

SYNLETT Spotlight 253

Diphenylphosphoryl Azide (DPPA) – A Reagent with Manifold Applications



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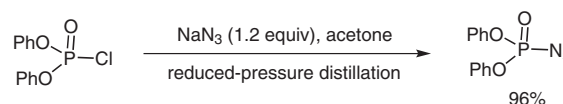
This feature focuses on a reagent chosen by a postgraduate, highlighting the uses and preparation of the reagent in current research

Introduction

Diphenylphosphoryl azide, originally developed by Yamada in 1972,¹ has shown significant synthetic versatility,² being used in isocyanate synthesis, especially in the Curtius rearrangement,¹ stereospecific conversion of alcohol into azide,³ as a coupling reagent in macrolactamization,⁴ in allylic amine synthesis,⁵ and in aziridination reactions.⁶

Diphenylphosphoryl azide, also called DPPA, diphenyl phosphorazidate or phosphoric acid diphenyl ester azide, is a colorless liquid with high boiling point (157 °C/0.17 mmHg), and can be easily prepared by the reaction be-

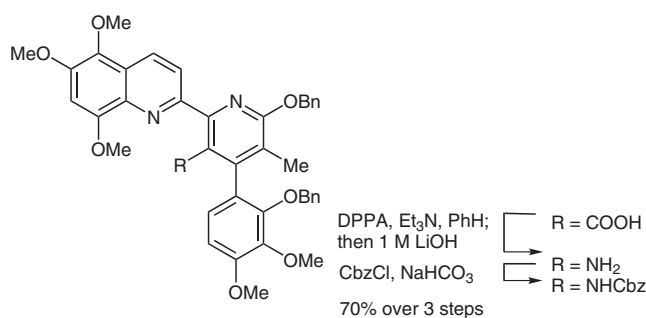
tween diphenylphosphoryl chloride and sodium azide in acetone in high yield.^{1,7} The Waldvogel group developed a reliable protocol for the large-scale (100 g) synthesis of DPPA, including purification by reduced-pressure distillation (Scheme 1).⁸ A polymer-supported form of the reagent has also been developed using phenol resin by the Taylor group.⁹



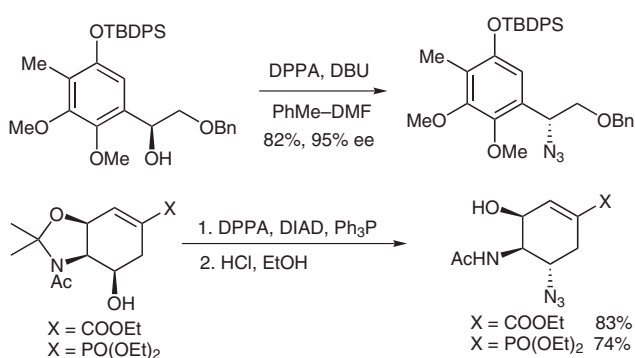
Scheme 1 Preparation of DPPA in 400 mmol scale

Abstracts

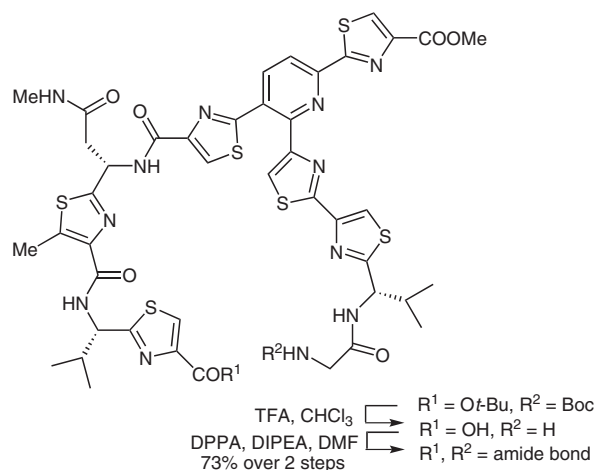
(A) Yamada and co-workers developed an improved method for the Curtius rearrangement reaction using DPPA, which was later named Yamada–Curtius rearrangement.¹ In 2007, the Ciufolini group employed this method in the total synthesis of streptonigrone, to transform a carboxylic acid group into a protected amino group through the hydrolysis of an isocyanate intermediate.¹⁰



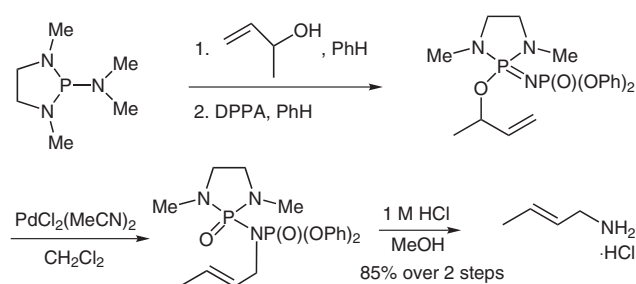
(B) A primary or secondary alcohol can be easily converted into an azide group by DPPA under mildly basic conditions or using Mitsunobu conditions for stereochemical inversion. In the total synthesis of cribrostatin VI, the Danishefsky group successfully employed DPPA to displace a benzyl alcohol in high yield and ee.¹¹ Another example was demonstrated in the synthesis of Tamiflu and its phosphonate congeners by the Wang group in 2007.¹²



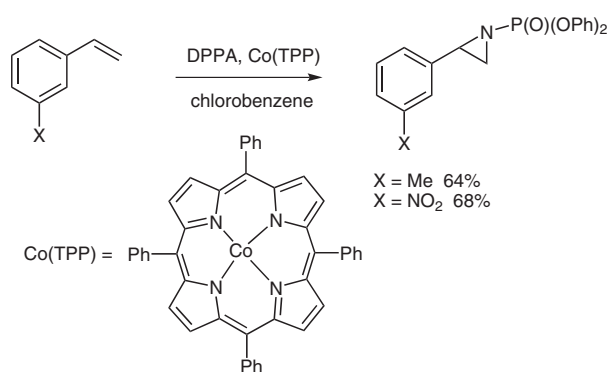
(C) Diphenylphosphoryl azide has also been widely used in peptide coupling reactions, particularly in macrolactamization.⁴ In 2005, the Moody group completed the synthesis of thiopeptide amythiamin D. In the final step, after global deprotection of *N*-Boc and *tert*-butyl groups, an α -amino ketone was successfully coupled with a thiazole carboxylic acid in DMF in 73% yield.¹³



(D) The Batey group has developed a stereoselective synthesis of allylic amines through a [3,3]-aza-phospha-oxa-Cope sigmatropic rearrangement.⁵ Methylvinylcarbinol was converted into crotylamine in 85% yield over two steps. DPPA was used as an amine source in these reactions, and excellent selectivity was achieved through addition of a catalytic amount of $\text{PdCl}_2(\text{MeCN})_2$ catalyst.



(E) A new catalytic aziridination reaction using cobalt tetraphenylporphyrin [Co(TPP)] as catalyst has been extensively studied by the Zhang group.⁶ DPPA functioned as a nitrene source in the reaction that proceeded in good to excellent yield.



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