3-Chloropropionyl Chloride

Magdalena Grabkowska-Drużyć
Bioorganic Chemistry Laboratory, Faculty of Pharmacy Medical University of Lodz, Muszyńskiego 1, 90-151 Lodz, Poland
magdalena.grabkowska-druzyc@umed.lodz.pl

Introduction

Acyl chlorides are highly reactive derivatives of carboxylic acids and therefore are applied widely in acylations. 3-Chloropropionyl chloride is an important bifunctional reagent. It is capable of acylation and possesses a 2-chloroethyl fragment (CH₂CH₂Cl), which can be subjected to nucleophilic substitution and serves as a masked vinyl group. It can be used as a starting material in many reactions to construct a variety of (hetero)cyclic compounds.

Preparation

3-Chloropropionyl chloride (1) is commercially available and can be prepared from β-propiolactone (2) and thionyl chloride. Other standard methods available for the preparation of acyl chlorides can also be applied: the reaction of acrylic acid (3) or 3-chloropropionic acid (4) with thionyl chloride, phosphoryl chloride, phosgene, or phosphorus trichloride.

Table 1 Use of 3-chloropropionyl chloride

(A) The Friedel–Crafts acylation of tert-butylbenzene (5) with 3-chloropropionyl chloride (1) followed by cyclization provided indanone 6, which was further transformed into urea derivative 7, a potent TRPV1 antagonist.

(B) A novel high-yielding one-pot microwave-assisted synthesis of condensed 5-substituted pyranoisoquinoline-1,6-diones 9 from 2-substituted isoquinoline-1,3-diones 8 and 3-chloropropionyl chloride (1) was reported.

(C) Aouf et al. reported the titanium tetrachloride mediated addition of 3-chloropropionyl chloride (1) to 2,3,6,7-tetramethyl-1,8-bis(trimethylsilyl)octa-2,6-diene (10) leading to cyclopentanol derivative 11, which contains three quaternary carbons.
(D) Acylation of 2-aminophenol (12) with 3-chloropropionyl chloride (1), followed by cyclization in the presence of polyphosphoric acid (PPA), gave benzoxazole 13, which was further reacted with 4-chlorophenyl-1-piperazine to yield the target benzodioxazole analogue 14, a selective dopamine D₄ receptor ligand.⁵

(E) Acylation of substituted nitriles 15 with 3-chloropropionyl chloride (1) and subsequent intramolecular cyclization afforded 2-aryl-2-pyrrolidinecarbonitriles 16 which were subsequently hydrolysed to 2-aryl-2-pyrrolidinecarboxamides 17, showing moderate anticancer activity.⁶

(F) 3-Chloropropionyl chloride (1) was applied in the preparation of intermediate 19 in the synthesis of cephalotaxine (20). The γ-lactam ring in 19 was constructed in a two-step sequence involving N-acylation and intramolecular alkylation.⁷

(G) Ozcan et al. reported the synthesis of oxadiazoloisopropylamide 23 as potent and noncovalent proteasome inhibitor. O-Acylation of N-hydroxyamidine 21 with 3-chloropropionyl chloride (1) and subsequent intramolecular cyclization afforded the intermediate oxadiazole 22, which was further transformed into 23 in good yield.⁸

(H) The synthesis of 2-imidazolidinones 25 and 26 (potential TACE inhibitors) started with the preparation of an unstable isocyanate 24 by reacting 3-chloropropionyl chloride (1) with sodium azide.⁹

References