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.

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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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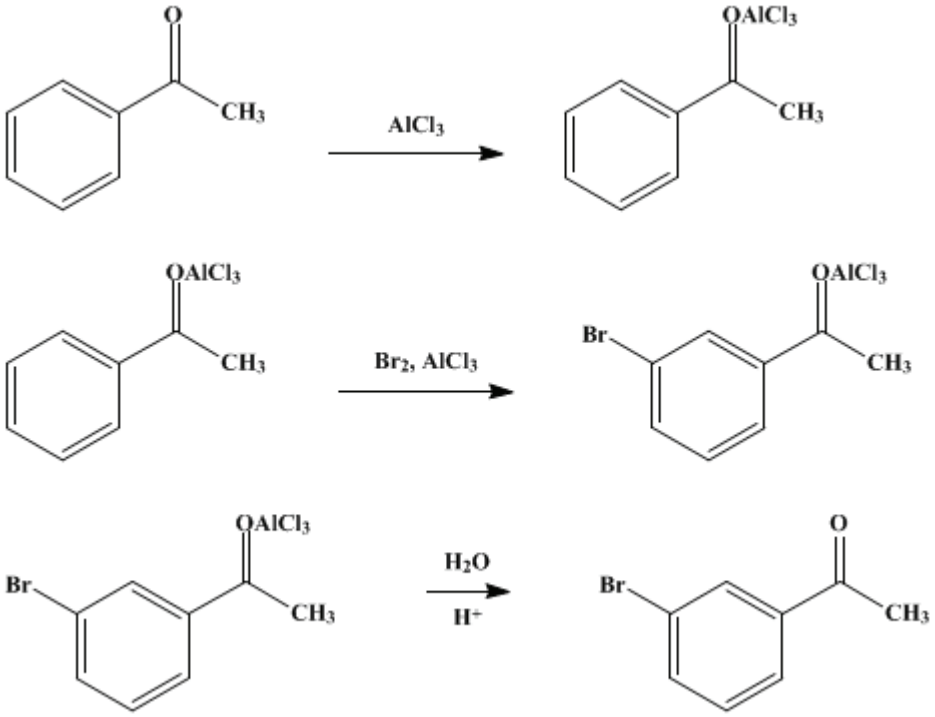
# 3-BROMOACETOPHENONE

## [Acetophenone, 3-bromo-]

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## 1. Procedure

The apparatus consists of a 1-l. three-necked flask equipped with a condenser, a dropping funnel, and a stirrer terminating in a stiff, crescent-shaped Teflon polytetrafluoroethylene paddle. The stirrer motor must have good torque (Note 1). The assembled apparatus, which is protected from moisture by means of drying tubes in the condenser and funnel, is preferably predried. About 216–224 g. (1.62–1.68 moles) of powdered anhydrous aluminum chloride is added to the apparatus with as little exposure to the moisture of the air as possible (Note 2). While the free-flowing catalyst is stirred (Note 3), 81 g. (0.67 mole) of acetophenone is added from the dropping funnel in a slow stream over a period of 20–30 minutes. Considerable heat is evolved, and, if the drops of ketone are not dispersed, darkening or charring occurs. When about one-third of the acetophenone has been added, the mixture becomes a viscous ball-like mass that is difficult to stir. Turning of the stirrer by hand or more rapid addition of ketone is necessary at this point. The addition of ketone, however, should not be so rapid as to produce a temperature above 180°. Near the end of the addition, the mass becomes molten and can be stirred easily without being either heated or cooled. The molten mass, in which the acetophenone is complexed with aluminum chloride, ranges in color from tan to brown.

Bromine (128 g., 0.80 mole) is added dropwise to the well-stirred mixture over a period of 40 minutes (Note 4). After all the bromine has been added, the molten mixture is stirred at 80–85° on a steam bath for 1 hour, or until it solidifies if that happens first (Note 5). The complex is added in portions to a well-stirred mixture of 1.3 l. of cracked ice and 100 ml. of concentrated hydrochloric acid in a 2-l. beaker (Note 6). Part of the cold aqueous layer is added to the reaction flask to decompose whatever part of the reaction mixture remains there, and the resulting mixture is added to the beaker. The dark oil that settles out is extracted from the mixture with four 150-ml. portions of ether. The extracts are combined, washed consecutively with 100 ml. of water and 100 ml. of 5% aqueous sodium

bicarbonate solution, dried with anhydrous sodium sulfate, and transferred to a short-necked distillation flask. The ether is removed by distillation at atmospheric pressure, and crude 3-bromoacetophenone is stripped from a few grams of heavy dark residue by distillation at reduced pressure. The colorless distillate is carefully fractionated in a column 20 cm. long and 1.5 cm. in diameter that is filled with Carborundum or Heli-Pak filling. The combined middle fractions of constant refractive index are taken as 3-bromoacetophenone; weight, 94–100 g. (70–75%); b.p. 75–76°/0.5 mm.; $n_D^{25}$ 1.5738–1.5742; m.p. 7–8° (Note 7) and (Note 8).

## 2. Notes

1. Among satisfactory motors are the Sargent Cone Drive and the Waco.
2. Exposure of the aluminum chloride to air is conveniently avoided by introducing the entire contents of two 4-ounce bottles of anhydrous resublimed aluminum chloride of the Baker and Adamson Company directly into the reaction flask.
3. If the paddle width is so small as to leave isolated, unagitated portions of aluminum chloride, it should be moved near the surface to disperse the ketone rapidly. If the ketone is not dispersed, condensation to dypnone occurs. Tars found in the stripping process are believed to originate from improper addition of the ketone to the aluminum chloride.
4. The rate of addition is regulated by the rate of evolution of hydrogen bromide. The yield of product is essentially the same whether the reaction mixture is held at 80–85° or at room temperature.
5. If the reaction mixture does not solidify during the heating, it is well to work it up at once while it can still be poured from the flask. Otherwise the work-up can be postponed to the next day. If the reaction mixture is too difficult to remove from the flask, the acid-ice slurry can be added *all at once* to the reaction flask immersed in ice. The vigorous surface decomposition is thus partly quenched. However, the cake is seldom difficult to remove unless polyhalogenation has occurred.
6. The acid prevents the formation of insoluble aluminum salts that make separation of ether-water layers difficult. It is helpful in this regard to stir the mixture of water, ketone, and acid for an hour or so before extracting the ketone with ether.
7. The present procedure has been used by the submitters to prepare the following 3-bromoacetophenones and benzaldehydes in the indicated yields:[2] 3-bromopropiophenone, m.p. 40–41°, 60%; 3-bromo-4-methylacetophenone, m.p. 42–43°, 56%; 3,4-dibromoacetophenone, m.p. 89–90°, 55%; 3-bromo-4-*tert*-butylacetophenone, b.p. 92°/0.1 mm., 30%; 3,5-dibromo-4-methylacetophenone, m.p. 102–103°, 57%; 3-bromobenzaldehyde, b.p. 105–106°/2 mm., 59%; 3-bromo-4-tolualdehyde, m.p. 48–49°, 44%.
8. The same procedure can be used to prepare 3-chloroacetophenones and benzaldehydes. The apparatus is modified by replacing the dropping funnel with a gas-inlet tube that permits chlorine to be introduced under the surface of the molten complex of acetophenone and aluminum chloride. For a run with 81 g. (0.67 mole) of acetophenone, 31 ml. (48 g., 0.67 mole) of liquid chlorine is condensed in a trap cooled with solid carbon dioxide and acetone. The gas is passed consecutively through a safety trap, a bubble counter containing concentrated sulfuric acid, and the inlet tube into the stirred complex. The rate of addition is controlled by gradually lowering the cooling bath surrounding the liquid chlorine trap. The internal temperature of the reaction mixture rises just above room temperature and the color of the complex changes from light brown to deep red-brown. The addition chlorine is complete in 10–14 hours; with a faster rate of addition, some chlorine escapes. Stirring is continued for another hour, and the reaction mixture is worked up. The submitters have prepared the following in this way:[2] 3-chloroacetophenone, b.p. 61–63°/0.5 mm., 54%; 3-chlorobenzaldehyde, b.p. 93–96°/15 mm., 43%; 2,3,5,6-tetrachloro-4-methylacetophenone, m.p. 98.5–99.5°, 67%.

## 3. Discussion

Nuclear halogenation of acetophenone depends on formation of the aluminum chloride complex. If less than one equivalent of aluminum chloride is used, side-chain halogenation occurs.[3] 3-Bromoacetophenone has been prepared from 3-aminoacetophenone by the Sandmeyer reaction.[4,5] The synthesis described here has been taken from work of the submitters,[2] who have used it to prepare many 3-bromo- and 3-chloroacetophenones and benzaldehydes, as well as more highly halogenated ones (Note 7) and (Note 8).

## References and Notes


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

3-Bromoacetophenone

Acetophenone, 3-bromo-

3-bromoacetophenones and benzaldehydes

3-bromo-4-methylacetophenone

3,4-dibromoacetophenone

3-bromo-4-tert-butylacetophenone

3,5-dibromo-4-methylacetophenone

3-chloroacetophenones and benzaldehydes

3-chloroacetophenone

2,3,5,6-tetrachloro-4-methylacetophenone

3-aminoacetophenone

3-bromo- and 3-chloroacetophenones and benzaldehydes

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

ether (60-29-7)

sodium bicarbonate (144-55-8)

hydrogen bromide (10035-10-6)

bromine (7726-95-6)

sodium sulfate (7757-82-6)

carbon dioxide (124-38-9)

acetone (67-64-1)

Acetophenone (98-86-2)

aluminum chloride (3495-54-3)

chlorine (7782-50-5)

3-bromopropiophenone

3-bromobenzaldehyde (3132-99-8)

3-bromo-4-tolualdehyde

3-chlorobenzaldehyde (587-04-2)