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Radical Addition of Hydrazones by α-Bromo Ketones To Prepare 1,3,5-Trisubstituted Pyrazoles via Visible Light Catalysis

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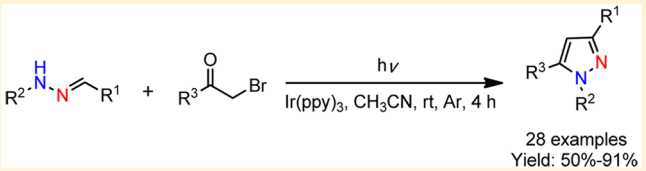
Supporting Information

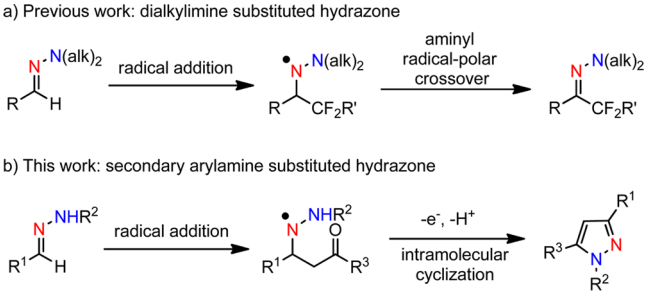
ABSTRACT: A novel efficient tandem reaction of hydrazones and α-bromo ketones is reported for the preparation of 1,3,5-trisubstituted pyrazoles by visible light catalysis. In this system, the monosubstituted hydrazones show wonderful reaction activity with alkyl radicals, generated from α-bromo ketones. A radical addition followed by intramolecular cyclization affords the important pyrazole skeleton in good to excellent yields. This efficient strategy under mild conditions with wide group tolerance provides a potential approach to the 1,3,5-trisubstituted pyrazoles.



INTRODUCTION

Visible light photoredox catalysis has attracted a great deal of attention in organic synthesis because of its low cost, easy availability, and environmental friendliness.[1] In particular, it features a unique ability to facilitate radical/polar crossover reactions via single-electron transfer. Following this strategy, many kinds of covalent bonds such as C═O, C═C, C−X, and even C−H have been activated into relative radical intermediates by photocatalysis,[2] and numerous significant chemical conversions have been realized, including radical addition, dehydrogen cross coupling, and cyclic reaction.[3] Recently, Zhu and Hashni independently reported visible light photoredox-catalyzed aminyl radical/polar crossover reaction to C−H difluoroalkylation of aldehyde-derived hydrazones.[4] They proposed that the addition of the generated CF_2 radical to the C═N bond leads to the aminyl radical intermediate, which then proceeds to singlet-electron oxidation and deprotonation to yield the product (Scheme 1a). In their work, the disubstituted groups on nitrogen are essential for the successful conversion; complex byproducts would be obtained if there is only one substitution. Herein, we report that the hydrazones which have monosubstituted group can react with α-bromo ketones to construct pyrazoles in an efficient way (Scheme 1b).

Scheme 1. Radical Addition to Carbon−Nitrogen π Bonds



Pyrazoles, with a wide range of biological activities and pharmacological properties,[5] are important structural motifs present in a wide range of natural products[6] and synthetic biologically active compounds such as Celebrex[5f,7] and Viagra.[8] In addition, pyrazoles can be used as ligands of metallic complexes for carbon−carbon coupling reaction.[9] Traditional strategies for the synthesis of 1,3,5-trisubstituted pyrazoles include oxidative aromatization of 1,3,5-triaryl pyrazolines,[10] cyclocondensation of hydrazines with 1,3-dicarbonyl compounds,[11] and intramolecular C−N coupling of acetylenic and alkenyl hydrazones.[12] Despite these great advances, the synthetic processes suffer from the use of toxic, expensive reagents and harsh reaction conditions. The strategy presented here is very attractive, because it shows the good to excellent yields of 1,3,5-trisubstituted pyrazole under mild conditions, short reaction time, and good function group tolerance.

RESULTS AND DISCUSSION

We started our investigation by using (*E*)-1-benzylidene-2-phenylhydrazine (**1a**) and α-bromoacetophenone (**2a**) as substrates (Table 1). Upon irradiation of **1a** (0.1 mmol), **2a** (0.15 mmol), $NaHCO_3$ (0.1 mmol), and $Ir(ppy)_3$ (2 mol %) in 2 mL of DMSO with blue LEDs (λ_{max} = 450 nm) under an Ar atmosphere for 2 h, an 80% yield of **3a** was obtained (Table 1, entry 1). The good yield stimulated us to explore and optimize the reaction conditions. Considering that DMSO was inconvenient during workup, we screened other different solvents and found CH_3CN to be the best medium for this conversion, which provided target compound **3a** in a 75% yield (Table 1, entries 2−

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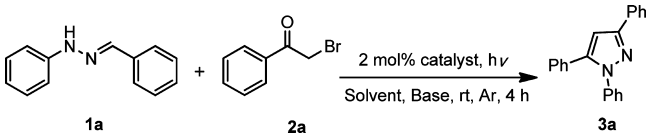
Table 1. Optimization of the Reaction Conditions[a]



1a 2a 3a

entry	solvent	catalyst	base (1 equiv)	yield (%)[b]
1[c]	DMSO	$Ir(ppy)_3$	$NaHCO_3$	80
2	dioxane	$Ir(ppy)_3$	$NaHCO_3$	51
3	$ClCH_2CH_2Cl$	$Ir(ppy)_3$	$NaHCO_3$	<5
4	CH_3CN	$Ir(ppy)_3$	$NaHCO_3$	75
5	CH_3CN	$Ir(ppy)_3$	K_2CO_3	71
6	CH_3CN	$Ir(ppy)_3$	Na_2CO_3	80
7[c]	DMSO	$Ir(ppy)_3$	Na_2CO_3	81
8[d]	CH_3CN	$Ir(ppy)_3$	Na_2CO_3	66
9[e]	CH_3CN	$Ir(ppy)_3$	Na_2CO_3	76
10[f]	CH_3CN	$Ir(ppy)_3$	Na_2CO_3	66
11[g]	CH_3CN	$Ir(ppy)_3$	Na_2CO_3	67
12	CH_3CN	Eosine	Na_2CO_3	<5
13	CH_3CN	$Ru(bpy)_3Cl_2·6H_2O$	Na_2CO_3	17
14[h]	CH_3CN	$Ir(ppy)_3$	Na_2CO_3	70
15[i]	CH_3CN	$Ir(ppy)_3$	Na_2CO_3	77
16[j]	CH_3CN	$Ir(ppy)_3$	Na_2CO_3	0
17	CH_3CN	–	Na_2CO_3	0

[a]Reaction conditions: 0.1 mmol of (*E*)-1-benzylidene-2-phenylhydrazine, 0.15 mmol of α-bromoacetophenone, 2 mol % catalyst, and 1 equiv of base in 2 mL of solvent irradiated by blue LEDs under Ar for 4 h. [b]Yields determined by ^1H NMR using diphenylacetonitrile as an internal standard. [c]Reaction time of 2 h. [d]0.5 equivalent of Na_2CO_3 was used. [e]2 equivalents of Na_2CO_3 was used. [f]1 equivalent of **2a** was used. [g]2 equivalents of **2a** was used. [h]The reaction concentration was 0.025 M. [i]The reaction concentration was 0.1 M. [j]In the dark.

4). When $NaHCO_3$ was replaced with K_2CO_3 and Na_2CO_3, the yields were 71% and 80%, respectively (Table 1, entries 5 and 6, respectively). When the reaction occurred in DMSO and Na_2CO_3, the product was achieved in 81% yield (Table 1, entry 7). Furthermore, the doses of Na_2CO_3 and **2a** were examined, and we found that 1 equiv of Na_2CO_3 and 1.5 equiv of **2a** in the reaction could produce the highest yield (Table 1, entries 8–11). However, Eosine and $Ru(bpy)_3Cl_2·6H_2O$ were inappropriate for this photoreaction (Table 1, entries 12 and 13, respectively), possibly because of the unfavorable redox potential[1,13] of the two photocatalysts relative to that of substrate **2a**. Then different reaction concentrations were screened, and we found that 0.05 M **1a** in the reaction is the best (Table 1, entries 14 and 15). Therefore, the optimized reaction conditions were confirmed to be 0.1 mmol of **1a**, 0.15 mmol of **2a**, 1 equiv of Na_2CO_3, and 2 mol % $Ir(ppy)_3$ in 2 mL of CH_3CN with the irradiation of blue LEDs under an Ar atmosphere for 4 h.

With the optimized reaction conditions in hand, we explored the scope of hydrazones with α-bromoacetophenone as a reaction partner, and the results are summarized in Table 2. Various substituted benzylidene phenylhydrazones were converted into the corresponding products in moderate to good yields. Comparison of the yields of **3b–3d** indicated the slightly steric effect in the phenyl group of R_1 (Table 2, **3b–3d**). The different functional groups of *para*-substituted benzylidene showed the electronic properties of the benzylidene phenylhydrazone substituents affected the efficiency of the reaction (Table 2, **3e–3j**). Electron-withdrawing substrates like F, Cl, and Br in the phenyl group of R_1 showed a higher reactivity than that of the electron-donating ones. Introducing a CN group promoted the yield of relative product to 91%. When R_1 was replaced with an ester group, the reaction also has a good yield (Table 2, **3k**). However, the substitution of R_2 decreased the reaction efficiency. The hydrazone with different groups in the phenyl group of R_2 could generate corresponding products in moderate yields (Table 2, **3l–3p**). Satisfyingly, the N-alkyl-substituted hydrazine could produce the corresponding products in moderate yields, as well (Table 2, **3q** and **3r**).

Further experiments were performed to understand the reaction efficiency of various α-bromo ketone derivatives (Table 3). A wide range of functional groups were tolerated in this system. *p*-CH_3-, *p*-OCH_3-, *p*-F-, *p*-Cl-, and *p*-Br-substituted α-bromoacetophenone and 2-(bromoacetyl)naphthalene could react with (*E*)-1-benzylidene-2-phenylhydrazine to yield the products in moderate yields (Table 3, **3s–3w** and **3a′**). Strong electron-withdrawing groups like *p*-CF_3Ph and *p*-NO_2Ph were tolerated in this system (Table 3, **3v–3y**). To our surprise, the *p*-hydroxyl α-bromoacetophenone could also react smoothly under the optimized condition to yield the hydroxyl product in 50% yield (Table 3, **3z**).

Under the optimized condition, the template reaction could produce the product with an isolated yield of 81% at room temperature. When 2 equiv of 2,2,6,6-tetramethyl piperidin-1-oxyl (TEMPO) was added, an only 9% yield of the target compound was obtained (Scheme 2). Furthermore, an addition product **4a** of acetophenone radical and TEMPO was observed, with an isolated yield of 68%. This result demonstrated that a radical procedure was involved in this system, and the acetophenone radical from **2a** was the key intermediate.

To elucidate more details about the reaction mechanism, spectroscopic experiments were performed. UV–vis absorption spectra of these three compounds showed only $Ir^{III}(ppy)_3$ could absorb visible light. When the photocatalyst $Ir^{III}(ppy)_3$ was irradiated with 405 nm light, a strong emission in 529 nm was observed. Progressive addition of **1a** or **2a** to the solution of excited $*Ir^{III}(ppy)_3$ demonstrated the degree of quenching caused by **2a** was much stronger than that caused by **1a** (for more details, see the Supporting Information). These results directly indicated the efficient interaction between **2a** and excited $Ir^{III}(ppy)_3$. According to the redox potential of **1a** (E_{red} < −2.0 V vs SCE, and E_{ox} = 0.94 V vs SCE), the electron transfer process between **1a** and $*Ir(ppy)_3$ ($E^{IV/III*}$ = −1.84 V vs SCE, and $E^{III*/II}$ = 0.26 V)[14] was less likely than that of **2a** (E_{ox} > 1.6 V vs SCE, and E_{red} = −1.2 V vs SCE).

On the basis of the results presented above, a plausible mechanism is proposed in Scheme 3. Under visible light irradiation, photocatalyst $Ir^{III}(ppy)_3$ is pumped to its excited state, $*Ir^{III}(ppy)_3$. Then this excited species transfers one electron to **2a**, which leads to the generation of alkyl radical **2a**$^•$ and $Ir^{IV}(ppy)_3^+$. As a highly electrophilic species, radical **2a**$^•$ tends to react with the electron-rich hydrazine and produces aminyl radical **A**. Further oxidation of **A** by $Ir^{IV}(ppy)_3^+$ affords intermediate **B** and regenerates $Ir^{III}(ppy)_3$. To our delight, this intermediate **B** could further cyclize to construct the pyrazole skeleton with mono N-substituted hydrazone.

In conclusion, a novel one-pot visible light-promoted singlet-electron transfer process has been developed for the facile synthesis of 1,3,5-trisubstituted pyrazoles from easily accessible starting materials. The reaction has been demonstrated to be general for a wide range of functional groups with electron-withdrawing and electron-donating ability, such as nitro, nitrile,

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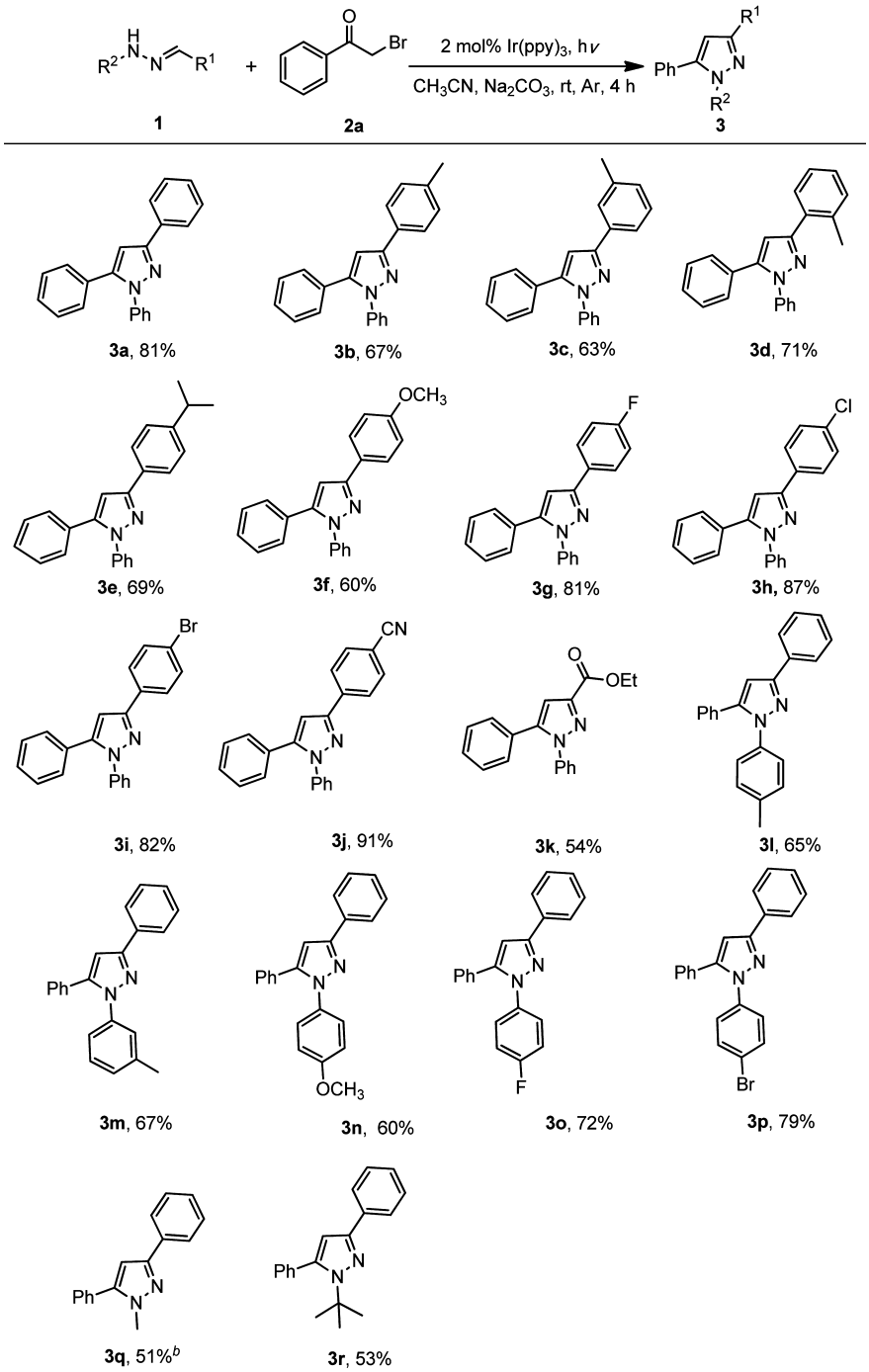
Table 2. Scope of Substituted Phenylhydrazone[a]



[a]Reaction conditions: 0.1 mmol of (*E*)-1-benzylidene-2-phenylhydrazine, 0.15 mmol of α-bromoacetophenone, 2 mol % $Ir(ppy)_3$, and 1 equiv of Na_2CO_3 in 2 mL of CH_3CN irradiated by blue LEDs under Ar for 4 h. [b]One-pot reaction of methyldrazine sulfate, benzaldehyde, and α-bromoacetophenone. For more details, see Experimental Section.

hydroxyl, etc., in hydrazones and α-bromo ketones. The good to excellent yields indicate the reaction potential of monosubstituted hydrazones in photocatalyzed radical addition. Such an approach enriches photoredox reaction and represents a lower-cost, milder, and greener process for the synthesis of 1,3,5-trisubstituted pyrazoles.

EXPERIMENTAL SECTION

General Experimental Procedure. ^1H and ^{13}C NMR spectra were recorded with 400 and 100 MHz NMR instruments. Chemical shifts (δ, parts per million) are given with tetramethylsilane (TMS) as an internal standard. The coupling constants (*J*) are reported in hertz. Flash column chromatography was performed over silica gel 200−300 mesh, and the eluent was a mixture of ethyl acetate (EA) and petroleum ether (PE). High-resolution mass spectra (HRMS-ESI) were recorded on a Q-TOF mass spectrometer. All the substituted α-bromo ketones, benzaldehydes, and phenylhydrazine hydrochloride salts were purchased from commercial sources and used without further purification. All the substituted phenylhydrazines were obtained from the neutralization reaction of corresponding hydrochloride salts with sodium hydroxide in a water and diethyl ether two-phase solution.

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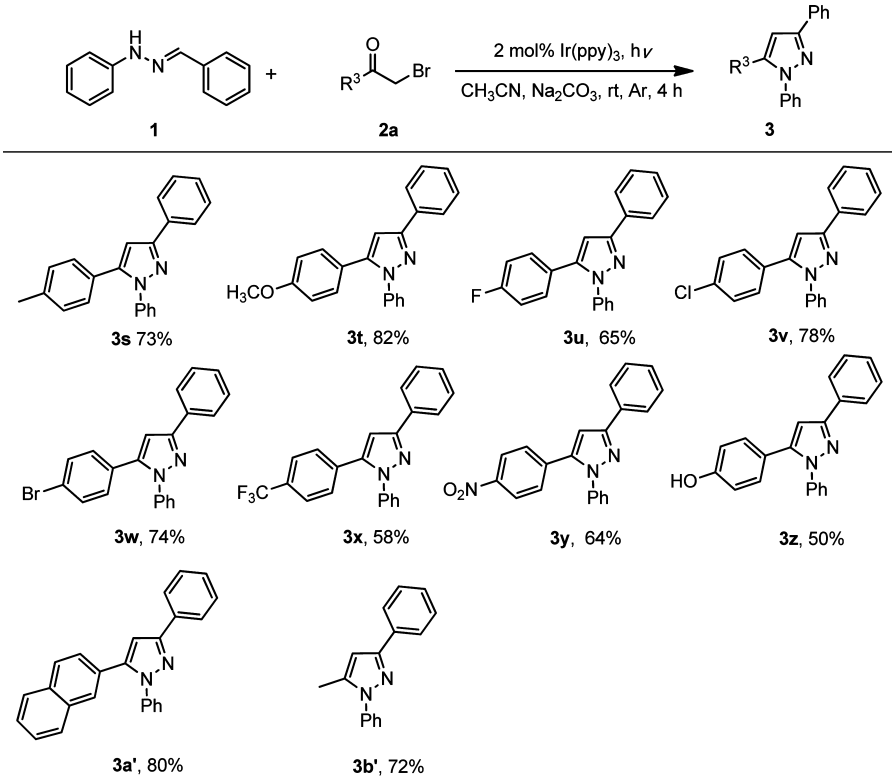
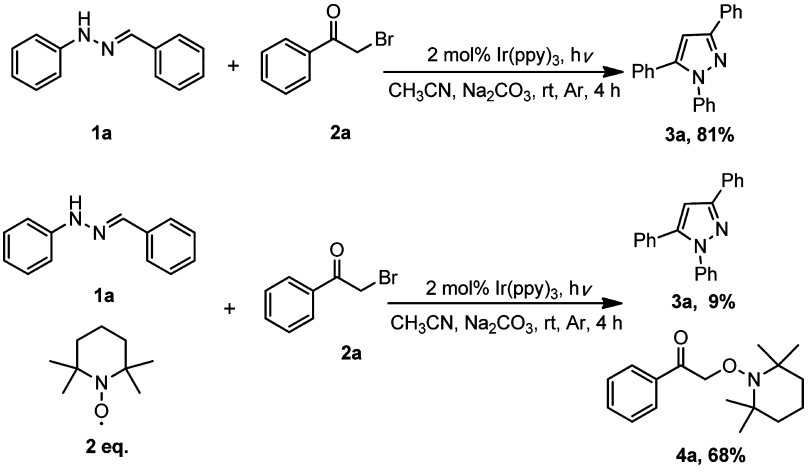
Table 3. Scope of the Substituted α-Bromo Ketone[a]



[a]Reaction conditions: 0.1 mmol of (*E*)-1-benzylidene-2-phenylhydrazine, 0.15 mmol of α-bromo ketone, 2 mol % $Ir(ppy)_3$, and 1 equiv of Na_2CO_3 in 2 mL of CH_3CN irradiated by blue LEDs under Ar for 4 h.

Scheme 2. Control Experiments



General Procedure for the Synthesis of Substituted Benzylidene Phenylhydrazones 1. To a stirred solution of substituted phenylhydrazine (5.5 mmol) in methanol (5 mL) were added benzaldehyde derivatives (5 mmol) dropwise. The mixture was then stirred at room temperature until the conversion was complete (disappearance of benzaldehydes, monitored by TLC). The solid was collected by filtration, washed with cooled MeOH, and then dried to afford product **1**.

General Procedure for the Synthesis of Pyrazoles. Benzylidene phenylhydrazone (0.1 mmol, 1 equiv), α-bromo ketone (0.15 mmol, 1.5 equiv), Na_2CO_3 (0.1 mmol, 1 equiv), and $Ir(ppy)_3$ (2 μmol, 0.02 equiv) were dissolved in CH_3CN (2 mL) in a 10 mL Pyrex tube equipped with a rubber septum and a magnetic stir bar, and then the argon-purged solution was irradiated with blue LEDs (λ_{max} = 450 nm) at room temperature for 4 h. The solvent was removed under reduced pressure after the reaction had reached completion. Then the residue was purified by column chromatography on silica gel via elution with ethyl acetate and petroleum ether to give the corresponding product.

One-Pot Synthesis of 3q. Methylhydrazine sulfate (0.1 mmol), benzaldehyde (0.15 mmol), and Na_2CO_3 (2 equiv) were dissolved in 1.5 mL of CH_3CN in a 10 mL Pyrex tube equipped with a rubber septum and a magnetic stir bar. After the solution had been purged with argon and stirred for 1 h, the reaction solution was supplemented with 0.15 mmol of α-bromoacetophenone in 0.5 mL of CH_3CN and then irradiated with blue LEDs for 4 h.

*1,3,5-Triphenyl-1H-pyrazole (**3a**).* White solid: yield 23.9 mg, 81%; mp 138−140 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 7.7 Hz, 2H), 7.45 (t, *J* = 7.4 Hz, 2H), 7.42−7.29 (m, 11H), 6.85 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.0, 144.4, 140.2, 133.1, 130.6, 128.9,

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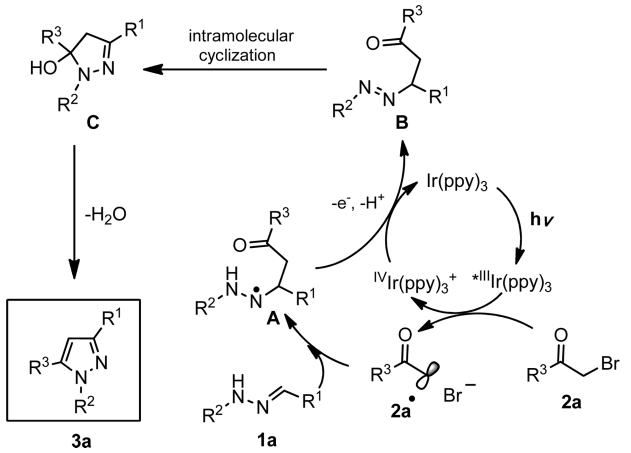
Scheme 3. Proposed Mechanism



128.8, 128.7, 128.5, 128.3, 128.0, 127.5, 125.9, 125.3, 105.2; HRMS (ESI) calcd for $C_{21}H_{17}N_2$ $[M + H]^+$ 297.1386, found 297.1386.

*1,5-Diphenyl-3-(p-tolyl)-1H-pyrazole (**3b**).* White solid: yield 20.8 mg, 67%; mp 127−128 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, J = 7.6 Hz, 2H), 7.30 (m, 12H), 6.79 (s, 1H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.0, 144.3, 140.2, 137.8, 130.7, 130.2, 129.4, 128.9, 128.8, 128.5, 128.3, 127.4, 125.8, 125.3, 105.1, 21.3; HRMS (ESI) calcd for $C_{22}H_{19}N_2$ $[M + H]^+$ 311.1543, found 311.1543.

*1,5-Diphenyl-3-(m-tolyl)-1H-pyrazole (**3c**).* White solid: yield 19.5 mg, 63%; mp 88−90 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (s, 1H), 7.72 (d, J = 7.6 Hz, 1H), 7.40−7.26 (m, 11H), 7.17 (d, J = 7.5 Hz, 1H) 6.83 (s, 1H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.1, 144.4, 140.2, 138.3, 132.9, 130.64, 128.9, 128.84, 128.78, 128.6, 128.5, 128.3, 127.5, 126.5, 125.4, 123.1, 105.3, 21.5; HRMS (ESI) calcd for $C_{22}H_{19}N_2$ $[M + H]^+$ 311.1543, found 311.1542.

*1,5-Diphenyl-3-(o-tolyl)-1H-pyrazole (**3d**).* Colorless oil: yield: 21.9 mg, 71%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (t, J = 3.8 Hz, 1H), 7.42−7.27 (m, 13H), 6.69 (s, 1H), 2.61 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.4, 143.4, 140.1, 136.2, 132.8, 130.9, 130.7, 129.4, 128.9, 128.8, 128.5, 128.3, 127.9, 127.3, 125.9, 125.2, 108.3, 21.4; HRMS (ESI) calcd for $C_{22}H_{19}N_2$ $[M + H]^+$ 311.1543, found 311.1543.

*3-(4-Isopropylphenyl)-1,5-diphenyl-1H-pyrazole (**3e**).* White solid: yield: 23.3 mg, 69%; mp 101−102 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, J = 7.4 Hz, 2H), 7.43−7.27 (m, 12H), 6.80 (s, 1H), 2.95 (m, 1H), 1.30 (s, 3H), 1.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.1, 148.8, 144.3, 140.2, 130.7, 130.6, 128.9, 128.8, 128.5, 128.3, 127.4, 126.7, 125.9, 125.3, 105.1, 34.0, 24.0; HRMS (ESI) calcd for $C_{24}H_{23}N_2$ $[M + H]^+$ 339.1856, found 339.1856.

*3-(4-Methoxyphenyl)-1,5-diphenyl-1H-pyrazole (**3f**).* White solid: yield 19.7 mg, 60%; mp 143−144 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, J = 8.0 Hz, 2H), 7.39−7.26 (m, 10H), 6.97 (d, J = 8.0 Hz, 2H), 6.76 (s, 1H), 3.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.7, 151.8, 144.4, 140.1, 130.6, 128.9, 128.8, 128.5, 128.3, 127.4, 127.2, 125.7, 125.3, 114.1, 104.8, 55.3; HRMS (ESI) calcd for $C_{22}H_{19}N_2O$ $[M + H]^+$ 327.1492, found 327.1491.

*3-(4-Fluorophenyl)-1,5-diphenyl-1H-pyrazole (**3g**).* White solid: yield 25.4 mg, 81%; mp 143−144 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (t, J = 6.72 Hz, 2H), 7.40−7.27 (m, 10H), 7.12 (t, J = 8.2 Hz, 2H), 6.78 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.8 (d, J = 246.6 Hz), 151.1, 144.6, 140.1, 130.5, 129.3 (d, J = 3.2 Hz), 129.0, 128.7, 128.5, 128.4, 127.5 (d, J = 8.0 Hz), 127.5, 125.3, 115.6 (d, J = 21.6 Hz), 105.0; HRMS (ESI) calcd for $C_{21}H_{16}FN_2$ $[M + H]^+$ 315.1292, found 315.1292.

*3-(4-Chlorophenyl)-1,5-diphenyl-1H-pyrazole (**3h**).* White solid: yield 28.9 mg, 87%; mp 138−139 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, J = 7.6 Hz, 2H), 7.42−7.24 (m, 12H), 6.79 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.9, 144.6, 140.0, 133.8, 131.6, 130.4, 129.0, 128.8, 128.7, 128.5, 128.4, 127.6, 127.1, 125.3, 105.1; HRMS (ESI) calcd for $C_{21}H_{16}ClN_2$ $[M + H]^+$ 331.0997, found 331.0996.

*3-(4-Bromophenyl)-1,5-diphenyl-1H-pyrazole (**3i**).* White solid: yield 30.8 mg, 82%; mp 152−154 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 8.1 Hz, 2H), 7.54 (d, J = 8.1 Hz, 2H), 7.37−7.24 (m, 10H), 6.79 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.9, 144.7, 140.0, 132.1, 131.8, 130.4, 129.0, 128.8, 128.54, 128.45, 127.6, 127.4, 125.3, 122.0, 105.1; HRMS (ESI) calcd for $C_{21}H_{16}BrN_2$ $[M + H]^+$ 375.0491, found 375.0490.

*4-(1,5-Diphenyl-1H-pyrazol-3-yl)benzonitrile (**3j**).* Light yellow solid: yield 29.1 mg, 91%; mp 168−170 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, J = 7.7 Hz, 2H), 7.70 (d, J = 7.7 Hz, 2H), 7.39−7.31 (m, 8H), 7.28−7.24 (m, 2H), 6.86 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.0, 145.0, 139.8, 137.5, 132.6, 130.1, 129.1, 128.8, 128.7, 128.6, 127.9, 126.2, 125.3, 119.1, 111.2, 105.6; HRMS (ESI) calcd for $C_{22}H_{16}N_3$ $[M + H]^+$ 322.1339, found 322.1337.

*Ethyl 1,5-Diphenyl-1H-pyrazole-3-carboxylate (**3k**).* Yellow oil: yield 15.8 mg, 54%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.27 (m, 8H), 7.21 (d, J = 7.4 Hz, 2H), 7.05 (s, 1H), 4.46 (q, J = 7.1 Hz, 2H), 1.43 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.5, 144.7, 144.4 139.6, 129.6, 129.0, 128.8, 128.7, 128.6, 128.3, 125.8, 109.9, 61.1, 14.4; HRMS (ESI) calcd for $C_{18}H_{17}N_2O_2$ $[M + H]^+$ 293.1285, found 293.1285.

*3,5-Diphenyl-1-(p-tolyl)-1H-pyrazole (**3l**).* Colorless oil: yield 20.3 mg, 65%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, J = 7.5 Hz, 2H), 7.42 (t, J = 7.4 Hz, 2H), 7.36−7.23 (m, 8H), 7.14 (d, J = 7.7 Hz, 2H), 6.81 (s, 1H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.7, 144.3, 137.7, 137.4, 133.1, 130.7, 129.5, 128.7, 128.6, 128.5, 128.2, 128.0, 125.8, 125.2, 104.9, 21.1; HRMS (ESI) calcd for $C_{22}H_{19}N_2$ $[M + H]^+$ 311.1543, found 311.1543.

*3,5-Diphenyl-1-(m-tolyl)-1H-pyrazole (**3m**).* White solid: yield 20.9 mg, 67%; mp 72−73 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, J = 7.6 Hz, 2H), 7.44 (t, J = 7.4 Hz, 2H), 7.34 (m, 7H), 7.20 (t, J = 7.7 Hz, 1H), 7.13 (d, J = 7.4 Hz, 1H), 7.05 (d, J = 7.8 Hz, 1H), 6.83 (s, 1H), 2.34 (d, J = 11.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.9, 144.4, 140.1, 139.1, 133.1, 130.7, 128.7, 128.64, 128.55, 128.4, 128.27, 128.25, 128.0, 126.0, 125.9, 122.5, 105.1, 21.4; HRMS (ESI) calcd for $C_{22}H_{19}N_2$ $[M + H]^+$ 311.1543, found 311.1543.

*1-(4-Methoxyphenyl)-3,5-diphenyl-1H-pyrazole (**3n**).* White solid: yield 19.6 mg, 60%; mp 109−111 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, J = 7.6 Hz, 2H), 7.43 (t, J = 7.4 Hz, 2H), 7.37−7.27 (m, 8H), 6.87 (d, J = 7.6 Hz, 2H), 6.82 (s, 1H), 3.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.9, 151.6, 144.4, 133.4, 133.1, 130.6, 128.7, 128.6, 128.5, 128.2, 127.9, 126.8, 125.8, 114.1, 104.7, 55.5; HRMS (ESI) calcd for $C_{22}H_{19}N_2O$ $[M + H]^+$ 327.1492, found 327.1492.

*1-(4-Fluorophenyl)-3,5-diphenyl-1H-pyrazole (**3o**).* Light yellow solid: yield 22.3 mg, 72%; mp 107−108 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, J = 7.7 Hz, 2H), 7.43 (t, J = 7.4 Hz, 2H), 7.34 (m, 6H), 7.29−7.23 (m, 2H), 7.04 (t, J = 7.9 Hz, 2H), 6.82 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.7 (d, J = 247.5 Hz), 152.1, 144.5, 136.3 (d, J = 3.0 Hz), 132.9, 130.4, 128.8, 128.7, 128.6, 128.5, 128.1, 127.1 (d, J = 8.6 Hz), 125.8, 115.8 (d, J = 22.9 Hz), 105.2; HRMS (ESI) calcd for $C_{21}H_{16}FN_2$ $[M + H]^+$ 315.1292, found 315.1291.

*1-(4-Bromophenyl)-3,5-diphenyl-1H-pyrazole (**3p**).* White solid: yield 29.5 mg, 79%; mp 100−101 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, J = 7.6 Hz, 2H), 7.36 (m, 4H), 7.27 (m, 4H), 7.18 (m, 4H), 6.73 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.3, 144.5, 139.2, 132.8, 132.0, 130.3, 128.8, 128.72, 128.69, 128.6, 128.2, 126.6, 125.9, 121.0, 105.7; HRMS (ESI) calcd for $C_{21}H_{16}BrN_2$ $[M + H]^+$ 375.0491, found 375.0490.

*1-Methyl-3,5-diphenyl-1H-pyrazole (**3q**).* Colorless oil: yield 11.9 mg, 51%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, J = 7.7 Hz, 2H), 7.51−7.43 (m, 5H), 7.41 (t, J = 7.5 Hz, 2H), 7.31 (t, J = 7.3 Hz, 1H), 6.61 (s, 1H), 3.93 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.5, 145.1, 133.3, 130.6, 128.8, 128.7, 128.63, 128.59, 127.7, 125.6, 103.3, 37.6; HRMS (ESI) calcd for $C_{16}H_{15}N_2$ $[M + H]^+$ 235.1230, found 235.1226.

*1-(tert-Butyl)-3,5-diphenyl-1H-pyrazole (**3r**).* White solid: yield 14.7 mg, 53%; mp 110−112 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, J = 7.8 Hz, 2H), 7.45−7.33 (m, 8H), 7.27 (t, J = 6.4 Hz, 1H), 6.45 (s, 1H), 1.51 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.8, 144.0, 134.4, 134.0, 130.5, 128.5, 128.4, 127.8, 127.2, 125.5, 106.5, 61.5, 31.2; HRMS (ESI) calcd for $C_{19}H_{21}N_2$ $[M + H]^+$ 277.1700, found 277.1700.

*1,3-Diphenyl-5-(p-tolyl)-1H-pyrazole (**3s**).* Yellow solid: yield 22.8 mg, 73%; mp 113−115 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, J = 7.5 Hz, 2H), 7.38 (m, 8H), 7.19 (d, J = 7.8 Hz, 2H), 7.14 (d, J = 7.8 Hz,

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J. Org. Chem. 2016, 81, 7127−7133

2H), 6.81 (s, 1H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.9, 144.5, 140.3, 138.3, 133.1, 129.2, 128.9, 128.7, 128.0, 127.7, 127.4, 125.9, 125.4, 105.0, 21.3; HRMS (ESI) calcd for $C_{22}H_{19}N_2$ $[M + H]^+$ 311.1542, found 311.1543.

*5-(4-Methoxyphenyl)-1,3-diphenyl-1H-pyrazole (**3t**).* White solid: yield 26.8 mg, 82%; mp 77−78 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, J = 7.7 Hz, 2H), 7.38 (m, 8H), 7.21 (d, J = 8.2 Hz, 2H), 6.85 (d, J = 8.2 Hz, 2H), 6.77 (s, 1H), 3.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.7, 151.9, 144.3, 140.2, 133.1, 130.1, 128.9, 128.6, 128.0, 127.4, 125.9, 125.4, 123.0, 114.0, 104.7, 55.3; HRMS (ESI) calcd for $C_{22}H_{19}N_2O$ $[M + H]^+$ 327.1492, found 327.1492.

*5-(4-Fluorophenyl)-1,3-diphenyl-1H-pyrazole (**3u**).* Yellow solid: yield 20.5 mg, 65%; mp 144−146 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, J = 7.5 Hz, 2H), 7.43 (t, J = 7.4 Hz, 2H), 7.38−7.30 (m, 6H), 7.24 (t, J = 6.3 Hz, 2H), 7.01 (t, J = 8.2 Hz, 2H), 6.79 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.7 (d, J = 248.8 Hz), 152.0, 143.4, 140.0, 133.0, 130.6 (d, J = 8.2 Hz), 129.0, 128.7, 128.1, 127.6, 126.8 (d, J = 3.4 Hz), 125.8, 125.3, 115.6 (d, J = 21.7 Hz), 105.2; HRMS (ESI) calcd for $C_{21}H_{16}FN_2$ $[M + H]^+$ 315.1292, found 315.1292.

*5-(4-Chlorophenyl)-1,3-diphenyl-1H-pyrazole (**3v**).* White solid: yield 26.8 mg, 81%; mp 103−105 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, J = 7.7 Hz, 2H), 7.44 (t, J = 7.3 Hz, 2H), 7.41−7.28 (m, 8H), 7.21 (d, J = 8.0 Hz, 2H), 6.82 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.1, 143.2, 139.9, 134.4, 132.9, 130.0, 129.08, 129.05, 128.8, 128.7, 128.1, 127.7, 125.9, 125.4, 105.3; HRMS (ESI) calcd for $C_{21}H_{16}ClN_2$ $[M + H]^+$ 331.0997, found 331.0997.

*5-(4-Bromophenyl)-1,3-diphenyl-1H-pyrazole (**3w**).* Yellow solid: yield 27.7 mg, 74%; mp 129−131 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, J = 7.6 Hz, 2H), 7.40 (m, 10H), 7.15 (d, J = 7.9 Hz, 2H), 6.83 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.1, 143.2, 139.9, 132.8, 131.8, 130.2, 129.5, 129.1, 128.7, 128.1, 127.7, 125.9, 125.4, 122.6, 105.3; HRMS (ESI) calcd for $C_{21}H_{16}BrN_2$ $[M + H]^+$ 375.0491, found 375.0492.

*1,3-Diphenyl-5-[4-(trifluoromethyl)phenyl]-1H-pyrazole (**3x**).* White solid: yield 21.3 mg, 58%; mp 154−156 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, J = 7.7 Hz, 2H), 7.59 (d, J = 8.0 Hz, 2H), 7.49−7.34 (m, 10H), 6.89 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.2, 142.9, 139.7, 134.0, 132.7, 130.3 (q, J = 32.4 Hz), 129.2, 128.9, 128.7, 128.3, 127.9, 125.9, 125.5 (q, J = 19.0 Hz), 125.4, 123.9 (q, J = 272.2 Hz), 105.8; HRMS (ESI) calcd for $C_{22}H_{16}F_3N_2$ $[M + H]^+$ 365.1260, found 365.1259.

*5-(4-Nitrophenyl)-1,3-diphenyl-1H-pyrazole (**3y**).* White solid: yield 21.8 mg, 64%; mp 136−137 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, J = 7.8 Hz, 2H), 7.92 (d, J = 7.6 Hz, 2H), 7.49−7.33 (m, 10H), 6.95 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.4, 147.3, 142.0, 139.6, 136.7, 132.5, 129.33, 129.27, 128.8, 128.4, 128.2, 125.8, 125.5, 123.8, 106.3; HRMS (ESI) calcd for $C_{21}H_{16}N_3O_2$ $[M + H]^+$ 342.1237, found 342.1237.

*4-(1,3-Diphenyl-1H-pyrazol-5-yl)phenol (**3z**).* White solid: yield 15.5 mg, 50%; mp 221−223 °C; ^{1}H NMR (400 MHz, acetone-d_6) δ 8.62 (s, 1H), 7.93 (d, J = 7.6 Hz, 2H), 7.43−7.27 (m, 8H), 7.13 (d, J = 7.4 Hz, 2H), 6.89 (s, 1H), 6.80 (d, J = 7.5 Hz, 2H); ^{13}C NMR (100 MHz, acetone-d_6) δ 157.7, 151.3, 144.6, 140.7, 133.6, 130.1, 128.8, 128.5, 127.7, 127.2, 125.5, 125.1, 121.9, 115.4, 104.4; HRMS (ESI) calcd for $C_{21}H_{17}N_2O$ $[M + H]^+$ 313.1335, found 313.1335.

*5-(Naphthalen-2-yl)-1,3-diphenyl-1H-pyrazole (**3a′**).* White solid: yield 27.8 mg, 80%; mp 102−103 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, J = 7.6 Hz, 2H), 7.88−7.74 (m, 4H), 7.54−7.41 (m, 6H), 7.34 (m, 5H), 6.95 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.1, 144.4, 140.2, 133.1, 133.0, 132.9, 129.0, 128.7, 128.2, 128.10, 128.06, 128.01, 127.98, 127.7, 127.5, 126.7, 126.6, 126.3, 125.9, 125.3, 105.6; HRMS (ESI) calcd for $C_{25}H_{19}N_2$ $[M + H]^+$ 347.1543, found 347.1543.

*5-Methyl-1,3-diphenyl-1H-pyrazole (**3b′**).* Colorless oil: yield 16.8 mg, 72%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93−7.84 (m, 2H), 7.57−7.46 (m, 4H), 7.40 (q, J = 7.6 Hz, 3H), 7.32 (t, J = 7.3 Hz, 1H), 6.54 (s, 1H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.7, 140.23, 140.18, 133.6, 129.2, 128.6, 127.8, 127.7, 125.9, 125.1, 104.5, 12.6; HRMS (ESI) calcd for $C_{16}H_{15}N_2$ $[M + H]^+$ 235.1230, found 235.1233.

*1-Phenyl-2-(2,2,6,6-tetramethylpiperidin-1-yl)ethanone (**4a**).* Colorless oil: yield 17.3 mg, 68%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, J = 7.6 Hz, 2H), 7.56 (t, J = 7.4 Hz, 1H), 7.46 (t, J = 7.5 Hz, 2H), 5.12 (s, 2H), 1.57 (dd, J = 19.5, 7.8 Hz, 1H), 1.52−1.44 (m, 4H), 1.37−1.30 (m, 1H), 1.19 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.8, 135.5, 133.2, 128.6, 128.0, 81.4, 60.2, 39.8, 32.8, 20.3, 17.1; HRMS (ESI) calcd for $C_{17}H_{26}NO_2$ $[M + H]^+$ 276.1958, found 276.1957.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00992.

Copies of ^{1}H and ^{13}C NMR spectra for all products, UV−vis absorption spectra of Ir(ppy)$_3$, **1a**, and **2a**, and steady state emission quenching spectra of *Ir(ppy)$_3$ excited by **1a** or **2a** (PDF)

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Notes

The authors declare no competing financial interest.

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