

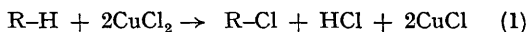
Selective α -Chlorination of Aliphatic Carboxylic Acids by Copper(II) Chloride

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"THE only satisfactory general method for the preparation of α -chloro-acids is that involving chlorination of an alkylmalonic acid, followed by decarboxylation".¹

Chlorination of active-hydrogen compounds by copper(II) chloride in polar media² (eqn. 1) is known for ketones, aldehydes (to give α -chloro-derivatives), and phenols (*o*- and *p*-substitution). Under analogous conditions, simple carboxylic acids and esters appear to be unreactive; to the author's knowledge, a useful synthesis of an α -chloro-acid based on eqn. 1 has not yet been described.³



Formation of CuCl from CuCl₂ and acetic

anhydride was observed forty years ago;⁴ the organic reaction products, however, were not determined.

It has now been found that copper(II) chloride in polar, inert solvents (*e.g.*, sulpholane) is able to convert acid chlorides, anhydrides, and carboxylic acids (containing anhydride or acid chloride as "catalyst") into α -chloro-derivatives with selectivities greater than 95%. Thus, isobutyric anhydride (206 mmole), CuCl₂ (400 mmole), and LiCl (470 mmole) in sulpholane (230 mmole), heated for 30 min. at 135° in a nitrogen atmosphere, gave a product containing 411 meq. of organic acid, including 195 meq. of chloro-derivative. After esterification, the latter was isolated and identified (g.l.c., ¹H n.m.r.) as ethyl α -chloroisobutyrate (b.p. 56°/25 mm).

Analogous results were obtained when isobutyric acid containing 10 mole % of the corresponding anhydride or acid chloride was employed (e.g., 5 hr. at 130°, 98% recovery of acid residues, conversion of $\text{CuCl}_2 > 80\%$).

As a further example, hexanoic acid (202 mmole), hexanoyl chloride (60 mmole), CuCl_2 (500 mmole), and LiCl (560 mmole) in sulpholane (590 mmole), kept at 135° for 2.5 hr., produced 262 mmole of

hydrogen chloride, and yielded a distillate containing 250 meq. of organic acid—including 220 meq. of chlorinated material—from which 2-chlorohexanoic acid¹ was isolated. The use of half the amount of organic substrate in the latter case leads to only a very small amount of dichloro-acid. Apparently, the method described here can be used to prepare pure α -monochloro-acids, regardless of the number of α -hydrogen atoms in the substrate.

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¹ R. H. Horn, R. B. Miller, and S. N. Slater, *J. Chem. Soc.*, 1950, 2900.

² C. E. Castro, E. J. Gaughan, and D. C. Owsley, *J. Org. Chem.*, 1965, **30**, 587, and references cited therein.

³ J. K. Kochi, *J. Amer. Soc.*, 1955, **77**, 5274; Fr. Pat. 1,294,996/1962.

⁴ J. B. Menke, *Rec. Trav. chim.*, 1926, **45**, 908.