

SYNLETT Spotlight 146

Diethyl Chlorophosphate

Compiled by Viviana Beatriz Dorn



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

Viviana B. Dorn was born in La Pampa (Argentina) in 1977. In 1996 she began her undergraduate course of Chemistry at the Universidad Nacional del Sur (Bahía Blanca). In 2001 she received her Diploma. She is currently working towards her Doctorate as a fellow of the CONICET in the group of Professor A. B. Chopa at the Instituto de Investigaciones en Química Orgánica, within a project on the Synthesis of Vinylstannanes from Carbonyl Compounds via $S_{RN}1$ reactions.

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Introduction

Diethyl chlorophosphate [CIP(O)(OEt)₂, DECP] is widely used in the synthesis of vinyl phosphates, which can be prepared regio- and stereoselectively by phosphorylation of enolate anions generated from the corresponding ketones under kinetically or thermodynamically controlled conditions.¹ Other important application, include the use of DECP for the phosphorylation of amide enolates to give α -phosphonoamides.²

Vinyl phosphates can also be synthesized by the Perkow reaction with trialkyl phosphites, but unlike the above-mentioned method, starting carbonyl compounds must be α -halo ketones, which are not commercially available and, in some cases very difficult to be synthesized. Moreover, the nature of the halogen atom and the reaction temperature have a crucial effect on the final products, i.e. both formation of vinyl phosphate and vinyl phosphonate can take place at the same time.^{1c,3}

Phenols are converted to the corresponding aryl phosphate in high yields by reaction of the phenoxide anion with DECP.⁴ This method is more successful in most cases than generating diethyl chlorophosphate *in situ*.⁵ In this sense, the selective phosphorylation of hydroxyphenols has recently been performed using DECP.⁶

On the other hand, the scope of phosphorylation in bioorganic chemistry includes amine precursors in the synthesis of phosphotriesters employing DECP. This synthetic strategy would make available some interesting unnatural phosphates derived from naturally occurring

amino sugars, alkaloids and amino acids.⁷ This reagent can also be used as a coupling agent in the synthesis of oligonucleoside phosphorodithionates⁸ and in the synthesis of diethylphosphoric anhydride employed in the N-protection of amino acids.⁹

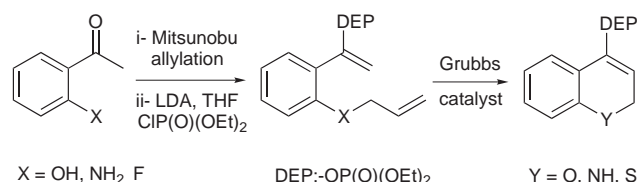
For the above exposed reasons, DECP has received added interest as phosphorylating reagent, in organic and bioorganic chemistry such as: synthesis of structurally specific olefins,^{1a,b,10} synthesis of acetylenes,¹¹ synthesis of phosphonates¹² and bisphosphonates,¹³ selective synthesis of thiol esters,¹⁴ cross-coupling reactions in the presence of various heteroatoms,^{15,1d} industrial scale synthesis of vinyl halides,¹⁶ displacement of phosphate as leaving group¹⁷ by an anion (e.g. organotin¹⁸ or tellurolate¹⁹ anions) or by alkyl cuprates.²⁰

DECP is commercially available. It can also be prepared by reaction of diethyl phosphite with chlorine until the liquid assumed a yellow coloration. Excess of gas is removed by bubbling dry air through the liquid under reduced pressure. The crude oil is vacuum-distilled. Yield 80–90%, bp 92 °C/17 mm Hg.²¹

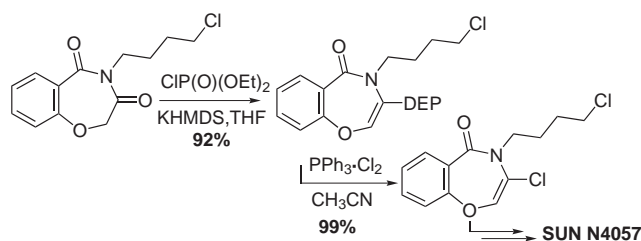
Caution! DECP is highly toxic by skin contact. It decomposes if exposed to moisture, and thermal decomposition may produce toxic fumes of phosphorus oxides and phosphines.

Abstract

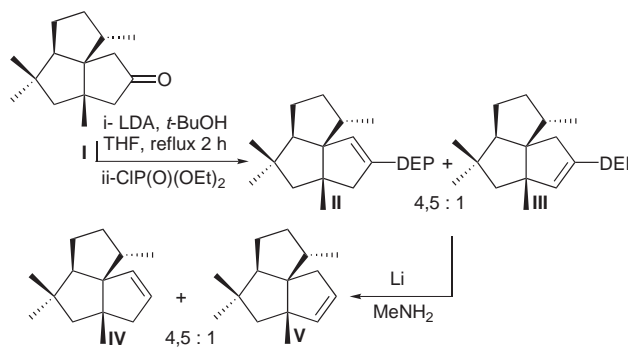
(A) A series of enol phosphates were synthesized starting from 2-substituted acetophenones. The ability of these compounds to undergo cross-coupling reactions in the presence of various heteroatoms, makes the enol phosphate an attractive functional group for the construction of various substituted heterocyclic systems via ring-closing metathesis.^{15c}



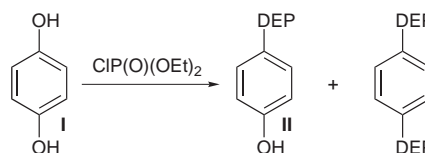
(B) A new practical synthetic method for the preparation of vinyl halides from acyclic and cyclic ketones and imides via the corresponding phosphate intermediates is proven. This process is satisfactory in an industrial scale production since the work-up procedure is easy to operate. Moreover, this method is applied to the industrial production of SUN N4057, a pharmaceutical candidate for the treatment of cerebral infarction.¹⁶



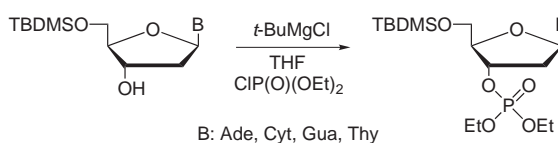
(C) A total synthesis of the silphinene **IV**, a natural product, has been accomplished in 12 steps. Since attempts to trap the ketone as its silyl enol ether in the cleavage reaction were unsuccessful, a study of the enolate formation of **I** was undertaken in hopes of selectively forming enol phosphate **II** as the direct precursor to silphinene. Thermodynamic enolization of **I** and quenching with DECP rendered enolphosphate **II** as major product. Reduction of this mixture, gave a mixture of silphinene **IV** and isosilphinene **V**. An efficient and regioselective formation of enol phosphate **II**, served to prepare the (\pm)-silphinene **IV** with high selectivity.^{10b}



(D) Monophosphorylated hydroxyphenols, which can be used as flame retardants in polycondensation reactions due to their free hydroxy group, were synthesized. The phosphorylation of hydroquinone **I** by DECP gave predominantly the monophosphate **II**.^{6b}



(E) DECP is used in the oligonucleotides synthesis via N-protected methods. The basis of this method is the activation of an hydroxyl group as an alkoxide which undergoes the O-selective reaction with DECP to give the nucleoside phosphate in almost quantitative yields.²²



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