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.

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.*
**MERCURY(II) OXIDE-MODIFIED HUNSDIECKER REACTION: 1-BROMO-3-CHLOROCYCLOBUTANE**

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1. **Procedure**

   In a 1-l., three-necked, round-bottomed flask, wrapped with aluminum foil to exclude light, and equipped with a mechanical stirrer, a reflux condenser, and an addition funnel, is suspended 37 g. (0.17 mole) of red mercury(II) oxide (Note 1) in 330 ml. of carbon tetrachloride (Note 2). To the flask is added 30.0 g. (0.227 mole) of 3-chlorocyclobutanecarboxylic acid (Note 3). With stirring, the mixture is heated to reflux before a solution of 40 g. (0.25 mole) of bromine in 180 ml. of carbon tetrachloride is added dropwise, but as fast as possible (4–7 minutes) without loss of bromine from the condenser (Note 4). After a short induction period, carbon dioxide is evolved at a rate of 150–200 bubbles per minute (Note 5). The solution is allowed to reflux for 25–30 minutes, until the rate of carbon dioxide evolution slows to about 5 bubbles per minute (Note 5). The mixture is cooled in an ice bath, and the precipitate is removed by filtration. The residue is washed with carbon tetrachloride, and the filtrates are combined. The solvent is removed by distillation using a modified Claisen distillation apparatus with a 6-cm. Vigreux column; vacuum distillation of the residual oil gives 13–17 g. (35–46%) of 1-bromo-3-chlorocyclobutane, b.p. 67–72° (45 mm.), \(n_2^\circ = 1.5065\) (Note 7) and (Note 8).

2. **Notes**

   1. Purified product is available from J. T. Baker Chemical Company.
   2. Reagent grade carbon tetrachloride was used.
   3. 3-Chlorocyclobutanecarboxylic acid was prepared as described in *Org. Synth., Coll. Vol. 6*, 271 (1988).
   4. The heating bath should be maintained at about 120° to ensure that the solution continues to reflux while the bromine solution is added.
   5. The gas evolution can be monitored by conducting the gas through rubber tubing from the condenser into a small amount of water where the bubbling can be observed. A small amount of bromine is lost because of entrainment by the gas.
   6. There is no increase in yield on heating the mixture under reflux for 3 hours.
   7. The submitters reported a 48–52% yield (18–20 g.) using the indicated scale, and a 35% yield when the reaction was carried out using twice the scale. The checkers obtained the product in 28–29% yield when the reaction was conducted on a scale 10 times that indicated.
   8. The product was analyzed by GC at 130° on a Beckman GC-2 chromatograph equipped with a 180 cm. × 6 mm. column (Beckman 17449) containing 42/60 Johns-Manville C-22 firebrick coated with Dow-Corning 550 silicone oil. The retention times are 12 and 14 minutes for the *trans* and *cis* compounds, respectively.

3. **Discussion**

   This procedure, a modified Hunsdiecker reaction based upon the method of Cristol and Firth,\(^2\) results in moderate to high yields of bromides and iodides from aliphatic\(^3\) and alicyclic carboxylic acids.\(^4,5,6\) Carbon tetrachloride is most frequently used as the solvent, but others can be employed.\(^3,6\) Attempts to prepare chlorides by the method have proved to be unsuccessful.\(^7\)

The main advantage of this procedure over that of the standard method\(^8\) is one of convenience. For
example, the present method is a one-step reaction while the usual method is a two-step sequence involving an intermediate silver salt. In addition, the presence of water produced in the reaction apparently does not reduce the yield in the present method while water markedly reduces the yield in that involving the silver intermediate.

Some variations of the method have been used to prepare cyclopropyl and cyclobutyl halides. Simultaneous addition of bromine and 3-bromocyclobutanecarboxylic acid to the suspension of mercury (II) oxide gives 1,3-dibromocyclobutane in good yield. Similarly, cyclopropanecarboxylic acid gives bromocyclopropane, and 3-(bromomethyl)cyclobutanecarboxylic acid gives 1-bromo-3-(bromomethyl) cyclobutane. In the latter reaction, it was found desirable to remove the water from the reaction as it is formed in order to obtain high yields. Another variation is the addition of a mixture of the acid and mercury (II) oxide to excess bromine in bromotrichloromethane.

The conversion of 1-bromo-3-chlorocyclobutane to bicyclo[1.1.0]butane is described in Organic Syntheses.

This preparation is referenced from:


References and Notes

1. Department of Chemistry, Western Washington University, Bellingham, Washington 98225.

Appendix

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

- bromine (7726-95-6)
- carbon tetrachloride (56-23-5)
- carbon dioxide (124-38-9)
- mercury(II) oxide, mercury (II) oxide (21908-53-2)
- Cyclopropanecarboxylic acid (1759-53-1)
Bromocyclopropane (4333-56-6)
1-Bromo-3-chlorocyclobutane (4935-03-9)
bromotrichloromethane (75-62-7)
Bicyclo[1.1.0]butane (157-33-5)
1-bromo-3-(bromomethyl)cyclobutane
3-Chlorocyclobutanecarboxylic acid (35207-71-7)
3-bromocyclobutanecarboxylic acid
1,3-dibromocyclobutane
3-(bromomethyl)cyclobutanecarboxylic acid