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of Organic Compounds

Working with Hazardous Chemicals

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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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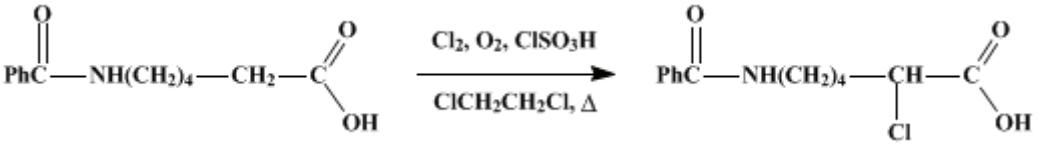
α-CHLORINATION OF CARBOXYLIC ACIDS MEDIATED BY CHLOROSULFONIC ACID: ε-BENZOYLAMINO-α-CHLOROCAPROIC ACID

[Hexanoic acid, 6-benzoylamino-2-chloro-]



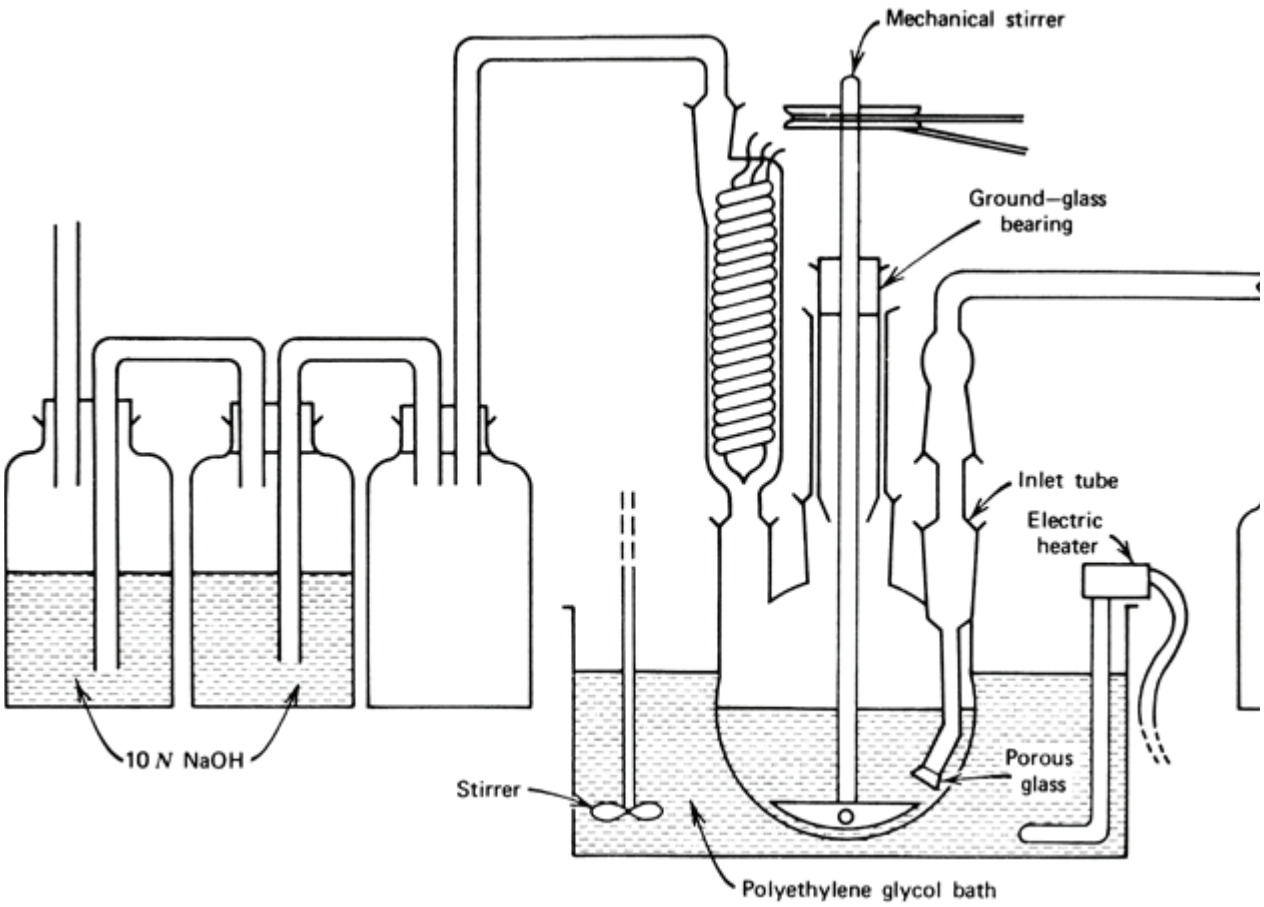
Submitted by Yoshiro Ogata, Toshiyuki Sugimoto, and Morio Inaishi[1].
Checked by Angela Hoppmann and George Büchi.

1. Procedure

Caution! Since chlorine is poisonous, this procedure should be conducted in an efficient hood. Chlorosulfonic acid is a strong skin irritant and should be handled with gloves and a protective face shield.

A 500-ml., four-necked, round-bottomed flask is equipped with an air-tight mechanical stirrer (Note 1), a gas dispersion tube with a porous glass frit, a Dimroth reflux condenser (Note 2), and a thermometer, making sure all joints are greased with silicone grease. The top of the condenser is connected to a series of three traps with polyvinyl chloride tubing (Figure 1). The first trap is empty, and the other two contain aqueous 10 *N* sodium hydroxide. The gas dispersion tube extends to near the bottom of the flask, just above the stirrer blade, and is connected to a gas-mixing chamber having two inlet tubes, one for oxygen and the other for chlorine. The flask is charged with 47.1 g. (0.200 mole) of ε-benzoylaminocaproic acid (Note 3) and 200 ml. of 1,2-dichloroethane. The solution is stirred and heated to 60–70°, before 25.5 g. (0.219 mole) of chlorosulfonic acid (Note 4) is added gradually. A 2:1 (v/v) mixture of gaseous chloride and oxygen (Note 5) is bubbled into the flask for 3 hours while the contents are stirred and heated at reflux. The chlorine-oxygen gas flow is discontinued, and nitrogen is passed through the reaction mixture for 1 hour at 60–70° to remove chlorine remaining in solution. The flask is stoppered, allowed to stand for 1 hour at room temperature, and stored in a refrigerator for 12 hours. The supernatant liquid is removed, and *ca.* 800 ml. of aqueous 1 *N* sodium hydroxide is added to the solid remaining in the flask with ice cooling. Nitrogen is bubbled through the alkaline solution for 30 minutes to expel 1,2-dichloroethane. The solution is decolorized with 5 g. of activated carbon, mixed with *ca.* 400 g. of ice, and acidified to a pH of *ca.* 6 with 6 *N* hydrochloric acid. If available, a few seed crystals of ε-benzoylamino-α-chlorocaproic acid are added to the solution to facilitate crystallization. After 1 hour, more 6 *N* hydrochloric acid (Note 6) is added gradually until the pH is lowered to 1. An hour later the precipitate is filtered and washed thoroughly with 300 ml. of cold water until sulfate ion in the aqueous wash is no longer detectable with a test solution of barium chloride.

Figure 1.



Drying under reduced pressure yields 39.1–43.1 g.. (72–80%) of crude, crystalline ε-benzoylamino-α-chlorocaproic acid, m.p. 138–140°. The product is dissolved in 320 ml. of hot 95% ethanol, 480 ml. of boiling water is added, and the resulting solution is allowed to cool slowly. The crystals are collected, washed with cold water, and dried, yielding 26.1–28.2 g. (48–52%) of pure ε-benzoylamino-α-chlorocaproic acid, m.p. 143–144° (Note 7).

2. Notes

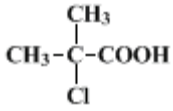
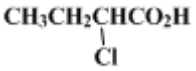
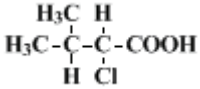
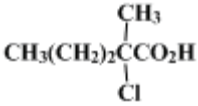
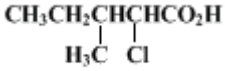
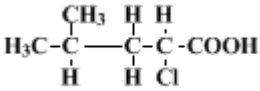
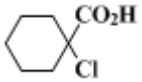
1. Vigorous stirring action is necessary to disperse the heavy, viscous mixture. The use of a magnetic stirrer is not advisable since the mixture may separate into two layers. A mechanical stirrer with ground-glass shaft and bearing lubricated with 1,2-dichloroethane is recommended.

2. A Dimroth condenser has an internal, spiral cooling tube with the inlet and outlet both connected at the top. Spiral condensers of this type are available from Ace Glass Incorporated, Vineland, New Jersey 08360. A Dimroth condenser is recommended for use with refluxing liquids that boil up to 160°.[2] Since the points of sealing are situated above the zone with a high temperature gradient, the risk of cracking from thermal stress is minimized. The α-chlorination of aliphatic acids by this procedure is usually carried out at 110–140° (see Table I). The submitters circulated ice-cold water through the condenser.

TABLE I

α-CHLORO CARBOXYLIC ACIDS PREPARED BY CHLORINATION IN THE PRESENCE OF CHLOROSULFONIC ACID AND OXYGEN[a]

Entry	α-Chloro Acid	Scale (mole)	Temperature (°)	Yield[b] (%)
1		0.45	120	75

				
2		0.45	120	82[c]
3		0.60	140	73
4		0.35	120	81
5		0.18	120	78
6		0.16	120	79[d]
7		0.23	110	73

[a]A 4:1:0.04 molar ratio of carboxylic acid, chlorosulfonic acid, and chloranil was used.
A 2:1 mixture of chlorine and oxygen was passed into the reaction for 3 hours.
[b]The yields were determined by gas chromatographic analysis after esterification of aliquots with sulfuric acid and methanol in 1,2-dichloroethane.
[c]β-Chloro acid was also formed in 1.6% yield.
[d]β-Chloro acid was also formed in 6.4% yield.

3. ε-Benzoylaminocaproic acid was prepared by the reaction of benzoyl chloride with ε-aminocaproic acid, as described in *Org. Synth.*, **Coll. Vol. 2**, 76 (1943).
4. Chlorosulfonic acid was purified by distillation before use, b.p. 86–88° (33 mm.).
5. The flow rates of the two gases are regulated by flow meters inserted in parallel between the gas-mixing chamber and the chlorine and oxygen tanks. Appropriate flow rates for chlorine and oxygen are 80–100 and 40–50 ml. per minute, respectively. The checkers purchased gas flow meters from Arthur H. Thomas Company, Philadelphia, Pennsylvania.
6. If the warm alkaline solution is acidified rapidly with 6 *N* hydrochloric acid, the product is likely to separate as an oil.
7. A melting point of 145–147° has been reported.[3] The submitters performed a high-pressure liquid chromatographic analysis on a 25 × 0.2 cm. column packed with porous, dichlorodimethylsilane-treated silica gel (Yanapak DMS). With 40:60 (v/v) methanol–water as carrier liquid and a flow rate of 80–100 ml. per hour, the product appeared as a single peak. IR (KBr) $cm.^{-1}$: 3360, 3040, 2920, 1700, 1600, 1550, 820, 770, 720, 690; ^1H NMR (dimethyl sulfoxide-d_6), δ (multiplicity, coupling constant J in Hz., number of protons, assignment): 1.2–2.2 (m, 6H, $CH_2CH_2CH_2$), 3.0–3.4 (m, 2H, CH_2N), 4.40 (t, J = 7, 1H, C*H*Cl), 7.2–7.9 (m, 5H, C_6H_5), 8.40 (broad t, J = 6, 1H, N*H*).

3. Discussion

The present procedure, a modification of one reported earlier by the submitters,[4] has been applied to the α-chlorination of a series of aliphatic carboxylic acids (Table I).[5] In these reactions solvent (1,2-dichloroethane) was unnecessary, 0.25 molar equivalents of chlorosulfonic acid was sufficient, and higher temperatures in the range of 110–140° were employed. The α-chloro acids were converted

efficiently to the corresponding methyl esters, for characterization, by reaction with methanol and a catalytic amount of concentrated sulfuric acid in 1,2-dichloroethane at reflux for 10 hours.[6] The methyl esters of the α-chloro acids shown in entries 3–6 have not been previously prepared.

Chlorosulfonic acid is particularly effective at mediating the α-chlorination of carboxylic acids, evidently owing to both its high acidity and its ability to render the reaction mixture more nearly homogeneous than other acidic catalysts. The function of oxygen is to scavenge free radicals, thereby suppressing the free radical chlorination at other positions of the carboxylic acid.[7] The chlorination of isovaleric acid (entry 3) in the absence of oxygen gives an appreciable amount of β-chloro acid. In the presence of oxygen only trace amounts (0–6.4%) of the β-chloro, or other isomers, were formed in the chlorinations shown in the table despite the tertiary hydrogens present in entries 3,5, and 6. This method, which uses chlorosulfonic acid and 1,2-dichloroethane, can be applied to α-bromination[8] and α-iodination[9] of carboxylic acids, where no radical trapper such as molecular oxygen is necessary.

ε-Benzoylamino-α-chlorocaproic acid has been previously prepared by chlorination of ε-benzoylaminocaproic acid with sulfuryl chloride in the presence of iodine.[3] The corresponding bromo analog has been obtained by reaction with bromine and red phosphorous and subsequent hydrolysis.[10,11] ε-Benzoylamino-α-halocaproic acid is an intermediate in the synthesis of *d,l*-lysine dihydrochloride.[3,12]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 8, 119

References and Notes

1. Department of Applied Chemistry, Faculty of Engineering, Nagoya University, Chikusa-ku, Nagoya, Japan.
2. B. J. Hazzard, "Organicum: Practical Handbook of Organic Chemistry," Addison-Wesley, Reading, Massachusetts, 1973, pp. 6–9.
3. A. Galat, *J. Am. Chem. Soc.*, **69**, 86 (1947).
4. Y. Ogata and T. Sugimoto, *Chem. Ind. (London)*, 538 (1977).
5. Y. Ogata, T. Harada, K. Matsuyama, and T. Ikejiri, *J. Org. Chem.*, **40**, 2960 (1975).
6. R. O. Clinton and S. C. Laskowski, *J. Am. Chem. Soc.*, **70**, 3135 (1948).
7. J. C. Little, A. R. Sexton, Y.-L. Tong, and T. E. Zurawic, *J. Am. Chem. Soc.*, **91**, 7098 (1969).
8. Y. Ogata and T. Sugimoto, *J. Org. Chem.*, **43**, 3684 (1978).
9. Y. Ogata and S. Watanabe, *J. Org. Chem.*, **44**, 2768 (1979); *J. Org. Chem.*, **45**, 2831 (1980); *Bull. Chem. Soc. Jpn.*, **53**, 2417 (1980).
10. J. C. Eck and C. S. Marvel, *Org. Synth.*, **Coll. Vol. 2**, 74 (1943).
11. E. E. Howe and E. W. Pietrusza, *J. Am. Chem. Soc.*, **71**, 2581 (1949).
12. J. C. Eck and C. S. Marvel, *Org. Synth.*, **Coll. Vol. 2**, 374 (1943).

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

silica gel

red phosphorous

ethanol (64-17-5)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

methanol (67-56-1)

sodium hydroxide (1310-73-2)

chlorosulfonic acid (7790-94-5)

bromine (7726-95-6)

oxygen (7782-44-7)

1,2-dichloroethane (107-06-2)

nitrogen (7727-37-9)

barium chloride (10361-37-2)

iodine (7553-56-2)

carbon (7782-42-5)

benzoyl chloride (98-88-4)

sulfuryl chloride (7791-25-5)

chlorine (7782-50-5)

ε-AMINOCAPROIC ACID (60-32-2)

ε-Benzoylaminocaproic acid (956-09-2)

isovaleric acid (503-74-2)

Hexanoic acid, 6-benzoylamino-2-chloro-,
ε-Benzoylamino-α-chlorocaproic acid (5107-15-3)

chlorine-oxygen

carboxylic acid, chlorosulfonic

d,l-lysine dihydrochloride