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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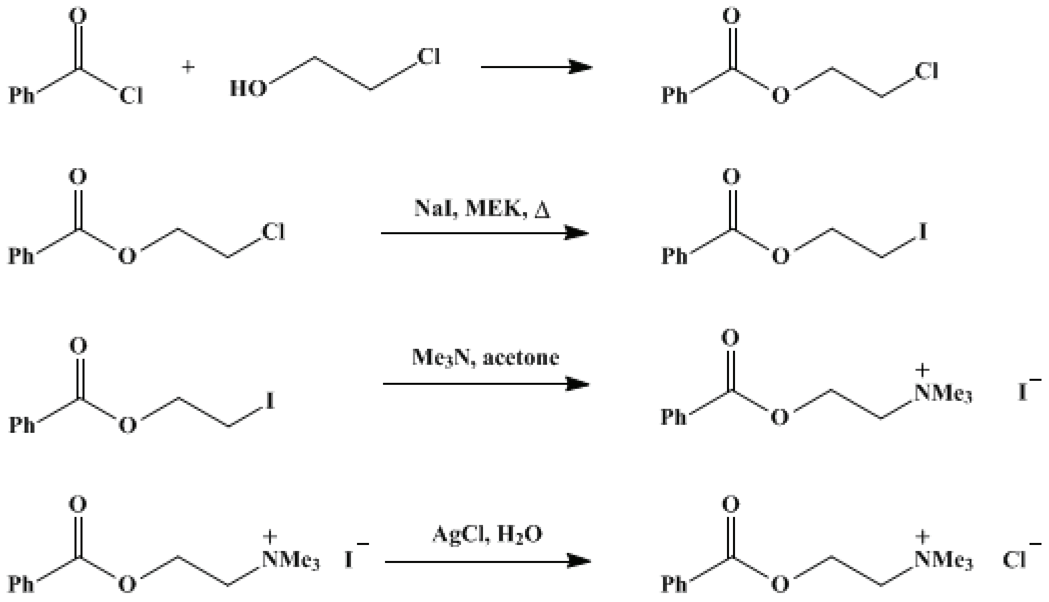
BENZOYLCHOLINE IODIDE AND CHLORIDE

[Choline, chloride benzoate, and Choline, iodide benzoate]



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1. Procedure

A. *2-Chloroethyl benzoate.* In a 500-ml. round-bottomed flask attached to a 100-cm. air condenser by a ground-glass joint are placed 80.5g. (66ml., 1 mole) of redistilled ethylene chlorohydrin (b.p. 128–129°) and 140.5 g. (115.5 ml., 1 mole) of benzoyl chloride. The apparatus is set up in a good hood, and the mixture is warmed gently with a low flame until the reaction starts (Note 1). The source of heat is withdrawn until the reaction moderates and is then again applied for an additional 30 minutes, during which time the temperature rises to about 200–215°. The flask is fitted with a short column (about 20 cm.) and arranged for distillation. After volatile material has been removed by evacuation with a water pump at a bath temperature of 100–110° the residual liquid is fractionated under reduced pressure. The yield of 2-chloroethyl benzoate boiling at 101–104°/2 mm. is 165–168 g. (89–91%), n_D^{19} 1.5298.

B. *2-Iodoethyl benzoate.* A mixture of 170 g. of anhydrous sodium iodide and 1.2 l. of methyl ethyl ketone (Note 2) is heated on a steam bath for 1 hour with occasional shaking in a 3-l. round-bottomed flask fitted with a water-cooled reflux condenser. 2-Chloroethyl benzoate (162 g., 0.88 mole) is added to the mixture, and heating is maintained for an additional 22–24 hours with occasional shaking. The mixture is cooled to room temperature and filtered through a 15-cm. Büchner funnel with suction. The inorganic salts on the filter are washed with 200 ml. of methyl ethyl ketone, and the filtrate is concentrated by distillation of about 1 l. of the solvent. The residue is poured into 1 l. of water contained in a separatory funnel, which is shaken, and the lower layer is withdrawn. The latter is washed successively with 200 ml. of 10% sodium bisulfite solution, 200 ml. of 5% sodium bicarbonate solution, and 100 ml. of water. It is dried with anhydrous magnesium sulfate (5–7 g.) and fractionated under reduced pressure. The yield of material boiling at 133–136°/2.5 mm., n_D^{15} 1.5820, is 190–196 g. (78–81%).

C. *Benzoylcholine iodide.* A solution of 194 g. (0.70 mole) of 2-iodoethyl benzoate in 200 ml. of dry acetone is treated with 270 ml. of a 19.5% solution of trimethylamine in acetone (Note 3) in a 1-l. Pyrex reagent bottle which is closed with a tightly fitting rubber stopper wired in place. The solution is allowed to stand at room temperature for 24 hours (Note 4), and at the end of this time the quaternary salt is separated by filtration with suction, washed with 200 ml. of dry acetone, and air-dried (Note 5). The weight of the quaternary iodide melting with decomposition at 247° is 200–210 g. (85–90%) (Note 6).

D. *Benzoylcholine chloride.* Silver chloride is prepared by dissolving 160 g. (0.94 mole) of silver nitrate in 500 ml. of boiling distilled water and adding 120 ml. of analytical reagent hydrochloric acid (sp. gr. 1.18) from a dropping funnel in a period of 15 minutes, with continuous stirring. The silver chloride is washed by decantation with three 300-ml. portions of boiling distilled water. The moist silver chloride is suspended in 750 ml. of water warmed to 50–60° in a 2-l. beaker, and 210 g. (0.63 mole) of benzoylcholine iodide is added in a period of 1 hour, with good mechanical stirring. After the addition is completed, stirring is continued for an additional 30 minutes without the application of heat. The mixture is cooled and filtered with suction. The silver salts on the filter are washed with 200 ml. of hot water (Note 7), and the combined filtrates are evaporated to dryness under reduced pressure (water pump). The residue is dried by twice distilling to dryness with 250 ml. of absolute ethanol and then once with 250 ml. of dry acetone, the last of the acetone being removed under reduced pressure. The product is recrystallized by dissolving it in 240 ml. of isopropyl alcohol (Note 8) and allowing the solution to cool in a refrigerator. It is filtered and dried, first at 100° and then in a vacuum desiccator over silica gel. The yield of pure product, m.p. 207° (dec.), is 125–132 g. (82–87%) (Note 9).

2. Notes

1. Usually the reaction starts at a temperature of 55° to 60° as evidenced by liberation of hydrogen chloride. If the reaction becomes too vigorous it may be moderated by applying a wet towel to the flask.
2. A purified grade of methyl ethyl ketone should be used. The technical material may be purified by allowing it to stand over solid anhydrous calcium chloride for 24 hours, decanting from the syrupy layer and solid through a filter, and then distilling; b.p. 79–80°.
3. The trimethylamine may be generated by the action of alkali on trimethylamine hydrochloride and dissolved in acetone.[2] The submitter prepared trimethylamine by the method of Sommelet and Ferrand[3] and obtained a 65% yield by the interaction of ammonia, formaldehyde, and formic acid. The checkers found that a commercial 25% solution of trimethylamine in methanol (210 ml.) gave the same yields as the acetone solution.
4. Increasing the reaction period to 48 hours gives an additional 5 to 7 g. of product.
5. If this preparation is carried out during periods of high humidity it is best to place the product in a vacuum desiccator, which is evacuated several times in order to remove the solvent. Anhydrous calcium chloride may be placed in the bottom of the desiccator.
6. This product is quite pure as shown by titration of iodide ion.
7. The silver residues are saved for the recovery of silver[4] and iodine.
8. The submitter states that the compound may be recrystallized by boiling with acetone under an upright condenser and adding ethanol cautiously down the condenser until the solid just dissolves. The substance is appreciably soluble in the cold solvent mixture. It is necessary to distil the mother liquor and recrystallize the residue from acetone-ethanol, for otherwise a considerable loss of product will occur. The checkers used isopropyl alcohol for crystallization.
9. Benzoylcholine chloride prepared by this method is pure as shown by titration of ionic chlorine. It is somewhat hygroscopic, though much less so than choline chloride. It is not appreciably hydrolyzed by boiling with water for 1 hour, although more prolonged heating leads to the formation of benzoic acid. Benzoylcholine chloride can be characterized as the picrate, m.p. 177°, formed by treating a strong aqueous solution with an appropriate amount of 0.5*N* calcium picrate and crystallizing the product from methyl ethyl ketone.

3. Discussion

2-Chloroethyl benzoate has been prepared from benzoyl chloride and ethylene chlorohydrin;[5,6,7] from benzoic acid, ethylene glycol, and hydrogen chloride[8] at 100°; from ethylene oxide and benzoyl chloride;[9] from benzoyl chloride and dioxane in the presence of titanium tetrachloride;[10] from benzoic acid, ethylene, and chlorine in the presence of various catalysts.[11] It has also been obtained by hydrolysis of 2-chloroethyl benzimidate;[12] by the action of bromomagnesium benzoate on 2-chloroethyl *p*-toluene-sulfonate;[13] and by the action of sodium benzoate on *bis*-(2-chloroethyl) sulfate.[14]

2-Iodoethyl benzoate has been obtained by the action of alcoholic sodium iodide on 2-chloroethyl benzoate.[5]

Benzoylcholine chloride has been prepared by heating choline chloride with benzoyl chloride[15] and by the action of trimethylamine on 2-chloroethyl benzoate.[16]

References and Notes

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

BENZOYLCHOLINE IODIDE AND CHLORIDE

Choline, chloride benzoate

Choline, iodide benzoate

ethanol (64-17-5)

calcium chloride (10043-52-4)

hydrogen chloride,
hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

methanol (67-56-1)

formaldehyde (50-00-0)

sodium bicarbonate (144-55-8)

silver chloride (7783-90-6)

silver nitrate (7761-88-8)

formic acid (64-18-6)

Benzoic acid (65-85-0)

sodium bisulfite (7631-90-5)

iodine (7553-56-2)

acetone (67-64-1)

benzoyl chloride (98-88-4)

chlorine (7782-50-5)

isopropyl alcohol (67-63-0)

sodium benzoate (532-32-1)

Ethylene oxide (75-21-8)

ethylene glycol (107-21-1)

ethylene (9002-88-4)

sodium iodide (7681-82-5)

ethylene chlorohydrin (107-07-3)

Trimethylamine (75-50-3)

Trimethylamine hydrochloride (593-81-7)

silver (7440-22-4)

magnesium sulfate (7487-88-9)

dioxane (123-91-1)

methyl ethyl ketone (78-93-3)

acetone-ethanol (1071-73-4)

BENZOYLCHOLINE IODIDE (17518-43-3)

choline chloride (67-48-1)

2-Chloroethyl benzoate (939-55-9)

2-iodoethyl benzoate (39252-69-2)

Benzoylcholine chloride,
D. Benzoylcholine chloride (2964-09-2)

calcium picrate

titanium tetrachloride (7550-45-0)

2-chloroethyl benzimidate

bromomagnesium benzoate

2-chloroethyl p-toluene-sulfonate (80-41-1)

bis-(2-chloroethyl) sulfate