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New synthetic methodology leading to a series of novel heterocyclic α-aminophosphonates: a very attractive expansion of Kabachnik–Fields reaction

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ABSTRACT

A convenient one-pot three-component approach leading to synthesis of a series of novel heterocyclic α-aminophosphonates starting either from 2-hydroxyacetophenones or 2-hydroxybenzaldehyes was developed.

1. Introduction

The chemistry of organophosphorus heterocycles has received considerable attention owing to their unique structural features and diverse potential biological properties. A large number of related compounds were synthesized in the past two decades.[1] 1,2-Oxaphosphol-3-enes (Fig. 1a), which were examined as potential precursors of stabilized C-centred radicals,[2] displayed diverse potential biological properties, such as antiviral activity,[3] cytotoxicity and genotoxicity,[4] antimicrobial activity.[5] It is well known that α-aminophosphonates, to a great extent, have received much attention because of their antifungal,[6] antitumoral,[7] and anti-Giardia.[8] Among numerous synthetic methodologies of α-aminophosphonate,[6–9] the most noteworthy and remarkable one is Kabachnik–Fields reaction,[10] generally using amines, dialkyl phosphites and carbonyl compounds as the reactants. Even though quite a lot research works, which focused on the synthesis and biological tests of α-aminophosphonates have been reported, but surprisingly 3-amino-2-hydroxy-2,3-dihydrobenzo[*d*][1,2]oxaphosphole 2-oxides, a kind of heterocyclic α-aminophosphonates (Fig. 1b), to the best of our knowledge, have not been described in the literature. The methodology towards synthesis of these 3-amino-2-hydroxy-2,3-dihydrobenzo[*d*][1,2]oxaphosphole 2-oxides, a new kind of organophosphorus heterocycles, was accidentally found by our research group in the process of an intentional synthesis of α-aminophosphonate through Kabachnik–Fields reaction through a one-pot, three-component procedure using carbonyl compound, amine and dialkyl phosphite. Herein, we disclose a facile methodology to prepare these novel organophosphorus heterocycles.

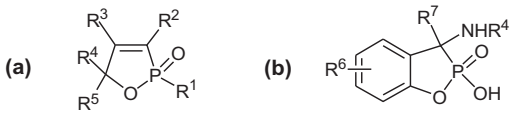

Fig. 1. The structures of 1,2-oxaphosphole 2-oxides derivatives.

2. Results and discussion

Instead of α-aminophosphonate **4a′**, a regular product of Kabachnik–Fields reaction, a cyclic α-aminophosphonate **4a** as shown in Scheme 1, namely 3-amino-2-hydroxy-6-methoxy-3-propyl-2,3-dihydrobenzo[*d*][1,2]-oxaphosphole 2-oxide, was

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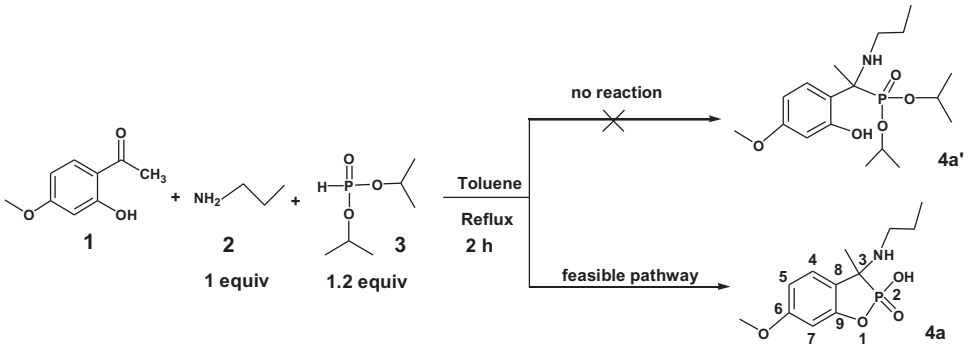


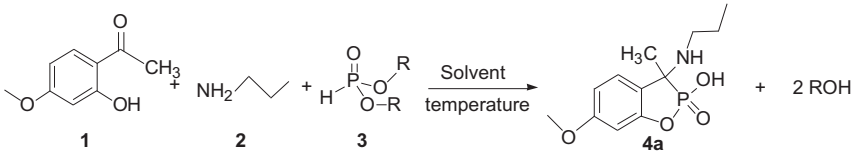
Scheme 1. Preparation of 2-hydroxy-6-methoxy-3-propylamino-2,3-dihydrobenzo[*d*][1,2]-oxaphosphole 2-oxide (compound **4a**).

accidentally obtained using 4-methyloxyl-2-hydroxyacetophenone **1**, propylamine **2** and diisopropyl phosphite **3** as reactants under reflux in toluene.

Using compounds **1**, **2** and diisopropyl phosphite as the reactants, the influence of the reaction temperature on the reaction was subsequently investigated in toluene solution at different temperatures 20, 30, 50, 80, 110 °C for 3 h (Table 1, entries 1–5). It can be seen that the yield was zero when the reaction temperature was below 30 °C, however increased slightly over the temperature range of 30–50 °C, and increased quickly over the temperature range of 50–110 °C, from 3% to 77%. It was especially worth mentioning that the reaction temperature was not increased further after the reactants began to reflux at approximate 110 °C, a boiling point of toluene. A relatively optimal condition towards synthesis of **4a** was further explored by using reactants **1**, **2** to react with any of the four other *H*-phosphonates besides diisopropyl phosphite **3** in toluene under reflux conditions for 3 h, respectively, as shown in Table 1 (entries 6–9). The results show that only cyclic product **4a** was obtained in each experimental case. It can be seen that even though **4a** could be synthesized by using any of the four given *H*-phosphonates, no yield obtained by using any of them was higher than 77%, a yield achieved by using diisopropyl phosphite as a phosphorus reactant under the same reaction conditions. Using compounds **1**, **2** and diisopropyl phosphite **3** as the reactants, several solvent systems together with a solvent-free system were further employed, respectively, to explore the optimal reaction condition for the preparation of cyclic compound **4a**. The reaction solutions were refluxed for 3 h at a temperature close to each boiling point of the used solvents, and maintained temperature at approximate 155 °C in the case of the solvent-free reaction system involved, respectively (Table 1, entries 10–15). The results show that the largest yield (yield: 77%) was obtained by refluxing the reactants in toluene.

The scope of the reactants was then enlarged to cover various 2-hydroxyacetophenones and amines as shown in Table 2. All the reactions were performed in toluene under reflux for 3 h using only diisopropyl phosphite as the phosphorus reagent. It is worth illustrating here that only the corresponding cyclic products, namely 3-amino-2-hydroxy-2,3-dihydrobenzo[*d*][1,2]-oxaphosphole 2-oxides (**4a**–**g**) were afforded in relatively good yields as shown in Table 2. Moreover, the fact that all the corresponding final cyclic products automatically precipitated from toluene solution as they were formed, significantly simplified the purification process. The final

Table 1
Optimization of conditions



Entry	Temperature (°C)	*H*-Phosphonates	Solvent	Yield[d] (%)
1	20	Diisopropyl phosphite	Toluene	0[a]
2	30	Diisopropyl phosphite	Toluene	0[a]
3	50	Diisopropyl phosphite	Toluene	3[a]
4	80	Diisopropyl phosphite	Toluene	38[a]
5	110	Diisopropyl phosphite	Toluene	77[a]
6	110	Dimethyl phosphite	Toluene	40[b]
7	110	Diethyl phosphite	Toluene	56[b]
8	110	Dibenzyl phosphite	Toluene	61[b]
9	110	Diphenyl phosphite	Toluene	49[b]
10	81	Diisopropyl phosphite	CH_3CN	0[c]
11	66	Diisopropyl phosphite	THF	6[c]
12	101	Diisopropyl phosphite	Dioxane	3[c]
13	117	Diisopropyl phosphite	n-C_4H_9OH	0[c]
14	152	Diisopropyl phosphite	DMF	34[c]
15	155	Diisopropyl phosphite	No solvent	41[c]

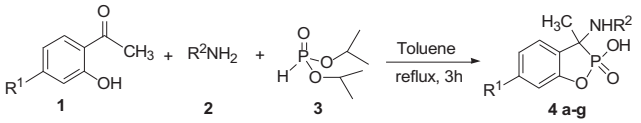
[a] Reaction conditions: using 4-methyloxyl-2-hydroxyacetophenone **1** (1 mmol), propylamine **2** (1 mmol) and diisopropyl phosphate **3** (1.2 mmol) in toluene (3 mL) at different temperature for 3 h.

[b] Reaction conditions: using 4-methyloxyl-2-hydroxyacetophenone **1** (1 mmol), propylamine **2** (1 mmol) to react with 5 different *H*-phosphonates **3** (1.2 mmol) in toluene (3 mL) under reflux for 3 h.

[c] Reaction conditions: using 4-methyloxyl-2-hydroxyacetophenone **1** (1 mmol), propylamine **2** (1 mmol) and diisopropyl phosphite **3** (1.2 mmol) as reactants, using different solvents (3 mL) under reflux conditions or at 155 °C when non-solvent system employed for 3 h, respectively.

[d] Isolated yields.

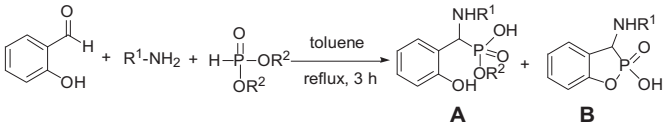
Table 2
Various 2-hydroxyacetophenones and amines were investigated to be reacted with diisopropyl phosphite[a]



Entry	R^1	R^2	Yield[b] (%)
4a	6-OCH_3	*n*-Pr	77
4b	6-OCH_3	CH_3	65
4c	6-OCH_3	C_2H_5	70
4d	6-OCH_3	H	75
4e	6-OCH_3	*n*-Bu	68
4f	H	*n*-Pr	70
4g	H	*n*-Bu	69

[a] Condition: *o*-hydroxyacetophenone and its derivatives **1** (1 mmol), diverse amines **2** (1 mmol), were reacted with diisopropyl phosphite **3** (1.2 mmol) in toluene (3 mL) under reflux for 3 h.
[b] Isolated yields.

Table 3
Ratio of products (**A**/**B**). *o*-Hydroxybenzaldehyde and its derivatives (1 mmol), diverse amines (1 mmol), different *H*-phosphonates (1.2 mmol) in toluene (3 mL) under reflux for 3 h



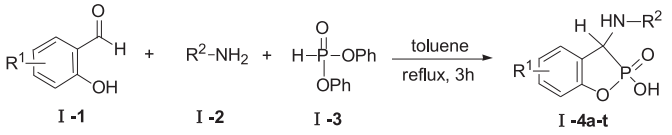
Entry	R^1, R^2	Ratio of products (**A**/**B**)
1	R^1=*n*-Pr, R^2=*i*-Pr	100:0
2	R^1=*n*-Pr, R^2=Et	60:40
3	R^1=*n*-Pr, R^2=Me	5:95
4	R^1=*n*-Pr, R^2=*n*-Bu	100:0
5	R^1=*n*-Pr, R^2=*i*-Bu	100:0
6	R^1=*n*-Pr, R^2=Ph	0:100
7	R^1=*n*-Pr, R^2=$PhCH_2$	0:100
8	R^1=Et, R^2=Ph	0:100
9	R^1=Et, R^2=$PhCH_2$	100:0

purification was accomplished by subsequent filtration followed by washing with methanol and drying in vacuum. It is also worth noticing that the methodology shown here exclude using aromatic amines as the reactants. It is proved that even though aromatic amines, such as aniline, 4-chloroaniline, *p*-methoxyaniline, 4-methylaniline, 3-methylaniline, 4-nitroaniline, could effectively react with 2-hydroxyacetophenones to afford the corresponding imines, the imines could not undergo the addition reaction further with *H*-phosphonates under the reaction condition, and let alone the subsequent intramolecular ester exchange reaction leading to heterocyclic α-aminophosphonates via a nucleophilic attack of *ortho*-hydroxyl group to the partially positive phosphorus atom of phosphoryl group.

It strongly suggests from the above experimental results that the heterocyclic α-aminophosphonates can be forced to form when using the relatively high steric hindrance of 2-hydroxyacetophenones. It is conceivable that even if the acyclic α-aminophosphonates possibly were formed via the reaction of 2-hydroxyacetophenones and the amines, they were to a great extent prone to undergo an intramolecular ester exchange reaction to reduce their relatively high steric hindrance.

It is known that aldehydes are usually more reactive towards nucleophilic additions than ketones because of both steric and electronic effects. Aldehydes and ketones usually display varying results when combined with chemical reagents. The reaction, using 2-hydroxybenzaldehye, instead of 2-hydroxyacetophenone, along with diisopropyl phosphite and propylamine as the reactants, was therefore performed intentionally under reflux operating conditions in toluene for 3 h as shown in Table 3. It is can be seen that instead of affording the cyclic product **B**, the reaction of 2-hydroxybenzaldehye with isopropyl phosphite and propylamine completely led to an α-amino monophosphonate **A**, a normal product of Kabachnik–Fields reaction (Table 3, entry 1). Synthetic methods possibly leading 2-hydroxybenzaldehye to the formation of the heterocyclic product **B** were subsequently investigated. The reactions using different amines and *H*-phosphonates along with 2-hydroxybenzaldehye as the reactants were investigated as shown in Table 3. The molar ratios of compounds **A** and **B** were determined from ^{31}P NMR integration of two phosphorus atom signals of the products **A** (about δ 22 ppm) and **B** (about δ 17 ppm) and the related results are repeatable. It is especially worth emphasizing that cyclic product **B** favoured reactions were practically realized by employing diphenyl phosphite as a phosphoryl reagent in both cases: propylamine and ethylamine being employed (Table 3, entries 6 and 8). It is concluded that in the case of *o*-hydroxybenzaldehydes, diphenyl phosphite can be used for heterocyclic α-aminophos phonates. The results may better be explained by the relatively high reaction activity of diphenyl phosphate in the related reactions. It may attribute to the better leaving group ability of the phenoxide anion relative to that of an alkoxide anion or more positive of phosphorus atom in case of diphenyl phosphite than dialkyl phosphite. The *ortho*-hydroxyl most possibly attack the positive phosphorus via the intramolecular ester exchange reaction to form the corresponding heterocyclic α-aminophosphonates in the case when diphenyl phosphite was employed. It is known that aldehydes are usually more reactive towards nucleophilic additions than ketones because of both steric and electronic effects. That's why 2-hydroxybenzaldehyes and 2-hydroxyacetophenones usually display varying results when combined with amines and dialkyl phosphates under the reaction conditions. It is also concluded from the results shown in Tables 2 and 4 that the yields of the corresponding heterocyclic products are not influenced obviously by various substituted groups attached to the

Table 4
Various *o*-hydroxybenzaldehydes and amines were investigated to be reacted with diphenyl phosphite[a]



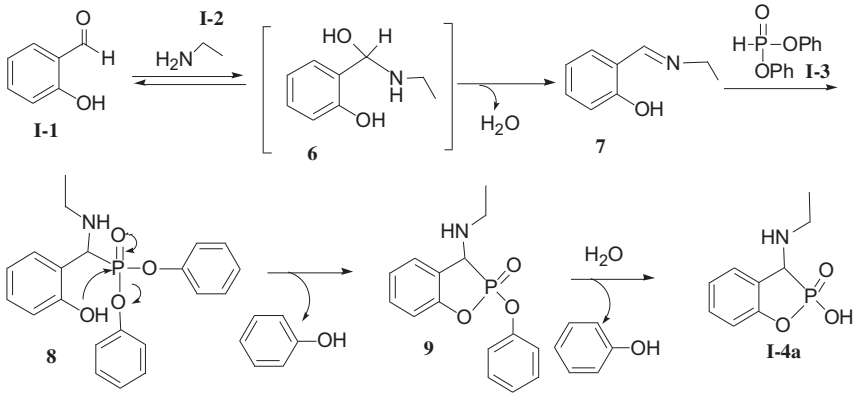
Entry	R^1	R^2	Yield[b] (%)
I-**4a**	H	Et	76
I-**4b**	H	*n*-Pr	80
I-**4c**	H	*n*-Bu	75
I-**4d**	H	*n*-Hex	70
I-**4e**	H	*n*-Oct	90
I-**4f**	5-NO_2	Et	65
I-**4g**	5-NO_2	*n*-Pr	85
I-**4h**	5-NO_2	*n*-Bu	81
I-**4i**	5-NO_2	*n*-Hex	76
I-**4j**	3-NO_2	Et	79
I-**4k**	3-NO_2	*n*-Pr	83
I-**4l**	3-NO_2	*n*-Bu	65
I-**4m**	3-NO_2	*n*-Hex	74
I-**4n**	5-Br	*n*-Pr	68
I-**4o**	3,5-Br	*n*-Pr	70
I-**4p**	3,5-I	*n*-Pr	75
I-**4q**	3,5-I	*n*-Bu	69
I-**4r**	5-I	*n*-Pr	67
I-**4s**	5-I	*n*-Bu	66
I-**4t**	H	$CH_2CH_2NH_2$	65

[a] Condition: *o*-hydroxybenzaldehyde and its derivatives I-**1** (1 mmol), various primary amines I-**2** (1 mmol) were reacted with diphenyl phosphite (1.2 mmol) in toluene (3 mL) under reflux for 3 h.
[b] Isolated yields.

benzene ring, no matter electron withdrawing groups such as $-NO_2$, $-X$, or electron donating group such as $-OCH_3$. It may be supported by the deduction that the reactivity of the carbonyl group, formaldehyde group for 2-hydroxybenzaldehyes and formyl group for 2-hydroxyacetophenones, are mainly affected by the hydroxyl group, a relatively strong activating electron releasing group at the *ortho* position.

Synthesis, using diphenyl phosphite, along with a variety of 2-hydroxybenzaldehyes and primary amines as the reactants, was further investigated by performing the reactions under reflux conditions in toluene for 3 h, respectively, as shown in Table 4. As expected, diphenyl phosphite unexceptionally brought about only the cyclic products in any given case. Twenty 2-hydroxy-3-alkylamino-2,3-dihydrobenzo[*d*][1,2]oxaphosphole 2-oxides(I-**4a**–**t**) were obtained in relatively good yields.

Obviously, this reaction should be, in reality, a multistep procedure having quite a complex mechanism involved. Here the related mechanism is reasonably proposed as shown in Scheme 2.



Scheme 2. A proposed reaction mechanism for compound I-**4a**.

The first step is the formation of the corresponding imine **7**. Because its formation is a reversible process, the application of any means, permitting the elimination of the water formed is helpful for the whole process. In the second step the compound diphenyl phosphite I-**3** having P–H bond adds to the C=N bond of the transient imine **7** to give the corresponding phosphonate **8**. In the third step, a novel five-membered ring intermediate **9** is formed by an intramolecular ester exchange reaction via a nucleophilic attack of *ortho*-hydroxyl group at the partially positive phosphorus atom of phosphoryl group. It is reasonable to assume that the ester exchange reaction would be favoured by forming a relatively stable intermediate **9** with a five-membered ring containing phosphorus atom. The final product I-**4a** is finally obtained followed by a subsequent hydrolysis of intermediate **9**.

3. Conclusion

Herein, we developed a convenient one-pot three-component approach to the synthesis of a series of novel heterocyclic α-aminophosphonates starting either from 2-hydroxyacetophenones or 2-hydroxybenzaldehyes. Using diisopropyl phosphite along with 2-hydroxyacetophenone or any of the substituted 2-hydroxyaceto phenones and primary amines, a wide range of the corresponding heterocyclic α-aminophosphonates could be synthesized in relatively high yields. In the case of using 2-hydroxybenzaldehye as the starting reactant, the chemical reactions, towards only in the cyclic product favoured direction, observably could be conducted by employing diphenyl phosphite as the phosphoryl reagent under the circumstances. The approaches described here obviously have significant advantages in terms of experimental simplicity, mild reaction conditions and easy work-up, and would surely represent a convenient tool for the synthesis of a variety of this novel type of organophosphorus heterocycles.

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Supplementary data

Supplementary data related to this article can be found in the online version, at doi:10.1016/j.tet.2012.02.059.

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