

# Synthesis, Reactivity and Biological Applications of Organophosphorus Heterocycles: A Review of Benzodiazaphosphorinones, Benzoxazaphosphorinones and Benzoxazaphosphinines

Neetu, University School of Basic & Applied Sciences, GGSIU, New Delhi

neetukumawat04@gmail.com

## *Abstract*

Organophosphorus heterocycles containing P–N and P–O bonds have attracted considerable attention due to their wide-ranging applications in medicinal chemistry, agriculture, and material science. This review presents a comprehensive analysis of the synthesis, structural features, and reactivity of benzodiazaphosphorinones, benzoxazaphosphorinones, and benzoxazaphosphinines. Various synthetic methodologies involving phosphorus reagents such as phosphorus trichloride ( $\text{PCl}_3$ ), phosphorus oxychloride ( $\text{POCl}_3$ ), and thiophosphoryl chloride ( $\text{PSCl}_3$ ) are critically discussed. The influence of reaction conditions, base catalysts, and substituents on product formation and yield is evaluated. Additionally, the biological significance of these compounds, particularly their anticancer and antimicrobial activities, is highlighted. A comparative analysis is presented to identify efficient synthetic strategies and future research directions.

## *Keywords*

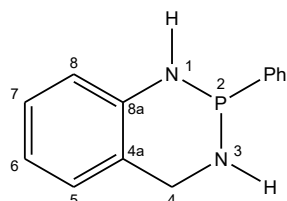
Organophosphorus compounds;  
Benzoxazaphosphorinones;  
Benzodiazaphosphorinones;  
Benzoxazaphosphinines; Anticancer activity;  $\text{PCl}_3$ ;  $\text{POCl}_3$

## I. INTRODUCTION

The preparation of P-heterocycles has been extensively reviewed over the years and the field has a great interest to study due to some applications. Organophosphorus compounds have wide spread use throughout the world, mainly in agriculture as insecticide, herbicides. They have also been used as nerve agent in chemical warfare and therapeutic agents. A large no. of different structural types of P-compounds has High level cancer activity. In contrast, Benzodiaza- and benzoxazaphosphinones are known only since 1978 and the interest in the classes of compounds has increased during the past few years. Selected synthesis of these compounds is an important part of this article.

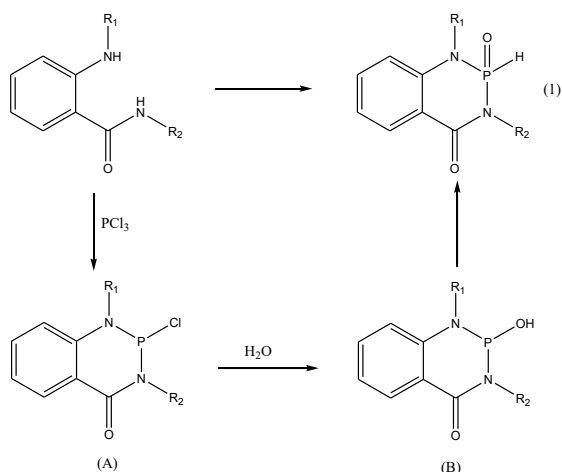
## II. STRUCTURE AND SYNTHESIS OF BENZODIAZAPHOSPHORINONES

In these heterocyclic compounds, two N-atom are bonded in  $\alpha$ -position to the phosphorus atom and a carbonyl group present in the ring.



2-Phenyl-1,2,3,4-tetrahydro-benzo[1,3,2]diazaphosphinine

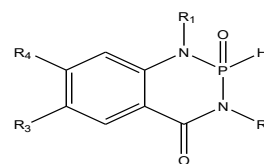
The study of the chemistry of benzodiazaphosphorinone was started in 1978 by GM Coppola [1], When N-substituted anthranillamide were allowed to react with phosphorus trichloride, benzodiazaphosphorinone of type (1) were produced through intermediate (A)



**Scheme-1**

Initially Hydrolysis product of type (B) were obtained instead of type (A). Type (A) was expected but it could not be isolated(scheme-1).

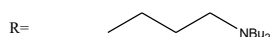
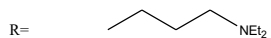
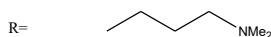
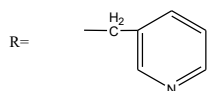
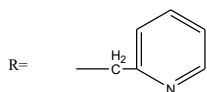
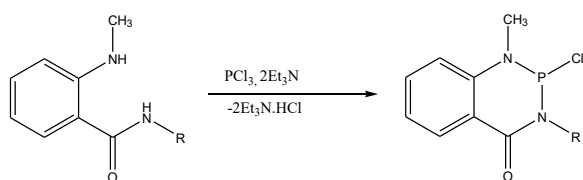
GM Coppola and co-workers have synthesized benzodiazaphosphorinone derivatives by reaction of substituted anthranillamide with  $\text{PCl}_3$ . Ten benzodiazaphosphorinones were prepared in yield upto 75%



	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	R <sub>4</sub>
1.	CH <sub>3</sub>	CH <sub>3</sub>	H	H
2.	CH <sub>3</sub>	CH <sub>3</sub>	Cl	H
3.	CH <sub>3</sub>	CH <sub>3</sub>	H	Cl
4.	CH <sub>3</sub>	CH <sub>2</sub> CH <sub>3</sub>	H	H
5.	CH <sub>3</sub>	CH <sub>3</sub>	O-CH <sub>2</sub> -O	
6.	CH <sub>3</sub>	CH <sub>2</sub> CH=CH <sub>2</sub>	H	H
7.	CH <sub>3</sub>	CH <sub>2</sub> CH <sub>2</sub> OCH <sub>2</sub> -C <sub>6</sub> H <sub>5</sub>	H	H
8.	CH <sub>2</sub> CH <sub>3</sub>	CH <sub>3</sub>	H	H
9.	CH <sub>2</sub> CH=CH <sub>2</sub>	CH <sub>3</sub>	H	H
10.		CH <sub>3</sub>	H	H

The above reaction were performed in inert atmosphere and without any base.

The presence of  $\text{Et}_3\text{N}$  as a base is necessary in some cases to avoid the formation of products which have difficult separation method. First fully characterized 1,3,2-benzodiazaphosphorinan-4-one was reported in 1993. I. Neda and co-workers performed these reactions in presence of  $\text{Et}_3\text{N}$  as base in 1993(scheme-2).



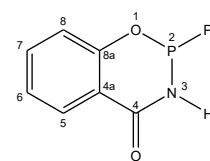
### Scheme-2

N-substituted Anthranillamide with  $\text{PCl}_3$  was first reported by GM Coppola et.al. As intermediate postulated N-substituted could not be isolated. Similar implementation has been carried out by R.Chen and R.Bao<sup>(2,3)</sup> and published in 1989-90. 1,3,2-benzodiazaphosphorinan-4-one intermediate phosphorus compound could not be isolated by none of them.

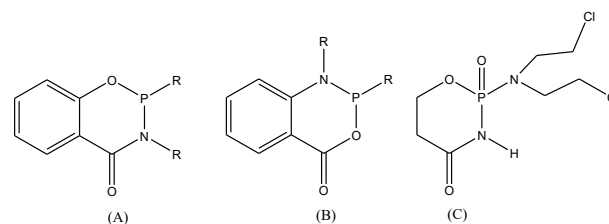
### III STRUCTURE AND SYNTHESIS OF BENZOXAZAPHOSPHORINONES:

Benzoxazaphosphorinones were known since 1960. In these heterocyclic compounds, one N-atom and one O-atom are bonded in  $\alpha$ -position to the phosphorus atom and a carbonyl group present in the ring. Benzoxazaphosphorinones can exist as two different structural isomers (**A**, **B**),

caused by different ring atoms (O, N) in  $\alpha$ -position to the phosphorus atom in the heterocyclic system:



2-Phenyl-2,3-dihydro-benzo[e][1,3,2]oxazaphosphinin-4-one

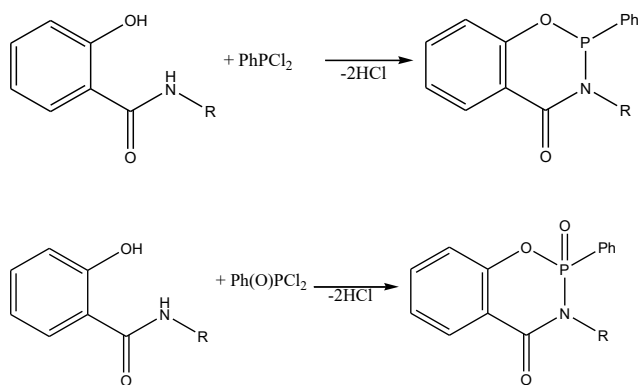


Compounds of type **A** can be synthesized easily by reaction of salicylamide with phosphorus (III) halides, while the formation of compounds of type **B** takes place via reaction of anthranilic acid with phosphorus (III) halides.

The pharmacological properties of benzoxazaphosphorinones were caused by the discovery of the cytostatic properties of the related compound Cyclophosphamide (**C**). Cyclophosphamide is a medication used as chemotherapy. Its further development by introducing different substituents in Cyclophosphamide and modification of the heterocyclic ring system gave rise to great interest in this class of compounds. Many benzoxazaphosphorinones of types **A** and **B** were described in research publications. A summary is given in the following.

In 1992, Kostka and co-workers used salicylamide and

dichlorophenylphosphine as well as dichlorophenylphosphine oxide for synthesis of different benzoxazaphosphorinones.

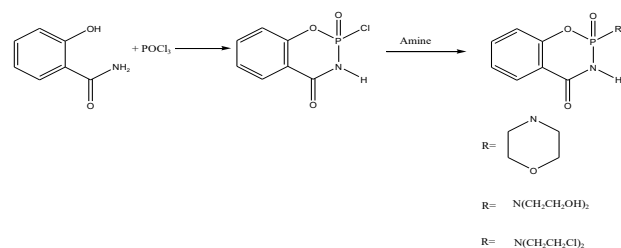
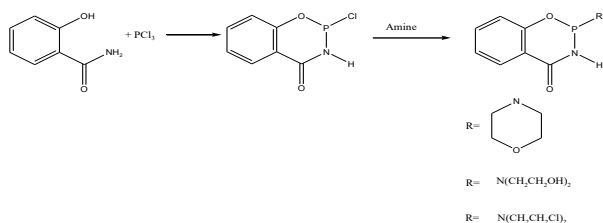


R= -H, -CH<sub>3</sub>, -C<sub>2</sub>H<sub>5</sub>, -(CH<sub>2</sub>)<sub>3</sub>CH<sub>3</sub>, -cyclohexyl, -CH<sub>2</sub>Ph, -Ph, -PhCH<sub>3</sub>, -NH<sub>2</sub>, -NH-CH<sub>3</sub>

### Scheme-3

By using Et<sub>3</sub>N as a base, the reaction time can be shortened, but at the same time the yield is reduced by 10-20% for some products(scheme-3).

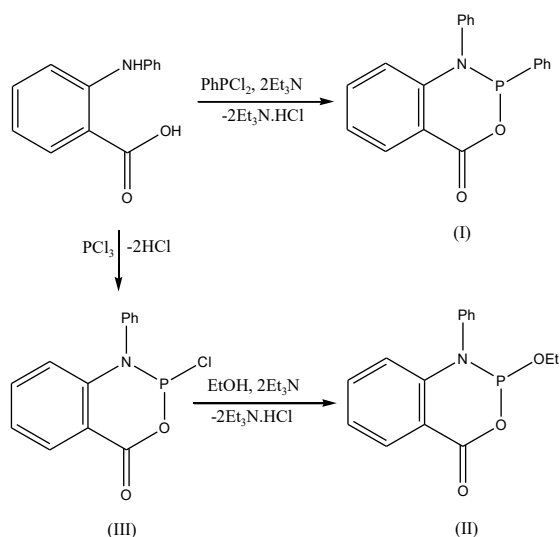
In 1994, Kostka and co-workers used salicylamide, POCl<sub>3</sub> or PCl<sub>3</sub> and proper amine: bis(2-chloroethyl) amine, bis(2-hydroxyethyl) amine and morpholine for synthesis of benzoxazaphosphorinones derivatives(scheme-4).



### Scheme-4

Six new compounds derivatives of 2-substituted 2,3-dihydro-1,3,2-benzoxazaphosphorin-4-on-2-oxide were obtained, with pharmacophoric groups, *i.e.* bis(2-chloroethyl) amine, bis(2-hydroxyethyl) amine and morpholine at 2-position. Out of the investigated compounds only those show antineoplastic activity which have the bis(2-chloroethyl) amine group in their molecule. This group is also present in cyclophosphamide. These compounds were further used in toxicity studies.

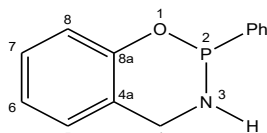
Compounds of type **B** can be obtained by reaction of anthranilic acid or its N- substituted derivatives and phosphorus halides [4]. As described for the reaction of salicylic acid amide and phosphorus trichloride the reaction of anthranilic acid or N-methyl anthranilic acid with phosphorus trichloride formed the corresponding 2-chlorobenzoxazaphosphorinones(scheme-5).



**Scheme-5**

#### IV. STRUCTURE AND SYNTHESIS OF BENZOXAZAPHOSPHININE

In these heterocyclic compounds, one N-atom and one O-atom are bonded in  $\alpha$ -position to the phosphorus atom.



2-Phenyl-3,4-dihydro-2H-benzo[e][1,3,2]oxazaphosphinine

Organo-phosphorus heterocyclic compounds containing P-N bond has significant medicinal and pesticidal activity, when linked with an amino acid ester moiety. The amino acid ester enhance chemotherapeutic properties. Simultaneously amino acid groups on phosphorus moiety have useful anti-neoplastic properties. Due to this property, new six membered Benzoxazaphosphinine heterocycles substituted with amino acids were synthesised and accomplished. In this

series, many different compounds synthesised due to N substituted phenol derivatives. There are so many research paper are published for this type of synthesis, some are summarised below:

TABLE I. COMPARATIVE DESCRIPTION OF DIFFERENT BENZOXAZAPHOSPHINE SYNTHESIS

S.no	Reaction condition	Reagents Used	Key Outcome
1	Step-1 <sup>(5)</sup> POCl <sub>3</sub> , Et <sub>3</sub> N, Toluene, 50-55 <sup>0</sup> C Step-2 Amino Acid Ester, THF, 40- 45 <sup>0</sup> C	POCl <sub>3</sub> , Et <sub>3</sub> N	Moderate yield, stable product
2	Step-1 <sup>(6)</sup> POCl <sub>3</sub> , Et <sub>3</sub> N, THF, 0 <sup>0</sup> C Step-2 ArOH, Et <sub>3</sub> N, THF	POCl <sub>3</sub>	Improved selectivity

3	<p>Step-1</p> <p>POCl<sub>3</sub>, 2Et<sub>3</sub>N, THF, 40- 45<sup>0</sup>C</p> <p>Step-2</p> <p>R-Na, THF, 40- 45<sup>0</sup>C</p>	POCl <sub>3</sub>	Good yield
4	<p>Step-1</p> <p>POCl<sub>3</sub>, 2Et<sub>3</sub>N, THF, 35- 45<sup>0</sup>C</p> <p>Step-2</p> <p>NH<sub>2</sub>R, THF, 35- 45<sup>0</sup>C</p>	POCl <sub>3</sub>	Functional derivatives
5	<p>Step-1</p> <p>PSCl<sub>3</sub>, 2Et<sub>3</sub>N, Toluene- THF, 35- 45<sup>0</sup>C</p> <p>Step-2</p> <p>HXR'R", Et<sub>3</sub>N, Toluene- THF, 40-</p>	PSCl <sub>3</sub>	Sulfide derivatives

	45 <sup>0</sup> C		
6	<p>Step-1</p> <p>PSCl<sub>3</sub>, 2Et<sub>3</sub>N, THF, 40- 45<sup>0</sup>C</p> <p>Step-2</p> <p>NH<sub>2</sub>R, Et<sub>3</sub>N, Toluene- THF, 40-45<sup>0</sup>C</p>		Bioactive compounds
7	<p>Step-1</p> <p>PhPCl<sub>2</sub>, 2Et<sub>3</sub>N, THF, 40- 45<sup>0</sup>C</p> <p>Step-2</p> <p>H<sub>2</sub>O<sub>2</sub>/S/Se THF, Reflux</p>		Oxide/sulfide/selenide derivatives

In 2008, an effective and simple Route adopted for the synthesis of novel amino acid ester linked, 2-oxobenzo[e][2H-1,3,2]-oxazaphosphinine derivatives(s.no-1). These derivatives were afforded through a two step synthetic route. Condensation of 2-[( $\alpha$ -methyl benzylamino) methyl]-4-bromophenol

with phosphorus oxychloride in equimolar quantities in the presence of triethylamine in dry toluene in 50-55°C produced the corresponding intermediate monochloride, 3-( $\alpha$ -methylbenzyl-6-bromo-2-chloro-3,4-dihydro-2-oxobenzo[e][2H-1,3,2-oxazaphosphinine], which was reacted with various aminoacid ester hydrochlorides in dry THF in the presence of triethylamine to give the product in moderate yields. The second step of the reaction was completed in 40-45 °C with stirring for 8-10 h

In 2008, organophosphorus heterocyclic compounds containing two six membered heterocyclic rings was accomplished successfully.

Cyclocondensation of 2-[[4-(2-hydroxybenzylamino)phenylamino]methyl]-phenol with phosphorus oxychloride in presence of triethylamine in dry tetrahydrofuran at 40–50 °C afforded 2-chloro-3-[4-(2-chloro-2-oxo-3,4-dihydro-2 $\lambda^5$ -benzo[e][1,3,2]oxazaphosphinine-2-oxide, which upon subsequent reaction with various phenols gave 3-[4-(2-aryloxy-2-oxo-3,4-dihydrobenzo[e][1,3,2]oxazaphosphinine-3-yl)phenyl]-2-aryloxy-3,4-dihydrobenzo[e][1,3,2]oxazaphosphinine-2-oxides in good yields(s.no-2). They used a different route in which direct condensation performed with aryl

phosphorodichloridates instead of POCl<sub>3</sub>. This route afforded good yields and more convenient than former method, because the intermediate is highly moisture sensitive and difficult to handle.

In 2011, some derivatives of benzoxazaphosphinin-2-ones were synthesised. It was a condensation reaction of 2-[(6-methyl-2-pyridyl) amino]methylphenol with phosphorus oxychloride in dry THF in the presence of triethylamine at 40–45 °C to afford the corresponding intermediate 2-chloro-3-(6-methyl-2-pyridyl)-3,4-dihydro-2H-1,3,2 $\lambda^5$ -benzoxazaphosphinin-2-one. In the next step the intermediate was reacted with respective sodium phenoxide in dry THF at 0-5°C. (s.no.-3)

In 2010, similar reaction performed for the synthesis of derivatives of benzoxazaphosphinin-2-ones. This reaction involves cyclo condensation of 2-[(3'-chloro-4'-nitrophenyl amino) methyl]phenol with phosphorusoxychloride in dry THF in the presence of TEA at 35-45°C to afford the corresponding monochloride intermediate.

Further step the intermediate was reacted with the respective aminoacid ester hydrochlorides in dry THF in the presence of TEA afforded products in good yields (s.no.-4).

In 2008, The synthesis process of substituted [1,3,2]oxazaphosphinine 2-

sulfides was published. The synthetic route involves preparation of the substituted [1,3,2]oxazaphosphinine 2-sulfides through a two-step process.

The intermediate 2-chloro-3-(4-chlorophenyl)-3,4-dihydrobenzo[*e*][1,3,2]oxa-zaphosphinine 2-sulfide was obtained from the cyclocondensation of 2-[(4-chlorophenylamino) methyl]phenol with thiophosphoryl chloride in equimolar quantities in the presence of triethylamine in dry toluene-tetrahydrofuran at 35°C for 2 h. Subsequent nucleophilic substitution of heterocyclic/acyclic amines/4'-acetamidophenol on this monochloride at 45-50 °C for 3h, yielded substituted [1,3,2]oxazaphosphinine 2-sulfides (s.no - 5).

In 2009, Thione derivatives of benzoxazaphosphinine synthesised and reported their antimicrobial activity.

The synthesis of 2-(aminoacid ester)-3-(6-methyl-2-pyridyl)- 3,4-dihydro-2*H*-1,3,2λ<sup>5</sup>-benzoxazaphosphinin-2-thiones is accomplished in a two-step process. The synthetic route involves the condensation of 2-[(6-methyl-2-pyridyl) amino] methylphenol with thiophosphoryl chloride in dry tetrahydrofuran in the presence of triethylamine at 40–45 °C to afford the corresponding intermediate 2-chloro-3-(6-methyl-2-pyridyl)-3,4-

dihydro-2*H*-1,3,2λ<sup>5</sup>-benzoxazaphosphinin-2-thione.

In the second step the intermediate was reacted with the respective aminoacid ester hydrochlorides in dry tetrahydrofuran- toluene in the presence of triethylamine to obtain the title compound in good yields(s.no-6).

They used PhPCl<sub>2</sub> instead of POCl<sub>3</sub>, and the intermediate used in further chalcogenides formation(O, S, Se).

The reaction mixture containing trivalent phosphorus intermediate was further converted to the corresponding oxide, sulphide and selenide without isolation by adding hydrogen peroxide, sulfur and selenium respectively at 0-50°C(s.no.-7).

## V. CONCLUSION

The description of the synthesis of organophosphorus heterocyclic compounds containing P-N bond are reviewed and reported. Synthesis of Benzodiaz-, oxazaphosphorinones, and benzoxazaphosphorinines reported during the last few years, forms an important part of this article. All reactions performed in inert atmosphere because some organophosphorus heterocyclic compounds are highly air sensitive and moisture sensitive and difficult to handle. A large no. of different structural types of organophosphorus compounds are synthesised and reported every year due to

their applications in different field like medicine, agriculture, biological etc.

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