3-Chloropropionyl Chloride

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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 ($\text{CH}_2\text{CH}_2\text{Cl}$), 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.¹ 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.²

(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.³

(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.⁴

(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 benzo[d]oxazole 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 anti-cancer 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*-hydroxyamide **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

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