

SYNLETT Spotlight 355

Phosphorus Oxychloride

Compiled by Fabien Caillé



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

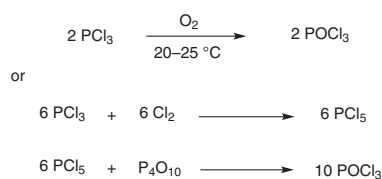
Fabien Caillé was born in 1986 in Tours, France. He graduated from the National Polytechnic School of Chemical Engineering and Technology of Toulouse in 2008 and is currently doing his PhD studies under the supervision of the Dr. F. Suzenet and the Dr. É. Jakab Tóth. His work deals with the synthesis and characterization of new bimodal probes for magnetic resonance and optical imaging.

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Introduction

Phosphorus oxychloride (POCl_3) 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,¹ such as the Bischler–Napieralski formation of isoquinolines² and its related cyclisations³, the Meth-Cohn approach to quinolines⁴ or the Robinson–Gabriel route to oxazole.⁵ Beyond the heterocyclic chemistry, phosphorus oxychloride is a powerful reagent for various

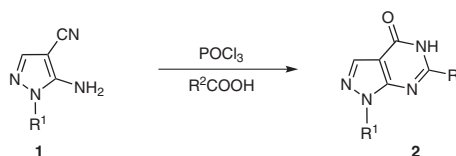
functionalization like chlorinations,⁶ Vilsmeier–Haack formylations⁷ or dehydrations.⁸ POCl_3 also appears as a key reagent in bioorganic chemistry to phosphorylate proteins⁹ or nucleosides,¹⁰ and enters in the preparation of some polymers.¹¹



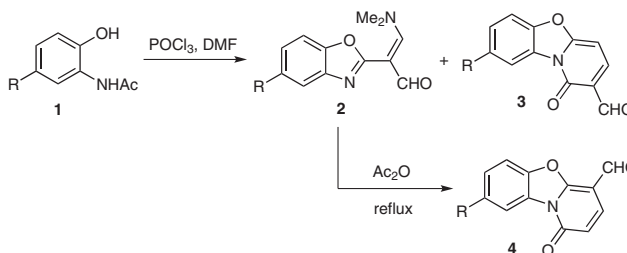
Scheme 1 Industrial preparation of phosphorus oxychloride

Abstracts

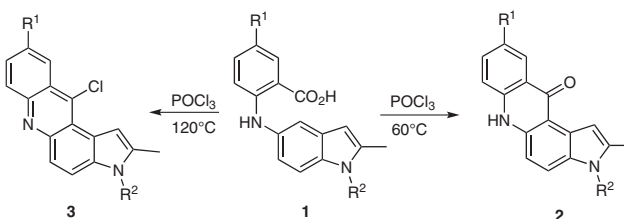
(A) An efficient one-pot synthesis of a library of 1-arylpyrazolo[3,4-*d*]pyrimidin-4-ones **2** has been reported.¹² Phosphorus oxychloride acts both as a chlorinating agent and an oxidant to generate in situ the reactive carboxamide and the acyl chloride. Intramolecular condensation thus afforded the targeted heterocycles **2** in high yields (70–97%) for potential biological applications.¹³



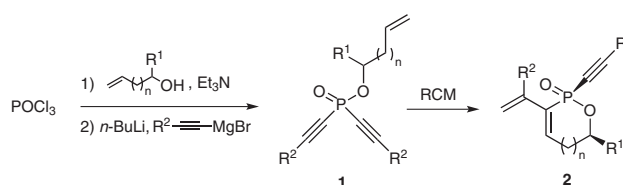
(B) Regioselective syntheses of 2- and 4-formylpyrido[2,1-*b*]benzoxazoles (**3** and **4**, respectively) from diverse acetaminophenols **1** have been studied.¹⁴ Surprisingly, reacting **1** with Vilsmeier reagent under Meth-Cohn conditions did not only yield expected aminoacroleins **2**, but also pyridobenzoxazoles **3** as side products. Refluxing **2** with acetic anhydride afforded compounds **4** in good to moderate yields. Efficient synthesis of pyrido[2,1-*b*]benzoxazoles is of primary interest for their potential bioactivities.¹⁵



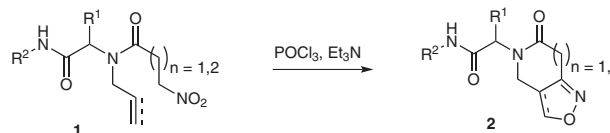
(C) Phosphorus oxychloride has been used to promote Friedel–Crafts intramolecular cyclization from indole derivatives **1**.¹⁶ Pyrroloacridones **2** were obtained under mild conditions (POCl_3 , 60 °C) whereas harsher ones resulted in the chlorination of the carbonyl followed by aromatization to give pyrroloacridines derivatives **3** in high yields (up to 91%).



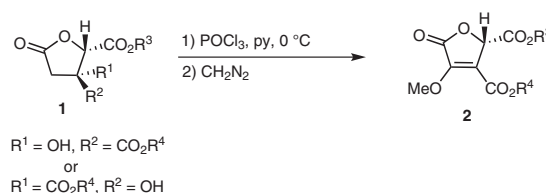
(D) P-Stereogenic heterocycles have been diastereoselectively synthesized from phosphorus oxychloride by ring-closing metathesis (RCM).¹⁷ POCl₃ is submitted to O-alkylation followed by double nucleophilic additions on alkyne magnesium bromide derivatives to form organophosphinate **1**. Diastereoselective enyne RCM in the presence of the Hoveyda catalyst afforded heterocycles **2** in high yields (>98%) and diastereoisomeric excess (18:1).



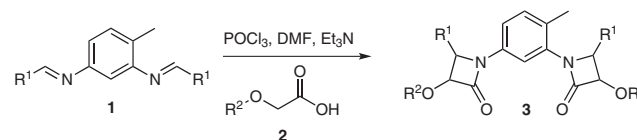
(E) The synthesis of novel fused isoxazole and isoxazoline rings **2** by POCl₃-mediated intramolecular nitrile oxide cycloadditions (INOC) has been reported.¹⁸ Compounds **1** synthesized by the Ugi reaction were submitted to INOC [2+3] addition in the presence of phosphorus oxychloride and triethylamine to afford a library of new heterocycles **2** in moderate yields (27–63%).



(F) An unusual α -hydroxylation of γ -butyrolactone in the presence of phosphorus oxychloride has been described.¹⁹ Compounds **1** obtained from chiral pool were submitted to POCl₃-mediated dehydration in the presence of pyridine at low temperature. A mechanism involving an enolization of the lactone followed by the formation of a POCl₃ cycloadduct is proposed. The hydroxyl intermediate is trapped with diazomethane to afford Quararibea metabolite analogs **2**.



(G) The Vilsmeier reagent has been selected to promote the synthesis of bis- β -lactam derivatives **3** by Staudinger cycloaddition.²⁰ 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 acids **2**.



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