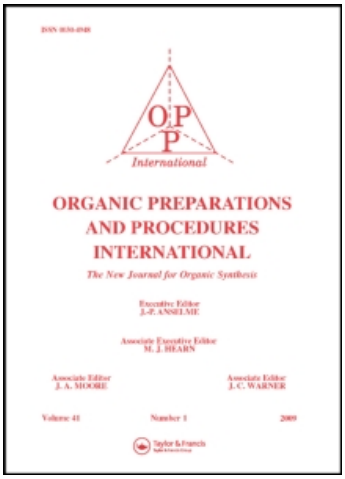

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Paula C. Miller[a]; John M. Molyneaux[a]
[a] Monsanto Company, St Louis, MO, USA

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"ONE-POT" SYNTHESIS OF DIMETHYL [1-SUBSTITUTED-5-HYDROXY-1*H*-PYRAZOL-4-YL]PHOSPHONATES

Paula C. Miller* and John M. Molyneaux

Monsanto Company, 800 N. Lindbergh Boulevard
St. Louis, MO 63167, USA

Dimethoxyphosphonyl substituted pyrazoles and pyrazolinones have been identified as agriculturally useful herbicides,[1] insecticides,[2] and more recently as chemical hybridizing agents for wheat.[3] We were particularly interested in dimethyl [1-aryl-5-hydroxy-1*H*-pyrazol-4-yl]phosphonates based on the similarity of these structures to carboxy-substituted analogs that are known chemical hybridizing agents.[4-8] There are, however, relatively few efficient preparations of phosphonyl heterocycles. The two previously reported methods to prepare these types of compounds are the addition of hydrazines to β-dicarbonyl functionalized phosphonates[9-11] or to their enamine derivatives.[2-12] In the former approach, the β-dicarbonyl functionalized phosphonates are often unstable and prepared in low yields. The overall yield of heterocyclic product is, therefore, low and generally, purification is required. In the latter method, the enamine intermediates can be prepared in good yields, but in some cases purification is required before completing the synthesis. The enamine intermediates are more stable than the carbonyl analogs but do undergo decomposition over time. Herein we report a simple one-pot procedure to prepare analytically pure dimethyl [1-aryl-5-hydroxy-1*H*-pyrazol-4-yl]phosphonates following a simple extractive workup. The intermediate 3-oxy-2-dimethylphosphonoacrylate sodium salt **2** can be isolated as a white solid in quantitative yield and stored indefinitely.

Dimethyl [1-aryl-5-hydroxy-1*H*-pyrazol-4-yl]phosphonates (**3**) were prepared as outlined below. Intermediate **2** was prepared in quantitative yield,[13] by a modified literature procedure starting with commercially available trimethyl phosphonoacetate (**1**); it was isolated as a mixture of isomers (E:Z; 1.8:1; J_{HP}(cis) = 2.7 Hz, J_{HP}(trans) = 35.7 Hz) as determined by ^{1}H and ^{31}P NMR spectroscopy and is stable to storage for years. Subsequent treatment of intermediate **2** with arylhydrazine hydrochlorides in water at 120°, after neutralization, resulted in 1,4-C-addition to the α,β-unsaturated π-system followed by elimination of water. The addition product was not isolated but was observed by HPLC analysis. Addition of a weak base then effected the cyclization to afford, after acidification, the phosphonopyrazole products **3**. For most examples, analytically pure products **3** were obtained by extracting the cyclization mixture with an organic solvent prior to acidification.

The same reaction was carried out with alkyl- and benzylhydrazine hydrochlorides.

However, in these cases the 3-hydroxy isomers **7r** and **7s** were isolated in addition to the 5-hydroxy isomers **3r** and **3s**, and chromatographic purification was required. The isomeric mixtures presumably result from the comparable nucleophilicity of the two hydrazine nitrogens. Representative examples of compounds synthesized by this route are given in Table 1.

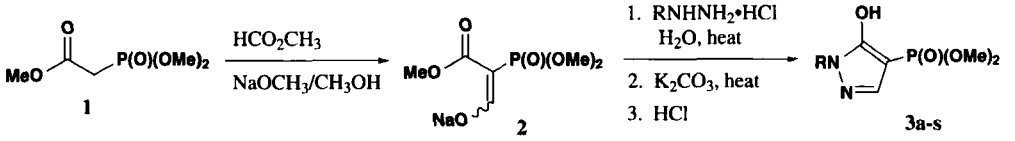


TABLE 1. Yield, mps and Elemental Analyses of Compounds **3** and **7**.

Compd	R	Yield (%)	mp. (°C)	Elemental Analysis (Found)[a] C	H	N
3a	C_6H_5	79	98-99	49.24 (49.30)	4.89 (4.89)	10.45 (10.43)
3b	2-ClC_6H_4[b]	58	157-158	43.71 (43.74)	4.00 (4.12)	9.27 (9.19)
3c	3-ClC_6H_4	70	—	43.71 (43.47)	4.00 (4.10)	9.27 (9.00)
3d	4-ClC_6H_4	78	133-135	43.71 (43.71)	4.00 (3.95)	9.27 (9.20)
3e	4-BrC_6H_4	70	138-140	38.15 (37.82)	3.50 (3.66)	8.09 (7.70)
3f	4-FC_6H_4[c]	70	121-123	46.15 (46.16)	4.23 (4.24)	9.79 (9.67)
3g	4-IC_6H_4	65	129-132	33.51 (33.62)	3.07 (3.10)	7.11 (7.01)
3h	4-$MeOC_6H_4$[c]	56	109-111	48.31 (48.34)	5.07 (5.10)	9.40 (9.31)
3i	4-$F_3CC_6H_4$	54	109-111	42.85 (42.57)	3.60 (3.70)	8.33 (8.34)
3j	4-$O_2NC_6H_4$[b]	79	165-168	42.17 (42.49)	3.86 (3.89)	13.42 (13.20)
3k	4-MeC_6H_4	79	98-100	51.05 (51.09)	5.36 (5.30)	9.93 (9.85)
3l	3-MeC_6H_4	84	83-84.5	51.05 (51.08)	5.36 (5.31)	9.93 (9.86)
3m	3,5-$Me_2C_6H_3$	70	101-103	52.69 (52.71)	5.79 (5.76)	9.46 (9.39)
3n	3,4-$Cl_2C_6H_3$	50	106-108	39.29 (39.07)	3.30 (3.25)	8.34 (8.22)
3o	3,5-$Cl_2C_6H_3$[d]	73	118-119	39.29 (39.15)	3.30 (3.28)	8.34 (8.27)
3p	2,6-$Cl_2C_6H_3$	70	156-158	39.29 (39.01)	3.30 (3.44)	8.34 (8.07)
3q	2,6-Cl_2-4-$CF_3C_6H_2$[c]	50	175-177	35.65 (35.69)	2.49 (2.53)	6.93 (6.83)
3r	$PhCH_2$	20[e]	—	(see experimental section)		
7r[f]	$PhCH_2$	18[g]	98-101	(see experimental section)		
3s	*c*-C_6H_{11}	6[e]	138-142	(see experimental section)		
7s[f]	*c*-C_6H_{11}	6[g]	156-159	(see experimental section)		

a) Except where cited, the crude products were sufficiently pure to give correct elemental analyses. All products could be used without further purification. b) Analytical sample recrystallized from EtOAc. c) Analytical sample obtained from chromatography (25% CH_2Cl_2/ethyl ether). d) The general procedure was modified as follows: The EtOAc wash was back extracted with H_2O and the combined aqueous layers were acidified and extracted with EtOAc. These EtOAc extractions were combined with the original EtOAc extractions and worked up to afford product. e) After partial chromatographic separation of the 3-hydroxy isomer. f) **7r** and **7s** are the 3-hydroxy isomers (see text). g) After partial chromatographic separation from the 5-hydroxy isomer.

In addition to the procedure described above (Method A), we explored the synthesis of these compounds by two other routes outlined below. The first (Method B) utilized the *N,N*-dimethylamino intermediate **4a** which was prepared by a previously described method as outlined below.[12] In the second route (Method C), we utilized intermediate **4b** which was prepared by alkylation of the corresponding sodium salt **2**. The intermediates **4a,b** were subjected to the addition/cyclization steps with no further purification to afford products **3**. The overall yields from these routes are compared to Method A in Table 2. In our hands, Method A consistently affords higher yields than the other two methods.

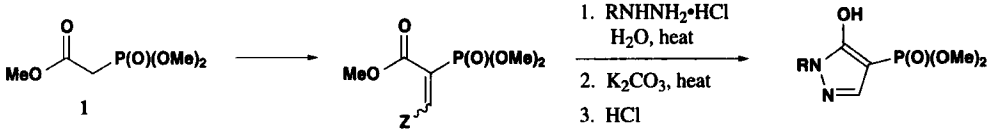


TABLE 2. Comparative Yields for Selected Compounds (**3**)

Entry	Ar	Yield (%)[a]	Method[b]
3d	4-ClC_6H_4	78	A
		64	B
		58	C
3l	3-MeC_6H_4	84	A
		42	B
3n	3,4-diClC_6H_3	50	A
		32	B

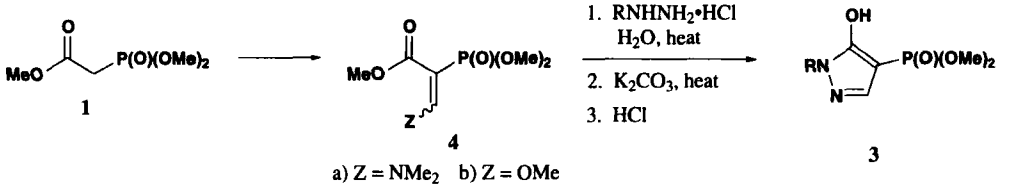
a) Overall yield including preparation of intermediates. b) Method A utilizes intermediate **2** as outlined in the first scheme, Methods B and C utilize intermediates **4a** and **4b**, respectively, as outlined in the second scheme.

Finally, we examined the tautomeric equilibrium of selected compounds by UV and IR spectroscopy. The N- and O-alkylated analogs of compound **3d** (compounds **5d** and **6d**, respectively) were prepared and used as spectroscopic references. The spectroscopic data for a series of compounds are shown in Table 3. The results indicate that **3d** exists as the enol tautomer in $CHCl_3$ solution. The UV spectroscopic data for related analogs show similar λ_{max} and ε values and, therefore, suggest that these analogs also exist as enol tautomers in solution. The 2-Cl analog **3b** did not exhibit a UV absorption maximum above 240 nm. The 4-NO_2 analog **3j** had a λ_{max} closer to the keto tautomer standard. The IR spectroscopic data for **3j**, however, did not show a carbonyl stretch and were consistent with the enol tautomer.

In conclusion, we have developed an efficient route to dimethyl [1-aryl-5-hydroxy-1*H*-pyrazol-4-yl]phosphonates. The alkyl and benzyl analogs were prepared as isomeric mixtures of the [3-hydroxy and 5-hydroxy-1*H*-pyrazol-4-yl]phosphonates in lower yields. The tautomeric equilibria, studied by UV and IR spectroscopy, suggest that the compounds exist as enol tautomers in the solid

state and in $CHCl_3$ solution.

TABLE 3. UV and IR Spectroscopic Data for Selected Compounds



Entry	λ_{max} (ε)	IR (cm^{-1})[a]
3b	not observed	1561, 1193
3d	248 (16,720)	1541, 1239
3h	248 (13,290)	1547, 1188
3j	306 (12,780)	1536, 1210
3n	252 (18,440)	—
5d	250 (16,621)	1547, 1250[b]
6d	284 (10,390) 250 (6,457)	1690, 1245

a) Diffuse reflectance spectroscopy unless otherwise noted. b) Polyethylene film.

EXPERIMENTAL SECTION

UV spectra were collected on a Varian Cary 5E spectrophotometer and IR spectra were collected on a Nicolet Magna 550 with omnic software, using a spectra tech collector accessory. ^1H NMR and ^{13}C NMR spectra were recorded on a Varian-400 (400 MHz ^1H, 100 MHz ^{13}C, 162 MHz ^{31}P, 376 MHz ^{19}F) spectrometer in deuterochloroform with tetramethylsilane (TMS) or chloroform as an internal reference unless otherwise stated.

Methyl (E)-2-(Dimethoxyphosphonyl)-3-hydroxy-2-propenoate, Sodium Salt (2).- To a mixture of trimethyl phosphonoacetate (5.0 g, 0.027 mol) and methyl formate (4 mL, 0.066 mol) in methanol (10 mL) was added sodium methoxide in methanol (25%, 7.0 g, 0.032 mol). The reaction flask was stoppered and stirred at ambient temperature for three days. The mixture was concentrated *in vacuo* to afford **2** as a white solid (6.20 g, 99%, E:Z = 1.8:1). ^1H NMR partial (CD_3OD): δ 9.43 (d, J = 35.7 Hz 1H, Z-isomer), 8.80 (d, J = 2.7 Hz 1H, E-isomer); ^{31}P NMR (CD_3OD): δ 27.18, (Z-isomer), 32.07 (E-isomer).

General Procedure for the Preparation (Method A) of Dimethyl [1-Aryl or Alkyl-5-hydroxy-1*H*-pyrazol-4-yl]phosphonates (3a-s).- A 100-mL, 1-necked round-bottomed flask was charged with 3-sodium alkoxy-2-dimethylphosphonoacrylate (**2**, 9.0 mmol) and an arylhydrazine hydrochloride (9.9 mmol, 1.1 equiv) dissolved in H_2O (50 mL) [in the case of **3a**, the hydrazine hydrochloride was generated from the free hydrazine by adding 1 equiv of concentrated HCl to the hydrazine dissolved in H_2O (5 mL) prior to the addition of the other reagents]. The mixture was heated in a 120° oil bath

with stirring under an atmosphere of N_2. After 5-10 min of heating, TLC (15% IPA/85% EtOAc) and HPLC (reverse phase) analysis indicated complete conversion to the intermediate adduct. The flask was removed from the oil bath, K_2CO_3 (9.9 mmol, 1.1 equiv) was added, and the mixture was again heated in a 120° oil bath with stirring under N_2 for 5-10 min or until TLC and HPLC analysis indicated the cyclization was complete. The mixture was cooled to room temperature and washed with EtOAc (2 x 30 mL). The aqueous phase was acidified with concentrated HCl, and the product was extracted with EtOAc (3 x 30 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated *in vacuo* to afford the product as a yellow solid. In most cases, the crude products were of analytical purity (tlc).

Dimethyl [1-Phenyl-5-hydroxy-1*H*-pyrazol-4-yl]phosphonate (3a).- The reaction was carried out using 8.6 mmol of intermediate **2** to afford the product as a yellow solid. ^{1}H NMR: δ 7.79 (d, *J* = 7.8 Hz, 1H, CH), 7.54 (s, 1H), 7.47-7.29 (m, 4H), 3.77 (d, *J* = 11.8 Hz, 6H); ^{13}C NMR: δ 158.7 (d, *J* = 22.1 Hz), 139.8 (d, *J* = 10.7 Hz), 137.5, 129.0, 127.1, 121.8, 83.6 (d, *J* = 222.0 Hz), 53.0 (d, *J* = 5.3 Hz); ^{31}P NMR: δ 20.15.

Dimethyl [1-(2-Chlorophenyl)-5-hydroxy-1*H*-pyrazol-4-yl]phosphonate (3b).- The reaction was carried out using 4.7 mmol of intermediate **2** to afford the product as a pale yellow solid. ^{1}H NMR: δ 9.20 (bs, 1H), 7.59 (s, 1H), 7.55-7.39 (m, 4H), 3.78 (d, *J* = 11.8 Hz, 6H); ^{13}C NMR: δ 159.8 (d, *J* = 21.4 Hz), 140.4 (d, *J* = 11.1 Hz), 134.3, 132.1, 130.7, 130.4, 129.3, 127.5, 82.6 (d, *J* = 222.4 Hz), 53.0 (d, *J* = 5.3 Hz); ^{31}P NMR: δ 19.80.

Dimethyl [1-(3-Chlorophenyl)-5-hydroxy-1*H*-pyrazol-4-yl]phosphonate (3c).- The reaction was carried out using 4.4 mmol of intermediate **2** to afford the product as a yellow oil. ^{1}H NMR: δ 9.42 (bs, 1H), 7.87 (t, *J* = 2 Hz, 1H), 7.74 (dq, *J* = 8.2, 1.0 Hz, 1H), 7.55 (d, *J* = 0.8 Hz, 1H), 7.39 (t, *J* = 8.1 Hz, 1H), 7.29 (dq, *J* = 7.1, 1.0 Hz, 1H), 3.78 (d, *J* = 11.6 Hz, 6H); ^{13}C NMR: δ 159.1 (d, *J* = 22.1 Hz), 140.0 (d, *J* = 10.3 Hz), 138.6, 134.8, 130.1, 127.0, 121.6, 119.3, 83.9 (d, *J* = 221.3 Hz), 53.1 (d, *J* = 5.0 Hz); ^{31}P NMR: δ 19.55.

Dimethyl [1-(4-Chlorophenyl)-5-hydroxy-1*H*-pyrazol-4-yl]phosphonate (3d).- The reaction was carried out using 8.8 mmol of intermediate **2** to afford the product as a yellow solid. ^{1}H NMR: δ 7.77 (d, *J* = 8.9 Hz, 2H), 7.54 (s, 1H), 7.43 (d, *J* = 8.9 Hz, 1H), 3.78 (d, *J* = 11.8 Hz, 6H); ^{13}C NMR: δ 158.9 (d, *J* = 22.1 Hz), 139.8 (d, *J* = 10.7 Hz), 136.2, 132.5, 129.2, 122.6, 83.8 (d, *J* = 220.5 Hz), 53.0 (d, *J* = 5.0 Hz)); ^{31}P NMR: δ 19.81.

Dimethyl [1-(4-Bromophenyl)-5-hydroxy-1*H*-pyrazol-4-yl]phosphonate (3e).- The reaction was carried out using 4.4 mmol of intermediate **2** to afford the product as a pale yellow solid. ^{1}H NMR: δ 9.40 (bs, 1H), 7.72 (d, *J* = 9.1 Hz, 2H), 7.58 (d, *J* = 8.9 Hz, 2H), 7.54 (d, *J* = 0.5 Hz, 1H), 3.77 (d, *J* = 11.6 Hz, 6H); ^{13}C NMR: δ 159.0 (d, *J* = 22.1 Hz), 139.9 (d, *J* = 10.7 Hz), 136.7, 132.1, 122.9, 120.4, 83.8 (d, *J* = 220.9 Hz), 53.0 (d, *J* = 5.3 Hz); ^{31}P NMR: δ 19.73.

Dimethyl [1-(4-Fluorophenyl)-5-hydroxy-1*H*-pyrazol-4-yl]phosphonate (3f).- The reaction was carried out using 4.4 mmol of intermediate **2** to afford the product as a pale yellow solid. ^{1}H NMR: δ 8.67 (bs, 1H), 7.76 (dd, *J* = 9.0, 4.7 Hz, 2H), 7.54 (s, 1H), 7.15 (t, *J* = 8.6 Hz, 2H), 3.78 (d, *J* = 11.8

Hz, 6H); ^{13}C NMR: δ 161.2 (d, *J* = 247.2 Hz), 158.7 (d, *J* = 22.1 Hz), 139.7 (d, *J* = 10.3 Hz), 133.7, 123.5 (d, *J* = 8.8 Hz), 115.9(d, *J* = 22.9 Hz), 83.6 (d, *J* = 220.9 Hz), 53.0 (d, *J* = 5.0 Hz); ^{31}P NMR: δ 19.85; ^{19}F NMR: δ -114.99 (heptet, *J* = 4.3 Hz).

Dimethyl [1-(4-Iodophenyl)-5-hydroxy-1*H*-pyrazol-4-yl]phosphonate (3g).- The reaction was carried out using 4.4 mmol of intermediate **2** to afford the product as a pale yellow solid. ^{1}H NMR: δ 8.80 (bs, 1H), 7.78 (d, *J* = 8.9 Hz, 2H), 7.59 (d, *J* = 8.9 Hz, 2H), 7.54 (s, 1H), 3.77 (d, *J* = 11.8 Hz, 6H); ^{13}C NMR: δ 159.1 (d, *J* = 22.5 Hz), 139.9 (d, *J* = 10.3 Hz), 138.1, 137.5, 123.1, 91.6, 83.9 (d, *J* = 220.9 Hz), 53.1 (d, *J* = 5.0 Hz); ^{31}P NMR: δ 19.76.

Dimethyl [1-(4-Methoxyphenyl)-5-hydroxy-1*H*-pyrazol-4-yl]phosphonate (3h).- The reaction was carried out using 4.7 mmol of intermediate **2** to afford the product as an amber solid. ^{1}H NMR: δ 9.00 (bs, 1H), 7.65 (d, *J* = 8.9 Hz, 2H), 7.53 (s, 1H), 6.97 (d, *J* = 8.9 Hz, 2H), 3.77 (s, 3H), 3.77 (d, *J* = 11.8 Hz, 6H); ^{13}C NMR: δ 158.5, 158.4 (d, *J* = 21.7 Hz), 139.4 (d, *J* = 10.3 Hz), 130.7, 123.5, 114.2, 83.2 (d, *J* = 220.0 Hz), 53.0 (d, *J* = 5.3 Hz); ^{31}P NMR: δ 19.98.

Dimethyl [1-(4-Trifluoromethylphenyl)-5-hydroxy-1*H*-pyrazol-4-yl]phosphonate (3i).- The reaction was carried out using 4.8 mmol of intermediate **2** to afford the product as a pale yellow solid. ^{1}H NMR (CD_3OD): δ 7.95 (d, *J* = 8.3 Hz, 2H), 7.81 (d, *J* = 1.9 Hz, 1H), 7.80 (d, *J* = 8.3 Hz, 2H), 3.79 (d, *J* = 11.6 Hz, 6H); ^{13}C NMR (CD_3OD): δ 158.9 (d, *J* = 19.1 Hz), 144.2 (d, *J* = 13.4 Hz), 129.9 (q, *J* = 32.4 Hz), 127.3 (q, *J* = 3.8 Hz), 125.3 (q, *J* = 271.2 Hz), 123.4, 123.1, 89.4 (d, *J* = 227.0 Hz), 53.5 (d, *J* = 5.3 Hz); ^{31}P NMR (CD_3OD): δ 18.01; ^{19}F NMR (CD_3OD): δ -64.29.

Dimethyl [1-(4-Nitrophenyl)-5-hydroxy-1*H*-pyrazol-4-yl]phosphonate (3j).- The reaction was carried out using 8.7 mmol of intermediate **2** to afford the product as a orange solid. ^{1}H NMR: δ 8.34 (d, *J* = 9.1 Hz, 2H), 8.11 (d, *J* = 9.2 Hz, 2H), 7.60 (s, 1H), 3.80 (d, *J* = 11.8 Hz, 6H); ^{13}C NMR: δ 160.2 (d, *J* = 21.75 Hz), 145.5, 142.7, 140.8 (d, *J* = 10.3 Hz), 124.8, 120.8, 84.6 (d, *J* = 220.1 Hz), 53.2 (d, *J* = 5.3 Hz)); ^{31}P NMR: δ 19.31.

Dimethyl [1-(4-Methylphenyl)-5-hydroxy-1*H*-pyrazol-4-yl]phosphonate (3k).- The reaction was carried out using 5.0 mmol of intermediate **2** to afford the product as a yellow solid. ^{1}H NMR: δ 7.64 (d, *J* = 6.7 Hz, 2H), 7.52 (s, 1H), 7.25 (d, *J* = 6.4 Hz, 2H), 3.76 (d, *J* = 11.8 Hz, 6H), 2.38 (s, 3H); ^{13}C NMR: δ 158.8 (d, *J* = 22.1 Hz), 139.4 (d, *J* = 10.3 Hz), 137.0, 135.1, 129.5, 121.6, 83.2 (d, *J* = 220.5 Hz), 53.0 (d, *J* = 4.2 Hz), 21.0); ^{31}P NMR: δ 20.24.

Dimethyl [1-(3-Methylphenyl)-5-hydroxy-1*H*-pyrazol-4-yl]phosphonate (3l).- The reaction was carried out using 8.8 mmol of intermediate **2** to afford the product as a yellow solid. ^{1}H NMR: δ 7.60-7.54 (m, 2H), 7.34 (t, *J* = 7.8 Hz, 2H), 7.14 (d, *J* = 7.6 Hz, 2H), 3.77 (d, *J* = 11.6 Hz, 6H), 2.41 (s, 6H); ^{13}C NMR: δ 158.9 (d, *J* = 21.7 Hz), 139.5 (d, *J* = 10.7 Hz), 137.5, 129.4, 128.8, 127.9, 122.3, 118.8, 83.3 (d, *J* = 220.9 Hz), 53.0 (d, *J* = 5.0 Hz), 21.4); ^{31}P NMR: δ 20.15.

Dimethyl [1-(3,5-Dimethylphenyl)-5-hydroxy-1*H*-pyrazol-4-yl]phosphonate (3m).-The reaction was carried out using 8.8 mmol of intermediate **2** to afford the product as a yellow solid. ^{1}H NMR: δ 7.53 (s, 1H), 7.39 (s, 2H), 6.96 (s, 1H), 3.77 (d, *J* = 11.8 Hz, 6H), 2.38 (s, 6H); ^{13}C NMR: δ 159.0 (d, *J* = 22.5 Hz), 139.5 (d, *J* = 10.3 Hz), 137.5, 129.5, 128.9, 119.6, 83.3 (d, *J* = 220.5 Hz), 53.0 (d, *J* =

5.3 Hz), 21.4; ^{31}P NMR: δ 20.23.

Dimethyl [(3,4-Dichlorophenyl)-5-hydroxy-1*H*-pyrazol-4-yl]phosphonate (3n).- The reaction was carried out using 8.6 mmol of intermediate **2** to afford the product as a yellow solid. ^{1}H NMR: δ 8.01 (d, *J* = 2.4 Hz, 1H), 7.74-7.72 (m, 1H), 7.55-7.51 (d, 1H), 3.78 (d, *J* = 11.5 Hz, 6H); ^{13}C NMR: δ 159.3 (d, *J* = 22.5 Hz), 140.2 (d, *J* = 10.3 Hz), 136.9, 133.1, 130.7, 129.4, 123.0, 120.2, 84.1 (d, *J* = 221.3 Hz), 53.1 (d, *J* = 5.35 Hz); ^{31}P NMR: δ 19.44.

Dimethyl [1-(3,5-Dichlorophenyl)-5-hydroxy-1*H*-pyrazol-4-yl]phosphonate (3o).- The reaction was carried out using 8.7 mmol of intermediate **2** to afford the product as a yellow solid. ^{1}H NMR: δ 7.83 (s, 1H), 7.55 (s, 1H), 7.30 (s, 1H), 3.78 (d, *J* = 11.8 Hz, 6H); ^{13}C NMR: δ 159.5 (d, *J* = 22.5 Hz), 140.3 (d, *J* = 10.3 Hz), 139.2, 135.4, 126.7, 119.4, 84.5 (d, *J* = 220.5 Hz), 53.1 (d, *J* = 5.0 Hz)); ^{31}P NMR: δ 19.41.

Dimethyl [1-(2,6-Dichlorophenyl)-5-hydroxy-1*H*-pyrazol-4-yl]phosphonate (3p).-The reaction was carried out using 4.6 mmol of intermediate **2** to afford the product as a pale yellow solid. ^{1}H NMR: δ 8.90 (bs, 1H), 7.65 (s, 1H), 7.46 (d, *J* = 8.2 Hz, 2H), 7.38 (dd, *J* = 9.0, 7.2 Hz, 1H), 3.78 (d, *J* = 11.5 Hz, 6H); ^{13}C NMR: δ 160.1 (d, *J* = 21.4 Hz), 141.2 (d, *J* = 10.7 Hz), 135.2, 132.4, 131.4, 128.6, 82.4 (d, *J* = 222.8 Hz), 53.0 (d, *J* = 5.0 Hz); ^{31}P NMR: δ 19.61.

Dimethyl [1-(2,6-Dichloro-4-trifluoromethylphenyl)-5-hydroxy-1*H*-pyrazol-4-yl]phosphonate (3q).- The reaction was carried out using 5.0 mmol of intermediate **2** to afford the product as a white solid. ^{1}H NMR: δ 8.33 (bs, 2H), 7.74 (s, 2H), 7.67 (d, *J* = 1.1 Hz, 1H), 3.79 (d, *J* = 11.6 Hz, 6H); ^{13}C NMR: δ 159.9 (d, *J* = 21.4 Hz), 142.0 (d, *J* = 10.7 Hz), 136.3, 135.6, 133.7 (q, *J* = 34.2 Hz), 125.8 (q, *J* = 3.7 Hz), 122.1 (q, *J* = 273.9 Hz), 83.1 (d, *J* = 224.3 Hz), 53.1 (d, *J* = 5.3 Hz); ^{31}P NMR: δ 18.98; ^{19}F NMR: δ -63.61.

Dimethyl [1-Benzyl-5-hydroxy-1*H*-pyrazol-4-yl]phosphonate (3r) and Dimethyl [1-benzyl-3-hydroxy-1*H*-pyrazol-4-yl]phosphonate (7r).- The reaction was carried out using 4.4 mmol of intermediate **2** to afford a mixture of the 3- and 5-hydroxy isomers (1:1, 49%). The products were purified by reverse phase chromatography; CH_3CN:H_2O, 15:85, hold 15 min; to 30:70 over 10 min; to 100:0 over 20 min (Note: all solvents contained 0.1% TFA). The 5-hydroxy product (F15-17) was isolated as a pale yellow oil after partial separation from the 3-hydroxy isomer (0.24 g, 0.9 mmol, 20%). The 3-hydroxy product (F19-20) was isolated as a white solid after partial separation from the 5-hydroxy isomer (0.22 g, 0.8 mmol, 18%). Both products crystallized with incorporation of TFA as judged by ^{19}F NMR spectroscopy.

Dimethyl [1-Benzyl-5-hydroxy-1*H*-pyrazol-4-yl]phosphonate (3r).- ^{1}H NMR: δ 9.04 (bs, 1H), 7.40 (s, 1H), 7.30 (m, 5H), 5.15 (s, 2H), 3.69 (d, *J* = 11.6 Hz, 6H); ^{13}C NMR: δ 158.1 (d, *J* = 21.0 Hz), 139.5 (d, *J* = 11.5 Hz), 135.7, 128.6, 127.81, 127.80, 82.8 (d, *J* = 224.7 Hz), 52.7 (d, *J* = 5.0 Hz), 50.3; ^{31}P NMR: δ 19.80.

Anal. Calcd for $C_{12}H_{15}N_2O_4P$ (0.1 TFA): C, 49.88; H, 5.19; N, 9.54. Found: C, 50.02; H, 5.36; N, 9.65 HRMS calcd for $C_{12}H_{15}N_2O_4P$ (M^+): 282.0769. Found: 282.0771.

Dimethyl [1-Benzyl-3-hydroxy-1*H*-pyrazol-4-yl]phosphonate (7r).- ^{1}H NMR: δ 11.90 (bs, 1H),

7.56 (d, J = 1.9 Hz, 1H), 7.34 (m, 3H), 7.26 (m, 2H), 5.08 (s, 2H), 3.75 (d, J = 11.8 Hz, 6H); ^{13}C NMR: δ 163.3 (d, J = 8.8 Hz), 136.7 (d, J = 21.7 Hz), 133.9, 128.9, 128.7, 128.3, 89.6 (d, J = 225.8 Hz), 56.0, 52.9 (d, J = 5.3 Hz); ^{31}P NMR: δ 16.87.

Anal. Calcd for $C_{12}H_{15}N_2O_4P$ (0.33 TFA): C, 47.49; H, 4.83; N, 8.75. Found: C, 47.69; H, 4.86; N, 8.75 HRMS calcd for $C_{12}H_{15}N_2O_4P$: 282.0769 (M^+), 281.0691 (M-H). Found: 282.0765 (M^+), 281.0692 (M-H).

Dimethyl [1-Cyclohexyl-5-hydroxy-1*H*-pyrazol-4-yl]phosphonate (3s) and Dimethyl [1-cyclohexyl-3-hydroxy-1*H*-pyrazol-4-yl]phosphonate (7s).- The reaction was carried out using 4.7 mmol of intermediate **2** to afford a mixture of the 3- and 5-hydroxy isomers (1.2:1.0, 22%). The products were purified by reverse phase chromatography; CH_3CN:H_2O, 10:90; to 40:60 over 20 min; to 100:0 over 5 min (Note: all solvents contained 0.1% TFA). The 5-hydroxy product (F15-17) was isolated as a white solid after partial separation from the 3-hydroxy isomer (0.07 g, 0.26 mmol, 6%). The 3-hydroxy product (F19-22) was isolated as a white solid after partial separation from the 5-hydroxy isomer (0.07 g, 0.26 mmol, 6%). Both products crystallized with incorporation of TFA as judged by ^{19}F NMR spectroscopy.

Dimethyl [1-Cyclohexyl-5-hydroxy-1*H*-pyrazol-4-yl]phosphonate (3s).- ^{1}H NMR: δ 11.45 (bs, 2H), 7.54 (s, 1H), 4.20 (m, 1H), 3.75 (d, J = 11.8 Hz, 6H), 1.96-1.71 (m, 7H), 1.41-1.24 (m, 3H); ^{13}C NMR: δ 157.5 (d, J = 21.2 Hz), 138.6 (d, J = 12.6 Hz), 82.6 (d, J = 225.8 Hz), 56.5, 53.2 (d, J = 5.3 Hz), 31.6, 25.5, 25.0; ^{31}P NMR: δ 19.23.

Anal. Calcd for $C_{11}H_{19}N_2O_4P$ (0.2 TFA): C, 46.08; H, 6.52; N, 9.43. Found: C, 46.15; H, 6.66; N, 9.30 HRMS calcd for $C_{11}H_{19}N_2O_4P$ (M^+): 274.1082. Found: 274.1079.

Dimethyl [1-Cyclohexyl-3-hydroxy-1*H*-pyrazol-4-yl]phosphonate (7s).- ^{1}H NMR: δ 12.15 (bs, 2H), 7.72 (d, J = 1.9 Hz, 1H), 3.94 (m, 1H), 3.81 (d, J = 11.6 Hz, 6H), 2.14 (bd, J = 11.0 Hz, 2H), 1.91 (bd, J = 13.7 Hz, 2H), 1.75 (bd, J = 12.9 Hz, 1H), 1.63 (dq, J = 12.4, 3.4 Hz, 2H), 1.41 (qm, J = 13.0 Hz, 2H), 1.25 (m, 1H); ^{13}C NMR: δ 162.5 (d, J = 8.4 Hz), 135.0 (d, J = 21.4 Hz), 88.5 (d, J = 227.7 Hz), 61.7, 53.3 (d, J = 5.3 Hz), 32.6, 25.0; ^{31}P NMR: δ 16.44.

Anal. Calcd for $C_{11}H_{19}N_2O_4P$ (0.13 TFA): C, 46.82; H, 6.68; N, 9.71. Found: C, 46.83; H, 6.68 N, 9.43 HRMS calcd $C_{11}H_{19}N_2O_4P$: 274.0182 (M^+), 273.1004 (M-H). Found: 274.1075 (M^+), 273.1000 (M-H).

Dimethyl [1-(4-Chlorophenyl)-5-hydroxy-1*H*-pyrazol-4-yl]phosphonate (3d) by Method B.- A mixture of trimethyl phosphonoacetate (13.4 g, 0.073 mol), *N,N*-dimethylformamide dimethyl acetal (13.2 g, 0.11 mol), and methanol (10 mL) was heated and held at reflux for 18 hours. The cool mixture was concentrated *in vacuo* to give trimethyl (dimethylaminomethylene) phosphonoacetate (**4a**) as light yellow solids/oil (22.4 g, 129%). A mixture of crude dimethylaminomethylene intermediate **4a**, (10.1 g, 0.032 mol), 4-chlorophenylhydrazine hydrochloride (5.8 g, 0.032 mol), and methanol (40 mL) was heated and held at reflux under nitrogen for one hour. TLC (EtOAc) analysis of an aliquot showed **4a** had been consumed. After the mixture had been cooled to 45°, water (15 mL) was added, followed by potassium carbonate (4.5 g, 0.032 mol). This mixture was heated and held at reflux for thirty minutes. TLC analysis of an aliquot showed complete conversion to product. The

reaction mixture was cooled to 25° and was worked up as described in Method A, to give **3d** (6.20 g, 64%) as a dark amber solid, ^{1}H and ^{31}P NMR spectra indicated pure product.

Methyl 2-(Dimethoxyphosphonyl)-3-methoxy-2-propenoate (4b).- To a slurry of methyl 3-oxy-2-dimethylphosphonoacrylate sodium salt (4.1 g, 0.017 mol) in anhydrous DMSO (25 mL) under nitrogen was added methyl iodide (4.5 g, 0.031 mol), and the reaction mixture was stirred for 18 hours at ambient temperature. The mixture was poured into dilute sodium chloride solution and was extracted with CH_2Cl_2 (6 x 75 mL). The extracts were washed with water (100 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo* to afford a brown oil (5.5 g). Partial separation by chromatography on silica gel (EtOAc) of half the crude product afforded pure E-isomer (0.27 g), a mixture of the E- and Z-isomers (0.75 g), and pure Z-isomer (0.14 g). The E- and Z-products were isolated in 52% overall yield.

Methyl (E)-2-(Dimethoxyphosphonyl)-3-methoxy-2-propenoate (4b, E-isomer).- ^{1}H NMR (300 MHz): δ 7.55 (d, J = 10.8 Hz, 1H), 4.06 (s, 3H), 3.78 (d, J = 2.7 Hz, 6H), 3.75 (s, 3H). ^{31}P NMR (121 MHz): δ 20.74.

Methyl (Z)-2-(Dimethoxyphosphonyl)-3-methoxy-2-propenoate (4b, Z-isomer).- ^{1}H NMR (300 MHz): δ 7.90 (d, J = 31.8 Hz, 1H), 4.03 (s, 3H), 3.78 (d, J = 5.1 Hz, 6H), 3.75 (s, 3H). ^{31}P NMR (121 MHz): δ 15.50.

Dimethyl [1-(4-chlorophenyl)-5-hydroxy-1*H*-pyrazol-4-yl]phosphonate (3d) by Method C.- A mixture of crude **4b** (6.9 g, 0.030 mol), 4-chlorophenylhydrazine hydrochloride (5.4 g, 0.030 mol), and methanol (40 mL) was heated and held at reflux under nitrogen for one hour. TLC (EtOAc) analysis of an aliquot showed **4b** had been consumed. After cooling to 45°, water (15 mL) was added, followed by potassium carbonate (4.1 g, 0.030 mol). This mixture was heated and held at 65° for one hour. TLC analysis of an aliquot showed complete conversion to product. The reaction mixture was cooled to 25° and worked up as described for Method A to afford **3d** as a red-amber solid (5.90 g, 65%), ^{1}H and ^{31}P NMR spectra indicated a 90% assay product, which results in a net 58% yield.

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