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One-Pot, Three-Component Approach to the Synthesis of 3,4,5-Trisubstituted Pyrazoles

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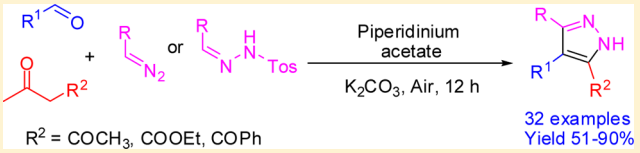
Supporting Information

ABSTRACT: An operationally simple and high yielding protocol for the synthesis of polyfunctional pyrazoles has been developed through one-pot, three-component coupling of aldehydes, 1,3-dicarbonyls, and diazo compounds as well as tosyl hydrazones. The reaction proceeds through a tandem Knoevenagel condensation, 1,3-dipolar cycloaddition, and transition metal-free oxidative aromatization reaction sequence utilizing molecular oxygen as a green oxidant. The scope of the reaction was studied by varying the aldehyde, 1,3-dicarbonyl, and diazo component individually.



INTRODUCTION

Pyrazole is among the most important privileged scaffolds found in synthetic and natural products[1] of medicinal interest. Pyrazole containing molecules possess a wide range of biological activities such as antibacterial,[2] antiviral,[3] anticancer,[4] antidiabetic,[5] antiobesity,[6] anti-inflammatory,[7] estrogen receptor agonistic,[8] cannabinoid receptor antagonistic,[9] etc. Apart from their medicinal values, polysubstituted pyrazoles have been utilized for many other purposes, such as ligands for cross coupling reactions[10] and dyes.[11] Considering the valuable potential of pyrazoles, numerous synthetic methods have been developed over the past decades.

There are two classical methods for the synthesis of pyrazoles, (1) 1,3-dipolar cycloaddition reaction of diazo compounds with alkynes and (2) condensation reaction of 1,3-dicarbonyls with hydrazines.[12] Although these methods provide pyrazoles in acceptable yields, they suffer from their own limitations such as the use of hazardous transition metals and carcinogenic hydrazines, limited substrate scope, and poor regioselectivity. Therefore, pyrazole synthesis was investigated extensively, and several improved synthetic routes were developed.[13−18] Most of these methods rely on the reaction of diazo compounds (isolated or generated in situ from corresponding tosyl hydrazones) with alkenes having an appropriate leaving group (Figure 1, eqs 1−3). Zhang et al. developed a synthetic route for pyrazoles through 1,3-dipolar cycloaddition reaction of in situ generated diazo compounds with vinyl azides.[14] The reaction of diazo compounds with β-nitrostyrenes has been reported for the synthesis of pyrazoles.[15] Furthermore, β-nitrostyrenes have been reacted with diazo compounds containing phosphonate and sulfonyl groups to provide pyrazoles with corresponding functionality.[16] Moreover pyrazoles have been synthesized via the reaction of enol triflates[17] or enaminones (generated in situ from carbonyls and amines)[18] with diazo compounds.

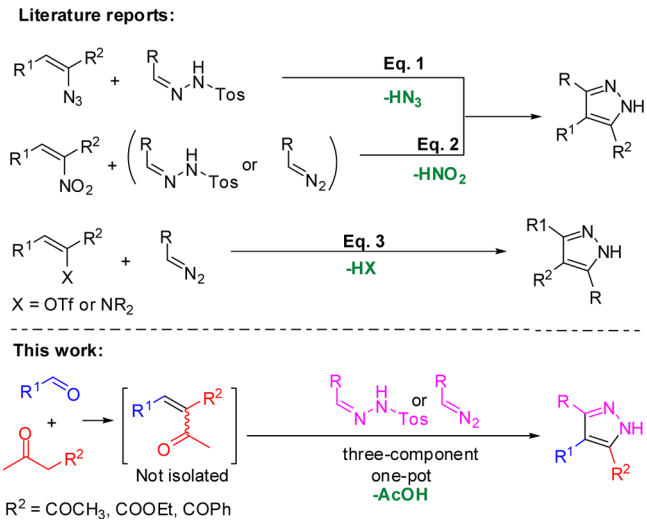


Figure 1. Various approaches for the synthesis of pyrazoles based on the reaction of alkenes with diazo compounds.

Many of the above-mentioned pyrazole synthetic routes require special substrates or reagents (vinyl azides, nitroalkenes, enol triflates, etc.) for the success of the reaction, which

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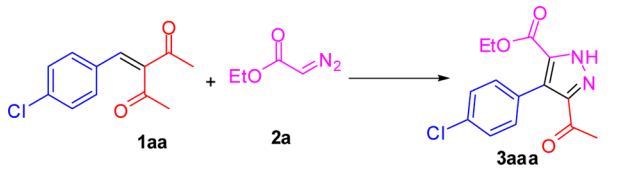
eventually limit the product diversity too. Therefore, a straightforward, operationally simple, and high yielding protocol for polysubstituted pyrazoles from easily available starting materials is highly needed. Presented in this paper are the results of one-pot, three-component coupling of aldehydes, 1,3-dicarbonyls, and diazo compounds or tosyl hydrazones to yield 3,4,5-trisubstituted pyrazoles.

RESULTS AND DISCUSSION

In order to study the feasibility of the cleavage of the acetyl group and aerobic aromatization, we started investigating a 1,3-dipolar cycloaddition reaction of 3-(4-chlorobenzylidene)-pentane-2,4-dione, **1aa**, with ethyl diazoacetate (EDA) **2a** (Table 1). First the reaction was attempted under open

Table 1. Optimization of Pyrazole Formation from 3-(4-Chlorobenzylidene)pentane-2,4-dione, 1aa, with EDA[a]



1aa 2a 3aaa

entry	solvent	temp (°C)	time (h)	yield[b] of **3aaa** (%)
1	toluene	rt	168	*d*
2	toluene	70	24	65
3[c]	toluene	70	24	68
4	CH_3CN	70	24	40
5	THF	reflux	24	55
6	EtOH	70	24	71
7	DMSO	70	12	84

[a]Reaction conditions: **1aa** (1 mmol), **2a** (1.01 mmol), solvent (1 mL), stir in open atmosphere. [b]Isolated yield. [c]Reaction was carried out under oxygen atmosphere. [d]Not determined.

atmospheric conditions in toluene. The reaction was very slow at room temperature, and the substrate remained unreacted even after a week (Table 1, entry 1). The reaction was accelerated at elevated temperature, and heating it at 70 °C for a period of 24 h lead to the complete consumption of the starting materials (Table 1, entry 2). The reaction performed under oxygen atmospheric conditions did not significantly improve the yield of **3aaa** 68% (Table 1, entry 3). Among the several solvents screened, DMSO was found to be the best in the terms of reaction time and yield (Table 1, entry 7). Since no base was needed for the formation of **3aaa**, one of the acetyl groups was presumably cleaved by the traces of water present in the reaction medium. Analyzing ^{1}H NMR spectrum of the crude reaction mixture revealed that acetic acid was a byproduct of the reaction.

After confirming the feasibility of acetyl cleavage and aerobic oxidative aromatization, we sought to develop a one-pot, three-component version of the pyrazole synthesis. Therefore, an equimolar mixture of 4-Cl-benzaldehyde (**4a**), acetyl acetone (**5a**), and EDA (ratio 1/1/1.01) containing 20 mol % of piperidinium acetate was heated at 70 °C in DMSO under open atmosphere for a period of 12 h. After workup and purification of the crude reaction mixture, pyrazole **3aaa** was obtained in 55% yield. Since the yield of pyrazole **3aaa** was not satisfactory, we attempted to carry out the reaction in a one-pot, two-step fashion. Hence an equimolar mixture of 4-Cl-benzaldehyde and acetyl acetone (1 mmol each) was treated with 20 mol % of piperidinium acetate under solvent-free conditions and stirred well. Formation of **1aa** was complete in about 10 min (TLC). Then 1 mL of DMSO and 1.01 mmol of EDA were added to the reaction mixture, and the mixture was heated at 70 °C for 12 h under open atmosphere. We were pleased to achieve a high yield of pyrazole **3aaa** (80%) using the one-pot, two-step strategy. Though the one-pot, multicomponent approach gave a slightly lower yield of the pyrazole **3aaa** (80%) compared with the direct approach (84%), the added advantages of the multicomponent approach make up for the loss in yield.

Further we tried to explore the scope of the one-pot, two-step, three-component approach for pyrazole synthesis by varying aldehyde, 1,3-dicarbonyl, and diazo components separately. The strategy was found to work well with both electron withdrawing and electron donating aromatic aldehydes (Table 2). However, the yields of pyrazoles were lower in case of electron donating aromatic aldehydes (Table 2, entry 10 and 11). This was presumably due to the incomplete conversion of the electron donating aromatic aldehydes to aldehyde−acetyl acetone adducts at the very first step of the reaction. Heteroaromatic aldehydes such as quinoline-4-carboxaldehyde, *N*-ethyl carbazole-3-carboxaldehyde, and furfural gave high yields of pyrazoles (75−82%) using the one-pot, three-component approach (Table 2, entry 12−14).

The one-pot, three-component protocol was successful with aliphatic aldehydes such as *n*-butanal (**4q**) and *n*-hexanal (**4r**) yielding the desired pyrazoles in moderate yields (Table 2, entry 17, 18). However, phenyl acetaldehyde (**4o**) and trimethylacetaldehyde (**4p**) did not lead to the pyrazole formation under our reaction conditions (Table 2, entry 15, 16). With phenyl acetaldehyde, the reaction mixture was too complex for purification. Purification of the reaction mixture derived from trimethylacetaldehyde yielded an oily compound (45%) the structure of which was assigned as **6aa** by analyzing its ^{1}H NMR, ^{13}C NMR, IR, and HRMS spectra (Figure 2). The compound **6aa** seems to be derived from the protonation of EDA followed by its coupling with acetyl acetone. However, it was surprising that compound **6aa** was not formed when a two component coupling of acetyl acetone and EDA was attempted under the same reaction conditions.

We, therefore, planned to synthesize pyrazoles by reacting the purified aliphatic aldehyde−acetyl acetone adducts **1oa** and **1pa** with EDA. The piperidinium acetate catalyzed reaction of phenyl acetaldehyde (**4o**) with acetyl acetone (**5a**) yielded **1oa′** (Scheme 1). Since the C−C double bond and carbonyls are not conjugated in **1oa′**, pyrazole formation did not occur with it. Despite many attempts, the trimethylacetaldehyde−acetyl acetone adduct **1pa** could not be isolated or characterized using either our piperidinium acetate catalyzed protocol or several other acid/base catalyzed methods commonly used for Knoevenagel condensation reactions. Therefore, the synthesis of the corresponding pyrazole could not be attempted from trimethylacetaldehyde.

Next, we started investigating the scope of the 1,3-dicarbonyls in the one-pot, three component pyrazole synthesis. Acetyl acetone (**5a**), benzoyl acetone (**5b**), ethyl acetoacetate (**5c**), and dibenzoyl methane (**5d**) were taken as four different 1,3-dicarbonyls for the study. The one-pot, three-component protocol optimized for acetyl acetone did not work for the rest of the 1,3-dicarbonyls, **5b**, **5c**, and **5d**. In the case of benzoyl acetone (**5b**), the acetyl group was partially cleaved yielding a mixture of pyrazole and dihydropyrazoles, which could not be separated by column chromatography. Under our

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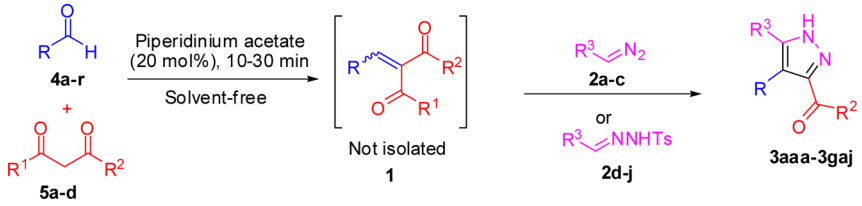
Table 2. Synthesis of Pyrazoles 3aaa−3gaj via One-Pot, Two-Step, Three-Component Reaction of Aldehydes 4a−s, 1,3-Dicarbonyls 5a−d, and Diazo-acetates 2a−c or Tosyl Hydrazones 2d−j



	aldehyde (4)		1,3-dicarbonyl (5)			diazo-ester or tosyl hydrazone (2)			
entry	compd no.	R	compd no.	R^1	R^2	compd no.	R^3	pyrazole (3)	yield[a] of pyrazole (%)
1[b]	**4a**	4-Cl-C_6H_4	**5a**	Me	Me	**2a**	COOEt	**3aaa**	80
2[b]	**4b**	4-Br-C_6H_4	**5a**	Me	Me	**2a**	COOEt	**3baa**	77
3[b]	**4c**	4-CF_3-C_6H_4	**5a**	Me	Me	**2a**	COOEt	**3caa**	80
4[b]	**4d**	4-Cl-3-F-C_6H_4	**5a**	Me	Me	**2a**	COOEt	**3daa**	81
5[b]	**4e**	1-naphthyl	**5a**	Me	Me	**2a**	COOEt	**3eaa**	75
6[b]	**4f**	2-naphthyl	**5a**	Me	Me	**2a**	COOEt	**3faa**	79
7[b]	**4g**	3-O_2N-C_6H_4	**5a**	Me	Me	**2a**	COOEt	**3gaa**	83
8[b]	**4h**	4-O_2N-C_6H_4	**5a**	Me	Me	**2a**	COOEt	**3haa**	85
9[b]	**4i**	4-CN-C_6H_4	**5a**	Me	Me	**2a**	COOEt	**3iaa**	81
10[b]	**4j**	3-4-methylenedioxy-C_6H_3	**5a**	Me	Me	**2a**	COOEt	**3jaa**	65
11[b]	**4k**	4-Me-C_6H_4	**5a**	Me	Me	**2a**	COOEt	**3kaa**	71
12[b]	**4l**	quinolin-4-yl	**5a**	Me	Me	**2a**	COOEt	**3laa**	78
13[b]	**4m**	9-ethyl-9*H*-carbazol-3-yl	**5a**	Me	Me	**2a**	COOEt	**3maa**	82
14[b]	**4n**	2-furyl	**5a**	Me	Me	**2a**	COOEt	**3naa**	75
15[b]	**4o**	$PhCH_2$	**5a**	Me	Me	**2a**	COOEt		*f*
16[b]	**4p**	$(CH_3)_3C$	**5a**	Me	Me	**2a**	COOEt		*f*
17[b]	**4q**	*n*-C_3H_7	**5a**	Me	Me	**2a**	COOEt	**3qaa**	51
18[b]	**4r**	*n*-C_5H_{11}	**5a**	Me	Me	**2a**	COOEt	**3raa**	57
19[c]	**4a**	4-Cl-C_6H_4	**5b**	Me	Ph	**2a**	COOEt	**3aba**	78
20[c]	**4g**	3-O_2N-C_6H_4	**5c**	Me	OEt	**2a**	COOEt	**3gca**	75
21[c]	**4i**	4-CN-C_6H_4	**5c**	Me	OEt	**2a**	COOEt	**3ica**	71
22[c]	**4s**	3-F-C_6H_4	**5d**	Ph	Ph	**2a**	COOEt	**3sda**	80
23[b]	**4g**	3-O_2N-C_6H_4	**5a**	Me	Me	**2b**	COO^{t}Bu	**3gab**	77
24[b]	**4i**	4-CN-C_6H_4	**5a**	Me	Me	**2b**	COO^{t}Bu	**3iab**	78
25[b]	**4g**	3-O_2N-C_6H_4	**5a**	Me	Me	**2c**	COOBn	**3gac**	81
26[b]	**4i**	4-CN-C_6H_4	**5a**	Me	Me	**2c**	COOBn	**3iac**	75
27[d]	**4g**	3-O_2N-C_6H_4	**5a**	Me	Me	**2d**	3-MeO-C_6H_4	**3gad**	90 (85)[e]
28[d]	**4g**	3-O_2N-C_6H_4	**5a**	Me	Me	**2e**	4-O_2N-C_6H_4	**3gae**	85
29[d]	**4i**	4-CN-C_6H_4	**5a**	Me	Me	**2d**	3-MeO-C_6H_4	**3iad**	89
30[d]	**4i**	4-CN-C_6H_4	**5a**	Me	Me	**2f**	3-Cl-4-O_2N-C_6H_3	**3iaf**	90
31[d]	**4i**	4-CN-C_6H_4	**5a**	Me	Me	**2e**	4-O_2N-C_6H_4	**3iae**	88
32[d]	**4k**	4-Me-C_6H_4	**5a**	Me	Me	**2e**	4-O_2N-C_6H_4	**3kae**	85
33[d]	**4q**	*n*-C_3H_7	**5a**	Me	Me	**2g**	3-O_2N-C_6H_4	**4qag**	70
34[d]	**4q**	*n*-C_3H_7	**5a**	Me	Me	**2h**	2-furyl		*f*
35[d]	**4g**	3-O_2N-C_6H_4	**5a**	Me	Me	**2h**	2-furyl		*f*
36[d]	**4g**	3-O_2N-C_6H_4	**5a**	Me	Me	**2i**	2-thienyl		*f*
37[d]	**4g**	3-O_2N-C_6H_4	**5a**	Me	Me	**2j**	9-ethyl-9*H*-carbazol-3-yl	**3gaj**	78
38[d]	**4g**	3-O_2N-C_6H_4	**5a**	Me	Me	**2k**	*n*-C_3H_7		*f*

[a]Isolated yield. [b]Reaction conditions: aldehyde (1 mmol), acetyl acetone (1 mmol), piperidinium acetate (20 mol %), solvent-free, stir, 10−30 min, then diazo-ester (1.01 mmol), DMSO (1 mL), 70 °C, 12 h. [c]Reaction conditions: aldehyde (1 mmol), 1,3-dicarbonyl (1 mmol), piperidinium acetate (20 mol %), solvent-free, stir, 10−30 min, then EDA (1.01 mmol), K_2CO_3 (1.5 mmol), EtOH (10 mL), reflux, 24 h. [d]Reaction conditions: aldehyde (1 mmol), acetyl acetone (1 mmol), piperidinium acetate (20 mol %), solvent-free, stir, 10−30 min, then tosyl hydrazone (1.5 mmol), K_2CO_3 (3.0 mmol), MeOH (10 mL), reflux, 12 h. [e]Yield in parentheses is for gram scale (10 mmol scale) reaction. [f]Not formed.

optimized conditions (Table 2, footnote *b*), the acetyl group of ethyl acetoacetate (**5c**) was not cleaved, and the reaction yielded a mixture of inseparable diastereomers of dihydropyrazole **7gca**. Similarly the benzoyl group of dibenzoyl methane (**5d**) was not cleaved yielding dihydropyrazoles **7ada** and **7hda** (Figure 3). These results indicated that water or piperidinium acetate were incapable of removing the acetyl (or benzoyl) group from the products (**7gca−7hda**). We, therefore, used K_2CO_3 as a base in EtOH for the reaction and achieved high yields (71−80%) of desired pyrazoles **3aba−3sda** under standard conditions (Table 2, entry 19−22). The combination of K_2CO_3 and DMSO was not suitable for the reaction because it hydrolyzed the ester, and the acid thus obtained could not be purified by column chromatography.

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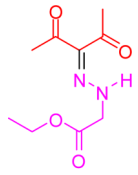
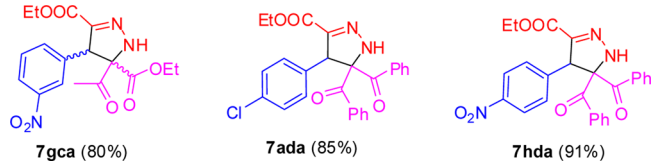


6aa

Figure 2. Chemical structure of compound **6aa**.



7gca (80%) **7ada** (85%) **7hda** (91%)

Figure 3. Chemical structures of dihydropyrazoles derived from three-component coupling of aldehyde, 1,3-dicarbonyl, and EDA under reaction conditions mentioned in footnote *b* of Table 2

Next we tried to explore the scope of the reaction in terms of the diazo component. The three-component reaction of aldehyde, acetyl acetone, and diazo esters such as *tert*-butyl diazoacetate (**2b**) and benzyl diazoacetate (**2c**) proceeded successfully (Table 2, entry 23−26). Following the optimized protocol, a number of pyrazoles **3gab**−**3iac** were synthesized in high yields (75−81%).

Finally the scope of the pyrazole synthesis was studied by taking tosyl hydrazones as an alternative to diazo compounds (Table 2, entry 27−38).[19] The use of tosyl hydrazones in the three-component reaction not only is exciting from a safety point of view but also extends the scope of the work toward a wide range of diazo compounds that are not commercially available. After screening several conditions, we found that refluxing the reaction mixture in MeOH using 3 equiv of K_2CO_3 as a base gave good yields of pyrazoles. Under basic reaction conditions (K_2CO_3) and heating, tosyl hydrazones were converted to corresponding diazo compounds, which reacted with aldehyde−acetyl acetone adducts. A series of substituted pyrazoles **3gad**−**3gaj** were synthesized using the one-pot, three-component protocol in high yields (70−90%). In order to further demonstrate the advantage of this method, a gram scale synthesis of **3gad** was performed under standard conditions. The desired pyrazole **3gad** was obtained in 85% yield, which indicates that there is potential industrial application (Table 2, entry 27). The three-component reaction was successful with aliphatic aldehyde (*n*-butanal) yielding a high yield (70%) of the desired pyrazole **4qag** (Table 2, entry 33). However, the reaction was not successful with tosyl hydrazone derived from aliphatic aldehyde (Table 2, entry 38). The reaction was also not successful with tosyl hydrazones derived from typical heteroaromatic aldehydes such as furfural (Table 2, entries 34 and 35) and 2-thenaldehyde (Table 2, entry 36). This was plausibly due to the fast decomposition of furfural tosyl hydrazones into highly reactive enynyl-ketones reported very recently.[20] Furthermore, high yield (78%) of the desired pyrazole **3gaj** was obtained with tosyl hydrazone derived from 9-ethyl-9*H*-carbazole-3-carbaldehyde as another heteroaromatic aldehyde.

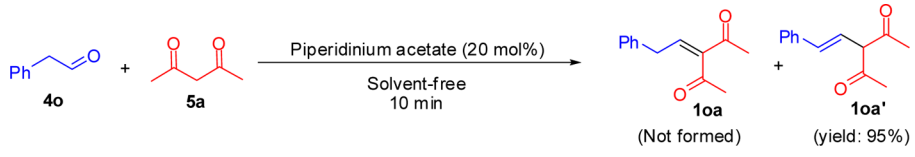
The high regioselectivity observed in our pyrazole synthesis is in accordance with previous literature reports involving 1,3-dipolar cycloaddition reactions of electron deficient olefins with diazo compounds.[15,16] It can be explained by considering atomic orbital coefficients of HOMO (diazo component)−LUMO (alkene) favored interactions expected for these type of 1,3-dipolar cycloaddition reactions. In many ^{1}H NMR spectra of pyrazoles, methyl hydrogen atoms of the acetyl group appeared as broad signals. And in many ^{13}C NMR spectra, C-3 and C-5 carbons of the pyrazole and carbonyl carbon were not resolved from the baseline. It is indeed due to the dynamic tautomeric forms that NH-pyrazole can adopt and is well documented in literature.[17,21]

The structural assignment for pyrazoles **3aaa**−**3gaj** and dihydropyrazoles **7gca**−**7hda** was based on the expected direction of the 1,3-dipolar cycloaddition reaction of diazo compounds with electron deficient alkenes reported in literature.[15,16] In order to give an unambiguous proof for the structural assignments, we attempted HMBC and 2D NOESY for several compounds (**3kaa**, **3gad**, and **3gae**). However, due to the dynamic tautomeric structures of the NH-pyrazoles (Scheme 2), these compounds did not give proper HMBC and 2D NOESY spectra. Furthermore, we attempted to collect single crystal X-ray analysis data for several pyrazoles, but unfortunately the diffraction patterns were not good enough. We, therefore, planned to eliminate the dynamic tautomerism of pyrazoles **3kaa**, **3gad**, and **3gae** by reacting them with ethyl α-bromoacetate (Scheme 2). The structural assignments for these pyrazole derivatives (**9kaaa**, **9gada**, and **9gaea**) were made through their HMBC and 2D NOESY spectra. Finally we succeeded in getting a single crystal X-ray analysis of the pyrazole derivative **9gaea** (Figure 4).

The structural characterization of pyrazole derivatives **9kaaa**, **9gada**, and **9gaea** reveals some interesting information. First, it confirms that the mode of the 1,3-dipolar cycloaddition reaction of diazo-acetates (**2a**−**c**), as well as aryl-diazomethanes derived from tosyl hydrazones (**2d**−**j**) toward aldehyde−acetyl acetone adducts is same. Second, electronic tuning of the tosyl hydrazone component (**3gad** and **3gae**) does not switch the regiochemical outcome of the reaction.

Formation of pyrazoles from the reaction of tosyl hydrazones with aldehyde−acetyl acetone adducts might be imagined to proceed without the intermediacy of corresponding aryl-diazomethanes. Such a stepwise addition−elimination reaction might give either a different regiomer or a mixture of regiomers. To get insight into such a possibility, (*p*-nitrophenyl)-diazomethane[22] was prepared and reacted with 3-nitro-benzaldehyde−acetyl acetone adduct. After workup and purification, we got the same pyrazole **3gae** (92%). This and the regiospecificity of the reaction, therefore, indirectly prove

Scheme 1. Knoevenagel Condensation Reaction of Phenyl Acetaldehyde with Acetyl Acetone



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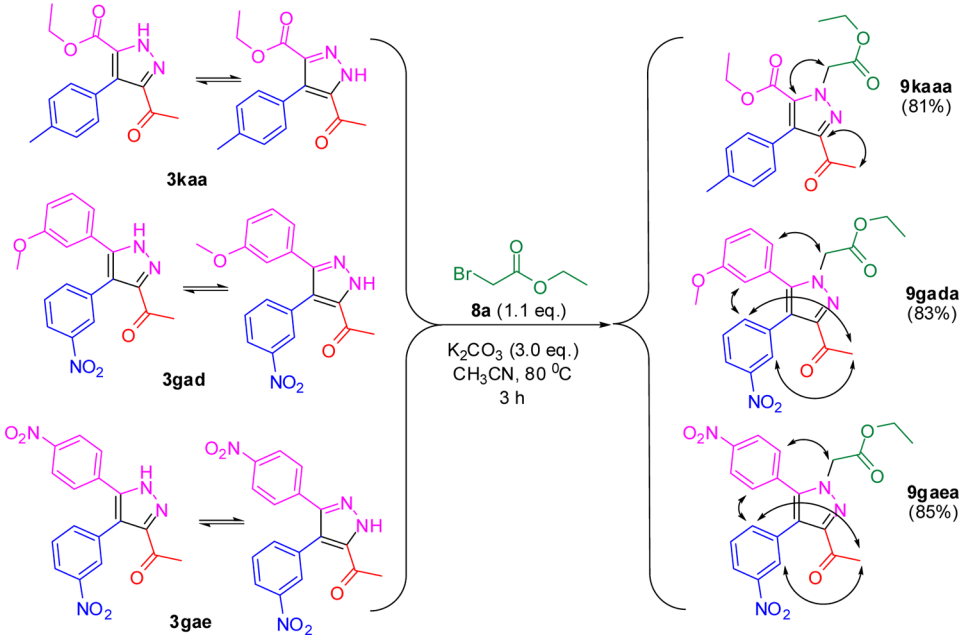
Scheme 2. Eliminating the Possibility of Dynamic Tautomers by Alkylating Pyrazoles 3kaa, 3gad, and 3gae by Ethyl α-Bromoacetate[a]



[a]Key $^{1}H-^{1}H$ (NOESY) correlations of the pyrazoles **9gada** and **9gaea** and $^{1}H-^{13}C$ (HMBC) correlations for the pyrazole **9kaaa** are shown by arrows.

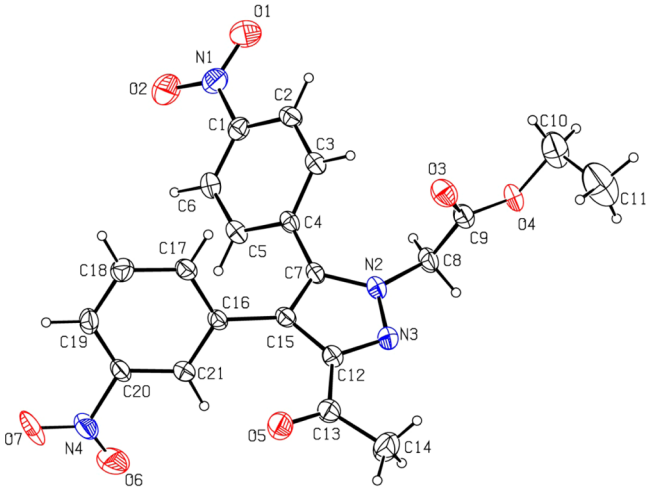


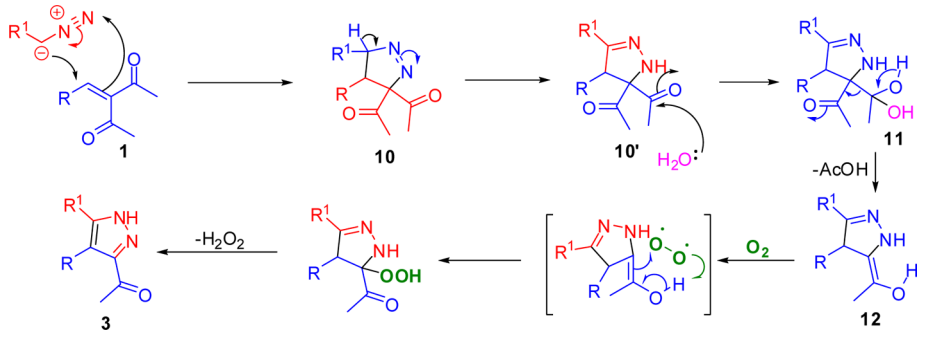
Figure 4. Single crystal X-ray analysis of compound **9gaea** (CCDC ref. No. 1050199; for details, see Supporting Information).

the intermediacy of aryl-diazomethanes in the pyrazole synthesis from tosyl hydrazones.

Formation of the pyrazoles can be explained by a plausible mechanism as depicted in Scheme 3. EDA (or the aryl diazomethane generated *in situ* from tosyl hydrazone) undergoes a 1,3-dipolar cycloaddition reaction with alkene **1** leading to the formation of an intermediate **10**, which isomerizes to **10′**. Next water (or K_2CO_3) attacks the intermediate **10′** leading to the formation of another intermediate **11**, which loses one acetyl group to form a dihydropyrazole **12**. Under aerobic conditions, the dihydropyrazole **12** aromatizes to pyrazole **3**. Attempts to isolate the dihydropyrazoles **12** by performing reactions under nitrogen atmosphere failed. This indicated that dihydropyrazoles **12** were very much prone to aerobic oxidative aromatization when exposed to air.

The proposed mechanism depicted in Scheme 3 raises several questions. First it is reasonable to argue whether the acetyl group is lost from the initially formed five member ring (**10**) or from the α,β-unsaturated compound itself. Second, is the additional acetyl group is necessary for the success of the

Scheme 3. A Plausible Mechanism for the Formation of Pyrazole 3



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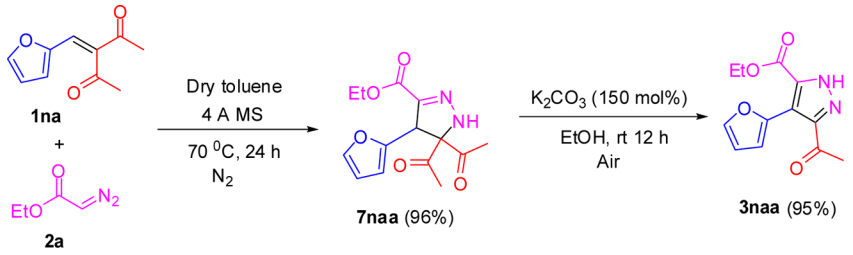
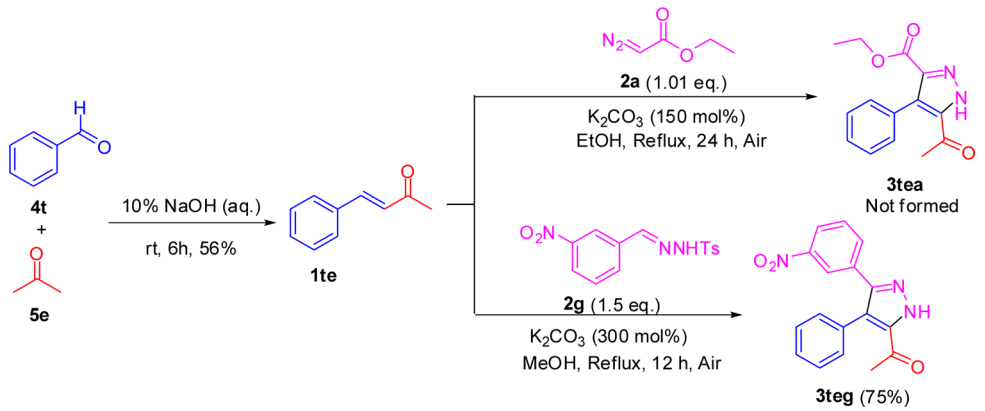
Scheme 4. Control Experiment: Isolation of the Initially Formed Five Member Adduct 7naa and Its Subsequent Conversion to Pyrazole 3naa



Scheme 5. Control Experiment: Preparation of Benzaldehyde−Acetone Adduct 1te and Its Reactions with EDA (2a) and Tosyl Hydrazone (2g)



pyrazole synthesis? In order to address the former query, we subjected the compound **1aa** under three different reaction conditions: (a) piperidinium acetate (20 mol %), DMSO, 70 °C, 24 h; (b) piperidinium acetate (20 mol %), K_2CO_3 (150 mol %), EtOH, reflux, 24 h; (c) piperidinium acetate (20 mol %), K_2CO_3 (300 mol %), MeOH, reflux, 24 h. In all three reaction conditions, **1aa** was almost completely recovered (≥90%). Next, we carried out a control reaction of furfural−acetyl acetone adduct **1na** with EDA in anhydrous toluene under nitrogen atmosphere as depicted in Scheme 4. The initially formed five member adduct **7naa** was isolated, and its treatment with K_2CO_3 (150 mol %) in EtOH yielded the desired pyrazole **3naa** in 95% yield. Similarly the dyhydropyrazoles **7gca**, **7ada**, and **7hda** were also converted to corresponding pyrazoles by treating them with K_2CO_3 (150 mol %) in EtOH. These experiments clearly support that the acetyl group is lost from the initially formed five member ring as depicted in Scheme 3.

In order to address the latter query regarding the necessity of the additional acetyl group, we carried out a few control experiments. First, benzaldehyde−acetone adduct **1te** was prepared and reacted with EDA as well as tosyl hydrazones (Scheme 5). Although formation of the desired pyrazole **1tea** was not observed (TLC and MS analysis) with EDA, the corresponding reaction with tosyl hydrazone gave a high yield of the corresponding pyrazole **3teg** (75%). These results suggest that the additional acetyl group is necessary for the success of pyrazole synthesis at least in the case of diazoacetates. Although we partially succeeded in synthesizing pyrazoles from aldehyde−acetone adduct **1te**, the overall reaction cannot be done in a one-pot fashion. Therefore, we conclude that an additional acetyl group is very much required in order to achieve a general one-pot, three-component synthesis of pyrazoles.

CONCLUSIONS

In conclusion, we have developed a one-pot protocol that affords excellent yields of highly substituted pyrazoles and several dihydropyrazoles from simple and inexpensive starting materials and catalysts, using the advantages of multicomponent reaction. This one-pot process does not require the purification of intermediates and eliminates the use of toxic transition metal based catalysts or oxidants. It generates two C−C and one C−N bonds through a cascade of several individual reactions and is mechanistically novel in that it involves the cleavage of an acetyl group for the pyrazole formation. A series of pyrazoles was synthesized using electron donating or withdrawing aromatic aldehydes, heteromatic aldehydes, 1,3-dicarbonyls, and diazo compounds in high yield. The direct use of tosyl hydrazones further extends the scope of the reaction and avoids handling of sensitive diazo compounds.

EXPERIMENTAL SECTION

General. The reagents, chemicals, and solvents were either purchased from commercial suppliers or prepared and purified by standard techniques. Column chromatography was carried out using silica gel 100−200 mesh. Infrared spectra were recorded using a FT-IR spectrophotometer, and values are reported in cm^{-1}. ^1H and ^{13}C NMR spectra were recorded with 300 and 500 MHz NMR instruments with tertramethylsilane (TMS) as an internal standard. High-resolution mass spectra (ESI-HRMS) were recorded on ESI-QTOP mass spectrometer.

Typical Experimental Procedure of the One-Pot, Three-Component Pyrazole Synthesis (3aaa−3raa). In a 10 mL round-bottom flask, aldehyde (1 mmol), acetyl acetone (1 mmol), and

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piperidinium acetate (0.2 mmol) were mixed, and reaction mixture was shaken under solvent-free conditions. The formation of aldehyde−acetyl acetone adduct was complete in about 10 min (monitored by TLC). Next EDA (1.01 mmol) and 1 mL of DMSO was added, and the reaction mixture was heated at 70 °C under open atmosphere until pyrazole formation was complete. Next the reaction mixture was diluted with dichloromethane (25 mL) and washed with brine (5 mL × 3). The organic layer was dried over anhydrous sodium sulfate and evaporated under reduced pressure to yield a crude reaction product. The crude was purified by silica-gel column chromatography using ethyl acetate−hexane as eluent in increasing polarity to yield the desired pyrazoles **3aaa**−**3raa**.

Ethyl 3-Acetyl-4-(4-chlorophenyl)-1H-pyrazole-5-carboxylate, ***3aaa***. A total of 234 mg (80%) of **3aaa** was obtained as a white solid, R_f = 0.55 (ethyl acetate/*n*-hexane, 3:7), mp 109−110 °C. IR (KBr, cm^{-1}): 3166, 2980, 1718, 1676, 1438, 1214, 1202. ^1H NMR ($CDCl_3$, 500 MHz) δ: 11.42 (bs, 1H), 7.40 (d, J = 8.4 Hz, 2H), 7.29 (d, J = 8.4 Hz, 2H), 4.27 (q, J = 7.2 Hz, 2H), 2.37 (s, 3H), 1.21 (t, J = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 191.8, 160.0, 134.2, 131.4, 129.2, 128.0, 125.5, 61.6, 28.2, 13.9. HRMS (ESI, Orbitrap): calcd for $C_{14}H_{14}ClN_2O_3$ $[M + H]^+$ 293.06930; found 293.06847.

Ethyl 3-Acetyl-4-(4-bromophenyl)-1H-pyrazole-5-carboxylate, ***3baa***. A total of 259 mg (77%) of **3baa** was obtained as a white solid, R_f = 0.51 (ethyl acetate/*n*-hexane, 3:7), mp 111−112 °C. IR (KBr, cm^{-1}): 3165, 2978, 1718, 1675, 1200, 1214. ^1H NMR ($CDCl_3$, 500 MHz) δ: 11.35 (bs, 1H), 7.55 (d, J = 7.8 Hz, 2H), 7.22 (d, J = 8.2 Hz, 2H), 4.27 (q, J = 7.2 Hz, 2H), 2.39 (bs, 3H), 1.21 (t, J = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 187.5, 158.5, 131.7, 131.0, 129.7, 122.5, 61.6, 28.2, 13.9. HRMS (ESI, Orbitrap): calcd for $C_{14}H_{13}BrN_2O_3Na$ $[M + Na]^+$ 359.00072; found 359.00041.

Ethyl 3-Acetyl-4-(4-(trifluoromethyl)phenyl)-1H-pyrazole-5-carboxylate, ***3caa***. A total of 261 mg (80%) of **3caa** was obtained as a white solid, R_f = 0.45 (ethyl acetate/*n*-hexane, 3:7), mp 111−112 °C. IR (KBr, cm^{-1}): 3248, 2988, 1714, 1335, 1221. ^1H NMR ($CDCl_3$, 300 MHz) δ: 11.51 (bs, 1H), 7.68 (d, J = 7.9 Hz, 2H), 7.48 (d, J = 7.9 Hz, 2H), 4.26 (q, J = 7.2 Hz, 2H), 2.41 (s, 3H), 1.19 (t, J = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 192.0, 159.7, 145.8, 136.0, 134.7, 130.5, 130.3 (q, J = 32.7 Hz), 127.3 (q, J = 272.5 Hz), 125.1, 124.6 (q, J = 3.6 Hz), 61.7, 28.0, 13.7. HRMS (ESI, Orbitrap): calcd for $C_{15}H_{14}F_3N_2O_3$ $[M + H]^+$ 327.09565; found 327.09596.

Ethyl 3-Acetyl-4-(4-chloro-3-fluorophenyl)-1H-pyrazole-5-carboxylate, ***3daa***. A total of 252 mg (81%) of **3daa** was obtained as a white solid, R_f = 0.35 (ethyl acetate/*n*-hexane, 3:7), mp 128−130 °C. IR (KBr, cm^{-1}): 3224, 1713, 1694, 1439, 1218. ^1H NMR ($CDCl_3$, 500 MHz) δ: 11.38 (bs, 1H), 7.42 (t, J = 7.9 Hz, 1H), 7.17 (dd, J = 1.8, 9.6 Hz, 1H), 7.07 (d, J = 8.2 Hz, 1H), 4.28 (q, J = 7.2 Hz, 2H), 2.44 (s, 3H), 1.22 (t, J = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 192.0, 159.5, 158.3 (d, J = 247.9 Hz), 131.1(d, J = 7.2 Hz), 129.8, 126.8 (d, J = 2.7 Hz), 124.2, 120.9 (d, J = 17.3 Hz), 118.7 (d, J = 21.7 Hz), 61.8, 28.0, 13.8. HRMS (ESI, Orbitrap): calcd for $C_{14}H_{13}ClFN_2O_3$ $[M + H]^+$ 311.05987; found 311.05984.

Ethyl 3-Acetyl-4-(naphthalen-1-yl)-1H-pyrazole-5-carboxylate, ***3eaa***. A total of 231 mg (75%) of **3eaa** was obtained as a white solid, R_f = 0.48 (ethyl acetate/*n*-hexane, 3:7), mp 103−104 °C. IR (KBr, cm^{-1}): 3219, 1730, 1682, 1440, 1235. ^1H NMR ($CDCl_3$, 300 MHz) δ: 11.70 (bs, 1H), 7.93 (t, J = 7.5 Hz, 2H), 7.57−7.40 (m, 5H), 4.05 (q, J = 7.2 Hz, 2H), 2.00 (s, 3H), 0.83 (t, J = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 190.4, 160.6, 133.4, 132.5, 129.0, 128.8, 128.4, 127.7, 126.4, 125.9, 125.1, 125.0, 124.6, 61.0, 27.8, 13.4. HRMS (ESI, Orbitrap): calcd for $C_{18}H_{17}N_2O_3$ $[M + H]^+$ 309.12392; found 309.12316.

Ethyl 3-Acetyl-4-(naphthalen-2-yl)-1H-pyrazole-5-carboxylate, ***3faa***. A total of 243 mg (79%) of **3faa** was obtained as a white solid, R_f = 0.51 (ethyl acetate/*n*-hexane, 3:7), mp 103−104 °C. IR (KBr, cm^{-1}): 3248, 2982, 1706, 1690, 1423, 1216. ^1H NMR ($CDCl_3$, 500 MHz) δ: 11.44 (bs, 1H), 7.94−7.87 (m, 2H), 7.84−7.80 (m, 2H), 7.53−7.48 (m, 2H), 7.45 (dd, J = 1.4, 8.4 Hz, 1H), 4.22 (q, J = 7.2 Hz, 2H), 2.27 (s, 3H), 1.10 (t, J = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 191.4, 160.5, 132.9, 132.8, 129.3, 128.2, 128.0, 127.8, 127.7, 127.4, 126.8, 126.4, 126.3, 61.3, 28.3, 13.8. HRMS (ESI, Orbitrap): calcd for $C_{18}H_{17}N_2O_3$ $[M + H]^+$ 309.12392; found 309.12302.

Ethyl 3-Acetyl-4-(3-nitrophenyl)-1H-pyrazole-5-carboxylate, ***3gaa***. A total of 252 mg (83%) of **3gaa** was obtained as a white solid, R_f = 0.35 (ethyl acetate/*n*-hexane, 3:7), mp 125−126 °C. IR (KBr, cm^{-1}): 3267, 2996, 1689, 1528, 1349, 1228. ^1H NMR ($CDCl_3$, 500 MHz) δ: 11.65 (bs, 1H), 8.27 (d, J = 8.4 Hz, 1H), 8.24 (s, 1H), 7.70 (d, J = 7.6 Hz, 1H), 7.60 (t, J = 7.9 Hz, 1H), 4.27 (q, J = 7.2 Hz, 2H), 2.53 (s, 3H), 1.17 (t, J = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 192.8, 159.2, 147.6, 136.5, 132.4, 128.4, 125.8, 123.8, 122.9, 61.9, 27.8, 13.7. HRMS (ESI, Orbitrap): calcd for $C_{14}H_{13}N_3NaO_5$ $[M + Na]^+$ 326.07529; found 326.07549.

Ethyl 3-Acetyl-4-(4-nitrophenyl)-1H-pyrazole-5-carboxylate, ***3haa***. A total of 258 mg (85%) of **3haa** was obtained as a white solid, R_f = 0.34 (ethyl acetate/*n*-hexane, 3:7), mp 141−142 °C. IR (KBr, cm^{-1}): 3161, 2979, 1721, 1677, 1603, 1517, 1346, 1214. ^1H NMR ($CDCl_3$, 300 MHz) δ: 11.44 (bs, 1H), 8.29 (d, J = 8.3 Hz, 2H), 7.53 (d, J = 8.3 Hz, 2H), 4.28 (q, J = 7.3 Hz, 2H), 2.50 (s, 3H), 1.21 (t, J = 7.3 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 192.6, 159.2, 147.5, 137.9, 131.2, 124.2, 122.7, 61.9, 27.8, 13.8. HRMS (ESI, Orbitrap): calcd for $C_{14}H_{14}N_3O_5$ $[M + H]^+$ 304.09335; found 304.09291.

Ethyl 3-Acetyl-4-(4-cyanophenyl)-1H-pyrazole-5-carboxylate, ***3iaa***. A total of 229 mg (81%) of **3iaa** was obtained as a white solid, R_f = 0.40 (ethyl acetate/*n*-hexane, 3:7), mp 158−160 °C. IR (KBr, cm^{-1}): 3224, 2924, 2230, 1731, 1693, 1440, 1227. ^1H NMR ($CDCl_3$, 500 MHz) δ: 11.84 (bs, 1H), 7.71 (d, J = 8.4 Hz, 2H), 7.47 (d, J = 8.4 Hz, 2H), 4.27 (q, J = 7.2 Hz, 2H), 2.49 (s, 3H), 1.18 (t, J = 7.3 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 192.5, 159.3, 146.5, 136.0, 134.8, 131.3, 130.9, 124.5, 118.7, 111.6, 61.8, 27.8, 13.7. HRMS (ESI, Orbitrap): calcd for $C_{15}H_{14}N_3O_3$ $[M + H]^+$ 284.10352; found 284.10226.

Ethyl 3-Acetyl-4-(benzo[d][1,3]dioxol-5-yl)-1H-pyrazole-5-carboxylate, ***3jaa***. A total of 196 mg (65%) of **3jaa** was obtained as a white solid, R_f = 0.30 (ethyl acetate/*n*-hexane, 3:7), mp 118−119 °C. IR (KBr, cm^{-1}): 3198, 2922, 1715, 1693, 1508, 1418, 1219. ^1H NMR ($CDCl_3$, 500 MHz) δ: 11.48 (bs, 1H), 6.89 (d, J = 7.9 Hz, 1H), 6.83 (s, 1H), 6.81 (d, J = 7.9 Hz, 1H), 6.04 (s, 2H), 4.30 (q, J = 7.2 Hz, 2H), 2.34 (s, 3H), 1.26 (t, J = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 191.3, 160.4, 147.6, 147.2, 126.5, 124.0, 123.7, 110.6, 107.0, 101.2, 61.3, 28.2, 13.9. HRMS (ESI, Orbitrap): calcd for $C_{15}H_{15}N_2O_5$ $[M + H]^+$ 303.09810; found 303.09823.

Ethyl 3-Acetyl-4-p-tolyl-1H-pyrazole-5-carboxylate, ***3kaa***. A total of 193 mg (71%) of **3kaa** was obtained as a light green oil, R_f = 0.45 (ethyl acetate/*n*-hexane, 3:7). IR (KBr, cm^{-1}): 3274, 2926, 1718, 1440, 1215. ^1H NMR ($CDCl_3$, 300 MHz) δ: 11.24 (bs, 1H), 7.25−7.20 (m, 4H), 4.25 (q, J = 7.2 Hz, 2H), 2.41 (s, 3H), 2.25 (s, 3H), 1.21 (t, J = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 191.2, 160.5, 143.5, 138.6, 138.0, 129.8, 128.6, 127.6, 127.1, 61.2, 28.3, 21.3, 13.9. HRMS (ESI, Orbitrap): calcd for $C_{15}H_{17}N_2O_3$ $[M + H]^+$ 273.12392; found 273.12422.

Ethyl 3-Acetyl-4-(quinolin-4-yl)-1H-pyrazole-5-carboxylate, ***3laa***. A total of 241 mg (78%) of **3laa** was obtained as a white solid, R_f = 0.32 (ethyl acetate/*n*-hexane, 3:7), mp 250−251 °C. IR (KBr, cm^{-1}): 3424, 1722, 1692, 1599, 1206. ^1H NMR ($CDCl_3$ + DMSO-d_6, 300 MHz) δ: 14.50 (bs, 1H), 8.94 (d, J = 4.5 Hz, 1H), 8.17 (d, J = 8.3 Hz, 1H), 7.72−7.67 (m, 1H), 7.47−7.40 (m, 2H), 7.31 (d, J = 4.5 Hz, 1H), 3.99 (q, J = 7.2 Hz, 2H), 2.44 (s, 3H), 0.73 (t, J = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$ + DMSO-d_6, 125 MHz) δ: 190.4, 159.5, 148.5, 146.9, 139.2, 130.2, 129.7, 128.6, 128.3, 126.9, 125.6, 121.4, 119.9, 119.3, 60.0, 26.6, 12.4. HRMS (ESI, Orbitrap): calcd for $C_{17}H_{16}N_3O_3$ $[M + H]^+$ 310.1192; found 310.1194.

Ethyl 3-Acetyl-4-(9-ethyl-9H-carbazol-3-yl)-1H-pyrazole-5-carboxylate, ***3maa***. A total of 308 mg (82%) of **3maa** was obtained as a white solid, R_f = 0.50 (ethyl acetate/*n*-hexane, 3:7), mp 172−173 °C. IR (KBr, cm^{-1}): 3247, 3049, 2974, 1712, 1683, 1443, 1231, 1207. ^1H NMR ($CDCl_3$, 500 MHz) δ: 8.07 (d, J = 8.1 Hz, 1H), 8.06 (s, 1H), 7.52−7.40 (m, 4H), 7.23 (t, J = 7.8 Hz, 1H), 4.42 (q, J = 7.2 Hz, 2H), 4.23 (q, J = 7.2 Hz, 2H), 2.84 (bs, 1H), 2.21 (s, 3H), 1.48 (t, J = 7.2 Hz, 3H), 1.14 (t, J = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 191.3, 160.9, 140.2, 139.7, 128.0, 127.7, 125.8, 122.7, 122.5, 122.1,

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120.7, 120.5, 118.9, 108.5, 107.8, 61.1, 37.7, 28.4, 13.9, 13.8. HRMS (ESI, Orbitrap): calcd for $C_{22}H_{22}N_3O_3$ $[M + H]^+$ 376.16612; found 376.16634.

Ethyl 3-Acetyl-4-(furan-2-yl)-1H-pyrazole-5-carboxylate, ***3naa****.* A total of 186 mg (75%) of **3naa** was obtained as a pale yellow oil, R_f = 0.43 (ethyl acetate/*n*-hexane, 3:7). IR (neat, cm^{-1}): 3247, 2983, 1727, 1694, 1441, 1229, 1211. ^1H NMR ($CDCl_3$, 500 MHz) δ: 11.70 (bs, 1H), 7.56 (d, J = 1.2 Hz, 1H), 6.76 (d, J = 3.4 Hz, 1H), 6.56−6.54 (m, 1H), 4.36 (q, J = 7.2 Hz, 2H), 2.44 (s, 3H), 1.32 (t, J = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 191.4, 160.0, 144.9, 142.8, 142.6, 137.9, 115.5, 112.5, 111.3, 61.6, 27.9, 13.9. HRMS (ESI, Orbitrap): calcd for $C_{12}H_{13}N_2O_4$ $[M + H]^+$ 249.08753; found 249.08781.

Ethyl 5-Acetyl-4-propyl-1H-pyrazole-3-carboxylate, ***3qaa****.* A total of 114 mg (51%) of **3qaa** was obtained as a pale oil, R_f = 0.50 (ethyl acetate/*n*-hexane, 3:7). IR (neat, cm^{-1}): 3268, 2928, 2869, 1723, 1688, 1455, 1208. ^1H NMR ($CDCl_3$, 300 MHz) δ: 12.07 (bs, 1H), 4.42 (q, J = 7.2 Hz, 2H), 3.05 (t, J = 7.4 Hz, 2H), 2.64 (s, 3H), 1.62−1.54 (m, 2H), 1.41 (t, J = 7.2 Hz, 3H), 0.94 (t, J = 7.4 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 194.7, 160.1, 148.5, 132.9, 128.4, 61.4, 27.7, 25.3, 23.8, 14.1, 13.8. HRMS (ESI, Orbitrap): calcd for $C_{11}H_{17}N_2O_3$ $[M + H]^+$ 225.1239; found 225.1257.

Ethyl 5-Acetyl-4-pentyl-1H-pyrazole-3-carboxylate, ***3raa****.* A total of 143 mg (57%) of **3raa** was obtained as a pale oil, R_f = 0.35 (ethyl acetate/*n*-hexane, 3:7). IR (neat, cm^{-1}): 3267, 2957, 1722, 1686, 1538, 1224. ^1H NMR ($CDCl_3$, 500 MHz) δ: 10.77 (bs, 1H), 4.42 (q, J = 7.2 Hz, 2H), 3.04 (t, J = 7.8 Hz, 2H), 2.60 (s, 3H), 1.41 (t, J = 7.2 Hz, 3H), 1.36−1.29 (m, 6H), 0.89 (t, J = 7.3 Hz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 194.6, 160.1, 128.8, 61.4, 31.8, 30.3, 27.7, 23.5, 22.4, 14.2, 14.9. HRMS (ESI, Orbitrap): calcd for $C_{13}H_{21}N_2O_3$ $[M + H]^+$ 253.1552; found 253.1561.

Experimental Procedure of the Synthesis of Compound 6aa. The typical one-pot, three-component synthetic protocol used for the pyrazoles **3aaa**−**3raa** was also used for the synthesis of compound **6aa**. Trimethylacetaldehyde was used as the aldehyde component, EDA as the diazo component, and acetyl acetone as 1,3-dicarbonyl component.

Ethyl 2-(2-(2,4-Dioxopentan-3-ylidene)hydrazinyl)acetate, ***6aa****.* A total of 96 mg (45%) of **6aa** was obtained as a red colored oil, R_f = 0.45 (ethyl acetate/*n*-hexane, 3:7). IR (neat, cm^{-1}): 3449, 2981, 2933, 1748, 1672, 1629, 1510, 1361, 1207. ^1H NMR ($CDCl_3$, 500 MHz) δ: 13.23 (bs, 1H), 4.39 (d, J = 4.7 Hz, 2H), 4.27 (q, J = 7.2 Hz, 2H), 2.53 (s, 3H), 2.32 (s, 3H), 1.32 (t, J = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 197.1, 196.9, 168.1, 134.2, 61.8, 54.1, 31.3, 26.2, 14.1. HRMS (ESI, Orbitrap): calcd for $C_9H_{15}N_2O_4$ $[M + H]^+$ 215.1032; found 215.1032.

Experimental Procedure of the Synthesis of Phenyl Acetaldehyde−Acetyl Acetone Adduct (1oa′). In a 10 mL round-bottom flask, phenyl acetaldehyde (1 mmol), acetyl acetone (1 mmol), and piperidinium acetate (0.2 mmol) were mixed, and the reaction mixture was shaken under solvent-free conditions. After the formation of the aldehyde−acetyl acetone adduct was complete (TLC), the reaction mixture was directly purified by silica-gel column chromatography using ethyl acetate−hexane as eluent in increasing polarity to yield the **1oa′**.

A total of 192 mg (95%) of **1oa′** was obtained as a pale yellow oil, R_f = 0.55 (ethyl acetate/*n*-hexane, 3:7), IR (neat, cm^{-1}): 3423, 3061, 2926, 1709, 1601, 1413, 1204. ^1H NMR ($CDCl_3$, 500 MHz) δ: 7.43 (dd, J = 1.3, 7.5 Hz, 2H), 7.35 (t, J = 7.5 Hz, 2H), 7.27 (tt, J = 1.2, 7.3 Hz, 1H), 6.76 (d, J = 16.2 Hz, 1H), 6.43 (d, J = 16.2 Hz, 1H), 2.22 (s, 6H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 191.1, 137.0, 134.2, 128.6, 127.6, 126.0, 122.7, 111.3, 24.2. HRMS (ESI, Orbitrap): calcd for $C_{13}H_{13}NaO_2$ $[M + Na]^+$ 224.08132; found 224.08015.

Typical Experimental Procedure of the One-Pot, Three-Component Dihydropyrazole Synthesis (7gca−7hda). The protocol used for the synthesis of pyrazoles **3aaa**−**3raa** was used for the synthesis of dihydropyrazoles **7gca**−**7hda**.

Diethyl 5-Acetyl-4-(3-nitrophenyl)-4,5-dihydro-1H-pyrazole-3,5-dicarboxylate, ***7gca****.* A total of 302 mg (80%) of **7gca** (mixture of inseparable diastereomers in 1:5 ratio) was obtained as an yellow oil, R_f = 0.34 (ethyl acetate/*n*-hexane, 3:7). IR (KBr, cm^{-1}): 3340, 2984, 1724, 1532, 1350, 1230. ^1H NMR ($CDCl_3$, 500 MHz) of the major diastereomer δ: 8.16 (dd, J = 1.9, 9.3 Hz, 1H), 8.06 (s, 1H), 7.54−7.44 (m, 2H), 7.19 (s, 1H), 5.37 (d, J = 1.3 Hz, 1H), 4.22−4.10 (m, 4H); 3.84−3.48 (m, 1H) 3.70−3.63 (m, 1H), 2.32 (s, 3H), 1.21 (t, J = 7.2 Hz, 3H), 0.78 (t, J = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 199.3, 196.7, 167.9, 166.4, 160.5, 148.2, 144.0, 137.7, 136.4, 134.5, 130.1, 129.6, 123.6, 122.9, 85.6, 63.7, 62.8, 61.5, 54.9, 53.5, 28.0, 25.0, 13.8, 13.3. HRMS (ESI, Orbitrap): calcd for $C_{17}H_{20}N_3O_7$ $[M + H]^+$ 378.13013; found 378.13112.

Ethyl 5,5-Dibenzoyl-4-(4-chlorophenyl)-4,5-dihydro-1H-pyrazole-3-carboxylate, ***7ada****.* A total of 339 mg (85%) of **7ada** was obtained as a white solid, R_f = 0.50 (ethyl acetate/*n*-hexane, 3:7), mp 160−161 °C. IR (KBr, cm^{-1}): 3350, 1682, 1668, 1595, 1230. ^1H NMR ($CDCl_3$, 500 MHz) δ: 7.84 (dd, J = 1.0, 8.4 Hz, 2H), 7.62 (dd, J = 1.0, 8.4 Hz, 2H), 7.50 (tt, J = 1.0, 7.5 Hz, 1H), 7.41−7.36 (m, 3H), 7.30 (bs, 1H), 7.22 (t, J = 8.4 Hz, 2H), 7.00 (d, J = 8.5 Hz, 2H), 6.92 (d, J = 8.5 Hz, 2H), 5.90 (d, J = 1.2 Hz, 1H), 4.22−4.10 (m, 2H), 1.21 (t, J = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 193.9, 190.3, 160.8, 146.0, 134.7, 134.2, 134.1, 133.8, 132.7, 130.8, 129.3, 129.1, 129.0, 128.4, 88.4, 61.4, 55.3, 13.9. HRMS (ESI, Orbitrap): calcd for $C_{26}H_{22}ClN_2O_4$ $[M + H]^+$ 461.12681; found 461.12763.

Ethyl 5,5-Dibenzoyl-4-(4-nitrophenyl)-4,5-dihydro-1H-pyrazole-3-carboxylate, ***7hda****.* A total of 372 mg (91%) of **7hda** was obtained as a white solid, R_f = 0.40 (ethyl acetate/*n*-hexane, 3:7), mp 161−162 °C. IR (KBr, cm^{-1}): 3327, 1679, 1596, 1526, 1350, 1232. ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.87 (d, J = 8.9 Hz, 2H), 7.83 (d, J 7.7 Hz, 2H), 7.62 (d, J = 7.6 Hz, 2H), 7.53 (t, J = 7.4 Hz, 1H), 7.43−7.38 (m, 4H), 7.25−7.16 (m, 4H), 6.01 (s, 1H), 4.24−4.07 (m, 2H), 1.22 (t, J = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 193.5, 189.8, 160.6, 147.2, 144.9, 141.7, 134.4, 134.0, 133.8, 130.4, 129.3, 129.2, 129.0, 128.6, 123.3, 88.8, 61.6, 55.3, 13.9. HRMS (ESI, Orbitrap): calcd for $C_{26}H_{22}N_3O_6$ $[M + H]^+$ 472.15086; found 472.15069.

Typical Experimental Procedure of the One-Pot, Three-Component Pyrazole Synthesis (3aba−3sda). In a 25 mL round-bottom flask, aldehyde (1 mmol), 1,3-dicarbonyl compound (1 mmol), and piperidinium acetate (0.2 mmol) were mixed, and the reaction mixture was shaken under solvent-free conditions. The formation of aldehyde−1,3-dicarbonyl adduct was complete in about 10−30 min (monitored by TLC). Next EDA (1.01 mmol), K_2CO_3 (1.5 mmol), and 10 mL of EtOH was added, and the reaction mixture was refluxed in open air until pyrazole formation was complete (24 h). Next the reaction mixture was concentrated and purified directly by silica-gel column chromatography using ethyl acetate−hexane as eluent in increasing polarity to yield the desired the pyrazoles **3aba**−**3sda**.

Ethyl 5-Benzoyl-4-(4-chlorophenyl)-1H-pyrazole-3-carboxylate, ***3aba****.* A total of 277 mg (78%) of **3aba** was obtained as a white solid, R_f = 0.40 (ethyl acetate/*n*-hexane, 1:3), mp 136−138 °C. IR (KBr, cm^{-1}): 3189, 2923, 1726, 1652, 1450, 1229. ^1H NMR ($CDCl_3$, 300 MHz) δ: 11.92 (bs, 1H), 7.89 (d, J = 6.5 Hz, 2H), 7.51 (t, J = 6.5 Hz, 1H), 7.40−7.17 (m, 6H), 4.32 (q, J = 6.9 Hz, 2H), 1.23 (t, J = 6.9 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 187.8, 159.7, 136.5, 133.8, 133.2, 131.7, 130.2, 128.8, 128.1, 127.7, 126.6, 61.7, 13.9. HRMS (ESI, Orbitrap): calcd for $C_{19}H_{16}ClN_2O_3$ $[M + H]^+$ 355.08495; found 355.08566.

Diethyl 4-(3-Nitrophenyl)-1H-pyrazole-3,5-dicarboxylate, ***3gca****.* A total of 250 mg (75%) of **3gca** was obtained as a white solid, R_f = 0.40 (ethyl acetate/*n*-hexane, 2:3), mp 174−176 °C. IR (KBr, cm^{-1}): 3117, 2929, 1732, 1533, 1349. ^1H NMR ($CDCl_3$, 500 MHz) δ: 8.25 (d, J = 8.2 Hz, 1H), 8.21 (s, 1H), 7.68 (d, J = 7.6 Hz, 1H), 7.55 (t, J = 7.8 Hz, 1H), 4.67 (bs, 1H), 4.24 (q, J = 7.2 Hz, 4H), 1.16 (t, J = 7.2 Hz, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 160.4, 147.3, 137.6, 136.7, 132.6, 128.1, 125.6, 124.9, 122.6, 61.6, 13.7. HRMS (ESI, Orbitrap): calcd for $C_{15}H_{16}N_3O_6$ $[M + H]^+$ 334.10391; found 334.10410.

Diethyl 4-(4-Cyanophenyl)-1H-pyrazole-3,5-dicarboxylate, ***3ica****.* A total of 222 mg (71%) of **3ica** was obtained as a white solid, R_f = 0.33 (ethyl acetate/*n*-hexane, 2:3), mp 174−175 °C. IR (KBr, cm^{-1}): 3440, 2925, 1732, 1606, 1538, 1440, 1281. ^1H NMR ($CDCl_3$, 500 MHz) δ: 11.53 (bs, 1H), 7.68 (d, J = 7.9 Hz, 2H), 7.48 (d, J = 7.9 Hz, 2H), 4.28 (q, J = 7.1 Hz, 4H), 1.20 (t, J = 7.1 Hz, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 159.8, 137.3, 135.8, 131.1, 131.0, 125.9, 118.7,

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111.6, 61.7, 13.8. HRMS (ESI, Orbitrap): calcd for $C_{16}H_{16}N_3O_4$ $[M + H]^+$ 314.11408; found 314.11451.

Ethyl 5-Benzoyl-4-(3-fluorophenyl)-1H-pyrazole-3-carboxylate, ***3sda.*** A total of 270 mg (80%) of **3sda** was obtained as a white solid, R_f = 0.45 (ethyl acetate/*n*-hexane, 1:3), mp 138−140 °C. IR (KBr, cm^{-1}): 3222, 2992, 1709, 1654, 1577, 1431, 1236. ^1H NMR ($CDCl_3$, 500 MHz) δ: 12.17 (bs, 1H), 7.98−7.77 (m, 2H), 7.49 (t, J = 7.2 Hz, 1H), 7.35 (t, J = 7.3 Hz, 2H), 7.26−7.20 (m, 1H), 7.10−7.01 (m, 2H), 6.97 (t, J = 7.2 Hz, 1H), 4.30 (q, J = 7.1 Hz, 2H), 1.22 (t, J = 7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 187.7, 162.9 (d, J = 245.2 Hz), 159.8, 136.4, 133.1, 132.5 (d, J = 8.2 Hz), 130.0, 129.0, 128.9 (d, J = 9.1 Hz), 126.3, 126.2, 117.5 (d, J = 22.7 Hz), 114.7 (d, J = 20.9 Hz), 61.7, 13.7. HRMS (ESI, Orbitrap): calcd for $C_{19}H_{16}FN_2O_3$ $[M + H]^+$ 339. 1145; found 339. 1145.

Typical Experimental Procedure of the One-Pot, Three-Component Pyrazole Synthesis (3gab−3iac). The protocol used for the synthesis of pyrazoles **3aaa−3raa** was used for the synthesis of compounds **3gab−3iac**.

tert-Butyl 5-Acetyl-4-(3-nitrophenyl)-1H-pyrazole-3-carboxylate, ***3gab.*** A total of 255 mg (77%) of **3gab** was obtained as a white solid, R_f = 0.40 (ethyl acetate/*n*-hexane, 3:7), mp 150−151 °C. IR (KBr, cm-1): 3213, 2981, 1725, 1684, 1524, 1349, 1234, 1157. ^1H NMR ($CDCl_3$, 500 MHz) δ: 11.80 (bs, 1H), 8.25 (d, J = 8.2 Hz, 1H), 8.21 (s, 1H), 7.67 (d, J = 7.8 Hz, 1H), 7.57 (t, J = 7.9 Hz, 1H), 2.60 (bs, 3H), 1.36 (s, 9H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 193.5, 158.4, 147.5, 136.5, 132.9, 128.3, 125.5, 123.2, 122.6, 84.0, 27.8 (2C). HRMS (ESI, Orbitrap): calcd for $C_{16}H_{18}N_3O_5$ $[M + H]^+$ 332.1247; found 332.1217.

tert-Butyl 5-Acetyl-4-(4-cyanophenyl)-1H-pyrazole-3-carboxylate, ***3iab.*** A total of 243 mg (78%) of **3iab** was obtained as a white solid, R_f = 0.45 (ethyl acetate/*n*-hexane, 3:7), mp 184−185 °C. IR (KBr, cm-1): 3213, 2978, 2236, 1716, 1692, 1223, 1157. ^1H NMR ($CDCl_3$, 500 MHz) δ: 11.90 (bs, 1H), 7.68 (d, J = 8.2 Hz, 2H), 7.44 (d, J = 8.2 Hz, 2H), 2.56 (bs, 3H), 1.36 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 193.2, 158.3, 136.6, 132.9, 131.2, 130.9, 127.7, 123.9, 118.8, 111.2, 83.8, 27.8 (2C). HRMS (ESI, Orbitrap): calcd for $C_{17}H_{18}N_3O_3$ $[M + H]^+$ 312.1348; found 312.1338.

Benzyl 5-Acetyl-4-(3-nitrophenyl)-1H-pyrazole-3-carboxylate, ***3gac.*** A total of 296 mg (81%) of **3gac** was obtained as a white solid, R_f = 0.35 (ethyl acetate/*n*-hexane, 3:7), mp 164−165 °C. IR (KBr, cm-1): 3234, 2926, 1731, 1685, 1525, 1350, 1188. ^1H NMR ($CDCl_3$, 500 MHz) δ: 11.90 (bs, 1H), 8.16 (d, J = 7.3 Hz, 1H), 8.15 (s, 1H), 7.61 (d, J = 7.6 Hz, 1H), 7.47 (t, J = 7.6 Hz, 1H), 7.32−7.24 (m, 3H), 7.09 (d, J = 7.0 Hz, 2H), 5.18 (s, 2H), 2.52 (bs, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 192.8, 159.1, 147.4, 136.3, 133.8, 132.3, 128.7, 128.5, 128.4, 128.3, 125.3, 123.9, 122.8, 67.7, 27.8. HRMS (ESI, Orbitrap): calcd for $C_{19}H_{16}N_3O_5$ $[M + H]^+$ 366.1090; found 366.1083.

Benzyl 5-Acetyl-4-(4-cyanophenyl)-1H-pyrazole-3-carboxylate, ***3iac.*** A total of 259 mg (75%) of **3iac** was obtained as a white solid, R_f = 0.30 (ethyl acetate/*n*-hexane, 3:7), mp 180−181 °C. IR (KBr, cm-1): 3448, 3205, 2923, 2229, 1734, 1666, 1446, 1223. ^1H NMR ($CDCl_3$, 500 MHz) δ: 11.78 (bs, 1H), 7.56 (d, J = 8.1 Hz, 2H), 7.38−7.30 (m, 6H), 7.08 (d, J = 6.8 Hz, 2H), 5.18 (s, 2H), 2.48 (bs, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 194.3, 159.1, 135.9, 134.0, 131.3, 130.8, 128.8, 128.5, 128.3, 126.9, 124.6, 118.6, 111.6, 67.6, 27.8. HRMS (ESI, Orbitrap): calcd for $C_{20}H_{16}N_3O_3$ $[M + H]^+$ 346.1192; found 346.1187.

Typical Experimental Procedure for the One-Pot, Three-Component Synthesis of Pyrazole (3gad−3gaj). In a 25 mL round-bottom flask, aldehyde (1 mmol), acetyl acetone (1 mmol), and piperidinium acetate (0.2 mmol) were mixed, and the reaction mixture was shaken under solvent-free conditions. The formation of the aldehyde−acetyl acetone adduct was complete in about 10 min (monitored by TLC). Next tosyl hydrazone (1.5 mmol), K_2CO_3 (3.0 mmol), and 10 mL of MeOH was added, and the reaction mixture was refluxed in open atmosphere until pyrazole formation was complete (12 h). Next the reaction mixture was concentrated and extracted with ethyl acetate/water. Next the organic layer was dried over anhydrous sodium sulfate, concentrated, and purified directly by silica-gel column chromatography using ethyl acetate−hexane as eluent in increasing polarity to yield the desired the pyrazoles **3gad−3gaj**.

1-(3-(3-Methoxyphenyl)-4-(3-nitrophenyl)-1H-pyrazol-5-yl)-ethanone, ***3gad.*** A total of 303 mg (90%) of **3gad** was obtained as a pale yellow solid, R_f = 0.50 (ethyl acetate/*n*-hexane, 1:1), mp 256−258 °C. IR (KBr, cm^{-1}): 3236, 3067, 2939, 1689, 1532, 1348, 1230, 1156. ^1H NMR ($CDCl_3$ + DMSO-d_6, 300 MHz) δ: 8.20−8.13 (m, 2H), 7.62−7.49 (m, 2H), 7.20 (t, J = 8.5 Hz, 1H), 6.90−6.80 (m, 3H), 3.68 (s, 3H), 2.60 (bs, 3H). ^{13}C NMR ($CDCl_3$ + DMSO-d_6, 75 MHz) δ: 193.9, 158.6, 146.9, 136.2, 134.0, 128.9, 128.6, 128.0, 124.6, 121.0, 119.3, 116.6, 113.5, 112.4, 54.2, 26.7. HRMS (ESI, Orbitrap): calcd for $C_{18}H_{16}N_3O_4$ $[M + H]^+$ 338.1141; found 338.1129.

1-(4-(3-Nitrophenyl)-3-(4-nitrophenyl)-1H-pyrazol-5-yl)ethanone, ***3gae.*** A total of 299 mg (85%) of **3gae** was obtained as a white solid, R_f = 0.53 (ethyl acetate/*n*-hexane, 1:1), mp 200−202 °C. IR (KBr, cm^{-1}): 3163, 2956, 1664, 1600, 1534, 1350, 1171, 1110. ^1H NMR ($CDCl_3$ + DMSO-d_6, 300 MHz) δ: 14.02 (bs, 1H), 8.28−8.10 (m, 4H), 7.64−7.55 (m, 2H), 7.52 (d, J = 8.5 Hz, 2H), 2.63 (bs, 3H). ^{13}C NMR ($CDCl_3$ + DMSO-d_6,, 75 MHz) δ: 193.1, 146.9, 146.0, 138.8, 135.7, 133.1, 128.3, 127.4, 124.3, 122.8, 121.3, 117.7, 26.7. HRMS (ESI, Orbitrap): calcd for $C_{17}H_{13}N_4O_5$ $[M + H]^+$ 353.0886; found 353.0879.

4-(5-Acetyl-3-(3-methoxyphenyl)-1H-pyrazol-4-yl)benzonitrile, ***3iad.*** A total of 282 mg (89%) of **3iad** was obtained as a white solid, R_f = 0.46 (ethyl acetate/*n*-hexane, 1:1), mp 208−210 °C. IR (KBr, cm^{-1}): 3264, 3061, 3008, 2922, 2229, 1682, 1607, 1433, 1391, 1263. ^1H NMR ($CDCl_3$ + DMSO-d_6, 300 MHz) δ: 7.77 (d, J = 7.9 Hz, 2H), 7.40 (d, J = 7.9 Hz, 2H), 7.25 (t, J = 7.9 Hz, 1H), 6.92 (d, J = 8.1 Hz, 1H), 6.80−6.76 (m, 2H), 3.66 (s, 3H), 2.53 (bs, 3H). ^{13}C NMR ($CDCl_3$ + DMSO-d_6, 75 MHz) δ: 191.9, 157.3, 145.8, 139.7, 136.3, 129.7, 129.5, 127.9, 127.3, 118.0, 116.9, 115.9, 112.4, 111.3, 107.7, 53.0, 25.4. HRMS (ESI, Orbitrap): calcd for $C_{19}H_{15}N_3O_2Na$ $[M + Na]^+$ 340.10415; found 340.10620.

4-(5-Acetyl-3-(3-chloro-4-nitrophenyl)-1H-pyrazol-4-yl)-benzonitrile, ***3iaf.*** A total of 330 mg (90%) of **3iaf** was obtained as a white solid, R_f = 0.59 (ethyl acetate/*n*-hexane, 1:1), mp 259−260 °C. IR (KBr, cm^{-1}): 3447, 3268, 2235, 1670, 1531, 1364, 1294. ^1H NMR ($CDCl_3$ + DMSO-d_6, 300 MHz) δ: 7.98 (s, 1H), 7.87−7.58 (bs, 2H), 7.52−7.26 (m, 4H), 2.59 (bs, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 192.2, 146.1, 137.1, 135.7, 130.5, 129.8, 127.0, 124.4, 122.8, 117.5, 117.0, 109.2, 25.8. HRMS (ESI, Orbitrap): calcd for $C_{18}H_{12}ClN_4O_3$ $[M + H]^+$ 367.0598; found 367.0597.

4-(5-Acetyl-3-(4-nitrophenyl)-1H-pyrazol-4-yl)benzonitrile, ***3iae.*** A total of 292 mg (88%) of **3iae** was obtained as a white solid, R_f = 0.40 (ethyl acetate/*n*-hexane, 1:1), mp 250−252 °C. IR (KBr, cm^{-1}): 3245, 2232, 1687, 1599, 1512, 1441, 1337, 1246. ^1H NMR ($CDCl_3$ + DMSO-d_6, 300 MHz) δ: 8.16 (d, J = 8.3 Hz, 2H), 7.68 (d, J = 6.5 Hz, 2H), 7.49 (d, J = 8.5 Hz, 2H), 7.42 (d, J = 7.4 Hz, 2H), 2.60 (bs, 3H). ^{13}C NMR ($CDCl_3$ + DMSO-d_6, 75 MHz) δ: 183.3, 146.2, 138.9, 136.7, 133.8, 131.0, 130.5, 127.6, 122.9, 117.7, 110.2, 26.7. HRMS (ESI, Orbitrap): calcd for $C_{18}H_{13}N_4O_3$ $[M + H]^+$ 333.09877; found 333.09681.

1-(3-(4-Nitrophenyl)-4-p-tolyl-1H-pyrazol-5-yl)ethanone, ***3kae.*** A total of 273 mg (85%) of **3kae** was obtained as a yellow solid, R_f = 0.42 (ethyl acetate/*n*-hexane, 1:1), mp 210−212 °C. IR (KBr, cm^{-1}): 3449, 3262, 2925, 1667, 1597, 1507, 1338, 1203. ^1H NMR ($CDCl_3$ + DMSO-d_6, 300 MHz) δ: 8.08 (d, J = 7.7 Hz, 2H), 7.73−7.48 (m, 2H), 7.40−7.07 (m, 4H), 2.42 (s, 3H), 2.13 (bs, 3H). ^{13}C NMR ($CDCl_3$ + DMSO-d_6, 75 MHz) δ: 189.9, 146.1, 137.2, 129.5, 128.9, 128.6, 127.4, 122.9, 122.0, 27.8, 20.7. HRMS (ESI, Orbitrap): calcd for $C_{18}H_{16}N_3O_3$ $[M + H]^+$ 322.1192; found 322.1196.

1-(5-(3-Nitrophenyl)-4-propyl-1H-pyrazol-3-yl)ethanone, ***3qag.*** A total of 191 mg (70%) of **3qag** was obtained as a white solid, R_f = 0.35 (ethyl acetate/*n*-hexane, 3:7), mp 155−156 °C. IR (KBr, cm^{-1}): 3447, 3189, 1652, 1528, 1346. ^1H NMR ($CDCl_3$ + DMSO-d_6, 300 MHz) δ: 13.42 (bs, 1H), 8.43 (s, 1H), 8.24 (d, J = 7.5 Hz, 1H), 7.95−7.85 (m, 1H), 7.68 (t, J = 7.4 Hz, 1H), 2.83 (t, J = 7.0 Hz, 2H), 2.61 (s, 3H), 1.63−1.55 (m, 2H) 0.94 (t, J = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$ + DMSO-d_6, 75 MHz) δ: 194.8, 147.2, 132.5, 128.9, 128.7, 127.2, 121.5,

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121.2, 120.3, 26.5, 24.4, 22.7, 13.0. HRMS (ESI, Orbitrap): calcd for $C_{14}H_{16}N_3O_3$ $[M + H]^+$ 274.1192; found 274.1195.

1-(5-(9-Ethyl-9H-carbazol-2-yl)-4-(3-nitrophenyl)-1H-pyrazol-3-yl)ethanone, ***3gaj.*** A total of 331 mg (78%) of **3gaj** was obtained as a yellow solid, R_f = 0.30 (ethyl acetate/*n*-hexane, 3:7), mp 160−161 °C. IR (KBr, cm^{-1}): 3257, 2925, 1672, 1530, 1470, 1347, 1231. ^1H NMR (DMSO-d_6, 300 MHz) δ: 13.09 (bs, 1H), 8.26 (d, J = 7.5 Hz, 1H), 8.15 (t, J = 7.5 Hz, 1H), 8.08 (d, J = 8.1 Hz, 1H), 7.96 (t, J = 8.1 Hz, 1H), 7.64 (t, J = 7.6 Hz, 1H), 7.54−7.40 (m, 3H), 7.33−7.22 (m, 3H), 4.39−7.32 (m, 2H), 2.65 (s, 3H), 1.45−1.40 (m, 3H). ^{13}C NMR (DMSO-d_6, 75 MHz) δ: 194.1, 147.3, 143.3, 139.8, 139.3, 137.2, 134.8, 131.3, 129.1, 128.3, 127.9, 126.2, 125.7, 125.2, 122.1, 121.6, 120.1, 119.1, 118.3, 116.3, 109.3, 36.9, 27.2, 13.6. HRMS (ESI, Orbitrap): calcd for $C_{25}H_{21}N_4O_3$ $[M + H]^+$ 425.1614; found 425.1619.

Typical Experimental Procedure for Alkylation of NH-Pyrazoles. In a 50 mL round-bottom flask, NH-pyrazole (1 mmol), ethyl α-bromoacetate (1.1 mmol), K_2CO_3 (3.0 mmol), and dry acetonitrile (20 mL) were mixed, and the reaction mixture was heated at 80 °C for 3 h. Next, the reaction mixture was evaporated to dryness, and the residue was extracted with ethyl acetate/water. The organic layer was dried over anhydrous sodium sulfate and concentrated to yield a crude reaction product, which was purified by silica-gel column chromatography using ethyl acetate/hexane in increasing polarity to yield the desired products (**9kaaa**−**9gaea**).

Ethyl 3-Acetyl-1-(2-ethoxy-2-oxoethyl)-4-p-tolyl-1H-pyrazole-5-carboxylate, ***9kaaa.*** A total of 290 mg (81%) of **9kaaa** was obtained as a white solid, R_f = 0.48 (ethyl acetate/*n*-hexane, 3:7), mp 110−111 °C. IR (KBr, cm^{-1}): 2993, 1749, 1703, 1465, 1229. ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.16 (s, 4H), 5.36 (s, 2H), 4.28 (q, J = 7.2 Hz, 2H), 4.10 (q, J = 7.2 Hz, 2H), 2.47 (s, 3H), 2.39 (s, 3H), 1.31 (t, J = 7.2 Hz, 3H), 0.98 (t, J = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 193.3, 167.4, 159.8, 147.1, 137.3, 132.1, 129.8, 128.5, 128.4, 128.1, 61.9, 61.3, 54.8, 28.1, 21.4, 14.1, 13.4. HRMS (ESI, Orbitrap): calcd for $C_{19}H_{23}N_2O_5$ $[M + H]^+$ 359.1607; found 359.1600.

Ethyl 2-(3-Acetyl-5-(3-methoxyphenyl)-4-(3-nitrophenyl)-1H-pyrazol-1-yl)acetate, ***9gada.*** A total of 351 mg (83%) of **9gada** was obtained as a pale solid, R_f = 0.56 (ethyl acetate/*n*-hexane, 3:7), IR (KBr, cm^{-1}): 2935, 1750, 1689, 1528, 1350. ^1H NMR ($CDCl_3$, 500 MHz) δ: 8.08−8.05 (m, 2H), 7.55 (d, J = 7.2 Hz, 1H), 7.38 (t, J = 7.6 Hz, 1H), 7.29 (t, J = 7.7 Hz, 1H), 6.93 (d, J = 7.6 Hz, 1H), 6.77 (d, J = 7.2 Hz, 1H), 6.72 (s, 1H), 4.88 (s, 2H), 4.25 (q, J = 6.9 Hz, 2H), 3.72 (s, 3H), 2.63 (s, 3H), 1.27 (t, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 194.2, 167.3, 159.7, 147.6, 147.1, 144.4, 136.6, 133.6, 130.2, 128.9, 128.4, 125.4, 122.3, 121.9, 120.2, 115.5, 115.3, 62.1, 52.2, 51.7, 27.8, 14.1. HRMS (ESI, Orbitrap): calcd for $C_{22}H_{22}N_3O_6$ $[M + H]^+$ 424.1509; found 424.1501.

Ethyl 2-(3-Acetyl-4-(3-nitrophenyl)-5-(4-nitrophenyl)-1H-pyrazol-1-yl)acetate, ***9gaea.*** A total of 372 mg (85%) of **9gaea** was obtained as a white solid, R_f = 0.52 (ethyl acetate/*n*-hexane, 3:7), mp 170−171 °C. IR (KBr, cm^{-1}): 3097, 2924, 2850, 1748, 1687, 1524, 1346. ^1H NMR ($CDCl_3$, 500 MHz) δ: 8.25 (d, J = 8.7 Hz, 2H), 8.11 (d, J = 8.1 Hz, 1H), 8.04 (s, 1H), 7.50 (d, J = 7.8 Hz, 1H), 7.45−7.40 (m, 3H), 4.89 (s, 2H), 4.26 (q, J = 7.1 Hz, 2H), 2.63 (s, 3H), 1.28 (t, J = 7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 193.8, 166.9, 148.4, 147.8, 147.3, 142.2, 136.4, 134.3, 132.8, 131.2, 128.8, 125.3, 124.2, 122.4, 121.1, 62.5, 51.9, 27.5, 14.0. HRMS (ESI, Orbitrap): calcd for $C_{21}H_{19}N_4O_7$ $[M + H]^+$ 439.1254; found 439.1268.

Synthesis of the Dihydropyrazole 7naa. In a 25 mL round-bottom flask, furfural−acetyl acetone adduct **1na** (1 mmol), EDA (1.01 mmol), 4 Å molecular sieves (500 mg), and anhydrous toluene (10 mL) were mixed under nitrogen atmosphere. The reaction mixture was heated at 70 °C for 24 h. Next, molecular sieves were filtered off, and the filtrate was concentrated to yield a crude reaction product, which was purified by silica-gel column chromatography to yield pure compound **7naa**.

Ethyl 5,5-Diacetyl-4-(furan-2-yl)-4,5-dihydro-1H-pyrazole-3-carboxylate, ***7naa.*** A total of 380 mg (96%) of **7naa** was obtained as a white solid, R_f = 0.48 (ethyl acetate/*n*-hexane, 3:7), mp 104−105 °C. ^1H NMR ($CDCl_3$, 500 MHz) δ: 7.44 (bs, 1H), 7.33 (m, 1H), 6.34 (m, 1H), 6.26 (m, 1H), 5.37 (s, 1H), 4.26−4.15 (m, 2H), 2.27 (s, 3H), 1.72 (s, 3H), 1.24−1.20 (m, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 201.5, 200.7, 160.5, 147.6, 142.7, 142.5, 111.3, 109.8, 90.2, 61.3, 48.4, 26.1, 25.7, 13.9. HRMS (ESI, Orbitrap): calcd for $C_{14}H_{17}N_2O_5$ $[M + H]^+$ 293.11375; found 293.11338.

1-(3-(3-Nitrophenyl)-4-phenyl-1H-pyrazol-5-yl)ethanone, ***3teg.*** A total of 230 mg (75%) of **3teg** was obtained as a white solid, R_f = 0.40 (ethyl acetate/*n*-hexane, 3:7), mp 190−191 °C. IR (KBr, cm^{-1}): 3255, 2925, 1662, 1527, 1341. ^1H NMR ($CDCl_3$, 500 MHz) δ: 11.50 (bs, 1H), 8.29 (s, 1H), 8.10 (d, J = 8.2 Hz, 1H), 7.73 (d, J = 7.8 Hz, 1H), 7.52−7.47 (m, 3H), 7.40 (t, J = 8.1 Hz, 1H), 7.37−7.30 (m, 2H), 2.13 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 147.5, 132.7, 131.7, 130.0, 129.7, 128.7, 128.1, 127.8, 127.5, 121.6, 27.7. HRMS (ESI, Orbitrap): calcd for $C_{17}H_{14}N_3O_3$ $[M + H]^+$ 308.1035; found 308.1040.

Synthesis of (*E*)-4-Phenylbut-3-en-2-one, 1te. Compound **1te** was synthesized from benzaldehyde and acetone using literature protocol.[23]

The compound **1te** was obtained as a white solid (0.82 g, 56%, 10 mmol scale reaction), mp 40−41 °C (lit 40−41 °C).[23] Spectroscopic data was found in accordance with literature.[24]

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Crystallographic data for compound **9gaea** and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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