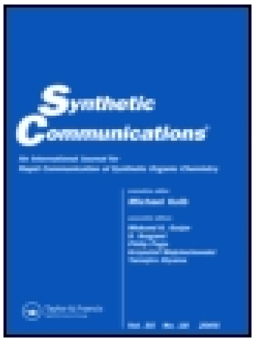

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Staudinger's Phosphazene as an Efficient Esterifying Reagent

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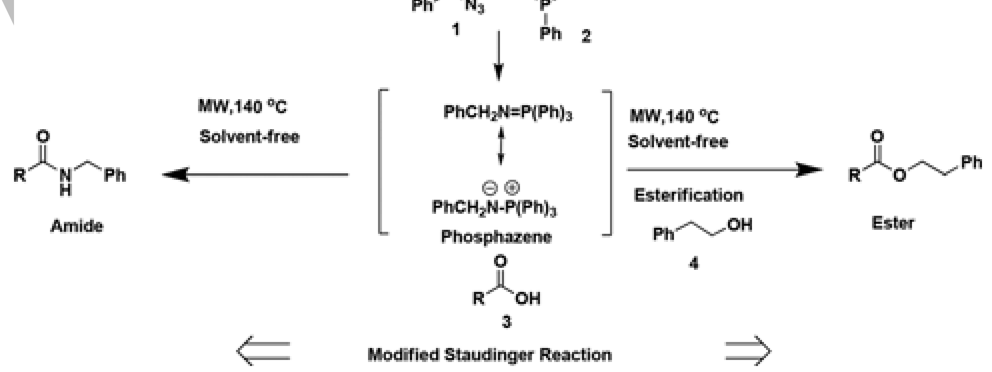
Abstract

A newer applicability of Staudinger's phosphazene as an efficient esterifying reagent is reported. Staudinger's phosphazene formed insitu by the reaction of organic mono-azide with triphenylphosphine is trapped by carboxylic acid to afford amide exclusively. In contrary, interestingly the same phosphazene behaves in a different way as an efficient esterifying reagent affording ester under a solvent-free microwave assisted protocol wherein in addition to the above reactants, alcohol is added as the another component. This discovery adds yet another new applicability of Staudinger's phosphazene to synthetic chemistry.

Graphical Abstract:



KEYWORDS: Mono azide; Staudinger's Phosphazene; Modified Staudinger Reaction; reagent; esterification.

INTRODUCTION

Extensive applications of Staudinger's phosphazene in organic syntheses since its discovery [1] are evident from its utility in the synthesis of potential organic compounds such as amine,[2] imine,[3] carbodiimide,[4] amide,[5] thioamide,[6] thiazolidone,[7] spirothiazolidones,[8] thiohydantoin,[9] isoquinolines.[10] Recently, we have discovered that bis-phosphazene,[11] also known as bis-iminophosphorane generated from Bis azide-Triphenylphosphine acts as an efficient esterifying reagent.

A deeper look on the proposed mechanism[11] of esterification using Bis azide/TPP clearly indicates that initially protonation of one of the nitrogens of the bis-phosphazene takes place in presence of carboxylic acid. This protonation leads to the formation of phosphonium ion (I) which is stabilized by the electron pair donated by the nitrogen of the second phosphazene in an intramolecular manner resulting in a cyclic phosphonium ion (II) (Scheme 1). This ion (II) eventually seems to drive the coupling of the carboxylic acid and the alcohol to achieve the esterification efficiently.

If the above proposed mechanism is true, then it is reasonable to question why not a similar but acyclic phosphonium ion shall be generated insitu (analogous to the cyclic phosphonium ion discussed vide scheme 1) by the intermolecular participation of two individual phosphazenes (instead of Bis-phosphazene discussed vide scheme 1) which can be prepared readily from mono-azide and triphenylphosphine (Scheme 2). Moreover, the feasibility of such a presumption seems to be favourable as the phosphazenes would be proximate to each other under solvent-free condition.

If this expectation turns to be true then it would be more remarkable in the sense that instead of bis azide-triphenylphosphine, one can expect the well-known commercially available mono azide-triphenylphosphine combination itself to behave as an efficient esterifying reagent via. the formation of the corresponding mono-phosphazene. In view of this, we were prompted to proceed with the reaction, the reactants being carboxylic acid, alcohol, triphenyl phosphine and organic mono-azide (instead of bis-azide of the earlier study[11]). To our delight, the attempt was successful thus disclosing yet another unknown applicability of the Staudinger's phosphazene as an esterifying reagent. The findings of our attempt are presented in the forthcoming pages.

RESULTS AND DISCUSSION

At the outset, to a mixture of triphenyl phosphine (1.0 mmol), carboxylic acid (1.0 mmol) and phenyl ethanol (1.0 mmol), benzyl azide (1.0 mmol) was added slowly in a drop wise manner (to avoid accumulation of azide) and the mixture was irradiated at 140 °C in microwave (CEM DISCOVER, Benchmate model, single-mode design with inbuilt IR sensor) to afford the corresponding ester[12-17] in good yield. (Caution! As azides are potentially explosive, all the reactions should be carried out behind a blast shield with personal protective equipment. In particular, the sequence of addition of the reactants should be strictly followed to avoid the accumulation of organic azides. This has been achieved in the present investigation by the slow drop wise addition of the benzyl azide to the reaction mixture containing triphenylphosphine during which the azide group is instantaneous converted to phosphazene and hence no difficulty was encountered). The synthesis of a library of esters has been accomplished by the optimised protocol (Table 1).

A plausible mechanism for the esterification is sketched below (Scheme 4). As already discussed vide supra, apparently the reaction proceeds via the reactive acylic phosphonium ion formed insitu which would have been trapped either by the carboxylate anion (Route A) or the alcohol (Route B) leading to the formation of the acyloxyphosphonium ion or alkoxy phosphonium ion respectively. Then these intermediates would have afforded the ester in good yield by dealkylation or deacylation.

As the reaction is very rapid and completes in 10 minutes under the solvent free condition, the intermediates could not be isolated. However, as a supporting evidence for the above sketched plausible mechanism, the byproduct viz. triphenylphosphine oxide has been isolated as white solid.

Having understood that both Bis phosphazene of our earlier report[11] and mono phosphazene of the present study behave as good esterifying reagents, it is pertinent to mention here the resemblance of their skeletal feature with that of the commercially available esterifying reagents like DCC and DEAD (Figure 1).

It is pertinent to mention here that phosphazene unlike DCC and DEAD, is an aza ylide with more of phosphonium ion character and thus acts efficiently as an esterifying reagent even at neutral condition. Also it could be realized that the mechanisms involved during the esterification using these commercial reagents are parallel to what has been discussed in the present investigation. Thus, our earlier study[11] and the present report add two more new reagents to the list of prevailing esterifying reagents.

Though many methods are available for activation of carboxylic acid during esterification, some of their disadvantages are (i) these methods often use organic solvents and/or reagents which results in hazardous/corrosive by-produts (ii) some of the reagents are expensive (iii) the work-up of the reaction is tedious(iv) some reactions need catalyst, scavenger or additive.(v) the reaction is time consuming. However, our present methodology involving Staudinger's Phospazene is advantageous than many other existing reagents as it is devoid of all the above said disadvantages.

EXPERIMENTAL

General

All chemicals, reagents and solvents were of commercially high purity grade purchased from Avra Synthesis Pvt. Ltd. and Merck Ltd. India. Silica gel (60–120 mesh) was used for column chromatographic isolation and purification of the compounds synthesized. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded in $CDCl_3$ on Bruker (Avance) (300 MHz) spectrometer and the chemical shifts are reported in δ values in parts per million (ppm) relative to tetramethylsilane, with coupling constant (J) values in Hertz. Microwave irradiation (CEM DISCOVER, Benchmate model, single-mode design with inbuilt IR sensor)

Procedure And Characterization

General Procedure For The Synthesis Of Alkyl Esters Under Microwave Irradiation (5a-P)

To a mixture of triphenylphosphine (1.0 mmol), benzyl azide (1.0 mmol) was added slowly in a phenylethanol (1.0 mmol) and carboxylic acid (1.0 mmol) (drop wise manner (to avoid accumulation of azide) and the mixture was place to microwave at 140°C for 10 minutes. (Caution! As azides are potentially explosive, all the reactions should be carried out behind a blast shield with personal protective equipment. In particular, the sequence of addition of the reactants should be strictly followed to avoid the accumulation of organic azides. This has been achieved in the present investigation by the slow drop wise addition of the benzyl azide to the reaction mixture containing triphenylphosphine during which the azide group is instantaneous converted to iminophosphorane and hence no difficulty was encountered). After the completion of the reaction (as monitored by TLC), the mixture was poured onto crushed ice. Then the reaction mixture was extracted with dichloromethane and the organic layer was dried over anhydrous Na_2SO_4. The solvent was removed and the residue was purified by column chromatography using silica gel as the adsorbent and petroleum ether: ethyl acetate (98:2) as the mobile phase to afford the corresponding carboxylic esters (5a-p) as colourless oily liquids. Yield (73-85%).

Phenethyl Benzoate (5a)[11]

Yield: 80 %; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (dd, *J* = 8.3, 1.1 Hz, 2H), 7.54 (d, *J* = 7.6 Hz, 2H), 7.43 (t, *J* = 7.7 Hz, 3H), 7.32 (d, *J* = 6.8 Hz, 3H), 7.29 – 7.23 (m, 2H), 4.53 (t, *J* = 7.0 Hz, 3H), 3.08 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.5, 137.8, 132.8, 130.2, 129.5, 128.9, 128.5, 128.3, 126.5, 65.4, 35.2.

CONCLUSIONS

In conclusion, herein we report a novel hitherto unknown applicability of Staudinger‘s Phosphazene as an efficient new reagent for esterification under neutral and solvent-free condition.

FUNDING

The authors thank IRHPA, DST for providing 300MHz NMR instrument for recording the NMR spectra for the compounds synthesized. One of the author thanks UGC and DST for the financial support.

SUPPORTING INFORMATION

Supplemental data for this article can be accessed on the publisher's website

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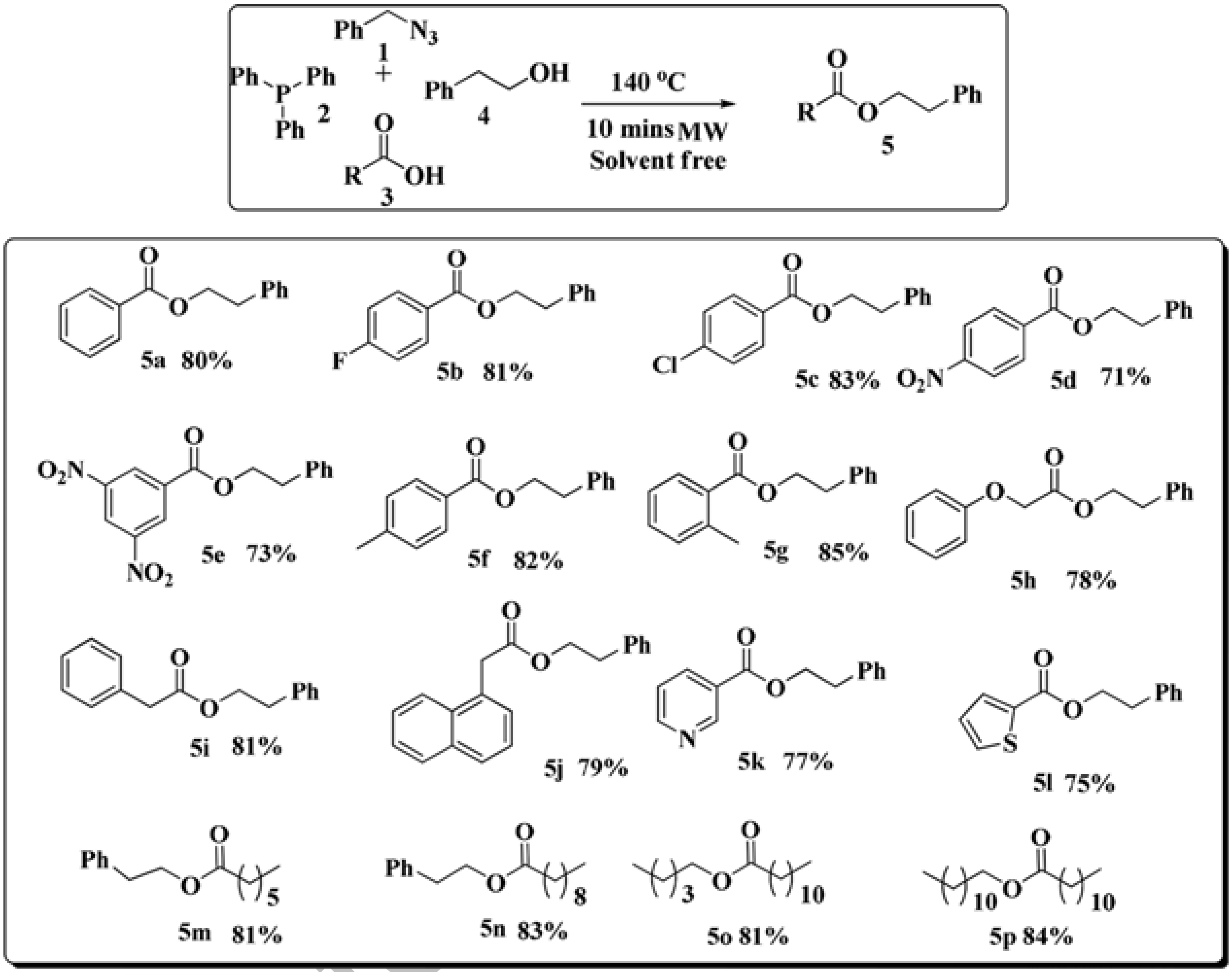
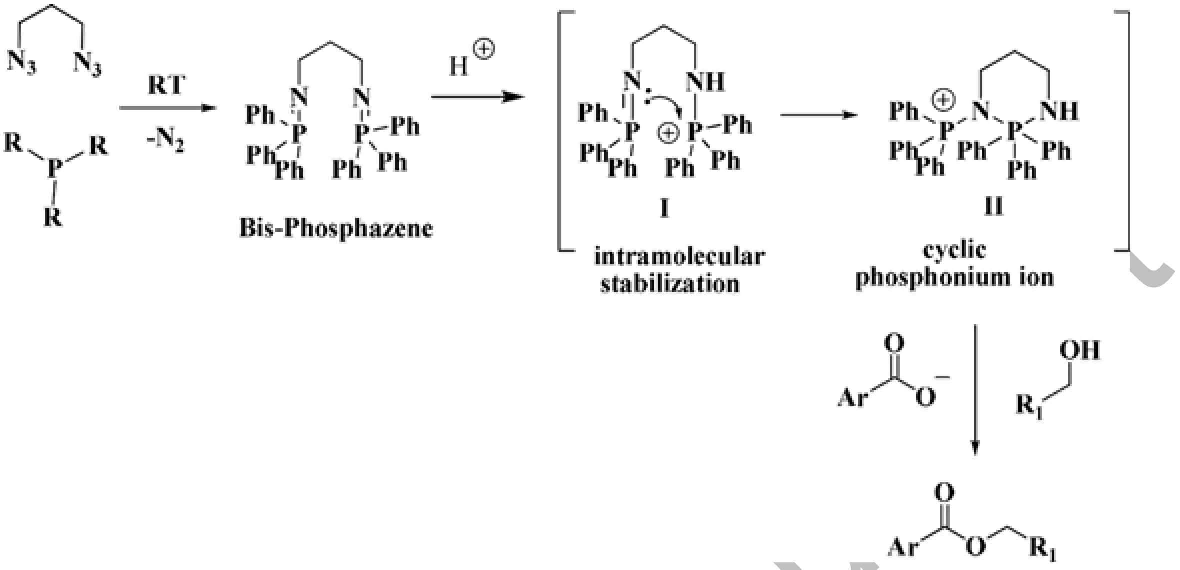
Table 1. Scope of Staudinger's phosphazene as esterifying reagent

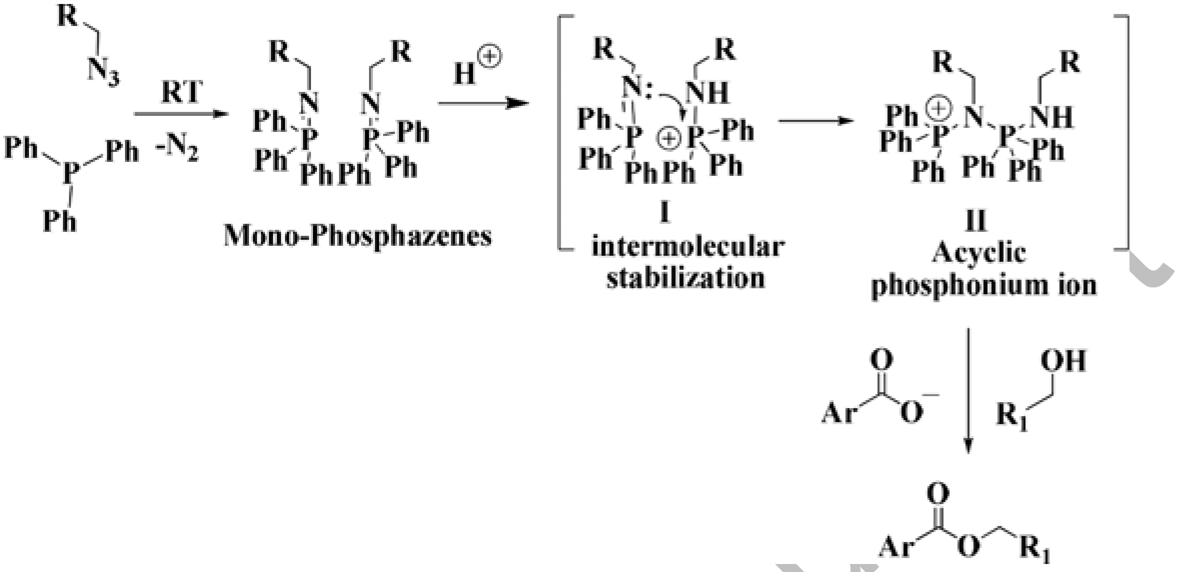


Reaction conditions: To a mixture of triphenylphosphine (1.0 mmol), 2-phenylethanol (1.0 mmol) and carboxylic acid (1.0 mmol), benzyl azide (1.0 mmol) was added slowly in a drop wise manner (to avoid accumulation of azide) and the mixture was irradiated (CEM DISCOVER, Benchmate model, single-mode design with inbuilt IR sensor) with microwave at 140 °C for 10 minutes.

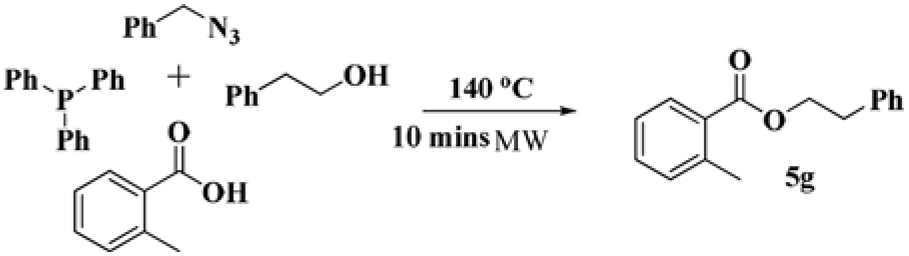
Scheme 1. Proposed mechanism for the esterification using bis –azide /TPP [11]



Scheme 2. Presumption leading to the present investigation



Scheme 3. Staudinger's phosphazene as an esterfying reagent



Scheme 4. Plausible mechanism of the Staudinger phosphazene

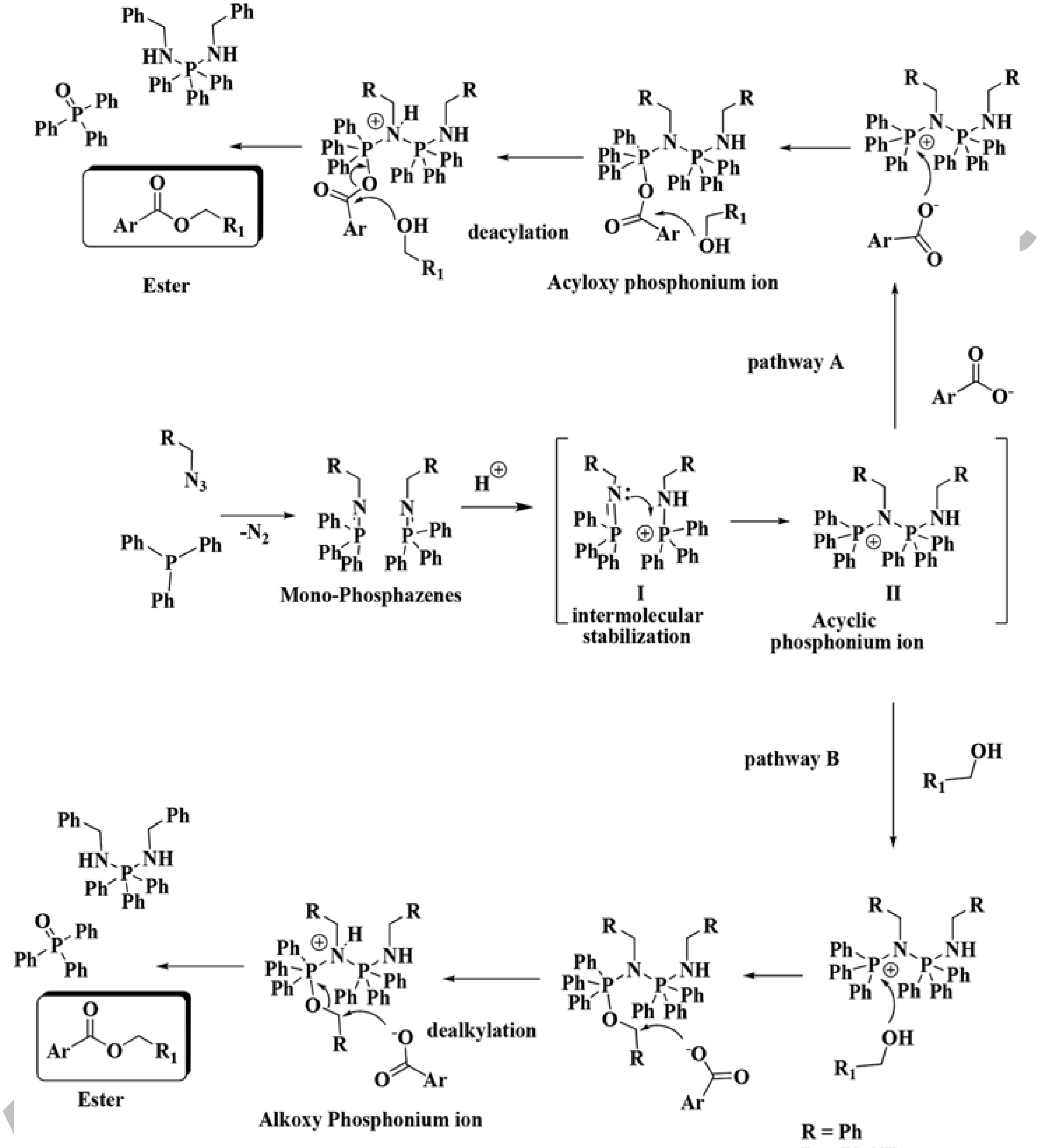


Fig. 1. Phosphazene resembles the partial structures of the esterifying reagent