

# Consecutive Condensation, C–N and N–N Bond Formations: A Copper-Catalyzed One-Pot Three-Component Synthesis of 2H-Indazole

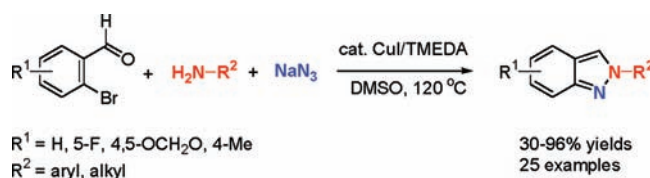
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## ABSTRACT



2H-Indazoles are synthesized using copper-catalyzed, one-pot, three-component reactions of 2-bromobenzaldehydes, primary amines, and sodium azide. A copper catalyst plays the key role in the formation of C–N and N–N bonds. This method has a broad substrate scope with a high tolerance for a variety of functional groups.

Over the past decade, researchers have been interested in the structure of indazoles in the field of drug discovery because indazoles act as efficient bioisosteres of indoles and benzimidazoles.<sup>1</sup> The indazole unit has been found in pharmaceutical materials with a broad range of biological properties, including antitumor activity,<sup>2</sup> HIV protease inhibition,<sup>3</sup> antimicrobial activity,<sup>4</sup> and anti-inflammatory activity.<sup>5</sup> A variety of synthetic methods for the production of indazoles have been reported. However, most studies have attempted to obtain the thermodynamically favored

1H-indazole, whereas much less attention has been paid to efficient methods of synthesizing 2H-indazole.<sup>6</sup>

Recently, a number of important biologically active compounds bearing 2H-indazole have been shown to have potent affinity for 5-HT<sub>1A</sub> receptors,<sup>7</sup> estrogen receptor  $\beta$ ,<sup>8</sup> and high affinity to the imidazoline I<sub>2</sub> receptor.<sup>9</sup>

Considering the potent bioactivities of compounds possessing a 2H-indazole core, the development of new strategies for the efficient synthesis of 2H-indazole is needed.<sup>10</sup> Recently, four newly developed approaches have been

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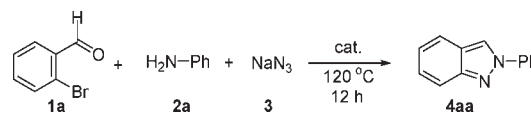
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reported for the assembly of 2*H*-indazole: (1) a Pd-catalyzed domino reaction of 2-halophenyl acetylenes with hydrazines,<sup>11</sup> (2) an Fe-catalyzed N–N bond formation of 2-azidophenyl ketoximes,<sup>12</sup> (3) a reaction of 2-chloromethylarylzinc reagents and aryldiazonium salts,<sup>13</sup> and (4) a [3 + 2] cycloaddition of arynes and sydrones.<sup>14</sup> However, all four have drawbacks, such as the generation of regioisomers, the requirement for expensive phosphine ligands, and a low tolerance toward functional groups such as alcohols. In addition, all of these methods require several steps to prepare the starting materials. A variety of one-pot multicomponent reactions have been developed because of their powerful ability to assemble complex structures with high efficiency using simple processes and their atom efficiency.<sup>15</sup> This type of reaction has especially been employed in the synthesis of heterocyclic compounds.<sup>16</sup> However, there have not previously been any reports on multicomponent reactions for the synthesis of 2*H*-indazoles.

Here, we report the first one-pot three-component reaction of 2-bromobenzaldehydes, primary amines, and sodium azide to produce 2*H*-indazoles through condensation and C–N and N–N bond formation. To achieve our goal, we initiated our studies by screening a variety of metal catalysts (Table 1).

Accordingly, we tested FeBr<sub>2</sub>, known to be an efficient catalyst for the synthesis of 2*H*-indazoles from 2-azidophenyl ketoximes.<sup>12</sup> However, this yielded no 2*H*-indazoles, the desired product (Table 1, entry 1). When the catalyst was changed to other metals such as Pd, Ni, and Co, only *N*-(2-bromobenzylidene)aniline (**7**) was found in the reaction mixture (Table 1, entries 3–6). Gratifyingly, using CuBr<sub>2</sub> and CuI yielded 41% and 61% of 2-phenyl-2*H*-indazole, respectively (Table 1, entries 7 and 8). After investigating the effect of ligands on the Cu-catalyzed reaction, we found *N,N,N',N'*-tetramethylethylenediamine (TMEDA) was the best ligand for this reaction (Table 1, entry 11). Among the solvents screened, polar solvents showed better results than nonpolar solvents (Table 1, entries 11–14). When the catalyst loading was decreased from 10 mol % to 5 mol %, the product yield decreased to 92% with trace amounts of imine intermediate, while 3 mol % of catalyst afforded a yield of 64% (entry 16). Considering a complete coupling of imine intermediate **7**, we continued with 10 mol % of catalyst for the subsequent investigation. We next examined the

**Table 1.** Optimized Conditions for the Synthesis of 2*H*-Indazole<sup>a</sup>



entry	cat.	ligand	solvent	yield (%) <sup>d</sup>
1	FeBr <sub>2</sub>	–	DMSO	0
2	FeCl <sub>3</sub>	–	DMSO	0
3	Pd(OAc) <sub>2</sub>	–	DMSO	0
4	Pd(PPh <sub>3</sub> ) <sub>2</sub> Cl <sub>2</sub>	–	DMSO	0
5	Ni(OAc) <sub>2</sub>	–	DMSO	0
6	CoBr <sub>2</sub>	–	DMSO	0
7	CuBr <sub>2</sub>	–	DMSO	41
8	CuI	–	DMSO	61
9	CuI	2-Bipyridyl	DMSO	65
10	CuI	L-Proline	DMSO	52
11	CuI	TMEDA	DMSO	98
12	CuI	TMEDA	DMF	72
13	CuI	TMEDA	<i>p</i> -Xylene	2
14	CuI	TMEDA	Diglyme	31
15	CuI <sup>b</sup>	TMEDA	DMSO	92
16	CuI <sup>c</sup>	TMEDA	DMSO	64

<sup>a</sup> Reaction conditions: **1a** (0.30 mmol), **2a** (0.36 mmol), **3** (0.60 mmol), and catalyst (0.03 mmol) in solvent (1.0 mL). <sup>b</sup> 0.015 mmol. <sup>c</sup> 0.009 mmol. <sup>d</sup> Determined by gas chromatography with internal standard.

scope of the reaction using various amines. We tested aromatic, heteroaromatic, and aliphatic amines in the above reaction which yielded a series of 2*H*-indazoles (Table 2). In the case of aromatic amines bearing electron-neutral and -donating groups, such as aniline, *p*-toluidine, and 4-methylthioaniline, good yields were seen (Table 2, entries 1–3). Heteroaromatic amines such as 2-aminopyridine produced the corresponding 2*H*-indazole **4ad** in 82% yield (Table 2, entry 4). However, sterically demanding anilines such as 2,4,6-trimethylaniline yielded only 46% of product **4ae** (Table 2, entry 5). Anilines with electron-withdrawing groups produced 2*H*-indazoles in moderate to good yields. Benzocaine, which bears a base sensitive ester group, also showed a 64% yield (Table 2, entry 6).

However, 4-trifluoromethyl- and 4-nitroaniline yielded 46% and 20% of their corresponding products, and the reaction mixture showed a variety of spots in thin layer chromatography (TLC). To increase the yield, the reactions of 2-bromoaldehyde and aniline derivatives were carried out first, and then NaN<sub>3</sub> with CuI/TMEDA was added to the reaction mixture. By using stepwise addition, their yields were increased to 72% and 48%, respectively (Table 2, entries 8 and 9). Aliphatic amines all showed good yields of 2*H*-indazoles. Even sterically demanding amines such as 1-adamantylamine yielded 84% of 2*H*-indazole **4aj** (Table 2, entry 10). In addition, an aliphatic amine with an alcohol group yielded 80% of the desired product (Table 2, entry 11). 2,2-Diethoxyethylamine and cyclopropylamine yielded 76% and 63% of 2*H*-indazole **4al** and **4am**, respectively (Table 2, entries 12 and 13).

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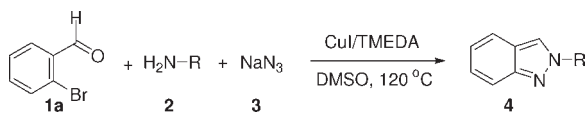
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**Table 2.** Synthesis of 2*H*-Indazole from 2-Bromobenzaldehyde<sup>a</sup>

entry	2 (R)	product	yield (%)
1	Ph		<b>4aa</b> 98
2	4-MeC <sub>6</sub> H <sub>4</sub>		<b>4ab</b> 81
3	4-MeSC <sub>6</sub> H <sub>4</sub>		<b>4ac</b> 84
4	2-Pyridyl		<b>4ad</b> 82
5	Mesityl		<b>4ae</b> 46
6	4-EtO <sub>2</sub> CC <sub>6</sub> H <sub>4</sub>		<b>4af</b> 64
7	4-ClC <sub>6</sub> H <sub>4</sub>		<b>4ag</b> 80
8	4-CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub>		<b>4ah</b> 46(72 <sup>b</sup> )
9	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>		<b>4ai</b> 20(48 <sup>b</sup> )
10	1-Adamantyl		<b>4aj</b> 84
11	3-(HO)Ad		<b>4ak</b> 80
12	CH <sub>2</sub> CH(OEt) <sub>2</sub>		<b>4al</b> 76
13	cyclopropyl		<b>4am</b> 63
14	HCO <sub>2</sub> NH <sub>4</sub> <sup>c</sup>		<b>4an</b> 30

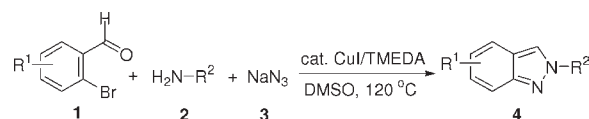
<sup>a</sup> Reaction conditions: 2-bromobenzaldehyde (1.5 mmol), aniline (1.8 mmol), NaN<sub>3</sub> (3.0 mmol), CuI (0.15 mmol), and TMEDA (0.15 mmol) were reacted in DMSO (5.0 mL) at 120 °C for 12 h. <sup>b</sup> 2-Bromobenzaldehyde and aniline derivative were first reacted, and then NaN<sub>3</sub>, CuI, and TMEDA were added. <sup>c</sup> Ammonium formate.

Surprisingly, ammonium formate was also coupled with 2-bromobenzaldehyde and NaN<sub>3</sub> to produce 1*H*-indazole (**4an**), which might be produced from the tautomerization of 2*H*-indazole, due to it being more thermodynamically stable than 2*H*-indazole (Table 2, entry 14).<sup>17</sup>

Encouraged by these results, we attempted to expand the scope of 2-bromobenzaldehydes by using substituted versions. Table 3 shows three-component coupling reactions using 2-bromo-5-fluorobenzaldehyde (**1b**), 6-bromo-1,3-benzodioxole-5-carboxaldehyde (**1c**), and 2-bromo-4-methylbenzaldehyde (**1d**).

All three reacted with amines and NaN<sub>3</sub> to produce the corresponding 2*H*-indazoles in moderate to good yields, although their yields were slightly lower than those from 2-bromobenzaldehyde. In the case of **2b**, anilines bearing electron-donating groups (**2b** and **2c**) and aliphatic amines (**2m** and **2o**) gave better yields than anilines bearing

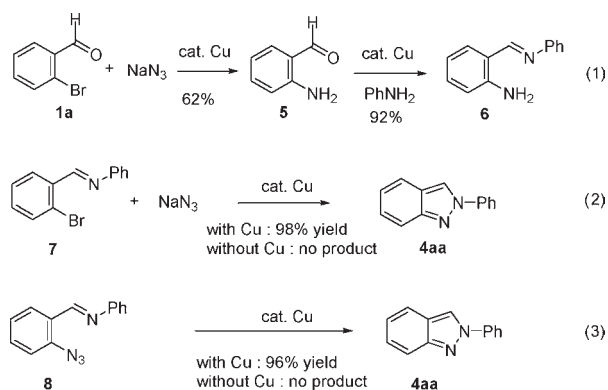
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**Table 3.** Synthesis of 2*H*-Indazole from Substituted 2-Bromobenzaldehyde<sup>a</sup>

entry	1 (R <sup>1</sup> )	product	yield (%)
1	<b>1b</b> (5-F)		<b>4bb</b> 78
2	<b>1b</b> (5-F)		<b>4bc</b> 88
3	<b>1b</b> (5-F)		<b>4bm</b> 86
4	<b>1b</b> (5-F)		<b>4bo</b> 80
5	<b>1b</b> (5-F)		<b>4bh</b> 57
6	<b>1b</b> (5-F)		<b>4bf</b> 61
7	<b>1b</b> (5-F)		<b>4bd</b> 55
8	<b>1c</b> (4,5-OCH <sub>2</sub> O)		<b>4cg</b> 40
9	<b>1c</b> (4,5-OCH <sub>2</sub> O)		<b>4cp</b> 65
10	<b>1c</b> (4,5-OCH <sub>2</sub> O)		<b>4cq</b> 62
11	<b>1d</b> (4-Me)		<b>4db</b> 70

<sup>a</sup> Reaction conditions: 2-bromobenzaldehyde (1.5 mmol), aniline (1.8 mmol), NaN<sub>3</sub> (3.0 mmol), CuI (0.15 mmol), and TMEDA (0.15 mmol) were reacted in DMSO (5.0 mL) at 120 °C for 12 h.

electron-withdrawing groups (**2h** and **2f**) and a heteroaromatic amine (**2d**) (Table 3, entries 1–7). We found similar trends with **1c** and **1d**: 4-chloroaniline provided a lower yield than electron-donating amines such as 3-phenylpropylamine or 4-methyl- and 4-ethylaniline (Table 3, entries 8–11). To understand the mechanism clearly, we further investigated the effect of a copper catalyst (Scheme 1).

**Scheme 1.** Cu-Catalyzed C–N and N–N Bond Formations

When 2-bromobenzaldehyde (**1a**) was reacted with  $\text{NaN}_3$  in the presence of  $\text{CuI/TMEDA}$ , 2-aminobenzaldehyde (**5**) was formed instead of the expected *N*-(2-azidobenzylidene)aniline (**8**).<sup>18,19</sup> The resulting product was reacted with aniline to yield 92% of *N*-(2-aminobenzylidene)aniline (**6**) (Scheme 1, eq 1); however, the desired 2*H*-indazole was not formed. *N*-(2-Bromobenzylidene)aniline (**7**) reacted with  $\text{NaN}_3$  in the presence of  $\text{CuI/TMEDA}$  and yielded 98% of the desired coupled product **4aa**. However, no conversion occurred in the absence of the copper catalyst (Scheme 1, eq 2). When the expected intermediate **8** was treated with  $\text{CuI/TMEDA}$  in DMSO, the desired product was formed in 96% yield (Scheme 1, eq 3).<sup>20</sup> Thus, copper may play an important role in both C–N bond formation between the aryl bromide and the azide and N–N bond formation between the imine and the azide.

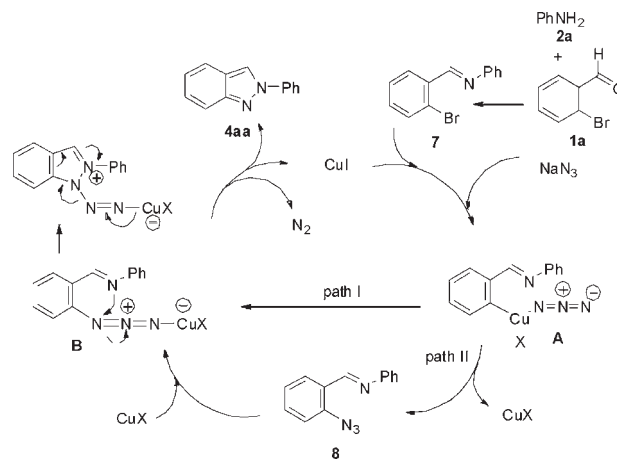
On the basis of these preliminary studies, we suggested a potential mechanism, as shown in Scheme 2. This three-component coupling reaction was hypothesized to occur first through the formation of **7**. The azide was then substituted with the bromide of **7** in the presence of the copper catalyst to form *N*-(2-azidobenzylidene)aniline (**8**).

The resulting intermediate **8** then went on to form copper(I)–azide complex **B**. A similar intermediate, an iron(II)–azide complex, has been proposed by Driver.<sup>12</sup> This azide was activated by means of the coordination of the terminal N-atom of the azide to the copper catalyst, and the activated azide was attacked by the N-atom of benzylideneaniline, resulting in N–N bond formation.<sup>21</sup>

The sequential procedure of the emission of  $\text{N}_2$  and the dissociation of the copper catalyst afforded the desired 2*H*-indazole **4aa**.<sup>22</sup> However, we do not exclude the mechanism of path I because intermediate **8** was not found in

the reaction mixture.<sup>23</sup> Further mechanistic studies of this three-component reaction are in progress in our laboratory.

**Scheme 2.** Proposed Mechanism



In conclusion, we have developed a novel method for the construction of the core structure of 2*H*-indazoles through a Cu-catalyzed sequential C–N and N–N bond formation. In contrast to existing methods, this method does not require special preparation of starting materials, because 2-bromobenzaldehydes, primary amines, and  $\text{NaN}_3$  are readily available. Moreover, the separation of the final products, 2*H*-indazoles, is very easy using column chromatography because of the large difference between the  $R_f$  values of the products and the starting materials in TLC. In addition, this three-component coupling reaction has a broad substrate scope with a high functional group tolerance. To the best of our knowledge, this method is the first example of the synthesis of 2*H*-indazole through a multi-component coupling reaction.

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**Supporting Information Available.** Experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

(23) The expected intermediate *N*-(2-azidobenzylidene)aniline (**8**) was not found in the reaction mixture by <sup>1</sup>H NMR study.

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