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Access to the Phosphorylindenopyrazole Scaffold via a Metal-Free Domino Reaction of Diazoalkylphosphonates with 3-Bromophthalides

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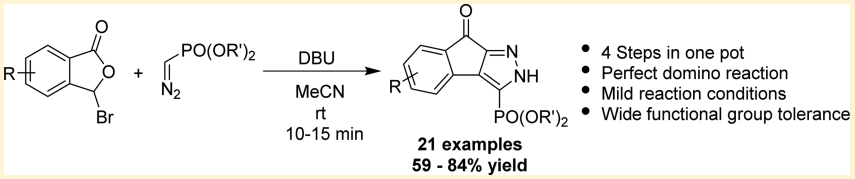
Supporting Information



ABSTRACT: A novel strategy is reported here for the synthesis of an indenopyrazole scaffold bearing a phosphonate group. The entire sequence includes nucleophilic addition−elimination, Seyferth−Gilbert homologation, transphosphorylation, and a 1,3-dipolar cycloaddition reaction of diazoalkylphosphonates in a perfect "domino" manner.

INTRODUCTION

The indenopyrazole framework has been implicated in cyclin-dependent kinase (CDK) inhibitors,[1] platelet-derived growth factor (PDGF-BB) receptor tyrosine kinase inhibitors,[2] hypoxia inducible factor (HIF)-1 inhibitors[3] and, more recently, as β1-adrenergic blockers (Figure 1).[4]

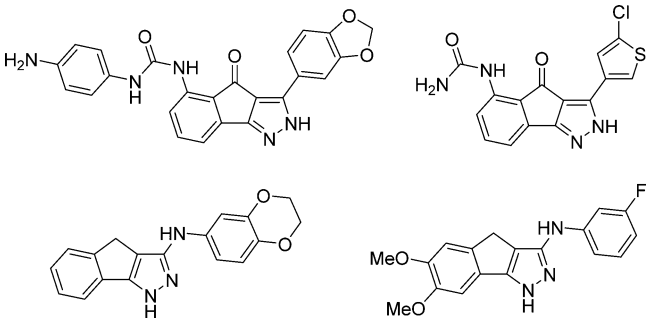
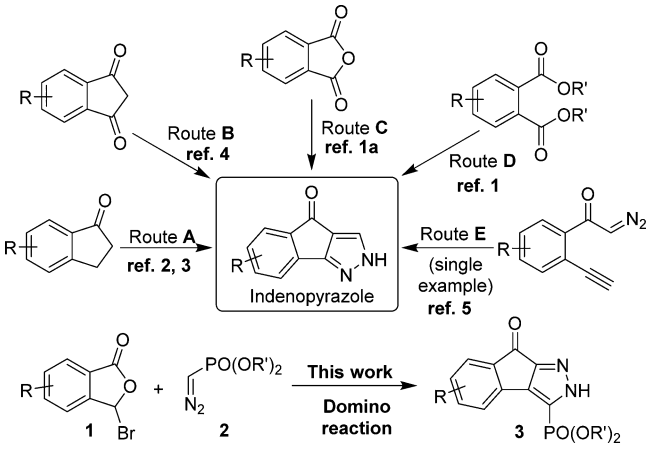


Figure 1. Indenopyrazole scaffold in biologically active molecules.

The routine synthetic methods reported for the indenopyrazole scaffold utilize corresponding indenones, phthalate esters, or phthalic anhydrides as starting substrates (Scheme 1, routes A−D).[1−4] In 1995, Kende and co-workers reported the synthesis of an indenopyrazole moiety from 2-diazo-1-(2-ethynylphenyl)ethan-1-one via a Ag(I)-catalyzed intramolecular dipolar cycloaddition reaction (Scheme 1, route E).[5] However, only a single example was reported, and the product was isolated in moderate yield. Therefore, all of the methods reported so far are multistep, provide indenopyrazoles in moderate yields, offer limited substitutions on the pyrazole moiety, and require elaborate synthetic procedures for accessing starting materials. Our group's ongoing research interest in investigating the effect of phosphonate groups in biologically active heterocyclic scaffolds[6,7] prompted us to design a strategy to introduce phosphonate group in the indenopyrazole scaffold. The diazoalkylphosphonate **2** was employed as the source of the phosphonate group in a domino reaction with 3-bromophthalides **1** serving as the template for the indenone moiety (Scheme 1; this work).

Scheme 1. Synthetic Methods for the Indenopyrazole Scaffold



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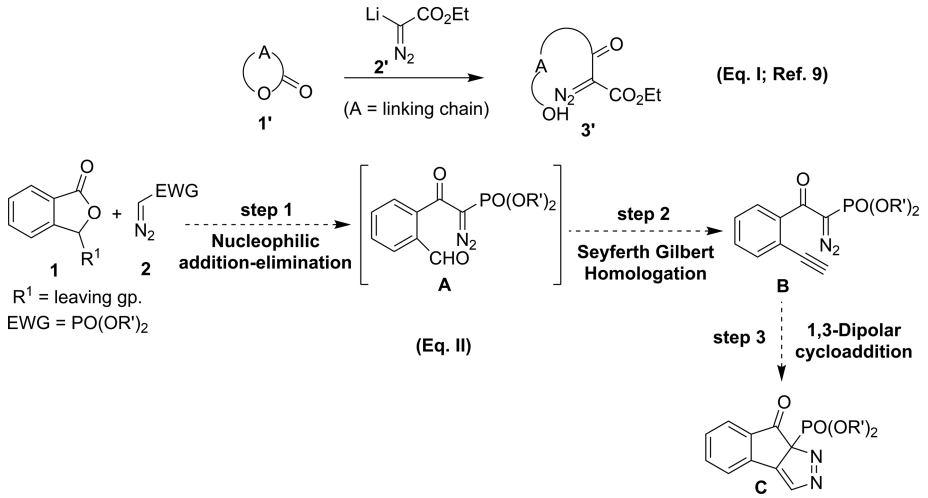
Scheme 2. Origin of the Idea



RESULTS AND DISCUSSION

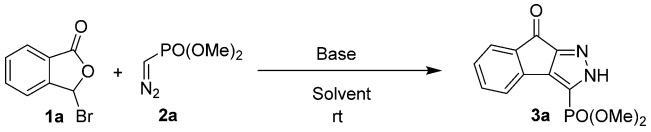
The diazocarbonyl compounds routinely participate in nucleophilic addition reactions with several electrophiles.[8] Moody and co-workers reported that the nucleophilic addition of ethyl lithiodiazoacetate **2′** with lactones **1′** is followed by ring opening, leading to the formation of corresponding alcohols **3′** (Scheme 2, eq I).[9] We envisaged that lactones such as isobenzofuranones or phthalides **1** bearing a suitable leaving group at the 3-position should also undergo nucleophilic addition and ring opening with diazocarbonyl compounds followed by elimination of the leaving group, resulting in the installation of a formyl group at the *o*-position (Scheme 2, eq II, step 1).[10] This newly introduced aldehyde functionality would undergo Seyferth−Gilbert homologation[11] in the case where diazo compound **2** is a diazoalkylphosphonate (Scheme 2, eq II, step 2). Once the alkyne and diazo functional groups are installed in the molecule **B**, an intramolecular 1,3-dipolar cycloaddition sequence (Pechmann reaction)[12] leading to the indenopyrazole scaffold **C** should be achievable under appropriate conditions (Scheme 2, eq II, step 3).[6d,13]

To test the feasibility of this method, we selected 3-bromophthalide **1a** and diazomethylphosphonate (DAMP) **2a** as model substrates (Table 1). The initial reactions with KOH, triethylamine, and K_2CO_3 as the base were not conclusive (entries 1−3). However, reaction with DBU and KO^{t}Bu resulted in a product in trace amounts which, upon spectroscopic analysis, showed the absence of formyl or alkyne moiety (entries 4 and 5). Additional spectroscopic and single-crystal X-ray analysis established the structure of the product as phosphonylated indenopyrazole **3a** unambiguously (Figure 2).[14]

The yield of **3a** increased to 42 and 69% with KO^{t}Bu and DBU in MeCN, respectively (entries 6 and 7). Further optimization established 2.5 equiv of DBU in MeCN to be the best condition in terms of reaction yield and time (entry 8).

The unusual reaction outcome can be rationalized mechanistically as shown in Scheme 3. The initial nucleophilic addition of **2a** on the phthalide **1a** is followed by elimination of HBr, leading to dialkyl (1-diazo-2-(2-formylphenyl)-2-oxoethyl)phosphonate **D**. The formyl group in **D** undergoes Seyferth−Gilbert homologation to afford dialkyl (1-diazo-2-(2-ethynylphenyl)-2-oxoethyl)phosphonate **E** in the presence of excess **2a**. The base-catalyzed deprotonation of the acetylenic proton in **E** triggers the transfer of the phosphonate group from the diazo carbon to the acetylenic carbon.[15] The resulting

Table 1. Optimization of Reaction Conditions[a]



	base	solvent	time (min)	yield of **3a** (%)[b]
1	KOH	MeOH	20	complex mixture
2	Et_3N	THF	120	no reaction
3	K_2CO_3	THF	120	no reaction
4	KO^t-Bu	THF	120	<10
5	DBU	THF	20	14
6	KO^t-Bu	MeCN	30	42
7	DBU	MeCN	10	69
8[c]	DBU	MeCN	10	84
9[d]	DBU	MeCN	10	82

[a]All reactions, unless otherwise mentioned, were performed with 0.5 mmol of **1a**, 1.0 mmol of **2a**, and 1.0 mmol of base in 5 mL of solvent. [b]Isolated yields. [c]**2a** (1.25 mmol) and DBU. [d]**2a** (1.5 mmol) and DBU.

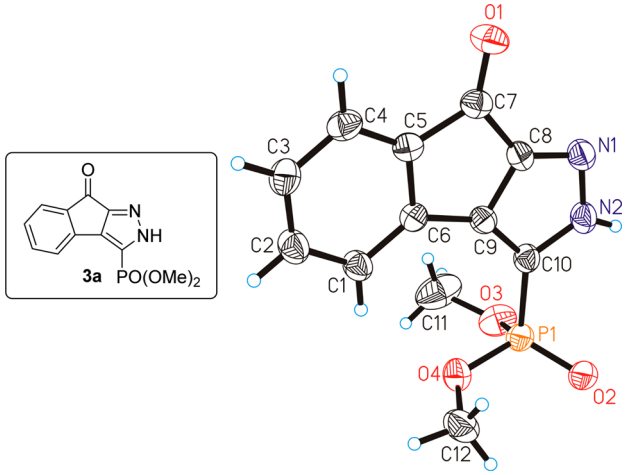


Figure 2. Thermal ellipsoid plot with 30% ellipsoid probability for non-H atoms of the crystal structure of compound **3a** determined at 293 K.

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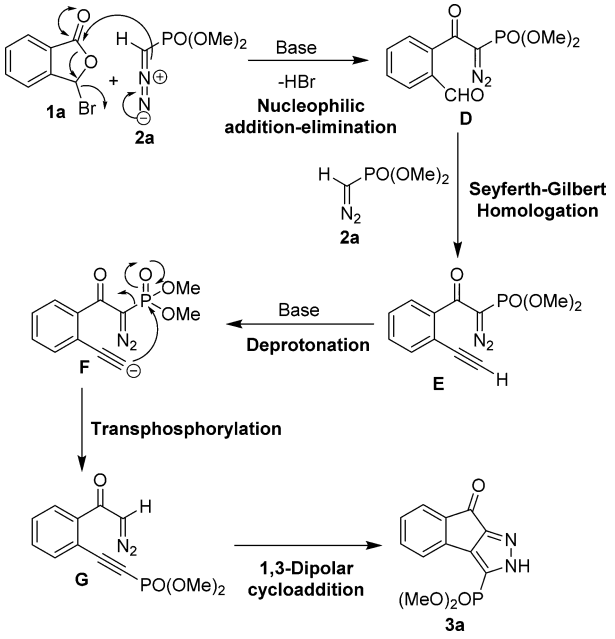
Scheme 3. Mechanistic Rationale



dialkyl ((2-(2-diazoacetyl)phenyl)ethynyl)phosphonate **G** in turn leads to the final **3a** via intramolecular 1,3-dipolar cycloaddition between the diazo group and alkynylphosphonate moiety.

We next aimed to expand the scope of the reaction with various 3-bromophthalides and diazoalkylphosphonates (Table 2).

The general nature of the reaction in terms of phthalides is evident from the wide range of substituted phthalides used in the reaction. The phthalides bearing substituents such as halides (F, Br, and Cl), nitro, cyano, and methyl as well as other aryl rings afford the corresponding indenopyrazoles in excellent yields. Also, the reaction proceeded smoothly with dimethyl-, diethyl-, and diisopropyl (diazomethyl)phosphonate, providing desired products in high yields.

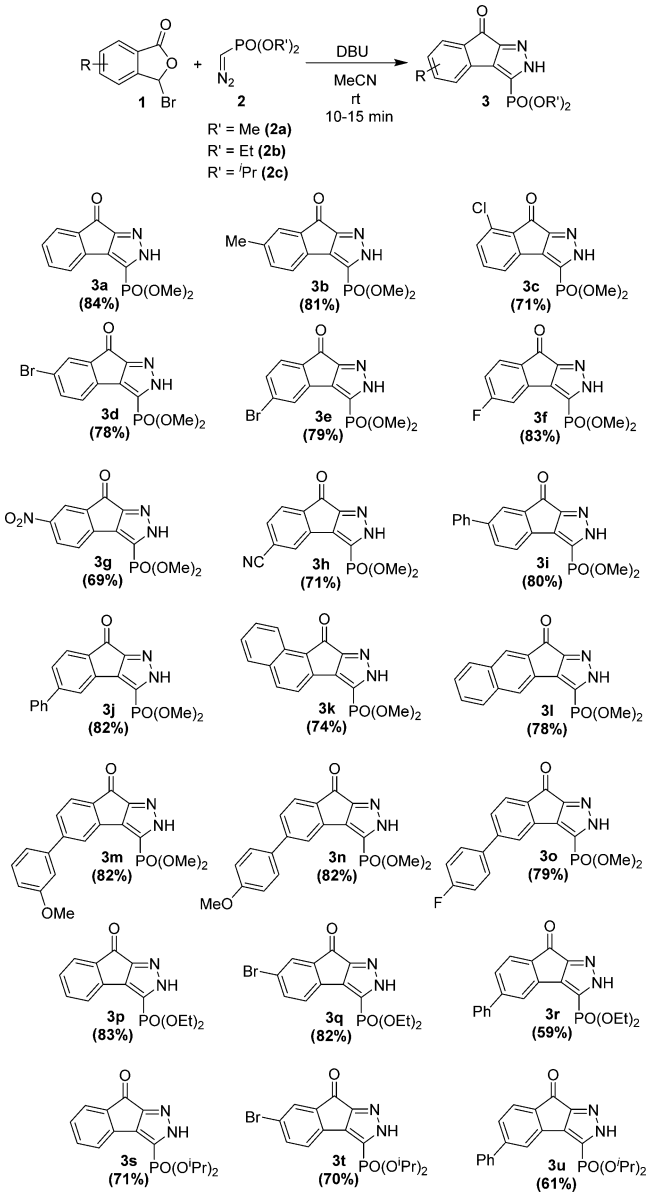
The validity of the proposed concept was tested by reacting **2a** with other cyclic electrophiles such as phthalic anhydride **4a** and *N*-methyl isatoic anhydride **4b** (Scheme 4).

As expected, nucleophilic addition of DAMP anion to the carbonyl group followed by ring opening in the case of **4a** and **4b** installs carboxyl and *N*-methyl amino functionality, respectively, at the *o*-position of the ring-opened products **5a** and **5b**.

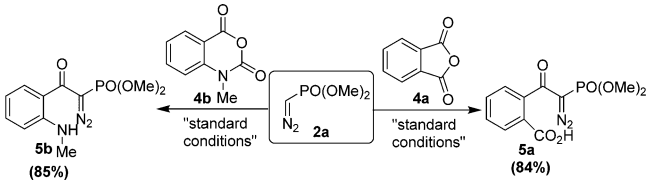
CONCLUSION

In conclusion, we devised an efficient strategy for the construction of a phosphoryl indenopyrazole scaffold by reacting diazophosphonates with phthalides bearing a leaving group at the 3-position. The reaction successfully exploits several known reactions of diazoalkylphosphonates, including nucleophilic addition−elimination, aldehyde to alkyne homologation, transphosphorylation, and 1,3-dipolar cycloaddition in a perfect "domino" manner.[16] The reaction proved to be fairly general because a wide range of substituted phthalides as well as diazo alkylphosphonates were successfully employed in the reaction. Also, other cyclic electrophiles such as phthalic anhydride and *N*-methylisatoic anhydride undergo nucleophilic addition with dimethyl(diazomethyl)phosphonate followed by ring opening, leading to the introduction of carboxyl and *N*-methyl amino functionalities, respectively, in the products.

Table 2. Substrate Scope



Scheme 4. Reaction of 2a with Other Cyclic Electrophiles



EXPERIMENTAL SECTION

General Information. All reactions were monitored by TLC; visualization was effected with UV and/or by development in iodine. Chromatography refers to column chromatography on silica gel (Merck, 100−200 mesh). NMR spectra were recorded at 400 (^{1}H), 100 (^{13}C), and 162 MHz (^{31}P). Chemical shifts are reported in δ (ppm) relative to TMS as the internal standard for ^{1}H and ^{13}C and phosphoric acid as the external standard for ^{31}P. The ^{13}C and ^{31}P

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spectra were proton decoupled and, in the case of ^{1}H NMR, the standard abbreviations such as s, d, t, q, m, and dd, referring to singlet, doublet, triplet, quartet, multiplet, and doublet of doublets, respectively, are used to describe spin multiplicity. The coupling constants (J) are given in Hz. The ESI-HRMS spectra were recorded on a Q-TOF LC/MS system.

Because diazo compounds are potentially hazardous (toxic and explosive), all of the reactions were performed in fume hood with proper safety measures. All reactions were conducted in oven-dried glassware under nitrogen. Diazomethyl-, diazoethyl-, and diazoisopropyl phosphonates were prepared according to the standard protocol.[17] The 3-bromophthalides (**1a−o**) were synthesized from corresponding phthalides following the literature procedure.[18] All other solvents and reagents were purchased from commercial sources and used as received.

General Procedure for the Reaction of Diazophosphonates (2a−c) with 3-Bromophthalides (1a−o) or Other Cyclic Electrophiles (4a and b). To a stirred solution of 3-bromophthalide **1** or other cyclic electrophiles **4** (0.5 mmol) in dry MeCN (5 mL) was added the diazophosphonate **2** (1.25 mmol) followed by DBU (1.25 mmol), and the reaction mixture was stirred at room temperature for 10−15 min (TLC monitoring). The reaction mixture was extracted with ethyl acetate (3 × 10 mL). The ethyl acetate layer was washed with 2 M HCl (2 × 10 mL) and water (2 × 10 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude residue was subjected to column chromatography on silica gel using hexane/ethyl acetate as eluent to afford the pure product **3**/**5**.

*Dimethyl 8-Oxo-2,8-dihydroindeno[2,1-c]pyrazol-3-ylphosphonate (**3a**).* Yellow solid (117 mg, 84%). R_f 0.50 (70% EtOAc/hexane); mp 144−146 °C; IR (KBr, cm^{-1}) 3401, 1719, 1607, 1385, 1219, 1068; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.75 (br s, 1H), 7.55 (d, J = 7.3 Hz, 1H), 7.38−7.40 (m, 2H), 7.19−7.22 (m, 1H), 3.83 (d, J_{H-P} = 11.7 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.7, 138.5, 137.3 (d, J_{C-P} = 17.4 Hz), 135.9, 135.2, 130.0, 128.9, 127.2, 125.1, 122.4, 53.7 (d, J_{C-P} = 5.3 Hz); ^{31}P NMR (161.9 MHz, $CDCl_3$) δ 8.27; HRMS for $C_{12}H_{11}N_2O_4P$: calcd (MH^+) 279.0529, found: 279.0524.

Selected X-ray crystallographic data for **3a**, $C_{12}H_{11}N_2O_4P$: M = 278.20, triclinic, P −1, a = 7.112(2) Å, b = 8.573(3) Å, c = 10.427(3) Å, V = 634.5(3)Å^3, α = 93.082(7)°, β = 90.137(8)°, γ = 91.869(8)°, Z = 2, D_c = 1.456 g cm^{-3}, μ(Mo Kα) = 0.228 mm^{-1}, F(000) = 288. Reflections collected: unique 4377/2183 [R(int) = 0.0334]. Final R indices: [$I > 2s(I)$], $R1$ = 0.0509, wR_2 = 0.1428.

*Dimethyl 6-Methyl-8-oxo-2,8-dihydroindeno[2,1-c]pyrazol-3-ylphosphonate (**3b**).* Yellow solid (118 mg, 81%). R_f 0.50 (70% EtOAc/hexane); mp 171−172 °C; IR (KBr, cm^{-1}) 3401, 3020, 2400, 1717, 1613, 1404, 1216, 1036; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.78 (br s, 1H), 7.44 (d, J = 7.6 Hz, 1H), 7.19 (s, 1H), 7.00 (d, J = 7.6 Hz, 1H), 3.83 (d, J_{H-P} = 11.7 Hz, 6H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.5, 146.5, 137.1 (d, J_{C-P} = 16.9 Hz), 136.1, 129.2, 125.1, 123.4, 53.7 (d, J_{C-P} = 5.0 Hz), 22.3; ^{31}P NMR (161.9 MHz, $CDCl_3$) δ 8.66; HRMS for $C_{13}H_{13}N_2O_4P$: calcd (MH^+) 293.0686, found: 293.0698.

*Dimethyl 7-Chloro-8-oxo-2,8-dihydroindeno[2,1-c]pyrazol-3-ylphosphonate (**3c**).* Pale yellow solid (111 mg, 71%). R_f 0.50 (70% EtOAc/hexane); mp 159−161 °C; IR (KBr, cm^{-1}) 3400, 3020, 2400, 1731, 1600, 1385, 1216, 1062; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, J = 7.2 Hz, 1H), 7.38 (d, J = 7.9 Hz, 1H), 7.16 (t, J = 7.8 Hz, 1H), 3.83 (d, J_{H-P} = 11.9 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.9, 155.5 (d, J_{C-P} = 14.8 Hz), 139.9, 136.0, 135.2, 133.0 (d, J_{C-P} = 15.2 Hz), 130.1, 128.9, 124.4 (d, J_{C-P} = 221.2 Hz), 123.1, 53.6 (d, J_{C-P} = 5.3 Hz); ^{31}P NMR (161.9 MHz, $CDCl_3$) δ 8.17; HRMS for $C_{12}H_{10}ClN_2O_4P$: calcd (MH^+) 313.0139, found: 313.0145.

*Dimethyl 6-Bromo-8-oxo-2,8-dihydroindeno[2,1-c]pyrazol-3-ylphosphonate (**3d**).* Yellow solid (139 mg, 78%). R_f 0.50 (70% EtOAc/hexane); mp 167−169 °C; IR (KBr, cm^{-1}) 3401, 3020, 2400, 1601, 1385, 1216, 1067; ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.04 (br s, 1H), 7.51 (s, 1H), 7.39 (2 d merged to appear as q, 2H), 3.86 (d, J_{H-P} = 11.6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.4, 137.5, 137.0, 135.9 (d, J_{C-P} = 16.8 Hz), 131.8, 130.0, 126.3, 125.8, 53.8 (d, J_{C-P} = 5.2 Hz); ^{31}P NMR (161.9 MHz, $CDCl_3$) δ 2.99; HRMS for $C_{12}H_{10}BrN_2O_4P$: calcd (MH^+) 356.9634, found: 356.9642.

*Dimethyl 5-Bromo-8-oxo-2,8-dihydroindeno[2,1-c]pyrazol-3-ylphosphonate (**3e**).* Yellow solid (141 mg, 79%). R_f 0.50 (70% EtOAc/hexane); mp 195−196 °C; IR (KBr, cm^{-1}) 3400, 3020, 2400, 1724, 1626, 1385,1067; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, J = 1.6 Hz, 1H), 7.53 (dd, J = 1.8, 7.9 Hz, 1H), 7.28 (d, J = 7.9 Hz, 1H), 3.83 (d, J_{H-P} = 11.7 Hz, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 183.7, 153.8, 140.1, 138.2, 137.6, 135.2, 127.8, 124.9, 123.0, 121.9, 53.8 (d, J_{C-P} = 5.0 Hz); ^{31}P NMR (161.9 MHz, $CDCl_3$) δ 7.78; HRMS for $C_{12}H_{10}BrN_2O_4P$: calcd (MH^+) 356.9634, found: 356.9630.

*Dimethyl 5-Fluoro-8-oxo-2,8-dihydroindeno[2,1-c]pyrazol-3-ylphosphonate (**3f**).* Yellow solid (123 mg, 83%). R_f 0.50 (70% EtOAc/hexane); mp 170−172 °C; IR (KBr, cm^{-1}) 3401, 3020, 2400, 1621, 1385, 1216, 1034; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.93 (br s, 1H), 7.36 (dd, J = 4.5, 8.0 Hz, 1H), 7.25 (dd, J = 1.9, 7.2 Hz, 1H), 7.05−7.10 (m, 1H), 3.84 (d, J_{H-P} = 11.7 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.2, 163.2 (d, J_{C-F} = 249.3 Hz), 154.5 (d, J_{C-F} = 13.9 Hz), 140.6 (d, J_{C-F} = 17.0 Hz), 136.9 (d, J_{C-P} = 17.2 Hz), 131.6 (d, J_{C-P} = 3.1 Hz), 123.8 (d, J_{C-F} = 7.7 Hz), 122.9 (d, J_{C-P} = 223.6 Hz), 121.1 (d, J_{C-F} = 22.8 Hz), 113.2 (d, J_{C-F} = 24.0 Hz), 53.7 (d, J_{C-P} = 5.2 Hz); ^{31}P NMR (161.9 MHz, $CDCl_3$) δ 8.04; HRMS for $C_{12}H_{10}FN_2O_4P$: calcd (MH^+) 297.0435, found: 297.0444.

*Dimethyl 6-Nitro-8-oxo-2,8-dihydroindeno[2,1-c]pyrazol-3-ylphosphonate (**3g**).* Yellow solid (111 mg, 69%). R_f 0.50 (75% EtOAc/hexane); mp 181−182 °C; IR (KBr, cm^{-1}) 3400, 3020, 1620, 1385, 1216, 1070; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (s, 1H), 8.11 (d, J = 8.0 Hz, 1H), 7.71 (d, J = 8.0 Hz, 1H), 3.90 (d, J_{H-P} = 11.6 Hz, 6H); ^{13}C NMR (100 MHz, CD_3OD) δ 187.9, 159.0, 156.9, 147.6, 142.3, 141.8 (d, J_{C-P} = 19.3 Hz), 130.6, 129.8, 128.5, 122.1, 58.7 (d, J_{C-P} = 4.3 Hz); ^{31}P NMR (161.9 MHz, $CDCl_3$) δ 7.47; HRMS for $C_{12}H_{10}N_3O_6P$: calcd (MH^+) 324.0380, found: 324.0375.

*Dimethyl 5-Cyano-8-oxo-2,8-dihydroindeno[2,1-c]pyrazol-3-ylphosphonate (**3h**).* Yellow solid (108 mg, 71%). R_f 0.50 (75% EtOAc/hexane); mp 211−213 °C; IR (KBr, cm^{-1}) 3400, 3020, 2400, 1645, 1404, 1216, 1069; ^{1}H NMR (400 MHz, DMSO-d_6) δ 14.76 (br s, 1H), 8.07 (d, J = 7.7 Hz, 1H), 7.97 (s, 1H), 7.77 (d, J = 7.8 Hz, 1H), 3.80 (d, J_{H-P} = 11.6 Hz, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 183.2, 154.4, 140.4, 140.2, 138.8, 136.8, 128.0, 124.2, 123.6, 118.6, 111.5, 52.7 (d, J_{C-P} = 4.5 Hz); ^{31}P NMR (161.9 MHz, DMSO-d_6) δ 6.50; HRMS for $C_{13}H_{10}N_3O_4P$: calcd (MH^+) 304.0482, found: 304.0481.

*Dimethyl 8-Oxo-6-phenyl-2,8-dihydroindeno[2,1-c]pyrazol-3-ylphosphonate (**3i**).* Yellow solid (142 mg, 80%). R_f 0.50 (75% EtOAc/hexane); mp 187−189 °C; IR (KBr, cm^{-1}) 3402, 3020, 2400, 1725, 1613, 1523, 1405, 1216, 1034; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (br s, 2H), 7.55 (d, J = 7.2 Hz, 2H), 7.35−7.45 (m, 4H), 3.86 (d, J_{H-P} = 11.6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.3, 148.3, 140.0, 137.3, 136.9 (d, J_{C-P} = 17.1 Hz), 136.6, 129.1, 128.6, 127.5, 127.1, 125.6, 121.3, 53.8 (d, J_{C-P} = 5.3 Hz); ^{31}P NMR (161.9 MHz, $CDCl_3$) δ 8.27; HRMS for $C_{18}H_{15}N_2O_4P$: calcd (MH^+) 355.0842, found: 355.0844.

*Dimethyl 8-Oxo-5-phenyl-2,8-dihydroindeno[2,1-c]pyrazol-3-ylphosphonate (**3j**).* Yellow solid (145 mg, 82%). R_f 0.50 (75% EtOAc/hexane); mp 185−186 °C; IR (KBr, cm^{-1}) 3401, 3020, 2400, 1621, 1385, 1216, 1069; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (s, 1H), 7.63 (d, J = 7.1 Hz, 1H), 7.52 (d, J = 6.8 Hz, 2H), 7.46 (d, J = 7.5 Hz, 1H), 7.39 (t, J = 6.6 Hz, 2H), 7.33 (d, J = 6.7 Hz, 1H), 3.86 (d, J_{H-P} = 11.6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.6, 142.2, 139.6, 139.2, 137.2 (d, J_{C-P} = 17.2 Hz), 134.5, 133.5, 129.0, 128.1, 126.8, 123.9, 122.7, 53.8 (d, J_{C-P} = 5.4 Hz); ^{31}P NMR (161.9 MHz, $CDCl_3$) δ 8.31; HRMS for $C_{18}H_{15}N_2O_4P$: calcd (MH^+) 355.0842, found: 355.0843.

*Dimethyl 7-Oxo-7,9-dihydrobenzo[6,7]indeno[2,1-c]pyrazol-10-ylphosphonate (**3k**).* Red solid (121 mg, 74%). R_f 0.50 (70% EtOAc/hexane); mp 185−187 °C; IR (KBr, cm^{-1}) 3401, 3020, 1645, 1403, 1217, 1070; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.29 (br s, 1H), 8.41−8.43 (m, 1H), 7.78−7.81 (m, 1H), 7.73, 7.66 (ABq, J = 8.2 Hz, 2H), 7.51−7.56 (m, 2H), 3.89 (d, J_{H-P} = 11.7 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 185.9, 156.1 (d, J_{C-P} = 15.2 Hz), 137.9, 137.0,

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135.3, 134.2 (d, J_{C-P} = 16.3 Hz), 129.7, 129.1, 128.9, 127.6, 127.5, 126.1, 123.2 (d, J_{C-P} = 216.9 Hz), 120.4, 53.8 (d, J_{C-P} = 5.1 Hz); ^{31}P NMR (161.9 MHz, $CDCl_3$) δ 9.43; HRMS for $C_{16}H_{13}N_2O_4P$: calcd (MH^+) 329.0686, found: 329.0695.

*Dimethyl 10-Oxo-2,10-dihydrobenzo[5,6]indeno[2,1-c]pyrazol-3-ylphosphonate (**3l**).* Pale yellow solid (128 mg, 78%). R_f 0.50 (70% EtOAc/hexane); mp 194−196 °C; IR (KBr, cm^{-1}) 3401, 3019, 1635, 1385, 1217, 1069; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.75−7.81(m, 3H), 7.40−7.52 (m, 2H), 3.88 (d, J_{H-P} = 11.6 Hz, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 137.3, 136.8, 132.9, 131.2, 130.4, 130.0, 129.3, 127.7, 126.7, 121.6, 53.8 (d, J_{C-P} = 5.2 Hz); ^{31}P NMR (161.9 MHz, $CDCl_3$) δ 8.48; HRMS for $C_{16}H_{13}N_2O_4P$: calcd (MH^+) 329.0686, found: 329.0696.

*Dimethyl 5-(3-Methoxyphenyl)-8-oxo-2,8-dihydroindeno[2,1-c]-pyrazol-3-ylphosphonate (**3m**).* Yellow solid (157 mg, 82%). R_f 0.50 (75% EtOAc/hexane); mp 164−165 °C; IR (KBr, cm^{-1}) 3400, 3019, 1725, 1607, 1385, 1218, 1036; ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.00 (br s, 1H), 7.79 (s, 1H), 7.63 (dd, J = 1.4, 7.7 Hz, 1H), 7.45 (d, J = 7.7 Hz, 1H), 7.30 (t, J = 8.0 Hz, 1H), 7.10 (d, J = 7.6 Hz, 1H), 7.04 (s, 1H), 6.86 (dd, J = 1.9, 8.2 Hz, 1H), 3.86 (d, J_{H-P} = 11.6 Hz, 6H), 3.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.6, 160.1, 142.0, 141.0, 139.2, 137.2 (d, J_{C-P} = 16.7 Hz), 134.7, 133.6, 130.0, 123.9, 122.7, 119.2, 113.6, 112.4, 55.4, 53.8 (d, J_{C-P} = 5.4 Hz); ^{31}P NMR (161.9 MHz, DMSO-d_6) δ 3.53; HRMS for $C_{19}H_{17}N_2O_5P$: calcd (MH^+) 385.0948, found: 385.0944.

*Dimethyl 5-(4-Methoxyphenyl)-8-oxo-2,8-dihydroindeno[2,1-c]-pyrazol-3-ylphosphonate (**3n**).* Yellow solid (157 mg, 82%). R_f 0.50 (75% EtOAc/hexane); mp 204−205 °C; IR (KBr, cm^{-1}) 3401, 3020, 2400, 1638, 1403, 1216, 1069, 1034; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (s, 1H), 7.58 (d, J = 7.4 Hz, 1H), 7.42−7.47 (m, 3H), 6.92 (d, J = 8.5 Hz, 2H), 3.85 (d, J_{H-P} = 11.6 Hz, 6H), 3.79 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 159.8, 140.9, 139.2, 134.3, 133.3, 131.6, 128.2, 123.6, 122.6, 115.0, 55.7, 53.8 (d, J_{C-P} = 5.0 Hz); ^{31}P NMR (161.9 MHz, $CDCl_3$) δ 8.16; HRMS for $C_{19}H_{17}N_2O_5P$: calcd (MH^+) 385.0948, found: 385.0942.

*Dimethyl 5-(4-Fluorophenyl)-8-oxo-2,8-dihydroindeno[2,1-c]-pyrazol-3-ylphosphonate (**3o**).* Yellow solid (147 mg, 79%). R_f 0.50 (75% EtOAc/hexane); mp 178−179 °C; IR (KBr, cm^{-1}) 3401, 3020, 2400, 1724, 1614, 1516, 1404, 1216, 1159, 1036; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (s, 1H), 7.58 (d, J = 7.1 Hz, 1H), 7.45−7.49 (m, 3H), 7.08 (t, J = 8.4 Hz, 2H), 3.86 (d, J_{H-P} = 11.6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.5, 162.9 (d, J_{C-F} = 247.0 Hz), 141.1, 139.2, 137.2 (d, J_{C-P} = 17.3 Hz), 135.7, 134.5, 133.3, 128.4 (d, J_{C-F} = 8.2 Hz), 123.7, 122.8, 116.0 (d, J_{C-F} = 21.6 Hz), 53.8 (d, J_{C-P} = 5.1 Hz); ^{31}P NMR (161.9 MHz, $CDCl_3$) δ 8.15; HRMS for $C_{18}H_{14}FN_2O_4P$: calcd (MH^+) 373.0748, found: 373.0744.

*Diethyl 8-Oxo-2,8-dihydroindeno[2,1-c]pyrazol-3-ylphosphonate (**3p**).* Pale yellow solid (127 mg, 83%). R_f 0.50 (70% EtOAc/hexane); mp 165−166 °C; IR (KBr, cm^{-1}) 3400, 3020, 1627, 1385, 1216, 1070; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, J = 7.2 Hz, 1H), 7.37−7.41 (m, 2H), 7.20−7.22 (m, 1H merged with $CDCl_3$ peak), 4.08−4.27 (m, 4H), 1.30 (t, J = 7.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.9, 154.6 (d, J_{C-P} = 13.2 Hz), 138.5, 136.8 (d, J_{C-P} = 16.7 Hz), 136.0, 135.0, 128.7, 125.0, 122.4, 63.8 (d, J_{C-P} = 5.0 Hz), 16.2 (d, J_{C-P} = 6.4 Hz); ^{31}P NMR (161.9 MHz, $CDCl_3$) δ 5.15; HRMS for $C_{14}H_{15}N_2O_4P$: calcd (MH^+) 307.0842, found: 307.0844.

*Diethyl (6-Bromo-8-oxo-2,8-dihydroindeno[2,1-c]pyrazol-3-yl)-phosphonate (**3q**).* Yellow solid (157 mg, 82%). R_f 0.50 (70% EtOAc/hexane); mp 190−191 °C; IR (KBr, cm^{-1}) 3401, 3020, 2400, 1726, 1602, 1404, 1216, 1025; ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.11 (br s, 1H), 7.56 (s, 1H), 7.41, 7.36 (ABq, J = 7.8 Hz, 2H), 4.13−4.31 (m, 4H), 1.34 (t, J = 7.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.7, 137.7, 137.1, 135.4 (d, J_{C-P} = 18.8 Hz), 131.6, 129.9, 126.2, 125.8, 63.9 (d, J_{C-P} = 5.3 Hz), 16.3 (d, J_{C-P} = 6.5 Hz); ^{31}P NMR (161.9 MHz, $CDCl_3$) δ 4.65; HRMS for $C_{14}H_{14}BrN_2O_4P$: calcd (MH^+) 384.9947, found: 384.9951.

*Diethyl (8-Oxo-6-phenyl-2,8-dihydroindeno[2,1-c]pyrazol-3-yl)-phosphonate (**3r**).* Yellow solid (113 mg, 59%). R_f 0.50 (60% EtOAc/hexane); mp 159−160 °C; IR (KBr, cm^{-1}) 3437, 3102, 2877, 2367, 2341, 1726, 1613, 1564, 1477, 1452, 1239, 1205, 1100, 1016; ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.08 (br s, 1H), 7.80 (s, 1H), 7.63 (d, J = 7.7 Hz, 1H), 7.52 (d, J = 7.4 Hz, 2H), 7.48 (d, J = 7.7 Hz, 1H), 7.39 (t, J = 7.6 Hz, 2H), 7.29−7.33 (m, 1H), 4.13−4.31 (m, 4H), 1.34 (t, J = 7.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.9, 153.9 (d, J_{C-P} = 158.6 Hz), 142.0, 139.6, 139.3, 136.8 (d, J_{C-P} = 16.1 Hz), 134.8, 133.4, 129.0, 128.0, 126.8, 124.3 (d, J_{C-P} = 221.5 Hz), 123.8, 122.8, 63.8 (d, J_{C-P} = 5.1 Hz), 16.3 (d, J_{C-P} = 6.5 Hz); ^{31}P NMR (161.9 MHz, $CDCl_3$) δ 5.20; HRMS for $C_{20}H_{19}N_2O_4P$: calcd (MH^+) 383.1155, found: 383.1152.

*Diisopropyl 8-Oxo-2,8-dihydroindeno[2,1-c]pyrazol-3-ylphosphonate (**3s**).* Yellow solid (119 mg, 71%). R_f 0.50 (70% EtOAc/hexane); mp 136−138 °C; IR (KBr, cm^{-1}) 3400, 3020, 2400, 1611, 1385, 1216, 1070; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.70 (br s, 1H), 7.53 (d, J = 7.2 Hz, 1H), 7.36−7.39 (m, 2H), 7.18 (t, J = 6.7 Hz, 1H), 4.70−4.78 (m, 2H), 1.36 (d, J = 6.0 Hz, 6H), 1.18 (d, J = 6.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 185.2, 138.6, 136.5, 136.2, 134.9, 128.6, 125.0, 122.6, 73.1 (d, J_{C-P} = 5.1 Hz), 24.1 (d, J_{C-P} = 4.2 Hz), 23.7 (d, J_{C-P} = 4.8 Hz); ^{31}P NMR (161.9 MHz, $CDCl_3$) δ 2.59; HRMS for $C_{16}H_{19}N_2O_4P$: calcd (MH^+) 335.1155, found: 335.1160.

*Diisopropyl 6-Bromo-8-oxo-2,8-dihydroindeno[2,1-c]pyrazol-3-ylphosphonate (**3t**).* Yellow solid (144 mg, 70%). R_f 0.50 (70% EtOAc/hexane); mp 209−210 °C; IR (KBr, cm^{-1}) 3428, 3102, 2366, 2341, 1794, 1727, 1240, 1100, 1041; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, J = 1.7 Hz, 1H), 7.53 (dd, J = 1.8, 7.9 Hz, 1H), 7.29 (d, J = 7.9 Hz, 1H), 4.70−4.81 (m, 2H), 1.38 (d, J = 6.2 Hz, 6H), 1.20 (d, J = 6.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.6, 140.0, 137.4, 136.7, 135.8 (d, J_{C-P} = 16.6 Hz), 134.8, 128.3, 126.1 (d, J_{C-P} = 220.3 Hz), 123.9, 122.4, 73.2 (d, J_{C-P} = 5.1 Hz), 24.1 (d, J_{C-P} = 3.8 Hz), 23.7 (d, J_{C-P} = 4.7 Hz); ^{31}P NMR (161.9 MHz, $CDCl_3$) δ 4.68; HRMS for $C_{16}H_{18}BrN_2O_4P$: calcd (MH^+) 413.0260, found: 413.0256.

*Diisopropyl (8-Oxo-5-phenyl-2,8-dihydroindeno[2,1-c]pyrazol-3-yl)phosphonate (**3u**).* Yellow solid (125 mg, 61%). R_f 0.50 (60% EtOAc/hexane); mp 201−202 °C; IR (KBr, cm^{-1}) 3428, 2980, 2365, 2342, 1798, 1726, 1617, 1563, 1460, 1377, 1232, 1101; ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.00 (br s, 1H), 7.79 (d, J = 1.4 Hz, 1H), 7.63 (dd, J = 1.7, 7.7 Hz, 1H), 7.52 (d, J = 7.3 Hz, 2H), 7.47 (d, J = 7.7 Hz, 1H), 7.38 (t, J = 7.2 Hz, 2H), 7.30 (t, J = 7.3 Hz, 1H), 4.72−4.83 (m, 2H), 1.40 (d, J = 6.2 Hz, 6H), 1.22 (d, J = 6.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 185.1, 141.9, 139.7, 139.3, 136.3 (d, J_{C-P} = 19.5 Hz), 134.9, 133.3, 129.0, 128.0, 126.8, 124.7, 123.7, 122.9, 73.1 (d, J_{C-P} = 5.0 Hz), 24.1 (d, J_{C-P} = 3.8 Hz), 23.8 (d, J_{C-P} = 4.6 Hz); ^{31}P NMR (161.9 MHz, $CDCl_3$) δ 2.43; HRMS for $C_{22}H_{23}N_2O_4P$: calcd (MH^+) 411.1468, found: 411.1463.

*2-(2-(Dimethoxyphosphoryl)-2-oxoacetyl)benzoic Acid (**5a**).* White gummy solid (125 mg, 84%). R_f 0.50 (5% MeOH/$CHCl_3$); IR (KBr, cm^{-1}) 3398, 2924, 2371, 1719, 1654, 1032; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, J = 7.8 Hz, 1H), 7.55−7.59 (m, 1H), 7.46−7.50 (m, 1H), 7.30 (d, J = 7.5 Hz, 1H), 3.73 (d, J_{H-P} = 11.5 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.1 (d, J_{C-P} = 10.0 Hz), 168.3, 139.8, 133.1, 130.9, 130.3, 127.7, 126.9, 54.2 (d, J_{C-P} = 5.0 Hz); ^{31}P NMR (161.9 MHz, $CDCl_3$) δ 13.48; HRMS for $C_{11}H_{11}N_2O_6P$: calcd (MH^+) 299.0427, found: 299.0433.

*Dimethyl (1-Diazo-2-(2-(methylamino)phenyl)-2-oxoethyl)-phosphonate (**5b**).*[6b] Yellow solid (99 mg, 85%). R_f 0.50 (70% EtOAc/hexane); mp 114−116 °C; IR (film, cm^{-1}) 1067, 1218, 1403, 1639, 3671, 3849; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (dd, J = 1.5, 7.9 Hz, 1H), 7.28−7.32 (m, 1H), 7.08 (br s, 1H), 6.64 (d, J = 8.5 Hz, 1H), 6.55 (t, J = 7.8 Hz, 1H), 3.80 (d, J = 11.9 Hz, 6H), 2.79 (d, J = 5.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.0 (d, J_{C-P} = 8.2 Hz), 150.3, 134.8, 129.6, 117.2, 114.3, 111.7, 61.2 (d, J_{C-P} = 218.7 Hz, CN_2), 54.0 (d, J_{C-P} = 5.5 Hz), 29.5; ^{31}P NMR (161.9 MHz, $CDCl_3$) δ 15.42; HRMS for $C_{11}H_{14}N_3O_4P$: calcd (MH^+) 284.0795, found: 284.0797.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02267.

X-ray data for compound **3a** (CIF)

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Copies of ^{1}H, ^{13}C, and ^{31}P NMR spectra of all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) (a) Yue, E. W.; Higley, C. A.; DiMeo, S. V.; Carini, D. J.; Nugiel, D. A.; Benware, C.; Benfield, P. A.; Burton, C. R.; Cox, S.; Grafstrom, R. H.; Sharp, D. M.; Sisk, L. M.; Boylan, J. F.; Muckelbauer, J. K.; Smallwood, A. M.; Chen, H.; Chang, C.-H.; Seitz, S. P.; Trainor, G. L. *J. Med. Chem.* **2002**, *45*, 5233. (b) Nugiel, D. A.; Vidwans, A.; Etzkorn, A.-M.; Rossi, K. A.; Benfield, P. A.; Burton, C. R.; Cox, S.; Doleniak, D.; Seitz, S. P. *J. Med. Chem.* **2002**, *45*, 5224. (c) Nugiel, D. A.; Etzkorn, A.-M.; Vidwans, A.; Benfield, P. A.; Boisclair, M.; Burton, C. R.; Cox, S.; Czerniak, P. M.; Doleniak, D.; Seitz, S. P. *J. Med. Chem.* **2001**, *44*, 1334.

(2) Ho, C. Y.; Ludovici, D. W.; Maharoof, U. S. M.; Mei, J.; Sechler, J. L.; Tuman, R. W.; Strobel, E. D.; Andraka, L.; Yen, H.-K.; Leo, G.; Li, J.; Almond, H.; Lu, H.; DeVine, A.; Tominovich, R. M.; Baker, J.; Emanuel, S.; Gruninger, R. H.; Middleton, S. A.; Johnson, D. L., Jr.; Galemmo, R. A. *J. Med. Chem.* **2005**, *48*, 8163.

(3) Minegishi, H.; Fukashiro, S.; Ban, H. S.; Nakamura, H. *ACS Med. Chem. Lett.* **2013**, *4*, 297.

(4) Angelone, T.; Caruso, A.; Rochais, C.; Caputo, A. M.; Cerra, M. C.; Dallemagne, P.; Filice, E.; Genest, D.; Pasqua, T.; Puoci, F.; Saturnino, C.; Sinicropi, M. S.; El-Kashef, H. *Eur. J. Med. Chem.* **2015**, *92*, 672.

(5) Kende, A. S.; Journet, M. *Tetrahedron Lett.* **1995**, *36*, 3087.

(6) For our group's work in phosphonate group chemistry, see: (a) Chaturvedi, A. K.; Rastogi, N. *J. Org. Chem.* **2016**, *81*, 3303. (b) Pramanik, M. M. D.; Rastogi, N. *Org. Biomol. Chem.* **2016**, *14*, 1239. (c) Pramanik, M. M. D.; Chaturvedi, A. K.; Rastogi, N. *Chem. Commun.* **2014**, *50*, 12896. (d) Pramanik, M. M. D.; Kant, R.; Rastogi, N. *Tetrahedron* **2014**, *70*, 5214.

(7) For the influence of phosphonate group on biological activity, see: (a) Shie, J.-J.; Fang, J.-M. *J. Chin. Chem. Soc.* **2014**, *61*, 127. (b) Ballatore, C.; Huryn, D. M.; Smith, A. B., III *ChemMedChem* **2013**, *8*, 385. (c) Mucha, A.; Kafarski, P.; Berlicki, L. *J. Med. Chem.* **2011**, *54*, 5955. (d) Kumar, T. S.; Zhou, S. Y.; Joshi, B. V.; Balasubramanian, R.; Yang, T.; Liang, B. T.; Jacobson, K. A. *J. Med. Chem.* **2010**, *53*, 2562. (e) Cosyn, L.; Van Calenbergh, S.; Joshi, B. V.; Ko, H.; Carter, R. L.; Harden, T. K.; Jacobson, K. A. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3002. (f) Shie, J.-J.; Fang, J.-M.; Wang, S.-Y.; Tsai, K.-C.; Cheng, Y.-S. E.; Yang, A.-S.; Hsiao, S.-C.; Su, C.-Y.; Wong, C.-H. *J. Am. Chem. Soc.* **2007**, *129*, 11892. (g) Schug, K. A.; Lindner, W. *Chem. Rev.* **2005**, *105*, 67.

(8) (a) Ford, A.; Miel, H.; Ring, A.; Slattery, C. N.; Maguire, A. R.; Mckervey, M. A. *Chem. Rev.* **2015**, *115*, 9981. (b) Hashimoto, T.; Maruoka, K. *Bull. Chem. Soc. Jpn.* **2013**, *86*, 1217. (c) Zhang, Y.; Wang, J. *Chem. Commun.* **2009**, 5350. (d) Zhang, Z.; Wang, J. *Tetrahedron* **2008**, *64*, 6577. (e) Regitz, M.; Maas, G. *Diazo Compounds; Properties and Synthesis*; Academic Press: Orlando, 1986. (f) Regitz, M. *The chemistry of Diazonium and Diazo Groups,Vol. 2*; Patai, S., Ed.; Wiley: New York, 1978; p 659. (g) Wulfman, D. S.; Linstrumelle, G.; Cooper, C. F. *The chemistry of Diazonium and Azo Groups*; Interscience: New York, 1978.

(9) Moody, C. J.; Taylor, R. J. *J. Chem. Soc., Perkin Trans. 1* **1989**, 721.

(10) For recent reactions of phthalides, see: (a) Mal, D.; Ghosh, K.; Jana, S. *Org. Lett.* **2015**, *17*, 5800. (b) Karmakar, R.; Pahari, P.; Mal, D. *Chem. Rev.* **2014**, *114*, 6213. (c) Naysmith, B. J.; Brimble, M. A. *Org. Lett.* **2013**, *15*, 2006. (d) Dinda, B. K.; Jana, A. K.; Mal, D. *Chem. Commun.* **2012**, *48*, 3999. (e) Zhong, F.; Luo, J.; Chen, G. − Y.; Dou, X.; Lu, Y. *J. Am. Chem. Soc.* **2012**, *134*, 10222. (f) Mal, D.; Pahari, P. *Chem. Rev.* **2007**, *107*, 1892.

(11) (a) Gilbert, J. C.; Weerasooriya, U. *J. Org. Chem.* **1982**, *47*, 1837. (b) Seyferth, D.; Marmor, R. S.; Hilbert, P. *J. Org. Chem.* **1971**, *36*, 1379. (c) Seyferth, D.; Marmor, R. S. *Tetrahedron Lett.* **1970**, *11*, 2493.

(12) (a) Mullins, R. J. In *Name Reactions in Heterocyclic Chemistry II*; Li, J. J., Ed.; Wiley: New York, 2011; p 327. (b) Zollinger, H. Diazo Chemistry II-Aliphatic. In *Inorganic and Organometallic Compounds*; VCH: Weinheim, 1995; p 11. (c) Regitz, M.; Heydt, H. *In 1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley Interscience: New York, 1984; Chapter 4.

(13) (a) Friscourt, F.; Fahrni, C. J.; Boons, G.-J. *Chem. - Eur. J.* **2015**, *21*, 13996. (b) McGrath, N. A.; Raines, R. T. *Chem. Sci.* **2012**, *3*, 3237. (c) Kumar, R.; Verma, D.; Mobin, S.; Namboothiri, I. N. N. *Org. Lett.* **2012**, *14*, 4070. (d) Lilienkampf, A.; Pieroni, M.; Wan, B.; Wang, Y.; Franzblau, S. G.; Kozikowski, A. P. *J. Med. Chem.* **2010**, *53*, 678. (e) Vuluga, D.; Legros, J.; Crousse, B.; Bonnet-Delpon, D. *Green Chem.* **2009**, *11*, 156. (f) He, S.; Chen, L.; Niu, Y.-N.; Wu, L.-Y.; Liang, Y.-M. *Tetrahedron Lett.* **2009**, *50*, 2443. (g) Krishna, P. R.; Sekhar, E. R.; Mongin, F. *Tetrahedron Lett.* **2008**, *49*, 6768. (h) Gao, D.; Zhai, H.; Parvez, M.; Back, T. G. *J. Org. Chem.* **2008**, *73*, 8057.

(14) Crystal structure of compound **3a** has been deposited at the Cambridge Crystallographic Data Center and allocated the reference no. CCDC 1490176.

(15) For examples of phosphonate group migration, see ref 6b and (a) Shen, C.; Yang, G.; Zhang, W. *Org. Lett.* **2013**, *15*, 5722. (b) Chang, W.-C.; Dey, M.; Liu, P.; Mansoorabadi, S. O.; Moon, S.-J.; Zhao, Z. K.; Drennan, C. L.; Liu, H. W. *Nature* **2013**, *496*, 114. (c) Jardine, A. M.; Vather, S. M.; Modro, T. A. *J. Org. Chem.* **1988**, *53*, 3983. (d) Dhawan, B.; Redmore, D. *J. Org. Chem.* **1986**, *51*, 179. (e) Dhawan, B.; Redmore, D. *J. Org. Chem.* **1984**, *49*, 4018. (f) Melvin, L. S. *Tetrahedron Lett.* **1981**, *22*, 3375. (g) Churi, R. H.; Griffin, C. E. *J. Am. Chem. Soc.* **1966**, *88*, 1824.

(16) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115.

(17) Du, T.; Du, F.; Ning, Y.; Peng, Y. *Org. Lett.* **2015**, *17*, 1308.

(18) (a) Mirabdolbaghi, R.; Dudding, T. *Org. Lett.* **2012**, *14*, 3748. (b) Wang, B.; Chai, X.; Zhu, W.; Wang, T.; Wu, Q. *Chem. Commun.* **2014**, *50*, 14374.

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