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Synthesis of 4-Arylidenepyrazolones by a Gold-Catalyzed Cyclization/Arylidene Group Transfer Cascade of *N*-Propioloyl Hydrazones

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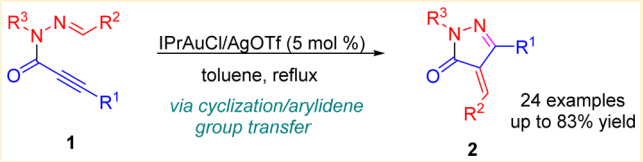
Supporting Information

ABSTRACT: An efficient gold-catalyzed cyclization/arylidene group transfer cascade reaction of *N*-propioloyl hydrazones has been developed. This method provides a novel approach for the synthesis of various functionalized 4-arylidenepyrazolones.



Pyrazolone is an important molecular motif and exists in many natural products, drugs, pharmaceutical candidates, and biologically important compounds.[1] Among those pyrazolone derivatives, 4-arylidenepyrazolones have been used as antagonists for a variety of biological targets (Figure 1)[2] such as effective inhibitors for HIV-1 integrase,[2a] orthopoxvirus,[2b] and inhibitor of H1N1 and H5N1 neuraminidases,[2c] as well as Farnesoid X Receptor.[2d] To date, the preparation of 4-arylidenepyrazolone derivatives usually relies on the condensation of substituted aldehydes[3] (or their acetal[4] or imine[5] precursors) with 2-pyrazolin-5-ones, which are, in turn, obtained by the Knorr condensation of β-ketoesters with substituted hydrazines. To the best of our knowledge, the use of a π-acidic transition-metal-catalyzed cyclization to access this family of compounds has not been disclosed.

Metal-catalyzed skeletal rearrangements provide an effective pathway for the construction of complex molecules.[6] In particular, the [3,3] rearrangement of various propargylic compounds has been well studied,[7] including the unique *N*-propargylic hydrazone derivatives. Such rearrangement reactions can be channeled to form different types of products by proper choice of substituents on the substrates. For example, we have reported the [3,3] sigmatropic rearrangement of *N*-propargylic sulfonylhydrazones for the stereoselective synthesis of sufonyldienes (Scheme 1, eq 1).[8] However, switching the *N*-sulfonyl group for an *N*-phenyl or *N*-alkyl group led to the formation of polysubstituted pyrazoles via a $PtCl_4$-catalyzed [3,3] sigmatropic rearrangement/cyclization cascade (Scheme 1, eq 2).[9] As part of our ongoing efforts in expanding the synthetic utility of *N*-propargylic hydrazones, we prepared the *N*-propioloyl hydrazones and envisioned that a similar rearrangement/cyclization sequence from these structures might afford pyridazinones (Scheme 1, eq 3).[10] However, when **1** was treated with a gold catalyst, the 4-arylidenepyrazolone **2** was obtained instead of the expected pyridazinone (Scheme 1, eq 4).[11,12] We report herein a novel method for the synthesis of various 4-arylidenepyrazolones from *N*-propioloyl hydrazones by gold-catalyzed cyclization/1,3-migration cascade.

We began our studies by reacting **1a** under the reaction conditions that we previously employed to convert *N*-propargylphenylhydrazones to pyrazoles (Scheme 1, eq 2). Treating **1a** with a catalytic amount of $PtCl_4$ in reflux toluene gave **2a** in 36% yield (Table 1, entry 1). A range of other transition-metal catalysts, including $Rh_2(Oct)_4$, $Rh_2(OAc)_4$, $Sc(OTf)_3$, CuI, $Cu(OAc)_2$, CuBr, and $CuBr{\cdot}SMe_2$, were tested to increase the yield of **2a**, but the results were unsatisfactory (Table 1, entries 2−8).

Recently, gold catalysis of organic reactions has become a highly active field.[13] The fact that gold has the unique catalytic activity on alkynes leads us to try gold catalysts. Interestingly, an improved 41% yield was obtained when $AuCl_3$ was used as the catalyst (Table 1, entry 9). Encouraged by these results, different gold catalyst systems (Table 1, entries 10−14) were screened, leading to the discovery that an optimal yield of 83% could be obtained by the use of a combination of the gold catalyst IPrAuCl and AgOTf (Table 1, entry 12). Other solvents, such as $PhCF_3$, DCE, DMSO, DMF, CCl_4, 1,4-dioxane, and THF, are less effective (entries 15−21). Therefore, the optimum reaction conditions were determined to be performing the reaction in toluene at reflux with 5 mol % IPrAuCl/AgOTf as the catalyst (Table 1, entry 12).

The substrate scope was explored, and the results are summarized in Scheme 2. Hydrazones derived from phenyl aldehydes bearing electron-donating groups (−OMe, −Me) or an electron-withdrawing halogen (Br) at different positions of the phenyl group, were successfully employed to give the corresponding products in moderate to good yields (Scheme 2, products **2a**−**2f**, 50−83% yields). The structure of **2d** was further confirmed by single-crystal X-ray structure analysis (Figure 2; see the Supporting Information). Heteroaryl aldehyde-derived hydrazones were also viable substrates (Scheme 2, products **2g** and **2h**, 51% and 61% yields). Hydrazone derived from 2-formylanaphthalene gave product **2i**

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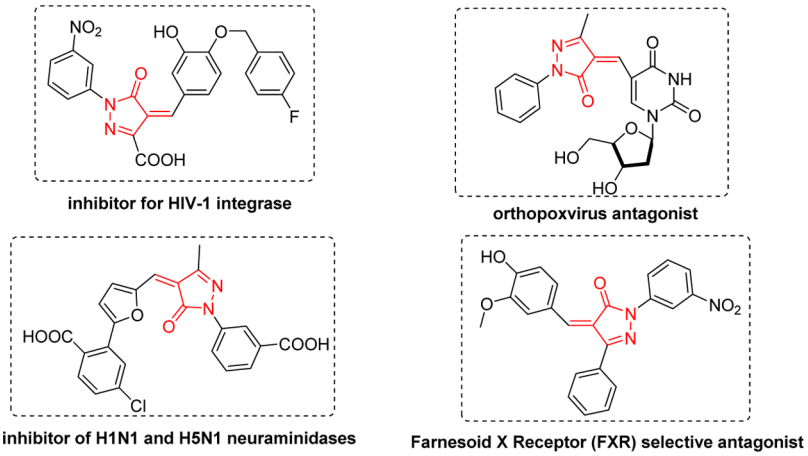
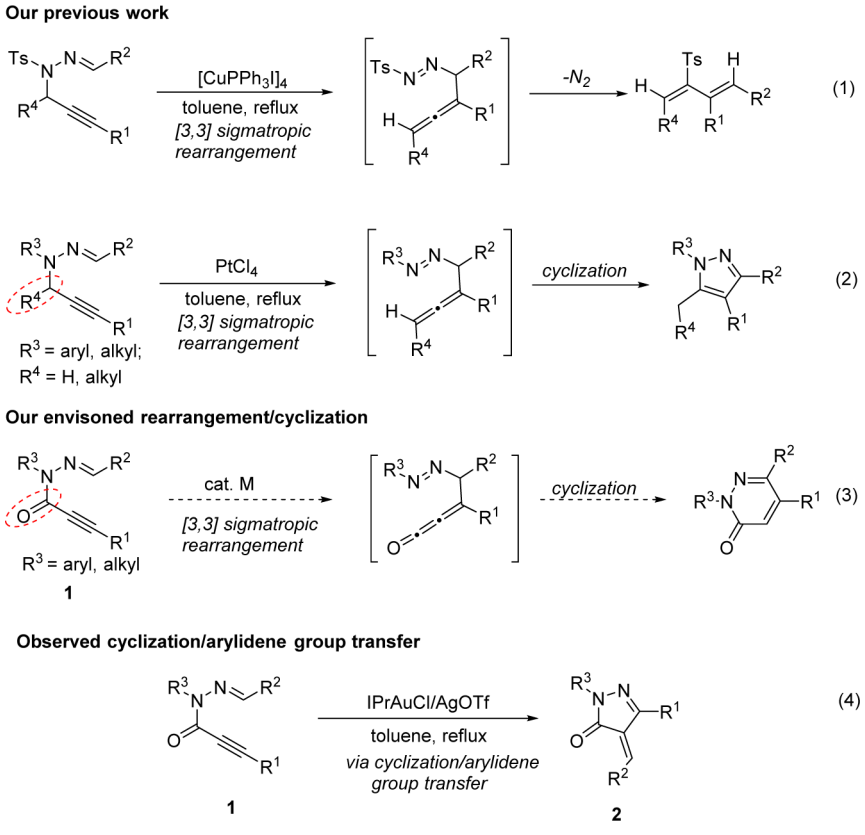


Figure 1. Biologically active 4-arylidenepyrazolone derivatives.

Scheme 1. [3,3] Rearrangement of *N*-Propargylhydrazones and Arylidene Group Transfer of *N*-Propioloyl Hydrazones



in 63% yield. Substrates with both electron-rich (−OMe) and electron-poor (−NO_2, −Br) phenyl groups at the R^3 position reacted smoothly to afford the desired products (Scheme 2, products **2j**−**2l**, 52−57% yields). Replacing the R^3 phenyl group with tosyl or a methyl group completely abolished the formation of the corresponding products due to the decomposition of the starting materials under the reaction conditions (Scheme 2, products **2m** and **2n**, 0% yield). The reaction seemed to be insensitive to the R^1 subsitutent. Hence, phenyl groups substituted with − Me, −COOMe, and − Cl, and numerous alkyl groups, such as *n*-propyl, cyclopropyl, cyclohexenyl, and the bulky *t*-butyl, were all tolerated (Scheme 2, products **2o**−**2u**, 40−70% yields). However, introducing a trimethylsilyl group at this position led to no reaction perhaps owing to that the triple bond could not be attacked by the nitrogen atom of the imine moiety because the trimethylsilyl group made it less electrophilic (Scheme 2, product **2v**, 0% yield). Interestingly, the present method was also compatible with the use of ketohydrazone as the substrate, albeit with moderate efficiency (Scheme 2, product **2w**, 41% yield). In addition, product **2x** was also prepared in moderate yield, which would be useful in the mechanism study experiment (Scheme 2, product **2x**, 51% yield).

To gain insight into the mechanism, a crossover experiment between equimolar amounts of reactants **1x** and **1c** was carried out, which yields the corresponding products **2x** and **2c**, and the crossover products **2a** and **2m** were also detected (Scheme 3, eq 1, determined by HPLC; Figure 3, see the Supporting

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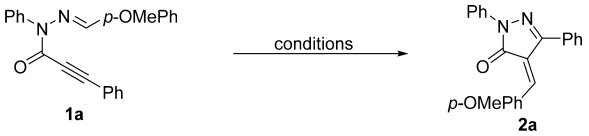
Table 1. Optimization of the Reaction Conditions[a]



entry	catalyst	solvent	t/h	result[b]
1	$PtCl_4$	$PhCH_3$	6	36%
2	$Rh_2(Oct)_4$	$PhCH_3$	6	NR[c]
3	$Rh_2(OAc)_4$	$PhCH_3$	6	NR
4	$Sc(OTf)_3$	$PhCH_3$	6	NR
5	CuI	$PhCH_3$	6	NR
6	$Cu(OAc)_2$	$PhCH_3$	6	NR
7	CuBr	$PhCH_3$	6	trace
8	$CuBr{\cdot}SMe_2$	$PhCH_3$	6	trace
9	$AuCl_3$	$PhCH_3$	1	41%
10	$Au(PPh_3)NTf_2$	$PhCH_3$	1	44%
11	$AuPPh_3Cl/AgOTf$	$PhCH_3$	6	60%
12	**IPrAuCl/AgOTf**	**$PhCH_3$**	**1**	**83%**
13	$IPrAuCl/AgBF_4$	$PhCH_3$	1	50%
14	$IPrAuCl/AgSbF_6$	$PhCH_3$	1	78%
15	IPrAuCl/AgOTf	$PhCF_3$	1	70%
16	IPrAuCl/AgOTf	DCE	6	33%
17[d]	IPrAuCl/AgOTf	DMSO	6	30%
18[d]	IPrAuCl/AgOTf	DMF	6	50%
19	IPrAuCl/AgOTf	CCl_4	6	57%
20	IPrAuCl/AgOTf	1,4-dioxane	1	complex
21	IPrAuCl/AgOTf	THF	1	complex

[a]Reaction conditions: The reaction was carried out using **1a** (0.3 mmol) and catalyst (5 mol %) in the solvent (3 mL) at reflux unless otherwise noted. [b]Isolated yield. [c]NR = no reaction. [d]The reaction was performed at 110 °C.

Information). This result clearly indicated that the 1,3-arylidene migration proceeds in an intermolecular manner. Moreover, the result led us to conjecture that trace amounts of water may participate in the reaction and 2-pyrazolin-5-one **6** may be a reactive intermediate. In order to verify our hypothesis, the reaction of **1c** with an equivalent of water was carried out, and **6a** was isolated as expected in 70% yield, together with the minor corresponding product **2c** and benzaldehyde (Scheme 3, eq 2). In addition, in the presence of **6a**, the reaction of **1p** afforded a nearly 1:1 mixture of **2c** and **2p** (Scheme 3, eq 3); these results indicated that **6** was produced as the reactive intermediate. It is noteworthy that the major product **2a** rather than the corresponding **2c** was obtained when **1a** reacted with equimolar amounts of *p*-anisaldehyde (Scheme 3, eq 4). Additionally, **6a** and *p*-anisaldehyde could smoothly give the condensation product **2a** in 84% yield under the optimized conditions (Scheme 3, eq 5), thus confirming the fact that the condensation reaction procedure of **6** with an aldehyde was included in the arylidene group transfer process.

On the basis of the above results, a proposed mechanism is illustrated in Scheme 4. First, coordination of the gold catalyst with the alkyne activates the triple bond of **1** for nucleophilic attack by the nitrogen atom of the hydrazone, leading to the cyclized vinyl gold intermediate **4**. In this process, the pyridazinone is not formed perhaps because of the weaker nucleophilicity of the carbon atom of the imine than the nitrogen atom. Then, **4** is hydrolyzed by advantageous water in the reaction system to give an aldehyde **7** and **5**, which is the enamine tautomer of **6**, and the gold catalyst is regenerated by protodemetalation of **4** at the same time. The *in situ* generated **5** then undergoes intermolecular nucleophilic attack at the carbonyl moiety of **7**, which affords the final product **2** and regenerates the water. As a note, the trace amounts of water plays a crucial role in the arylidene group transfer course. What's more, the high *Z* selectivity of **2** is probably owing to that the *E* isomer is destabilized because of the steric repulsion between R^1 and R^2.

In summary, we have developed a novel approach for the synthesis of 4-arylidenepyrazolone derivatives from *N*-propioloylhydrazones by a gold-catalyzed cyclization/1,3-migration cascade. The reaction is broad in substrate scope and provides convenient access to a variety of highly functionalized 4-arylidenepyrazolones. The present method complements traditional condensation reactions to prepare this family of compounds and shall find its potential applications in medicinal chemistry.

EXPERIMENTAL SECTION

General Information. Unless otherwise noted, all reagents were obtained commercially and used without further purification. Propargylic acid was prepared according to known references.[14]All reaction mixtures were stirred with a magnetic bar in flame-dried tubes. ^1H and ^{13}C spectra were recorded on a 400 or 500 MHz spectrometer. Chemical shifts were reported in ppm. ^1H NMR spectra were referenced to $CDCl_3$ (7.26 ppm), and ^{13}C NMR spectra were referenced to $CDCl_3$ (77.0 ppm). All ^{13}C NMR spectra were measured with complete proton decoupling. Peak multiplicities were designated by the following abbreviations: s, singlet; d, doublet; t, triplet; m, multiplet; brs, broad singlet, and *J*, coupling constant in Hz. IR spectra were recorded on an FTIR spectrometer as thin film. Absorptions were given in wavenumbers (cm^{-1}). HRMS spectra were recorded with a Micromass QTOF2 Quadrupole/Time-of-Flight Tandem mass spectrometer using electron spray ionization. HPLC separation and purification of the crossover experimental products were all conducted on an HPLC instrument at room temperature using toluene as elution solvent, and the chromatogram was monitored at 450 nm.

General Procedure for Synthesis of *N*-Propioloyl Hydrazones 1. A propynoic acid (5.5 mmol, 1.1 equiv) in $SOCl_2$ (5 mL) was heated at 60 °C for 3 h, and then the excess $SOCl_2$ was removed under reduced pressure. The resulting acid chloride was used without further purification. To the solution of the corresponding hydrazone (5 mmol, 1.0 equiv) in 15 mL of THF was added 1.6 M *n*-butyl lithium in hexane (4.68 mL, 7.5 mmol, 1.5 equiv) at −78 °C under the protection of N_2. A yellow solid was formed during the addition. The mixture was stirred for 15 min, and then propynoic acid chloride in 5 mL of THF was added. The resulting solution was warmed to rt over 30 min and quenched by adding H_2O. The solution was extracted with diethyl ether. The extracts were combined, washed with H_2O, and dried over anhydrous Na_2SO_4. The solvent was removed by vacuum, and the crude residue was purified by silica gel column chromatography (eluent: petroleum ether/EtOAc = 20/1), and the resulting *N*-propioloyl hydrazones **1** were further purified by recrystallyzation from ethyl acetate and hexane.

General Procedure for Synthesis of 4-Arylidenepyrazolones 2. The corresponding *N*-propioloyl hydrazones **1** (0.3 mmol), IPrAuCl (0.015 mmol, 9.3 mg), and AgOTf (0.015 mmol, 3.85 mg) were added to a 10 mL Schlenk tube, followed by the addition of $PhCH_3$ (3 mL), and the reaction mixture was stirred at reflux under the protection of N_2. Upon completion (monitored by TLC), the reaction mixture was cooled to room temperature and purified by silica gel column chromatography to afford the corresponding 4-arylidenepyrazolones **2** (eluent: petroleum ether/EtOAc = 30/1).

(*Z*)-4-(4-Methoxybenzylidene)-2,5-diphenyl-2,4-dihydro-3*H*-pyrazol-3-one (2a). An orange solid (88 mg, 83% yield, mp: 175−176 °C); **^1H NMR** (400 MHz, $CDCl_3$) δ 3.87 (s, 3H), 6.97−7.00 (m, 2H), 7.20−7.24 (m, 1H), 7.42−7.46 (m, 2H), 7.52−7.55 (m, 4H), 7.66−7.68 (m, 2H), 8.08 (dd, 2H, J_1 = 8.8 Hz, J_2 = 1.1 Hz), 8.53−8.56

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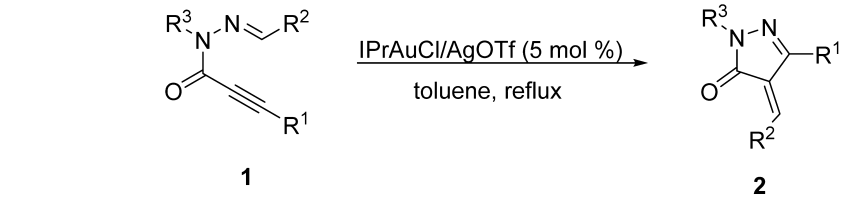
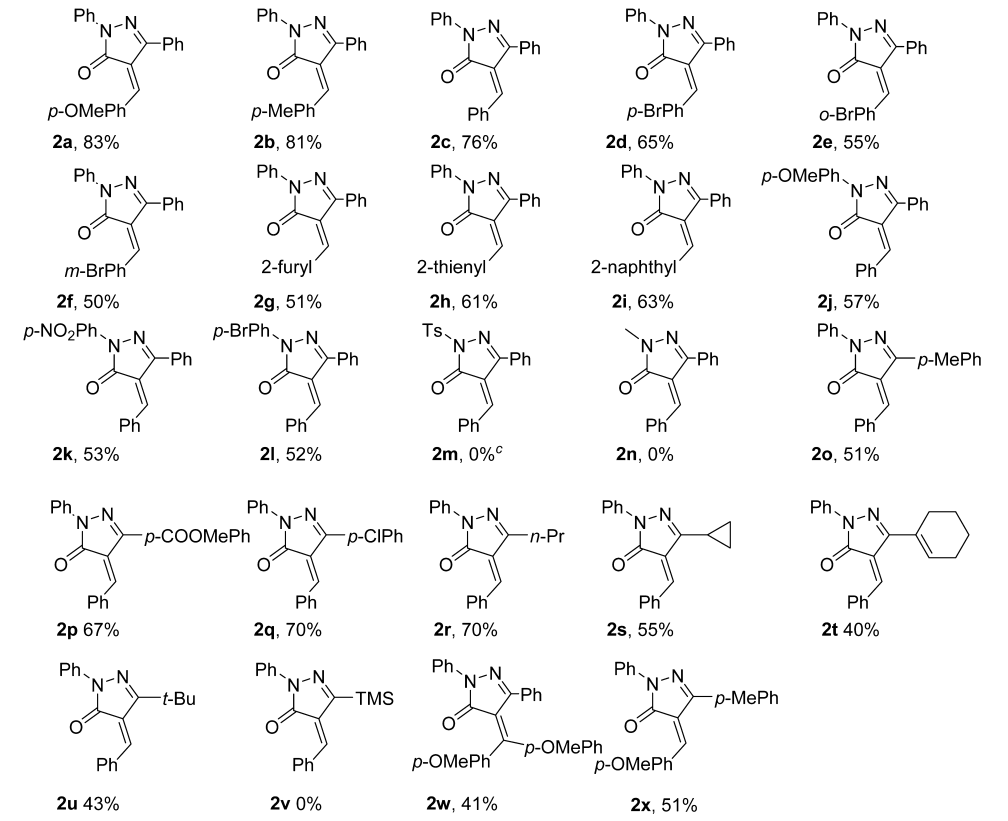
Scheme 2. Gold-Catalyzed Synthesis of 4-Arylidenepyrazolones[a,b]





[a]Reaction conditions: The reaction was carried out using **1** (0.3 mmol) and catalyst (5 mol %) in $PhCH_3$ (3 mL) at reflux in a Schlenk tube. [b]Isolated yields. [c]Ts = *p*-toluenesulfonyl.

(m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 55.6, 114.2, 119.5, 123.71, 125.0, 126.4, 128.8, 128.9, 129.0, 131.2, 136.9, 138.7, 139.8, 149.8, 153.3, 162.5, 164.0; **IR** (film): 3080, 2839, 1682, 1585 cm^{-1}; **HRMS** (ESI) *m*/*z* Calculated for $C_{23}H_{19}N_2O_2$ $[M + H]^+$ 355.1441, found: 355.1443.

(*Z*)-4-(4-Methylbenzylidene)-2,5-diphenyl-2,4-dihydro-3*H*-pyrazol-3-one (2b). A red solid (82 mg, 81% yield, mp: 154−155 °C); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.44 (s, 3H), 7.20−7.25 (m, 1H) 7.31 (d, 2H, *J* = 8.1 Hz), 7.43−7.47 (m, 2H), 7.54−7.56 (m, 3H), 7.61(s, 1H), 7.67−7.70 (m, 2H), 8.08 (dd, 2H, J_1 = 8.5 Hz, J_2 = 1.0 Hz), 8.39 (d, 2H, *J* = 8.2 Hz); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 22.0, 118.9, 119.5, 125.1, 125.5, 128.8, 128.9, 129.5, 129.8, 130.6, 130.9, 134.2, 138.5, 144.7, 150.2, 153.1, 162.2; **IR** (film): 3063, 2959, 1687, 1593 cm^{-1}; **HRMS** (ESI) *m*/*z* Calculated for $C_{23}H_{19}N_2O$ $[M + H]^+$ 339.1492, found: 339.1495.

(*Z*)-4-Benzylidene-2,5-diphenyl-2,4-dihydro-3*H*-pyrazol-3-one (2c). A red solid (73.8 mg, 76% yield, mp: 144−145 °C); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.22−7.25 (m, 1H) 7.44−7.57 (m, 8H), 7.64(s, 1H), 7.69−7.71 (m, 2H), 8.09 (dd, 2H, J_1 = 8.7 Hz, J_2 = 1.1 Hz), 8.44−8.46 (m, 2H; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 119.3, 125.0, 126.4, 128.5, 128.7, 128.8, 128.9, 129.7, 130.7, 132.8, 133.1, 133.7, 138.3, 149.9, 152.8, 161.9; **IR** (film): 3062, 1683, 1593 cm^{-1}; **HRMS** (ESI) *m*/*z* Calculated for $C_{22}H_{17}N_2O$ $[M + H]^+$ 325.1335, found: 325.1331.

(*Z*)-4-(4-Bromobenzylidene)-2,5-diphenyl-2,4-dihydro-3*H*-pyrazol-3-one (2d). A red solid (78.6 mg, 65% yield, mp: 167−169 °C); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.21−7.24 (m, 1H), 7.42−7.46 (m, 2H), 7.54−7.56 (m, 4H), 7.61−7.64 (m, 2H), 7.66−7.68 (m, 2H), 8.03 (dd, 2H, J_1 = 8.7 Hz, J_2 = 1.0 Hz), 8.31−8.34 (m, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 119.4, 125.3, 126.9, 128.3, 128.8, 128.9, 129.0, 129.9, 130.5, 131.7, 131.9, 135.0, 138.2, 148.2, 152.8, 161.8; **IR** (film): 3063, 1686, 1596 cm^{-1}; **HRMS** (ESI) *m*/*z* Calculated for $C_{22}H_{16}BrN_2O$ $[M + H]^+$ 403.0441 and 405.0420, found: 403.0446 and 405.0425.

(*Z*)-4-(2-Bromobenzylidene)-2,5-diphenyl-2,4-dihydro-3*H*-pyrazol-3-one (2e). A red solid (66.5 mg, 55% yield, mp: 150−151 °C); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.22−7.23 (m, 1H), 7.35−7.37 (m, 1H), 7.42−7.47 (m, 3H), 7.55−7.56 (m, 3H), 7.66−7.68 (m, 1H), 7.75−7.77 (m, 2H), 8.01−8.06 (m, 3H), 8.73 (d, 1H, *J* = 7.6 Hz); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 119.3, 125.3, 126.8, 127.1, 127.3, 128.7, 128.8, 129.0, 130.0, 130.5, 132.0, 132.9, 133.3, 133.4, 138.2, 147.5, 152.4, 161.7; **IR** (film): 3092, 1687, 1597 cm^{-1}; **HRMS** (ESI) *m*/*z* Calculated for $C_{22}H_{16}BrN_2O$ $[M + H]^+$ 403.0441 and 405.0420, found: 403.0446 and 405.0425.

(*Z*)-4-(3-Bromobenzylidene)-2,5-diphenyl-2,4-dihydro-3*H*-pyrazol-3-one (2f). A red solid (60.5 mg, 50% yield, mp: 112−113 °C); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.21−7.25 (m, 1H), 7.35−7.39 (m, 1H), 7.42−7.46 (m, 2H), 7.53 (s, 1H), 7.55−7.56 (m, 3H), 7.65−7.67 (m, 3H), 8.03 (d, 2H, *J* = 8.2 Hz), 8.43 (d, 1H, *J* = 7.7 Hz), 8.55

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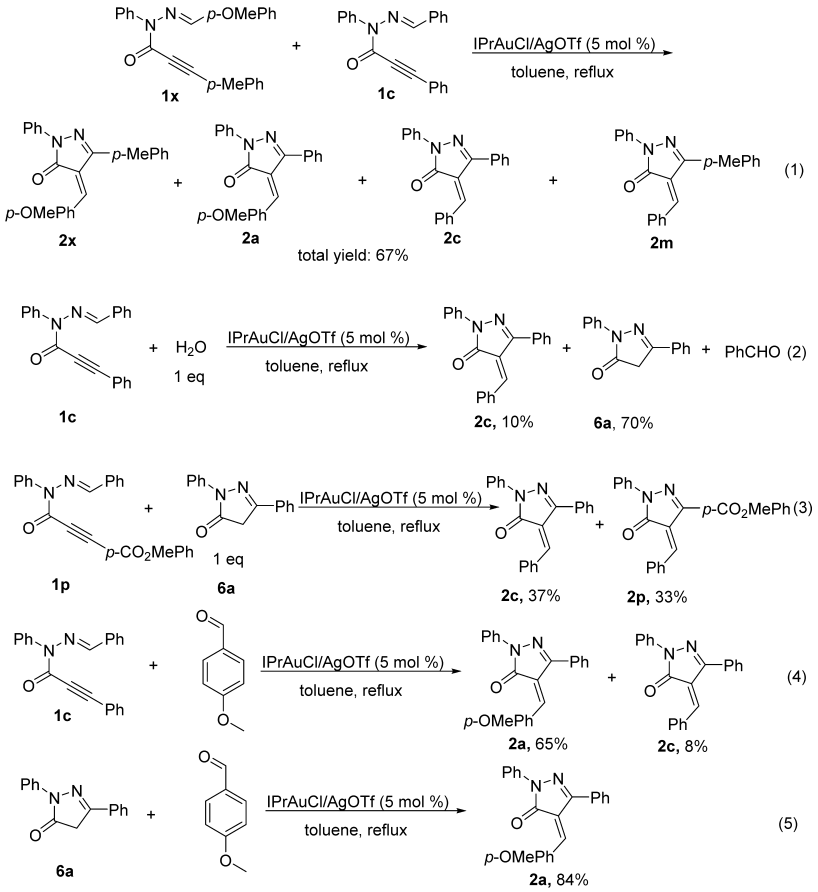
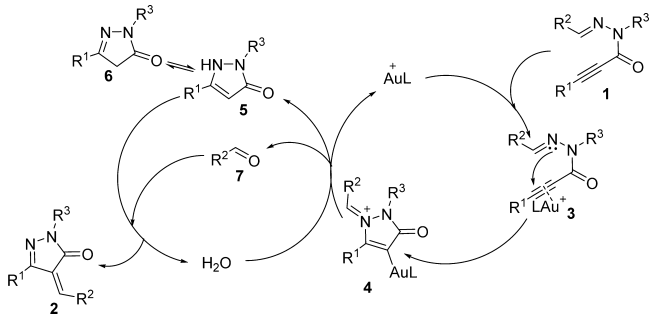
Scheme 3. Mechanism Study



Scheme 4. Proposed Mechanism



(s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 119.5, 122.5, 125.3, 127.8, 128.8, 128.9, 129.0, 129.9, 130.0, 130.5, 131.9, 134.7, 135.6, 136.0, 138.2, 147.7, 152.6, 161.7; **IR** (film): 3062, 1686, 1596 cm^{-1}; **HRMS** (ESI) m/z Calculated for $C_{22}H_{16}BrN_2O$ $[M + H]^+$ 403.0441 and 405.0420, found: 403.0446 and 405.0425.

(*Z*)-4-(Furan-2-ylmethylene)-2,5-diphenyl-2,4-dihydro-3*H*-pyrazol-3-one (2g). A red solid (48.1 mg, 51% yield, mp: 162−163 °C); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.73−6.74 (m, 1H), 7.21−7.24 (m, 1H), 7.43−7.47 (m, 2H), 7.52−7.54 (m, 3H), 7.59(s, 1H), 7.68−7.70 (m, 2H), 7.75 (dd, 1H, J_1 = 1.5 Hz, J_2 = 0.5 Hz), 8.06−8.08 (m, 2H), 8.84 (d, 1H, J = 3.8 Hz) ; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 114.9, 119.3, 121.2, 125.1, 125.5, 128.6, 128.8, 129.0, 129.7, 130.9, 131.7, 138.5, 148.8, 150.9, 151.8, 162.3; **IR** (film): 3134, 1682, 1609 cm^{-1}; **HRMS** (ESI) m/z Calculated for $C_{20}H_{15}N_2O_2$ $[M + H]^+$ 315.1128, found: 315.1133.

(*Z*)-2,5-Diphenyl-4-(thiophen-2-ylmethylene)-2,4-dihydro-3*H*-pyrazol-3-one (2h). A brownness solid (60.4 mg, 61% yield, mp: 139−140 °C); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.20−7.24 (m, 2H), 7.42−7.47 (m, 2H), 7.52−7.57 (m, 3H), 7.67−7.70 (m, 2H), 7.83(s, 1H), 7.86−7.88 (m, 1H), 7.95 (dd, 1H, J_1 = 3.8 Hz, J_2 = 0.5 Hz), 8.09−8.13 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 119.1, 121.0, 124.9, 128.1, 128.6, 128.7, 128.9, 129.6, 130.9, 136.8, 138.4, 138.7,138.9, 141.4, 151.9, 162.4; **IR** (film): 3062, 1682, 1593 cm^{-1}; **HRMS** (ESI) m/z Calculated for $C_{20}H_{15}N_2OS$ $[M + H]^+$ 331.0900, found: 331.0904.

(*Z*)-4-(Naphthalen-2-ylmethylene)-2,5-diphenyl-2,4-dihydro-3*H*-pyrazol-3-one (2i). A red solid (70.8 mg, 63% yield, mp: 151−152 °C); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.22−7.25 (m, 1H), 7.45−7.48 (m, 2H), 7.51−7.62 (m, 5H), 7.71−7.73 (m, 2H), 7.77(s, 1H), 7.86 (d, 1H, J = 8.1 Hz), 7.91 (d, 1H, J = 8.6 Hz), 7.98 (d, 1H, J = 8.0 Hz), 8.09 (dd, 2H, J_1 = 8.6 Hz, J_2 = 1.0 Hz), 8.58 (dd, 1H, J_1 = 8.7 Hz, J_2 = 1.6 Hz), 8.94 (s, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$); δ 119.5, 125.1, 126.3, 126.7, 127.7, 128.2, 128.8, 128.9, 129.0, 129.7, 129.8, 130.7, 130.9, 132.8, 135.4, 136.2, 138.4, 149.9, 153.0, 162.0; **IR** (film): 3057, 1684, 1595 cm^{-1}; **HRMS** (ESI) m/z Calculated for $C_{26}H_{19}N_2O$ $[M + H]^+$ 375.1492, found: 375.1493.

(*Z*)-4-Benzylidene-2-(4-methoxyphenyl)-5-phenyl-2,4-dihydro-3*H*-pyrazol-3-one (2j). A red solid (60.6 mg, 57% yield, mp: 153−154 °C); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.83 (s, 3H), 6.97 (d, 2H, J = 8.7 Hz), 7.49−7.54 (m, 6H), 7.64 (s, 1H), 7.67−7.68 (m, 2H), 7.93 (d, 2H, J = 8.7 Hz), 8.45 (d, 2H, J = 7.3 Hz); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 55.5, 114.0, 121.3, 126.5, 128.6, 128.9, 129.0, 129.7, 130.8, 131.8, 133.0, 133.1, 133.8, 149.9, 152.7, 157.2, 161.7; **IR** (film): 3066, 2932, 1683, 1615 cm^{-1}; **HRMS** (ESI) m/z Calculated for $C_{23}H_{19}N_2O_2$ $[M + H]^+$ 355.1441, found: 355.1443.

(*Z*)-4-Benzylidene-2-(4-nitrophenyl)-5-phenyl-2,4-dihydro-3*H*-pyrazol-3-one (2k). A bisque solid (58.7 mg, 53% yield, mp: 192−193 °C); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.51−7.55 (m, 2H), 7.58−7.61 (m, 4H), 7.68−7.70 (m, 3H), 8.28−8.30 (m, 2H), 8.33−8.35(m, 2H), 8.41 (d, 2H, J = 7.4 Hz); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 118.0, 124.7, 125.4, 128.7, 128.8, 129.0, 130.1, 130.3, 132.5, 133.8, 133.9, 143.5, 143.8, 151.5, 154.5, 162.4; **IR** (film): 3113, 1697, 1590

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J. Org. Chem. 2015, 80, 9307−9313

cm^{-1}; **HRMS** (ESI) m/z Calculated for $C_{22}H_{16}N_3O_3$ $[M + H]^+$ 370.1186, found: 370.1188.

(*Z*)-4-Benzylidene-2-(4-bromophenyl)-5-phenyl-2,4-dihydro-3*H*-pyrazol-3-one (2l). A red solid (63 mg, 52% yield, mp: 171−173 °C); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.48−7.53 (m, 3H), 7.54−7.59 (m, 5H), 7.64−7.69 (m, 3H), 7.98−8.02 (m, 2H), 8.40−8.42(m, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 117.9, 120.6, 126.2, 128.6, 128.9, 129.0, 129.9, 130.5, 131.7, 132.8, 133.3, 133.8, 137.5, 150.5, 153.3, 161.9; **IR** (film): 3063, 1689, 1597 cm^{-1}; **HRMS** (ESI) m/z Calculated for $C_{22}H_{16}BrN_2O$ $[M + H]^+$ 403.0441 and 405.0420, found: 403.0446 and 405.0425.

(*Z*)-4-Benzylidene-2-phenyl-5-(*p*-tolyl)-2,4-dihydro-3*H*-pyrazol-3-one (2o). A red solid (52 mg, 51% yield, mp: 162−163 °C); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 2.47 (s, 3H), 7.21−7.24 (m, 1H), 7.36 (d, 2H, J = 7.7 Hz), 7.43−7.46 (m, 2H), 7.49−7.52 (m, 2H), 7.54 (d, 1H, J = 7.0 Hz), 7.58 (d, 2H, J = 7.78 Hz), 7.64 (s, 1H), 8.07 (d, 2H, J = 7.9 Hz), 8.44 (d, 2H, J = 7.3 Hz); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 21.4, 119.4, 125.0, 126.6, 127.9, 128.6, 128.7, 128.8, 129.6, 132.9, 133.0, 133.7, 138.4, 139.9, 149.9, 152.9, 161.9; **IR** (film): 3065, 2919, 1684, 1615 cm^{-1}; **HRMS** (ESI) m/z Calculated for $C_{23}H_{19}N_2O$ $[M + H]^+$ 339.1492, found: 339.1496.

Methyl (*Z*)-4-(4-Benzylidene-5-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazol-3-yl)benzoate (2p). An orange solid (76.8 mg, 67% yield, mp: 199−200 °C); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 3.97 (s, 3H), 7.21−7.24 (m, 1H), 7.42−7.45 (m, 2H), 7.48−7.51 (m, 2H), 7.54−7.55 (m, 1H), 7.62 (s, 1H), 7.76 (d, 2H, J = 8.2 Hz), 8.03 (m, 2H), 8.21 (d, 2H, J = 8.3 Hz), 8.43 (d, 2H, J = 7.4 Hz); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 52.3, 119.4, 125.3, 126.0, 128.6, 128.7, 128.8, 130.1, 131.2, 132.7, 133.4, 133.8, 135.0, 138.2, 150.0, 151.7, 161.8, 166.4; **IR** (film): 3069, 2950, 1725, 1687, 1594 cm^{-1}; **HRMS** (ESI) m/z Calculated for $C_{24}H_{19}N_2O_3$ $[M + H]^+$ 383.1390, found: 383.1395.

(*Z*)-4-Benzylidene-5-(4-chlorophenyl)-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one (2q). A red solid (75 mg, 70% yield, mp: 180−181 °C); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.21−7.24 (m, 1H), 7.42−7.45 (m, 2H), 7.49−7.52 (m, 3H), 7.53 (s, 1H), 7.55 (s, 1H), 7.58 (s, 1H), 7.62 (d, 2H, J = 8.3 Hz), 8.03 (d, 2H, J = 7.8 Hz), 8.43 (d, 2H, J = 7.4 Hz); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 119.4, 125.3, 126.2, 128.7, 128.8, 129.2, 129.3, 130.1, 132.8, 133.4, 133.8, 136.0, 138.3, 150.0, 151.8, 161.8; **IR** (film): 3070, 1686, 1593 cm^{-1}; **HRMS** (ESI) m/z Calculated for $C_{22}H_{16}ClN_2O$ $[M + H]^+$ 359.0946, found: 359.0947.

(*Z*)-4-Benzylidene-2-phenyl-5-propyl-2,4-dihydro-3*H*-pyrazol-3-one (2r). An orange solid (61 mg, 70% yield, mp: 108−109 °C); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.10 (t, 3H, J = 7.4 Hz), 1.83 (sext, 2H, J = 7.4 Hz), 2.65 (t, 2H, J = 7.3 Hz), 7.17−7.21 (m, 1H), 7.38−7.44 (m, 3H), 7.47−7.55 (m, 3H), 8.01 (d, 2H, J = 7.7 Hz), 8.48 (dd, 2H, J_1 = 8.0 Hz, J_2 = 1.4 Hz); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 13.9, 20.6, 29.1, 119.0, 124.7, 127.1, 128.5, 128.6, 132.7, 132.8, 133.5, 138.4, 146.3, 153.7, 161.9; **IR** (film): 3068, 2957, 1678, 1614 cm^{-1}; **HRMS** (ESI) m/z Calculated for $C_{19}H_{19}N_2O$ $[M + H]^+$ 291.1492, found: 291.1493.

(*Z*)-4-Benzylidene-5-cyclopropyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one (2s). A red solid (48 mg, 55% yield, mp: 123−124 °C); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 1.00−1.04 (m, 2H), 1.07−1.13 (m, 2H), 1.86−1.92 (m, 1H), 7.15−7.19 (m, 1H), 7.38−7.42 (m, 2H), 7.49−7.55 (m, 3H), 7.66 (s, 1H), 7.96−7.98 (m, 2H), 8.51 (dd, 2H, J_1 = 8.3 Hz, J_2 = 1.0 Hz); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 6.8, 7.3, 119.0, 124.7, 127.8, 128.7, 132.9, 133.0, 133.6, 138.5, 146.6, 154.8, 162.1; **IR** (film): 3071, 3005, 1683, 1597 cm^{-1}; **HRMS** (ESI) m/z Calculated for $C_{19}H_{17}N_2O$ $[M + H]^+$ 289.1335, found: 289.1338.

(*Z*)-4-Benzylidene-5-(cyclohex-1-en-1-yl)-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one (2t). A red solid (40 mg, 40% yield, mp: 129−130 °C); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 1.73−1.78 (m, 2H), 1.81−1.85 (m, 2H), 2.30−2.32 (m, 2H), 2.52−2.55 (m, 2H), 6.16−6.18 (m, 1H), 7.17−7.20 (m, 1H), 7.39−7.43(m, 2H), 7.48−7.55 (m, 3H), 7.68 (s, 1H), 8.01 (dd, 2H, J_1 = 8.7 Hz, J_2 = 1.0 Hz), 8.40 (dd, 2H, J_1 = 8.2 Hz, J_2 = 1.4 Hz); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 21.9, 22.4, 25.9, 26.9, 119.3, 124.9, 126.3, 128.5, 128.7, 129.7, 132.7, 132.9, 133.6, 138.5, 149.3, 153.9, 162.0; **IR** (film): 3065, 2931, 2857, 1687, 1596 cm^{-1}; **HRMS** (ESI) m/z Calculated for $C_{22}H_{21}N_2O$ $[M + H]^+$ 329.1648, found: 329.1645.

(*Z*)-4-Benzylidene-5-(*tert*-butyl)-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one (2u). A red liquid (39 mg, 43% yield); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 1.52 (s, 9H), 7.17−7.21 (m, 1H), 7.41−7.44(m, 2H), 7.48−7.54 (m, 3H), 7.85 (s, 1H), 8.02−8.04 (m, 2H), 8.35 (dd, 2H, J_1 = 8.0 Hz, J_2 = 1.4 Hz); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 29.5, 34.9, 118.9, 124.6, 125.9, 128.3, 128.6, 132.3, 132.5, 133.1, 138.4, 147.8, 158.8, 162.3; **IR** (film): 3067, 2971, 2930, 1688, 1597 cm^{-1}; **HRMS** (ESI) m/z Calculated for $C_{20}H_{21}N_2O$ $[M + H]^+$ 305.1648, found: 305.1648.

4-(Bis(4-methoxyphenyl)methylene)-2,5-diphenyl-2,4-dihydro-3*H*-pyrazol-3-one (2w). A purple solid (56 mg, 41% yield, mp: 203−204 °C); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.69 (s, 3H), 3.90 (s, 3H), 6.51 (d, 2H, J = 8.5 Hz), 6.96−6.99 (m, 4H), 7.02−7.08 (m, 3H), 7.15−7.17 (m, 3H), 7.35−7.40 (m, 2H), 7.51 (d, 2H, J = 8.7 Hz), 8.06 (d, 2H, J = 7.8 Hz); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 55.3, 55.4, 113.1, 113.4, 119.2, 120.5, 124.2, 124.5, 127.6, 127.7, 127.9, 128.6, 129.8, 131.8, 132.8, 135.1, 135.4, 138.8, 152.6, 162.4, 163.4, 165.7; **IR** (film): 3061, 2931, 1680, 1597 cm^{-1}; **HRMS** (ESI) m/z Calculated for $C_{30}H_{25}N_2O_3$ $[M + H]^+$ 461.1860, found: 461.1863.

(*Z*)-4-(4-Methoxybenzylidene)-2-phenyl-5-(*p*-tolyl)-2,4-dihydro-3*H*-pyrazol-3-one (2x). A red solid (56 mg, 51% yield, mp: 178−179 °C); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 2.45 (s, 3H), 3.87 (s, 3H), 6.97−7.00 (m, 2H), 7.19−7.22 (m, 1H), 7.34 (d, 2H, J = 8.1 Hz), 7.42−7.46 (m, 2H), 7.55−7.57 (m, 3H), 8.07−8.10 (m, 2H), 8.52−8.55(dd, 2H, J_1 = 7.1 Hz, J_2 = 1.8 Hz); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 21.3, 55.4, 114.1, 119.4, 123.8, 124.8, 126.4, 128.2, 128.6, 128.8, 129.5, 136.8, 138.6, 139.7, 149.6, 153.2, 162.4, 163.8; **IR** (film): 3084, 2847, 1687, 1584 cm^{-1}; **HRMS** (ESI) m/z Calculated for $C_{24}H_{21}N_2O_2$ $[M + H]^+$ 369.1598, found: 369.1601.

2,5-Diphenyl-2,4-dihydro-3*H*-pyrazol-3-one (6a). A white solid (49.7 mg, 70% yield, mp: 88−90 °C); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 3.79 (s, 2H), 7.20−7.24 (m, 1H), 7.40−7.47 (m, 5H,), 7.74−7.77 (m, 2H), 7.96−7.99 (m, 2H), **^{13}C NMR** (125 MHz, $CDCl_3$) δ 39.6, 119.0, 125.3, 125.9, 128.8, 128.9, 130.7, 130.8, 138.1, 154.6, 170.2. **IR** (film): 2965, 1705, 1593 cm^{-1}. **HRMS** (ESI) m/z Calculated for $C_{15}H_{13}N_2O$ $[M + H]^+$ 237.1022, found: 237.1026.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01366.

Crystallographic data of **2d** (CIF)

^{1}H and ^{13}C NMR spectra of all products, crystallographic data of **2d**, and the HPLC experiment (PDF)

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Notes

The authors declare no competing financial interest.

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