3-Chloropropionyl Chloride

Magdalena Grabkowska-Drużyć

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

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Magdalena Grabkowska-Drużyć was born in Starażowice (Poland) in 1985. She received her M.Sc. in chemistry in 2009 working in the group of Professor Grzegorz Młostowski 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, phosgene, or phosphorus trichloride.

Table 1 Use of 3-chloropropionyl chloride

<table>
<thead>
<tr>
<th>Reaction Scheme</th>
<th>Details</th>
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<tbody>
<tr>
<td>(A)</td>
<td>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</td>
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<td>(B)</td>
<td>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</td>
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<td>(C)</td>
<td>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</td>
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</table>

Scheme 1

1. AlCl₃, CH₂Cl₂, 0 °C
2. H₂SO₄, 90 °C
3. NaH, THF

R = hydrogen, halogen, alkyl or alkoxy
(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 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-hydroxamidine 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