JOC The Journal of Organic Chemistry

Article

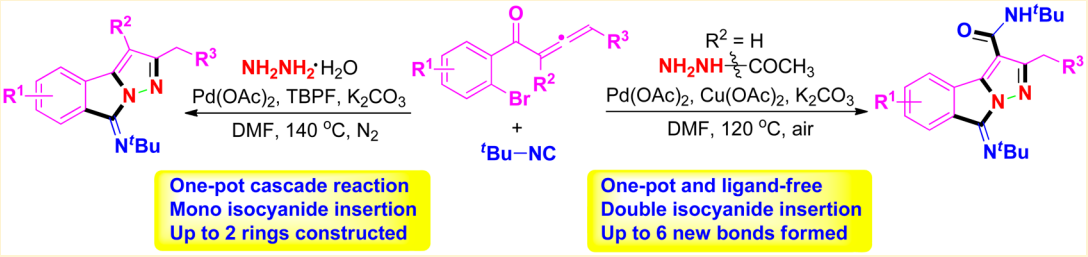
pubs.acs.org/joc

Synthesis of Pyrazolo[5,1-*a*]isoindoles and Pyrazolo[5,1-*a*]isoindole-3-carboxamides through One-Pot Cascade Reactions of 1-(2-Bromophenyl)buta-2,3-dien-1-ones with Isocyanide and Hydrazine or Acetohydrazide

Miaomiao Tian, Yan He, Xinying Zhang,* and Xuesen Fan*

School of Chemistry and Chemical Engineering, Collaborative Innovation Center of Henan Province for Green Manufacturing of Fine Chemicals, Key Laboratory of Green Chemical Media and Reactions, Ministry of Education, Henan Key Laboratory for Environmental Pollution Control, Henan Normal University, Xinxiang, Henan 453007, China

Supporting Information



ABSTRACT: A novel and efficient method for the construction of the pyrazolo[5,1-*a*]isoindole scaffold via a one-pot three-component cascade reaction of 1-(2-bromophenyl)buta-2,3-dien-1-one with hydrazine and isocyanide promoted by a Pd catalyst is described. This cascade process proceeds through initial condensation of the allenic ketone with hydrazine followed by Pd-catalyzed isocyanide insertion into the C−Br bond and intramolecular C−N bond formation. Interestingly, when acetohydrazide was used in place of hydrazine, a more sophisticated procedure involving condensation, isocyanide insertion into C−H and C−Br bonds, deacetylation, and formation of C−C, C−O, and C−N bonds occurred to afford pyrazolo[5,1-*a*]isoindole-3-carboxamides with good efficiency.

INTRODUCTION

Fused pyrazoles have stimulated considerable attention, as they are key structural motifs in compounds with important biological activities.[1,2] In particular, pyrazolo[5,1-*a*]isoindoles are endowed with plant growth regulating,[3] antihypertensive,[4] antiamoebic,[5] and antidepressant activities.[6] Because of their importance, a number of approaches have been developed for the synthesis of pyrazolo[5,1-*a*]isoindoles, including reaction of iminophosphoranes with acetylenic compounds,[7] intramolecular Wittig reaction of phosphorus ylides,[8] condensation of phthalaldehydic acid with acetophenones followed by condensation with hydrazine hydrate,[9] Suzuki cross-coupling reaction of pyrazolylboronic esters,[10] intramolecular C−H bond activation of 1-(2-halobenzyl)pyrazoles,[11] photochemical intramolecular [3 + 2] cycloaddition of stilbene-methylene-sydnones,[12] and intramolecular Friedel−Crafts acylation of chalcone-based *N*-formylpyrazolines.[13] While these literature procedures are generally efficient and reliable, some of them still suffer from difficult-to-obtain substrates, tedious operation procedures, and harsh reaction conditions. Therefore, efficient and convenient new strategies for the synthesis of pyrazolo[5,1-*a*]isoindole derivatives starting from simple and easily obtainable substrates are still in great demand.

In the past several decades, isocyanides have emerged as powerful and versatile building blocks in organic synthesis. Earlier studies on the reactivity of isocyanides were mainly focused on the potential utility of their nucleophilicity and electrophilicity in multicomponent reactions (MCRs). Recently, transition-metal-catalyzed isocyanide insertion as a novel reaction pattern is rapidly prevailing.[14] Isocyanide insertion (also called imidoylative reaction) refers to the direct insertion of isocyanide into a heteroatom−hydrogen, carbon−halogen, or carbon−hydrogen bond to give an imidoylative intermediate, which can be then trapped by various nucleophiles to afford different classes of organic compounds, including some biologically significant heterocycles.[15]

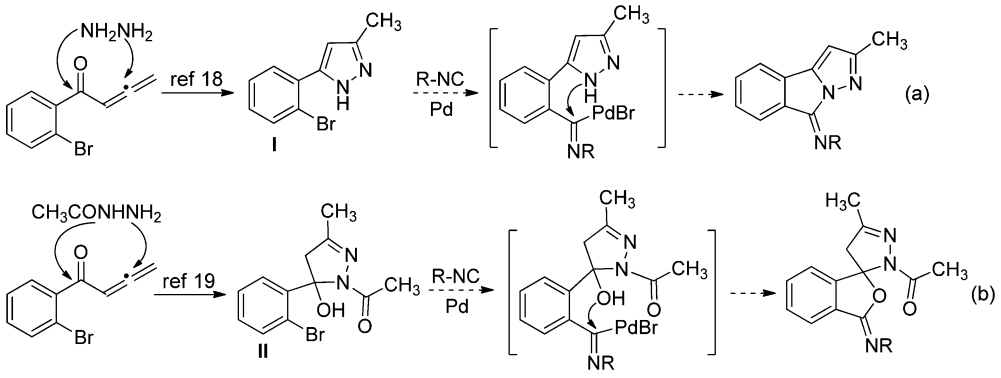
Meanwhile, allene derivatives are valuable intermediates in synthetic chemistry because of their diverse reactivity.[16] Among them, electron-deficient allenic ketones are highly active in receiving nucleophilic addition to form C−C and C−X bonds.[17] In recent studies, we have disclosed that cascade nucleophilic addition of hydrazine to allenic ketones can lead to the formation of substituted pyrazoles with ease in high efficiency.[18] We have also found that the tandem reaction

Received: May 7, 2015
Published: July 8, 2015

ACS Publications © 2015 American Chemical Society

DOI: 10.1021/acs.joc.5b00997
J. Org. Chem. 2015, 80, 7447−7455

Scheme 1. Our Envisioned One-Pot Synthesis of Fused or Spiropyrazoles

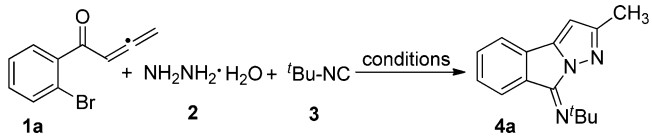


between a 1,2-allenic ketone and acetohydrazine provides a highly regioselective synthesis of 1-acetyl-5-hydroxypyrazolines.[19] Inspired by these pioneering results, we hypothesized that the pyrazolo[5,1-*a*]isoindole scaffold could be constructed via a one-pot three-component reaction of 1-(2-bromophenyl)-buta-2,3-dien-1-one with hydrazine and isocyanide featuring Pd-catalyzed isocyanide insertion into the C−Br bond of the in situ-formed 5-(2-bromophenyl)-1*H*-pyrazole (**I**) followed by C−N bond formation (Scheme 1a). Moreover, spiro-(isobenzofuran-1,3′-pyrazole) might also be formed via isocyanide insertion into the C−Br bond of 1-(5-(2-bromophenyl)-5-hydroxy-3-methyl-4,5-dihydro-1*H*-pyrazol-1-yl)ethanone (**II**), formed in situ from the reaction of 1-(2-bromophenyl)buta-2,3-dien-1-one with acetohydrazide, followed by an intramolecular C−O bond formation (Scheme 1b). Herein we report our preliminary results in this regard.

RESULTS AND DISCUSSION

Our studies were initiated by treatment of 1-(2-bromophenyl)-buta-2,3-dien-1-one (**1a**) with hydrazine (**2**) in DMF at room temperature for 10 min. Then *tert*-butyl isocyanide (**3**), $Pd(OAc)_2$, and K_2CO_3 were added. The resulting mixture was stirred at 120 °C for 6 h. As expected, 2-methyl-*N*-(2-methyl-8*H*-pyrazolo[5,1-*a*]isoindol-8-ylidene)propan-2-amine (**4a**) was obtained in a yield of 30% (Table 1, entry 1). To improve the efficiency, PPh_3 was used as a ligand to assist this Pd-catalyzed process. As a result, the yield of **4a** increased to 45% (entry 2). Next, different palladium catalysts were screened, but none of them gave higher yield of **4a** than that with $Pd(OAc)_2$ (entries 2−5). Under these circumstances, other ligands including XPhos, SPhos, TFP, and TBPF were tried (entries 6−9). Among them, TBPF turned out to be the most efficient, giving **4a** in a yield of 65% (entry 9). Subsequently, the effect of different bases on this cascade reaction was also studied. It was found that while the reactions using Cs_2CO_3 and KOH gave yields similar to that with K_2CO_3, the use of Na_2CO_3, Et_3N, or DBU resulted in decreased efficiency (entries 10−14). Next, various solvents including dioxane, THF, CH_3CN, and toluene were also tried, but they were less favorable for this reaction than DMF (entries 15−18 vs 9). In further screening, we were pleased to find that elevating the reaction temperature from 120 to 140 °C improved the yield to 85% (entry 19). Further increasing the reaction temperature, however, did not give positive results (entry 20). In summary of the optimization study, initial treatment of **1a** with **2** (1.1 equiv) in DMF at ambient temperature for 10 min followed by reaction of the resulting mixture with **3** (1.5 equiv) in the presence of 0.05 equiv of $Pd(OAc)_2$, 0.1 equiv of TBPF, and 2 equiv of K_2CO_3 at 140 °C for 6 h under nitrogen gave **4a** in a yield of 85% (Table 1, entry 19).

Table 1. Optimization Studies on the Formation of 4a[a]



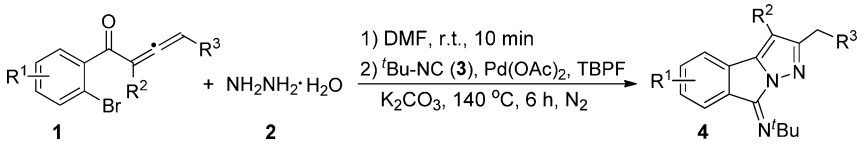
entry	catalyst	ligand[b]	base	solvent	*T* (°C)	yield (%)[c]
1	$Pd(OAc)_2$	–	K_2CO_3	DMF	120	30
2	$Pd(OAc)_2$	PPh_3	K_2CO_3	DMF	120	45
3	$PdCl_2$	PPh_3	K_2CO_3	DMF	120	42
4	$PdCl_2(PPh_3)_2$	PPh_3	K_2CO_3	DMF	120	20
5	$Pd_2(dba)_3$	PPh_3	K_2CO_3	DMF	120	36
6	$Pd(OAc)_2$	XPhos	K_2CO_3	DMF	120	40
7	$Pd(OAc)_2$	SPhos	K_2CO_3	DMF	120	53
8	$Pd(OAc)_2$	TFP	K_2CO_3	DMF	120	43
9	$Pd(OAc)_2$	TBPF	K_2CO_3	DMF	120	65
10	$Pd(OAc)_2$	TBPF	Et_3N	DMF	120	32
11	$Pd(OAc)_2$	TBPF	DBU	DMF	120	40
12	$Pd(OAc)_2$	TBPF	Na_2CO_3	DMF	120	48
13	$Pd(OAc)_2$	TBPF	Cs_2CO_3	DMF	120	60
14	$Pd(OAc)_2$	TBPF	KOH	DMF	120	63
15	$Pd(OAc)_2$	TBPF	K_2CO_3	dioxane	reflux	50
16	$Pd(OAc)_2$	TBPF	K_2CO_3	THF	reflux	40
17	$Pd(OAc)_2$	TBPF	K_2CO_3	CH_3CN	reflux	43
18	$Pd(OAc)_2$	TBPF	K_2CO_3	toluene	reflux	55
19	**$Pd(OAc)_2$**	**TBPF**	**K_2CO_3**	**DMF**	**140**	**85**
20	$Pd(OAc)_2$	TBPF	K_2CO_3	DMF	160	80

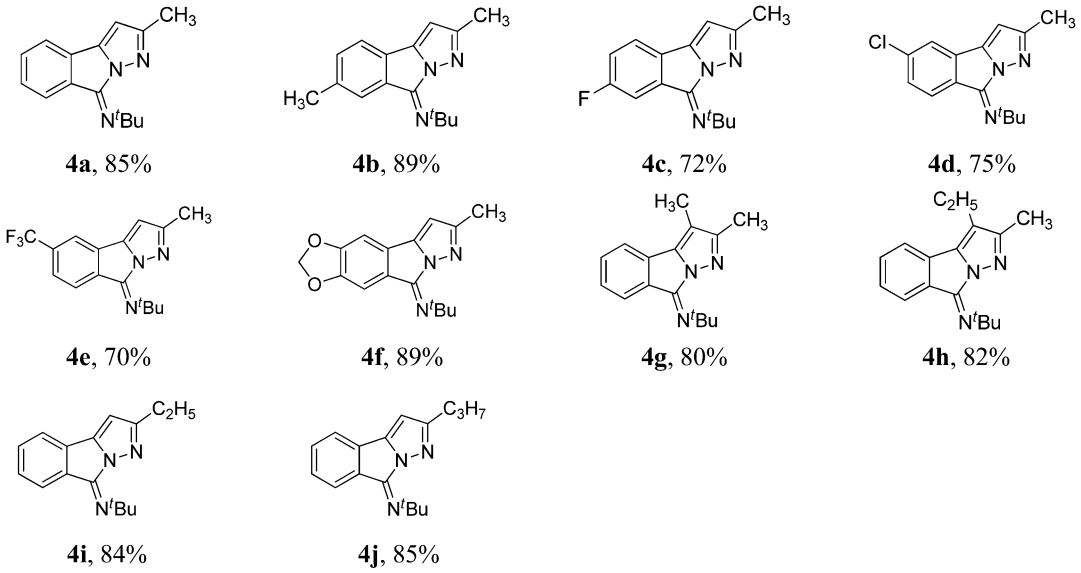
[a]Reaction conditions: **1a** (0.2 mmol), **2** (0.22 mmol), solvent (1 mL), r.t., 10 min; then **3** (0.3 mmol), catalyst (0.01 mmol), ligand (0.02 mmol), base (0.4 mmol), 6 h, under N_2. [b]Ligands: XPhos = 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl; SPhos = 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl; TFP = tris(2-furanyl)-phosphine; TBPF = tri-(*tert*-butyl)phosphonium tetrafluoroborate. [c]Isolated yields.

With the optimized reaction conditions in hand, we screened a range of 1-(2-bromophenyl)buta-2,3-dien-1-ones **1** to probe the scope of this new synthetic strategy toward pyrazolo[5,1-*a*]isoindoles. It turned out that allenic ketone substrates with various substituents attached on the phenyl ring underwent this tandem reaction smoothly to afford the desired pyrazolo[5,1-*a*]isoindoles **4a−f** in good to excellent yields (Table 2). Various functional groups, from electron-donating methoxy to electron-

DOI: 10.1021/acs.joc.5b00997
J. Org. Chem. 2015, 80, 7447−7455

Table 2. Synthesis of Pyrazolo[5,1-*a*]isoindoles 4[a,b]





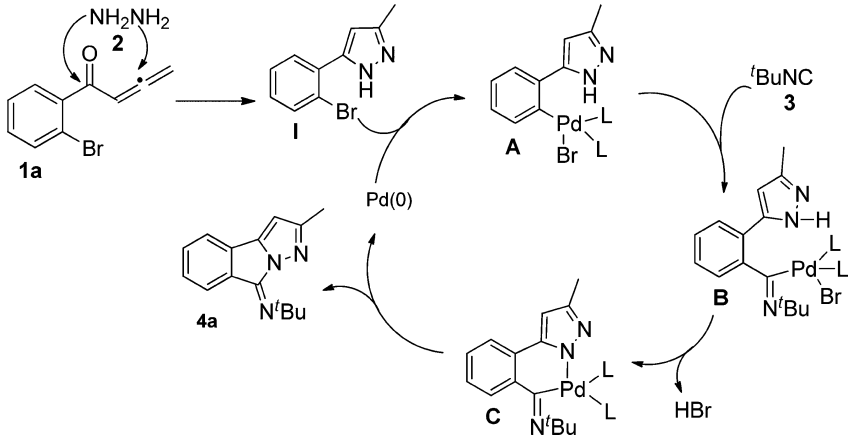
4a, 85% **4b**, 89% **4c**, 72% **4d**, 75%

4e, 70% **4f**, 89% **4g**, 80% **4h**, 82%

4i, 84% **4j**, 85%

[a]Reaction conditions: **1** (0.5 mmol), **2** (0.55 mmol), DMF (2.5 mL), r.t., 10 min; then **3** (0.75 mmol), $Pd(OAc)_2$ (0.025 mmol), TBPF (0.05 mmol), K_2CO_3 (1 mmol), 140 °C, 6 h, under N_2. [b]Isolated yields are shown.

Scheme 2. Plausible Pathway for the Formation of 4a



withdrawing trifluoromethyl, were well-tolerated. Fluoro- or chloro-substituted aromatic moieties survived the reaction conditions, allowing possible subsequent elaboration of the products (**4c** and **4d**). It was also observed that the electronic nature of the substrate affected the yield of **4** in that substrates with electron-donating groups were more favorable than those with electron-withdrawing groups (**4b** and **4f** vs **4c**–**e**). Interestingly, when substrates bearing a methyl or ethyl group at the internal or terminal position of the allene moiety were used, the reaction still proceeded smoothly to give the corresponding products (**4g**–**j**) with good efficiency.

On the basis of the above results and previous reports,[14,15] a plausible pathway to account for the formation of **4a** is proposed in Scheme 2. Initially, condensation of **1a** with **2** affords **I**. Oxidative insertion of Pd(0) into the C–Br bond of **I** gives Pd(II) intermediate **A**. Next, insertion of **3** into the Pd–C bond of **A** provides imidoyl intermediate **B**. Subsequent N-coordination of Pd gives the new complex **C**. Finally, reductive elimination and intramolecular cyclization take place with **C** to give **4a** and regenerate the Pd(0) catalyst.

Having established an efficient synthesis of pyrazolo[5,1-*a*]isoindoles via the Pd-catalyzed one-pot cascade reaction of 1-(2-bromophenyl)buta-2,3-dien-1-ones with hydrazine and isocyanide, we moved forward to study our envisioned synthesis of spiro(isobenzofuran-1,3′-pyrazole) as described in Scheme 1b. Thus, **1a** (0.2 mmol) was first allowed to react with acetohydrazide (**5a**) (0.22 mmol) in DMF at room temperature for 1 h. The resulting mixture was then treated with **3** (0.3 mmol) in the presence of 0.05 equiv of $Pd(OAc)_2$, 0.1 equiv of TBPF, and 2 equiv of K_2CO_3 at 120 °C for 8 h under nitrogen. To our surprise, the envisioned 1-(3-(*tert*-butylimino)-5′-methyl-3*H*-spiro[isobenzofuran-1,3′-pyrazole]-2′(4′*H*)-yl)-

DOI: 10.1021/acs.joc.5b00997
J. Org. Chem. 2015, 80, 7447–7455

Scheme 3. Unexpected Formation of 6a from the Reaction of 1a with 5a and 3

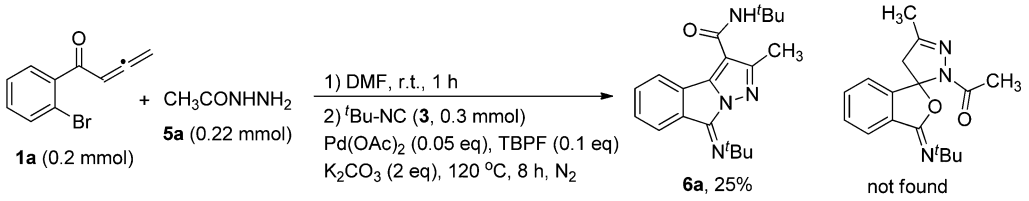
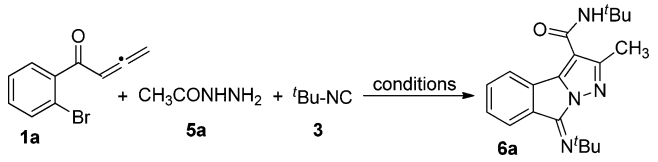


Table 3. Optimization Studies on the Formation of 6a[a]



entry	catalyst	ligand	oxidant	base	solvent	T (°C)	yield (%)[b]
1	$Pd(OAc)_2$	TBPF	–	K_2CO_3	DMF	120	44
2	$Pd(OAc)_2$	PPh_3	–	K_2CO_3	DMF	120	40
3	$Pd(OAc)_2$	XPhos	–	K_2CO_3	DMF	120	33
4	$Pd(OAc)_2$	SPhos	–	K_2CO_3	DMF	120	35
5	$PdCl_2$	TBPF	–	K_2CO_3	DMF	120	42
6	$PdCl_2(PPh_3)_2$	TBPF	–	K_2CO_3	DMF	120	30
7	$Pd_2(dba)$	TBPF	–	K_2CO_3	DMF	120	32
8	$Pd(PPh_3)_4$	TBPF	–	K_2CO_3	DMF	120	25
9	$Pd(OAc)_2$	TBPF	O_2 (balloon)	K_2CO_3	DMF	120	46
10	$Pd(OAc)_2$	TBPF	AgOAc	K_2CO_3	DMF	120	58
11	$Pd(OAc)_2$	TBPF	Ag_2CO_3	K_2CO_3	DMF	120	52
12	$Pd(OAc)_2$	TBPF	$Cu(OAc)_2$	K_2CO_3	DMF	120	72
13[c]	$Pd(OAc)_2$	TBPF	$Cu(OAc)_2$	K_2CO_3	DMF	120	52
14[d]	$Pd(OAc)_2$	TBPF	$Cu(OAc)_2$	K_2CO_3	DMF	120	70
15	**$Pd(OAc)_2$**	**–**	**$Cu(OAc)_2$**	**K_2CO_3**	**DMF**	**120**	**82**
16	–	–	$Cu(OAc)_2$	K_2CO_3	DMF	120	–
17	$Pd(OAc)_2$	–	$Cu(OAc)_2$	K_2CO_3	DMF	140	72
18	$Pd(OAc)_2$	–	$Cu(OAc)_2$	K_2CO_3	DMF	100	62
19	$Pd(OAc)_2$	–	$Cu(OAc)_2$	K_2CO_3	dioxane	reflux	56
20	$Pd(OAc)_2$	–	$Cu(OAc)_2$	K_2CO_3	toluene	reflux	52

[a]Reaction conditions: **1a** (0.2 mmol), **5a** (0.22 mmol), solvent (1 mL), r.t., 1 h; then **3** (0.44 mmol), catalyst (0.01 mmol), ligand (0.02 mmol), oxidant (0.2 mmol), K_2CO_3 (0.4 mmol), 120 °C, 8 h, under air. [b]Isolated yields. [c]$Cu(OAc)_2$ (0.1 mmol). [d]$Cu(OAc)_2$ (0.4 mmol).

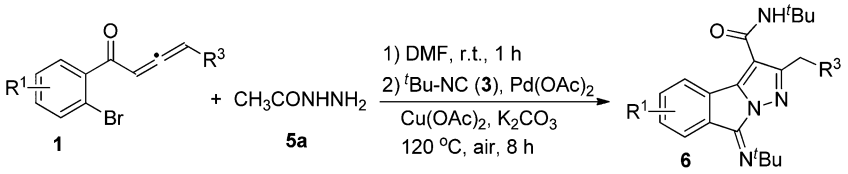
ethanone was not found. Instead, *N*-*tert*-butyl-8-(*tert*-butylimino)-2-methyl-8*H*-pyrazolo[5,1-*a*]isoindole-3-carboxamide (**6a**) was obtained in 25% yield (Scheme 3).

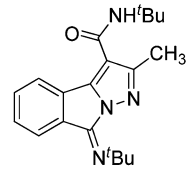
It occurred to us that the unexpected formation of **6a** might be more rewarding for the following reasons. First, the pyrazole-4-carboxamide scaffold has been found in a number of compounds showing significant biological and pharmaceutical activities.[20] For the construction of this privileged structure, the most frequently used strategy is the reaction of pyrazole-4-carboxylic acid with amines under the assistance of activating reagents such as 1,1′-carbonyldiimidazole or (benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate (BOP reagent).[21] In another example, Pendri reported a solid-phase synthesis of 1,5-diarylpyrazole-4-carboxamides, which act as antagonists of the CB-1 receptor, through acylation of a resin-bound secondary amine with a β-keto ester via transamidation, conversion of the resulting β-keto amide to the corresponding vinylogous amide, and pyrazole formation upon reaction with an aryl hydrazine, followed by cleavage of the product from the resin.[22] In view of more sustainable chemistry, the development of new synthetic methods for pyrazole-4-carboxamides featuring a simplified procedure and starting from economical reagents should definitely benefit the synthetic community and pharmaceutical chemistry. Second, it was noticed that the formation of **6a** should have involved a direct carboxamidation of the C−H bond at the 4-position of the in situ-formed pyrazole moiety. In recent years, transition-metal-catalyzed C−H bond activation and subsequent functionalization has evolved as a powerful tool for the formation of C−C and C−X bonds since this strategy has advantages such as step economy and environmental sustainability due to the avoidance of using halogenated materials as the substrates. Among various functionalizations following the initial C−H bond activation, however, direct carboxamidation is only scarcely found in the literature.[23] To the best of our knowledge, direct carboxamidation onto the pyrazole ring via C−H bond cleavage has not been previously reported.

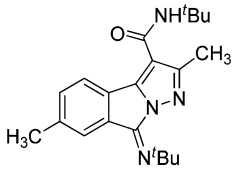
Inspired by the above facts, we thoroughly studied the reaction of **1a**, **5a**, and **3**. As the structure of **6a** indicated that 2 equiv of isocyanide **3** participated in the formation of **6a**, the reaction was then rerun with 2.2 equiv of **3** under air while the other conditions were kept unchanged. In this case, **6a** was obtained in a yield of 44% (Table 3, entry 1). Next, different

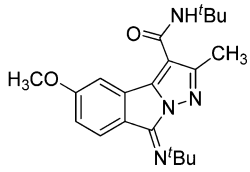
DOI: 10.1021/acs.joc.5b00997
J. Org. Chem. 2015, 80, 7447−7455

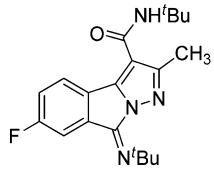
Table 4. Synthesis of Pyrazolo[5,1-*a*]isoindole-3-carboxamides 6[a,b]

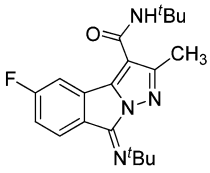


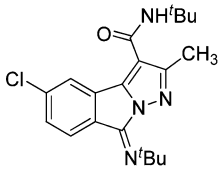

6a, 82%

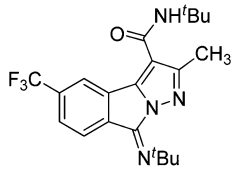

6b, 86%

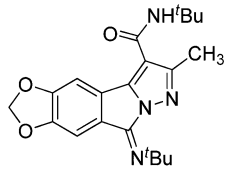

6c, 89%

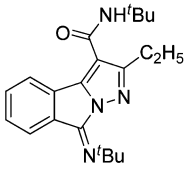

6d, 72%

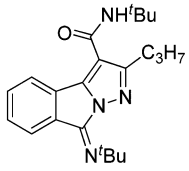

6e, 70%


6f, 76%


6g, 67%

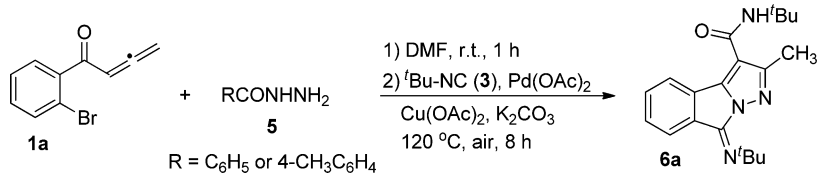

6h, 87%


6i, 81%


6j, 83%

[a]Reaction conditions: **1** (0.2 mmol), **5a** (0.22 mmol), DMF (1 mL), r.t., 1 h; then **3** (0.44 mmol), $Pd(OAc)_2$ (0.01 mmol), $Cu(OAc)_2$ (0.2 mmol), K_2CO_3 (0.4 mmol), 120 °C, 8 h, under air. [b]Isolated yields are shown.

Scheme 4. Reactions of 1a, 3, and Benzohydrazides 5



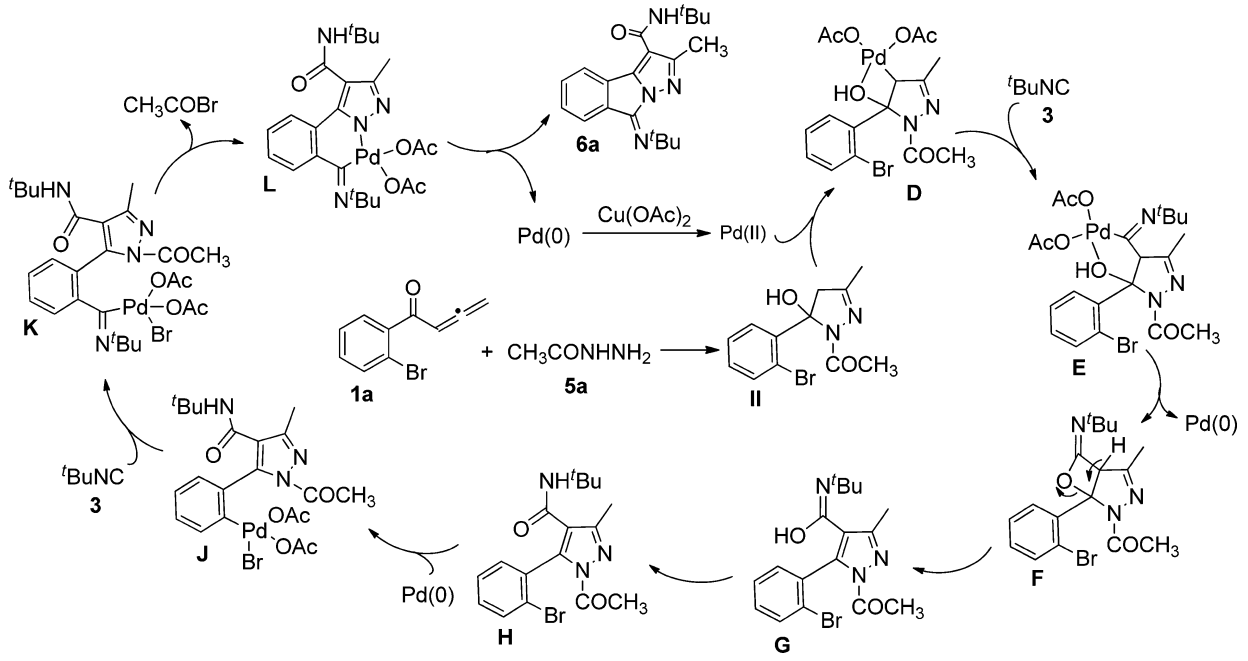
ligands and Pd catalysts were tried with the aim of improving the efficiency (entries 2−8). Unfortunately, no better results were obtained. Since in previously reported C−H activation processes promoted by Pd catalysts an added oxidant is usually needed to oxidize the in situ-formed Pd(0) into Pd(II), several oxidants were tried, including molecular oxygen, AgOAc, Ag_2CO_3, and $Cu(OAc)_2$ (entries 9−14). Among them, $Cu(OAc)_2$ gave the best yield, and its optimum amount turned out to be 1 equiv. Interestingly, a subsequent control experiment disclosed that the reaction could afford **6a** in a yield of 82% in the absence of any added ligand (entry 15). When the Pd catalyst was removed, however, the formation of **6a** was not observed (entry 16). Next, the reaction was tried at 140 or 100 °C, but no increase in the yield of **6a** was obtained (entries 17 and 18). When the reaction was carried out in another solvent such as dioxane or toluene, the yield of **6a** decreased dramatically (entries 19 and 20). In summary of the optimization process, treatment of **1a** with **5a** (1.1 equiv) in DMF at ambient temperature for 1 h followed by reaction of the resulting mixture with **3** (2.2 equiv) in the presence of 0.05 equiv of $Pd(OAc)_2$, 1 equiv of $Cu(OAc)_2$, and 2 equiv of K_2CO_3 at 120 °C under air for 8 h gave **6a** in a yield of 82% (Table 3, entry 15).

To confirm the generality of this one-pot synthesis of pyrazolo[5,1-*a*]isoindole-3-carboxamides **6**, we examined several 1-(2-bromophenyl)buta-2,3-dien-1-ones **1** under the optimized reaction conditions. The results listed in Table 4 show that **1** with electron-donating methoxy or methyl groups or electron-withdrawing trifluoromethyl or halide groups on the phenyl ring could take part in this cascade reaction smoothly to afford the corresponding pyrazolo[5,1-*a*]isoindole-3-carboxamides **6a−j** in good to excellent yields. Meanwhile, the R^3 unit could be either a methyl or ethyl group without showing an obvious effect (**6i** and **6j**).

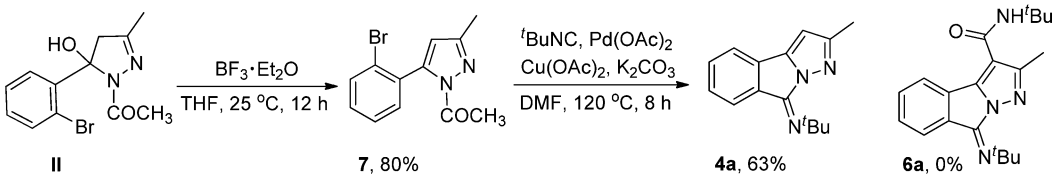
As a further aspect, the scope of hydrazide substrates was studied. In addition to acetohydrazide, this reaction was found also to be compatible with benzohydrazide and 4-methylbenzohydrazide, which gave **6a** in 52% and 45% yield, respectively (Scheme 4). Comparison with the results listed in Table 4 indicated that aryl-substituted hydrazides were less

DOI: 10.1021/acs.joc.5b00997
J. Org. Chem. 2015, 80, 7447−7455

Scheme 5. Plausible Pathway for the Formation of 6a



Scheme 6. Control Experiment Supporting the Mechanism for the Formation of 6a



efficient than acetohydrazide as substrates for this cascade reaction.

As shown in Scheme 5, the formation of **6a** starts with the condensation of **1a** with **5a** to afford **II**. Subsequent C–H activation and palladation of **II** with the assistance of the vicinal hydroxyl group yields cyclopalladation intermediate **D**.[24] Insertion of isocyanide into the C–Pd bond in **D** gives intermediate **E**. Reductive elimination occurs with **E** to give **F** and generate Pd(0). The ensuing ring opening of **F** gives **G**, which tautomerizes to afford **H**. Next, oxidative insertion of Pd(0) into the C–Br bond in **H** gives intermediate **J**. Subsequent isocyanide insertion into the Pd–C bond in **J** provides another imidoyl intermediate, **K**, and then N-coordination of Pd in **K** along with the elimination of acetyl bromide affords complex **L**. Finally, reductive elimination occurs with **L** to release **6a** and liberate Pd(0). The Pd(0) species is then oxidized by $Cu(OAc)_2$ to regenerate Pd(II) for the next catalytic cycle.

The plausible pathway for the formation of **6a** as shown in Scheme 5 was partly supported by the following experiment. 1-(5-(2-Bromophenyl)-3-methyl-1*H*-pyrazol-1-yl)ethanone (**7**) was prepared through $BF_3{\cdot}Et_2O$-promoted dehydration of **II**. When **7** was subjected to the standard reaction conditions used for the preparation of **6a**, **4a** was obtained in a yield of 63% while no formation of **6a** was observed (Scheme 6). This result indicated that the presence of the vicinal hydroxyl group is crucial for the carboxamination of the pyrazole unit.

■ CONCLUSION

We have developed a novel and efficient synthesis of pyrazolo[5,1-*a*]isoindoles via a palladium-catalyzed one-pot three-component cascade reaction of 1-(2-bromophenyl)buta-2,3-dien-1-ones with hydrazine and isocyanide. More interestingly, when hydrazine was replaced by acetohydrazide, a more complex version of the cascade process took place, and biologically and synthetically valuable pyrazolo[5,1-*a*]isoindole-3-carboxamides were obtained with good efficiency. Notably, this is the first example of direct carboxamidation onto a pyrazole ring via C–H bond cleavage. Compared with literature procedures to obtain pyrazolo[5,1-*a*] isoindoles and pyrazolo-[5,1-*a*]isoindole-3-carboxamides, the strategies developed herein showed advantages such as readily available starting materials, practical reaction conditions, and multiple bond formation to give advanced structures in one pot with high atom economy. Further studies to gain deeper insight into the reaction mechanism for the formation of pyrazolo[5,1-*a*]isoindole-3-carboxamides are currently underway.

■ EXPERIMENTAL SECTION

General Methods. Unless otherwise noted, all of the commercial reagents were used without further purification. The solvents were dried prior to use. 1-(2-Bromophenyl)buta-2,3-dien-1-ones **1** were synthesized through oxidation of the corresponding homopropargyl alcohols,[25] which were prepared through zinc-promoted propargylation of aldehydes.[26] ^{1}H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively. Chemical shifts (in ppm) were referenced to tetramethylsilane in $CDCl_3$ or DMSO-d_6. ^{13}C NMR spectra were calibrated with $CDCl_3$ (δ = 77.00 ppm) or DMSO-d_6 (δ = 39.50

DOI: 10.1021/acs.joc.5b00997
J. Org. Chem. 2015, 80, 7447–7455

ppm). Multiplicities are indicated as follows: s (singlet); d (doublet); t (triplet); m (multiplet); dd (doublet of doublets), etc. Coupling constants are given in hertz. High-resolution mass spectrometry (HRMS) was performed in ESI mode using a MicrOTOF mass spectrometer. The conversion of starting materials was monitored by thin-layer chromatography (TLC) using silica gel plates (silica gel 60 F254, 0.25 mm), and the components were visualized by observation under UV light (254 and 365 nm).

Typical Procedure for the Synthesis of 4a and Spectroscopic Data for 4a–j. To a flask containing 1-(2-bromophenyl)buta-2,3-dien-1-one (**1a**) (111 mg, 0.5 mmol) and hydrazine hydrate (**2**) (28 mg, 0.55 mmol) was added DMF (2.5 mL), and the mixture was stirred at room temperature for 10 min. Then *tert*-butyl isocyanide (**3**) (62 mg, 0.75 mmol), $Pd(OAc)_2$ (6 mg, 0.025 mmol), TBPF (15 mg, 0.05 mmol), and K_2CO_3 (138 mg, 1 mmol) were added, and the resulting mixture was stirred at 140 °C under a nitrogen atmosphere. Upon completion of the reaction, the reaction mixture was diluted with brine (10 mL) and extracted with EtOAc (6 mL × 3). The combined organic phases were dried with anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by column chromatography on silica gel with EtOAc/hexane (5%) as the eluent to give 2-methyl-*N*-(2-methyl-8*H*-pyrazolo[5,1-*a*]isoindol-8-ylidene)-propan-2-amine (**4a**) in 85% yield. **4b–j** were obtained in a similar manner.

*2-Methyl-N-(2-methyl-8H-pyrazolo[5,1-a]isoindol-8-ylidene)-propan-2-amine (**4a**).* Eluent: ethyl acetate/hexanes (5%). White solid (102 mg, 85%), mp 133–134 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.68 (s, 9H), 2.37 (s, 3H), 6.08 (s, 1H), 7.30–7.39 (m, 3H), 7.80 (d, J = 7.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.6, 28.9, 55.3, 98.6, 119.6, 123.8, 128.3, 129.9, 130.9, 133.9, 137.2, 148.1, 156.0. HRMS: calcd for $C_{15}H_{18}N_3$ 240.1495 $[M + H]^+$, found 240.1508.

*N-(2,6-Dimethyl-8H-pyrazolo[5,1-a]isoindol-8-ylidene)-2-methylpropan-2-amine (**4b**).* Eluent: ethyl acetate/hexanes (5%). White solid (113 mg, 89%), mp 175–176 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.65 (s, 9H), 2.35 (s, 3H), 2.39 (s, 3H), 6.02 (s, 1H), 7.18 (d, J = 8.0 Hz, 1H), 7.24 (d, J = 8.0 Hz, 1H), 7.58 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.5, 21.5, 28.9, 55.2, 98.1, 119.4, 124.3, 127.3, 131.4, 137.4, 138.5, 138.8, 148.3, 155.9. HRMS: calcd for $C_{16}H_{19}N_3Na$ 276.1471 $[M + Na]^+$, found 276.1479.

*N-(6-Fluoro-2-methyl-8H-pyrazolo[5,1-a]isoindol-8-ylidene)-2-methylpropan-2-amine (**4c**).* Eluent: ethyl acetate/hexanes (5%). White solid (93 mg, 72%), mp 144–145 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.62 (s, 9H), 2.34 (s, 3H), 6.04 (s, 1H), 7.05–7.10 (m, 1H), 7.30 (dd, J_1 = 8.0 Hz, J_2 = 4.4 Hz, 1H), 7.45 (dd, J_1 = 8.0 Hz, J_2 = 2.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.5, 28.8, 55.4, 98.4, 111.4, 111.7, 117.5, 117.7, 120.9, 121.0, 126.0, 137.5, 137.6, 139.6, 139.7, 147.4, 156.2, 161.8, 164.3. HRMS: calcd for $C_{15}H_{17}FN_3$ 258.1401 $[M + H]^+$, found 258.1409.

*N-(5-Chloro-2-methyl-8H-pyrazolo[5,1-a]isoindol-8-ylidene)-2-methylpropan-2-amine (**4d**).* Eluent: ethyl acetate/hexanes (5%). White solid (102 mg, 75%), mp 168–169 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.62 (s, 9H), 2.35 (s, 3H), 6.08 (s, 1H), 7.25 (dd, J_1 = 8.4 Hz, J_2 = 2.4 Hz, 1H), 7.33 (d, J = 2.4 Hz, 1H), 7.66 (d, J = 7.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.6, 28.8, 55.5, 99.1, 119.9, 124.9, 128.2, 131.3, 135.4, 136.9, 137.5, 146.7, 156.1. HRMS: calcd for $C_{15}H_{16}ClN_3Na$ 296.0925 $[M + Na]^+$, found 296.0915.

*2-Methyl-N-(2-methyl-5-(trifluoromethyl)-8H-pyrazolo[5,1-a]-isoindol-8-ylidene)propan-2-amine (**4e**).* Eluent: ethyl acetate/hexanes (5%). White solid (107 mg, 70%), mp 127–128 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.63 (s, 9H), 2.37 (s, 3H), 6.16 (s, 1H), 7.56 (d, J = 8.0 Hz, 1H), 7.61 (s, 1H), 7.85 (d, J = 8.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.5, 28.8, 55.7, 99.4, 116.56, 116.59, 122.5, 124.1, 125.1, 125.2, 130.4, 132.7, 133.0, 137.2, 140.2, 146.7, 156.5. HRMS: calcd for $C_{16}H_{16}F_3N_3Na$ 330.1189 $[M + Na]^+$, found 330.1190.

*2-Methyl-N-(8-methyl-5H-[1,3]dioxolo[4,5-f]pyrazolo[5,1-a]-isoindol-5-ylidene)propan-2-amine (**4f**).* Eluent: ethyl acetate/hexanes (5%). White solid (126 mg, 89%), mp 225–226 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.60 (s, 9H), 2.32 (s, 3H), 5.94 (s, 1H), 6.00 (s, 2H), 6.79 (s, 1H), 7.19 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.5, 28.8, 55.1, 97.7, 100.8, 101.7, 105.0, 124.7, 131.6, 138.3, 147.8, 148.0, 150.1, 155.6. HRMS: calcd for $C_{16}H_{18}N_3O_2$ 284.1394 $[M + H]^+$, found 284.1403.

*N-(2,3-Dimethyl-8H-pyrazolo[5,1-a]isoindol-8-ylidene)-2-methylpropan-2-amine (**4g**).* Eluent: ethyl acetate/hexanes (5%). White solid (101 mg, 80%), mp 132–133 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.65 (s, 9H), 2.17 (s, 3H), 2.27 (s, 3H), 7.24–7.28 (m, 1H), 7.38 (d, J = 4.0 Hz, 2H), 7.76 (d, J = 7.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 8.2, 12.5, 28.8, 55.1, 109.0, 118.9, 123.8, 127.6, 130.5, 130.7, 137.2, 138.6, 144.4, 155.9. HRMS: calcd for $C_{16}H_{20}N_3$ 254.1652 $[M + H]^+$, found 254.1663.

*N-(3-Ethyl-2-methyl-8H-pyrazolo[5,1-a]isoindol-8-ylidene)-2-methylpropan-2-amine (**4h**).* Eluent: ethyl acetate/hexanes (5%). White solid (109 mg, 82%), mp 52–54 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.22–1.26 (m, 3H), 1.61 (s, 9H), 2.29 (s, 3H), 2.59–2.65 (m, 2H), 7.26–7.28 (m, 1H), 7.29–7.40 (m, 2H), 7.75 (dd, J_1 = 6.8 Hz, J_2 = 0.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 12.6, 14.9, 16.8, 28.8, 55.0, 115.8, 119.1, 123.8, 127.6, 130.5, 130.8, 137.3, 138.6, 144.1, 155.3. HRMS: calcd for $C_{17}H_{22}N_3$ 268.1808 $[M + H]^+$, found 268.1818.

*N-(2-Ethyl-8H-pyrazolo[5,1-a]isoindol-8-ylidene)-2-methylpropan-2-amine (**4i**).* Eluent: ethyl acetate/hexanes (5%). White solid (106 mg, 84%), mp 51–53 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.33 (t, J = 7.2 Hz, 3H), 1.66 (s, 9H), 2.73 (q, J = 7.2 Hz, 2H), 6.12 (s, 1H), 7.30 (t, J = 7.6 Hz, 1H), 7.32–7.39 (m, 2H), 7.77 (d, J = 7.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.3, 22.3, 28.9, 55.3, 97.2, 119.6, 123.7, 128.2, 130.0, 130.9, 137.2, 138.6, 147.9, 161.8. HRMS: calcd for $C_{16}H_{20}N_3$ 254.1652 $[M + H]^+$, found 254.1663.

*2-Methyl-N-(2-propyl-8H-pyrazolo[5,1-a]isoindol-8-ylidene)-propan-2-amine (**4j**).* Eluent: ethyl acetate/hexanes (5%). White solid (113 mg, 85%), mp 199–200 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.05 (t, J = 7.6 Hz, 3H), 1.69 (s, 9H), 1.77 (q, J = 8.6 Hz, 2H), 2.69 (t, J = 7.6 Hz, 2H), 6.10 (s, 1H), 7.28–7.39 (m, 3H), 7.79 (d, J = 7.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.9, 22.4, 28.9, 31.0, 55.3, 97.7, 119.6, 123.7, 128.2, 130.1, 130.9, 137.2, 138.6, 147.8, 160.5. HRMS: calcd for $C_{17}H_{22}N_3$ 268.1808 $[M + H]^+$, found 268.1820.

Typical Procedure for the Synthesis of 6a and Spectroscopic Data for 6a–j. To a flask containing 1-(2-bromophenyl)buta-2,3-dien-1-one (**1a**) (44 mg, 0.2 mmol) and acetohydrazide (**5a**) (16 mg, 0.22 mmol) was added DMF (1 mL), and the mixture was stirred at room temperature for 1 h. Then *tert*-butyl isocyanide (**3**) (37 mg, 0.44 mmol), $Pd(OAc)_2$ (2 mg, 0.01 mmol), $Cu(OAc)_2$ (36 mg, 0.2 mmol), and K_2CO_3 (55 mg, 0.4 mmol) were added, and the resulting mixture was stirred at 120 °C under air. Upon completion of the reaction, the reaction mixture was diluted with brine (10 mL) and extracted with EtOAc (6 mL × 3). The combined organic phases were dried with anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by column chromatography on silica gel with EtOAc/hexane (5%) as the eluent to give *N*-*tert*-butyl-8-(*tert*-butylimino)-2-methyl-8*H*-pyrazolo[5,1-*a*]isoindole-3-carboxamide (**6a**) in 82% yield. **6b–j** were obtained in a similar manner.

*N-tert-Butyl-8-(tert-butylimino)-2-methyl-8H-pyrazolo[5,1-a]-isoindole-3-carboxamide (**6a**).* Eluent: ethyl acetate/hexanes (5%). White solid (55 mg, 82%), mp 200–201 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.50 (s, 9H), 1.60 (s, 9H), 2.50 (s, 3H), 5.69 (s, 1H), 7.36 (t, J = 7.6 Hz, 1H), 7.44–7.48 (m, 1H), 7.76 (d, J = 7.2 Hz, 1H), 8.04 (d, J = 7.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.7, 29.0, 29.1, 51.8, 55.6, 111.3, 118.3, 122.5, 123.7, 129.3, 131.3, 136.9, 152.8, 157.3, 162.7. HRMS: calcd for $C_{20}H_{27}N_4O$ 339.2179 $[M + H]^+$, found 339.2189.

*N-tert-Butyl-8-(tert-butylimino)-2,6-dimethyl-8H-pyrazolo[5,1-a]-isoindole-3-carboxamide (**6b**).* Eluent: ethyl acetate/hexanes (5%). White solid (61 mg, 86%), mp 206–207 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.50 (s, 9H), 1.60 (s, 9H), 2.40 (s, 3H), 2.49 (s, 3H), 5.67 (s, 1H), 7.25 (d, J = 6.0 Hz, 1H), 7.58 (s, 1H), 7.90 (d, J = 7.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.6, 21.6, 28.9, 29.1, 51.7, 55.5, 111.8, 117.9, 122.2, 124.3, 126.7, 131.9, 138.1, 139.7, 148.5, 152.8, 162.8. HRMS: calcd for $C_{21}H_{29}N_4O$ 353.2336 $[M + H]^+$, found 353.2347.

*N-tert-Butyl-8-(tert-butylimino)-5-methoxy-2-methyl-8H-pyrazolo[5,1-a]isoindole-3-carboxamide (**6c**).* Eluent: ethyl acetate/

DOI: 10.1021/acs.joc.5b00997
J. Org. Chem. 2015, 80, 7447–7455

hexanes (5%). White solid (66 mg, 89%), mp 188−189 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.50 (s, 9H), 1.59 (s, 9H), 2.49 (s, 3H), 3.89 (s, 3H), 5.67 (s, 1H), 6.85 (d, J = 9.2 Hz, 1H), 7.58 (s, 1H), 7.66 (d, J = 8.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.5, 29.0, 29.1, 51.7, 55.4, 55.7, 107.9, 111.6, 114.6, 125.0, 129.1, 130.8, 137.5, 147.6, 152.6, 162.4, 162.7. HRMS: calcd for $C_{21}H_{29}N_4O_2$ 369.2285 $[M + H]^+$, found 369.2296.

*N-tert-Butyl-8-(tert-butylimino)-6-fluoro-2-methyl-8H-pyrazolo-[5,1-a]isoindole-3-carboxamide (**6d**).* Eluent: ethyl acetate/hexanes (5%). White solid (51 mg, 72%), mp 197−199 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.49 (s, 9H), 1.58 (s, 9H), 2.50 (s, 3H), 5.67 (s, 1H), 7.11−7.15 (m, 1H), 7.44 (dd, J_1 = 7.6 Hz, J_2 = 2.0 Hz, 1H), 8.11 (dd, J_1 = 8.4 Hz, J_2 = 0.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.8, 28.9, 29.0, 51.8, 55.7, 111.2, 111.4, 111.5, 117.9, 118.1, 124.7, 124.8, 125.4, 139.4, 148.5, 152.2, 162.5. HRMS: calcd for $C_{20}H_{26}FN_4O$ 357.2085 $[M + H]^+$, found 357.2097.

*N-tert-Butyl-8-(tert-butylimino)-5-fluoro-2-methyl-8H-pyrazolo-[5,1-a]isoindole-3-carboxamide (**6e**).* Eluent: ethyl acetate/hexanes (5%). White solid (50 mg, 70%), mp 201−202 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.50 (s, 9H), 1.59 (s, 9H), 2.51 (s, 3H), 5.67 (s, 1H), 7.00−7.05 (m, 1H), 7.71 (dd, J_1 = 8.4 Hz, J_2 = 4.8 Hz, 1H), 7.86 (dd, J_1 = 8.0 Hz, J_2 = 2.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.8, 28.8, 28.9, 51.8, 55.7, 110.5, 110.8, 112.2, 115.8, 116.1, 125.23, 125.25, 125.3, 131.3, 132.3, 136.8, 147.7, 152.1, 162.3, 163.6. HRMS: calcd for $C_{20}H_{26}FN_4O$ 357.2085 $[M + H]^+$, found 357.2098.

*N-tert-Butyl-8-(tert-butylimino)-5-chloro-2-methyl-8H-pyrazolo-[5,1-a]isoindole-3-carboxamide (**6f**).* Eluent: ethyl acetate/hexanes (5%). White solid (57 mg, 76%), mp 228−229 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.50 (s, 9H), 1.58 (s, 9H), 2.51 (s, 3H), 5.67 (s, 1H), 7.32 (dd, J_1 = 8.4 Hz, J_2 = 2.0 Hz, 1H), 7.67 (d, J = 8.0 Hz, 1H), 8.13 (d, J = 1.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.8, 28.9, 29.0, 51.8, 54.5, 112.2, 123.1, 124.7, 129.2, 130.7, 134.9, 137.4, 147.6, 152.3, 162.3. HRMS: calcd for $C_{20}H_{25}ClN_4ONa$ 395.1609 $[M + Na]^+$, found 395.1624.

*N-tert-Butyl-8-(tert-butylimino)-2-methyl-5-(trifluoromethyl)-8H-pyrazolo[5,1-a]isoindole-3-carboxamide (**6g**).* Eluent: ethyl acetate/hexanes (5%). White solid (54 mg, 67%), mp 185−186 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.51 (s, 9H), 1.60 (s, 9H), 2.53 (s, 3H), 5.67 (s, 1H), 7.63 (d, J = 8.0 Hz, 1H), 7.87 (d, J = 8.8 Hz, 1H), 8.36 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.7, 28.9, 29.1, 29.7, 51.9, 56.1, 112.5, 119.69, 119.73, 119.8, 124.0, 126.15, 126.19, 130.0, 133.4, 136.6, 139.8, 147.4, 153.0, 162.2. HRMS: calcd for $C_{21}H_{26}F_3N_4O$ 407.2053 $[M + H]^+$, found 407.2065.

*N-tert-Butyl-5-(tert-butylimino)-8-methyl-5H-[1,3]dioxolo[4,5-f]-pyrazolo[5,1-a]isoindole-9-carboxamide (**6h**).* Eluent: ethyl acetate/hexanes (5%). White solid (66 mg, 87%), mp 224−226 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.48 (s, 9H), 1.57 (s, 9H), 2.47 (s, 3H), 5.63 (s, 1H), 6.02 (s, 2H), 7.18 (s, 1H), 7.62 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.8, 28.9, 29.0, 51.7, 55.5, 101.8, 104.0, 104.7, 106.7, 110.8, 115.2, 124.2, 131.5, 148.7, 150.2, 151.7, 162.7. HRMS: calcd for $C_{21}H_{27}N_4O_3$ 383.2078 $[M + H]^+$, found 383.2089.

*N-tert-Butyl-8-(tert-butylimino)-2-ethyl-8H-pyrazolo[5,1-a]-isoindole-3-carboxamide (**6i**).* Eluent: ethyl acetate/hexanes (5%). White solid (57 mg, 81%), mp 207−208 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.37 (t, J = 7.6 Hz, 3H), 1.50 (s, 9H), 1.60 (s, 9H), 2.87 (q, J = 7.2 Hz, 2H), 5.72 (s, 1H), 7.34−7.38 (m, 1H), 7.43−7.47 (m, 1H), 7.77 (d, J = 8.0 Hz, 1H), 7.97 (d, J = 8.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 12.6, 22.2, 28.9, 29.0, 51.8, 55.6, 111.1, 122.1, 123.7, 129.2, 129.4, 131.3, 136.9, 137.9, 147.9, 158.3, 162.8. HRMS: calcd for $C_{21}H_{29}N_4O$ 353.2336 $[M + H]^+$, found 353.2349.

*N-tert-Butyl-8-(tert-butylimino)-2-propyl-8H-pyrazolo[5,1-a]-isoindole-3-carboxamide (**6j**).* Eluent: ethyl acetate/hexanes (5%). White solid (61 mg, 83%), mp 197−199 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.02−1.06 (m, 3H), 1.50 (s, 9H), 1.60 (s, 9H), 1.79−1.82 (m, 2H), 2.81 (t, J = 6.8 Hz, 2H), 5.71 (s, 1H), 7.36 (t, J = 7.2 Hz, 1H), 7.45 (t, J = 7.2 Hz, 1H), 7.76 (d, J = 8.0 Hz, 1H), 7.97 (d, J = 8.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.9, 21.7, 29.0, 29.1, 30.5, 51.8, 55.7, 111.3, 122.1, 123.7, 129.2, 129.4, 131.3, 136.9, 137.9, 147.8, 157.0, 162.8. HRMS: calcd for $C_{22}H_{31}N_4O$ 367.2492 $[M + H]^+$, found 367.2487.

Synthetic Procedure and Spectroscopic Data for II. To a solution of 1-(2-bromophenyl)buta-2,3-dien-1-one (**1a**) (222 mg, 1 mmol) in EtOH (10 mL) was added acetohydrazide (**5a**) (74 mg, 1 mmol). The mixture was then stirred at 25 °C until **1a** was consumed completely. The solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel with EtOAc/hexane (20%) as the eluent to afford 1-(5-(2-bromophenyl)-5-hydroxy-3-methyl-4,5-dihydro-1*H*-pyrazol-1-yl)ethanone (**II**) in 85% yield.

*1-(5-(2-Bromophenyl)-5-hydroxy-3-methyl-4,5-dihydro-1H-pyrazol-1-yl)ethanone (**II**).* Eluent: ethyl acetate/hexanes (20%). White solid (252 mg, 85%), mp 117−118 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.12 (s, 3H), 2.30 (s, 3H), 3.16−3.24 (m, 2H), 5.02 (s, 1H), 7.15−7.19 (m, 1H), 7.34−7.38 (m, 1H), 7.59 (d, J = 7.6 Hz, 1H), 7.78 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 15.8, 22.0, 52.1, 92.0, 119.9, 127.3, 127.8, 129.6, 134.8, 140.8, 154.8, 170.5. HRMS: calcd for $C_{12}H_{14}BrN_2O_2$ 297.0233 $[M + H]^+$, found 297.0225.

Synthetic Procedure and Spectroscopic Data for 7. To a solution of 1-(5-(2-bromophenyl)-5-hydroxy-3-methyl-4,5-dihydro-1*H*-pyrazol-1-yl)ethanone (**II**) (148 mg, 0.5 mmol) in dry THF (5 mL) was added $BF_3{\cdot}Et_2O$ (14 mg, 0.1 mmol), and the mixture was then stirred at 25 °C for 12 h. The resulting mixture was concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel with EtOAc/hexane (5%) as the eluent to afford 1-(5-(2-bromophenyl)-3-methyl-1*H*-pyrazol-1-yl)ethanone (**7**) in 80% yield.

*1-(5-(2-Bromophenyl)-3-methyl-1H-pyrazol-1-yl)ethanone (**7**).* Eluent: ethyl acetate/hexanes (5%). White solid (111 mg, 80%), mp 105−106 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.38 (s, 3H), 2.68 (s, 3H), 6.21 (s, 1H), 7.26−7.29 (m, 2H), 7.35 (d, J = 8.0 Hz, 1H), 7.63 (d, J = 7.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.0, 23.1, 112.7, 123.8, 127.0, 130.1, 130.4, 132.4, 133.5, 144.0, 152.0, 169.7. HRMS: calcd for $C_{12}H_{12}BrN_2O$ 279.0128 $[M + H]^+$, found 279.0121.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b00997.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: xuesen.fan@htu.cn.

*E-mail: xinyingzhang@htu.cn.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful to the National Natural Science Foundation of China (Grants 21272058 and 21172057), the Program for Innovative Research Team in Science and Technology in University of Henan Province (15IRTSTHN003), the Program for Science and Technology Innovation Talents in Universities of Henan Province (15HASTIT005), and PCSIRT (IRT 1061) for financial support.

■ REFERENCES

(1) Li, M.; Zhao, B.-X. *Eur. J. Med. Chem.* **2014**, *85*, 311.

(2) (a) Jiang, B.; Fan, W.; Sun, M.-Y.; Ye, Q.; Wang, S.-L.; Tu, S.-J.; Li, G. *J. Org. Chem.* **2014**, *79*, 5258. (b) Merchant, R. R.; Allwood, D. M.; Blakemore, D. C.; Ley, S. V. *J. Org. Chem.* **2014**, *79*, 8800. (c) Zhu, Y.; Hong, J.-J.; Zhou, Y.-B.; Xiao, Y.-W.; Lin, M.; Zhan, Z.-P. *Org. Biomol. Chem.* **2014**, *12*, 3797.

(3) Watanabe, K.; Kamuro, Y.; Taniguchi, E. *J. Agric. Food Chem.* **1994**, *42*, 2311.

DOI: 10.1021/acs.joc.5b00997
J. Org. Chem. 2015, 80, 7447−7455

(4) Toja, E.; Omodei-Sale, A.; Cattaneo, C.; Galliani, G. *Eur. J. Med. Chem., Chim. Ther.* **1982**, *17*, 223.
(5) Abid, M.; Azam, A. *Bioorg. Med. Chem.* **2005**, *13*, 2213.
(6) Wolf, J. G.; Voitenko, Z. V.; Pokholenko, O. A.; Kondratov, I. S.; Kovtunenko, V. O.; André, C. *Phosphorus, Sulfur Silicon Relat. Elem.* **2005**, *180*, 163.
(7) Merot, P.; Gadreau, C.; Foucaud, A. *Tetrahedron* **1981**, *37*, 2595.
(8) Islami, M. R.; Abedini-Torghabeh, J.; Fatemi, S. J.; Hassani, Z.; Amiry, A. *Synlett* **2004**, 1707.
(9) Bousquet, E.; Moran, M.; Harmon, J.; Johnson, A.; Summers, J. *J. Org. Chem.* **1975**, *40*, 2208.
(10) Gérard, A.-L.; Mahatsekake, C.; Collot, V.; Rault, S. *Tetrahedron Lett.* **2007**, *48*, 4123.
(11) Choi, Y. L.; Lee, H.; Kim, B. T.; Choi, K.; Heo, J.-N. *Adv. Synth. Catal.* **2010**, *352*, 2041.
(12) Butkovic, K.; Marinic, Z.; Molcanov, K.; Kojic-Prodic, B.; Sindler-Kulyk, M. *Beilstein J. Org. Chem.* **2011**, *7*, 1663.
(13) Ahmed, N.; Dev, D. *Synth. Commun.* **2013**, *43*, 689.
(14) For selected reviews of the chemistry of isocyanide, see: (a) Lygin, A. V.; de Meijere, A. *Angew. Chem., Int. Ed.* **2010**, *49*, 9094. (b) Vlaar, T.; Ruijter, E.; Maes, B. U. W.; Orru, R. V. A. *Angew. Chem., Int. Ed.* **2013**, *52*, 7084. (c) Lang, S. *Chem. Soc. Rev.* **2013**, *42*, 4867. (d) Qiu, G.; Ding, Q.; Wu, J. *Chem. Soc. Rev.* **2013**, *42*, 5257.
(15) (a) Zhang, S.; Zhang, W.; Xi, Z. *Chem. - Eur. J.* **2010**, *16*, 8419. (b) Van Baelen, G.; Kuijer, S.; Rýček, L.; Sergeyev, S.; Janssen, E.; De Kanter, F. J. J.; Maes, B. U. W.; Ruijter, E.; Orru, R. V. A. *Chem. - Eur. J.* **2011**, *17*, 15039. (c) Vlaar, T.; Ruijter, E.; Znabet, A.; Janssen, E.; de Kanter, F. J. J.; Maes, B. U. W.; Orru, R. V. A. *Org. Lett.* **2011**, *13*, 6496. (d) Tyagi, V.; Khan, S.; Giri, A.; Gauniyal, H. M.; Sridhar, B.; Chauhan, P. M. S. *Org. Lett.* **2012**, *14*, 3126. (e) Soeta, T.; Tamura, K.; Ukaji, Y. *Org. Lett.* **2012**, *14*, 1226.
(16) For recent reviews of the chemistry of allenes, see: (a) Brasholz, M.; Reissig, H. U.; Zimmer, R. *Acc. Chem. Res.* **2009**, *42*, 45. (b) Ma, S. *Acc. Chem. Res.* **2009**, *42*, 1679. (c) Aubert, C.; Fensterbank, L.; Garcia, P.; Malacria, M.; Simonneau, A. *Chem. Rev.* **2011**, *111*, 1954. (d) Krause, N.; Winter, C. *Chem. Rev.* **2011**, *111*, 1994. (e) Yu, S.; Ma, S. *Angew. Chem., Int. Ed.* **2012**, *51*, 3074. (f) Ye, J.; Ma, S. *Acc. Chem. Res.* **2014**, *47*, 989. (g) Le Bras, J.; Muzart, J. *Chem. Soc. Rev.* **2014**, *43*, 3003.
(17) (a) Miao, M.; Cao, J.; Huang, X.; Wu, L. *J. Org. Chem.* **2013**, *78*, 5999. (b) Zhang, F.-G.; Wei, Y.; Yi, Y.-P.; Nie, J.; Ma, J.-A. *Org. Lett.* **2014**, *16*, 3122. (c) Cui, L.; Guo, S.; Li, B.; Zhang, X.; Fan, X. *Chin. Chem. Lett.* **2014**, *25*, 55. (d) Zhang, X.; Jia, X.; Fang, L.; Liu, N.; Wang, J.; Fan, X. *Org. Lett.* **2011**, *13*, 5024.
(18) Guo, S.; Wang, J.; Guo, D.; Zhang, X.; Fan, X. *RSC Adv.* **2012**, *2*, 3772.
(19) Guo, S.; Wang, J.; Guo, D.; Zhang, X.; Fan, X. *Tetrahedron* **2012**, *68*, 7768.
(20) Küçükgüzel, Ş. G.; Şenkardeş, S. *Eur. J. Med. Chem.* **2015**, *97*, 786.
(21) (a) Manvar, D.; Pelliccia, S.; La Regina, G.; Famiglini, V.; Coluccia, A.; Ruggieri, A.; Anticoli, S.; Lee, J.-C.; Basu, A.; Cevik, O.; Nencioni, L.; Palamara, A. T.; Zamperini, C.; Botta, M.; Neyts, J.; Leyssen, P.; Kaushik-Basu, N.; Silvestri, R. *Eur. J. Med. Chem.* **2015**, *90*, 497. (b) Donohue, B. A.; Michelotti, E. L.; Reader, J. C.; Reader, V.; Stirling, M.; Tice, C. M. *J. Comb. Chem.* **2002**, *4*, 23.
(22) Pendri, A.; Dodd, D. S.; Chen, J.; Cvijic, M. E.; Kang, L.; Baska, R. A.; Carlson, K. E.; Burford, N. T.; Sun, C.; Ewing, W. R.; Gerritz, S. W. *ACS Comb. Sci.* **2012**, *14*, 197.
(23) (a) Hesp, K. D.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2011**, *133*, 11430. (b) He, T.; Li, H.; Li, P.; Wang, L. *Chem. Commun.* **2011**, *47*, 8946. (c) Peng, J.; Liu, L.; Hu, Z.; Huang, J.; Zhu, Q. *Chem. Commun.* **2012**, *48*, 3772.
(24) Zhang, C.; Ji, J.; Sun, P. *J. Org. Chem.* **2014**, *79*, 3200.
(25) Sniady, A.; Morreale, M. S.; Dembinski, R. *Org. Synth.* **2007**, *84*, 199.
(26) Wu, W. L.; Yao, Z. J.; Li, Y. L.; Li, J. C.; Xia, Y.; Wu, Y. L. *J. Org. Chem.* **1995**, *60*, 3257.

DOI: 10.1021/acs.joc.5b00997
J. Org. Chem. 2015, 80, 7447−7455