3-Chloropropionyl Chloride

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Magdalena Grabkowska-Drużyc was born in Starachowice (Poland) in 1985. She received her M.Sc. in chemistry in 2009 working in the group of Professor Grzegorz Mostoń at the University of Lodz (Poland). She has been employed as a Teaching Assistant at the Bioorganic Chemistry Laboratory, Faculty of Pharmacy, Medical University of Lodz since 2010 under the guidance of Dr. Dorota G. Piotrowska. Her research interests focus on the synthesis of new isoxazolidine analogues of C-nucleotides of the potential anticancer and antiviral activity.

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, phosphogene, or phosphorus trichloride.

Table 1 Use of 3-chloropropionyl chloride

<table>
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<th>Reaction Scheme</th>
<th>Chemical Structure</th>
<th>Conditions</th>
<th>Yield</th>
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| (A)            | ![Acid Chloride]   | 1. AlCl₃, CH₂Cl₂, 0 °C  
2. H₂SO₄, 90 °C | 36% yield |
| (B)            | ![Microwave-Assisted Synthesis] | 1. AlCl₃, CH₂Cl₂, 0 °C  
2. H₂SO₄, 90 °C | 75–88% yield |
| (C)            | ![Titanium Tetrachloride Mediation] | 1. NaH, THF  
2. TICl₃, MeNO₂ | 44% yield |

Scheme 1

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(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 benzoxazol 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-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