reported syntheses. The earlier syntheses of this compound consist of the reaction of the hazardous diazomethane with ketene[8] and the oxidative degradation[9] or the ozonization of methylenecyclobutane.[10] Recent syntheses involve the dithiane method of Corey and Seebach,[11,12] the solvolytic cyclization of 3-butyn-1-yl trifluoromethanesulfonate,[13] the ring enlargement of protected cyclopropanone cyanohydrin[14] and of 1-(phenylthio)cyclopropanemethanol,[15] and finally, the cyclodialkylation of tosylmethyl isocyanide.[16] These methods are most or less laborious, time-consuming, and based on expensive starting materials. Most of them present the disadvantage of producing an aqueous solution of the highly water-miscible and volatile cyclobutanone (b.p. 100°C).

The availability of methylenecyclopropane, its facile oxidation to oxaspiropentane, and the lithium

iodide-induced ring enlargement to cyclobutanone described here remains the best laboratory scale preparation of cyclobutanone. Furthermore, this rearrangement of oxaspiropentanes appears to be general for the preparation of substituted cyclobutanones.[2,17]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 7, 114

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

m-chloroperbenzoic acid (MCPBA)

Oxaspiropentanes

4-nitroperbenzoic acid

sulfuric acid (7664-93-9)

ammonia (7664-41-7)

sodium thiosulfate (7772-98-7)

nitrogen (7727-37-9)

allyl chloride (107-05-1)

dichloromethane (75-09-2)

phenolphthalein (77-09-8)

magnesium sulfate (7487-88-9)

Diazomethane (334-88-3)

sodium amide (7782-92-5)

Tetrahydrofuran (109-99-9)

lithium aluminium hydride (16853-85-3)

3-buten-2-one (78-94-4)

2-methylpropenal (78-85-3)

tert-butyl alcohol (75-65-0)

calcium hydride (7789-78-8)

methallyl chloride,
3-chloro-2-methyl-1-propene (563-47-3)

lithium iodide (10377-51-2)

Cyclobutanone (1191-95-3)

methylenecyclobutane (1120-56-5)

Methylenecyclopropane (6142-73-0)

Oxaspiropentane (157-41-5)

4-nitrobenzoic acid (62-23-7)

4-nitroperoxybenzoic acid (943-39-5)

3-Butyn-1-yl trifluoromethanesulfonate (32264-79-2)

cyclopropanone cyanohydrin

1-(phenylthio)cyclopropanemethanol

tosylmethyl isocyanide (36635-61-7)