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of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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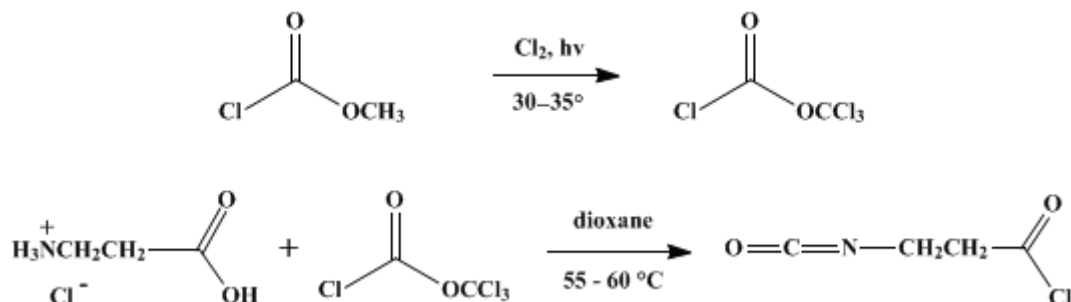
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TRICHLOROMETHYL CHLOROFORMATE AS A PHOSGENE EQUIVALENT: 3-ISOCYANATOPROANOYL CHLORIDE

[Propanoyl chloride, 3-isocyanato-]



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1. Procedure

Caution! Trichloromethyl chloroformate is toxic. These reactions should both be carried out in a well-ventilated hood (Note 1).

A. *Trichloromethyl chloroformate*. A 100-ml., three-necked, round-bottomed Pyrex flask is equipped with a thermometer, a reflux condenser protected at the top with a calcium chloride tube, and a gas-inlet tube with a coarse fritted-glass tip extending almost to the bottom of the flask. In the flask are placed 37.8 g. (0.400 mole) of freshly distilled *methyl chloroformate* (Note 2) and a Teflon-coated magnetic stirring bar. The flask is illuminated with a 100-W., high-pressure, mercury-vapor lamp (Note 3) placed beside it (Note 4) and (Note 5). The *methyl chloroformate* is stirred and irradiated as a slow stream of *chlorine* (Note 6) is passed into the flask through the gas-inlet tube (Note 7). When the temperature reaches 30° due to the exothermic reaction, the flask is immersed in a water bath (Note 8). The *chlorine* is then passed into the solution more rapidly so as to maintain the temperature at 30–35° (Note 9). After *ca.* 6.5–7 hours the colorless solution assumes the pale yellow-green color of *chlorine*, which indicates that the end point of the reaction has been reached (Note 10). Distillation under reduced pressure affords 65–72 g. (82–91%) of *trichloromethyl chloroformate* as a colorless liquid, b.p. 53–55° (53 mm.) (Note 11).

B. *3-Isocyanatopropanoyl chloride*. A 500-ml., two-necked flask is equipped with a thermometer and a reflux condenser protected at its top by a calcium chloride tube. A Teflon-coated magnetic stirring bar, 250 ml. of anhydrous *dioxane* (Note 12), 12.6 g. (0.100 mole) of finely pulverized *3-aminopropanoic acid hydrochloride* (Note 13), and 23.8 g. (14.4 ml., 0.120 mole) of *trichloromethyl chloroformate* (Note 14) are placed in the flask in the order specified. The mixture is stirred and heated at 55–60°. After *ca.* 5 hours, the solid has completely dissolved, leaving a clear solution. The heating is discontinued after a total of 7 hours (Note 15), and the solvent is removed under reduced pressure. The residual oil is distilled rapidly under reduced pressure, yielding 11.2–12.4 g. (84–93%) of distillate at 75–85° (20 mm.) (Note 16). Redistillation affords 10.5–11.8 g. (79–88%) of *3-isocyanatopropanoyl chloride* as a colorless liquid, b.p. 92–94° (25 mm.) (Note 17).

2. Notes

1. Vapors of all of the polychlorinated *methyl chloroformates* are toxic.^{2,3,4} *Trichloromethyl chloroformate* has a phosgene-like odor and is known to decompose to *phosgene* at elevated temperature⁵ or on contact with *iron(III) oxide* or charcoal.⁶

2. [Methyl chloroformate](#) is available from Aldrich Chemical Company, Inc.
3. The checkers used a 200-W., high-pressure, mercury-vapor lamp and the corresponding transformer which are available from the Hanovia Lamp Division, Canrad-Hanovia, Inc., 100 Chestnut St., Newark 5, New Jersey 07105. The lamp was suspended vertically in a cylindrical, double-walled, Pyrex jacket cooled by flowing water. The inside diameter, outside diameter, and length of the cooling jacket were 3, 4, and 22 cm., respectively. The cooling jacket was clamped in place *ca.* 5 cm. from the reaction vessel to allow the cooling bath to be raised into position. The use of the 200-W. lamp did not alter the reaction time.
4. It is advisable to wrap the entire apparatus with aluminum foil to avoid exposure to UV light. The reaction solution can be observed through a small hole in the aluminum foil which is shielded from the direct radiation of the lamp.
5. The irradiation should be started before the flow of [chlorine](#) gas is begun to avoid the risk of explosion.
6. The checkers used [chlorine](#) from a lecture bottle supplied by the Linde Division, Union Carbide Chemical Corp.
7. [Chlorine](#) should be introduced slowly at first to prevent an accumulation of unreacted [chlorine](#) in the solution and avoid the risk of a rapid, exothermic reaction. The accumulation of [chlorine](#) is indicated by the appearance of its characteristic yellow-green color.
8. The checkers used a 15 × 7.5 cm. Pyrex crystallizing dish as a transparent water bath.
9. Once the [chlorine](#) gas flow is properly adjusted, the solution remains colorless and the temperature stays in the 30–35° range without further adjustment until the end point is approached. However, the color and temperature should be observed frequently during the 6.5- to 7-hour reaction time. Although this reaction can be carried out at higher temperatures, the yields are reduced, probably owing to loss of the volatile [methyl chloroformate](#), b.p. 71°, and/or decomposition of the product. For example, the yields of [trichloromethyl chloroformate](#) are *ca.* 75% and 55% when the chlorination is carried out at 50–55° and 85–90°, respectively.
10. The checkers judged that the end point had been reached when the yellow-green color persisted for 2–3 minutes after the [chlorine](#) flow had been stopped. At the first appearance of the yellow-green color, the gas stream was shut off, and the color faded within *ca.* 15 sec. The [chlorine](#) flow was resumed at a slow rate until the end point was reached.
11. The product has the following spectral properties: IR (neat) cm^{-1} : 1815 (C=O), 1054, 968, 912, 814, 764; ^{13}C NMR (CDCl_3), δ (assignment): 108.37 (CCl_3), 143.93 (C=O). [Trichloromethyl chloroformate](#) is stable at room temperature, but decomposes to [phosgene](#) when heated above 300°⁵ or on contact with [iron\(III\) oxide](#) or charcoal.⁶ Decomposition to [carbon tetrachloride](#) and [carbon dioxide](#) occurs on exposure to alumina, [aluminum chloride](#), or [iron\(III\) chloride](#).^{5,6,7,8}
12. The checkers dried and purified [dioxane](#) by distillation from the [sodium](#)–benzophenone ketyl.
13. [3-Aminopropanoic acid](#) (β -alanine) is available from Aldrich Chemical Company, Inc., and from the Nutritional Biochemical Division, ICN Products. The hydrochloride salt is prepared in the following manner. A solution of 89 g. (1.0 mole) of [3-aminopropanoic acid](#) in 200 ml. of water is acidified by addition of 100 ml. (1.20 mole) of concentrated [hydrochloric acid](#) and concentrated to a white solid with a rotary evaporator. The solid is pulverized to a fine powder and dried at 60° under reduced pressure, yielding 113–125 g. (90–100%) of [3-aminopropanoic acid hydrochloride](#).
14. Although the reaction can be carried out with an equimolar amount of [trichloromethyl chloroformate](#), a longer time (15–20 hours) is required to reach completion, and the yield is reduced somewhat. If a 1.5–2.0-fold excess of [trichloromethyl chloroformate](#) is used, the reaction time is decreased to *ca.* 5 hours and the yield is increased to 90–95%.
15. The checkers heated the suspension for a total of 10 hours, 7–8 hours having been required to dissolve the solid completely. The reaction time may depend on the particle size of the hydrochloride salt and the rate of stirring.
16. The submitters advise that the distillation be carried out rapidly to avoid the formation of a tarry residue.
17. The spectral properties of [3-isocyanatopropanoyl chloride](#) are as follows: IR (liquid film) cm^{-1} : 2278 (N=C=O), 1795 (O=C-Cl); ^1H NMR (CDCl_3), δ (multiplicity, coupling constant J in Hz., number of protons, assignment): 3.17 (t, J = 6, 2H, $\text{CH}_2\text{CH}_2\text{N}=\text{C}=\text{O}$), 3.67 (t, J = 6, 2H, $\text{CH}_2\text{CH}_2\text{N}=\text{C}=\text{O}$); ^{13}C NMR (CDCl_3), δ (assignment): 38.3 ($\text{CH}_2\text{CH}_2\text{N}=\text{C}=\text{O}$), 47.6 ($\text{CH}_2\text{CH}_2\text{N}=\text{C}=\text{O}$), 123.0 (N=C=O), 171.6 (O=C-Cl). A small peak at δ 67.1 in the ^{13}C NMR spectrum of the product obtained by the checkers was

attributed to a small amount of dioxane.

3. Discussion

The chlorination of methyl chloroformate in sunlight was first reported by Hentschel, but without a detailed description of either the procedure or the results.⁵ The first step of the present procedure for the preparation of trichloromethyl chloroformate utilizes a UV light source and affords a simple, reproducible way to obtain this reagent. Although trichloromethyl chloroformate may also be synthesized by photochemical chlorination of methyl formate,^{9,10,11} the volatility of methyl formate causes losses during the reaction and increases the hazard of forming an explosive mixture of its vapor and chlorine gas. The preparation of trichloromethyl chloroformate by chlorination of methyl chloroformate in the dark with diacetyl peroxide as initiator has been reported;¹² however, the procedure consists of several steps, and the overall yield is rather low.

Trichloromethyl chloroformate is synthetically useful as a substitute for phosgene, which, owing to its high volatility and toxicity, presents a severe hazard in the laboratory. Although trichloromethyl chloroformate is toxic, it is a dense and less volatile liquid (b.p. 128°, d_{4}^{25} 1.65), having a vapor pressure of only 10 mm. at 20°. Consequently it is more easily handled in a safe manner than phosgene.

Trichloromethyl chloroformate has proven effective in the preparation of *N*-carboxy- α -amino acid anhydrides from amino acids,¹³ and various compounds having isocyanate, acid chloride, and chloroformate groups.^{14,15} For example, trichloromethyl chloroformate may be used instead of phosgene in the preparation of 2-*tert*-butoxycarbonyloxyimino-2-phenylacetonitrile.¹⁵ The use of this reagent is illustrated here by the synthesis of 3-isocyanatopropanoyl chloride from 3-aminopropanoic acid hydrochloride.

3-Isocyanatopropanoyl chloride has also been prepared by the reaction of 3-aminopropanoic acid hydrochloride with phosgene;¹⁶ however, the yield is only 36%, and hydrogen chloride must be introduced to increase the yield to 92%. The present procedure effects this reaction without additional hydrogen chloride and avoids the hazards of handling phosgene. This procedure has been successful in the synthesis of isocyanato acid chlorides and isocyanato chloroformates from amino acids and amino alcohols, respectively.¹⁴ For example, 6-isocyanatohexanoyl chloride can be prepared in good yield with trichloromethyl chloroformate, although it is obtained in only trace amounts with phosgene unless additional hydrogen chloride is used. Isocyanato acid chlorides such as 3-isocyanatopropanoyl chloride, having two different, highly reactive electrophilic groups, are novel reagents for introducing amino acid residues into organic compounds¹⁴ and polymers.¹⁷

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 199
- Org. Syn. Coll. Vol. 9, 242

References and Notes

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

alumina

benzophenone ketyl

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

carbon tetrachloride (56-23-5)

carbon dioxide (124-38-9)

aluminum chloride (3495-54-3)

chlorine (7782-50-5)

sodium (13966-32-0)

phosgene (75-44-5)

iron(III) chloride (7705-08-0)

methyl formate (107-31-3)

iron(III) oxide (1309-37-1)

β -Alanine,
3-aminopropanoic acid (107-95-9)

dioxane (123-91-1)

methyl chloroformate,
methyl chloroformates (79-22-1)

diacetyl peroxide (110-22-5)

Trichloromethyl chloroformate (503-38-8)

2-tert-Butoxycarbonyloxyimino-2-phenylacetonitrile (58632-95-4)

3-Isocyanatopropanoyl chloride,
Propanoyl chloride, 3-isocyanato- (3729-19-9)

3-aminopropanoic acid hydrochloride

6-isocyanatohexanoyl chloride