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# Exceptional Effect of Nitro Substituent on the Phosphonation of Imines: The First Report on Phosphonation of Imines to α-Iminophosphonates and α-(*N*-phosphorylamino)phosphonates

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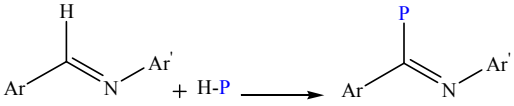
A novel and chemoselective method is reported for the simple phosphonation of imines. By change of the electronic effects of the substituents, this method offers the selective synthesis of either α-iminophosphonates or α-(*N*-phosphorylamino)phosphonates. The mild reaction condition makes this protocol very attractive for synthesis of these two classes of phosphorous compounds.

## Introduction

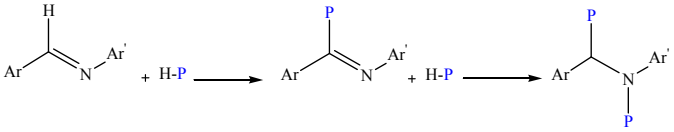
Organic phosphorus compounds, particularly phosphonates and their derivatives are considered as an important class of organophosphorus compounds with widespread applications in medicinal[1] and agricultural chemistry.[2] In biological chemistry, phosphonate compounds play an important role as pharmaceuticals due to their unique structure and charge distribution.[3] In addition, there are reports for their uses in organic synthetic blocks[4] and as phophorous-containing ligands for metal-catalyzed C-C bond formation.[5] Therefore, development of more convenient and efficient methods to form the C-P bond is a current topic and challengeable to researchers in organic chemistry. The Michaelis-Arbuzov reaction is a well-known and classical method for C−P bond formation discovered by August Michaelis in 1898.[6] During the last few years significant advances have been achieved in the development of cross-coupling methodologies for the synthesis of different classes of aromatic phosphonate compounds. For example, the first cross-coupling arylboronic acids and *H*-phosphonate diesters using catalytic amounts of copper(II) oxide and phenanthroline catalyst in order to yield aryl phosphonates have been reported by Zhuang and co-workers.[7] Recently, metal-catalyzed direct C-H bond functionalization has offered one of the most effective and efficient pathways for C-P bond construction.[8-11] There are some examples in the literature in the development of C-P bond forming reactions via direct C-H bond cleavage. A pyridine-directed C-H phosphonation reaction with *H*-phosphonates by palladium catalyst is an example for the preparation of aryl phosphonates by C-H bond activation.[11] The palladium-catalyzed C-3 dehydrogenative phosphonation of coumarin derivatives is a typical example for the regioselective $sp^2$C-H bond functionalization.[10] Since α-aminophosphoric acids are the most widely studied classes of biologically active compounds[12] as well as important surrogates for carboxylic amino acids,[13] chemists have been encouraged in the progress of methods for their synthesis. The phosphonation of $sp^3$ C-H bonds of adjacent to tertiary amines is an operative oxidative protocol to afford α-aminophosphonates.[9, 14-15] In this regard, metal catalysts such as Cu,[9, 15a,b,c] Fe,[15d,e,f] Ru,[15g, h] V,[15i,k] and Mo[15l] in the presence of an oxidant have been applied. α-Iminophosphonates are direct precursors of α-aminophosphonates through the conversion of the imine moiety into amine. In order to serve this purpose, simple reduction of the C-N double bond or addition of nucleophiles to the imine carbon has been applied.[16] Hence, direct approach to α-aminophosphonates based on the rhodium-, palladium- and ruthenium-catalyzed hydrogenation of the corresponding olefinic precursors are developing remarkably in recent years.[12, 17] Beletskaya and co-workers have achieved success for the hydrogenation of α-iminophosphonatesto optically active α-aminophosphonates with enantiomeric excesses up to 94% by $[Rh(COD)_2]^+SbF^{6-}$/(R)-BINAP complex.[12] In continuation of our work on the Pd catalyzed coupling reactions and phosphonation of aryl halides,[18] we were interested in oxidative phosphorylation of C-H bond of ortho position of benzylidene moiety of Schiff bases, mainly due to the importance of oxidative cross-coupling reactions from the atom- and step-economical points of view and environmentally friendly synthetic approach.[19] In addition, Schiff bases as an important class of organic compounds possess a wide variety of applications in many fields including analytical, biological, and inorganic chemistry.[20] However, to our surprise, the separated products from this protocol showed that instead of C-H activation, C=N bond of imine underwent phosphorylation, and

produced α-iminophosphonatesand α-(*N*-phosphorylamino)phosphonates. Since α-iminophosphonates are precursors of α-aminophosphonic acids, their simple and easy synthesis is of importance. According to the literature review, various methods for the synthesis of α-iminophosphonates have been reported.[12, 16, 21] For example, α-iminophosphonates were synthesized at 120-170°C via the Arbuzov reaction of triethylphosphite with imidoyl chlorides prepared by reacting thionyl chloride and amides.[12] Addition of sodium salt of dialkylphosphites to the triple bond of nitriles represents another route to form such compounds as reaction intermediates to produce phosphoryl aminophosphonates; however, in the reactions of nitriles with *H*-phosphonate dialkyl esters, the iminophosphonates were never isolated as the reaction intermediates.[21] Also, α-iminophosphonates were prepared by aza-Wittig reaction of phosphazenes derived from the addition of trimethylphosphineto azides with α-ketophosphonates.[16] In this article, we disclose a novel metal free reaction for direct oxidative phosphonation of imines to α-iminophosphonates (Scheme 1a) or oxidative phosphonation followed by addition process to offer α-(*N*-phosphorylamino)phosphonates (Scheme 1b). To the best of our knowledge, direct α-phosphonation of imines leading to α-iminophosphonates and also α-(*N*-phosphorylamino)phosphonates has not been reported before. In this work, we report for the first time on the effect of substituents on the aromatic ring for phosphonation of imines to offer either α-iminophosphonates or α-(*N*-phosphorylamino)phosphonates.

a.




b.

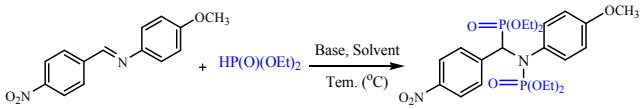



**Scheme 1**

## Results and discussion

Our initial study for Pd catalyzed C-H activation was on the reaction of (4-nitro-benzylidene)-(4-methoxy-phenyl)-imine (**1a**), with *H*-phosphonate diethylester in the presence of 4.0 equiv. of DBU (1,8-diazabicyclo[5.4.0]undec-7-ene), $Pd(OAc)_2$ (10 mol%), and AgOAc (1.5 equiv.) as an oxidant in $CH_3CN$ at 80 °C (Table 1, entry 1). When the reaction was worked up, the obtained product was found to be diethyl [α-(*N*-phosphoryl)-(4-methoxy-phenyl)-amino]4-nitro-benzyl phosphonate (**2a**) in moderate yield. We decided to eliminate both the Pd catalyst and the oxidant from the reaction mixture. The obtained result showed that again the product **2a** is obtained in the same yield (Table 1, entry 2). Further optimization of the reaction conditions was focused on producing the product **2a** in higher yield. Therefore, the effects of different parameters were studied. The reaction underwent with various solvent screenings and the best result was acquired in toluene (Table 1, entry 5). According to the results of Table 1, entry 6; the reaction did not work well under solvent-free condition. In our optimization, several bases were also studied for this reaction such as DABCO (1,4-diazabicyclo[2.2.2]octane), $Et_3N$, $K_2CO_3$, NaOAc, and $LiNH_2$. The reaction did not proceed by using DABCO, $Et_3N$, $K_2CO_3$ and $LiNH_2$ (Table 1, entries 7, 8, 9, 10) and using NaOAc as a base, the product was obtained in low yield (Table 1, entry 11). According to these results, we selected DBU as the most suitable base. Furthermore, by replacing the *H*-phosphonate diethyl ester with triethylphosphite, the reaction failed under our optimized conditions (Table 1, entry 12). Decreasing the amount of *H*-phosphonate diethyl ester and DBU from four equimolar to two resulted in very low yield (Table 1, entries 13, 14). Performing the reaction at 60 °C led to very good yield of the phosphonated product **2a** (Table 1, entry 15), while lowering the temperature to 35°C and room temperature, the reaction either was very slow or did not occur at all (Table 1, entries 16, 17). One pot reaction of 4-nitrobenzaldehyde, 4-methoxyaniline with *H*-phosphonate diethyl ester and DBU in toluene at 60 °C gives a complex mixture.

**Table 1.** Effect of different reaction parameters on phosphonation of (4-nitro-benzylidene)-(4-methoxy-phenyl)-amine.[a]



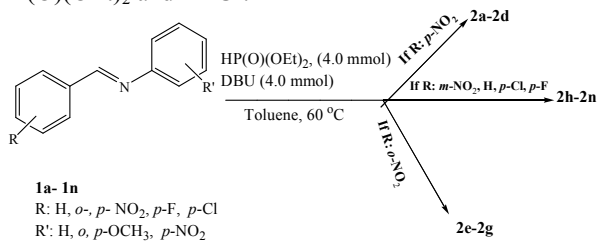

**1a** **2a**

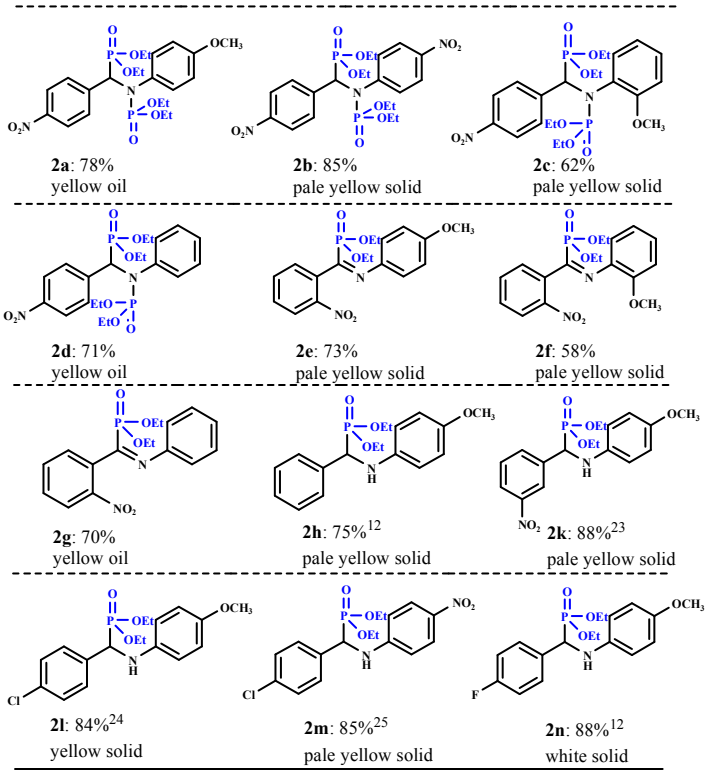
| Entry | Base | Solvent | Tem. (°C) | Yield[b] **(%)** |
|---|---|---|---|---|
| 1[c] | DBU | $CH_3CN$ | 80 | 58 |
| 2 | DBU | $CH_3CN$ | 80 | 60 |
| 3 | DBU | PEG200 | 80 | 0 |
| 4 | DBU | EtOH | 80 | 0 |
| 5 | DBU | Toluene | 80 | 77 |
| 6 | DBU | Solvent free | 80 | 22 |
| 7 | DABCO | Toluene | 80 | 0 |
| 8 | $Et_3N$ | Toluene | 80 | 0 |
| 9 | $K_2CO_3$ | Toluene | 80 | 0 |
| 10 | $LiNH_2$ | Toluene | 80 | 0 |
| 11 | NaOAc | Toluene | 80 | 25 |
| 12[d] | DBU | Toluene | 80 | 80 |
| 13[e] | DBU | Toluene | 80 | 10 |
| 14[f] | DBU | Toluene | 80 | 15 |
| 15 | DBU | Toluene | 60 | 75 |
| 16 | DBU | Toluene | 35 | trace |
| 17 | DBU | Toluene | RT | 0 |

[a]Reaction conditions: (4-nitro-benzylidene)-(4-methoxy-phenyl)-amine (**1a**) (1mmol), *H*-phosphonate diethyl ester (4mmol), base (4mmol), solvent (4ml). [b]Isolated yield. [c]$Pd(OAc)_2$ (10 mol%, 10 mg) as a catalyst, AgOAc as an oxidant (1.5 equiv., 0.25g) were added to the reaction mixture. [d]Triethylphosphite was added to the mixture in place of *H*-phosphonate diethyl ester. [e]The amount of *H*-phosphonate diethyl ester is 2mmol. [f]The amount of used DBU is 2mmol. All of the reactions were monitored by TLC after 24h.

With optimized reaction conditions in hand; imine (1mmol), *H*-phosphonate diethyl ester (4mmol), DBU (4mmol), and toluene (4ml) at 60 °C, we examined various imines so as to gauge the scope of the reaction (Table 2). Initially, various *N*-aryl groups of (4-nitro-benzylidene)amines (**1a-d**) were investigated. When the substituent groups were placed on the *para*-position of the imino unit, we obtained higher yields of the diphosphonates, especially for those imines having electron-withdrawing substituents (Table 2, 2a, 2b). (4-Nitro-benzylidene) amine bearing an electron-donating group at the ortho-position such as $-OCH_3$ has some steric effect and therefore, slightly decreases the yield of the product (Table 2, 2c). The phosphonation reaction proceeded smoothly for 4-nitrobenzylidene amine (**1d**) and the product was obtained in 71% yield (Table 2, 2d). We extended the phosphonation reaction to (2-nitro-benzylidene) amines in order to study the orientation effect on the yield and the scope of the reaction. When the $-NO_2$ group was placed in the ortho position of the ring, a very distinct steric effect was observed which changed the scope of the reaction. The characterization of the isolated products showed that in these cases, instead of diphosphonates, the corresponding α-iminophosphonates have been obtained (Table 2, 2e, 2f, 2g). In this study, imines of (2-nitro-benzylidene)-(4-methoxy-phenyl)-amine (**1e**) and (2-nitro-benzylidene)-phenylamine (**1g**) produced their corresponding α-iminophosphonates in 73% and 70%, respectively (Table 2, 2e, 2g). We also evaluated imines bearing electron withdrawing groups other than $-NO_2$ linked on the *para*-position of benzylidene unit such as -Cl, and -F. First, the phosphonation reaction of (4-chloro-benzylidene)-(4-methoxy-phenyl)-amine (**1l**) was carried out under the same reaction conditions as with **1a**. Formation of α-aminophosphonate (Table 2, 2l) from **1l** directed us toward studying the electronic effect of the substitutions. Since $-NO_2$ as a strong withdrawing group has electronically impact on the phosphorylated products **2a-2g**, we did the phosphonation of (4-chloro-benzylidene)-(4-nitro-phenyl)-amine (**1m**) with *H*-phosphonate diethyl ester and DBU as a base in toluene at 60 °C. The product was the corresponding α-aminophosphonate (Table 2, 2m). (4-Fluoro-benzylidene)-(4-methoxy-phenyl)-amine (**1n**) as an imine possessing more electron-withdrawing halogen than **1l** was also applied in this cross-coupling reaction and the only obtained product was found to be diethyl α-(4-methoxyphenylamino)-(4-flurorobenzyl)phosphonate in slightly higher yield than **2l** (Table 2, 2n). According to the observed results, the attachment of $-NO_2$ group on benzylidene unit of imine shows distinguishing electronic effect to product α-iminophosphonates and α-(*N*-phosphorylamino)phosphonates (**2a-2g**). Encouraged by these results, (3-nitro-benzylidene)-(4-methoxy-phenyl)-amine (**1k**) was chosen as another example to study the orientation and electronic effects of phosphonation reaction. It was converted into the corresponding α-aminophosphonate with excellent yield (Table 2, 2k). As a result, the reaction is applicable to substrates bearing $-NO_2$ group in ortho and *para* position of imines in order to generate α-iminophosphonate and α-(*N*-phosphorylamino)phosphonates, and becauseof subtle steric and electronic effects, it is highly chemoselective.

**Table 2.** Phosphonation of imines in toluene using $HP(O)(OEt)_2$ and DBU[a].

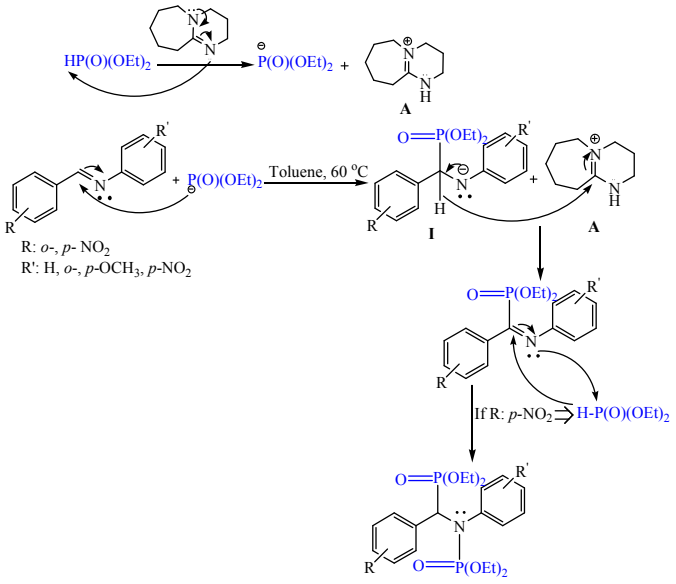


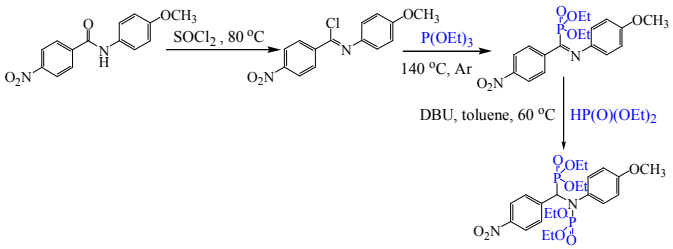

All of the reactions have been monitored by TLC after 24h.

Although the mechanism for this reaction is unclear, we proposed the following probable mechanism. In the first step, diethyl phosphonate anion and salt **A** is formed from the reaction of *H*-phosphonate diethyl ester and DBU as a base. Then, the attack of diethyl phosphonate anion to imine in toluene at 60 °C produces adduct **I** which may be a key intermediate in the reaction. The next step includes oxidation of adduct **I** by salt **A** as shown in Scheme 2 and α-iminophosphonate forms in this stage. In the case of *para*-nitro derivatives, subsequently, the obtained α-iminophosphonate reacts with another equimolar of *H*-phosphonate diethyl ester to produce α-(*N*-phosphorylamino)phosphonates. DBU is a chemical compound used in organic synthesis as a catalyst, a

complexing ligand, and a well-known non-nucleophilic base. Herein, we introduce dual possible role of DBU both as base and as oxidant. To prove the possible role of DBU as an oxidant in the reaction, we carried out four control experiments. According to the results of these transformations, we conducted the first control experiment involving phosphonation of (4-nitro-benzylidene)-(4-methoxy-phenyl)-amine **1a** in the absence of DBU in EtOH as a solvent at 60 °C. The reaction monitoring showed that **1a** was converted almost completely into the corresponding α-aminophosphonate within 24h. Then, DBU was added to the reaction mixture and the desired product **2a** was produced. In the second control experiment, the reaction **1a** with *H*-phosphonate diethyl ester proceeded in toluene and in the absence of DBU at 60 °C. TLC analysis represented that the reaction did not occur. We expanded the control experiments using **1e** as a starting material in both EtOH and toluene in the absence of DBU at 60 °C. The corresponding α-aminophosphonate was obtained in EtOH and then the addition of DBU produced α-iminophosphonate **2e**. However, the reaction failed in toluene in the absence of DBU. Therefore, the presence of DBU plays a synergic role to produce the desired products. In order to get more insight into the proposed mechanism, the reaction of **1g** with *H*-phosphonate diethyl ester and DBU in toluene at 60 °C was done. The analysis of the reaction mixture supports the hypothesis that DBU acts as an oxidant through recognizing the reduced form of DBU in the reaction mixture. According to the $^{1}$H- and $^{13}$C-NMR (see the supporting information), the presence of N-H and C-H signals at 4.9 and 3.18 ppm, respectively and the absence of the signal for the carbon of C=N and the presence of C-H signal at 77.2 ppm in the reduced form of DBU are strong evidences for the reduction of DBU in this processes. Additionally, to prove the second phosphorylation in the proposed manner, we prepared the α-iminophosphonate of imine **1a** by described procedure in the literature.[12] Then, the purified α-iminophosphonate was allowed to react with *H*-phosphonate diethyl ester and DBU in toluene at 60 °C. After 24h, bisphosphonate **2a** was obtained as the main product (Scheme 3).




**Scheme 2.** Proposed mechanism.




**Scheme 3**

## Experimental Section

Melting points were determined and recorded in open capillaries with Buchi B-545 melting point instrument and were not corrected. $^{1}$H and $^{13}$C NMR spectra were recorded on a Brucker Avance DPX-250 spectrometers using $CDCl_3$ and tetramethylsilane (TMS) as internal standard in pure deuterated solvents. $^{31}$P NMR spectra were recorded on a Brucker Avance DPX-400 Ultra sheild. FTIR spectra were run on a Shimadzu FTIR-8300 spectrophotometer. Mass spectra were acquired on a Shimadzu GCMS-QP 1000 EX instrument at 70 eV. CHN analyses were performed with a Vario EL, ElementarAnalyser system GmbH (Hanau). The reaction monitoring was carried out on silica gel analytical sheets. Purification of products was carried out by column chromatography on the column of silica gel 60 Merck (230-240 mesh) in glass columns (2 or 3 cm diameter).

### General procedure for the preparation of imines[22]

Aldehyde (5.0 mmol) and 5.0 mmol of amine in ethanol (10.0 mL) were placed in a flask equipped with a magnetic stirrer, andrefluxcondenser. The reaction mixture was refluxed with stirring for 24 h. After completion, the reaction mixture was cooled to room temperature, and then mixture was left for crystallization. After recrystallization from ethanol, the pure products were obtained with excellent yield (**1a-n**).

### General procedure for phosphorylation of imines

A mixture of imine (1.0 mmol), *H*-phosphonate diethyl ester (0.5 mL, 4.0 mmol), and DBU (0.48 mL, 4.0 mmol), in toluene (4 mL) was heated at 60 °C for 24h. After completion, the reaction mixture was cooled to room temperature and the solvent was evaporated under vacuum. Then, the crude organic mixture was purified by silica gel column chromatography (petroleumether/ethyl acetate 4:1) to obtain the desired products in moderate to excellent yield.

### Typical procedure for the preparation of *N*-(4-methoxyphenyl)-4-nitrobenzamide[26]

To a refluxing solution of $Ph_2PCl$ (0.27 mL, 1.5 mmol) and imidazole (0.30 g, 4.5 mmol) in 5 mL dichloromethane, iodine (0.37 g, 1.5 mmol) and 4-nitrobenzoic acid (0.33 g, 2.0 mmol) were added consecutively. After few minutes, *p*-anisidine (0.24 g, 2.0 mmol) was added to the reaction mixture and was left stirring at reflux for 20 min. Then, the organic layer was washed with saturated aqueous sodium carbonate (3 × 5 mL) and aqueous sodium thiosulfate (2 × 5 mL), and driedover $Na_2SO_4$. The desired product was obtained by column chromatography over silica gel with n-hexane / ethyl acetate (5:1) as eluent (yield: 88%).

**Typical procedure for the preparation of *N*-(*p*-anisyl)-4-nitrobenzenecarboxyimidoyl chloride[12]**

A mixture of *N*-(4-methoxyphenyl)-4-nitrobenzamide (0.27 g, 1.0 mmol) and thionylchloride (0.38 mL, 5.3 mmol) were stirred at 80 $^oC$ for 8h. Excess $SOCl_2$ was removed under reduced pressure, and the residue was purified by column chromatography over silica gel using n-hexane / ethyl acetate as eluent (7:1) affording the product as pale yellow crystals; yield: 0.24 g (75%).

**Typical procedure for the preparation of Diethyl α-(*p*-anisylimino)-4-nitrobenzylphosphonate[12]**

To a 3-necked round flask equipped with a magnetic stirrer, *N*-(*p*-anisyl)-4-nitrobenzenecarboxyimidoyl chloride (0.32 g, 1.0 mmol) and triethylphosphite (0.25mL, 1.5 mmol) was added under Ar. The reaction mixture was stirred at 140 $^oC$ for 8h and then purified by column chromatography over silica gel with n-hexane / ethyl acetate as eluent (4:1) giving iminophosphonate as a yellow oil; yield: 0.3 g (70%).

**Typical procedure for the preparation of Diethyl [α-(*N*-phosphoryl)-(4-methoxy-phenyl)-amino]4-nitro-benzyl phosphonate (2a)**

To a 25-ml round flask containing α-iminophosphonate (0.21 g, 0.5 mmol) prepared from previous reaction was added *H*-phosphonate diethyl ester (0.125 mL, 1.0 mmol), and DBU (0.145 mL, 1.0 mmol), in toluene (2 mL) and heated at 60 °C for 24h. The solvent was removed in vacuo. Then, the crude organic mixture was purified by silica gel column chromatography (petroleumether/ethyl acetate 4:1) to obtain the bisphosphonate product.

Diethyl [α-(*N*-phosphoryl)-(4-methoxy-phenyl)-amino]4-nitro-benzyl phosphonate (**2a**) was obtained as yellow oil; yield: 0.414 g, 78%; $^1$H-NMR ($CDCl_3$, 250 MHz) δ (ppm): 8.06 (d, 2H, J= 9Hz), 7.49 (d, 2H, J= 9Hz), 6.82 (d, 2H, J= 9Hz), 6.66 (d, 2H, J= 9Hz), 5.63 (dd, 1H, $^2$J (H-P)= 23.1Hz, $^3$J (H-P)= 11Hz), 4.23-3.78 (m, 8H), 3.70 (d, 3H, J= 1Hz), 1.30 (t, 3H, J= 7Hz), 1.20 (mt, 3H, ), 1.10 (mt, 3H), 1.02 (t, 3H, J= 7Hz); $^{13}$C-NMR ($CDCl_3$, 62.9 MHz) δ (ppm): $^{13}$C-NMR ($CDCl_3$, 62.9 MHz) δ (ppm): 159.0, 147.7 , 142.1 (d, $^2$J(C-P)= 6.0Hz), 132.9, 131.9 (d, $^2$J(C-P)= 8.4Hz), 129.4, 123.2, 113.4, 62.6- 63.0 (m, 4C, -$CH_2$-,), 58.5 (dd, -CH-, $^2$J (C-P)= 8.3Hz, $^1$J (C-P)= 162.1Hz), 55.2 (1C, -$OCH_3$), 15.9-16.4 (m, 4C, -$CH_3$); $^{31}$P-NMR ($CDCl_3$, 162 MHz) δ (ppm): 19.94 (d, $^3$J(P-P)= 21.8 Hz), 5.71(d, $^3$J (P-P)= 21.8 Hz); IR (KBr): ν [$cm^{-1}$] 2985.6, 2931.6, 2869.9, 1604.7, 1519.8, 1350.1, 1249.8, 1026.1, 964.3, 864.1; Anal. Calcd for $C_{22}H_{32}N_2O_9P_2$: C, 49.81; H, 6.08; N, 5.28. Found: C, 49.42; H, 5.83; N, 4.98.

Diethyl [α-(*N*-phosphoryl)-(4-nitro-phenyl)-amino] 4-nitro-benzyl phosphonate (**2b**): Pale yellow solid (mp: 87-88 ºC); $^1$H-NMR ($CDCl_3$, 250 MHz) δ (ppm): 8.16 (d, 2H, J= 9Hz), 8.08 (d, 2H, J= 9Hz), 7.63 (d, 2H, J= 9Hz), 7.21 (d, 2H, J= 9Hz), 5.83 (dd, 1H, $^2$J(H-P)= 24.6Hz, $^3$J(H-P)=11.8Hz), 4.31-3.85 (m, 8H), 1.35 (t, 3H, J= 7Hz), 1.29 (mt, 3H), 1.20 (t, 3H), 1.12 (t, 3H, J= 7Hz); $^{13}$C-NMR ($CDCl_3$, 62.9 MHz) δ (ppm): 147.8, 146.2, 144.5, 141.5 (d, $^3$J(C-P)= 3.5Hz), 131.1 (d, $^2$J(C-P)=7.9Hz), 130.4, 123.6 (d, $^2$J(C-P)= 7.9Hz), 63.0-63.7 (m, 4C, -$CH_2$-), 58.4 (dd, -CH-, $^2$J (C-P)= 5.5Hz, $^1$J (C-P)= 161.0Hz), 15.9-16.4 (m, 4C, -$CH_3$); $^{31}$P-NMR ($CDCl_3$, 162 MHz)δ (ppm): 19.28 (d, $^3$J(P-P)= 20.5 Hz), 4.51 (d, $^3$J(P-P)= 20.5 Hz); IR (KBr): ν [$cm^{-1}$] 2977.9, 2916.2, 1595.9, 1519.8, 1350.1, 1249.8, 1026.1, 972.1; MS (70 eV, EI): m/z (%): 545, $M^+$ (0.4), 408 (100.0); Anal. Calcd for $C_{21}H_{29}N_3O_{10}P_2$: C, 46.24; H, 5.36; N, 7.70. Found: C, 46.25; H, 5.75; N, 8.00.

Diethyl [α-(*N*-phosphoryl)-(2-methoxy-phenyl)-amino]4-nitro-benzyl phosphonate (**2c**): Pale yellow solid (mp: 115-115.5 ºC); $^1$H-NMR ($CDCl_3$, 250 MHz) δ (ppm): 8.12-8.09 (m, 2H), 7.91-7.88 (m, 2H), 6.76-6.60 (m, 2H), 6.49- 6.41 (m, 1H), 6.10 (d, 1H, J= 7.5Hz), 5.68-5.64 (m, 1H), 4.21-3.96 (m, 11H), 1.23-1.09 (m, 12H); $^{13}$C-NMR ($CDCl_3$, 62.9 MHz) δ (ppm): $^{13}$C-NMR ($CDCl_3$, 62.9 MHz) δ (ppm): 158.2, 143.2, 136.3, 130.2 (d, $^2$J(C-P)= 4.1Hz), 129.6, 122.5, 119.6, 118.6, 116.6, 64.1-64.4 (m, 4C, -$CH_2$-), 57.8 (broad s, 1C, -CH-), 55.7 (1C, -$OCH_3$), 16.2 (broad s, 4C, -$CH_3$); $^{31}$P-NMR ($CDCl_3$, 162 MHz)δ (ppm): 20.76, 17.51; IR (KBr): ν [$cm^{-1}$] 2985.6, 2931.6, 1596.9, 1519.8, 1458.1, 1342.4, 1249.8, 1164.9, 1118.6, 1026.1, 972.1, 856.3, 740.6; MS (70 eV, EI): m/z (%): 530, $M^+$ (5.7), 255 (100.0); Anal. Calcd for $C_{22}H_{33}N_2O_9P_2$: C, 49.81; H, 6.08; N, 5.28. Found: C, 49.50; H, 5.78; N, 5.08.

Diethyl [α-(*N*-phosphoryl)-(phenyl)-amino]4-nitro-benzyl phosphonate (**2d**): Yellow oil; $^1$H-NMR ($CDCl_3$, 250 MHz) δ (ppm): 8.06 (d, 2H, J= 8.2Hz), 7.51 (d, 2H, J= 8.7Hz), 7.20-7.14 (m, 3H), 6.95-6.90 (m, 2H), 5.66 (dd, 1H, $^2$J (H-P)= 23.5Hz, $^3$J (H-P)= 11.5Hz), 4.25-3.74 (m, 8H), 1.28 (t, 3H, J= 7Hz), 1.21 (mt, 3H), 1.09 (mt, 3H), 1.02 (t, 3H, J= 7Hz); $^{13}$C-NMR ($CDCl_3$, 62.9 MHz) δ (ppm): 147.9, 131.8 (d, $^2$J(C-P)= 8.4Hz, two peaks), 131.6, 128.3, 128.0, 123.2, 123.0, 62.6-63.1 (m, 4C, -$CH_2$-), 59.6-59.7 (m, 1C, -CH-), 54.3 (broad s, 1C, -CH-), 15.9-16.4 (m, 4C, -$CH_3$); $^{31}$P-NMR ($CDCl_3$, 162 MHz)δ (ppm): 19.60, 3.08; IR (KBr): ν [$cm^{-1}$] 2985.6, 2931.6, 1596.9, 1527.5, 1490.1, 1442.7, 1350.1, 1257.5, 1164.9, 1026.1, 972.1, 864.1, 794.6; MS (70 eV, EI): m/z (%): 500, $M^+$ (1.0), 363 (100.0); Anal. Calcd for $C_{21}H_{31}N_2O_8P_2$: C, 50.40; H, 6.04; N, 5.60. Found: C, 50.12; H, 5.72; N, 5.30.

Diethyl α-(p-anisylimino)-2-nitrobenzylphosphonate (**2e**): Pale yellow solid (mp: 77-78 ºC); $^1$H-NMR ($CDCl_3$, 250 MHz) δ

(ppm): 8.09-8.07 (m, 1H), 7.75-7.73 (m, 1H), 7.43-7.24 (m, 4H), 7.07-7.03 (m, 2H), 4.01-3.87 (m, 7H), 1.21-1.18 (m, 6H); $^{13}$C-NMR ($CDCl_3$, 62.9 MHz) δ (ppm): 161.4, 159.3, 149.7, 132.5, 130.0, 126.8 (d, $^4$J(C-P)= 4.0Hz), 122.8, 121.2, 120.0, 114.2, 113.6, 62.7 (d, $2CH_2$, $^2$J(C-P)= 5.3Hz), 55.6 ($OCH_3$), 16.0 (d, $2CH_3$, $^3$J(C-P)= 6.4Hz); $^{31}$P-NMR ($CDCl_3$, 162 MHz)δ (ppm): 2.76; IR (KBr): ν [$cm^{-1}$] 2985.6, 2931.6, 2839.0, 1643.2, 1604.7, 1512.1, 1450.4, 1388.7, 1296.1, 1249.8, 1172.6, 1026.1, 972.1, 833.2, 756.0; Anal. Calcd for $C_{18}H_{21}N_2O_6P$: C, 55.10; H, 5.39; N, 7.14. Found: C, 54.85; H, 5.04; N, 6.84.

Diethyl α-(ortho-anisylimino)-2-nitrobenzylphosphonate (**2f**): Pale yellow solid (mp: 147-148 ºC); $^1$H-NMR ($CDCl_3$, 250 MHz) δ (ppm): 8.13-8.08 (m, 1H), 7.79-7.75 (m, 1H), 7.62-7.54 (m, 1H), 7.40-7.25 (m, 4H), 7.12-7.11 (m, 1H), 7.10-7.08 (m, 1H), 4.08-3.81 (m, 4H), 3.78 (d, 3H, J= 1.8 Hz), 1.22 (mt, 3H), 1.13 (mt, 3H); $^{13}$C-NMR ($CDCl_3$, 62.9 MHz) δ (ppm): 157.6, 156.2, 147.9, 133.0, 132.3, 130.6, 128.6, 126.6, 126.4, 121.3, 120.4, 113.8, 111.9, 62.6 (d, $2CH_2$, $^2$J(C-P)= 4.8Hz), 55.8 ($OCH_3$), 15.9-16.1 (m, $2CH_3$); $^{31}$P-NMR ($CDCl_3$, 162 MHz) δ (ppm): 2.50; IR (KBr): ν [$cm^{-1}$] 2977.9, 2893.0, 1604.7, 1504.4, 1473.3, 1300.1, 1280.6, 1249.8, 1164.9, 1010.6, 979.8, 840.9, 763.8; MS (70 eV, EI): m/z (%): 392, $M^+$ (1.1), 223 (100.0); Anal. Calcd for $C_{18}H_{21}N_2O_6P$: C, 55.10; H, 5.39; N, 7.14. Found: C, 55.38; H, 5.74; N, 7.46.

Diethyl α-(phenylimino)-2-nitrobenzylphosphonate (**2g**): Yellow oil, $^1$H-NMR ($CDCl_3$, 250 MHz) δ (ppm): 8.12-8.09 (m, 1H), 7.78-7.74 (m, 1H), 7.60-7.50 (m, 5H), 7.33-7.30 (m, 2H), 4.03-3.91(m, 4H), 1.16 (t, 6H, J= 7Hz); $^{13}$C-NMR ($CDCl_3$, 62.9 MHz) δ (ppm): 157.9, 156.8, 151.8, 141.3, 132.9, 131.0, 129.0, 128.7, 126.9 (d, $^3$J(C-P)= 6.3Hz), 121.3, 113.7, 62.8 (d, $2CH_2$, $^2$J(C-P)= 5.6Hz), 16.0 (d, $2CH_3$, $^3$J(C-P)= 6.7Hz); $^{31}$P-NMR ($CDCl_3$, 162 MHz) δ (ppm): 4.49; IR (KBr): ν [$cm^{-1}$] 2985.6, 2931.6, 1658.7, 1596.9, 1504.4, 1473.5, 1388.7, 1257.5, 1164.9, 1110.9, 1049.2, 1010.6, 979.8, 840.9, 748.3; MS (70 eV, EI): m/z (%): 362, $M^+$ (0.4), 179 (100.0); Anal. Calcd for $C_{17}H_{19}N_2O_5P$: C, 56.35; H, 5.29; N, 7.73. Found: C, 56.05; H, 5.01; N, 7.50.

Diethyl α-(*p*-anisylimino)-4-nitrobenzylphosphonate: Yellow oil; $^1$H-NMR ($CDCl_3$, 250 MHz) δ (ppm): 8.17 (d, 2H, J= 16.7Hz), 7.77 (d, 2H, J= 16.7Hz), 7.19-6.90 (m, 4H), 4.73-4.23 (m, 4H), 3.91 (s, 3H), 1.39-1.14 (m, 6H); $^{13}$C-NMR ($CDCl_3$, 62.9 MHz) δ (ppm): 198.7, 160.5, 151.5, 145.0 , 137.5 (d, $^2$J(C-P)= 4.9Hz), 129.3 (d, $^2$J(C-P)= 4.5Hz), 122.7, 122.6, 115.5, 60.2 (d, -$CH_2$-,$^2$J (C-P)= 5.7Hz), 53.0 (1C, -$OCH_3$), 16.6 (d, -$CH_3$, $^3$J (C-P)= 4.7Hz); $^{31}$P-NMR ($CDCl_3$, 162 MHz)δ (ppm): 4.85.

## Conclusions

In summary, we have developed a novel and efficient method of oxidative phosphonation of imines with *H*-phosphonate diethyl ester using DBU both as base and as oxidant with high chemoselectivity.Also, we studied the electronic and orientation effects of substituents on the phosphonation of imines.

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# Exceptional Effect of Nitro Substituent on the Phosphonation of Imines: The First Report on Phosphonation of Imines to α-Iminophosphonates and α-(*N*-phosphorylamino)phosphonates

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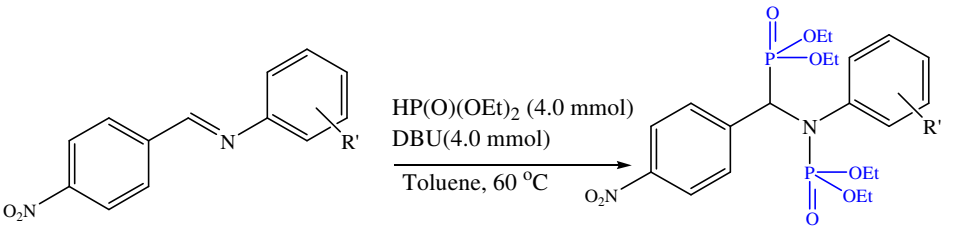
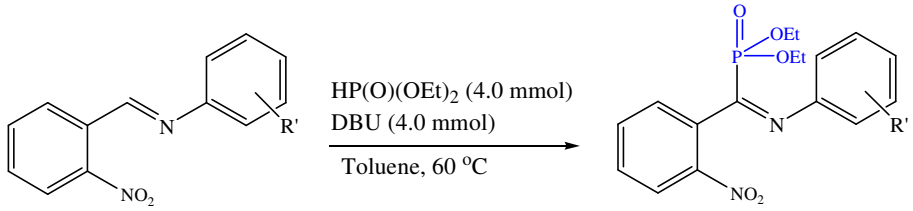
A novel chemoselective method for the simple phosphonation of imines with *H*-phosphonate diethyl ester and study of the electronic and orientation effects of the substituents on phosphorylation reaction.



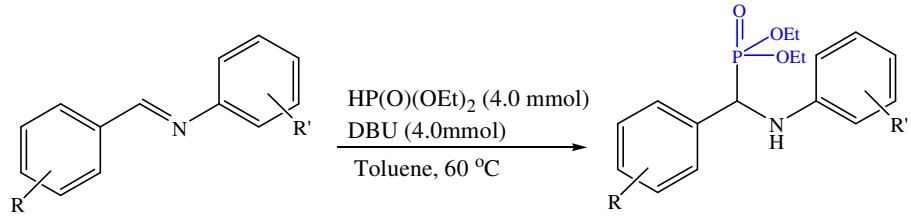

**1a- 1d**
R': H, *o, p*-$OCH_3$, *p*-$NO_2$

**2a- 2d**




**1e- 1g**
R': H, *o, p*-$OCH_3$

**2e-2g**




**1h- 1n**
R: H, *m*-$NO_2$, *p*-F, *p*-Cl
R': *p*-$OCH_3$, *p*-$NO_2$

**2h-2n**