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A regioselective route to 5-substituted pyrazole- and pyrazoline-3-phosphonic acids and esters

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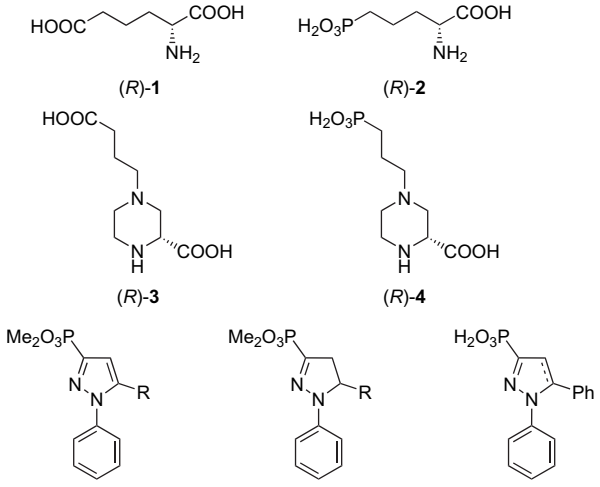
Abstract—The regioselective synthesis of 5-substituted-3-dimethoxyphosphono-pyrazoles and -2-pyrazolines has been accomplished through the 1,3-dipolar cycloaddition of a suitable nitrile imine to monosubstituted alkynes and alkenes. Examples of hydrolysis of the heterocyclic phosphonic esters to the corresponding acids are described.

1. Introduction

1,3,5-Trisubstituted pyrazoles are synthetic targets of utmost importance in the pharmaceutical industry, since such a heterocyclic moiety represents the core structure of numerous drugs,[1] including the widely prescribed Celebrex and Viagra.[2] Furthermore, recent reports indicate the pyrazole chemotype as the structural motif of a number of highly potent inhibitors of coagulation factor Xa.[3] Among them, Rivaroxaban[4] and Apixaban[5] were selected for clinical development for the prevention and treatment of thrombotic diseases. If we focus our attention on pyrazole- and 2-pyrazoline acids, we can find a huge number of derivatives with antimicrobial,[6] herbicide,[7] hypoglycemic,[8] and hypolipidemic[9] activities. Furthermore, pyrazole 3-carboxylates were also identified as selective antagonists of subtype 1 PGE2 receptors (EP1).[10] These compounds showed efficacy in numerous preclinical model of pain, including allodynia, neuropathic pain, and are expected to be devoid of the gastrointestinal effects associated with non-steroidal anti-inflammatory drugs (NSAIDS)[11] and the cardiovascular side effects typical of COX-2 selective inhibitors.[12]

Bioisosterism is a common strategy applied in medicinal chemistry to increase the potency and/or selectivity, as well as to ameliorate the overall pharmacokinetic profile of drugs. In particular, the carboxylate group can be fruitfully replaced by an array of moieties characterized by similar physico-chemical properties, e.g., hydroxamate, tetrazole, 3-hydroxyisoxazole, 3-hydroxythiadiazole, and phosphonate. As an example, in the glutamatergic systems the replacement of the distal carboxylate group with the phosphonate moiety is responsible for a substantial increase in potency. As a matter of fact, such a bioisosteric modification transforms a weak NMDA antagonist such as (*R*)-2-amino-adipic acid **1** into the quite potent (*R*)-2-amino-5-phosphonopentanoate **2** (Fig. 1).[13] The same trend is observed on passing from 4-carboxypropyl-piperazine-2-carboxylic acid **3** to



5a: R = Ph
5b: R = CO_2Me
5c: R = C_4H_9
5d: R = C_9H_{19}

6a: R = Ph
6b: R = CO_2Me
6c: R = C_4H_9
6d: R = C_9H_{19}

7: pyrazole
8: 2-pyrazoline

Figure 1. Structures of reference [(*R*)-**1**, (*R*)-**2**, (*R*)-**3**, and (*R*)-**4**] and target compounds [**5a–d**, **6a–d**, **7**, and **8**].

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4-phosphonopropyl-piperazine-2-carboxylic acid (CPP) **4** (Fig. 1), which is a commonly used pharmacological tool to characterize NMDA receptors.[13]

In connection with our medicinal chemistry project aimed at the discovery of new NMDA antagonists, we needed to prepare a series of 3-phosphono-2-pyrazolines as well as 3-phosphono-pyrazoles. Among the numerous methods developed to synthesize pyrazoles and 2-pyrazolines,[14] the most applied protocol is the reaction of hydrazines with either 1,3-dicarbonyl compounds, α,β-ethynyl ketones, or α,β-unsaturated ketones. We did not take into account this methodology due to the uncertainty of the reaction outcome, i.e., by using 1,3-dicarbonyl compounds a mixture of regioisomers is usually formed, the difficulty in the preparation of the substrates, and the limited possibility to generate a library of compounds. A valid synthetic alternative is represented by the 1,3-dipolar cycloaddition of diazoalkanes or nitrile imines with alkynes or alkenes. The advantage of this procedure is that it is often highly regioselective and, in addition, the 1,3-dipole can be reacted with an array of unsaturated substrates to produce a number of different heterocyclic entities.[15]

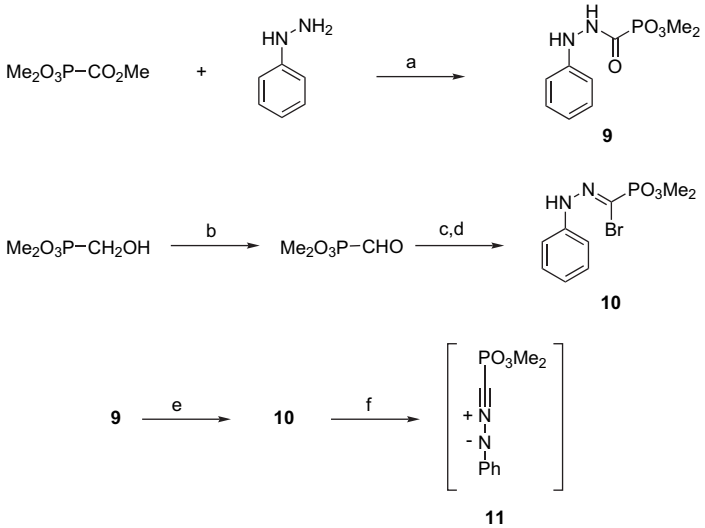
Herein, we describe a highly regioselective synthesis of 5-substituted 1-phenyl-pyrazoles **5a–d** and 2-pyrazolines **6a–d** bearing at the 3-position the dimethyl phosphonic ester moiety (Fig. 1). Examples of their transformation into the corresponding phosphonic acids as well as the oxidation of a 2-pyrazoline to the related pyrazole derivative are also reported.

2. Results and discussion

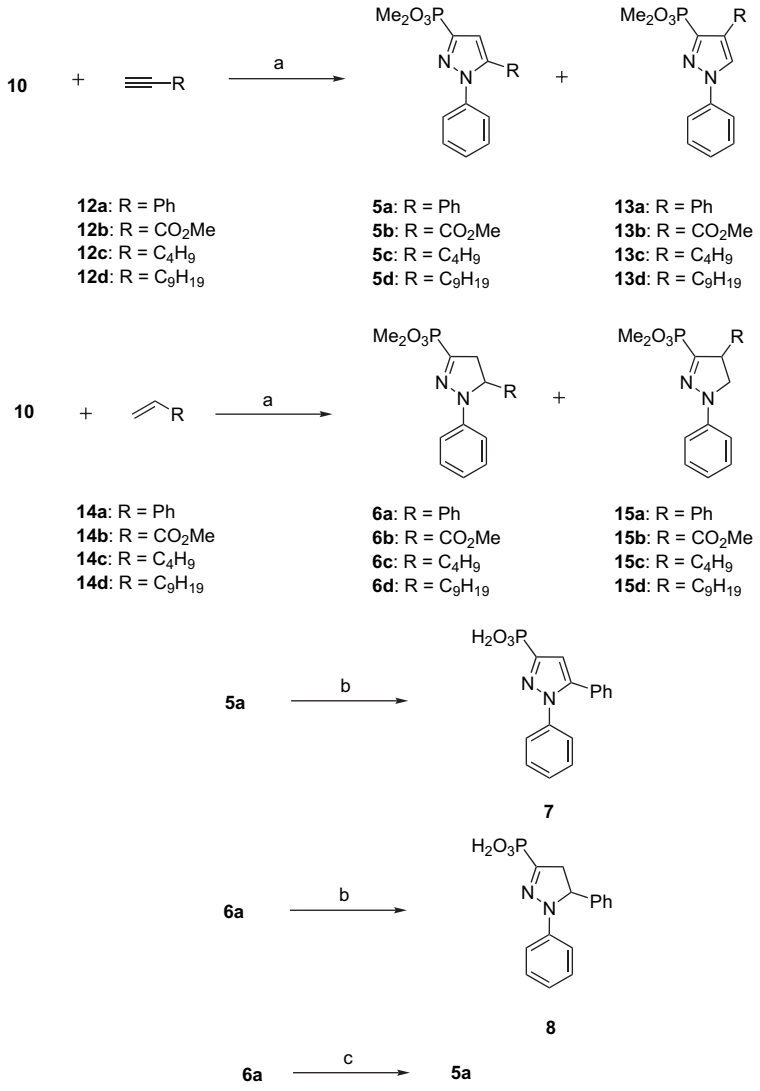
Nitrile imines can be generated in a variety of ways, e.g., by oxidation of aldehyde hydrazones, thermolysis of 2,5-disubstituted tetrazoles or oxadiazolin-5-ones, and photochemical degradation of sydnones. Usually, the most practical and scalable method is the in situ technique based on the dehydrohalogenation of hydrazonoyl halides, such as **10**, by treatment with a base (Scheme 1). Therefore, we prepared the phenylhydrazide of dimethyl formylphosphonate by condensing phenylhydrazine with trimethyl phosphonoformate under vacuum to remove methanol. As shown in Scheme 1, intermediate **9** was transformed into hydrazonoyl bromide **10** by treatment with a mixture of carbon tetrabromide and triphenylphosphine.[16] In parallel, we devised an alternative route to hydrazonoyl bromide **10** through the condensation of phenylhydrazine with dimethyl formylphosphonate followed by treatment with *N*-bromo succinimide (NBS). Dimethyl formylphosphonate, obtained by Swern oxidation of dimethyl (hydroxymethyl)phosphonate,[17] was not characterized but directly condensed with phenylhydrazine, since it is chemically unstable and at −10 °C undergoes decomposition to carbon monoxide and dimethyl phosphite.[18]

Nitrile imine **11**, generated in situ by reacting hydrazonoyl bromide **10** with sodium bicarbonate, was evaluated for its reactivity toward representative alkynes **12a–d** and alkenes **14a–d**. All the cycloaddition reactions, reported in Scheme 2, were run under comparable conditions with a threefold excess of dipolarophile. The reactions progressed until the disappearance of the hydrazonoyl bromide. The outcome of the reactions was carefully analyzed by LC–MS to evaluate the ratio among the couple of regioisomers **5a–d/13a–d** and **6a–d/15a–d**. The relative percentages of the two regioisomers are reported in Table 1. Major isomers **5a–d** and **6a–d** were fully characterized by spectroscopic and analytical methods, whereas minor regioisomers **13a–d** and **15a–d** were detected by HPLC and identified through their MS spectrum.

The almost unidirectional behavior observed in the cycloaddition of nitrile imine **11** to monosubstituted alkynes and alkenes parallels the results obtained with the thoroughly studied diphenylnitrile imine.[15] The regioselectivity of such a 1,3-dipole has been explained on the basis of the Frontier orbital theory where the dominant interaction involves the



Scheme 1. (a) Neat, 40 °C, 20 mbar, 2 h; (b) $(COCl)_2$, DMSO, TEA, −60 °C/CH_2Cl_2; (c) $PhNHNH_2$, −40 °C/CH_2Cl_2; (d) NBS/AcOEt, Δ; (e) CBr_4, PPh_3/CH_2Cl_2; (f) $NaHCO_3$/AcOEt.



Scheme 2. (a) $NaHCO_3$/AcOEt, Δ; (b) TMSBr, CH_2Cl_2; (c) PDC, DMF.

LUMO of the 1,3-dipole and the HOMO of the dipolarophile.[19,20] According to the principle of the maximum overlap, the preferred isomer comes from the union of the two sites of the reactants having the largest coefficients. Since the dipolarophile HOMO of monosubstituted alkynes and alkenes has the larger coefficient at the β carbon, regardless of the substitution pattern, and the nitrilium carbon is the terminus endowed with the highest LUMO coefficient, the formation of cycloadducts **5a**–**d** and **6a**–**d** as the major regioisomers is fully accounted for.[19]

To check the applicability of the present methodology to the synthesis of pyrazole- and 2-pyrazoline-3-phosphonic acids, we treated the representative cycloadducts **5a** and **6a** with a 10-fold excess of trimethylsilyl bromide; heterocyclic phosphonic acids **7** and **8**, respectively, were obtained in quantitative yield.[21] Finally, the conversion of 2-pyrazolines into the corresponding pyrazole derivatives was proved to be effective by reacting **6a** with a 15-fold excess of pyridinium dichromate (PDC) in DMF at room temperature to produce pyrazole **5a** in high yield.

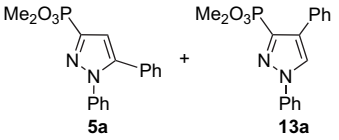
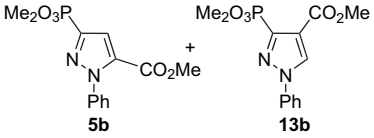
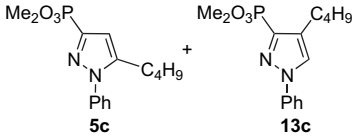
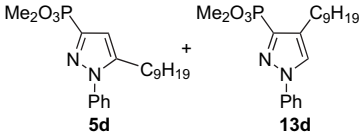
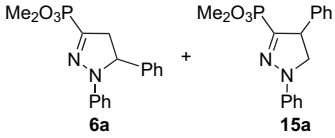
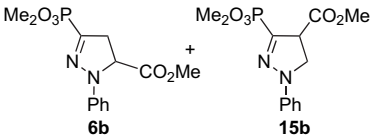
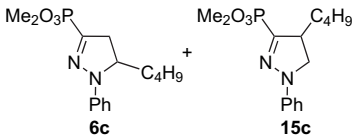
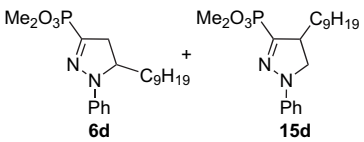
3. Experimental

3.1. Materials and methods

All reagents were purchased from Sigma. Dimethyl (hydroxymethyl)phosphonate was prepared according to a literature procedure.[17] ^{1}H NMR (300 MHz), ^{13}C NMR (75.5 MHz), and ^{31}P NMR (121.5 MHz) spectra were recorded with a Varian Mercury 300 spectrometer in $CDCl_3$ or DMSO-d_6 solution at 20 °C. Chemical shifts (δ) are expressed in parts per million and coupling constants (J) in hertz. IR spectra were recorded with a Perkin–Elmer FTIR spectrometer Paragon 1000 PC. TLC analyses were performed on commercial silica gel 60 F_{254} aluminum sheets; spots were visualized by spraying with a dilute alkaline potassium permanganate solution. Melting points were determined on a model B 540 Büchi apparatus and are uncorrected.

HPLC–MS analyses were carried out using an Agilent 1100 HPLC coupled with an ESI (+) Bruker Esquire 3000 ionic

Table 1. Regioisomeric ratio of the cycloaddition between nitrile imine **11** and dipolarophiles **12a–d** and **14a–d**

Dipolarophile	Products	Regioisomeric ratio[a]	Yield[b] (%)
Ph—≡ **12a**	 **5a** + **13a**	90:10	40
MeOOC—≡ **12b**	 **5b** + **13b**	78:22	34
C_4H_9—≡ **12c**	 **5c** + **13c**	95:5	18
C_9H_{19}—≡ **12d**	 **5d** + **13d**	81:19	12
Ph **14a**	 **6a** + **15a**	97:3	30
MeO_2C **14b**	 **6b** + **15b**	97:3	20
C_4H_9 **14c**	 **6c** + **15c**	98:2	20
C_9H_{19} **14d**	 **6d** + **15d**	95:5	27

[a] Determined by LC–MS analysis of the crude reaction mixture.
[b] Yield of isolated product **5** or **6**.

trap. The instrument was fitted with a Waters Atlantis column (4.6×50 mm, 3 μm). Analyses were carried out using mobile phases A and B according to one of the following methods:

Phase A: H_2O+0.1% TFA; phase B: acetonitrile+0.1% TFA.
Method 1: t=0, A: 80%, B: 20%; t=10 min, A: 50%, B: 50%.
Method 2: t=0, A: 60%, B: 40%; t=10 min, A: 0%, B: 100%.
Method 3: t=0, A: 90%, B: 10%; t=6 min, A: 10%, B: 90%.
Method 4: t=0, A: 40%, B: 60%; t=10 min, A: 10%, B: 90%.

3.2. Dimethyl [(2-phenylhydrazino)carbonyl]-phosphonate (9)

Trimethyl phosphonoformate (1 mL, 7.6 mmol) and phenylhydrazine (0.75 mL, 7.6 mmol) were mixed in a round bottom flask. The mixture was promptly stirred at 40 °C under reduced pressure (20 mbar). After 3 h, the crude material

was purified by flash chromatography (petroleum ether/AcOEt 1:1) to obtain **9** (250 mg, 1.03 mmol, yield 14%) as a white solid.

Phosphonate **9**: crystallized from $(i\text{-Pr})_2O$ as white prisms; mp 142–144 °C. R_f=0.4 (AcOEt). ^{1}H NMR ($CDCl_3$): δ= 3.87 (d, J_{H-P}=11.0, 3H), 3.88 (d, J_{H-P}=11.0, 3H), 6.42 (br s, 1H), 6.86 (d, J=7.7, 2H), 6.94 (t, J=7.7, 1H), 7.25 (dd, J= 7.7, 7.7, 2H), 9.5 (br s, 1H); ^{13}C NMR ($CDCl_3$): 55.1 (J_{C-P}= 7.0), 114.3, 122.1, 129.5, 146.9, 164.5 (d, J_{C-P}=223.0); ^{31}P NMR ($CDCl_3$): 1.12; ν_{max} (neat) 3251, 2958, 1676, 1659, 1602, 1498, 1248, 1036. Anal. Calcd for $C_9H_{13}N_2O_4P$: C, 44.27; H, 5.37; N, 11.47. Found: C, 44.63; H, 5.50; N, 11.09.

3.3. Dimethyl [bromo(phenylhydrazono)methyl]-phosphonate (10)

To a solution of **9** (3.0 g, 12 mmol) in CH_2Cl_2 (20 mL) a solution of CBr_4 (6.0 g, 18 mmol) in CH_2Cl_2 (10 mL) was added dropwise, followed by a solution of PPh_3 (3.9 g, 15 mmol) in CH_2Cl_2 (10 mL) at 0 °C. The reaction mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure and the crude material was purified by flash chromatography (petroleum ether/AcOEt 1:1) to give **10** (2.6 g, 8.5 mmol, yield 70%) as a white solid.

Hydrazonoyl bromide **10**: crystallized from $(i\text{-Pr})_2O$ as white prisms; mp (dec) >108 °C; R_f=0.6 (AcOEt); ^{1}H NMR ($CDCl_3$): 3.92 (d, J_{H-P}=11.0, 6H), 7.05 (t, J=7.7, 1H), 7.2 (d, J=7.7, 2H), 7.32 (dd, J=7.7, 7.7, 2H), 8.55 (br s, 1H); ^{13}C NMR ($CDCl_3$): 54.3 (J_{C-P}=6.0), 107.6 (d, J_{C-P}=280.0), 114.1, 122.8, 129.3, 141.1; ^{31}P NMR ($CDCl_3$): 5.78; ν_{max} (neat) 3197, 2954, 1602, 1556, 1510, 1251, 1039. Anal. Calcd for $C_9H_{12}BrN_2O_3P$: C, 35.20; H, 3.94; N, 9.12. Found: C, 35.51; H, 4.05; N, 9.02.

3.4. Preparation of 10 from dimethyl (hydroxymethyl)-phosphonate

To a solution of oxalyl chloride (0.48 mL, 5.5 mmol) in dry CH_2Cl_2 (13 mL) cooled at −60 °C, under N_2, was added DMSO (0.79 mL, 11 mmol). After 2 min, a solution of dimethyl (hydroxymethyl)phosphonate[17] (0.70 g, 5 mmol), in dry CH_2Cl_2 (5 mL), was added slowly with stirring. After 15 min, TEA (3.5 mL, 25 mmol) was added dropwise. The temperature was then let to rise at −40 °C and stirred for 1 h. After that time phenylhydrazine (0.38 mL, 10 mmol) was added and the mixture was let to warm to room temperature. The solvent was evaporated under vacuum, and the crude material was purified by flash chromatography (petroleum ether/AcOEt 1:1) to give the intermediate dimethyl [(phenylhydrazono)methyl]phosphonate (0.24 g, 1.06 mmol), which was directly submitted to bromination with NBS (0.21 g, 1.17 mmol) in AcOEt (5 mL) at reflux. After 1 h, the solvent was evaporated under vacuum and the crude material was purified by flash chromatography (petroleum ether/AcOEt 1:1) to give **10** (0.30 g, 0.98 mmol, overall yield 20%).

3.5. General procedure for the cycloaddition of 11 to alkynes 12

To a solution of alkyne **12** (3 mmol) in AcOEt (5 mL) were added **10** (0.31 g, 1 mmol) and $NaHCO_3$ (0.34 g, 4 mmol). The reaction mixture was refluxed for 24 h and the progress of the reaction was followed by TLC (AcOEt). Water (1 mL) was added and the organic layer was separated and dried over anhydrous Na_2SO_4. HPLC–MS analysis of the crude material, obtained after evaporation of the solvent, showed the formation of regioisomers **5** and **13** in the relative ratio reported in Table 1. The crude material was purified by flash chromatography on silica gel (petroleum ether/AcOEt 2:3) to give pyrazole **5**.

Pyrazole **5a**: R_f=0.22 (petroleum ether/AcOEt 2:3); yellow oil; ^{1}H NMR ($CDCl_3$): 3.90 (d, J_{H-P}=11.0, 6H), 6.97 (d, J_{H-P}=1.5, 1H), 7.17–7.23 (m, 2H), 7.25–7.40 (m, 8H); ^{13}C NMR ($CDCl_3$): 53.2 (d, J_{C-P}=6.0), 53.2 (d, J_{C-P}=6.0), 112.8 (d, J_{C-P}=23.0), 125.3, 128.1, 128.4, 128.5, 128.7, 129.1, 139.1, 141.2 (d, J_{C-P}=233.0), 144.0 (d, J_{C-P}=10.0); ^{31}P NMR ($CDCl_3$): 14.21; ν_{max} (neat) 3470, 2953, 1498, 1256, 1031; HPLC retention time: 5.01 min (method 3). Anal. Calcd for $C_{17}H_{17}N_2O_3P$: C, 62.19; H, 5.22; N, 8.53. Found: C, 62.03; H, 5.31; N, 8.35.

Pyrazole **5b**: R_f=0.31 (petroleum ether/AcOEt 3:7); yellow oil; ^{1}H NMR ($CDCl_3$): 3.82 (s, 3H), 3.88 (d, J_{H-P}=11.3, 6H), 7.40–7.55 (m, 6H); ^{13}C NMR ($CDCl_3$): 52.4, 53.4 (d, J_{C-P}=6.0), 118.0 (d, J_{C-P}=24.0), 126.0, 128.7, 129.4, 132.0, 139.5, 141.4 (d, J_{C-P}=234.0), 158.8; ^{31}P NMR ($CDCl_3$): 12.19; ν_{max} (neat) 3473, 2956, 1737, 1499, 1280, 1035; HPLC retention time: 5.03 min (method 1). Anal. Calcd for $C_{13}H_{15}N_2O_5P$: C, 50.33; H, 4.87; N, 9.03. Found: C, 50.04; H, 5.02; N, 8.90.

Pyrazole **5c**: R_f=0.29 (petroleum ether/AcOEt 3:7); yellow oil; ^{1}H NMR ($CDCl_3$): 0.87 (t, J=7.3, 3H), 1.20–1.40 (m, 2H), 1.55–1.65 (m, 2H), 2.63 (t, J=7.7, 2H), 3.86 (d, J_{H-P}= 11.4, 6H), 6.68 (s, 1H), 7.35–7.50 (m, 5H); ^{13}C NMR ($CDCl_3$): 13.7, 22.2, 25.8, 30.6, 53.2 (d, J_{C-P}=6.0), 111.0 (d, J_{C-P}=24.0), 125.8, 128.8, 129.2, 132.0, 139.2, 140.6 (d, J_{C-P}=233.0), 145.4 (d, J_{C-P}=10.0); ^{31}P NMR ($CDCl_3$): 14.83; ν_{max} (neat) 3431, 2954, 1500, 1255, 1031; HPLC retention time: 3.08 min (method 2). Anal. Calcd for $C_{15}H_{21}N_2O_3P$: C, 58.43; H, 6.87; N, 9.09. Found: C, 58.15; H, 6.95; N, 8.88.

Pyrazole **5d**: R_f=0.31 (petroleum ether/AcOEt 1:1); yellow oil; ^{1}H NMR ($CDCl_3$): 0.86 (t, J=7.0, 3H), 1.15–1.40 (m, 12H), 1.55–1.65 (m, 2H), 2.62 (t, J=8.0, 2H), 3.85 (d, J_{H-P}= 11.2, 6H), 6.70 (s, 1H), 7.40–7.60 (m, 5H); ^{13}C NMR ($CDCl_3$): 14.4, 23.0, 26.4, 28.9, 29.4, 29.5, 29.7, 30.0, 32.2, 53.4 (d, J_{C-P}=6.3), 53.5 (d, J_{C-P}=6.3), 111.1 (d, J_{C-P}=24.0), 125.9, 128.9, 129.3, 139.4, 140.9 (d, J_{C-P}=233.0), 145.5 (d, J_{C-P}=9.7); ^{31}P NMR ($CDCl_3$): 14.96; ν_{max} (neat) 3368, 2926, 1501, 1258, 1034; HPLC retention time: 3.99 min (method 4). Anal. Calcd for $C_{20}H_{31}N_2O_3P$: C, 63.47; H, 8.26; N, 7.40. Found: C, 63.15; H, 8.42; N, 7.37.

3.6. General procedure for the cycloaddition of 11 to alkenes 14

To a solution of alkene **14** (3 mmol) in AcOEt (5 mL) were added **10** (0.31 g, 1 mmol) and $NaHCO_3$ (0.34 g, 4 mmol). The reaction mixture was refluxed for 24 h and the progress of the reaction was followed by TLC (AcOEt). Water (1 mL)

was added and the organic layer was separated and dried over anhydrous Na_2SO_4. HPLC–MS analysis of the crude material, obtained after evaporation of the solvent, showed the formation of regioisomers **6** and **15** in the relative ratio reported in Table 1. The crude material was purified by flash chromatography on silica gel (petroleum ether/AcOEt 2:3) to give pyrazoline **6**.

Pyrazoline **6a**: R_f=0.4 (petroleum ether/AcOEt 3:7); white prisms from *i*-PrOH, mp (dec) >122 °C; ^{1}H NMR ($CDCl_3$): 3.00 (dd, J=7.4, 18.0, 1H), 3.68 (dd, J=13.0, 18.0, 1H), 3.88 (d, J_{H-P}=11.3, 3H), 3.90 (d, J_{H-P}=11.3, 3H), 5.30 (dd, J=7.4, 13.0, 1H), 6.85 (t, J=7.3, 1H), 7.04 (d, J=8.4, 2H), 7.10–7.40 (m, 7H); ^{13}C NMR ($CDCl_3$): 45.0 (d, J_{C-P}=20.0), 53.2 (d, J_{C-P}=6.6), 53.3 (d, J_{C-P}=6.6), 64.0 (d, J_{C-P}=4.3), 114.0, 120.6, 125.4, 127.7, 128.7, 129.1, 136.8 (d, J_{C-P}=236.0), 140.9, 142.6; ^{31}P NMR ($CDCl_3$): 13.43; ν_{max} (neat) 3474, 2953, 1599, 1499, 1258, 1119; 1032; HPLC retention time: 9.61 min (method 1). Anal. Calcd for $C_{17}H_{19}N_2O_3P$: C, 61.81; H, 5.80; N, 8.48. Found: C, 61.58; H, 5.86; N, 8.40.

Pyrazoline **6b**: R_f=0.18 (petroleum ether/AcOEt 2:3); yellow oil; ^{1}H NMR ($CDCl_3$): 3.27 (ddd, J=1.5, 7.0, 18.0, 1H), 3.51 (ddd, J=1.5, 13.2, 18.0, 1H), 3.73 (s, 3H), 3.85 (d, J_{H-P}=11.3, 3H), 3.86 (d, J_{H-P}=11.3, 3H), 4.83 (dd, J=7.0, 13.2, 1H), 6.95 (t, J=7.3, 1H), 7.07 (d, J=8.4, 2H), 7.27 (dd, J=7.3, 8.4, 2H); ^{13}C NMR ($CDCl_3$): 40.4 (d, J_{C-P}=22.0), 53.3, 53.8 (d, J_{C-P}=6.0), 53.9 (d, J_{C-P}=6.0), 61.5 (d, J_{C-P}=4.0), 113.8, 121.7, 129.5, 137.6 (d, J_{C-P}=203.0), 142.8, 170.9; ^{31}P NMR ($CDCl_3$): 12.15; ν_{max} (neat) 3474, 2956, 1745, 1599, 1501, 1261, 1124, 1035; HPLC retention time: 5.78 min (method 1). Anal. Calcd for $C_{13}H_{17}N_2O_5P$: C, 50.00; H, 5.49; N, 8.97. Found: C, 49.75; H, 5.68; N, 8.70.

Pyrazoline **6c**: R_f=0.29 (petroleum ether/AcOEt 2:3); yellow oil; ^{1}H NMR ($CDCl_3$): 0.88 (t, J=7.0, 3H), 1.20–1.40 (m, 4H), 1.42–1.62 (m, 1H), 1.70–1.82 (m, 1H), 2.90 (ddd, J=1.4, 5.3, 17.3, 1H), 3.25 (ddd, J=1.4, 12.0, 17.3, 1H), 3.85 (d, J_{H-P}=11.3, 3H), 3.86 (d, J_{H-P}=11.3, 3H), 4.41 (dddd, J=2.7, 5.3, 8.5, 12.0, 1H), 6.92 (t, J=7.5, 1H), 7.14 (d, J=7.5, 2H), 7.27 (dd, J=7.5, 7.5, 2H); ^{13}C NMR ($CDCl_3$): 14.2, 22.7, 26.9, 31.6, 39.8 (d, J_{C-P}=20.0), 53.5 (d, J_{C-P}=3.5), 60.0 (d, J_{C-P}=4.6), 114.6, 121.0, 129.4, 137.2 (d, J_{C-P}=237.0), 142.7; ^{31}P NMR ($CDCl_3$): 14.18; ν_{max} (neat) 3470, 2955, 1599, 1499, 1258, 1124, 1033; HPLC retention time: 4.06 min (method 2). Anal. Calcd for $C_{15}H_{23}N_2O_3P$: C, 58.05; H, 7.47; N, 9.03. Found: C, 57.80; H, 7.72; N, 8.81.

Pyrazoline **6d**: R_f=0.32 (petroleum ether/AcOEt 1:1); yellow oil; ^{1}H NMR ($CDCl_3$): 0.86 (t, J=7.0, 3H), 1.15–1.30 (m, 14H), 1.40–1.60 (m, 1H), 1.65–1.80 (m, 1H), 2.87 (ddd, J=1.4, 5.3, 17.3, 1H), 3.51 (ddd, J=1.4, 12.0, 17.3, 1H), 3.82 (d, J_{H-P}=11.3, 3H), 3.83 (d, J_{H-P}=11.3, 3H), 4.38 (dddd, J=2.4, 5.3, 8.5, 12.0, 1H), 6.90 (t, J=7.5, 1H), 7.12 (d, J=7.5, 2H), 7.26 (dd, J=7.5, 7.5, 2H); ^{13}C NMR ($CDCl_3$): 14.4, 23.0, 24.8, 29.6, 29.7, 29.8, 29.8, 32.0, 32.2, 39.9 (d, J_{C-P}=20.0), 53.5 (d, J_{C-P}=3.5), 60.2 (d, J_{C-P}=4.8), 114.6, 121.0, 129.3, 137.2 (d, J_{C-P}=237.0), 142.7; ^{31}P NMR ($CDCl_3$): 14.30; ν_{max} (neat) 3399, 2926, 1599, 1499, 1259, 1124; 1033; HPLC retention time: 5.07 min (method 4). Anal. Calcd for $C_{20}H_{33}N_2O_3P$: C, 63.14; H, 8.74; N, 7.36. Found: C, 62.79; H, 9.03; N, 7.10.

3.7. Preparation of 1,5-diphenyl-1*H*-pyrazole-3-phosphonic acid (7)

To a solution of **5a** (164 mg, 0.5 mmol) in CH_2Cl_2 (3 mL) was added bromotrimethylsilane (0.66 mL, 5 mmol). The reaction mixture was then stirred at room temperature for 4 h. Methanol (2 mL) was added and the reaction mixture was stirred for 1 h and then the solvent was evaporated under vacuum to give **7** (150 mg, 0.5 mmol, yield 100%) as a white powder.

Phosphonic acid **7**: white prisms from *i*-PrOH, mp (dec) >210 °C; ^{1}H NMR (DMSO-d_6): 6.82 (d, J_{H-P}=1.5, 1H), 7.18–7.48 (m, 10H); ^{13}C NMR (DMSO-d_6): 112.0 (d, J_{C-P}=22.0), 126.2, 129.0, 129.2, 129.3, 129.4, 129.9, 130.1, 140.1, 143.8 (d, J_{C-P}=9.2), 148.2 (d, J_{C-P}=221.0); ^{31}P NMR (DMSO-d_6): 5.45; ν_{max} (neat) 3245, 2972, 2290, 1596, 1499, 1132, 1001. Anal. Calcd for $C_{15}H_{13}N_2O_3P$: C, 60.00; H, 4.36; N, 9.33. Found: C, 59.74; H, 4.69; N, 9.09.

3.8. Preparation of 1,5-diphenyl-4,5-dihydro-1*H*-pyrazole-3-phosphonic acid (8)

Compound **6a** was treated as described for **5a** to give the corresponding phosphonic acid **8** as a white powder in quantitative yield.

Phosphonic acid **8**: white prisms from *i*-PrOH, mp (dec) >160 °C; ^{1}H NMR (DMSO-d_6): 2.78 (dd, J=6.0, 17.5, 1H), 3.64 (dd, J=12.6, 17.5, 1H), 5.40 (dd, J=6.0, 12.6, 1H), 6.73 (t, J=7.6, 1H), 6.92 (d, J=7.6, 2H), 7.13 (t, J=7.6,7.6, 2H), 7.17–7.27 (m, 3H), 7.32 (t, J=7.0, 7.0, 2H); ^{13}C NMR (DMSO-d_6): 46.1 (d, J_{C-P}=20.0), 63.1 (d, J_{C-P}=4.5), 114.0, 120.1, 126.4, 128.1, 129.6, 129.6, 142.7, 144.1, 145.2 (d, J_{C-P}=220.0); ^{31}P NMR (DMSO-d_6): 4.84; ν_{max} (neat) 3296, 2974, 2297, 1599, 1499, 1120, 1031. Anal. Calcd for $C_{15}H_{15}N_2O_3P$: C, 59.60; H, 5.00; N, 9.27. Found: C, 59.62; H, 4.84; N, 8.97.

3.9. Oxidation of dimethyl 1,5-diphenyl-4,5-dihydro-1*H*-pyrazole-3-phosphonate (6a) to dimethyl 1,5-diphenyl-1*H*-pyrazole-3-phosphonate (5a)

To a solution of **6a** (165 mg, 0.5 mmol) in DMF (3 mL) was added PDC (2.8 g, 7.5 mmol). The solution was stirred at room temperature for 4 h. The reaction was followed by TLC (petroleum ether/AcOEt 3:7). Water (6 mL) was then added and the solution was extracted with AcOEt (3×5 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The crude material was purified by column chromatography on silica gel (petroleum ether/AcOEt 2:3) to give **5a** (131 mg, 0.4 mmol, 80% yield) as a yellow oil.

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