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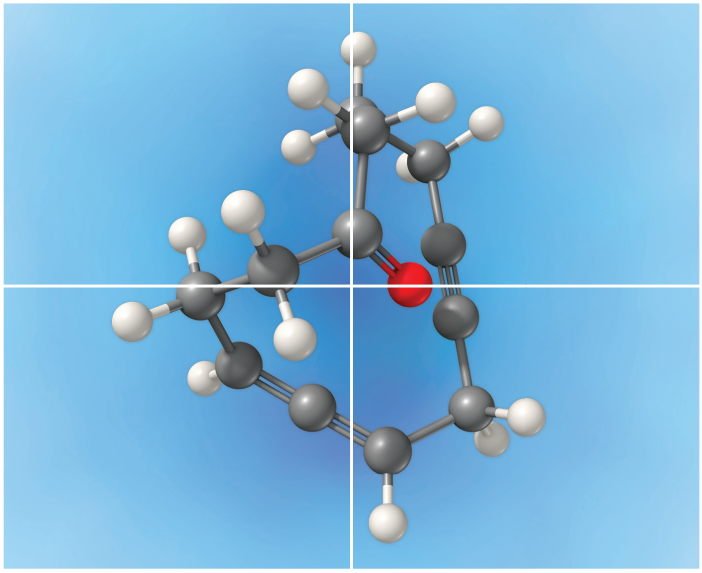

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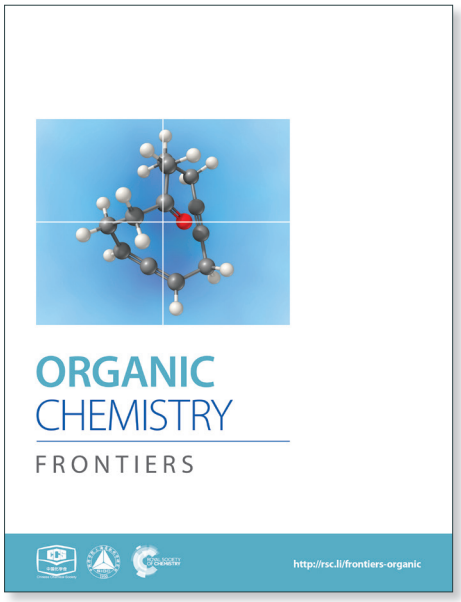

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ARTICLE TYPE

Efficient Access to *1H*-Indazoles via Copper-Catalyzed Cross-Coupling/Cyclization of 2-Bromoaryl Oxime Acetates and Amines

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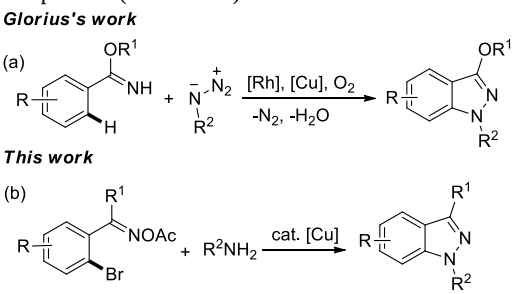
We describe a novel and useful method to provide *1H*-indazoles via copper-catalyzed tandem reaction which is triggered by Ullmann-type reaction and followed by N-N bond formation. Arylamines, alkylamines and sulfonamides could smoothly couple with 2-bromoaryl oxime acetates and various 1*H*-indazoles were formed in good to excellent yields under mild reaction conditions.

Due to a wide range of pharmaceutical activities, the 1*H*-indazole subunit has caused much attention of synthetic chemists and they have been widely used for anticancer, anti-inflammatory, anti-HIV, antifertility, and contraceptive drugs.[1] Consequently, many methods have been developed for the construction of 1*H*-indazole frameworks, including classical diazotizations and nitrosation reactions,[2] condensation of hydrazine with *ortho*-substituted benzaldehydes,[3a,b] [3 + 2] cycloaddition of arynes with diazo compounds or hydrazones[3c-e] and cyclization of arylamino oximes.[3f-g] With the development of transition metal catalysis, some transition metal-catalyzed routes to 1*H*-indazole unit also have been realized. For examples, Voskoboynikov *et al.* reported a palladium-catalyzed cyclization of arylhydrazones to form the 1*H*-indazole derivatives.[4a] Copper-catalyzed amination reactions were also used for 1*H*-indazole subunits.[5] Olmo and coworkers have developed an efficient synthesis for indazoles via *N*-arylation of hydrazines, followed by intramolecular dehydration.[5a] However, most of these methods have some limitations, such as long reaction time, poor functional group tolerance, low conversion. In addition, the biggest problem is the use of toxic organo-hydrazines. To the best of our knowledge, few examples of constructing 1*H*-indazoles via the formation of N-N bonds have been reported.[3f-g,6] Recently, Glorius *et al.* described an efficient synthesis of 1*H*-indazoles from arylimidates and organo azides via Rh^{III}/Cu^{II}-cocatalyzed C-H activation and C-N/N-N bond formations (Scheme 1a).[6] As to such fact, we thought a method which utilized the N−N bond formation to obtain the 1*H*-indazole unit only using the cheap metal (copper) as catalyst and without use of carcinogenic hydrazines is desired and challenging.

Copper-mediated Ullmann-type reaction was discovered a century ago.[7] However, it has not been fully utilized due to high reaction temperature, limitations of the substrates, and need of stoichiometric copper salts. In recent years, great breakthroughs have been achieved by some research groups,[8] which made Ullmann-type reactions come up with a catalytic amount of copper salts and low temperature. And these breakthroughs also made Ullmann-type reaction a good method to construct C-C, C-O and C-N bonds. In the past several years, oxime esters have been used for the nitrogen-containing heterocycles, such as pyridines,[9] pyrroles,[10] and imidazo[1,2-a]pyridines[11] in the presence of copper salts. Based on our previous work on oxime esters[10a, 11, 12] and the development of Ullmann-type reactions, we envisioned that we could obtain nitrogen-containing heterocycles via tandem reaction which is triggered by Ullmann-type reactions and then undergo N-N bond formation using oxime acetates not only as substrate but also internal oxidant. Herein, we disclose a novel and efficient strategy for 1*H*-indazoles from 2-bromoaryl oxime acetates and amines via copper-catalyzed tandem reaction involving a sequential Ullmann-type reaction and N-N bond formation process (Scheme 1b).

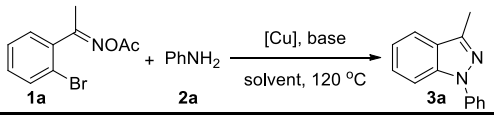


Scheme 1. Glorius's work and this work.

Initially, we took the transformation of 1-(2-bromophenyl)ethanone oxime acetate (**1a**) and aniline (**2a**) as the model system to screen reaction parameters (Table 1). To our delight, product **3a** could be obtained in 71% GC yield when we utilized CuBr (10 mol %) as catalyst and K_2CO_3 as base in DMSO at 120 °C under N_2 atmosphere after 6 h (Table 1, entry 1). Different copper salts such as CuI, CuCl, $Cu(OAc)_2$, and $Cu(OTf)_2$ were also examined in this process (entries 2-5) and CuCl was proved to be the best catalyst, affording product **3a** in 86% isolated yield. No product could be observed without copper catalyst (entry 6). The investigation of different bases, including Cs_2CO_3, Na_2CO_3, $NaHCO_3$, $NaHSO_3$, and Et_3N, indicated that K_2CO_3 was the best choice (entries 7-11). And the yield was decreased to 18% in the absence of base (entry 12). Decreasing the temperature to 100 °C, the yield sharply decreased to 53% and the reason was the Ullmann-type reaction could not proceed smoothly at lower temperature (entry 13). Different solvents such as toluene, DMF, DMA, NMP and MeCN were screened. Except

acetonitrile could obtain 85% yield, other solvents were not good for this reaction (entries 14-18). Thus, the optimal reaction conditions were **1a** (0.5 mmol), **2a** (0.6 mmol), CuCl (10 mol %), K_2CO_3 (1.0 mmol), in 2 mL DMSO at 120 °C under N_2 atmosphere for 6 h.

Table 1. Optimization of the reaction conditions.[a]

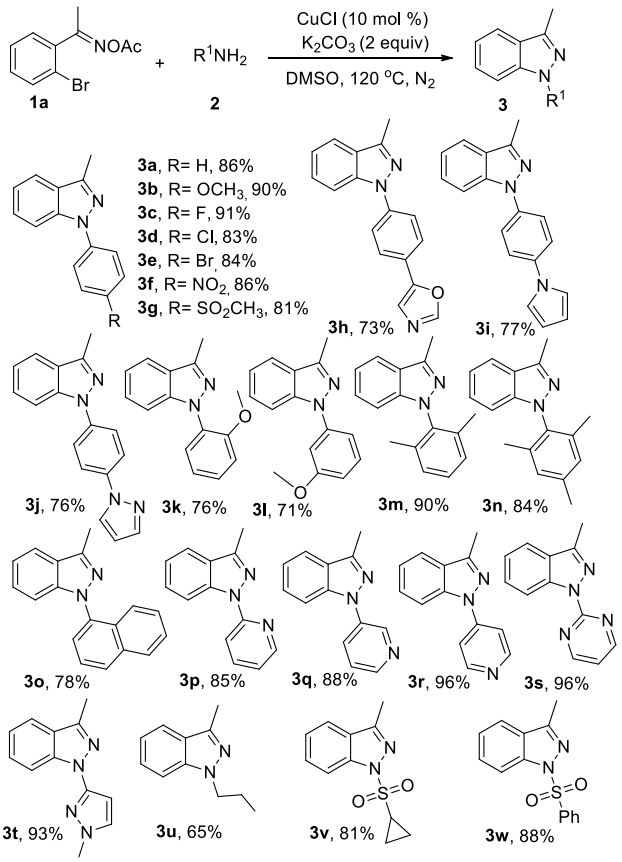


entry	[Cu]	base	solvent	yield [b](%)
1	CuBr	K_2CO_3	DMSO	71
2	CuI	K_2CO_3	DMSO	86
3	**CuCl**	**K_2CO_3**	**DMSO**	**92 (86)**
4	$Cu(OTf)_2$	K_2CO_3	DMSO	11
5	$Cu(OAc)_2$	K_2CO_3	DMSO	60
6	---	K_2CO_3	DMSO	0
7	CuCl	Cs_2CO_3	DMSO	63
8	CuCl	Na_2CO_3	DMSO	33
9	CuCl	$NaHCO_3$	DMSO	42
10	CuCl	$NaHSO_3$	DMSO	11
11	CuCl	NEt_3	DMSO	6
12	CuCl	---	DMSO	18
13[c]	CuCl	K_2CO_3	DMSO	53
14	CuCl	K_2CO_3	toluene	8
15	CuCl	K_2CO_3	DMF	41
16	CuCl	K_2CO_3	DMA	69
17	CuCl	K_2CO_3	NMP	37
18	CuCl	K_2CO_3	MeCN	85

[a] Reaction conditions: unless otherwise noted, all reactions were performed with **1a** (0.5 mmol), **2a** (0.6 mmol), catalyst (10 mol %), base (1 mmol) and solvent (2 mL) at 120 °C under N_2 atmosphere for 6 h. [b] Determined by GC based on **1a**. [c] Take the reaction at 100 °C.

With the optimum reaction conditions in hand, we started to investigate the scope of amines (Table 2). Various functional groups including methoxyl, fluoro, chloro, bromo, nitro, and methylsulfonyl could be tolerated at the *para*-position of aniline and the desired 1*H*-indazoles **3a**-**3g** were formed in good to excellent yields. 4-Heterocyclic-substituted anilines, such as 4-(oxazol-5-yl)aniline, 4-(1*H*-pyrrol-1-yl)aniline, and 4-(1*H*-pyrazol-1-yl)aniline, were also suitable substrates to afford the corresponding 1*H*-indazoles (**3h**-**3j**). When 2-methoxyaniline, 3-methoxyaniline, 2,6-dimethylaniline and 2,4,6-trimethylaniline were subjected to the reaction system, **3k**-**3n** could be isolated in 76%, 71%, 90% and 84% yields, respectively. In addition, other aromatic or heterocyclic amines even including pyridine ring, which were not usually applicable in copper-catalyzed reactions, could also be transformed to the target products in yields ranging from 78% to 96% (**3o**-**3t**). It was exiting that the alkyl amines were good starting materials and the corresponding products could be generated in moderate yields (**3u**). It was worth mentioning that sulfonamide derivatives could transform into products in good yields, which could bring in useful sulfone functional group (**3v**-**3w**).

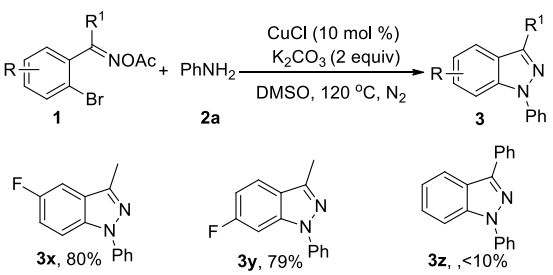
Table 2 Cu(I)-catalyzed synthesis of 1*H*-indazoles from 1-(2-bromophenyl)ethanone oxime acetate and amine.[a]



[a] The reactions were carried out at 120 ℃, using **1a** (0.5 mmol), **2** (0.6 mmol), CuCl (10 mol %), K_2CO_3 (1.0 mmol), in DMSO (2 mL) under N_2 atmosphere for 6 h. Yields refer to isolated yields.

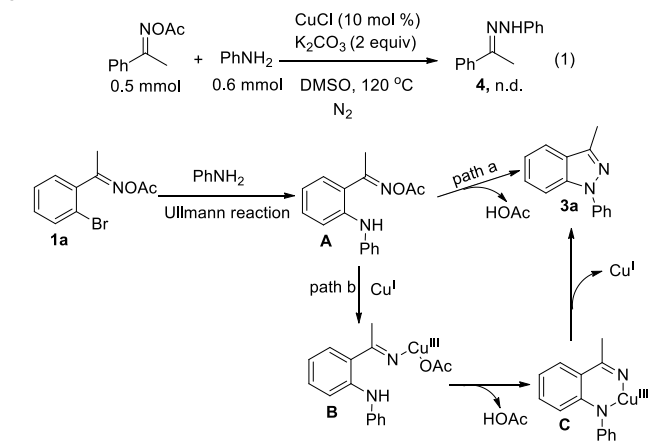
Subsequently, we examined various oxime acetates in Table 3. 2-Bromoaryl oxime acetates such as 1-(2-bromo-4-fluorophenyl)ethanone oxime acetate and 1-(2-bromo-5-fluorophenyl)ethanone oxime acetate also reacted well with aniline to afford the corresponding products (**3x**-**3y**) in 80% and 79% yields, respectively. However, when (2-bromophenyl)(phenyl)methanone oxime acetate was used as the substrate, the corresponding product **3z** was obtained in lower yield and the 3-phenylbenzo[*d*]isoxazole was formed via (2-bromophenyl)(phenyl)methanone oxime acetate turning into (2-bromophenyl)(phenyl)methanone oxime and then intramolecular Ullmann-type reaction.[13a]

Table 3 Cu(I)-catalyzed synthesis of *1H*-indazoles from oxime acetate and aniline.[a]



[a] The reactions were carried out at 120 ℃, using **1** (0.5 mmol), **2a** (0.6 mmol), CuCl (10 mol %), K_2CO_3 (1.0 mmol), in DMSO (2 mL) under N_2 atmosphere for 6 h. Yields refer to isolated yields.

Control experiment was conducted to gain more insight into the mechanism. When we coupled acetophenone oxime acetate with aniline under the standard conditions, product **4** could not be obtained [Eq. (1)], and the analogue of **1a** easily went through Ullmann-type reaction,[13g] suggesting that this reaction should be triggered by Ullmann-type reaction. Based on this experiment and previous reports,[13-16] a plausible mechanism of the present reaction is described in Scheme 2. Firstly, **1a** was coupled with aniline to form intermediate **A** via copper-catalyzed Ullmann reaction.[13] Then intermediate **A** might go through two possible pathways for the observed product. In path a, the amino group attacked the oxime acetate to form the desired 1*H*-indazole product **3a** with releasing of a molecule of HOAc.[3f, 3g, 14] The other pathway might go through a organocopper(III) process (path b). Oxidative addition of CuI to the N-O bond gave intermediate **B**.[15] Subsequently, intermediate **C** was formed via the coordination of nitrogen atom to copper(III), which simultaneously produced a molecule of HOAc which was neutralized by base. Finally, intermediate **C** could transfer to the desired product via reductive elimination (path b).[16]



Scheme 2. Possible reaction mechanism

In conclusion, we have developed a novel and useful method for the construction of 1*H*-indazoles. This transformation is supposed to be triggered by Ullmann-type reaction and then undergo N-N bond formation process. Various arylamines, alkylamines and sulfonamides could be applied to this reaction system and the desired 1*H*-indazole products were formed in good to excellent yields. In this process, the oxime acetates were not only used as substrate but also internal oxidant. Moreover, the use of a catalytic amount of copper salts and no need for additional ligands make this method attractive and practical. Further studies on the reaction scope and mechanism are currently on progress in our laboratory.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental section, characterization of all compounds, copies of ^1H and ^{13}C NMR spectra for selected compounds. See DOI: 10.1039/b000000x/

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