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Aza-Wittig reaction of *N*-phosphorylalkyl phosphazenes with carbonyl compounds and phenylisocyanate. Synthesis of 4-amino-3-phosphoryl-2-azadienes and pyrazine-phosphonates

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Abstract—Simple and functionalized *N*-phosphorylalkyl imines and *N*-phosphorylalkyl-*N'*-phenyl-carbodiimides are obtained by aza-Wittig reaction of phosphazenes derived from aminophosphonates with carbonyl compounds and phenyl isocyanate. The reaction with dimethylformamide diethyl acetal (DMF–DEA) of these functionalized imines leads to the synthesis of 4-amino-3-phosphoryl-2-azadienes. *N*-Phosphorylmethyl imine derived from benzaldehyde can be used for the preparation of substituted pyrrole-phosphonates, while acid treatment of 4-dimethylamino-3-diethylphosphoryl-1-phenyl-2-azadiene gives diethyl 5-diethylphosphorylpyrazin-2-ylphosphonate.

1. Introduction

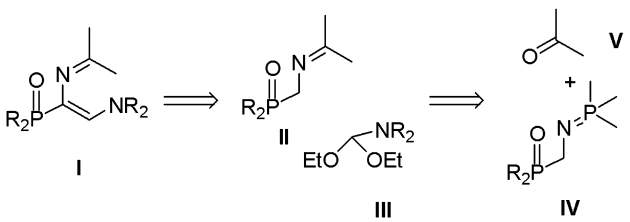
Substituted 2-azabutadiene systems have proved to be efficient key intermediates in organic synthesis for the construction of heterocycles.[1] The great majority of 2-azadienes studied are substituted with strong electron-donating groups,[1,2] while the chemistry of neutral[3,4] and electron-poor 2-azadienes have received much less attention.[5,6] Furthermore, α-aminophosphonates can be considered as surrogates for α-aminoacids,[7a] and have been used as haptens for the generation of catalytic antibodies,[7b] as enzyme inhibitors[7c,d] as well as antibacterial agents.[7e] Therefore, the introduction of organophosphorus functionalities in azadienes may be very interesting[8] because molecular modifications involving these substrates could afford new aminophosphorus derivatives. However, only the synthesis of 2-azadienes containing a phosphine oxide group in position 4[9a] and a phosphonate group in positions 1[9b] and 3[9c,d] have been reported and, as far as we know, the preparation of azadienes containing a phosphorus substituent and an electron-donating group such an amino group has not been described.

On the other side, phosphazenes[10,11] represent an important class of compounds and have attracted a great deal of attention in recent years because of their broad range of uses in the building of acyclic compounds[12] and in the preparation of heterocycles.[13] In this context, we have been involved in the study of simple and functionalized phosphazenes[10e] as well as their use in the construction of carbon–nitrogen double bonds (aza-Wittig reaction)[4,5] and in the preparation of acyclic[14] and heterocyclic compounds.[15] Following our previous studies on the reactivity and synthetic utility of phosphazenes, here we aim to explore a new and effective strategy for the preparation of 2-azadienes containing an electron-withdrawing and an electron-donating group (**I**, Scheme 1) from functionalized imines **II**, easily prepared by aza-Wittig reaction of *N*-phosphonylalkyl phosphazenes **IV** and carbonyl compounds **V**. The use of functionalized imines and azadienes for the preparation of phosphorylated pyrroles and pyrazines is also explored.

2. Results and discussion

2.1. Synthesis of *N*-phosphorylalkyl imines

Imines are obtained by aza-Wittig reaction of phosphazenes



Scheme 1.

Keywords: phosphazenes; aza-Wittig; aminophosphonates; azadienes; pyrroles; pyrazines.

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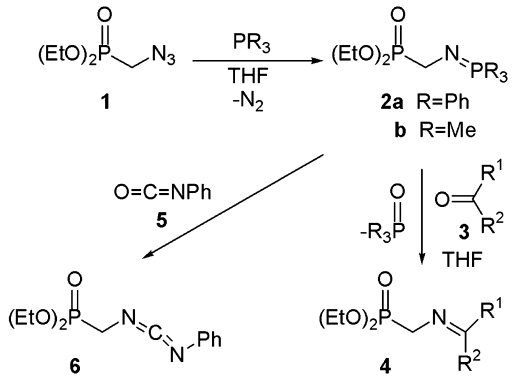
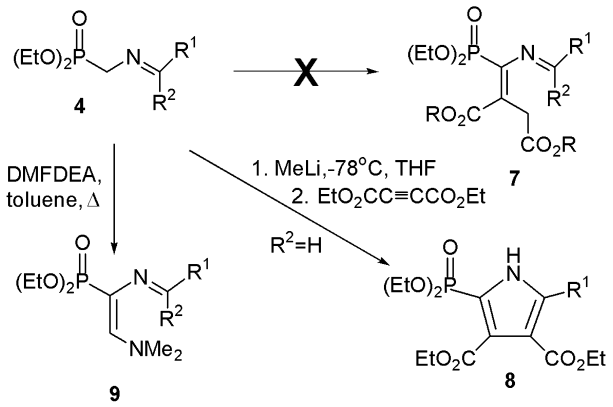


Scheme 2.



Scheme 3.

and carbonyl compounds.[4,5,10] In our case, the required phosphazenes **2** are very unstable compounds.[10e,16] Therefore, phosphazene **2a** (R=C_6H_5) was generated in situ by Staudinger reaction of diethyl azidomethylphosphonate[17] **1** with triphenylphosphine (Scheme 2) and the crude reaction mixture, without further purification, was heated with aldehydes in THF at 60°C to give *N*-phosphorylalkylaldimines **4a**–**d** in good yields (Scheme 2, Table 1, entries 1–4). The presence of phosphazene **2a** in the crude reaction mixture was monitored by ^{31}P NMR spectroscopy.[†] Compounds **4** were characterized on the basis of their spectroscopic data. Thus, the ^{31}P NMR spectrum of compound **4a** showed an absorption at δ_P=21.6 ppm, while the ^1H NMR showed a doublet for the methylene group (δ_H=4.1 ppm; $^2J_{PH}$=16.0 Hz) and another doublet at δ_H=8.36 ppm with a long-range coupling constant $^4J_{HP}$=4.0 Hz for the imine proton.

The reaction was not limited to simple aldehydes as *N*-phosphorylalkyl phosphazene **2a** also reacted with piruvonitrile **3e** (R^1=CH_3, R^2=CN) and ethyl cyanoformate **3f** (R^1=OC_2H_5, R^2=CN) in THF at 60°C to afford functionalized imines **4e** (R^1=CH_3, R^2=CN) and **4f** (R^1=OC_2H_5, R^2=CN), respectively (Scheme 2, Table 1, entries 5, 6). The use of a more reactive phosphazene **2b** (R=CH_3) derived from trimethylphosphine and generated in situ allowed to perform the process in milder reaction conditions (25°C) when this phosphazene **2b** reacted with piruvonitrile **3e** (Scheme 2, Table 1, entry 7). The aza-Wittig reaction of these phosphorylated phosphazenes **2** can also be extended to isocyanates. Thus, treatment of the in situ generated phosphazene **2a** with phenyl isocyanate **5** at room temperature led to the formation of *N*-phosphorylmethyl carbodiimide **6** in 75% yield (Scheme 2, Table 1, entry 8).

2.2. Synthesis of 3-phosphoryl-2-azadienes

With these results in hand, we next tried to study whether functionalized imines containing a phosphonate group **4** could be used as intermediates in the preparation of phosphorylated azadienes.[18] We thought that the reaction of imines **4** with acetylenic esters could be used for this goal and azadienes **7** could be obtained (Scheme 3) through a similar pathway to that observed in the case of *N*-alkoxycarbonylalkylimines.[19] However, the expected azadiene **7** was not formed when imine **4a** (R^1=*p*-CH_3–C_6H_4, R^2=H) reacted with dimethyl acetylenedicarboxylate in the presence of methyl lithium at −78°C, and the substituted pyrrole **8** was obtained instead. Spectroscopic data were in agreement with the structure of compound **8**. The formation of pyrrole **8** suggests that the process could begin by conjugated addition of the carbanion derived from the imine to the acetylenic ester followed by intramolecular cyclization. Therefore, the first synthesis of a pyrrole-phosphonate with carboxylate groups is described. In this context, as far as we know, the synthesis of this kind of compounds has been limited to the preparation of 3,4-disubstituted pyrrole-phosphonates from nitroalkenes and

Table 1. Imines **4** and carbodiimide **6** obtained

Entry	Compound	R^1	R^2	Conditions	Yield (%)[a]
1	**4a**	H	*p*-CH_3-C_6H_4	THF, reflux, 10 h	85
2	**4b**	H	*p*-NO_2-C_6H_4	THF, reflux, 10 h	70
3	**4c**	H	*p*-CH_3O-C_6H_4	THF, reflux, 10 h	61
4	**4d**	H	*o*-CH_2=$CHCH_2OC_6H_4$	THF, reflux, 10 h	70
5	**4e**	CH_3	CN	THF, reflux, 10 h	76
6	**4f**	OC_2H_5	CN	THF, reflux, 23 h	80
7	**4e**[b]	CH_3	CN	THF, room temperature, 12 h	70
8	**6**			THF, room temperature, 42 h	75

[a] Yield after purification by flash chromatography.
[b] Prepared from the phosphazene derived from trimethylphosphine.

[†] The reaction was monitored by ^{31}P NMR showing the disappearance of triphenylphosphine (δ_P=−6.00 ppm) and the formation of phosphazene **2a** (δ_P=22.6 and 40.5 ppm, $^3J_{PP}$=14.1 Hz), which disappeared after the addition of aldehydes with the formation of the triphenylphosphine oxide (δ_P=29.50 ppm).

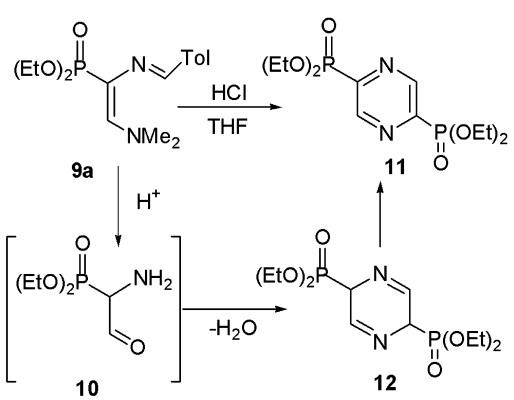
Table 2. Heterodienes **9** and pyrazine **11** obtained

Entry	Compound	R^1	R^2	Conditions	Yield (%)[a]
1	**9a**	H	*p*-CH_3-C_6H_4	THF, reflux, 5 d	60
2	**9b**	H	*p*-NO_2-C_6H_4	THF, reflux, 3 d	70
3	**9c**	H	*o*-CH_2=$CHCH_2OC_6H_4$	THF, reflux, 48 h	50
4	**9d**	CN	OC_2H_5	THF, reflux, 12 h	60
5	**11**			HCl (dil), room temperature, 10 h	40

[a] Yield after purification by flash chromatography.

isocyanates[20] and 5-ketopyrrolephosphonates from alkenes and nitrile ylides.[21]

A second alternative for the preparation of azadienes from imines **4** could be also explored, for instance the condensation reaction of these imines with dimethylformamide diethyl acetal (DMF–DEA). A related reaction in which some imines react with this reagent (DMF–DEA) has been recently used for the preparation of quinolines[22a] or imidazoles.[22b] In addition, this process could introduce an electron-releasing amino group in the azadiene. Therefore, thermal treatment of aldimines **4** (R^1=H) with dimethylformamide diethyl acetal (DMF–DEA) in refluxing toluene was carried out to give the 4-dimethylamino-3-phosphoryl heterodienes **9** (Scheme 3, Table 2, entries 1–3) as expected. Compounds **9** were purified by flash chromatography and characterized on the basis of their spectroscopic data. Thus, the ^{31}P NMR spectrum of compound **9a** showed an absorption at δ_P=20.6 ppm whereas, the ^{1}H NMR spectrum gave doublets for the imine and the olefinic proton at δ_H=8.17 ($^4J_{HP}$=4.0 Hz) and at δ_H=6.85 ($^3J_{HP}$=9.3 Hz). This coupling constant is consistent with the *cis* configuration of the vinylic proton and the phosphonate group,[23] and therefore, with the *trans* configuration of the enamine double bond. The formation of azadienes **9** could be explained by a condensation reaction of the imines with DMF–DEA with the loss of two molecules of ethanol and construction of the carbon–carbon double bond. This process is not restricted to phosphorylated aldimines **4** (R^1=H) and can also be extended to iminoester **4f** (R^1=CN, R^2=OC_2H_5) to give azadiene **9d** (R^1=CN, R^2=OC_2H_5) which contains two electron-donor (OC_2H_5, $(NCH_3)_2$) and two electron-withdrawing (CN, $PO(OC_2H_5)_2$) substituents (Scheme 3, Table 2, entry 4).



Scheme 4.

Continuing with our interest in the chemistry of new three,[24] five[25] and six[26] membered phosphorus substituted heterocyclic compounds, we explored the use of the functionalized imine **9a** as an intermediate in the preparation of phosphorylated pyrazines, since compound **9a** may be considered as a synthetic equivalent of phosphorylated aminoaldehyde **10** (Scheme 4). Pyrazines are widely used intermediates in Medicinal Chemistry.[27,28] In addition, pyrazines which are biosynthesized from amino acids, are common units in a wide variety of marine natural products showing cytostatic and antitumor properties,[29] while pyrazinamides[30] and more recently pyrazinesters[31] have been successfully evaluated 'in vitro' and 'in vivo' for antituberculosis activity. Therefore, the development of new methods of synthesis of pyrazines acquired relevance in recent years. However, although it is known that phosphorus substituents regulate important biological functions,[7] only very recently the first synthesis of pyrazine-phosphonates by dimerization of azirines has been disclosed.[26b]

Then, a pyrazine containing two phosphonate groups **11** was obtained by acid treatment (2N HCl) of functionalized imine **9a** (Scheme 4, Table 2, entry 5). Spectroscopic data were in agreement with the assigned structure **11**. Mass spectrometry of the compound showed the molecular ion peak (*m/z* 352, 2%), while in the ^{31}P NMR spectrum the phosphonate groups resonated at δ_P=7.3 ppm. The ^{1}H NMR spectrum of pyrazine **11** displayed a singlet at δ_H=9.15 ppm corresponding to protons in position 2 and 5, whereas, the ^{13}C NMR spectrum of **11** showed a triplet at δ_C=147.4 ppm (J_{CP}=22.2 Hz) for C-3 and C-6 and a doublet at δ_C=150.1 ppm ($^1J_{CP}$=220.1 Hz) for C-2 and C-5. The formation of pyrazine **11** can be rationalized by an acid hydrolysis of both enamine and imine groups of compound **9a**, followed by the dimerization-condensation of the aminoaldehyde intermediate **10** with loss of two molecules of water and formation of dihydropyrazine **12**. Oxidation of this heterocycle in the reaction medium would give pyrazine **11** (Scheme 4). As far as we know, this method is the first synthesis of pyrazine-phosphonates without substituents in the carbon atom adjacent to the heteroatom.

In conclusion, functionalized imines **4** and carbodiimides derived from aminophosphonates **6** can be prepared, respectively, by the aza-Wittig reaction of *N*-phosphorylalkylphosphazenes **2** and carbonyl compounds or isocyanates. Thermal treatment of phosphorylated imines **4** with DMF–DEA provides an efficient and easy access to azadienes **9** containing both electron-withdrawing and electron-releasing groups, which have been used for the preparation of pyrazine-phosphonates. Azadienes[1–5] and pyrazines[27–31] are important synthons in organic synthesis

and in the preparation of biologically active compounds of interest in Medicinal Chemistry.

3. Experimental

3.1. General

Chemicals were purchased from Aldrich Chemical Company. Solvents for extraction and chromatography were of technical grade. All solvents used in reactions were freshly distilled from appropriate drying agents before use. All other reagents were recrystallized or distilled as necessary. All reactions were performed under an atmosphere of dry nitrogen. Analytical TLC was performed with Merck silica gel 60 F_{254} plates. Visualization was accomplished by UV light. Flash chromatography was carried out using Merck silica gel 60 (230–400 mesh ASTM). Melting points were determined with a Electrothermal IA9100 Digital Melting Point Apparatus and are uncorrected. ^{1}H (300 MHz), ^{13}C (75 MHz) and ^{31}P NMR (120 MHz) spectra were recorded on a Varian Unity Plus 300 MHz spectrometer using $CDCl_3$ or CD_3OD solutions with TMS as internal reference for ^{1}H and ^{13}C NMR spectra and phosphoric acid (85%) for ^{31}P NMR spectra. Chemical shifts (δ) are reported in ppm. Coupling constants (J) are reported in Hertz. Low-resolution mass spectra (MS) were obtained at 50–70 eV by electron impact (EIMS) on a Hewlett Packard 5971 or 5973 spectrometer. Data are reported in the form m/z (intensity relative to base=100). Infrared spectra (IR) were taken on a Nicolet IRFT Magna 550 spectrometer, and were obtained as solids in KBr or as neat oils. IR absorptions are reported in cm^{-1}. Elemental analyses were performed in a LECO CHNS-932 apparatus. Diethyl azidomethylphosphonate **1** was synthesized according to literature procedures.[17]

3.2. General procedure for the synthesis of phosphorylalkyl aldimines 4

Diethyl azidomethylphosphonate **1** (0.95 g, 5 mmol) in THF (5 mL) was added dropwise to a solution of triphenylphosphine (1.18 g, 4.5 mmol) in THF (10 mL) at 0°C. The formation of the phosphazene **2a** was monitored by ^{31}P NMR spectroscopy (see Section 2.1). After stirring the mixture at room temperature for 10 h, carbonyl derivatives **3** or **5** (5 mmol) were added and the solution stirred at room temperature or under reflux for 10–23 h. The solvent was removed at reduced pressure and the residue containing imines **4** or **6** and triphenylphosphine oxide was extracted with cool diethyl ether (4×15 mL). The combined organic extracts were evaporated under reduced pressure and the residue was purified by column chromatography to afford compounds **4**.

3.2.1. Diethyl (*E*)-*N*-(4-methylbenzyliden)aminomethylphosphonate (4a). According to the general procedure, *p*-tolylaldehyde **3** (0.54 g, 4.5 mmol) was used. The crude residue was purified by chromatography eluting with hexane/ethyl acetate 3:1 to yield 1.03 g (85%) of **4a** as a yellow oil. ^{1}H NMR δ: 8.21 (1H, d, $^4J_{HP}$=4.7 Hz, CH=N), 7.57 (2H, d, $^3J_{HH}$=7.9 Hz, Harom), 7.14 (2H, d, $^3J_{HH}$=7.9 Hz, Harom), 4.10 (4H, m, 2×OCH_2), 4.03 (2H, d, $^2J_{HP}$=17.7 Hz, NCH_2), 2.31 (3H, s, CH_3Tolyl), 1.26 (6H, t, $^3J_{HH}$=7.0 Hz, 2×CH_3); ^{13}C NMR δ: 165.3 (d, $^3J_{CP}$=16.6 Hz, CH=N), 141.3 (*C*arom–C), 133.0 (*C*arom–C), 129.1–128.1 (Carom), 62.4 (OCH_2), 62.3 (OCH_2), 57.3 (d, $^1J_{CP}$=154.1 Hz, NCH_2), 21.3 (CH_3tolyl), 16.3 (CH_3), 16.2 (CH_3); ^{31}P NMR δ: 22.6. IR (NaCl, ν_{max}): 1633 (C=N), 1241 (P=O), 1036 (P–O); EIMS, (m/z): 269 (M^+, 2). Anal. calcd for $C_{13}H_{20}NO_3P$: C, 57.99; H, 7.49; N, 5.20. Found: C, 57.95; H, 7.40; N, 5.15.

3.2.2. Diethyl (*E*)-*N*-(4-nitrobenzyliden)aminomethylphosphonate (4b). According to the general procedure, *p*-nitrobenzaldehyde **3** (1.61 g, 10 mmol) was used. The crude residue was purified by chromatography eluting with hexane/ethyl acetate 3:1 and 2.1 g (70%) of **4b** were obtained as a yellow oil. ^{1}H NMR δ: 8.36 (1H, d, $^4J_{HP}$=4.0 Hz, CH=N), 8.20 (2H, d, $^3J_{HH}$=6.8 Hz, Harom), 7.88 (2H, d, $^3J_{HH}$=6.8 Hz, Harom), 4.16 (4H, m, 2×OCH_2), 4.10 (2H, d, $^2J_{HP}$=16.0 Hz, NCH_2), 1.26 (6H, t, $^3J_{HH}$=7.0 Hz, 2×CH_3); ^{13}C NMR δ: 163.2 (d, $^3J_{CP}$=16.6 Hz, CH=N), 149.3 (*C*arom–C), 140.8 (*C*arom–C), 129.8–123.6 (Carom), 62.6 (OCH_2), 62.5 (OCH_2), 57.4 (d, $^1J_{CP}$=153.6 Hz, NCH_2), 16.3 (CH_3), 16.2 (CH_3); ^{31}P NMR δ: 21.6. IR (NaCl, ν_{max}): 1520 (C=N), 1347 (P=O), 1029 (P–O); EIMS, (m/z): 163 (M^+– P(O)(OCH_2CH_3)$_2$), 7). Anal. calcd for $C_{12}H_{17}N_2O_5P$: C, 48.00; H, 5.71; N, 9.33. Found: 48.30; H, 5.45; N, 9.65.

3.2.3. Diethyl (*E*)-*N*-(4-methoxybenzyliden)aminomethyl-phosphonate (4c). According to the general procedure, *p*-methoxybenzaldehyde **3** (1.4 g, 10 mmol) was used. The crude residue was purified by chromatography eluting with hexane/ethyl acetate 3:1 and 1.8 g (61%) of **4c** were obtained as a yellow oil. ^{1}H NMR δ: 8.16 (1H, d, $^4J_{HP}$=4.5 Hz, CH=N), 7.63 (2H, d, $^3J_{HH}$=8.2 Hz, Harom), 6.87 (2H, d, $^3J_{HH}$=8.3 Hz, Harom), 4.12 (4H, m, 2×OCH_2), 4.04 (2H, d, $^2J_{HP}$=17.5 Hz, NCH_2), 3.77 (3H, s, OCH_3), 1.27 (6H, t, $^3J_{HH}$=7.0 Hz, 2×CH_3); ^{13}C NMR δ: 164.7 (d, $^3J_{CP}$=16.1 Hz, CH=N), 161.8 (*C*arom–C), 131.7–129.6 (Carom), 128.2 (*C*arom–C), 62.3 (OCH_2), 57.3 (d, $^1J_{CP}$=154.1 Hz, NCH_2), 55.1 (OCH_3), 16.2 (CH_3); ^{31}P NMR δ: 22.8. IR (NaCl, ν_{max}): 1599 (C=N), 1255 (P=O), 1023 (P–O); EIMS, (m/z): 285 (M^+, 1). Anal. calcd for $C_{13}H_{20}NO_4P$: C, 54.73; H, 7.07; N, 4.91. Found: C, 54.45; H, 7.15; N, 4.85.

3.2.4. Diethyl (*E*)-*N*-(2-allyloxybenzyliden)aminomethylphosphonate (4d). According to the general procedure, *o*-allyloxybenzaldehyde **3** (1.6 g, 10 mmol) was used. The crude residue was purified by chromatography eluting with hexane/ethyl acetate 3:1 and 2.2 g (70%) of **4d** were obtained as a yellow oil. ^{1}H NMR δ: 8.72 (1H, d, $^4J_{HP}$=4.8 Hz, CH=N), 7.91–6.80 (4H, m, Harom), 6.01 (1H, m, CH_2=C*H*), 5.37 (1H, dd, $^3J_{HH}$=17.2 Hz, $^4J_{HH}$=1.3 Hz, CH=C*Htrans*), 5.26 (1H, dd, $^3J_{HH}$=10.5 Hz, $^4J_{HH}$=1.3 Hz, CH=C*Hcis*), 4.53 (2H, dd, $^3J_{HH}$=5.2 Hz, $^4J_{HH}$=1.3 Hz, OCH_2), 4.15 (4H, m, 2×OCH_2), 4.05 (2H, d, $^2J_{HP}$=14.2 Hz, NCH_2), 1.27 (6H, t, $^3J_{HH}$=7.0 Hz, 2×CH_3); ^{13}C NMR δ: 161.4 (d, $^3J_{CP}$=16.6 Hz, CH=N), 132.2 (=CH), 157.8, 124.4 (*C*arom–C), 128.3, 127.3, 120.8, 112.2 (Carom), 117.6 (=CH_2), 69.0 (OCH_2), 62.4 (OCH_2), 57.7 (d, $^1J_{CP}$=153.6 Hz, NCH_2), 16.4 (CH_3); ^{31}P NMR δ: 22.7. IR (NaCl, ν_{max}): 1593 (C=N), 1241 (P=O), 1023 (P–O); EIMS,

(*m*/*z*): 311 (M^+, 13). Anal. calcd for $C_{15}H_{22}NO_4P$: C, 57.87; H, 7.12; N, 4.50. Found: C, 57.65; H, 7.25; N, 4.65.

3.2.5. Diethyl *N*-(1-cyanoethyliden)aminomethylphosphonate (4e). According to the general procedure, piruvonitrile **3** (0.31 g, 4.5 mmol) was used. The crude residue was purified by chromatography eluting with hexane/ethyl acetate 3:1 and 0.75 g (76%) of **4e** were obtained as a yellow oil. ^{1}H NMR δ: 4.08 (4H, m, 2×OCH_2), 3.65 (2H, dd, $^2J_{HP}$=12.0 Hz, $^2J_{HH}$=5.9 Hz, NCH_2), 1.97 (3H, s, CH_3), 1.31 (6H, t, $^3J_{HH}$=7.0 Hz, 2×CH_3); ^{13}C NMR δ: 170.5 (C=N), 115.1 (C≡N), 62.4 (OCH_2), 62.3 (OCH_2), 34.3 (d, $^1J_{CP}$=158 Hz, NCH_2), 22.3 (CH_3), 16.2 (CH_3), 16.1 (CH_3); ^{31}P NMR δ: 23.8. IR (NaCl, ν_{max}): 2236 (C≡N), 1228 (P=O), 1023 (P–O); EIMS, (*m*/*z*): 218 (M^+, 3%). Anal. calcd for $C_8H_{15}N_2O_3P$: C, 44.04, H, 6.93, N, 12.84. Found: C, 43.95, H, 6.80, N, 12.95.

3.2.6. Diethyl *N*-(1-cyano-1-ethoxymethyliden)aminomethyl-phosphonate (4f). According to the general procedure, ethyl cyanoformiate **3** (0.45 g, 4.5 mmol) was used. The crude residue was purified by chromatography eluting with hexane/ethyl acetate 3:1 and 0.90 g (80%) of **4f** were obtained as a yellow oil. ^{1}H NMR δ: 4.17 (2H, q, $^3J_{HH}$=7.1 Hz, OCH_2), 4.09 (4H, m, 2×OCH_2), 3.91 (2H, d, $^2J_{HP}$=17.2 Hz, NCH_2), 1.26 (9H, s, 3×CH_3); ^{13}C NMR δ: 139.8 (d, $^3J_{CP}$=15.8 Hz, C=N), 106.5 (d, $^4J_{CP}$=3.2 Hz, C≡N), 64.3 (OCH_2), 62.3 (OCH_2), 47.3 (d, $^1J_{CP}$=158.5 Hz, NCH_2), 16.0 (CH_3), 15.9 (CH_3), 13.2 (CH_3); ^{31}P NMR δ: 20.9. IR (NaCl, ν_{max}): 2238 (C≡N), 1255 (P=O); EIMS, (*m*/*z*): 248 (M^+, 10%). Anal. calcd for $C_9H_{17}N_2O_4P$: C, 43.55, H, 6.90, N, 11.29. Found: C, 43.50, H, 6.80, N, 11.20.

3.2.7. *N*-Diethoxyphosphorylmethyl-*N′*-phenylcarbodiimide (6). According to the general procedure, phenylisocyanate **5** (0.54 g, 4.5 mmol) was used. The crude residue was purified by chromatography eluting with hexane/ethyl ether 3:1 and 0.90 g (75%) of **6** were obtained as a yellow oil. ^{1}H NMR δ: 7.24–7.01 (5H, m, arom), 4.14 (4H, m, OCH_2), 3.59 (2H, d, $^2J_{HP}$=13.3 Hz, NCH_2), 1.17 (6H, m, CH_3); ^{13}C NMR δ: 142.9 (C=), 129.3–124.2 (CNarom), 62.9 (OCH_2), 62.8 (OCH_2), 41.5 (d, $^1J_{CP}$=151.7 Hz, NCH_2), 16.4 (CH_3), 16.3 (CH_3); ^{31}P NMR ($CDCl_3$)δ: 24.5. IR (NaCl, ν_{max}): 2094, 1221 (P=O); EIMS, (*m*/*z*): 268 (M^+, 24%). Anal. calcd for $C_{12}H_{17}N_2O_3P$: C, 53.73, H, 6.39, N, 10.44. Found: C, 53.70, H, 6.35, N, 10.30.

3.2.8. Dimethyl 2-(diethoxyphosphoryl)-5-*p*-tolyl-1*H*-pyrrole-3,4-dicarboxylate 8. Methyl lithium (1.8 mmol) was added to a solution of the imine **4a** (0.3 g, 1.1 mmol) in THF (5 mL) at −78°C. After stirring 1 h at −78°C, dimethylacetylenedicarboxylate (1.8 mmol) was added, the mixture was allowed to warm to room temperature and stirred overnight. The solvent was removed at reduced pressure and the residue was purified by flash chromatography eluting with hexane/ethyl acetate 3:1 to yield 0.16 g (36%) of **8** as a yellow oil. ^{1}H NMR δ: 10.8 (1H, s, NH), 7.20–711 (4H, m, Harom), 4.00 (4H, m, 2×OCH_2), 3.78 (3H, s, OCH_3), 3.68 (3H, s, OCH_3), 2.31 (3H, s, CH_3Tolyl), 1.28 (6H, t, $^3J_{HH}$=7.0 Hz, 2×CH_3); ^{13}C NMR δ: 164.6 (*C*arom–C), 138.8 (*C*arom–C), 128.8, 128.7 (Carom), 127.2 (*C*arom–C), 125.8 (d, $^2J_{CP}$=21.6 Hz, P–C=*C*), 118.7 (d, $^1J_{CP}$=224 Hz, P–C–NH), 114.2 (d, $^3J_{CP}$=11.5 Hz, Tol-C–NH), 63.0 (OCH_2), 62.1 (OCH_2), 52.0 (CH_3), 51.7 (CH_3), 21.2 (CH_3tolyl), 16.5 (CH_3); ^{31}P NMR δ: 6.85. IR (NaCl, ν_{max}): 1650 (C=N), 1241 (P=O), 1023 (P–O); EIMS, (*m*/*z*): 409 (M^+, 100). Anal. calcd for $C_{19}H_{24}NO_7P$: C, 55.74; H, 5.91; N, 3.42. Found: C, 55.65; H, 5.55; N, 3.55.

3.3. General procedure for the synthesis of 3-phosphoryl-2-azadienes 9

Dimethylformamide diethyl acetal was added to an equimolecular amount of imine **4** (5 mmol) in toluene (20 mL) and the mixture was heated at reflux until the starting imine was not detected (TLC). The solvent was removed at reduced pressure and the residue was purified by flash chromatography eluting with hexane/ethyl acetate to yield compounds **9**.

3.3.1. Diethyl (*E*,*E*)-{2-dimethylamino-1-[(4-methyl benzylidene)amino]vinyl}phosphonate (9a). According to the general procedure, imine **4a** (1.3 g, 4.8 mmol) was used. The crude residue was purified by flash chromatography eluting with hexane/ethyl acetate 1:1 to yield a yellow solid that was crystallized from hexane yielding 0.93 g (60%) of **9a** as a yellow solid; mp 90–95°C. ^{1}H NMR δ: 8.17 (1H, d, $^4J_{HP}$=4.0 Hz, CH=N), 7.47–7.10 (4H, m, Harom), 6.85 (1H, d, $^3J_{HP}$=9.3 Hz, PC=CH), 4.03 (4H, m, 2×OCH_2), 3.26 (6H, s, $(NCH_3)_2$), 2.31 (3H, s, CH_3Tolyl), 1.22 (6H, t, $^3J_{HH}$=7.0 Hz, 2×CH_3); ^{13}C NMR δ: 149.0 (d, $^3J_{CP}$=9.5 Hz, CH=N), 147.6 (d, $^2J_{CP}$=41.3 Hz, PC=*C*), 138.8 (*C*arom–C), 135.7 (*C*arom–C), 129.0–126.7 (Carom), 103.8 (d, $^1J_{CP}$=181.3 Hz, P*C*=C), 60.7 (OCH_2), 43.5 (NCH_3), 21.3 (CH_3tolyl), 16.1 (CH_3); ^{31}P NMR δ: 20.6. IR (NaCl, ν_{max}): 3144 (NMe_2), 1633 (C=N), 1414 (P=O), 1029 (P–O); EIMS, (*m*/*z*): 324 (M^+, 100). Anal. calcd for $C_{16}H_{25}N_2O_3P$: C, 59.25; H, 7.77; N, 8.64. Found: C, 59.30; H, 7.55; N, 8.90.

3.3.2. Diethyl (*E*,*E*)-{2-dimethylamino-1-[(4-nitrobenzylidene)amino]vinyl}phosphonate (9b). According to the general procedure, imine **4b** (1.5 g, 5 mmol) was used. The crude residue was purified by flash chromatography eluting with hexane/ethyl acetate 2:1 to yield a yellow solid that was crystallized from hexane yielding 1.25 g (70%) of **9b** as a yellow solid; mp 108–109°C. ^{1}H NMR δ: 8.19 (1H, d, $^4J_{HP}$=3.6 Hz, CH=N), 8.27–7.60 (4H, m, Harom), 7.03 (1H, d, $^2J_{HP}$=8.8 Hz, PC=CH), 4.03 (4H, m, 2×OCH_2), 3.30 (6H, s, $(NCH_3)_2$), 1.27 (6H, t, $^3J_{HH}$=7.0 Hz, 2×CH_3); ^{13}C NMR δ: 149.3 (d, $^2J_{CP}$=41.5 Hz, PC=*C*), 147.0 (*C*arom–C), 145.1 (d, $^3J_{CP}$=8.5 Hz, C=N), 144.0 (*C*arom–C), 126.8–123.7 (Carom), 104.8 (d, $^1J_{CP}$= 183.3 Hz, P*C*=C), 60.7 (OCH_2), 43.5 (NCH_3), 16.1 (CH_3); ^{31}P NMR δ: 18.8. IR (NaCl, ν_{max}): 3137 (NMe_2), 1619 (C=N), 1394 (P=O), 1029 (P–O); EIMS, (*m*/*z*): 355 (M^+, 100). Anal. calcd for $C_{15}H_{22}N_3O_5P$: C, 50.70; H, 6.24; N, 11.83. Found: 50.90; H, 6.05; N, 11.45.

3.3.3. Diethyl (*E*,*E*)-{2-dimethylamino-1-[(2-allyloxybenzylidene)amino]vinyl}phosphonate (9c). According to the general procedure, imine **4c** (1.6 g, 5 mmol) was used. The crude residue was purified by flash chromatography eluting with hexane/ethyl acetate 2:1 to yield 0.9 g (50%) of **9c** as a yellow oil. ^{1}H NMR δ: 8.68 (1H, d,

$^4J_{HP}$=4.8 Hz, CH═N), 7.75–6.90 (4H, m, Harom), 6.81 (1H, d, $^3J_{HP}$=8.4 Hz, PC═CH), 6.02 (1H, m, CH_2═C*H*), 5.40 (1H, dd, $^3J_{HH}$=17.2 Hz, $^4J_{HH}$=1.5 Hz, CH═C*Htrans*), 5.19 (1H, dd, $^3J_{HH}$=9.0 Hz, $^4J_{HH}$=1.3 Hz, CH═C*Hcis*), 4.50 (2H, dd, $^3J_{HH}$=6.3 Hz, $^4J_{HH}$=1.6 Hz, OCH_2), 4.05 (4H, m, 2×OCH_2), 3.30 (6H, s, $(NCH_3)_2$), 1.27 (6H, t, $^3J_{HH}$=7.0 Hz, 2×CH_3); ^{13}C NMR δ: 148.0 (d, $^2J_{CP}$= 41.8 Hz, PC═*C*), 145.5 (d, $^3J_{CP}$=9.0 Hz, CH═N), 133.1 (═CH), 129.9 (Carom), 127.5 (*C*arom–C), 125.7, 120.8 (Carom), 116.9 (═CH_2), 112.6 (Carom), 104.0 (d, $^1J_{CP}$= 182.8 Hz, P*C*═C), 69.0 (OCH_2), 61.4 (CH_2), 43.8 (NCH_3), 16.4 (CH_3); ^{31}P NMR δ: 20.4. IR (NaCl, ν_{max}): 3400 (NMe_2), 1745 (C═N), 1241 (P═O), 1023 (P–O); EIMS, (*m*/*z*): 366 (M^+, 45). Anal. calcd for $C_{18}H_{27}N_2O_4P$: C, 59.01; H, 7.43; N, 7.65. Found: C, 59.25; H, 7.25; N, 7.50.

3.3.4. Ethyl *N*-[1-(diethoxyphosphoryl)-2-dimethylamino-vinyl]cyanoformimidate (9d). According to the general procedure, imine **4f** (1.25 g, 5 mmol) was used. The crude residue was purified by flash chromatography eluting with ethyl acetate to yield 0.9 g (50%) of **9d** as a yellow-brown oil. ^{1}H NMR δ: 6.49 (1H, d, $^3J_{HP}$=11.1 Hz, PC═CH), 4.13 (2H, m, OCH_2), 3.93 (4H, m, 2×OCH_2), 2.79 (6H, s, $(NCH_3)_2$), 1.20 (6H, m, 3×CH_3); ^{13}C NMR δ: 139.5 (d, $^2J_{CP}$=27.7 Hz, PC═*C*), 131.7 (C≡N), 128.2 (d, $^3J_{CP}$=12.0 Hz, CH═N), 98.5 (d, $^1J_{CP}$=219.0 Hz, P*C*═C), 62.1 (OCH_2), 61.2 (OCH_2), 42.4 (NCH_3), 16.1 (CH_3), 16.0 (CH_3); ^{31}P NMR δ: 18.6. IR (NaCl, ν_{max}): 2250 (C≡N), 1626 (C═N), 1241 (P═O), 1023 (P–O); EIMS, (*m*/*z*): 303 (M^+, 60). Anal. calcd for $C_{12}H_{22}N_3O_4P$: C, 47.52; H, 7.31; N, 13.85. Found: C, 47.75; H, 7.05; N, 13.55.

3.3.5. 2,5-Bis(diethoxyphosphoryl)pyrazine (11). 2 M HCl (1 mL) was added to a solution of azadiene **9a** (0.2 g, 0.6 mmol) in THF (5 mL) and the mixture was stirred 15 min at room temperature. After removing the solvent at reduced pressure, the crude residue was purified by flash chromatography eluting with ethyl acetate to yield 0.085 g (40%) of **11** as a yellow oil. ^{1}H NMR δ: 9.15 (1H, s, Hpyrazine), 4.24 (4H, m, 2×OCH_2), 1.32 (6H, t, $^3J_{HH}$= 7.1 Hz, 2×CH_3); ^{13}C NMR δ: 150.1 (d, $^1J_{CP}$=220.1 Hz, CP), 147.4 (t, J_{CP}=22.2 Hz, CHpyrazine), 63.7 (OCH_2), 16.2 (CH_3), 16.0 (CH_3); ^{31}P NMR δ: 7.4. IR (NaCl, ν_{max}): 1635 (C═N), 1235 (P═O), 1026 (P–O); EIMS, (*m*/*z*): 352 (M^+, 2). Anal. calcd for $C_{12}H_{22}N_2O_6P_2$: C, 40.92; H, 6.30; N, 7.95. Found: C, 40.65; H, 6.55; N, 7.60.

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