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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.*
TRICHLOROMETHYL CHLOROFORMATE AS A PHOSGENE EQUIVALENT: 3-ISOCYANATOPROPAANOYL CHLORIDE

[Propanoyl chloride, 3-isocyanato-]

\[
\begin{align*}
\text{H}_3\text{NCH}_2\text{CH}_2\text{OH} + \text{Cl}_3\text{CCl}_3 & \xrightarrow{\text{dioxane}, 55 - 60^\circ \text{C}} \text{Cl}^+ \text{C} = \text{N} - \text{CH}_2\text{CH}_2\text{OCCl}_3 \\
\text{Cl}_3\text{CCl}_3 & \xrightarrow{\text{Cl}_2, \text{hv}, 30 - 35^\circ} \text{OCCl}_3
\end{align*}
\]

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1. Procedure

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; 13C NMR (CDCl3), δ (assignment): 108.37 (CCl3), 143.93 (C=O). Trichloromethyl chloroformate is stable at room temperature, but decomposes to phosgene when heated above 300° or on contact with iron(III) oxide or charcoal. Decomposition to carbon tetrachloride and carbon dioxide occurs on exposure to alumina, aluminum chloride, or iron(III) chloride.

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 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.

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 (CDCl3), δ (multiplicity, coupling constant J in Hz., number of protons, assignment): 3.17 (t, J = 6, 2H, CH2CH2N=C=O), 3.67 (t, J = 6, 2H, CH2CH2N=C=O); 13C NMR (CDCl3), δ (assignment): 38.3 (CH2CH2N=C=O), 47.6 (CH2CH2N=C=O), 123.0 (N=C=O), 171.6 (O=C-Cl). A small peak at δ 67.1 in the 13C 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. 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, 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; 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$_{15}$ 1.65), having a vapor pressure of only 10 mm. at 20°. Consequently it is more easily handled in a safer manner than phosgene.

Trichloromethyl chloroformate has proven effective in the preparation of N-carboxy-α-amino acid anhydrides from amino acids, and various compounds having isocyanate, acid chloride, and chloroformate groups. For example, trichloromethyl chloroformate may be used instead of phosgene in the preparation of 2-tert-butoxycarbonyloxymino-2-phenylacetonitrile. 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; 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 isocyanate acid chlorides and isocyanato chloroformates from amino acids and amino alcohols, respectively. 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 compounds and polymers.

This preparation is referenced from:


References and Notes

1. Department of Industrial Chemistry, Faculty of Engineering, Seikei University, Musashino-shi, Tokyo, Japan.

**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 (5703-46-8)
- 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