SYNLETT
Spotlight 355

This feature focuses on a reagent chosen by a postgraduate, highlighting the uses and preparation of the reagent in current research.

Phosphorus Oxychloride

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Introduction

Phosphorus oxychloride (POCl3) is a common and intensively used inorganic compound industrially prepared from phosphorus trichloride either by oxidation with oxygen or chlorination followed by treatment with phosphorus pentoxide (Scheme 1). Despite it reacts violently with water, this stable colorless liquid has been extensively studied for decades to promote the synthesis of diverse heterocycles, such as the Bischler–Napieralski formation of isoquinolines and its related cyclisations, the Meth-Cohn approach to quinolines or the Robinson–Gabriel route to oxazole. Beyond the heterocyclic chemistry, phosphorus oxychloride is a powerful reagent for various functionalization like chlorinations, Vilsmeier–Haack formylations or dehydratations. POCl3 also appears as a key reagent in bioorganic chemistry to phosphorylate proteins or nucleosides, and enters in the preparation of some polymers.

Abstracts

(A) An efficient one-pot synthesis of a library of 1-arylpyrazolo[3,4-d]pyrimidin-4-ones has been reported. Phosphorus oxychloride acts both as a chlorinating agent and an oxidant to generate in situ the reactive carboxamide and the acyl chloride. Intramolecular condensation thus afforded the targeted heterocycles in high yields (70–97%) for potential biological applications.

(B) Regioselective syntheses of 2- and 4-formylpyrido[2,1-b]benzoxazoles from diverse acetaminophenols have been studied. Surprisingly, reacting with Vilsmeier reagent under Meth-Cohn conditions did not only yield expected aminoacroleins, but also pyridobenzoxazoles as side products. Refluxing with acetic anhydride afforded compounds in good to moderate yields. Efficient synthesis of pyrido[2,1-b]benzoxazoles is of primary interest for their potential bioactivities.

(C) Phosphorus oxychloride has been used to promote Friedel–Crafts intramolecular cyclization from indole derivatives. Pyrroloacridones were obtained under mild conditions (POCl3, 60°C) whereas harsher ones resulted in the chlorination of the carbonyl followed by aromatization to give pyrroloacridines derivatives in high yields (up to 91%).
P-Stereogenic heterocycles have been diastereoselectively synthesized from phosphorus oxychloride by ring-closing metathesis (RCM).\textsuperscript{17} POCl\textsubscript{3} is submitted to O-alkylation followed by double nucleophilic additions on alkylene magnesium bromide derivatives to form organophosphinate. Diastereoselective enyne RCM in the presence of the Hoveyda catalyst afforded heterocycles in high yields (>98%) and diastereoisomeric excess (18:1).

The synthesis of novel fused isoxazole and isoxazoline rings by POCl\textsubscript{3}-mediated intramolecular nitrile oxide cycloadductions (INOC) has been reported.\textsuperscript{18} Compounds 1 synthesized by the Ugi reaction were submitted to INOC [2+3] addition in the presence of phosphorus oxychloride and triethylamine to afford a library of new heterocycles in moderate yields (27–63%).

The Vilsmeier reagent has been selected to promote the synthesis of bis-fused isoxazole ring derivatives 3 by Staudinger cycloaddition.\textsuperscript{19} Bis-imines 1, prepared from the corresponding diamine and aldehydes, underwent a [2+2]-ketene-imine cycloaddition. Ketenes were generated in situ by action of the Vilsmeier reagent on the carboxylic acid.

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**References**


