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Regioselective Synthesis of 3-Carbo-5-phosphonylpyrazoles through a One-Pot Claisen–Schmidt/1,3-Dipolar Cycloaddition/Oxidation Sequence

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A one-pot reaction involving an aldehyde, a methyl ketone, and the Bestmann–Ohira reagent has been developed for the synthesis of variously substituted 3-carbo-5-phosphonylpyrazoles. Our synthetic methodology features a domino Claisen–Schmidt/1,3-dipolar cycloaddition/oxidation sequence, which leads to the target compounds in excellent yields. We further demonstrated that this unprecedented sequence could also be combined with a copper-catalyzed azide–alkyne cycloaddition in a one-pot, four-step cascade process generating five new bonds and two heterocyclic rings.

Introduction

Dimethyl (1-diazo-2-oxopropyl)phosphonate (**1**; Bestmann–Ohira reagent, BOR) is a valuable reagent that allows a one-carbon chain homologation of an aldehyde into a terminal alkyne under mild reaction conditions. Readily prepared from commercially available precursors, this reagent is the outcome of a story that began in the early 1970s with the discovery by Seyferth and co-workers of dimethyl (diazomethyl)phosphonate (**2**; Figure 1).[1] Over the years, Colvin et al.[2] demonstrated the ability of **2** to transform carbonyl compounds into the corresponding acetylenic derivatives, while Gilbert and Weerasooriya[3] extended the scope of the reaction and studied its mechanism. Nevertheless, **2** was still not easily accessible, requiring five steps from the starting phthalimide, and stability issues prevented many groups from using it. A major breakthrough was made when Ohira found that the anion of **2** could be generated in situ by treatment of **1** under mild basic conditions.[4] A few years later, Bestmann and co-workers examined in more detail the reactivity of **1** and described major improvements in its synthesis.[5] Since then, the so-called Bestmann–Ohira reagent has been used as an efficient alternative to the Corey–Fuchs procedure.[6] The BOR-based homologation of aldehydes has been used on many sensitive substrates, including modified nucleosides and amino acids,[7] and many one-pot procedures rely on its versatility.[8]

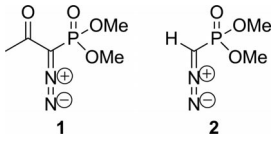

Figure 1. Dimethyl (1-diazo-2-oxopropyl)phosphonate (**1**; BOR) and dimethyl (diazomethyl)phosphonate (**2**).

Recently, the BOR has found new applications in organic synthesis as a cycloaddition partner for the synthesis of phosphonyloxazoles[9] and -pyrazoles.[10] This latter class of compounds is particularly attractive, because appropriately functionalized pyrazoles have emerged as enzyme inhibitors, fungicides, and insecticides.[11] The pyrazole scaffold is also found in best-selling drugs such as Celebrex, Viagra, and Acomplia. In the multitude of existing methods available for the synthesis of pyrazole derivatives, classical approaches are based on either the condensation of hydrazine on 1,3-dicarbonyl compounds or on the cycloaddition of 1,3-dipoles to triple bonds.[12] Due to the decisive role played by the C–P bond in isosteric, biologically active phosphate analogues,[13] the synthesis of phosphonylpyrazoles has attracted considerable attention over the years. Hence, the development of a synthetic route towards 5-phosphonylpyrazoles involving the reaction of the BOR with aryl- or heteroaryl nitroalkenes[10] was welcomed and provided an efficient alternative to the previously reported methodologies, which were often limited by the number of steps and the harsh conditions required.[14]

In this context, we recently described a new multicomponent reaction (MCR) that allowed the regioselective synthesis of phosphonylpyrazoles **3** by combining an aldehyde, a cyano acid derivative, and the BOR (Scheme 1).[15] Based on a domino Knoevenagel condensation/formal 1,3-dipolar

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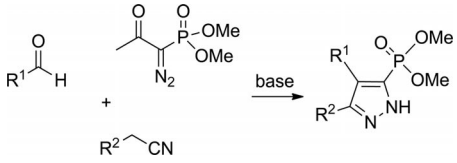
cycloaddition sequence, this process afforded 5-phosphonylpyrazole scaffolds through the formation of two C–C bonds and one C–N bond (Scheme 1). This study provided the first example of an MCR featuring the BOR, thus paving the way for new applications in diversity-oriented synthesis.



Scheme 1. Three-component synthesis of phosphonylpyrazoles.[15]

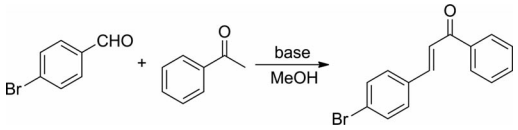
In a continuation of our work, we sought to extend the scope and applications of the BOR to a diverse array of 3-substituted 5-phosphonyl heterocycles. Herein, we wish to report a novel one-pot, sequential, multicomponent, regioselective synthesis of 3-carbo-5-phosphonylpyrazoles based on a domino Claisen–Schmidt/1,3-dipolar cycloaddition/oxidation sequence.

Results and Discussion

Because the Claisen–Schmidt condensation offers an efficient way to synthesize enones under alcoholic alkaline conditions, we envisioned that it would be possible to combine this approach with a 1,3-dipolar cycloaddition in a one-pot sequential process. The significance of the present protocol relies on the possibility of building α,β-unsaturated ketone intermediates starting from a methyl ketone and an aldehyde, and on the ability of these intermediates to act as dipolarophiles in the presence of the BOR. Acetophenone and *p*-bromobenzaldehyde were selected as model substrates to establish optimum experimental conditions for the formation of the corresponding chalcone. Because the dimethyl (diazomethyl)phosphonate anion of **2** is generated under mild reaction conditions ($MeOH/K_2CO_3$), we conducted a base screen; the results are summarized in Table 1. Interestingly, organic bases failed to catalyze the formation of the expected chalcone, whereas inorganic bases gave better results, particularly KOH, which, upon heating at 60 °C in MeOH, afforded the desired compound in 95% yield within 2 h (Table 1, Entry 11). With these results in hand, we next explored the use of the BOR in the conversion of the resulting α,β-unsaturated ketones into the corresponding phosphonylpyrazolines through a cycloaddition reaction. This sequential process is particularly challenging due to the inherent reactivity of the BOR in the presence of aldehydes.

Our initial attempt was carried out with acetophenone and *p*-bromobenzaldehyde. After complete conversion of the starting materials into the corresponding α,β-unsaturated ketone as determined by TLC, the BOR was added to the reaction mixture. Optimum conditions were obtained

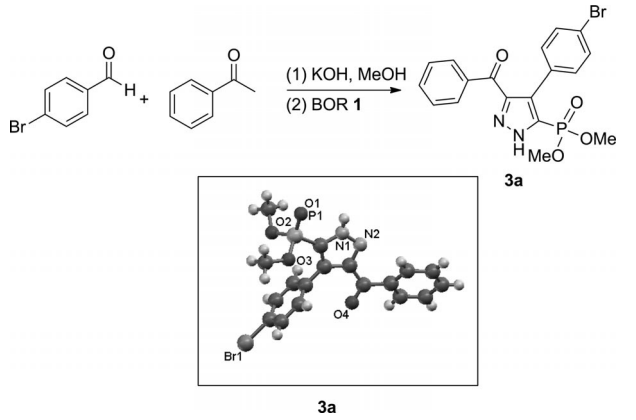
Table 1. Base screening and optimization of the reaction conditions.



Entry	Base	Temp. [°C]	Time [h]	Yield [%][a]
1	piperidine	r.t.	4	–
2	TEA	r.t.	4	–
3	DIEA	r.t.	4	–
4	K_2CO_3	r.t.	4	20
5	KOH	r.t.	4	35
6	piperidine	60	4	–
7	TEA	60	4	–
8	DIEA	60	4	–
9	K_2CO_3	60	4	35
10	NaOH	60	2	90
11	KOH	60	2	95

[a] Isolated yield.

with 2 equiv. of BOR, because it was observed that some decomposition of the BOR might occur over time. Surprisingly, instead of the expected pyrazoline, we observed the exclusive formation of phosphonylpyrazole **3a**. The structure, as well as the regioselectively of the process, was eventually secured by spectroscopic and crystallographic analyses (Scheme 2).[16] This result was unexpected, because the reaction of α,β-unsaturated ketones with diazo compounds usually leads to pyrazolines,[17] which are then readily converted into pyrazoles through an oxidative dehydrogenation in the presence of an oxidizing agent.[18] It is worth noting that in our previously reported Knoevenagel condensation/formal 1,3-dipolar cycloaddition sequence,[15] the aromatization was promoted by the elimination of hydrogen cyanide. In contrast, in the present process, although there is no leaving group, the pyrazoline could not be isolated regardless of whether the reaction was carried out under air or nitrogen. Whereas spontaneous air oxidation of pyrazolines is not frequently encountered in the literature, a few reports indicate that such oxidation might take place depending on the nature of the substituents on the resulting pyrazoles.[19] We thus suspected that oxidation of the phosphonylpyrazoline to the corresponding pyrazole proceeded upon exposure to air during the workup. A control experiment was performed with cyclopentanone and *p*-bromobenzaldyde. This should lead to a bis(pyrazoline), which is not able to be oxidized. Although the bis(α,β-unsaturated ketone) was observed, we were not able to identify any cycloaddition products. An unprecedented one-pot Claisen–Schmidt/1,3-dipolar cycloaddition/oxidation sequence was therefore unveiled. We further demonstrated that this one-pot sequential process compared favorably with the two-step procedure. Indeed, whereas the two-step protocol afforded phosphonylpyrazole **3a** in 70% yield after two purification steps, and required almost 2 d of bench work, the one-pot sequential process generated **3a** with 77% yield in 10 h, purification included.

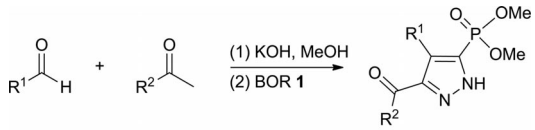


Scheme 2. One-pot access to phosphonylpyrazoles and X-ray structure of **3a**.[16]

With these initial results in hand, we then investigated the scope of this unique one-pot sequence; the results are summarized in Table 2. Interestingly, α,β-unsaturated ketone formation was usually complete within 1–3 h, whereas the cycloaddition at room temperature required 6–12 h unless otherwise specified. A survey of the scope with regards to the aldehyde component revealed that aromatic or heteroaromatic aldehydes were needed to afford the corresponding pyrazoles in good to excellent yields (Table 2). In addition, we noticed significant electronic effects, because faster reactions and higher yields were observed with arenecarbaldehydes bearing electron-withdrawing groups. In contrast, the reactions of aldehydes substituted with electron-donating groups were slightly more sluggish and less efficient (Table 2, Entries 1–5). Similarly, steric effects were found to play a decisive role in the formation of the target phosphonylpyrazoles. Whereas *p*-, *m*-, or *o*-methoxybenzaldehydes reacted with acetophenone to give the corresponding α,β-unsaturated ketone intermediates (TLC monitoring), we observed that after adding **1**, the cycloaddition only took place with the less constrained structures (Table 2, Entries 3 and 4). Indeed, in the case of *o*-methoxybenzaldehyde, the corresponding chalcone was recovered mostly unreacted. This result suggested that hindered α,β-unsaturated ketones are not reactive enough to lead to the expected phosphonylpyrazoles. It is worth noting that the reaction using 2-thiophenecarbaldehyde together with acetophenone also provided good yields of the desired pyrazoles under the optimized reaction conditions (Table 2, Entry 7).

We next examined the scope of the reaction with regard to the methyl ketone component. The electronic properties of the substituents also appeared to be a dominant factor controlling the reactivity. This is not unexpected, because the rate-determining step of the reaction is proportional to the concentration of the enolate anion, which, in turn, should be dependent upon the acidity of the α-proton of the substituted acetophenone. For example, whereas the reaction of *p*-methoxyacetophenone with *p*-bromobenzaldehyde and **1** leads to the formation of phosphonylpyrazole **3h** in good yield (Table 2, Entry 8), we found that *p*-nitroacetophenone was too reactive under these reaction conditions, leading mostly to autocondensation products (data not shown). These results suggest that fine-tuning of the pK_a value of the α-proton is essential. Interestingly, the pyrazole formation reaction also proceeds smoothly with heterocyclic methyl ketones. Nevertheless, as observed with acetophenone, *ortho* substituents are not well tolerated, because, in the presence of 2,4-dichlorobenzaldeyde, the corresponding phosphonylpyrazole **3m** is obtained with only 30% yield (Table 2, Entries 11 and 12). Finally, we demonstrated that sterically hindered aliphatic methyl ketones were also good substrates for this one-pot sequential process (Table 2, Entries 13 and 14).

Table 2. Three-component, sequential synthesis of 3-oxo-5-phosphonylpyrazoles.

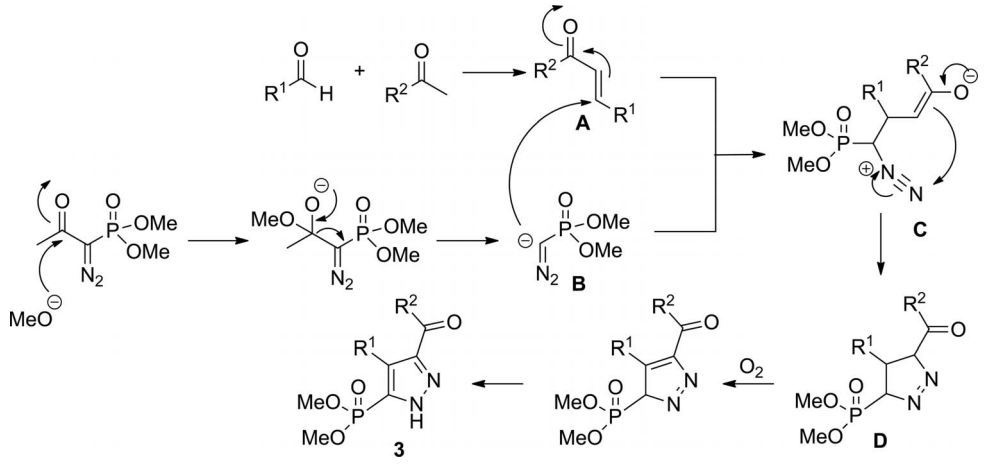


Entry	R^1	R^2	3	Yield [%][a]
1	4-Br-C_6H_4	Ph	**3a**	77
2	Ph	Ph	**3b**	71
3	4-MeO-C_6H_4	Ph	**3c**	67
4	3-MeO-C_6H_4	Ph	**3d**	61
5	4-(HC≡C)-C_6H_4	Ph	**3e**	70
6	4-O_2N-C_6H_4	Ph	**3f**	91
7	2-thiophenyl	Ph	**3g**	70
8	4-Br-C_6H_4	4-MeO-C_6H_4	**3h**	70
9	4-O_2N-C_6H_4	4-MeO-C_6H_4	**3i**	81
10	2-thiophenyl	4-MeO-C_6H_4	**3j**	65
11	4-Br-C_6H_4	*N*-Me-pyrrol-2-yl	**3k**	71
12	2,4-Cl_2-C_6H_3	*N*-Me-pyrrol-2-yl	**3l**	30
13	Ph	*t*Bu	**3m**	65
14	4-O_2N-C_6H_4	*t*Bu	**3n**	65

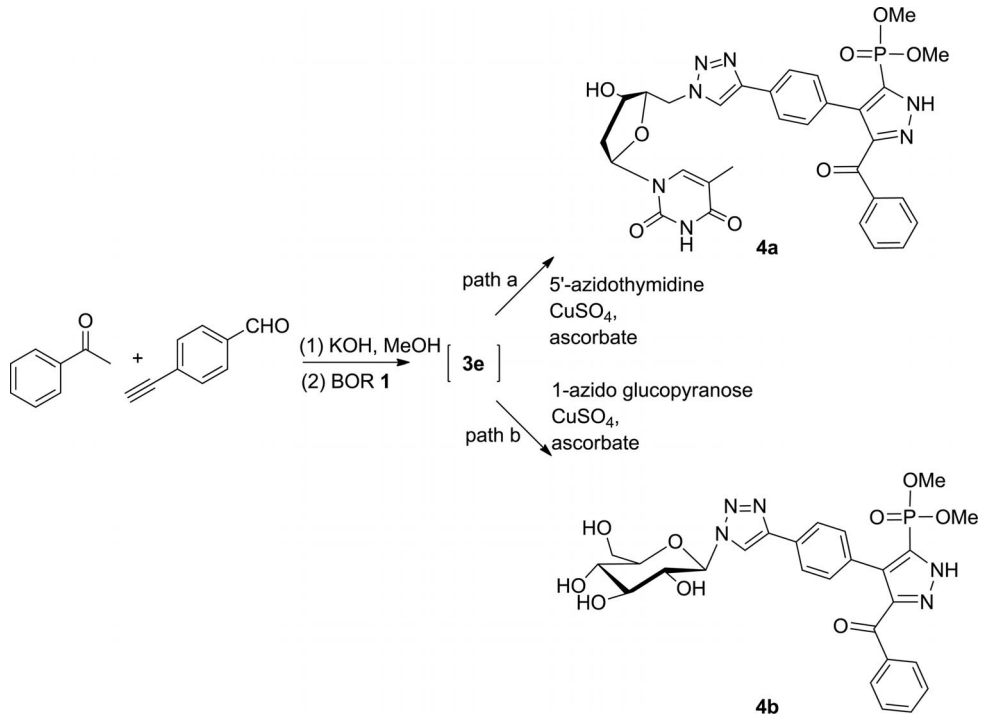
[a] Isolated yield.

On the basis of these results, a plausible mechanism accounting for this novel three-component sequential reaction is devised in Scheme 3. The first step would be the formation of α,β-unsaturated ketone **A**, which would be attacked by the dimethyl (diazomethyl)phosphonate anion **B**. We assume a stepwise cycloaddition based on a Michael-type 1,4-addition leading to intermediate **C**. An intramolecular cyclization would then proceed to afford the highly reactive intermediate pyrazoline **D**, which would then undergo an O_2-promoted oxidative aromatization to furnish, after tautomerization, the pyrazole product **3**.

The prospect of discovering compounds with pharmacological activity prompted us to combine this one-pot sequence of two divergent reaction pathways with click chemistry. As shown in Scheme 4, 4-ethynylbenzaldehyde was sequentially submitted to the optimized reaction conditions. Treatment of the phosphonylpyrazole intermediate **3e** with



Scheme 3. Proposed mechanism for the three-component sequential process.



Scheme 4. One-pot, sequential MCR/CuAAC.

5′-azidothymidine through a copper-catalyzed azide–alkyne 1,3-dipolar cycloaddition (CuAAC) gave the thymidine–pyrazol **4a** with 61% yield and 85% atom economy (Path a).[20] Alternatively, **3e** reacts quickly with 1-azidoglucopyranose, leading to phosphonylpyrazole **4b** with 55% yield and 82% atom economy (Path b). In each case, the cascade sequence generates five new bonds and two heterocyclic rings in a one-pot fashion, thus further demonstrating the versatility of the BOR. Moreover, because chemical processes are expected to maximize the formation of the target products, the BOR is significantly more atom-economical when used as a cycloaddition partner than as a homologation reagent.[21]

Conclusions

We have developed a general and straightforward procedure for the regioselective preparation of 3-carbo-5-phosphonylpyrazoles. Based on an unprecedented Claisen–Schmidt/1,3-dipolar cycloaddition/oxidation sequence, these results broaden the emerging role of the BOR as a 1,3-dipolar precursor in one-pot reactions. Moreover, this sequence has been efficiently coupled to a CuAAC reaction for the rapid synthesis of potential biologically active compounds. Given the importance played by substituted pyrazoles in the pharmaceutical and agrochemical industry, and in light of the considerable challenges faced by re-

searchers to develop sustainable chemical processes, the readily available starting materials, combined with the rapid one-pot assembly of this complex scaffold, should be useful in drug discovery.

Experimental Section

General Remarks: All reactions were conducted in oven-dried glassware. Methanol was distilled from sodium and benzophenone. Dimethyl (oxopropyl)phosphonate was purchased from Alfa Aesar and used as received for the synthesis of the Bestmann–Ohira reagent.[4,5] All other reagents were purchased from local suppliers and used without purification. All reactions were monitored by TLC; visualization was effected with UV and/or by developing in iodine. Chromatography refers to open column chromatography on silica gel (Merck, 40–63 μm). Melting points were recorded with a Bibby Stuart Scientific SMP3 melting point apparatus. NMR spectra were recorded with a Bruker DRX-300 MHz spectrometer at 300 (^{1}H), 75 (^{13}C), and 121 MHz (^{31}P) at 298°K. Chemical shifts are reported in δ units (ppm) relative to the solvent residual peak as internal standard (^{1}H and ^{13}C) and H_3PO_4 as external standard for ^{31}P NMR measurements. High-resolution mass spectra (ESI$^+$) were recorded with a Micromass apparatus.

General Procedure for the Synthesis of Pyrazoles 3a–n: To a solution of aldehyde (0.4 mmol) and ketone (0.8 mmol) in MeOH (5 mL), was added powdered KOH (2 mmol), and the reaction mixture was stirred at 55 °C for 1–3 h. When the starting aldehyde was completely converted into the intermediate chalcone (TLC monitoring), the Bestmann–Ohira reagent (0.8 mmol) diluted with MeOH (1 mL) was added at room temperature, and stirring was continued until completion of the reaction (2–16 h; TLC monitoring). The solvent was then evaporated, and the crude product was dissolved in ethyl acetate (50 mL), washed with saturated ammonium chloride (1 × 20 mL), and brine (1 × 20 mL). The organic layer was dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude residue was finally purified by column chromatography (acetone/CH_2Cl_2, 0–30%) to afford the desired product.

Dimethyl [5-Benzoyl-4-(4-bromophenyl)-1*H*-pyrazol-3-yl]phosphonate (3a): Colorless crystals (133 mg, 77% yield). M.p. 214–216 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.66 (s, 3 H, OCH_3), 3.70 (s, 3 H, OCH_3), 7.22–7.25 (m, 2 H, ArH), 7.34–7.53 (m, 5 H, ArH), 7.95 (d, J = 7.3 Hz, 2 H, ArH) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 53.6, 53.7, 122.6, 128.4, 129.7, 130.6, 131.3, 131.8, 133.4, 137.0, 188.3 ppm. ^{31}P NMR ($CDCl_3$, 121 MHz): δ = 8.73 ppm. HRMS (ESI): calcd. for $C_{18}H_{17}BrN_2O_4P$ [M + H]$^+$ 435.0109; found 435.0103.

Dimethyl (5-Benzoyl-4-phenyl-1*H*-pyrazol-3-yl)phosphonate (3b): Colorless solid (101 mg, 71% yield). M.p. 154–156 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.64 (s, 3 H, OCH_3), 3.68 (s, 3 H, OCH_3), 7.28–7.39 (m, 7 H, ArH), 7.47 (t, J = 7.4 Hz, 1 H, ArH), 7.95 (d, J = 7.4 Hz, 2 H, ArH) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 53.5, 53.6, 128.0, 128.1, 128.2, 130.1, 130.5, 130.6, 130.7, 133.1, 137.1, 188.5 ppm. ^{31}P NMR ($CDCl_3$, 121 MHz): δ = 9.06 ppm. HRMS (ESI): calcd. for $C_{18}H_{18}N_2O_4P$ [M + H]$^+$ 357.1004; found 357.1001.

Dimethyl [5-Benzoyl-4-(4-methoxyphenyl)-1*H*-pyrazol-3-yl]phosphonate (3c): Colorless solid (103 mg, 67% yield). M.p. 187–190 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.66 (s, 3 H, OCH_3), 3.70 (s, 3 H, OCH_3), 3.79 (s, 3 H, Ar-OCH_3), 6.84 (d, J = 8.7 Hz, 2 H, ArH), 7.28–7.38 (m, 4 H, ArH), 7.49 (t, J = 7.4 Hz, 1 H, ArH), 7.95 (d, J = 7.2 Hz, 2 H, ArH) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 53.5, 53.6, 55.4, 113.6, 122.7, 128.2, 130.6, 131.4, 133.1, 137.2, 159.5, 188.7 ppm. ^{31}P NMR ($CDCl_3$, 121 MHz): δ = 9.51 ppm. HRMS (ESI): calcd. for $C_{19}H_{20}N_2O_5P$ [M + H]$^+$ 387.1110; found 387.1106.

Dimethyl [5-Benzoyl-4-(3-methoxyphenyl)-1*H*-pyrazol-3-yl]phosphonate (3d): Colorless solid (94 mg, 61% yield). M.p. 156–158 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.64 (s, 3 H, OCH_3), 3.68 (s, 3 H, OCH_3), 3.72 (s, 3 H, Ar-OCH_3), 6.79–6.82 (m, 1 H, ArH), 6.91–6.93 (m, 2 H, ArH), 7.18 (t, J = 8.1 Hz, 1 H, ArH), 7.32 (t, J = 7.6 Hz, 2 H, ArH), 7.46 (t, J = 7.4 Hz, 1 H, ArH), 7.92 (d, J = 7.5 Hz, 2 H, ArH) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 53.5, 53.6, 55.3, 113.9, 115.6, 122.6, 128.2, 129.0, 130.3, 130.5, 131.9, 133.2, 137.1, 159.1, 188.5 ppm. ^{31}P NMR ($CDCl_3$, 121 MHz): δ = 9.31 ppm. HRMS (ESI): calcd. for $C_{19}H_{20}N_2O_5P$ [M + H]$^+$ 387.1110; found 387.1116.

Dimethyl [5-Benzoyl-4-(4-ethynylphenyl)-1*H*-pyrazol-3-yl]phosphonate (3e): Colorless solid (106 mg, 70% yield). M.p. 196–199 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.08 (s, 1 H, ≡CH), 3.65 (s, 3 H, OCH_3), 3.69 (s, 3 H, OCH_3), 7.30–7.52 (m, 7 H, ArH), 7.94 (d, J = 6.0 Hz, 2 H, ArH) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 53.6, 53.7, 78.1, 83.6, 122.0, 128.4, 128.6, 130.2, 130.6, 131.4, 131.9, 133.4, 137.0, 188.2 ppm. ^{31}P NMR ($CDCl_3$, 121 MHz): δ = 8.76 ppm. HRMS (ESI): calcd. for $C_{20}H_{18}N_2O_4P$ [M + H]$^+$ 381.1004; found 381.1006.

Dimethyl [5-Benzoyl-4-(4-nitrophenyl)-1*H*-pyrazol-3-yl]phosphonate (3f): Yellowish solid (146 mg, 91% yield). M.p. 180–183 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.72 (s, 3 H, OCH_3), 3.75 (s, 3 H, OCH_3), 7.36–7.41 (m, 2 H, ArH), 7.52–7.58 (m, 3 H, ArH), 8.00 (d, J = 7.3 Hz, 2 H, ArH), 8.19 (d, J = 8.8 Hz, 2 H, ArH) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 53.7, 53.8, 123.1, 128.4, 128.7, 130.6, 131.0, 133.6, 136.8, 138.1, 147.5, 188.0 ppm. ^{31}P NMR ($CDCl_3$, 121 MHz): δ = 8.05 ppm. HRMS (ESI): calcd. for $C_{18}H_{17}N_3O_6P$ [M + H]$^+$ 402.0855; found 402.0849.

Dimethyl [5-Benzoyl-4-(thiophen-2-yl)-1*H*-pyrazol-3-ylphosphonate] (3g): Colorless solid (101 mg, 70% yield). M.p. 124–126 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.72 (s, 3 H, OCH_3), 3.75 (s, 3 H, OCH_3), 6.98–7.01 (m, 1 H, ArH), 7.18–7.20 (m, 1 H, ArH), 7.31–7.40 (m, 3 H, ArH), 7.52 (t, J = 7.3 Hz, 1 H, ArH), 7.98 (d, J = 7.2 Hz, 2 H, ArH) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 53.7, 53.8, 122.7, 123.0, 127.0, 127.3, 128.3, 129.5, 130.6, 133.3, 137.1, 188.5 ppm. ^{31}P NMR ($CDCl_3$, 121 MHz): δ = 8.53 ppm. HRMS (ESI): calcd. for $C_{16}H_{16}N_2O_4PS$ [M + H]$^+$ 363.0568; found 363.0566.

Dimethyl [4-(4-Bromophenyl)-5-(4-methoxybenzoyl)-1*H*-pyrazol-3-yl]phosphonate (3h): Colorless solid (130 mg, 70% yield). M.p. 179–180 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.65 (s, 3 H, OCH_3), 3.69 (s, 3 H, OCH_3), 3.80 (s, 3 H, Ar-OCH_3), 6.83 (d, J = 7.6 Hz, 2 H, ArH), 7.24 (s, 2 H, ArH), 7.42 (d, J = 6.9 Hz, 2 H, ArH), 7.96 (d, J = 7.4 Hz, 2 H, ArH) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 53.6, 53.7, 55.7, 113.7, 122.4, 129.0, 129.3, 129.8, 129.9, 131.3, 131.8, 133.1, 147.2, 164.0, 186.8 ppm. ^{31}P NMR ($CDCl_3$, 121 MHz): δ = 8.89 ppm. HRMS (ESI): calcd. for $C_{19}H_{19}BrN_2O_5P$ [M + H]$^+$ 465.0215; found 465.0207.

Dimethyl [5-(4-Methoxybenzoyl)-4-(4-nitrophenyl)-1*H*-pyrazol-3-yl]-phosphonate (3i): Pale-yellow solid (139 mg, 81% yield). M.p. 108–110 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.68 (s, 3 H, OCH_3), 3.72 (s, 3 H, OCH_3), 3.79 (s, 3 H, Ar-OCH_3), 6.84 (d, J = 8.7 Hz, 2 H, ArH), 7.54 (d, J = 8.9 Hz, 2 H, ArH), 7.99 (d, J = 8.7 Hz, 2 H, ArH), 8.15 (d, J = 8.9 Hz, 2 H, ArH) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 53.7, 53.8, 55.6, 113.7, 123.2, 128.0, 128.3, 129.5, 131.0, 133.1, 138.2, 147.4, 186.3 ppm. ^{31}P NMR ($CDCl_3$, 121 MHz): δ = 8.51 ppm. HRMS (ESI): calcd. for $C_{19}H_{19}N_3O_7P$ [M + H]$^+$ 432.0961; found 432.0945.

Dimethyl [5-(4-Methoxybenzoyl)-4-(thiophen-2-yl)-1*H*-pyrazol-3-yl]-phosphonate (3j): Pale-yellow solid (102 mg, 65% yield). M.p. 117–120 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.68 (s, 3 H, OCH_3), 3.72 (s, 3 H, OCH_3), 3.77 (s, 3 H, Ar-OCH_3), 6.82 (d, J = 8.9 Hz, 2 H, ArH), 6.95 (dd, J = 5.1, 3.6 Hz, 1 H, ArH), 7.16 (dd, J = 3.5, 1.1 Hz, 1 H, ArH), 7.26 (dd, J = 5.1, 1.0 Hz, 1 H, ArH), 7.95 (d, J = 8.7 Hz, 2 H, ArH) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 53.6, 53.7, 55.5, 113.6, 122.2, 122.4, 126.9, 127.0, 129.2, 129.8, 130.4, 132.9, 163.9, 186.9 ppm. ^{31}P NMR ($CDCl_3$, 121 MHz): δ = 9.13 ppm. HRMS (ESI): calcd. for $C_{17}H_{18}N_2O_5PS$ $[M + H]^+$ 393.0674; found 393.0665.

Dimethyl [4-(4-Bromophenyl)-5-(1-methyl-1*H*-pyrrol-2-ylcarbonyl)-1*H*-pyrazol-3-yl]phosphonate (3k): Colorless crystalline solid (124 mg, 71% yield). M.p. 172–175 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.65 (s, 3 H, OCH_3), 3.69 (s, 3 H, OCH_3), 3.92 (s, 3 H, NCH_3), 6.09 (dd, J = 2.4, 4.1 Hz, 1 H, ArH), 6.82–6.88 (m, 1 H, ArH), 7.01–7.06 (m, 1 H, ArH), 7.24–7.30 (m, 2 H, ArH), 7.43–7.49 (m, 2 H, ArH) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 37.8, 53.5, 53.6, 108.8, 122.3, 124.4, 128.1, 128.4, 130.1, 130.7, 131.3, 131.7, 132.6, 177.5 ppm. ^{31}P NMR ($CDCl_3$, 121 MHz): δ = 9.20 ppm. HRMS (ESI): calcd. for $C_{17}H_{18}BrN_3O_4P$ $[M + H]^+$ 438.0218; found 438.0219.

Dimethyl [4-(2,4-Dichlorophenyl)-3-(1-methyl-1*H*-pyrrol-2-ylcarbonyl)-1*H*-pyrazol-5-yl]phosphonate (3l): Colorless solid (52 mg, 30% yield). M.p. 186–188 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.68 (d, J = 11.8 Hz, 3 H, OCH_3), 3.75 (d, J = 11.7 Hz, 3 H, OCH_3), 3.92 (s, 3 H, NCH_3), 6.14 (dd, J = 2.4, 4.0 Hz, 1 H, ArH), 6.87–6.88 (m, 1 H, ArH), 7.29–7.36 (m, 3 H, ArH), 7.44 (d, J = 1.8 Hz, 1 H, ArH) ppm. ^{13}C NMR (CDCl3, 75 MHz): δ = 37.7, 53.5, 53.8, 108.7, 124.0, 125.5, 125.7, 126.9, 129.3, 129.6, 130.2, 132.3, 132.7, 134.7, 134.9, 176.8 ppm. ^{31}P NMR ($CDCl_3$, 121 MHz): δ = 8.58 ppm. HRMS (ESI): calcd. for $C_{17}H_{17}Cl_2N_3O_4P$ $[M + H]^+$ 432.0961; found 432.0945.

Dimethyl [4-Phenyl-5-pivaloyl-1*H*-pyrazol-3-yl]phosphonate (3m): Colorless solid (87 mg, 65% yield). M.p. 139–141 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.32 [s, 9 H, $(CH_3)_3C$], 3.60 (s, 3 H, OCH_3), 3.65 (s, 3 H, OCH_3), 7.25–7.37 (m, 5 H, ArH) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 27.3, 45.0, 53.5, 53.6, 127.9, 128.0, 129.9, 130.6, 131.5, 147.6, 147.9, 202.4 ppm. ^{31}P NMR ($CDCl_3$, 121 MHz): δ = 9.09 ppm. HRMS (ESI): calcd. for $C_{16}H_{22}N_2O_4P$ $[M + H]^+$ 337.1317; found 337.1302.

Dimethyl [4-(4-Nitrophenyl)-5-pivaloyl-1*H*-pyrazol-3-yl]phosphonate (3n): Pale-yellow solid (99 mg, 65% yield). M.p. 163–166 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.34 [s, 9 H, $(CH_3)_3C$], 3.67 (s, 3 H, OCH_3), 3.70 (s, 3 H, OCH_3), 7.45 (d, J = 8.7 Hz, 2 H, ArH), 8.22 (d, J = 8.7 Hz, 2 H, ArH) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 27.3, 44.9, 53.6, 53.7, 123.1, 128.7, 128.9, 130.9, 139.1, 147.5, 201.9 ppm. ^{31}P NMR ($CDCl_3$, 121 MHz): δ = 8.42 ppm. HRMS (ESI): calcd. for $C_{16}H_{21}N_3O_6P$ $[M + H]^+$ 382.1168; found 382.1173.

General Procedure for the Synthesis of Pyrazoles 4a–b: 4-Ethynylbenzaldehyde (0.4 mmol) was subjected to the pyrazole synthesis according to the general procedure. When the starting aldehyde was completely converted into the intermediate (ethynylphenyl)pyrazole (TLC monitoring), $CuSO_4$ (0.5 mmol) and sodium ascorbate (0.8 mmol) dissolved in water (1 mL) were poured into the reaction media, followed by the addition of the azido compound (0.4 mmol). After completion of the reaction, the reacting mixture was filtered through a Büchner funnel. The solvent was evaporated, and the crude residue was directly subjected to silica gel column chromatography (CH_2Cl_2/MeOH, 0–20%) to afford the desired product.

Dimethyl (5-Benzoyl-4-{4-[1-(2′,5′-dideoxythymidin-5′-yl)-1*H*-1,2,3-triazol-4-yl]phenyl}-1*H*-pyrazol-3-yl)phosphonate(4a): Colorless solid (158 mg, 61% yield). M.p. 220–223 °C. ^{1}H NMR ([D$_6$]DMSO, 300 MHz): δ = 1.70 [s, 3 H, CH_3(thymine)], 2.14–2.19 (m, 2 H, 2′-H and 2"-H), 3.40–3.43 (m, 2 H, OH and NH), 3.60 (s, 3 H, OCH_3), 3.64 (s, 3 H, OCH_3), 4.12–4.17 (m, 1 H, 4′-H), 4.33–4.34 (m, 1 H, 3′-H), 4.70 (dd, J = 6.5, 14.4 Hz, 1 H, 5′-H), 4.79 (dd, J = 4.5, 14.4 Hz, 1 H, 5′′-H), 6.21 (t, J = 6.9 Hz, 1 H, 1′-H), 7.24 (s, 1 H, 6-H), 7.38–7.47 (m, 4 H, ArH), 7.56–7.60 (m, 1 H, ArH), 7.78–7.86 (m, 4 H, ArH), 8.59 (s, 1 H, $H_{triazole}$), 11.32 (s, 1 H, $NH_{pyrazole}$) ppm. ^{13}C NMR ([D$_6$]DMSO, 75 MHz): δ = 12.0, 38.0, 51.2, 53.1, 53.1, 54.9, 70.6, 83.8, 83.9, 110.0, 122.4, 124.5, 128.3, 129.8, 130.0, 130.5, 133.2, 136.0, 146.1, 150.5, 163.7 ppm. ^{31}P NMR ([D$_6$]DMSO, 121 MHz): δ = 9.31 ppm. HRMS (ESI): calcd. for $C_{30}H_{31}N_7O_8P$ $[M + H]^+$ 648.1972; found 648.1988.

Dimethyl {5-Benzoyl-4-[4-(1-β-D-glucopyranosyl-1*H*-1,2,3-triazol-4-yl)phenyl]-1*H*-pyrazol-3-yl}phosphonate (4b): Colorless solid (129 mg, 55% yield). M.p. 122–124 °C. ^{1}H NMR (MeOD, 300 MHz): δ = 3.54–3.61 (m, 2 H, H_{Gluc}), 3.68–3.77 (m, 1 H, H_{Gluc}), 3.80 (d, J = 3.1 Hz, 3 H, OCH_3), 3.84 (d, J = 3.2 Hz, 3 H, OCH_3), 3.88–3.99 (m, 2 H, H_{Gluc}), 4.28 (dd, J = 3.9, 7.8 Hz, 1 H, H_{Gluc}), 5.66 (d, J = 9.2 Hz, 1 H, H_{Gluc}), 7.33–7.44 (m, 4 H, ArH), 7.53 (t, J = 7.9 Hz, 1 H, ArH), 7.77–7.80 (m, 2 H, ArH), 8.03–8.12 (m, 2 H, ArH), 8.51 (d, J = 1.2 Hz, 1 H, $H_{triazole}$) ppm. ^{13}C NMR (MeOD, 75 MHz): δ = 54.6, 54.7, 62.5, 71.0, 74.2, 78.5, 81.2, 89.8, 121.7, 127.4, 129.2, 129.7, 131.0, 131.2, 133.7, 138.7, 142.4, 142.6, 148.5, 150.3, 150.4, 188.5 ppm. ^{31}P NMR (MeOD, 121 MHz): δ = 8.41 ppm. HRMS (ESI): calcd. for $C_{26}H_{29}N_5O_9P$ $[M + H]^+$ 586.1709; found 586.1683.

Supporting Information (see footnote on the first page of this article): Copies of ^{1}H, ^{13}C, and ^{31}P NMR spectra for all reported compounds.

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[16] CCDC-779600 (**3a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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