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A Convenient Microwave-Assisted Propylphosphonic Anhydride (T3P®) Mediated One-Pot Pyrazolone Synthesis

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This paper describes a facile, efficient, and clean synthesis of various pyrazolones by employing T3P® as a catalyst and performing the reaction under microwave irradiation. This two-step, one-pot reaction proceeded readily and tolerated a variety of functional groups. A wide range of pyrazolone derivatives were obtained in good to excellent yields.

Introduction

Propylphosphonic anhydride (T3P®) has been commonly used as a water scavenger and coupling reagent for the synthesis of amides.[1] Because of its properties, which include a broad functional group tolerance, low toxicity, and easy workup procedures, new applications have recently been developed for this reagent.[2] For instance, T3P® has been used in dehydration chemistry that involves the conversion of carboxylic acids and amides into nitriles as well as in the synthesis of alkenes, isonitriles, and several substituted heterocycles.[3] More recently, T3P® was used as an efficient catalyst for the acetalization or thioacetalization of aldehydes, for the reduction of carboxylic acids into alcohols, and for the synthesis of 4-thiazolidinones and 5,6-dihydrophenanthridine derivatives.[4]

In continuation of our work on the development of useful synthetic methodologies,[3a] we reasoned that T3P® could be employed for the construction of the pyrazolone ring. Pyrazolones are traditionally synthesized by treatment of a β-keto ester with hydrazine under acidic conditions at high temperature for a long reaction time.[5–8] Consequently, new, mild, and expedient protocols for these derivatives are of significant importance. The pyrazolone ring is an important scaffold that is found in pharmaceuticals that exhibit widespread pharmacological properties. One of the most relevant examples, edaravone (3-methyl-1-phenyl-2-pyrazolin-5-one, Radicut®, Mitsubishi Tanabe Pharma Corporation) is used to treat patients in the acute stages of cerebral thrombosis or embolism and stroke. Moreover, because of its antioxidant properties, edaravone might be useful for managing many oxidative stress-related diseases.[9]

During the last decade, compounds that contain a pyrazolone moiety, or its related analogues, have received considerable attention in medicinal chemistry. These compounds exhibit antitubercular,[5] antifungal,[6] anti-infectious,[8] anticancer,[10] antipyretic and analgesic,[11] antioxidant,[12] and antimicrobial properties.[13] Finally, some of the pyrazolone derivatives have been developed to treat a variety of disorders that are caused by human immunodeficiency virus (HIV)[14] and hereditary hemochromatosis.[15]

Results and Discussion

Initially, a model reaction was conducted by treating ethyl benzoylacetate (**1a**, 0.5 mmol) with phenylhydrazine (**2a**, 0.5 mmol) in the presence of an excess amount of T3P® (50% solution in EtOAc, 4 equiv.) at 100 °C under microwave irradiation (MW) for 15 min (see Table 1, Entry 1). We were pleased to find that T3P® did mediate this cyclization. The reaction conditions were then optimized by fine-tuning the equivalents of T3P®, the reaction time, and the temperature.

Decreasing the amount of T3P® from 4 to 2 equiv. did not affect the outcome of the reaction, which indicated that it was sufficient to have 2 equiv. of T3P® (see Table 1, Entry 2). We then decided to evaluate the impact of changing the reaction time, and a series of experiments were carried out for periods of 10 and 5 min (see Table 1, Entries 3 and 4). Using T3P® (2 equiv.), the reaction of **1a** and **2a** in EtOAc at 100 °C for only 5 min proved to be optimal for this cyclodehydration, and the isolated yield from this conversion was excellent (90%, see Table 2, Entry 1). Furthermore, decreasing the amount of T3P® from 2 equiv. to 1.5 equiv. or the reaction temperature to 90 °C lowered the conversion yield (see Table 1, Entries 5 and 6, respectively).

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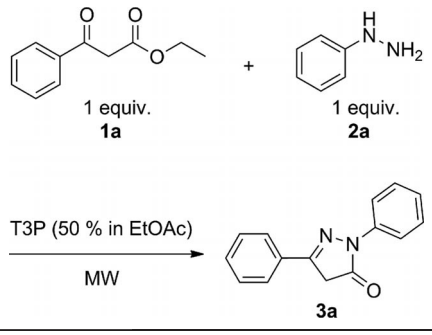
Table 1. Optimization of reaction conditions.



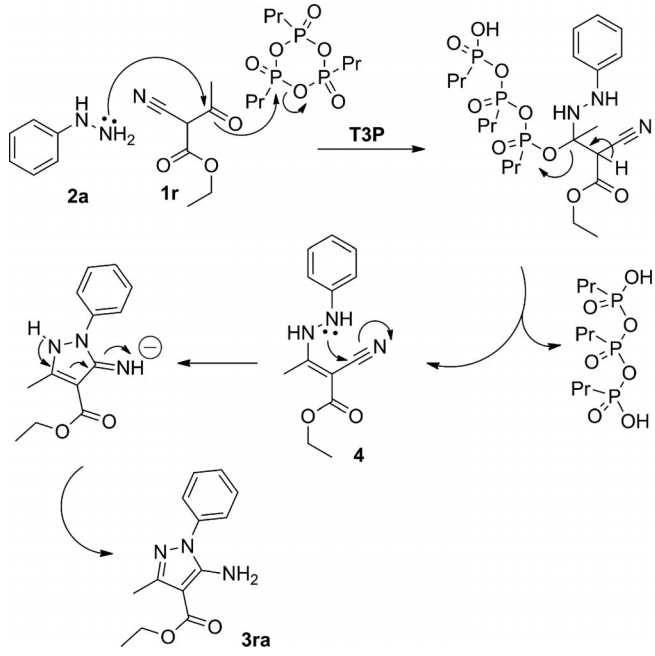
Entry	T3P® [equiv.]	Time [min]	*T* [°C]	% Conversion[a]
1	4	15	100	100
2	2	15	100	100
3	2	10	100	99
4	2	5	100	98
5	1.5	5	100	77
6	2	5	90	87
7	0	5	100	14
8[b]	1.5 + AcOH	5	100	87
9[c]	1.5 + AcOH	5	100	89
10	0 + AcOH	5	100	86

[a] Determined by LC–MS analysis (for details, see Exp. Sect.). [b] Reaction conducted in EtOAc. [c] Reaction conducted in EtOH.

Finally, to validate that the ring-closing dehydration was mediated by T3P® and not by a thermal process only, a control experiment was conducted. As expected, heating the mixture of **1a** and **2a** at 100 °C in EtOAc without T3P® for 5 min under microwave irradiation gave only 14% conversion (see Table 1, Entry 7). With the goal to decrease the amount of required T3P®, we carried out the reaction with 1.5 equiv. of T3P® and two drops of acetic acid in either EtOAc or EtOH (see Table 1, Entries 8 and 9). No significant difference was observed when the reaction was carried out in either of these two solvents (87% conversion in EtOAc, 89% in EtOH). These conversions were similar to that obtained by using only two drops of acetic acid without T3P® (e.g., 86%, see Table 1, Entry 10). Thus, under our reaction conditions, no synergistic effect was obtained by combining T3P® and acetic acid. The probable degradation of T3P® in acidic media to produce phosphoric acid could explain this result.

The optimized conditions [e.g., T3P® (2 equiv.), MW, 5 min at 100 °C] were then used to explore the scope of this reaction. The results in Table 2 show that a variety of β-keto esters that contain electron-donating (see Table 2, Entries 2–5), electron-withdrawing (see Table 2, Entries 8–11), heteroaromatic, and aliphatic groups (see Table 2, Entries 6 and 7 as well as 12–17, respectively) were successfully employed to prepare the corresponding pyrazolone derivatives in good to excellent yields. We were pleased to see that the reaction worked well with electron-donating and electron-withdrawing substituents as well as heteroaromatic β-keto esters (see Table 2, Entries 2–11). Only ethyl (3-chlorobenzoyl)acetate (**1k**, see Table 2, Entry 11) led to a small decrease in the yield to 75%, which indicated the limited influence of an electron-withdrawing substituent on the yield of the reaction. Several aliphatic β-keto esters were also suitable substrates for the reaction (i.e., **1l**–**1q**, see Table 2, Entries 12–17). In these cases, steric effects appear to influence the rate and yield of the reaction. Indeed, when ethyl pivaloylacetate (**1n**) and phenylhydrazine (**2a**) were used as substrates, the synthesis of 3-*tert*-butyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (**3n**) required a higher temperature and longer reaction time (e.g., 120 °C and 10 min). Furthermore, this methodology was employed to synthesize edaravone (3-methyl-1-phenyl-2-pyrazolin-5-one, **3l**), in a good yield of 83% (see Table 2, Entry 12).

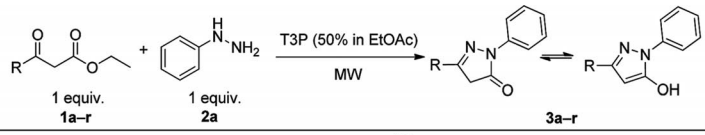
Notably, the use of ethyl 2-cyanoacetoacetate (**1r**) led to the formation of **3ra** instead of expected pyrazolone **3r** (see Table 2, Entry 18). Under similar conditions, aminopyrazoles were obtained by condensation of keto esters with hydrazine derivatives.[16] This presumably proceeds as depicted in Scheme 1.

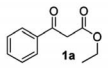
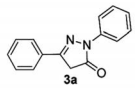
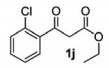
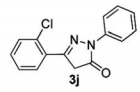
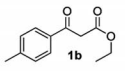
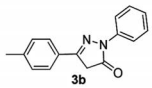
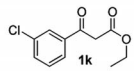
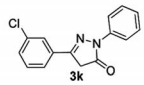
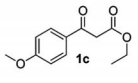
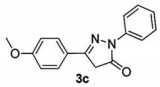
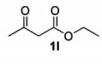
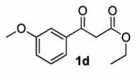
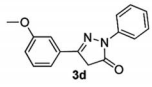
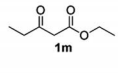
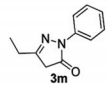
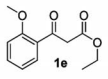
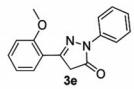
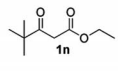
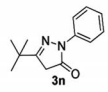
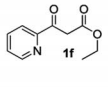
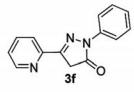
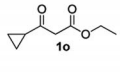
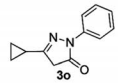
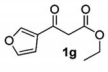
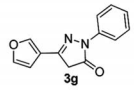
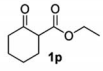
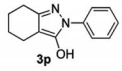
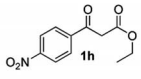
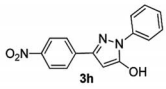
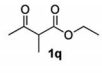
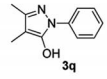
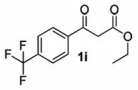
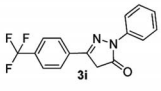
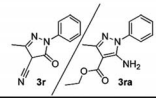


Scheme 1. Plausible mechanism of formation of **3ra**.

The first step of this mechanism is the condensation of hydrazine **2a** with ethyl 2-cyanoacetoacetate **1r** (a Knoevenagel-type condensation) to produce intermediate **4**. This condensation could be assisted by the presence of T3P®. Subsequently, **4** could undergo an intramolecular cyclization, which upon tautomerization would lead to **3ra**. In this plausible mechanism, only 1 equiv. of T3P® is needed. To confirm this hypothesis, two reactions were conducted, that is, one with only 1 equiv. of T3P® and one without T3P®. These reactions were monitored by LC–MS analysis. To our pleasure, no product was formed when the reactants were irradiated under microwave conditions at 100 °C for 5 min in EtOAc in the absence of T3P®. With only 1 equiv. of T3P®, a conversion yield of 81% was obtained after 15 min of reaction time. More experiments with regard to the use of T3P® in Knoevenagel-type condensations are under investigation and will be reported soon.

Table 2. Pyrazolone synthesis in the presence of T3P®: scope of β-keto esters.

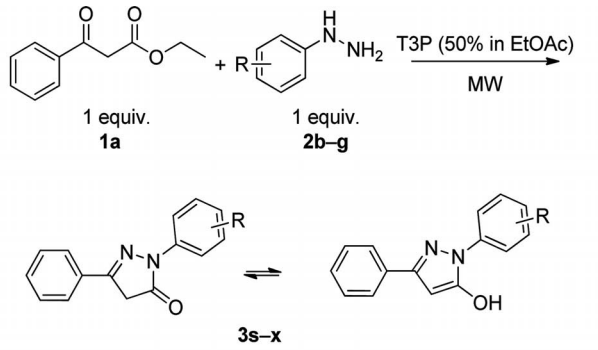


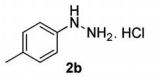
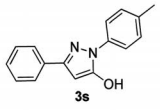
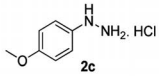
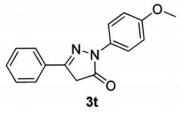
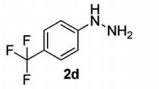
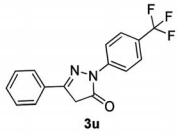
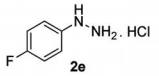
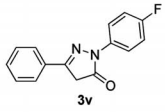
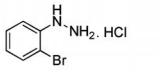
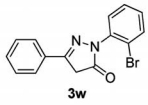
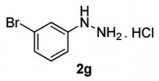
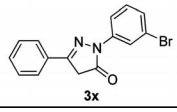
Entry	β-Keto ester	Product	Time [min]	*T* [°C]	Yield[a]	Entry	β-Keto ester	Product	Time [min]	*T* [°C]	Yield[a]
1			5	100	90% 96%[b]	10			5	100	96%
2			5	100	89%	11			5	100	75%
3			5	100	98%	12			5	100	83%
4			5	100	97%	13			5	100	91%
5			5	100	99%	14			10	120	72%
6			5	100	83%	15			5	100	92%
7			5	100	98%	16			5	100	88%
8			5	100	99%	17			5	100	87%
9			5	100	95%	18			5	100	0/42%

[a] Reactions conducted on a 0.5 mmol scale, isolated yield. [b] Reaction conducted on a 5 mmol scale, isolated yield.

The substrate scope of the reaction was further extended to various substituted hydrazines. Thus, ethyl benzoylacetate **1a** was treated with a range of hydrazines under our optimized reaction conditions (see Table 3). To our delight, hydrazines that contain either electron-donating (see Table 3, Entries 1 and 2) or electron-withdrawing groups (see Table 3, Entries 3–6) were well tolerated to afford the corresponding pyrazolones in good yields. Surprisingly, the substitution of the phenylhydrazine at the *para* position with the electron-withdrawing trifluoromethyl group (see Table 3, Entry 3) did not require any adjustment to the reaction conditions, whereas *para*-methoxyphenylhydrazine needed a longer reaction time (2 × 5 min) and a higher temperature (120 °C) to achieve full conversion (see Table 3, Entry 2). Other *para* substitutents (i.e., 4-methyl and 4-fluoro) furnished the expected derivatives by following the previously optimized conditions (see Table 3, Entries 1 and 4). Furthermore, *ortho*- and *meta*-substituted hydrazines

Table 3. Pyrazolone synthesis in the presence of T3P®: scope of substituted hydrazines.



Entry	Hydrazine	Product	Time [min]	T [°C]	Yield[a]
1	 2b	 3s	5	100	76%
2	 2c	 3t	2×5	120	77%
3	 2d	 3u	5	100	79%
4	 2e	 3v	5	100	73%
5	 2f	 3w	5	100	79%
6	 2g	 3x	5	100	84%

[a] Reactions conducted on a 0.5 mmol scale, isolated yield.

also performed well (see Table 3, Entries 5 and 6), which indicated the limited influence of steric factors on the reaction outcome.

Conclusions

In summary, we have developed a new, efficient, and easily reproducible T3P® mediated microwave-assisted procedure to construct pyrazolone analogues. With this simple and rapid method, a series of compounds were synthesized to examine the extension and limitations of this methodology. This approach offers a notable alternative to the strongly acidic conditions that are generally applied with other synthetic methods and, therefore, may have application to the syntheses of biological and pharmaceutical molecules that contain a pyrazolone scaffold. During this study, we also identified the potential use of T3P® in Knoevenagel-type condensations. Further studies with regard to this new employment of T3P® are currently under investigation and will be reported soon.

Experimental Section

General Methods: All the reagents were commercially available and used without further purification. Analytical thin layer chromatography was performed on silica gel 60 F-254 plates (E. Merck) and visualized by using UV light. Flash column chromatography was performed with Merck silica gel 60 (40–63 mm). The ^{1}H NMR spectroscopic data were recorded at 400 MHz, and the ^{13}C NMR spectroscopic data were recorded at 100 MHz. The chemical shifts for the ^{1}H and ^{13}C NMR are referenced to the residual solvent signals [^{1}H NMR: $CDCl_3$ at δ = 7.26 ppm, CD_3OD at δ = 3.31 ppm, deuterated dimethyl sulfoxide ([D_6]DMSO) at δ = 2.50 ppm; ^{13}C NMR: $CDCl_3$ at δ = 77.16 ppm, CD_3OD at δ = 49.01 ppm, and [D_6]DMSO at δ = 39.52 ppm]. The microwave reactions were performed in a Biotage Initiator that produced a controlled irradiation at 2450 MHz with a power of 0–300 W. The reaction temperature was determined by using a built-in online IR sensor. All reactions were performed in sealed microwave-transparent process vials that were designed for reaction volumes of 0.5–2 mL. Analytical LC–MS data were recorded with an Agilent MSD mass spectrometer that was connected to an Agilent 1100 system with: (i) System A: Column ACE 3 C8 (50 × 3.0 mm), H_2O [+ 0.1% trifluoroacetic acid (TFA)] and MeCN as mobile phases, flow rate: 1 mL/min, and a gradient time of 3.0 min or (ii) System B: Column Xterra MSC18 (50 × 3.0 mm), H_2O [containing NH_4HCO_3 (10 mM solution), pH = 10] and MeCN as mobile phases, flow rate: 1 mL/min, and a gradient time of 3.0 min. Preparative HPLC analyses were performed with a Gilson HPLC System with Column Xbridge Prep C18, 5 μM CBD (30 × 75 mm), H_2O [containing NH_4HCO_3 (50 mM solution), pH = 10] and MeCN as mobile phases, flow rate: 45 mL/min, and a gradient time of 9 min. UV (254 or 214 nm) and MS (ESI+) detection were used for both the LC–MS and preparative HPLC analyses. The percent conversion in Table 1 was estimated by comparing the peak area of **3a** to the combined peak area(s) of **1a** and/or **2a**. Compounds **3a**,[17] **3h**,[18] **3l**,[17] **3n**,[19] **3q**,[20] **3ra**,[16] **3t**,[17] and **3v**[21] are known compounds, and the spectroscopic data that were obtained are in agreement with the proposed structures and match those reported. Compounds **3b**,[22] **3c**,[18] **3d**,[23] **3e**,[24] **3f**,[25] **3g**,[26] **3j**,[27] **3k**,[28] **3m**,[29] **3o**,[30] **3p**,[31] and **3s**[32] are known compounds, but their complete NMR spectroscopic data have not been previously reported. Melting points were obtained with a Stuart Scientific SMP3 apparatus. It is well-known that the pyrazolone ring exists in various prototropic tautomeric forms. From the ^{1}H and ^{13}C NMR chemical shifts, we assume that the keto form predominates in low polarity solvent such as $CDCl_3$, whereas the enol form predominates in the [D_6]DMSO and CD_3OD solutions. Furthermore, this is in agreement with literature data.[33]

General Experimental Procedure for Compounds 3a–3j: T3P® (50% in EtOAc, 1 mmol, 2 equiv.) was added to a mixture of the β-keto ester (0.5 mmol) and hydrazine (0.5 mmol) in a microwave vial. The reaction volume was then adjusted to 0.5 mL with EtOAc, and the vessel was sealed under air. The mixture was then heated under microwave irradiation at 100 °C for 5 min. The residue was suspended in water, and CH_2Cl_2 was then added. The organic layer was washed with a saturated solution of $NaHCO_3$. The aqueous layers were combined and extracted with CH_2Cl_2. The combined organic layers were then washed with brine and dried with Na_2SO_4. Evaporation of the solvent afforded the required product in sufficient purity.

1,3-Diphenyl-1*H*-pyrazol-5(4*H*)-one (3a): Yellow-orange solid (107 mg, 90% yield), m.p. 138–140 °C (EtOH); ref.[17] m.p. 136–138 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.99 (dd, J = 7.6, 1.0 Hz, 2 H), 7.79–7.77 (m, 2 H), 7.48–7.42 (m, 5 H), 7.25 (t, J = 7.6 Hz, 1 H), 3.86 (s, 2 H) ppm. LC–MS: m/z = 237 $[M + H]^+$.

3-(4-Methylphenyl)-1-phenyl-1*H*-pyrazol-5(4*H*)-one (3b): Yellow solid (112 mg, 89% yield), m.p. 154–156 °C (EtOH); ref.[22] m.p. 154 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.99 (dd, J = 7.5, 1.0 Hz, 2 H), 7.67 (d, J = 8.1 Hz, 2 H), 7.45 (t, J = 7.5 Hz, 2 H), 7.27 (d, J = 8.1 Hz, 2 H), 7.23 (t, J = 7.5 Hz, 1 H), 3.82 (s, 2 H), 2.41 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.2, 154.7, 141.1, 138.1, 129.6, 128.8, 128.1, 125.9, 125.2, 119.0, 39.7, 21.5 ppm. LC–MS: m/z = 251 $[M + H]^+$.

3-(4-Methoxyphenyl)-1-phenyl-1*H*-pyrazol-5(4*H*)-one (3c): Red-orange solid (131 mg, 98% yield), m.p. 134–136 °C (EtOH); ref.[18] m.p. 133 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.98 (dd, J = 7.8, 1.0 Hz, 2 H), 7.72 (d, J = 8.9 Hz, 2 H), 7.44–7.40 (m, 2 H), 7.23–7.20 (m, 1 H), 6.97 (d, J = 8.9 Hz, 2 H), 3.86 (s, 3 H), 3.80 (s, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.2, 161.6, 154.4, 138.2, 128.8, 127.6, 125.1, 123.6, 121.3, 119.0, 114.3, 113.5, 55.4, 39.7 ppm. LC–MS: m/z = 267 $[M + H]^+$.

3-(3-Methoxyphenyl)-1-phenyl-1*H*-pyrazol-5(4*H*)-one (3d): Orange solid (129 mg, 97% yield), m.p. 124–125 °C (EtOH); ref.[23] m.p. 137–138 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.98 (dd, J = 7.6, 1.3 Hz, 2 H), 7.45–7.41 (m, 2 H), 7.37–7.35 (m, 2 H), 7.30 (dt, J = 8.1, 1.1 Hz, 1 H), 7.25–7.20 (m, 1 H), 7.02 (ddd, J = 8.1, 2.6, and 1.0 Hz, 1 H), 3.88 (s, 3 H), 3.83 (s, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.2, 160.0, 154.5, 138.1, 132.2, 130.0, 128.9, 125.4, 119.1, 118.7, 116.7, 110.8, 55.4, 39.8 ppm. LC–MS: m/z = 267 $[M + H]^+$.

3-(2-Methoxyphenyl)-1-phenyl-1*H*-pyrazol-5(4*H*)-one (3e): Orange solid (132 mg, 99% yield), m.p. 133–134 °C (EtOH); ref.[24] m.p. 133–134 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.09 (dd, J = 7.8, 1.8 Hz, 1 H), 8.01 (dd, J = 7.6, 1.0 Hz, 2 H), 7.45–7.40 (m, 3 H), 7.23–7.19 (m, 1 H), 7.07 (td, J = 7.6, 1.0 Hz, 1 H), 6.98 (d, J = 7.6 Hz, 1 H), 4.03 (s, 2 H), 3.89 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.7, 158.2, 154.1, 138.7, 132.3, 129.2 (2 C), 128.3, 125.5, 121.4, 120.4, 119.4 (2 C), 111.9, 55.8, 44.3 ppm. LC–MS: m/z = 267 $[M + H]^+$.

2-Phenyl-5-pyridin-2-yl-1,2-dihydro-pyrazol-3-one (3f): Light brown solid (99 mg, 83% yield), m.p. 179–181 °C (EtOH); ref.[25] m.p. 178–179 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.64 (d, J = 4.8 Hz, 1 H), 8.15 (d, J = 7.8 Hz, 1 H), 7.98 (d, J = 7.6 Hz, 2 H), 7.81 (td, J = 7.8, 1.7 Hz, 1 H), 7.46 (t, J = 7.6 Hz, 2 H), 7.36–7.32 (m, 1 H), 7.25 (t, J = 7.6 Hz, 1 H), 4.02 (s, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.9, 155.9, 149.9, 149.5, 138.0, 138.5, 138.0, 136.5, 128.8, 125.4, 124.6, 120.2, 119.1, 39.7 ppm. LC–MS: m/z = 238 $[M + H]^+$.

3-(Furan-3-yl)-1-phenyl-1*H*-pyrazol-5(4*H*)-one (3g): Purple solid (111 mg, 98% yield), m.p. 140–141 °C (EtOH); ref.[26] m.p. 182 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94 (dd, J = 7.5, 1.2 Hz, 2 H), 7.75 (s, 1 H), 7.51 (t, J = 1.5 Hz, 1 H), 7.44 (t, J = 7.5 Hz, 2 H), 7.23 (t, J = 7.5 Hz, 1 H), 6.87 (d, J = 1.5 Hz, 1 H), 3.73 (s, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.4, 148.8, 144.4, 142.6, 137.9, 128.8, 125.2, 116.4, 119.1, 107.3, 40.1 ppm. LC–MS: m/z = 227 $[M + H]^+$.

3-(4-Nitrophenyl)-1-phenyl-1*H*-pyrazol-5(4*H*)-ol (3h): Yellow powder (140 mg, quantitative yield), m.p. 187–188 °C (EtOH); ref.[18] m.p. 190–191 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 12.02 (br. s, 1 H), 8.28 (d, J = 9.1 Hz, 2 H), 8.11 (d, J = 9.1 Hz, 2 H), 7.84 (dd, J = 7.6, 1.1 Hz, 2 H), 7.53 (t, J = 7.6 Hz, 2 H), 7.35 (tt, J = 7.6, 1.1 Hz, 1 H), 6.21 (s, 1 H) ppm. LC–MS: m/z = 282 $[M + H]^+$.

1-Phenyl-3-[4-(trifluoromethyl)phenyl]-1*H*-pyrazol-5(4*H*)-one (3i): Yellow powder (144 mg, 95% yield); m.p. 164–166 °C (diisopropyl ether). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.97 (dd, J = 7.5, 1.1 Hz, 2 H), 7.90 (d, J = 8.0 Hz, 2 H), 7.73 (d, J = 8.0 Hz, 2 H), 7.47 (t, J = 7.5 Hz, 2 H), 7.27–7.23 (m, 1 H), 3.87 (s, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.1, 153.3, 138.1, 134.3, 129.1, 126.4, 126.3, 126.2, 126.1, 125.9, 119.4, 39.7 ppm. LC–MS: m/z = 305 $[M + H]^+$.

3-(2-Chlorophenyl)-1-phenyl-1*H*-pyrazol-5(4*H*)-one (3j): Yellow solid (130 mg, 96% yield); m.p. 139–141 °C (diisopropyl ether). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.00–7.95 (m, 3 H), 7.48–7.42 (m, 3 H), 7.41–7.35 (m, 2 H), 7.25 (tt, J = 7.5, 1.1 Hz, 1 H), 4.14 (s, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.5, 153.5, 138.0, 132.7, 131.3, 131.0, 129.9, 129.8, 128.9 (2 C), 127.2, 125.5, 119.1 (2 C), 43.2 ppm. LC–MS: m/z = 271 $[M + H]^+$, 273.

General Experimental Procedure for Compounds 3k–3p, 3t, and 3u: T3P® (50% in EtOAc, 1 mmol, 2 equiv.) was added to a mixture of the β-keto ester (0.5 mmol) and hydrazine (0.5 mmol) in a microwave vial. The reaction volume was then adjusted to 0.5 mL with EtOAc, and the vessel was sealed under air. The mixture was then heated under microwave irradiation for the time and temperature that are indicated in Table 2. The solvent was removed under reduced pressure, and the residue was purified by filtration through a plug of silica gel.

3-(3-Chlorophenyl)-1-phenyl-1*H*-pyrazol-5(4*H*)-one (3k): Purification by filtration through silica gel (gradient 5–30% EtOAc in hexanes) afforded **3k** (102 mg, 75% yield) as a light yellow foam. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94 (d, J = 7.8 Hz, 2 H), 7.77 (t, J = 1.6 Hz, 1 H), 7.59 (dt, J = 7.3, 1.6 Hz, 1 H), 7.46–7.36 (m, 4 H), 7.25–7.19 (m, 1 H), 3.79 (s, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.1, 153.4, 138.1, 135.2, 132.7, 130.7, 130.3, 129.0, 126.0, 125.6, 124.2, 119.2, 39.6 ppm. LC–MS: m/z = 271 $[M + H]^+$, 273.

3-Methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (3l): Purification by filtration through silica gel (gradient 5–40% EtOAc in hexanes) afforded **3l** (72 mg, 83% yield) as a white powder, m.p. 120–122 °C (EtOH); ref.[17] m.p. 127–129 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.89–7.81 (m, 2 H), 7.42–7.35 (m, 2 H), 7.21–7.14 (m, 1 H), 3.43 (s, 2 H), 2.19 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.7, 156.5, 138.1, 128.9 (2 C), 125.2, 119.0 (2 C), 43.2, 17.1 ppm. LC–MS: m/z = $[M + H]^+$ 175.

3-Ethyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (3m): Purification by filtration through silica gel (gradient 5–30% EtOAc in hexanes) afforded **3m** (86 mg, 91% yield) as a light yellow solid; m.p. 99–101 °C (EtOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.91–7.82 (m, 2 H), 7.43–7.33 (m, 2 H), 7.21–7.12 (m, 1 H), 3.41 (s, 2 H), 2.52 (q, J = 7.5 Hz, 2 H), 1.25 (t, J = 7.5 Hz, 3 H) ppm. ^{13}C NMR (100 MHz,

$CDCl_3$): δ = 170.7, 160.9, 138.2, 128.9 (2 C), 125.1, 118.9 (2 C), 41.6, 24.7, 10.8 ppm. LC–MS: *m*/*z* = 189 $[M + H]^+$.

3-*tert*-Butyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (3n): Purification by filtration through silica gel (gradient 5–15% EtOAc in hexanes) afforded **3n** (78 mg, 72% yield) as a white powder, m.p. 112–113 °C (EtOH); ref.[19] m.p. 117–119 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.93–7.86 (m, 2 H), 7.41–7.34 (m, 2 H), 7.19–7.12 (m, 1 H), 3.44 (s, 2 H), 1.27 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.9, 166.6, 138.4, 128.8, 124.9, 118.9, 39.0, 35.0, 28.2 ppm. LC–MS: *m*/*z* = 217 $[M + H]^+$.

3-Cyclopropyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (3o): Purification by filtration through silica gel (gradient 5–30% EtOAc in hexanes) afforded **3o** (92 mg, 92% yield) as a light yellow solid; m.p. 114–115 °C (EtOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.88–7.83 (m, 2 H), 7.41–7.35 (m, 2 H), 7.20–7.14 (m, 1 H), 3.31 (s, 2 H), 1.87 (tt, *J* = 8.3, 5.0 Hz, 1 H), 1.06–1.00 (m, 2 H), 0.91–0.86 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.1, 161.6, 138.1, 128.8 (2 C), 125.0, 118.9 (2 C), 40.1, 12.2, 7.9 (2 C) ppm. LC–MS: *m*/*z* = 201 $[M + H]^+$.

2-Phenyl-4,5,6,7-tetrahydro-2*H*-indazol-3-ol (3p): Purification by filtration through silica gel (pentane/EtOAc, 5:1) afforded **3p** (94 mg, 88% yield) as a yellow solid. ^{1}H NMR (400 MHz, CD_3OD): δ = 7.65–7.61 (m, 2 H), 7.53–7.48 (m, 2 H), 7.38–7.34 (m, 1 H), 2.63 (t, *J* = 6.0 Hz, 2 H), 2.39 (t, *J* = 6.0 Hz, 2 H), 1.90–1.78 (m, 4 H) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ = 151.0, 149.8, 137.0, 130.4 (2 C), 128.3, 123.0 (2 C), 104.5, 23.4, 22.9, 22.7, 19.6 ppm. LC–MS: *m*/*z* = $[M + H]^+$ 215.

3-Phenyl-1-(4-methoxyphenyl)-pyrazol-5(4*H*)-one (3t): Purification by filtration through silica gel (pentane/EtOAc, 5:1) afforded **3t** (103 mg, 77% yield) as an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.86 (d, *J* = 9.0 Hz, 2 H), 7.78–7.74 (m, 2 H), 7.48–7.42 (m, 3 H), 6.97 (d, *J* = 9.0 Hz, 2 H), 3.83 (s, 3 H), 3.82 (s, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.9, 157.2, 154.5, 131.4, 130.9, 130.6, 128.9 (2 C), 125.9 (2 C), 121.0 (2 C), 114.0 (2 C), 55.4, 39.4 ppm. LC–MS: *m*/*z* = $[M + H]^+$ 267.

3-Phenyl-1-(4-trifluorophenyl)-pyrazol-5(4*H*)-one (3u): Purification by filtration through silica gel (pentane/EtOAc, 5:1) afforded **3u** (120 mg, 79% yield) as a white solid; m.p. 149–150 °C (diisopropyl ether). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.17 (d, *J* = 8.6 Hz, 2 H), 7.80–7.77 (m, 2 H), 7.69 (d, *J* = 8.6 Hz, 2 H), 7.49–7.47 (m, 3 H), 3.88 (s, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.6, 155.0, 141.0, 129.2, 127.4, 126.5 (2 C), 126.3 (q, *J* = 32.6 Hz), 125.6 (q, *J* = 3.8 Hz, 2 C), 122.9 (2 C), 120.2 (q, *J* = 269.9 Hz), 118.5 (2 C), 39.9 ppm. LC–MS: *m*/*z* = 305 $[M + H]^+$.

5-Hydroxy-3,4-dimethyl-1-phenylpyrazole (3q): T3P® (50% in EtOAc, 1 mmol, 2 equiv.) was added to a mixture of ethyl 2-methylacetoacetate (**1q**, 0.5 mmol) and phenylhydrazine (**2a**, 0.5 mmol) in a microwave vial. The reaction volume was then adjusted to 0.5 mL with EtOAc, and the vessel was sealed under air. The mixture was then heated under microwave irradiation at 100 °C for 5 min. The residue was suspended in water, and then CH_2Cl_2 was added. The organic layer was washed with a saturated solution of $NaHCO_3$. The aqueous layers were combined and extracted with CH_2Cl_2. The combined organic layers were then washed with brine and dried with Na_2SO_4. After evaporation of the solvent, the obtained residue was purified by flash chromatography on silica gel (hexane/EtOAc, 1:1 and then 100% ethyl acetate) to afford **3q** (82 mg, 87% yield) as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.88 (dd, *J* = 7.4, 1.3 Hz, 2 H), 7.42–7.37 (m, 2 H), 7.21 (tt, *J* = 7.4, 1.3 Hz, 1 H), 3.27 (br. s, 1 H), 2.19 (s, 3 H), 1.53 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.9, 162.4, 137.6, 128.8 (2 C), 125.2, 118.7 (2 C), 22.3, 12.6 ppm. LC–MS: *m*/*z* = 189 $[M + H]^+$.

General Experimental Procedure for Compounds 3s and 3v–3x: T3P® (50% in EtOAc, 1 mmol, 2 equiv.) was added to a mixture of the β-keto ester (0.5 mmol) and hydrazine (0.5 mmol) in a microwave vial. The reaction volume was then adjusted to 0.5 mL with EtOAc, and the vessel was sealed under air. The mixture was then heated at 100 °C for 5 min under microwave irradiation. The residue was suspended in water, and then CH_2Cl_2 was added. The organic layer was washed with a saturated solution of $NaHCO_3$. The aqueous layers were combined and extracted with CH_2Cl_2. The combined organic layers were then washed with brine and dried with Na_2SO_4. After evaporation of the solvent, the obtained residue was purified by flash chromatography on silica gel (pentane/EtOAc, 4:1).

3-Phenyl-1-(4-methylphenyl)-pyrazol-5(4*H*)-ol (3s): White powder (95 mg, 76% yield). ^{1}H NMR (400 MHz, $[D_6]$DMSO): δ = 7.81 (dd, *J* = 7.0, 1.3 Hz, 2 H), 7.72 (d, *J* = 8.6 Hz, 2 H), 7.42–7.38 (m, 2 H), 7.33–7.29 (m, 1 H), 7.28 (dd, *J* = 8.6, 0.5 Hz, 2 H), 5.99–5.91 (br. s, 1 H), 2.34 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $[D_6]$DMSO): δ = 154.3, 149.2, 137.2, 136.6, 134.6, 133.5, 129.2, 128.5, 127.7, 125.0, 120.9, 20.51 ppm. LC–MS: *m*/*z* = 251 $[M + H]^+$.

3-Phenyl-1-(4-fluorophenyl)-pyrazol-5(4*H*)-one (3v): White solid (93 mg, 73% yield), m.p. 147–149 °C (diisopropyl ether); ref.[21] m.p. 149–153 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.98–7.93 (m, 2 H), 7.79–7.76 (m, 2 H), 7.48–7.46 (m, 3 H), 7.14–7.09 (m, 2 H), 3.86 (s, 2 H) ppm. LC–MS: *m*/*z* = 255 $[M + H]^+$.

3-Phenyl-1-(2-bromophenyl)pyrazol-5(4*H*)-one (3w): Light brown solid (125 mg, 79% yield); m.p. 162–164 °C (diisopropyl ether). ^{1}H NMR (400 MHz, $[D_6]$DMSO): δ = 7.81 (d, *J* = 8.3 Hz, 1 H), 7.76 (d, *J* = 7.3 Hz, 2 H), 7.55–7.50 (m, 2 H), 7.45–7.36 (m, 3 H), 7.31–7.28 (m, 1 H), 5.90 (br. s, 1 H) ppm. ^{13}C NMR (100 MHz, $[D_6]$DMSO): δ = 154.3, 149.9, 137.5, 133.7, 133.1, 130.6, 130.2, 128.5 (2 C), 128.4, 127.6, 124.9 (2 C), 121.6, 83.3 ppm. LC–MS: *m*/*z* = 315 $[M + H]^+$, 317.

3-Phenyl-1-(3-bromophenyl)pyrazol-5(4*H*)-one (3x): Light brown powder (132 mg, 84% yield); m.p. 111–113 °C (diisopropyl ether). ^{1}H NMR (400 MHz, $[D_6]$DMSO): δ = 12.13 (br. s, 1 H), 8.04 (s, 1 H), 7.90–7.83 (m, 3 H), 7.46–7.33 (m, 5 H), 6.03 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $[D_6]$DMSO): δ = 154.4, 150.3, 140.2, 133.0, 131.0, 128.6 (2 C), 128.2 (2 C), 125.3 (2 C), 122.9, 121.7, 119.4, 85.6 ppm. LC–MS: *m*/*z* = 315 $[M + H]^+$, 317.

Ethyl 5-Amino-3-methyl-1-phenyl-1*H*-pyrazole-4-carboxylate (3ra): T3P® (50% in EtOAc, 1 mmol, 2 equiv.) was added to a mixture of ethyl 2-cyanoacetoacetate (**1r**, 0.5 mmol) and phenylhydrazine (**2a**, 0.5 mmol) in a microwave vial. The reaction volume was then adjusted to 0.5 mL with EtOAc, and the vessel was sealed under air. The mixture was then heated under microwave irradiation at 100 °C for 5 min. The solvent was removed under reduced pressure, and the residue was purified by preparative HPLC (XBridge C18, MeCN/NH_4CO_3, gradient 25–95% MeCN) to afford **3ra** (52 mg, 42% yield) as a buff-colored solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.52–7.46 (m, 4 H), 7.38–7.34 (m, 1 H), 5.33 (br. s, 2 H), 4.33 (q, *J* = 7.2 Hz, 2 H), 2.40 (s, 3 H), 1.38 (t, *J* = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.2, 150.2, 149.9, 137.5, 129.6, 127.8, 123.8, 94.6, 59.4, 14.5 ppm. LC–MS: *m*/*z* = 246 $[M + H]^+$.

Supporting Information (see footnote on the first page of this article): General experimental procedure and ^{1}H and ^{13}C spectra of compounds.

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