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Phosphonylpyrazoles from Bestmann−Ohira Reagent and Nitroalkenes: Synthesis and Dynamic NMR Studies

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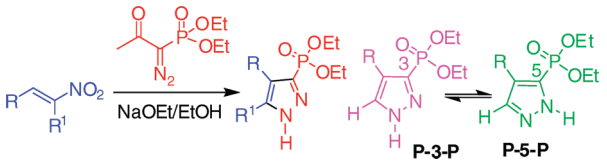

Application of diethyl 1-diazo-2-oxopropylphosphonate (Bestmann−Ohira reagent) as a cycloaddition partner with nitroalkenes has been extensively investigated. Base-mediated reaction of the Bestmann−Ohira reagent with various nitroalkenes such as β-substituted, α,β-disubstituted, and nitroethylene that are part of a carbocyclic or heterocyclic ring provided functionalized phosphonylpyrazoles through a one-pot regioselective reaction at room temperature in high yield. The substituted nitroalkenes employed in these reactions also included Morita−Baylis−Hillman adducts of conjugated nitroalkenes with various electrophiles. Detailed dynamic NMR studies were performed on the prototropic tautomerism exhibited by the phosphonylpyrazoles using $CDCl_3$ and DMSO-d_6 as solvents and ^1H and ^{31}P as the probe nuclei. These studies unraveled the existence of two tautomers in solution with a small energy difference but considerable barrier to interconversion.

Introduction

Heterocyclic compounds are popular targets for synthetic chemists primarily because of their diverse and potent biological properties.[1] Pyrazoles, in particular, have been reported to exhibit a wide range of biological properties.[2] Their therapeutic effects in areas such as CNS diseases, metabolic diseases, endocrine functions, and oncology have been highlighted.[3] The efficacy of pyrazoles to behave as non-nucleoside HIV-1 reverse transcriptase inhibitors,[4] COX-2 inhibitors,[5] antihyperglycemic agents,[6] cannabinoid antagonists,[7] and cytotoxic agents[8] has been reported in the recent literature. Other enzyme inhibitory,[9] antimicrobial, antiviral, and anticancer[10] properties of pyrazoles also made them a prominent class of heterocycles. The natural product withasomnine, which is an analgesic and a CNS depressant,

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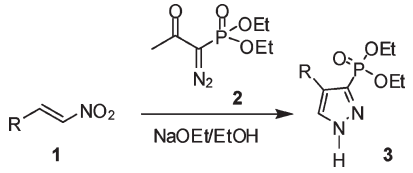
possesses a pyrazole moiety.[11] Several pyrazole-containing compounds such as Viagra, Celebrex, and Acomplia are much sought after drugs in the world market. The versatility of pyrazoles as ligands in coordination chemistry has been recently reviewed.[12]

The pivotal role of organophosphorus compounds[13] as biomolecules, metabolic probes,[14] peptide mimetics,[15] antibiotic and pharmacological agents,[16] and other molecules of biological relevance[17] is well-documented. The organophosphorus compounds to which a heterocyclic moiety is attached often display greater biological activity.[18] Among phosphorus compounds, phosphonates regulate important biological functions by mimicking carboxylic acid groups.[19] Various heterocyclic phosphonates[20] exhibit a wide range of bioactivities such as Edg receptor antagonistic,[21] bone-resorption inhibitory,[22] antibiotic,[23] antibacterial, and antifungal properties.[24]

Synthesis of phosphonylpyrazoles appeared an attractive objective in view of the above-mentioned properties of the individual components and the possible and unpredictable changes in such properties in the hybrid system. The reported methods for the synthesis of phosphonylpyrazoles are by and large based on the cyclocondensation of 1,3-difunctional species bearing phosphorus substituent with hydrazine derivatives[25] or 1,3-dipolar cycloaddition of alkenyl or alkynyl phosphonate with diazo compounds.[26] Although these are based on the methods for the synthesis of pyrazoles,[27,28] synthesis of the phosphorus/phosphonate precursors involves multisteps and the key cyclization/cycloaddition step often proceeds with poor regioselectivity.[29]

SCHEME 1



We recently disclosed a one-pot regioselective synthesis of phosphonylpyrazoles **3** via base-mediated reaction of the Bestmann−Ohira reagent **2** with nitroalkenes **1** (Scheme 1).[30] In fact, the reaction of **2**,[31] which is a synthetic equivalent of diethyl diazomethylphosphonate (Seyferth−Colvin−Gilbert reagent),[32] with aldehydes in the presence of a suitable base is a convenient way of generating acetylenes.[33,34] However, possible application of **2** as a cycloaddition partner received scant attention.[35] This article, which is a full version of our preliminary communication,[30] describes the scope and applications of our methodology and the tautomerism exhibited

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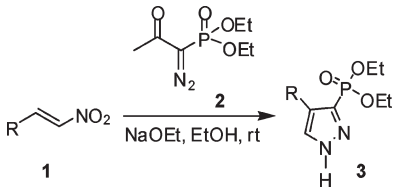
TABLE 1. 1,3-DC Reaction of β-Substituted Nitroethylenes 1 with BOR 2 in the Presence of NaOEt in EtOH at Room Temperature



entry	1	R	time	% yield[a]
1	**1a**	benzo[*d*][1,3]dioxole	15 min	77
2	**1b**	4-OMe-Ph	15 min	66
3	**1c**	4-Cl-Ph	15 min	61
4	**1d**	4-NO_2-Ph	15 min	64
5	**1e**	3-NO_2-Ph	15 min	61
6	**1f**	2-NO_2-Ph	15 min	67
7	**1g**	Ph	15 min	62
8	**1h**	2-furyl	15 min	55[b]
9	**1i**	2-thienyl	15 min	49[b]
10	**1j**	NMe_2	15 min	64
11	**1k**	cyclohexyl	30 min	53
12	**1l**	PhCH=CH[c]	2 h	58
13	**1m**	2-MeO-PhCH=CH[c]	2 h	60

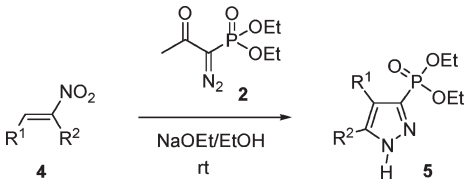
[a]Isolated yield after purification by silica gel column chromatography. [b]Part of **1** polymerized. [c](*E*) configuration.

by **3**. Multinuclear (^{1}H and ^{31}P), variable-temperature (VT), and solvent-dependent NMR studies were performed on a representative system to unravel the tautomeric equilibrium in phosphonylpyrazoles.

Results and Discussion

The commercially available 2-oxopropylphosphonate was transformed in one step to the Bestmann−Ohira reagent (BOR) **2**.[34] Our extensive optimization studies using **1a** as the model substrate revealed that the regioselective formation of pyrazole **3a** in 77% yield from nitroalkene **1a** and BOR **2** takes place in the presence of sodium ethoxide in ethanol at room temperature in 15 min (Table 1). The requirement of a nucleophilic base and protic solvent was apparent from our experiments. According to the proposed mechanism,[30] the nucleophilic base mediated acyl cleavage of BOR **2** followed by cycloaddition of the resulting diazomethylphosphonate anion with nitroalkene **1a** provides initial cycloadduct which undergoes elimination to afford phosphonylpyrazole **3a**. After confirming the structure of **3a** by ^{1}H−^{1}H-NOESY and single-crystal X-ray diffraction analysis,[30] we reacted a variety of other nitroalkenes **1b**−**m** with BOR **2** under the optimized conditions (Table 1). Examination of Table 1 suggests that while aromatic nitroalkenes **1a**−**g** with a variety of substituents (entries 1−7) provide pyrazoles **3a**−**g** in 61−77% yield, the product yields are marginally lower in the case of heteroaromatic nitroalkenes **1h**−**i**. The pyrazoles **3j**−**m** were isolated in satisfactory yields in the case of enaminonitroalkene **1j**, β-alkyl nitroethylene **1k**, and nitrodienes **1l**−**m** (entries 10−13, Table 1).

TABLE 2. 1,3-DC Reaction of α,β-Disubstituted Nitroethylenes 4 with BOR 2 in the Presence of NaOEt in EtOH at Room Temperature



entry	nitroalkene	R^1	R^2	time	% yield[a]
1	**4a**	benzo[*d*][1,3]dioxole	Me	15 min	70
2	**4b**	4-Cl-Ph	Me	15 min	65
3	**4c**	4-NO_2-Ph	Me	15 min	68
4	**4d**	Ph	Me	15 min	62
5	**4e**	Ph	Ph	2 h	56

[a]Isolated yield after purification by recrystallization.

Having successfully employed a diverse array of β-substituted nitroethylenes **1a**−**m**, we proceeded to investigate the reactivity of BOR **2** with a variety of α,β-disusbtituted nitroethylenes **4a**−**e**[36,37] under the optimized conditions (Table 2). It may be noted that nitroethylenes **4a**−**e** with methyl and phenyl substituents at the α-position and aromatic rings with electron-withdrawing and -donating groups at the β-position react with BOR **2** to afford pyrazoles **5a**−**e** in good yield (56−70%, entries 1−5, Table 2).

Reaction of BOR **2** with nitroethylenic moiety **6** which is part of various carbo- and heterocyclic rings appeared to be an attractive strategy for the synthesis of phosphonylpyrazoles **7** which are fused to carbo- and heterocycles (Table 3). Thus, we were pleased to observe the formation of phosphonyl pyrazoles angularly fused to chromene skeleton **7a**−**c** in good yield when nitrochromenes **6a**−**c**[38] were reacted with BOR **2** (entries 1−3, Table 3). While nitroquinoline **6d** and nitronaphthalene **6e** also reacted with BOR **2** over 24 h and delivered the pyrazoles **7d** and **7e**, respectively, in good to moderate yield (entries 4 and 5), our attempts to react nitrobenzene **6f** and *m*-dinitrobenzene **6g** with BOR **2** under similar conditions were unsuccessful (entries 6 and 7, Table 3). The inertness of nitrobenzene **6f** and *m*-dinitrobenzene **6g** in their base-mediated reaction with BOR **2** is attributable to their greater aromaticity as compared to nitroquinoline **6d** and nitronaphthalene **6e**.

It should be noted that in the reactions discussed so far, the pyrazoles are formed via elimination of the NO_2 group, a

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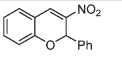
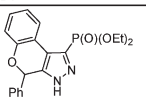
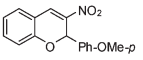
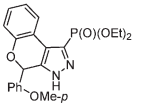
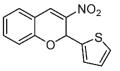
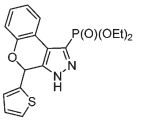
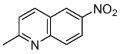
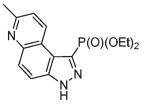
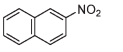
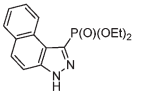
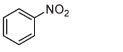
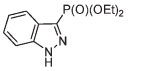
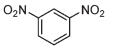
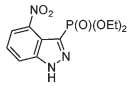
(38) (a) Deshpande, S. R.; Mathur, H. H.; Trivedi, G. K. *Indian J. Chem.* **1983**, *22B*, 166. (b) Yan, M.-C.; Jang, Y.-J.; Yao, C.-F. *Tetrahedron Lett.* **2001**, *42*, 2717. (c) See also: Xu, D.-Q.; Wang, Y.-F.; Luo, S.-P.; Zhang, S.; Zhong, A.-G.; Chen, H.; Xu, Z.-Y. *Adv. Synth. Catal.* **2008**, *350*, 2610.

TABLE 3. 1,3-DC Reaction of Nitroheterocycles and Aromatics 6 with BOR 2 in the Presence of NaOEt in EtOH at Room Temperature

entry	6	nitroalkene	time	7	pyrazole	% yield[a]
1	**6a**		0.5 h	**7a**		64
2	**6b**		1 h	**7b**		57
3	**6c**		12 h	**7c**		59
4	**6d**		24 h	**7d**		52
5	**6e**		24 h	**7e**		38[b]
6	**6f**		24 h	**7f**		-[c]
7	**6g**		24 h	**7g**		-[c]

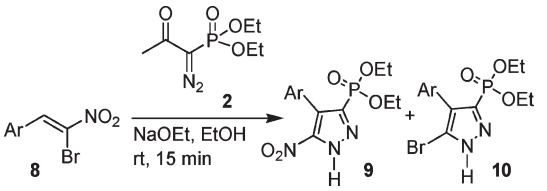
[a]Isolated yield after purification by silica gel column chromatography. [b]22% of **6e** was recovered. [c]No reaction. *m*- and *p*-nitrotoluene also did not react under our experimental conditions.

synthetically useful functionality, from the initial cycloadduct. Therefore, it was felt that in the event of the starting nitroalkene possessing a leaving group that is better than NO_2 group at the α-position, it would be possible to isolate nitropyrazole. In order to achieve this objective, α-bromonitroalkenes **8a**−**d**[37] were reacted with BOR **2** under the optimized conditions (Table 4). These reactions proceeded in moderate to good yield (38−54%). Interestingly, nitroalkenes **8a** and **8c** provided nitropyrazoles **9a** and **9c** as the exclusive products (entries 1 and 3, Table 4). On the other hand, in the case of α-bromonitrostyrenes with electron-donating groups on the aromatic ring mixtures of nitropyrazole and bromopyrazole were isolated (entries 2 and 4, Table 4). This was explained primarily in terms of the elimination of HBr by an E2 mechanism and HNO_2 by an E1cB mechanism from the initial cycloadducts. It turns out that in the case of **8a** and **8c** E2 elimination leads to the exclusive formation of **9a** and **9c**, respectively. However, in the case of **8b** and **8d**, a competing E1cB mechanism is also operative which leads to the formation of a mixture of **9** and **10**.[30]

Our methodology found applications in the synthesis of fully functionalized pyrazoles. At the outset, α-hydroxymethylated nitroalkenes **11a**−**c**,[39] which were conveniently generated via Morita−Baylis−Hillman (MBH) reaction of nitroalkenes with formaldehyde, were employed as the cycloaddition partners with BOR **2** under the optimized conditions (Table 5). The fully functionalized pyrazoles **12a**−**c** were isolated in good yield (55−61%).

(39) (a) Rastogi, N.; Namboothiri, I. N. N.; Cojocaru, M. *Tetrahedron Lett*. **2004**, *45*, 4745. (b) Mohan, R.; Rastogi, N.; Namboothiri, I. N. N.; Mobin, S. M.; Panda, D. *Bioorg. Med. Chem*. **2006**, *14*, 8073.

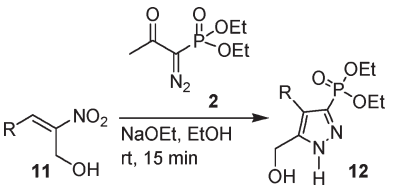
TABLE 4. 1,3-DC Reaction of α-Bromonitrostyrenes 8 with BOR 2 in the Presence of NaOEt in EtOH



entry	8	Ar	% yield of **9** + **10**[a]	**9**/**10** ratio[b]
1	**8a**	Ph	47	100:0
2	**8b**	4-OMe-Ph	54	61:39
3	**8c**	4-Cl-Ph	38	100:0
4	**8d**	benzo[*d*][1,3]dioxole	50	52:48

[a]Isolated yield after purification by silica gel column chromatography. Part of **8** polymerized. [b]Determined by ^{31}P NMR of the crude mixture.

TABLE 5. 1,3-DC Reaction of α-Hydroxymethylated Nitrostyrenes 11 with BOR 2 in the Presence of NaOEt in EtOH



entry	11	R	% yield[a]
1	**11a**	benzo[*d*][1,3]dioxole	61
2	**11b**	4-OMe-Ph	55
3	**11c**	2-furyl	57

[a]Isolated yield after purification by silica gel column chromatography.

The above strategy was extended to other MBH adducts arising from reaction of nitroalkenes with electrophiles such as tosyl imines, methyl vinyl ketone, azo dicarboxylate, and acrylate[40] (Table 6). Reaction of these MBH adducts **13a**−**f** with BOR **2** proceeded well to afford pyrazoles **14a**−**f** in good to excellent yield (51−75%). In the case of MBH adducts **13e**−**f** the initial cycloadduct underwent spontaneous cyclization to the lactams **14e**−**f**.

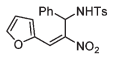
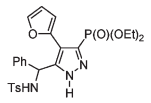
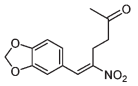
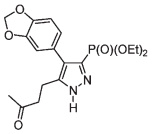
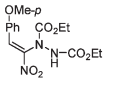
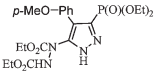
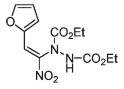
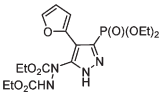
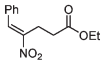
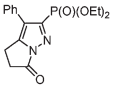
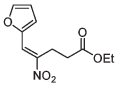
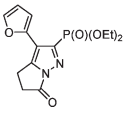
Dynamic NMR Studies. Besides biological and ligand properties (vide supra), an interesting property of pyrazoles is their tautomerism,[41] but the energy difference between the two tautomers is generally small.[42] Additionally, the

(40) MBH adducts of nitroalkenes with: (a) Tosyl imines: Rastogi, N.; Mohan, R.; Panda, D.; Mobin, S. M.; Namboothiri, I. N. N. *Org. Biomol. Chem*. **2006**, *4*, 3211. (b) Activated alkenes such as MVK and acrylate: Dadwal, M.; Mohan, R.; Panda, D.; Mobin, S. M.; Namboothiri, I. N. N. *Chem. Commun*. **2006**, 338. (c) Azodicarboxylates: Dadwal, M.; Mobin, S. M.; Namboothiri, I. N. N. *Org. Biomol. Chem*. **2006**, *4*, 2525.

(41) (a) Elguero, J.; Marzin, C.; Linda, P.; Katritzky, A. R. *The Tautomerism of Heterocycles*; Academic Press: New York, 1976; pp 655. (b) Cornago, P.; Cabildo, P.; Claramunt, R. M.; Bouissane, L.; Pinilla, E.; Torres, M. R.; Elguero, J. *New J. Chem*. **2009**, *33*, 125 and references cited therein. (c) O'Connell, M. J.; Ramsay, C. G.; Steel, P. J. *Aust. J. Chem*. **1985**, *38*, 401 and references cited therein. (d) Fahmy, H. M.; Elnagdi, M. H.; Mahgoub, A. E.; Kasem, A.; Ghali, E. A. *J. Chin. Chem. Soc*. **1985**, *32*, 99. (e) Witanowski, M.; Stefaniak, L.; Januszewski, H.; Elguero, J. *J. Chim. Phys. Phys.-Chim. Biol*. **1973**, *70*, 697; *Chem. Abstr*. **1973**, *79*, 31082.

(42) Abboud, J. L. M.; Cabildo, P.; Canada, T.; Catalan, J.; Claramunt, R. M.; De Paz, J. L. G.; Elguero, J.; Homan, H.; Notario, R. *J. Org. Chem*. **1992**, *57*, 3938.

TABLE 6. 1,3-DC Reaction of Various MBH Adducts of Nitroalkenes 13 with BOR 2 in the Presence of NaOEt in EtOH

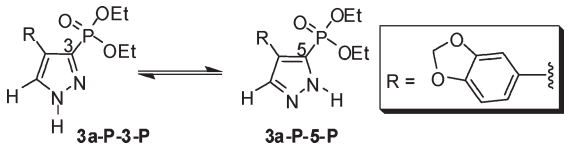
entry	13	nitroalkene	time	14	pyrazole	% yield[a]
1	**13a**		2 h	**14a**		62
2	**13b**		2 h	**14b**		51
3	**13c**		1 h	**14c**		75
4	**13d**		1 h	**14d**		63
5	**13e**		2 h	**14e**		55
6	**13f**		2 h	**14f**		62

[a]Isolated yield after purification by silica gel column chromatography.

activation barrier for the interconversion between the tautomers is also generally low. The tautomerism involving exclusively the ring proton attached to the nitrogen has been extensively investigated both experimentally[41] and theoretically.[43] Although pyrazole tautomeric equilibrium constants can be determined by NMR spectroscopy, to our knowledge, the method has scarcely been used.[44] An interesting case of a tautomeric mixture whose equilibrium constant has been determined by NMR spectroscopy is that of 3(5)-methyl- and phenylpyrazoles.[45] In this study, 3(5)-methylpyrazole was found to exist in hexamethylphosphorotriamide (HMPT) at −20 °C as a mixture of 46% of 3-methylpyrazole and 54% of 5-methylpyrazole. To our knowledge, there was no study on the tautomerism of pyrazole phosphonates. Further, ^{31}P NMR was rarely utilized to study the pyrazole tautomerism.[46] In this scenario, we decided to investigate the tautomerism of our phosphonylpyrazoles by ^{1}H NMR and ^{31}P NMR analysis.

The ^{1}H NMR spectrum of compound **3a** recorded in $CDCl_3$ showed two peaks centered at ∼7.80 ppm in a 1:1 ratio and separated by 2.0 Hz for the C5-H (Figure S1a, Supporting Information). These peaks remained unaffected when the spectrum was recorded in $CDCl_3$ + D_2O. Therefore, the possibility of these two peaks arising due to coupling of C5−H with the adjacent NH proton was ruled out. However, appearance of these two peaks as a doublet (J = 2.0 Hz) due to coupling of C5-H with phosphorus could not be ruled out. When the spectrum was recorded in DMSO-d_6, the pattern dramatically changed to the two peaks appearing at 7.86 and 8.10 ppm, respectively, in 1:4 ratio (Figure S1b, Supporting Information). Additionally, there was no characteristic peak for the N-H proton when the spectrum was recorded in $CDCl_3$, but it appeared at ∼13.60 ppm in DMSO-d_6 (Figures S1a and S1b, Supporting Information). From the above observation it appeared that the two peaks centered at ∼7.80 ppm in $CDCl_3$ (a) corresponded to the C5-H of the two equally populated but fast interconverting tautomers **3a-P-3-P** (pyrazole-3-phosphonate) and **3a-P-5-P** (pyrazole-5-phosphonate) of phosphonylpyrazole **3a** on the NMR time scale (Scheme 2) or (b) due to coupling of C5−H with phosphorus. In any event, if tautomerism does exist in $CDCl_3$ at room temperature and the process is fast on the NMR time scale, it would slow down in a strong hydrogen bonding acceptor solvent such as DMSO-d_6 with concomitant appearance of the N-H signal and shifting of the equilibrium in favor of one of the tautomers (Scheme 2).

SCHEME 2. Tautomerism in Phosphonylpyrazoles



To further understand the tautomerism exhibited by phosphonyl pyrazole **3** in solution, variable-temperature NMR experiments (230−330 K) were performed both in $CDCl_3$ and in DMSO-d_6 by choosing phosphonyl pyrazole **3a** as the model substrate.

First, we recorded the ^{1}H NMR spectra of **3a** in the temperature range of 228−318 K in $CDCl_3$ (Figure 1a). The pyrazole proton C5-H in **3a** showed two peaks of equal intensities at room temperature due to intermediate exchange on NMR time scale (vide supra, see also Figure S1a). The two peaks are visible, though not clearly separated due to fast exchange at 318 K as well. The same experiment was performed at different low temperatures (up to 228 K) at which the interconversion, if any, was expected to gradually slow down so that the two peaks corresponding to the two tautomeric pyrazoles **3a-P-3-P** and **3a-P-5-P** could be followed by NMR. Unfortunately, the peaks overlapped to form a single broad peak at lower temperature. Appearance of a single peak even at the lowest temperature studied is attributable either to accidental overlap of the two peaks corresponding to two tautomers or existence of only one tautomer (very slow or no exchange on NMR time scale). However, considerable deshielding of the peak for the C5-H was observed on lowering the temperature, suggesting that intermolecular H-bonding with the participation of C5-H, besides N-H, becomes stronger at lower temperature. An infinite network of phosphonylpyrazole **3a** involving intermolecular hydrogen bonding and π-stacking was observed in the solid state (Figure S2, Supporting Information)[30] which

(43) (a) Alkorta, I.; Elguero, J.; Liebman, J. F. *Struct. Chem.* **2006**, *17*, 439. (b) Alkorta, I.; Elguero, J. *Heteroatom Chem.* **2005**, *16*, 628.

(44) (a) Nesmeyanov, A. N.; Zavelovich, E. B.; Babin, V. N.; Kochetkova, N. S.; Fedin, E. I. *Tetrahedron* **1975**, *31*, 1461. (b) Nesmeyanov, A. N.; Babin, V. N.; Zavelovich, E. V.; Kochetkova, N. S. *Chem. Phys. Lett.* **1976**, *37*, 184.

(45) (a) Cativiela, C.; Garcia-Laureiro, J. I.; Elguero, J.; Elguero, E. *Gazz. Chim. Ital.* **1991**, *121*, 477. (b) Aguilar-parrilla, F.; Cativiela, C.; Diaz de Villegas, M. D.; Elguero, J.; Foces-Foces, C.; Garcia, L.; Jose, I.; Hernandez, C. F.; Limbach, H. H.; Smith, J. A. S.; Toiron, C. *J. Chem. Soc., Perkin Trans. 2* **1992**, 1737.

(46) Claramunt, R. M.; López, C.; Elguero, J.; Rheingold, A. L.; Zakharov, L. N.; Trofimenkoc, S. *ARKIVOC* **2003**, 209.

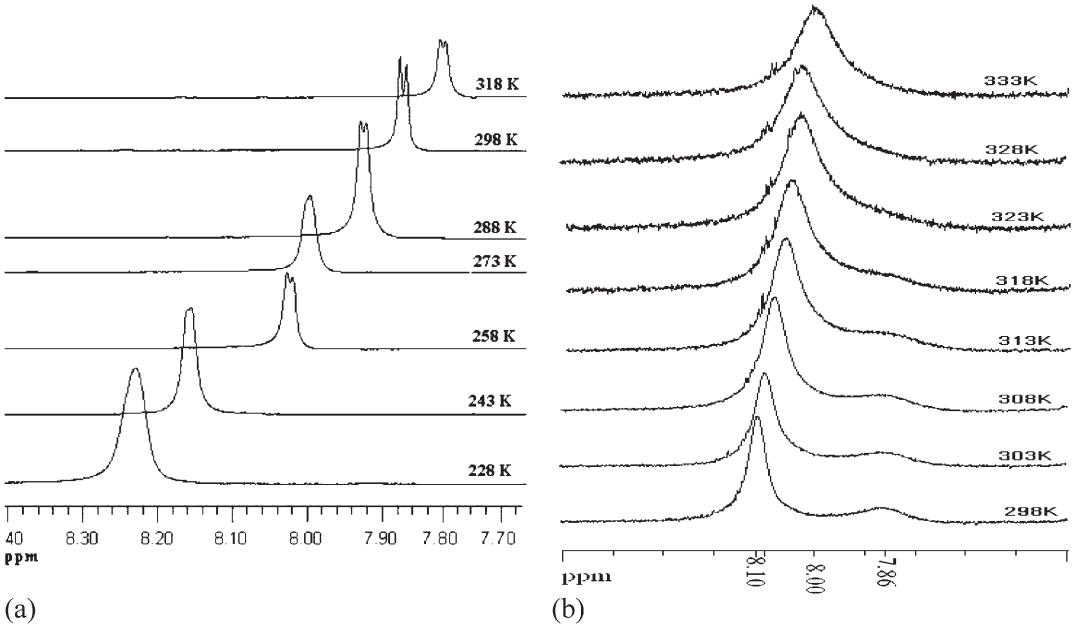


FIGURE 1. VT ^{1}H NMR spectra of **3a** (a) in $CDCl_3$ and (b) DMSO-d_6.

is likely to be present in solution ($CDCl_3$) as well at low temperature.

After completing our VT ^{1}H NMR analysis of **3a** in $CDCl_3$, we proceeded to investigate the behavior of **3a** in a strong H-bonding acceptor solvent such as DMSO-d_6 in anticipation that the two tautomers that interconverted rapidly (fast exchange on NMR time scale) in $CDCl_3$ at different temperatures would exhibit differential stability and population as a result of selective stabilization of one of them by DMSO-d_6.[47] Thus, the ^{1}H NMR spectra of **3a** were recorded in the temperature range of 298−333 K in DMSO-d_6 (Figure 1b). The spectrum recorded at 298 K showed two signals appearing at 7.86 ppm and 8.10 ppm with a ratio of ∼1:4 (see also Figure S1b, Supporting Information). When the temperature was raised, the two peaks coalesced at 318 K and became a broad single peak. The VT ^{1}H NMR spectra recorded in DMSO-d_6 (Figure 1b) allow us to estimate the average rate constant k_{av} and average lifetime τ_{av} at the coalescence temperature T_c by the following equation:[48]

$$k_{av} = 2.22(\Delta\nu) \text{ and } \tau_{av} = 1/k_{av} \quad (1)$$

This relates to two given signals absorbing with a frequency difference $\Delta\nu$. However, since two kinetic processes are involved for unequally populated two-site exchange between **3a-P-3-P** and **3a-P-5-P**, the following modified Eyring's equations were used for calculating the kinetic constants at coalescence.[49]

$$k_A = 1/2\tau_{av}(1\text{-}\Delta n) \text{ and } \tau_A = 1/k_A \quad (2)$$

$$k_B = 1/2\tau_{av}(1+\Delta n) \text{ and } \tau_B = 1/k_B \quad (3)$$

$$\Delta G_A^* = 4.57T_c[10.62 + \log 2\pi\Delta\nu\tau_A/2\pi(1-\Delta n) + \log(T_c/\Delta\nu)] \quad (4)$$

$$\Delta G_B^* = 4.57T_c[10.62 + \log 2\pi\Delta\nu\tau_B/2\pi(1+\Delta n) + \log(T_c/\Delta\nu)] \quad (5)$$

where Δn is $n_B - n_A$, the difference in mole fractions of the two species.

Using the above equations, we calculated the free energies of activation at coalescence (T_c = 318 K) for the tautomerism of **3a-P-3-P** to **3a-P-5-P** and vice versa from ^{1}H NMR recorded in DMSO-d_6 as 17.52 and 15.66 kcal mol^{-1}, respectively (Tables S1 and S3, Supporting Information).

The ^{31}P NMR spectrum recorded in $CDCl_3$ at room temperature shows a single peak at 7.03 ppm, while in DMSO-d_6 two signals at 7.78 and 12.07 ppm corresponding to two tautomers with relative intensity of ∼1:3 are observed (Figure S3, Supporting Information).

Subsequently, we recorded the variable-temperature ^{31}P NMR spectrum in two different solvents, i.e., $CDCl_3$ and DMSO-d_6 (Figure 2). In the case of DMSO-d_6 at room temperature, the rate of tautomerism between **3a-P-5-P** and **3a-P-3-P** was found to be slow on the NMR time scale showing two clearly distinguishable peaks in ∼1:3 ratio (Figure 2a and Figure S3, Supporting Information). When the temperature was gradually raised from 298 to 343 K, the peaks turned broad, especially the one corresponding to the minor tautomer, making it extremely difficult to assess the coalescence.

The ^{31}P NMR spectra of **3a** were then recorded in $CDCl_3$ over the temperature range 223−300 K (Figure 2b). The RT

(47) For NMR studies on the tautomerism of pyrazoles in strong hydrogen bonding acceptor solvents such as DMSO and HMPT, see: (a) Gonzalez, E.; Faure, R.; Vincent, E. J.; Espada, M.; Elguero, J. *Org. Magn. Reson.* **1979**, *12*, 587. (b) Litchman, W. M. *J. Am. Chem. Soc.* **1979**, *101*, 545. (c) Chenon, M. T.; Coupry, C.; Grant, D. M.; Pugmire, R. J. *J. Org. Chem.* **1977**, *42*, 659.

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(49) Shanan-Atidi, H.; Bar-Eli, K. H. *J. Phys. Chem.* **1970**, *74*, 961. This is a convenient method to calculate kinetic constants at coalescence for unequally populated two site exchange as compared to the cumbersome line shape analysis. For a discussion, see: Eliel, E. L.; Wilen, S. H.; Mander, L. S. *Stereochemistry of Organic Compounds*; John Wiley and Sons, Singapore, 2003, pp 504. For an application, see: Zhang, P. C.; Wang, Y. H.; Liu, X.; Yi, X.; Chen, R. Y.; Yu, D. Q. *Chin. Chem. Lett.* **2002**, *13*, 645.

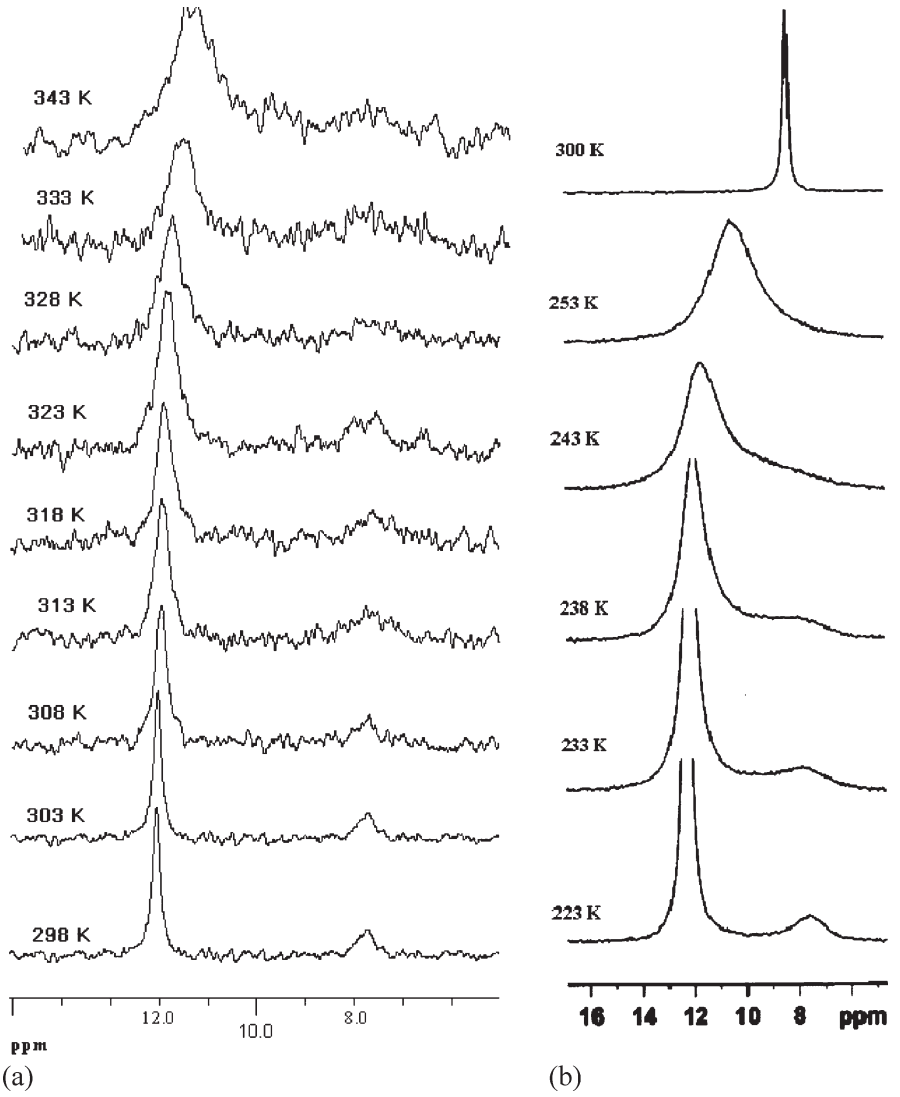


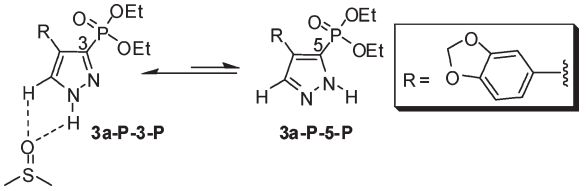
FIGURE 2. VT ^{31}P NMR spectra of **3a** in (a) DMSO-d_6 and (b) $CDCl_3$.

^{31}P NMR spectrum (300 K) showed a single peak either due the fast interconversion between the two tautomers **3a-P-5-P** and **3a-P-3-P** or due to the existence of only one tautomer. Interestingly, when the spectrum was recorded at 223 K, the slow interconversion on the NMR time scale between the two tautomers was evident from the appearance of two peaks, respectively, at 7.61 and 12.29 ppm in a ratio of ~1:7 (Figure 2b). These two peaks coalesced at 238 K and became a single peak, due to fast exchange on NMR time scale, centered at δ 8.36 at higher temperature. This confirmed that two tautomers do exist in $CDCl_3$ as well, but they interconvert slowly at low temperature enabling us to distinguish between them. An averaged single peak, indicating their faster interconversion on the NMR time scale, is observed at higher temperature. The activation barriers for the interconversion of **3a-P-3-P** to **3a-P-5-P** and vice versa calculated from ^{31}P NMR recorded in $CDCl_3$ at coalescence (T_c = 238 K) are, respectively, 13.48 and 10.81 kcal mol^{-1} (Tables S2 and S3, Supporting Information).

Variable-temperature ^{1}H NMR spectra suggested that, in DMSO-d_6 at room temperature, intermolecular hydrogen bonding involving the N-H and C5-H of the phosphonylpyrazole and DMSO-d_6 could stabilize **3a-P-3-P** over **3a-P-5-P** (Scheme 3). This intermolecular hydrogen bonding becomes weaker as the temperature is increased. Hence, ^{1}H NMR in DMSO-d_6 at room temperature showed two peaks of unequal intensities for C5-H corresponding to major and minor tautomers. It is important to note that the peak for the major tautomer is deshielded as compared to that for the minor tautomer in all the analogues **3a**−**m** (Table S4, Supporting Information). On the other hand, it showed an average signal for two tautomers at elevated temperature. The same trend was observed in the case of ^{31}P NMR as well.

As a consequence of overlapping of peaks for C5-H in ^{1}H NMR at low temperature in $CDCl_3$ (Figure 1a), we cannot unambiguously assign the major tautomer. However, ^{31}P NMR in $CDCl_3$ clearly shows two separate peaks in ~1:7 ratio for two different tautomers due to slow exchange on NMR time scale at lower temperature (Figure 2b). This is presumably due to the intermolecular hydrogen bonding between C5-H of one molecule and P=O of another molecule

SCHEME 3. Stabilization of Pyrazole 3-Phosphonate of 3a in DMSO-d_6



becoming stronger with lowering of temperature. This type of hydrogen bonding is also present in the solid state (see the crystal structure of **3a**, Figure S2, Supporting Information), and hence, we believe that **3a-P-3-P** is stabilized over **3a-P-5-P** in $CDCl_3$ at lower temperature as well. This is consistent with the general trend that the tautomer in the solid state and the most stable tautomer in solution are identical.[50]

Analysis of ^1H and ^{31}P NMR spectra of pyrazoles **3b**−**m** recorded in $CDCl_3$ and in DMSO-d_6 at room temperature revealed that **3b**−**m** also exhibit tautomerism similar to that of **3a** (Table S4, Supporting Information).[51]

Conclusions

The regioselective synthesis of fused and highly functionalized phosphonylpyrazoles through a one-pot base-mediated reaction at room temperature between the Bestmann−Ohira reagent (BOR) and nitroalkenes has been carried out. These studies establish the hitherto unexplored role of BOR as a 1,3-dipolar cycloaddition partner with nitroalkenes. The scope and potential of the cycloaddition has been demonstrated with a variety of nitroethylenes and nitrodienes. The tautomerism exhibited by many of the pyrazole phosphonates in solution was investigated in detail by dynamic NMR studies which showed that the two tautomers underwent faster interconversion in $CDCl_3$. But, in a hydrogen bonding acceptor solvent such as DMSO-d_6, selective stabilization of one of the tautomers, which was identical to the only tautomer observed in solid state (X-ray), was discernible. Investigations on the base-mediated cycloaddition of BOR with other activated alkenes are currently underway in our laboratory.

Experimental Section

General Procedure for the 1,3-DC Reaction of Nitroalkenes and Nitrodienes with Bestmann−Ohira Reagent.[52] NaOEt (102 mg, 1.5 mmol) was added to a stirred solution of nitroalkene **1**, **4**, **6**, **8**, **11**, or **13** (1 mmol) and BOR **2** (264 mg, 1.2 mmol) in dry EtOH (5 mL) at room temperature under N_2. The resulting mixture was stirred until the reaction was complete (monitored by TLC, see also Tables 1−6) which was then diluted with water (15 mL), neutralized with 5% HCl (10 mL), and extracted with ethyl acetate (3 × 15 mL). The combined organic layers were then washed with brine (2 × 10 mL), dried over anhyd Na_2SO_4, and then concentrated in vacuo. The crude residue was purified by column chromatography (silica gel, *n*-hexane/ethylacetate 3:1) to afford pure pyrazole **3**, **5**, **7**, **9**−**10**, **12**, or **14**. Representative experimental data are provided below. For complete data, see the Supporting Information.

Diethyl 4-cyclohexyl-1*H*-pyrazol-3-ylphosphonate (3k): colorless solid; yield 151 mg (53%); mp 136 °C; IR (KBr, cm^{-1}) 3170 (m), 2926 (s), 1240 (m), 1225 (s), 1023 (s), 974 (m), 576 (m); ^1H NMR (400 MHz, $CDCl_3$) δ 1.32 (t, J = 7.0 Hz, 6H), 1.35−1.40 (m, 6H), 1.72−1.92 (m, 4H), 2.77−2.83 (m, 1H), 4.04−4.24 (m, 4H), 7.64 (d, J = 2.0 Hz, 1H); ^1H NMR (300 MHz, DMSO-d_6) δ 1.22 (t, J = 6.9 Hz, 6H), 1.28−1.31 (m, 5H), 1.72−1.85 (m, 5H), 2.76 (m, 1H), 3.95 (dq collapsed to quintet, J = 7.0 Hz, 4H), 7.54/7.70 (br s/br s, minor/major, 1H), 13.28 ((br s/br s, major/minor, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.2 (d, J_{C-P} = 6.9 Hz), 26.0, 26.7, 33.9, 34.9, 62.2 (d, J_{C-P} = 4.6 Hz), 130.2 (br), 133.2 (d, J_{C-P} = 22.8 Hz), 134.7 (d, J_{C-P} = 220.0 Hz); ^{31}P NMR (121.4 MHz, $CDCl_3$) δ 10.04; ^{31}P NMR (121.4 MHz, DMSO-d_6) δ 12.35 (br); MS (ES+) *m*/*e* (rel intensity) 325 (MK^+, 5), 309 (MNa^+, 100), 287 (MH, 5); HRMS (ES+) calcd for $C_{13}H_{23}N_2O_3PNa$ (MNa^+) 309.1344, found 309.1340.

Diethyl 4-(benzo[*d*][1,3]dioxol-5-yl)-5-methyl-1*H*-pyrazol-3-yl-3-phosphonate (5a): colorless solid; yield 235 mg (70%); mp 153 °C; IR (KBr, cm^{-1}) 3412 (br, m), 3081 (w), 2980 (w), 2925 (w), 1693 (s), 1604 (m), 1541 (s), 1462 (w), 1291 (w), 1260 (w), 1172 (m), 1027 (s), 760 (m); ^1H NMR (400 MHz, $CDCl_3$) δ 1.19 (t, J = 7.0 Hz, 6H), 2.30 (s, 3H), 3.96−4.15 (m, 4H), 5.99 (s, 2H), 6.79−6.88 (m, 3H); ^1H NMR (300 MHz, DMSO-d_6) δ 1.10 (t, J = 6.9 Hz, 6H), 2.16/2.21 (s/s, minor/major in 1:4.6 ratio, 3H), 4.03 (dq collapsed to quintet, J = 7.3 Hz, 4H), 6.02 (s, 2H), 6.89 (ABq, J = 6.2 Hz, 2H), 6.92 (s, 1H), 13.30 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.8, 16.0 (d, J_{C-P} = 6.9 Hz), 62.6 (d, J_{C-P} = 4.6 Hz), 101.0, 108.0, 110.4, 123.4, 124.8 (d, J_{C-P} = 21.3 Hz), 125.9, 134.0 (d, J_{C-P} = 210.5 Hz), 142.7 (br), 146.7, 147.2; ^{31}P NMR (161.8 MHz, $CDCl_3$) δ 7.76; ^{31}P NMR (121.4 MHz, DMSO-d_6) δ 7.37/11.76 (minor/major in 1:3.6 ratio); MS (ES+) *m*/*e* (rel intensity) 339 (MH^+, 100); HRMS (ES+) calcd for $C_{15}H_{20}N_2O_5P$ (MH^+) 339.1110, found 339.1112.

Diethyl-7-methyl-3*H*-pyrazolo[4,3-*f*]quinolin-1-ylphosphonate (7d): light yellow solid; yield 165 mg (52%); mp 190 °C; IR (KBr, cm^{-1}) 3440 (br, m), 2989 (w), 1596 (w), 1545 (w), 1441 (w), 1375 (w), 1246 (m), 1232 (s), 1048 (vs), 1023 (vs); ^1H NMR (300 MHz, $CDCl_3$) δ 1.33 (t, J = 7.1 Hz, 6H), 2.78 (s, 3H), 4.17−4.37 (m, 4H), 7.46 (d, J = 8.5, Hz, 1H), 7.96 (ABq, J = 9.1, the upfield half is further split into d, J = 2.2 Hz, 2H), 9.26 (d, J = 8.5 Hz, 1H); ^1H NMR (300 MHz, DMSO-d_6) δ 1.24 (t, J = 7.1 Hz, 6H), 2.60 (s, 3H), 4.15 (dq collapsed to quintet, J = 7.3 Hz, 4H), 7.59 (d, J = 8.4 Hz, 1H), 7.94 (ABq, J = 9.1 Hz, the downfield half is further split into d, J = 1.8 Hz, 2H), 9.27 (d, J = 8.4 Hz, 1H), 14.34 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.2 (d, J_{C-P} = 6.6 Hz), 24.7, 63.1 (d, J_{C-P} = 5.4 Hz), 115.1, 119.9 (d, J_{C-P} = 23.7 Hz), 120.3, 122.7, 129.4, 134.0, 134.6 (d, J_{C-P} = 232.6), 139.9, 146.0, 157.0; ^{31}P NMR (121.4 MHz, $CDCl_3$) δ 9.21; ^{31}P NMR (121.4 MHz, DMSO-d_6) δ 11.4; MS (ES+) *m*/*e* (rel intensity) 320 ((MH^+, 100); HRMS (ES+) calcd for $C_{15}H_{19}N_3O_3P$ (MH^+) 320.1164, found 320.1153.

Diethyl 4-(4-Chlorophenyl)-1*H*-pyrazol-3-ylphosphonate (9c): colorless solid; yield 137 mg (38%); mp 216−218 °C; IR (KBr, cm^{-1}) 3440 (br, m), 3093 (br, w), 2983 (w), 2923 (m), 1679 (m), 1523 (m), 1413 (w), 1388 (w), 1247 (m), 1026 (s), 842 (m), 769 (m); ^1H NMR (300 MHz, $CDCl_3$) δ 1.20 (t, J = 7.1 Hz, 6H), 3.99−4.17 (m, 4H), 7.32 (ABq, J = 8.4 Hz, 4H), 14.05 (br s, 1H); ^1H NMR (300 MHz, DMSO-d_6) δ 1.09 (t, J = 6.9 Hz, 6H), 3.87−4.02 (m, 4H), 7.46 (ABqt, J = 7.7, 2.1 Hz, 4H), 15.01 (br s,

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(51) For a detailed discussion on the tautomerism of **3b**−**m**, **5**, **7**, **9**, **10**, **12**, and **14** based on their room-temperature ^1H and/or ^{31}P NMR recorded in $CDCl_3$ and in DMSO-d_6, see the Supporting Information.

(52) The reactions of all the nitroalkenes **1**, **4**, **6**, **8**, **11**, and **13** with BOR **2** were carried out under identical conditions, at 1 mmol scale under N_2 (for reaction times, see Tables 1−6). All the pyrazole phosphonates are stable and can be stored in the refrigerator for several months without any decomposition. The yields dropped gradually on scale up of the reaction between **1a** and BOR **2** as follows: 1 mmol, 77%; 3 mmol, 68% and 5 mmol, 61%.

1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.0 (d, J_{C-P} = 6.8 Hz), 64.2 (d, J_{C-P} = 5.3 Hz), 122.2 (d, J_{C-P} = 17.6 Hz), 126.9, 128.5, 131.5, 132.7 (d, J_{C-P} = 217.3 Hz), 135.2, 154.0 (d, J_{C-P} = 18.3 Hz); ^{31}P NMR (121.4 MHz, $CDCl_3$) δ 0.29; ^{31}P NMR (121.4 MHz, DMSO-d_6) δ 3.02; MS (ESI) *m*/*e* (rel intensity) 360 (MH^+, 78), 332 (10); (ES+) calcd for $C_{13}H_{16}N_3O_5PCl$ (MH^+) 360.0516, found 360.0517.

Diethyl 4-(benzo[*d*][1,3]dioxol-5-yl)-5-(hydroxymethyl)-1*H*-pyrazol-3-ylphosphonate (12a): dark brown liquid; yield 216 mg (61%); IR (KBr, cm^{-1}) 3429 (br, w), 2983 (m), 2935 (w), 1614 (s), 1560 (m), 1513 (m), 1465 (m), 1443 (m), 1371 (m), 1249 (s), 1027 (s), 839 (s), 738 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.16 (t, J = 6.9 Hz, 6H), 3.91−4.11 (m, 4H), 4.64 (s, 2H), 5.99 (s, 2H), 6.83−6.96 (m, 3H); ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.11 (t, J = 7.0 Hz, 6H), 3.89−4.05 (m, 4H), 4.41 (s, 2H), 5.38 (br s, 1H), 6.03 (s, 2H), 6.90−7.10 (m, 3H), 13.61 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 16.1 (d, J_{C-P} = 6.1 Hz), 54.6, 62.9, 101.3, 108.2, 110.7, 123.8, 124.7 (d, J_{C-P} = 21.3 Hz), 125.0, 136.4 (d, J_{C-P} = 226.5 Hz), 144.9, 147.2, 147.5; ^{31}P NMR (121.4 MHz, $CDCl_3$) δ 8.80; ^{31}P NMR (121.4 MHz, DMSO-d_6) δ 11.47; MS (ES+) *m*/*e* (rel intensity) 355 (MH^+, 100), 337 (12); HRMS (ES+) calcd for $C_{15}H_{20}N_2O_6P$ (MH^+) 355.1059, found 355.1044.

Diethyl 6-oxo-3-phenyl-5,6-dihydro-4*H*-pyrrolo[1,2-*b*]pyrazol-2-ylphosphonate (14e): colorless solid; yield 183 mg (55%); mp 148 °C; IR (KBr, cm^{-1}) 3056 (m), 2986 (m), 1717 (s), 1654 (w), 1438 (m), 1397 (m), 1264 (s), 1221 (s), 1026 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.14 (t, J = 7.0 Hz, 6H), 2.70 (t, J = 5.9 Hz, 2H), 2.98 (t, J = 5.9 Hz, 2H), 3.92−4.10 (m, 4H), 7.33−7.43 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.0 (d, J_{C-P} = 6.7 Hz), 19.0, 33.7, 62.7 (d, J_{C-P} = 5.3 Hz), 125.4 (d, J_{C-P} = 22.1 Hz), 127.7, 128.3, 130.2, 131.4, 137.2 (d, J_{C-P} = 220.0 Hz), 142.5 (d, J_{C-P} = 11.2 Hz), 176.4; ^{31}P NMR (121.4 MHz, $CDCl_3$) δ 8.09; MS (ES+) *m*/*e* (rel intensity) 353 ($[MH\cdot H_2O]^+$, 100), 335 (MH^+, 5), 279 (90), 253 (8); HRMS (ES+) calcd for $C_{16}H_{20}N_2O_4P$ (MH^+) 335.1161, found 335.1169.

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Supporting Information Available: Complete characterization data, tables of energy calculations, copies of NMR spectra for all new compounds, and ^{1}H and ^{31}P VT NMR spectra for a representative compound **3a**. This material is available free of charge via the Internet at http://pubs.acs.org.