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Palladium-Catalyzed Synthesis of 5-Iminopyrrolones through Isocyanide Double Insertion Reaction with Terminal Alkynes and Water

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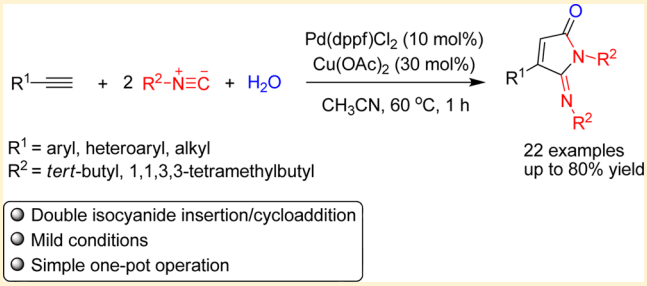
Supporting Information

ABSTRACT: With the combination of $Pd(dppf)Cl_2$ and $Cu(OAc)_2$, a variety of 5-iminopyrrolones were synthesized in moderate to good yields from terminal alkynes, isocyanide, and water via isocyanide double insertion and cycloaddition reaction. A plausible reaction mechanism for this process is depicted. Furthermore, selected compounds **3c**, **3e**, and **3h** exhibited good activities against HepG2 (human liver cancer), NCI-H460 (human lung cancer), and SK-OV-3 (human ovarian cancer) cell lines with IC_{50} values in the range of 10.63−22.63 μmol L^{-1}.



INTRODUCTION

The pursuit of concise strategies for the preparation of nitrogen-containing heterocycles continues to be a long sought after target because of their wide existence in biological and medicinal chemistry.[1,2] It is also an attractive and challenging area of research in organic synthesis to get a direct route to a final compound from readily available substrates. Isocyanides have been widely applied to construct various nitrogen heterocyclic compounds due to their superior capability to rapidly create molecular diversity, however, most reported achievements mainly focus on the utility of isocyanides single insertion for the synthesis of nitrogen-containing compounds.[3] Only a few examples of metal-catalyzed double isocyanides insertion have been reported.[4] For example, in 2015, Tu and Jiang[5] disclosed a palladium-catalyzed double isocyanide insertion−cyclization between 2-haloanilines and isocyanides to form 3-iminoindol-2-amines (Scheme 1a). Recently, Li and Jia[6] reported a temperature-dependent selective double insertion of isocyanides with the aid of $KAuCl_4$ to construct a polycyclic skeleton (Scheme 1b). More recently, Zhu and Shen[7] illustrated palladium-catalyzed synthesis of α-iminonitrile via *tert*-butyl isocyanide double insertion and elimination (Scheme 1c).

Alkynes, another important class of organic compounds, have been extensively applied in organic synthesis as building blocks and versatile synthons.[8] As our interest in the study of the conversions alkynes to heterocycles continues,[9] to our delight, we found that the reaction of terminal alkynes, isocyanides, and H_2O in the presence of $Pd(dppf)Cl_2/Cu(OAc)_2$ could offer 5-iminopyrrolones (Scheme 1d), which are well-known compounds because of their wide occurrence in nature,[10] profound pharmaceutical activities,[11] and considerable applications in drug development.[12]

RESULTS AND DISCUSSION

We commenced our study by using phenylacetylene (**1a**), *tert*-butyl isocyanide (**2a**), and H_2O as model substrates under various conditions, and the results are summarized in Table 1. At first, the reaction of **1a**, **2a**, and H_2O in the presence of $Pd(PPh_3)_4$ (10 mol %) and $Cu(OAc)_2$ (30 mol %) in CH_3CN, heated at 60 °C for 1 h, gave the desired product of 5-iminopyrrolone (**3a**) in 41% yield (Table 1, entry 1). In the absence of $Cu(OAc)_2$, TLC analysis indicated that no desired product formed (Table 1, entry 2). Other copper salts such as $CuCl_2$, CuBr, $CuSO_4$, CuO, and other metal-free oxidants such as TBHP, $K_2S_2O_8$, and O_2 were also attempted, respectively, however, the results were not encouraging, as no desired product was observed in these cases (Table 1, entries 3−9). Subsequent evaluation of Pd-catalysts and the results proved that $Pd(dppf)Cl_2$ is the optimal one, providing the product **3a** in 71% yield (Table 1, entry 10 vs entries 11−13). Screening of different solvents revealed that CH_3CN was found to be the best solvent for this process (Table 1, entry 10 vs entries 14−17). In addition, it is worth noting that 10 mol % of $Pd(dppf)Cl_2$ with 30 mol % $Cu(OAc)_2$ was sufficient to promote the reaction, and the yield of **3a** was decreased when 1 equiv of $Pd(dppf)Cl_2$ or 1 equiv of $Cu(OAc)_2$ was used, clearly indicating that the reaction proceeded in a catalytic manner (Table 1, entry 10 vs entries 18−19). Besides, the reaction was

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Scheme 1. Metal-Catalyzed Isocyanide Double Insertion Reaction

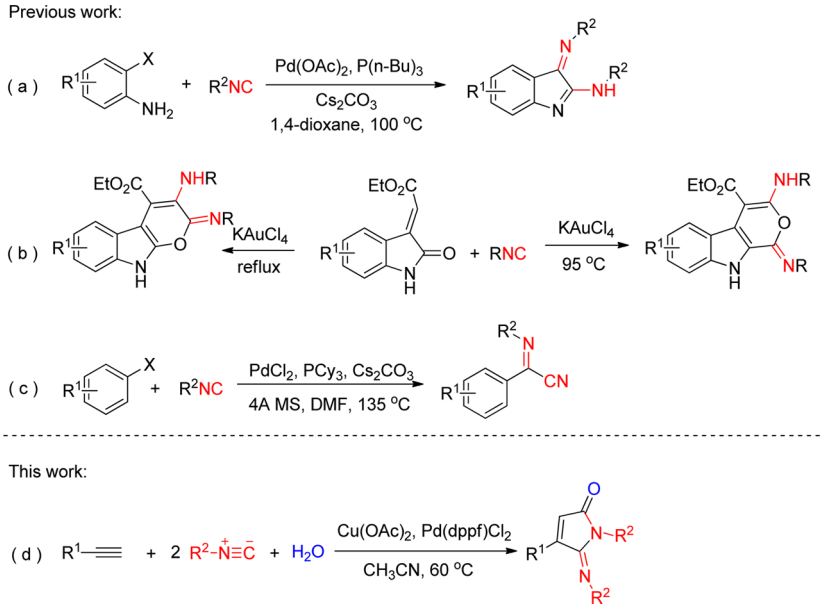
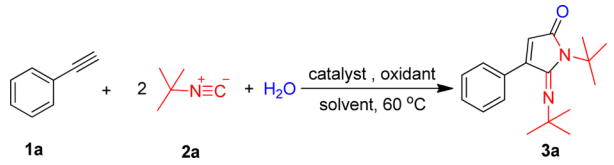


Table 1. Optimization of Reaction Conditions[a]



1a 2a 3a

entry	catalyst	oxidant	solvent	yield[b] (%)
1	$Pd(PPh_3)_4$	$Cu(OAc)_2$	CH_3CN	41
2	$Pd(PPh_3)_4$	none	CH_3CN	0
3	$Pd(PPh_3)_4$	$CuCl_2$	CH_3CN	0
4	$Pd(PPh_3)_4$	CuBr	CH_3CN	0
5	$Pd(PPh_3)_4$	$CuSO_4$	CH_3CN	0
6	$Pd(PPh_3)_4$	CuO	CH_3CN	0
7	$Pd(PPh_3)_4$	TBHP	CH_3CN	0
8	$Pd(PPh_3)_4$	$K_2S_2O_8$	CH_3CN	0
9	$Pd(PPh_3)_4$	O_2 (1 atm)	CH_3CN	0
10	**$Pd(dppf)Cl_2$**	**$Cu(OAc)_2$**	**CH_3CN**	**71**
11	$Pd(OAc)_2$	$Cu(OAc)_2$	CH_3CN	55
12	$PdCl_2$	$Cu(OAc)_2$	CH_3CN	21
13	$Pd(NH_3)Cl_2$	$Cu(OAc)_2$	CH_3CN	15
14	$Pd(dppf)Cl_2$	$Cu(OAc)_2$	DMSO	65
15	$Pd(dppf)Cl_2$	$Cu(OAc)_2$	DMF	55
16	$Pd(dppf)Cl_2$	$Cu(OAc)_2$	1,4-dioxane	51
17	$Pd(dppf)Cl_2$	$Cu(OAc)_2$	toluene	30
18[c]	$Pd(dppf)Cl_2$	$Cu(OAc)_2$	CH_3CN	45
19[d]	$Pd(dppf)Cl_2$	$Cu(OAc)_2$	CH_3CN	32
20[e]	$Pd(dppf)Cl_2$	$Cu(OAc)_2$	CH_3CN	60

[a]Reaction conditions: **1a** (0.1 mmol), *t*-BuNC (0.3 mmol), H_2O (0.1 mmol), catalyst (10 mol %), and oxidant (30 mol %) in solvent (2 mL) at 60 °C for 1 h under air. [b]Isolated yield of pure product based on **1a**. [c]$Pd(dppf)Cl_2$ (1.0 equiv). [d]$Cu(OAc)_2$ (1.0 equiv). [e]Conditions: **1a** (5 mmol), **2a** (15 mmol), H_2O (5 mmol), $Pd(dppf)Cl_2$ (10 mol %), $Cu(OAc)_2$ (30 mol %), and CH_3CN (60 mL), 1 h.

scalable and practical since a satisfactory yield (60%) could be obtained in the presence of $Pd(dppf)Cl_2$ (10 mol %), $Cu(OAc)_2$ (30 mol %) and H_2O (5 mmol) when the reaction was performed on a 5 mmol scale (Table 1, entry 20).

With the optimized conditions in hand, various terminal alkynes were employed for this transformation to the synthesis of 5-iminopyrrolones. As illustrated in Table 2, with regard to aromatic terminal alkynes, both electron-rich and electron-poor functional groups on the benzene ring can be tolerated in this transformation, generating the corresponding 5-iminopyrrolones in moderate to good yields (Table 2, **3b**−**3n**). Different substituted aromatic terminal alkynes, including some with electron-donating groups (OMe, OH, NH_2, alkyl) and some with electron-withdrawing groups (F, Cl, Br, NO_2, CN, CF_3), could be converted into the corresponding products, and electron-donating groups showed a positive effect to this reaction. To our delight, a single crystal of product **3b** was obtained by slow crystallization from a mixture of dichloromethane and ethyl acetate, and its structure was 1-(*tert*-butyl)-5-(*tert*-butylimino)-4-(4-chlorophenyl)-1*H*-pyrrol-2(5*H*)-one.[13] Figure 1 illustrates the molecular structure of the 5-iminopyrrolone **3b**.

Additionally, polycyclic aromatic and heteroaromatic alkynes worked well and afforded the corresponding 5-iminopyrrolone in good yields (Table 2, **3o**−**3q**). Fortunately, bifunctional substrates 1,4-diethynylbenzene can gave good results under the standard conditions (Table 2, **3r**). In particular, the reactivity of the cyclization reaction of alkyl-substituted terminal alkynes appears to be higher than that of the aryl-substituted terminal alkynes, presumably due to the fact that a less hindered group is in favor of migratory insertion of isocyanides (Table 2, **3s**−**3u**). Moreover, different isocyanides such as 1,1,3,3-tetramethylbutyl isocyanide (**2b**), isocyanobenzene (**2c**), benzyl isocyanide (**2d**), tosylmethyl isocyanide (**2e**), isocyanocyclohexane (**2f**), and ethylisocyanoacetate (**2g**) were investigated, and only the 1,1,3,3-tetramethylbutyl isocyanide can smoothly transform, affording the desired product of **3v** in 69% yield (Scheme 2). The results suggested that the quaternary carbon of isocyanide played an important role in the isocyanide double insertion reaction.[7]

Some control experiments were carried out in order to explore the possible reaction pathway. The reaction of **1a** and **2a** in the presence of 10 mol % $Pd(dppf)Cl_2$ and 30 mol % $Cu(OAc)_2$ in ultradry CH_3CN under N_2 only generated trace

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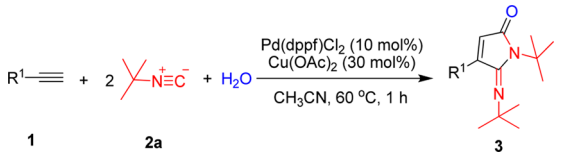
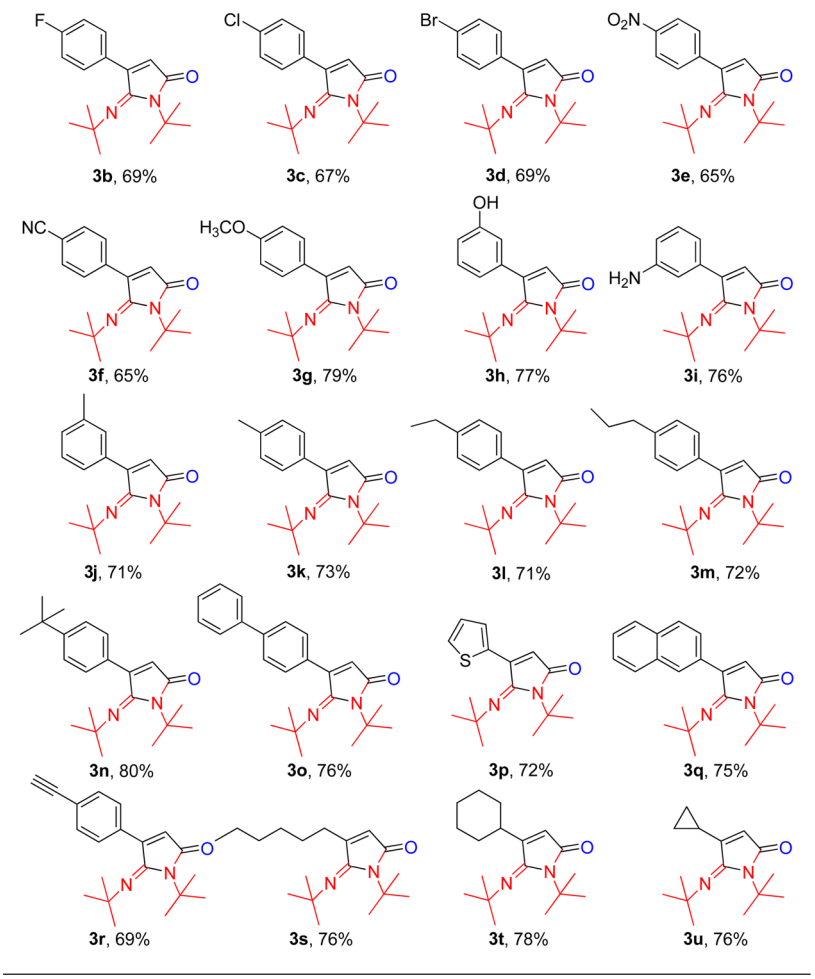
Table 2. Substrate Scope for the Reaction of Terminal Alkynes 1 and *t*-BuNC 2a[a,b]





[a]Reaction conditions: terminal alkyne 1 (0.1 mmol), isocyanide 2 (0.3 mmol), H_2O (0.1 mmol), $Pd(dppf)Cl_2$ (10 mol %), $Cu(OAc)_2$ (30 mol %) in CH_3CN (2 mL) at 60 °C for 1 h under air. [b]Isolated yield of pure product based on **1**.

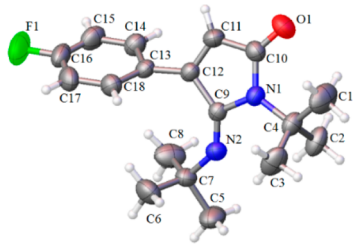
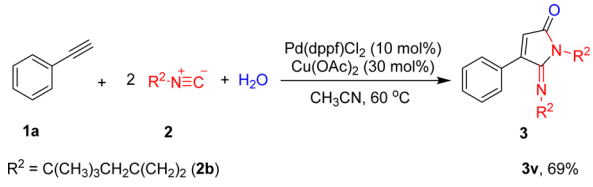


Figure 1. X-ray crystal structure of 5-iminopyrrolone **3b**. The thermal ellipsoids are at the 30% probability level.

amounts of **3a** [Scheme 3, eq 1]. The reaction of **1a** and **2a** in the presence of $H_2{}^{18}O$ generated ^{18}O-labeled product [^{18}O]-**3a** in 70% isolated yield under the standard conditions [Scheme 3, eq 2, the ^{18}O was determined by HRMS], indicating that the oxygen atom of the 5-iminopyrrolones product originated from H_2O. Treatment of a CH_3CN solution of *tert*-butyl isocyanide **2a** in the presence of $Pd(dppf)Cl_2$ (10 mol %), $Cu(OAc)_2$ (30 mol %) at 60 °C for 30 min, phenylacetylene **1a**, and water were then added, and 5-iminopyrrolone **3a** was obtained 73% yield [Scheme 3, eq 3]. However, only a trace amount of desired product was detected when phenylacetylene **1a** was first added [Scheme 3, eq 4].

Scheme 2. Scope of Isocyanide Double Insertion



On the basis of literature reports and our experimental results, a plausible mechanism for this reaction is shown in Scheme 4. The isocyanide-complexed Pd species **A** is first formed, acts as an active catalyst in our system,[14] and then

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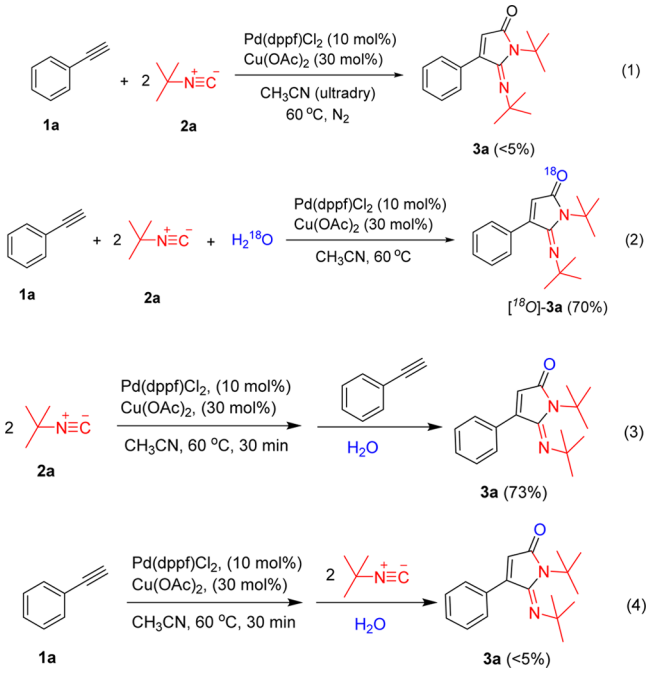
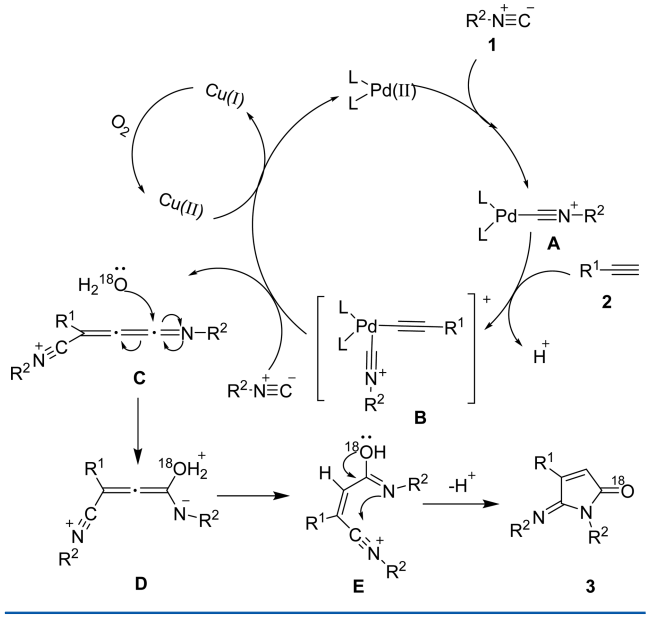
Scheme 3. Control Experiments



Scheme 4. Proposed Mechanism



reacts with terminal alkyne **1** to form intermediate **B**. Subsequently, the second isocyanide insertion takes place to generate intermediate **C**, meanwhile the palladium(0) species is reoxidized to palladium(II) by Cu(II) in the system to complete the cycle. Intermediate **C** then reacts with water to give the diene **D**, and the electron rearrangement of **D** occurs to afford its resonance isomer **E**. Finally, cycloaddition of **E** through deprotonation leads to the desired 5-iminopyrrolone **3**.

Subsequently, the *in vitro* antitumor activities with selected compounds **3c**, **3e**, and **3h** were evaluated by the MTT assay against HepG2, NCI-H460, and SK-OV-3 tumor cell lines, using 5-fluorouracil (5-FU) as the positive control. As shown in Table 3, compounds **3c**, **3e**, and **3h** exhibited moderate to good cytotoxicities. Especially, compound **3e** exhibited the best

Table 3. *In Vitro* Anticancer Activities of 3c, 3e, and 3h

	IC_{50}[a] (μmol L^{-1})		
compd	HepG2	NCI-H460	SK-OV-3
3c	13.52 ± 1.15	13.87 ± 1.35	13.14 ± 1.27
3e	10.63 ± 1.09	13.32 ± 0.90	14.69 ± 1.06
3h	11.74 ± 0.97	14.39 ± 1.12	22.63 ± 0.87
5-Fu	29.98 ± 0.37	44.04 ± 0.54	26.43 ± 0.41

[a]IC_{50} (μmol L^{-1}) values are presented as the mean ± SD (standard error of the mean) from the three separate experiments.

cytotoxicities against HepG2, NCI-H460, and SK-OV-3 cells with IC_{50} values of 10.63, 13.32, and 14.69 μmol L^{-1}.

CONCLUSIONS

In summary, we have successfully presented a synthetic route for the synthesis of 5-iminopyrrolones via isocyanide double insertion and cycloaddition reaction with the one-pot combination of Pd(dppf)Cl_2/Cu$(OAc)_2$. Simple starting material and reagents, mild reaction conditions, a simple experimental procedure, and good yields are some of the attractive attributes of the present protocol. Furthermore, the 5-iminopyrrolones showed promising anticancer potency through preliminary biological studies. Further work concerning synthetic applications and biological assessment of these 5-iminopyrrolones is underway, and the results shall be reported in due course.

EXPERIMENTAL SECTION

General Experimental Procedure for Synthesis of 5-Iminopyrrolones 3. To the mixture of terminal alkynes (1.0 equiv, 0.1 mmol) and isocyanides (3.0 equiv, 0.3 mmol) are added H_2O (1.0 equiv, 0.1 mmol), Pd(dppf)Cl_2 (10 mol %), Cu$(OAc)_2$ (30 mol %), and 2.0 mL CH_3CN at 60 °C for 1 h in the air. The progress of the reaction was monitored by thin-layer chromatography. Upon completion, the mixture was evaporated under reduced pressure, and the residue was separated by column chromatography (ethyl acetate/petroleum ether = 1:50 to 1:30) to give the pure product. See Supporting Information for additional information.

*1-(tert-Butyl)-5-(tert-butylimino)-4-phenyl-1H-pyrrol-2(5H)-one (**3a**).* Yellow solid (19.8 mg, 71%); mp 58−61 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.36 (m, 3H), 7.24−7.21 (m, 2H), 6.21 (s, 1H), 1.67 (s, 9H), 1.04 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.8, 147.4, 142.7, 135.3, 133.6, 128.7, 128.6, 128.1, 57.4, 56.0, 32.1, 29.9, 29.0, 28.4 ppm; HRMS (m/z) (ESI): calcd for $C_{18}H_{25}N_2O$285.1967 [M + H^+]; found 285.1958.

*1-(tert-Butyl)-5-(tert-butylimino)-4-(4-fluorophenyl)-1H-pyrrol-2(5H)-one (**3b**).* Light yellow solid (20.0 mg, 69%); mp 129−132 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.19 (dd, J = 8.5, 5.4 Hz, 2H), 7.07 (t, J = 8.6 Hz, 2H), 6.20 (s, 1H), 1.65 (s, 9H), 1.04 (s, 9H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.6, 162.8 (d, $^1J_{C-F}$ = 248.0 Hz), 147.2, 141.6, 134.1, 131.2 (d, $^4J_{C-F}$ = 3.6 Hz), 130.5 (d, $^3J_{C-F}$ = 8.0 Hz), 115.3 (d, $^2J_{C-F}$ = 22.0 Hz), 57.5, 56.0, 32.2, 29.8. HRMS (m/z) (ESI): calcd for $C_{18}H_{24}FN_2O$ 303.1873 [M + H^+]; found 303.1868. See additional information in Supporting Information.

*1-(tert-Butyl)-5-(tert-butylimino)-4-(4-chlorophenyl)-1H-pyrrol-2(5H)-one (**3c**).* Light yellow solid (21.0 mg, 67%); mp 68−71 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39−7.36 (m, 2H), 7.18−7.15 (m, 2H), 6.22 (s, 1H), 1.66 (s, 9H), 1.07 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 147.0, 141.4, 134.7, 134.1, 133.7, 130.0, 128.4, 57.5, 56.0, 32.2, 29.8 ppm; HRMS (m/z) (ESI): calcd for $C_{18}H_{24}ClN_2O$ 319.1577 [M + H^+]; found 319.1565.

*4-(4-Bromophenyl)-1-(tert-butyl)-5-(tert-butylimino)-1H-pyrrol-2(5H)-one (**3d**).* Light yellow oil (24.8 mg, 69%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, J = 8.4 Hz, 2H), 7.11 (d, J = 8.4 Hz, 2H), 6.22 (s, 1H), 1.66 (s, 9H), 1.07 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 147.0, 141.4, 134.2, 134.1, 131.4, 130.3, 122.9, 57.6, 56.1, 32.2,

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29.8 ppm; HRMS (m/z) (ESI): calcd for $C_{18}H_{24}BrN_2O$ 363.1072, 365.1052 [M + H$^+$]; found 363.1066, 365.1044.

1-(tert-Butyl)-5-(tert-butylimino)-4-(4-nitrophenyl)-1H-pyrrol-2(5H)-one (**3e**). Light yellow solid (21.0 mg, 65%); mp 86−88 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, J = 8.7 Hz, 2H), 7.43 (d, J = 8.7 Hz, 2H), 6.29 (s, 1H), 1.66 (s, 9H), 1.05 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8, 147.9, 146.2, 142.0, 140.3, 134.7, 129.7, 123.4, 57.8, 56.2, 32.2, 29.7 ppm; HRMS (m/z) (APCI): calcd for $C_{18}H_{24}N_3O_3$ 330.1818 [M + H$^+$]; found 330.1825.

4-(1-(tert-Butyl)-2-(tert-butylimino)-5-oxo-2,5-dihydro-1H-pyrrol-3-yl)benzonitrile (**3f**). Light yellow solid (20.0 mg, 65%); mp 113−115 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, J = 8.3 Hz, 2H), 7.37 (d, J = 8.3 Hz, 2H), 6.27 (s, 1H), 1.66 (s, 9H), 1.05 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.0, 146.3, 140.6, 140.1, 134.6, 132.2, 132.0, 129.5, 118.1, 112.7, 57.8, 56.2, 32.2, 29.8 ppm; HRMS (m/z) (APCI): calcd for $C_{19}H_{24}N_3O$ 310.1919 [M + H$^+$]; found 310.1925.

1-(tert-Butyl)-5-(tert-butylimino)-4-(4-methoxyphenyl)-1H-pyrrol-2(5H)-one (**3g**). Light yellow solid (24.4 mg, 79%); mp 102−104 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (d, J = 8.7 Hz, 2H), 6.89 (d, J = 8.7 Hz, 2H), 6.17 (s, 1H), 3.83 (s, 3H), 1.65 (s, 9H), 1.06 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.9, 159.8, 147.6, 142.6, 133.4, 129.9, 127.5, 113.5, 57.3, 55.9, 55.3, 32.1, 29.8 ppm; HRMS (m/z) (ESI): calcd for $C_{19}H_{27}N_2O_2$ 315.2073 [M + H$^+$]; found 315.2067.

1-(tert-Butyl)-5-(tert-butylimino)-4-(3-hydroxyphenyl)-1H-pyrrol-2(5H)-one (**3h**). Light yellow solid (23.0 mg, 77%); mp 111−114 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.19 (t, J = 7.8 Hz, 1H), 6.89 (dd, J = 8.1, 1.5 Hz, 1H), 6.71 (t, J = 5.2 Hz, 2H), 6.21 (s, 1H), 1.66 (s, 9H), 1.08 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 156.4, 146.9, 143.0, 136.0, 132.8, 129.3, 120.2, 116.1, 115.7, 57.8, 56.5, 32.0, 29.9 ppm; HRMS (m/z) (ESI): calcd for $C_{18}H_{25}N_2O_2$ 301.1916 [M + H$^+$]; found 301.1909.

4-(3-Aminophenyl)-1-(tert-butyl)-5-(tert-butylimino)-1H-pyrrol-2(5H)-one (**3i**). Light yellow solid (22.1 mg, 76%); mp 100−103 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (t, J = 7.8 Hz, 1H), 6.67 (ddd, J = 8.1, 2.3, 0.8 Hz, 1H), 6.61−6.57 (m, 1H), 6.53−6.48 (m, 1H), 6.18 (s, 1H), 3.77 (s, 2H), 1.65 (s, 9H), 1.09 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9, 147.3, 146.1, 143.0, 136.1, 132.9, 129.0, 118.8, 115.1, 115.0, 57.3, 56.2, 32.0, 29.8 ppm; HRMS (m/z) (ESI): calcd for $C_{18}H_{26}N_3O$ 300.2076 [M + H$^+$]; found 300.2070.

1-(tert-Butyl)-5-(tert-butylimino)-4-(m-tolyl)-1H-pyrrol-2(5H)-one (**3j**). Light yellow oil (20.9 mg, 71%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (t, J = 7.5 Hz, 1H), 7.17 (d, J = 7.7 Hz, 1H), 7.02 (d, J = 8.5 Hz, 2H), 6.19 (s, 1H), 2.36 (s, 3H), 1.66 (s, 9H), 1.05 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.8, 147.5, 142.8, 137.7, 135.1, 133.2, 129.2, 127.9, 125.7, 57.3, 56.0, 32.0, 29.8, 21.3 ppm; HRMS (m/z) (ESI): calcd for $C_{19}H_{27}N_2O$ 299.2123 [M + H$^+$]; found 299.2112.

1-(tert-Butyl)-5-(tert-butylimino)-4-(p-tolyl)-1H-pyrrol-2(5H)-one (**3k**). Light yellow solid (20.2 mg, 73%); mp 70−73 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (d, J = 7.9 Hz, 2H), 7.12−7.08 (m, 2H), 6.17 (s, 1H), 2.37 (s, 3H), 1.66 (s, 9H), 1.05 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.8, 147.5, 142.8, 138.5, 133.4, 132.3, 128.7, 128.5, 57.3, 55.9, 32.0, 29.8, 21.2 ppm; HRMS (m/z) (ESI): calcd for $C_{19}H_{27}N_2O$ 299.2123 [M + H$^+$]; found 299.2116.

1-(tert-Butyl)-5-(tert-butylimino)-4-(4-ethylphenyl)-1H-pyrrol-2(5H)-one (**3l**). Light yellow solid (22.0 mg, 71%); mp 41−43 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (d, J = 8.2 Hz, 2H), 7.13 (d, J = 8.2 Hz, 2H), 6.19 (s, 1H), 2.68 (q, J = 7.6 Hz, 2H), 1.67 (s, 9H), 1.25 (t, J = 7.6 Hz, 3H), 1.06 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.8, 147.5, 144.8, 142.9, 133.3, 132.5, 128.6, 127.4, 57.3, 55.9, 32.0, 29.8, 28.5, 15.3 ppm; HRMS (m/z) (ESI): calcd for $C_{20}H_{29}N_2O$ 313.2280 [M + H$^+$]; found 313.2280.

1-(tert-Butyl)-5-(tert-butylimino)-4-(4-propylphenyl)-1H-pyrrol-2(5H)-one (**3m**). Light yellow oil (22.9 mg, 72%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (d, J = 8.2 Hz, 2H), 7.12 (d, J = 8.2 Hz, 2H), 6.19 (s, 1H), 2.64−2.59 (m, 2H), 1.67 (s, 9H), 1.64 (d, J = 6.9 Hz, 2H), 1.05 (s, 9H), 0.93 (t, J = 7.3 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9, 147.6, 143.3, 142.9, 133.3, 132.5, 128.6, 128.1, 57.3, 56.0, 37.7, 32.1, 29.9, 24.4, 13.6 ppm; HRMS (m/z) (ESI): calcd for $C_{21}H_{31}N_2O$ 327.2436 [M + H$^+$]; found 327.2459.

1-(tert-Butyl)-4-(4-(tert-butyl)phenyl)-5-(tert-butylimino)-1H-pyrrol-2(5H)-one (**3n**). Light yellow solid (26.9 mg, 80%); mp 129−131 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, J = 8.3 Hz, 2H), 7.14 (d, J = 8.3 Hz, 2H), 6.19 (s, 1H), 1.66 (s, 9H), 1.33 (s, 9H), 1.04 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.9, 151.9, 147.5, 142.8, 133.3, 132.2, 128.3, 124.8, 57.3, 55.9, 34.7, 32.0, 31.2, 29.8 ppm; HRMS (m/z) (ESI): calcd for $C_{22}H_{33}N_2O$ 341.2593 [M + H$^+$]; found 341.2587.

4-([1,1′-Biphenyl]-4-yl)-1-(tert-butyl)-5-(tert-butylimino)-1H-pyrrol-2(5H)-one (**3o**). Light yellow solid (27.1 mg, 76%); mp 125−127 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66−7.61 (m, 4H), 7.47 (t, J = 7.5 Hz, 2H), 7.39 (d, J = 7.3 Hz, 1H), 7.30 (d, J = 8.2 Hz, 2H), 6.27 (s, 1H), 1.69 (s, 9H), 1.10 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7, 147.4, 142.5, 141.4, 140.0, 134.2, 133.6, 129.1, 128.9, 127.7, 127.0, 126.6, 57.4, 56.1, 32.1, 29.8 ppm; HRMS (m/z) (ESI): calcd for $C_{24}H_{29}N_2O$ 361.2280 [M + H$^+$]; found 361.2275.

1-(tert-Butyl)-5-(tert-butylimino)-4-(thiophen-2-yl)-1H-pyrrol-2(5H)-one (**3p**). Light yellow solid (20.5 mg, 72%); mp 96−98 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, J = 4.7 Hz, 1H), 7.06−6.99 (m, 2H), 6.35 (s, 1H), 1.65 (s, 9H), 1.14 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.0, 146.2, 135.9, 135.4, 135.0, 128.3, 127.1, 126.7, 57.6, 56.1, 31.9, 29.8 ppm; HRMS (m/z) (ESI): calcd for $C_{16}H_{23}N_2OS$ 291.1531 [M + H$^+$]; found 291.1525.

1-(tert-Butyl)-5-(tert-butylimino)-4-(naphthalen-2-yl)-1H-pyrrol-2(5H)-one (**3q**). Light yellow solid (24.9 mg, 75%); mp 125−127 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89−7.82 (m, 3H), 7.71 (s, 1H), 7.54 (dd, J = 6.2, 3.2 Hz, 2H), 7.34 (d, J = 8.4 Hz, 1H), 6.30 (s, 1H), 1.70 (s, 9H), 1.05 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.7, 147.4, 142.8, 134.0, 132.9, 132.7, 132.5, 128.0, 127.8, 127.7, 126.8, 126.8, 126.5, 57.5, 56.1, 32.1, 29.8 ppm; HRMS (m/z) (ESI): calcd for $C_{22}H_{27}N_2O$ 335.2123 [M + H$^+$]; found 335.2109.

(E)-1-(tert-Butyl)-5-(tert-butylimino)-3-(4-ethynylphenyl)-1H-pyrrol-2(5H)-one (**3r**). Light yellow oil (20.9 mg, 69%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, J = 8.2 Hz, 2H), 7.19 (d, J = 8.3 Hz, 2H), 6.22 (s, 1H), 3.14 (s, 1H), 1.65 (s, 9H), 1.05 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.5, 147.0, 141.9, 135.7, 133.8, 131.8, 128.6, 122.6, 82.9, 78.5, 57.5, 56.1, 32.1, 29.8 ppm; HRMS (m/z) (ESI): calcd for $C_{20}H_{25}N_2O$ 309.1967 [M + H$^+$]; found 309.1958.

1-(tert-Butyl)-5-(tert-butylimino)-4-hexyl-1H-pyrrol-2(5H)-one (**3s**). Light yellow oil (22.1 mg, 76%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.13 (t, J = 1.8 Hz, 1H), 2.52−2.47 (m, 2H), 1.59 (s, 9H), 1.43 (s, 9H), 1.40−1.32 (m, 4H), 1.30 (dd, J = 6.8, 3.7 Hz, 4H), 0.90−0.87 (m, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.7, 149.6, 143.0, 130.7, 57.1, 54.4, 32.3, 31.6, 30.3, 29.9, 28.9, 28.5, 22.5, 14.0 ppm; HRMS (m/z) (ESI): calcd for $C_{18}H_{33}N_2O$ 293.2593 [M + H$^+$]; found 293.2582.

1-(tert-Butyl)-5-(tert-butylimino)-4-cyclohexyl-1H-pyrrol-2(5H)-one (**3t**). Light yellow solid (21.1 mg, 78%); mp 94−97 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.12 (s, 1H), 2.74−2.65 (m, 1H), 1.82−1.72 (m, 5H), 1.57 (s, 9H), 1.41 (s, 9H), 1.25−1.17 (m, 5H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 149.5, 148.7, 129.9, 57.0, 54.4, 37.3, 34.2, 32.3, 29.8, 26.3, 25.6 ppm; HRMS (m/z) (ESI): calcd for $C_{18}H_{31}N_2O$ 291.2436 [M + H$^+$]; found 291.2442.

1-(tert-Butyl)-5-(tert-butylimino)-4-cyclopropyl-1H-pyrrol-2(5H)-one (**3u**). Light yellow solid (18.4 mg, 76%); mp 85−89 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.76 (d, J = 0.8 Hz, 1H), 1.92−1.83 (m, 1H), 1.61 (s, 9H), 1.52 (s, 9H), 1.11−1.03 (m, 2H), 0.79−0.70 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.6, 149.1, 146.0, 125.5, 57.2, 54.5, 32.2, 29.9, 12.0, 11.8 ppm; HRMS (m/z) (ESI): calcd for $C_{15}H_{25}N_2O$ 249.1967 [M + H$^+$]; found 249.1955.

4-Phenyl-1-(2,4,4-trimethylpentan-2-yl)-5-((2,4,4-trimethylpentan-2-yl)imino)-1H-pyrrol-2(5H)-one (**3v**). Red brown oil (24.9 mg, 69%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.35 (m, 3H), 7.22−7.18 (m, 2H), 6.20 (s, 1H), 2.04 (s, 2H), 1.76 (s, 6H), 1.38 (s, 2H), 1.16 (s, 6H), 0.99 (s, 9H), 0.84 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2, 146.6, 141.8, 134.5, 133.3, 128.2, 127.5, 126.9, 60.0, 59.4, 53.8, 49.5, 31.6, 30.7, 30.6, 30.6, 30.5, 30.2 ppm; HRMS (m/z) (ESI): calcd for $C_{26}H_{41}N_2O$ 397.3219 [M + H$^+$]; found 397.3217.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02288.

X-ray data for compound **3b** (CIF)

General experimental methods; ^{1}H and ^{13}C NMR spectra of compounds **3a**−**3v** (PDF)

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Notes

The authors declare no competing financial interest.

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