Chloroacetylchloride: A Versatile Reagent in Heterocyclic Synthesis

Compiled by Ramesh Yella

Ramesh Yella was born in Sircilla, Karimnagar District, Andhra Pradesh, India in 1981. He received his B.Sc. in 2003 and M.Sc. (Organic Chemistry) in 2005 from Kakatiya University, Warangal, Andhra Pradesh, India. He then joined the Indian Institute of Technology Guwahati (IITG) as a Junior Research Fellow. Currently, he is working as a Senior Research Fellow (CSIR-SRF) for his Ph.D. dissertation under the supervision of Prof. Bhisma K. Patel. His research interest mainly focuses on the synthesis of heterocyclic compounds.

Department of Chemistry, Indian Institute of Technology Guwahati, 781 039 Guwahati, India
E-mail: ramesh@iitg.ernet.in
Dedicated to my mentor Professor B. K. Patel for providing me the great opportunity to work with him.

Introduction

Chloroacetylchloride is widely used in organic synthesis as a bifunctional reagent because acyl chloride (hard electrophile) easily forms esters1 or amides,2–4 while the other end the chloromethyl site (soft electrophile) can form other linkages.2–7 It is a convenient reagent for the preparation of heterocyclic compounds and is utilized as an important building block in the synthesis of natural and therapeutically active compounds.10,11

The reagent is used in the preparation of alachlor, butachlor, and the local anesthetic and antiarrhythmic drug lidocaine.12 Furthermore, it is also used to produce phenacyl chloride, another chemical intermediate used as a tear gas via Friedel–Crafts acylation of benzene using AlCl3 as catalyst.13 Chloroacetylchloride must be handled with precaution because it reacts readily with nucleophiles, such as amines, alcohols, and water generating hydrochloric acid, making it a lachrymator.

Preparation

Industrially, chloroacetylchloride is prepared by carbonylation of methylene chloride, oxidation of vinylidene chloride, or the addition of chlorine to ketene. In another approach, it can also be prepared by the reaction of chloroacetic acid with thionyl chloride, phosphorus pentachloride, or phosgene.

Properties

Chloroacetylchloride is a colorless liquid (mp –22 °C, bp 106 °C). Some of the important uses of this reagent are depicted below.

Abstracts

(A) A highly efficient method has been developed for the synthesis of 2-imino-4-thiazolidinones from both symmetrical and unsymmetrical thioureas using chloroacetylchloride under solvent-free conditions at room temperature.2

(B) A new, one-pot preparation of benzo[1,4]thiazin-3(4H)-one derivatives in high yields from substituted 2-chlorobenzothiols, chloroacetylchloride, and primary amines via Smiles rearrangement under microwave irradiation has been achieved.3

(C) A facile cycloaddition has been developed for the synthesis of antifungal fluorne containing azeto[2,1-d][1,5]benzotheizazepine derivatives on the surface of potassium carbonate under microwave irradiation.4

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(D) A green synthesis of benzothiazoles has been reported by the condensation of \( \text{o-amin thio phen ol and chloroac etyl chloride re-} \) 
resulting in 2-chloromethylbenzothiazole, which underwent S-alkylation with different benzenesulfonic acids in water under microwave irradiation.\(^5\)

(E) The condensation of 2-pyrazolin-5-ones with phenyl isothio
cyanate, followed by reaction of the resulting thiolate ions with chlo
roacetyl chloride resulted in cyclized \( \text{N,S-heterocycles, i.e., 2-} \) 
iminothiazolidin-4-ones.\(^6\)

(F) N-Heterocyclic carbene precursors, i.e., imidazoline or tetra
hydropyrimidine frameworks, were prepared from chloroalkanoyl chlorides and sequential attack of nitrogen nucleophiles. The resulting amide on the subsequent ring closure gave dihydroimidazolium and tetrahydropyrimidinium salts.\(^7\)

(G) Wei et al. have synthesized antifungal novel triazoles containing the thioamide moiety. The introduction of the thioamide group to the triazole molecule enhances the activity.\(^8\)

(H) The acylation of (1-methyl-4\( (1\text{H})\)-pyridinylidene)acetonitrile with chloroacetyl chloride leads to 4-chloro-2-(1-methyl-4\( (1\text{H})\)-pyridinylidene)-3-oxobutane nitrile. This furnished 4-(2-amino-4,5-
dihydro-4-oxo-1\( \text{H}\)-pyrrol-3-yl)-1-methylpyridinium chlorides on further reaction with primary amines. The hydrogenation of these quaternary salts afforded 5-amino-1,2-dihydro-4-(1-methyl-4-piperidinyl)-3\( \text{H}\)-pyrrol-3-ones in nearly quantitative yields.\(^9\)

References