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

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## ABSTRACT


**2*H*-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.[1] The indazole unit has been found in pharmaceutical materials with a broad range of biological properties, including antitumor activity,[2] HIV protease inhibition,[3] antimicrobial activity,[4] and anti-inflammatory activity.[5] A variety of synthetic methods for the production of indazoles have been reported. However, most studies have attempted to obtain the thermodynamically favored 1*H*-indazole, whereas much less attention has been paid to efficient methods of synthesizing 2*H*-indazole.[6]

Recently, a number of important biologically active compounds bearing 2*H*-indazole have been shown to have potent affinity for 5-$HT_{1A}$ receptors,[7] estrogen receptor $\beta$,[8] and high affinity to the imidazoline $I_2$ receptor.[9]

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

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(10) The derivatization of 2*H*-indazoles has been reported. See: (a) Slade, D. J.; Pelz, N. F.; Bodnar, W.; Lampe, J. W.; Watson, P. S. *J. Org. Chem.* **2009**, *74*, 6331. (b) Ohnmacht, S. A.; Culshaw, A. J.; Greaney, M. F. *Org. Lett.* **2010**, *12*, 224.

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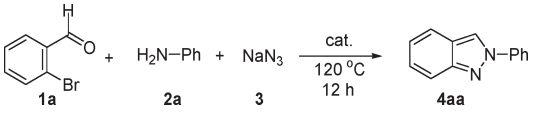
reported for the assembly of 2*H*-indazole: (1) a Pd-catalyzed domino reaction of 2-halophenyl acetylenes with hydrazines,[11] (2) an Fe-catalyzed N−N bond formation of 2-azidophenyl ketoximes,[12] (3) a reaction of 2-chloromethylarylzinc reagents and aryldiazonium salts,[13] and (4) a [3 + 2] cycloaddition of arynes and sydnones.[14] 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.[15] This type of reaction has especially been employed in the synthesis of heterocyclic compounds.[16] 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 $FeBr_2$, known to be an efficient catalyst for the synthesis of 2*H*-indazoles from 2-azidophenyl ketoximes.[12] 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 $CuBr_2$ 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[a]




| entry | cat. | ligand | solvent | yield (%)[d] |
|---|---|---|---|---|
| 1 | $FeBr_2$ | – | DMSO | 0 |
| 2 | $FeCl_3$ | – | DMSO | 0 |
| 3 | $Pd(OAc)_2$ | – | DMSO | 0 |
| 4 | $Pd(PPh_3)_2Cl_2$ | – | DMSO | 0 |
| 5 | $Ni(OAc)_2$ | – | DMSO | 0 |
| 6 | $CoBr_2$ | – | DMSO | 0 |
| 7 | $CuBr_2$ | – | 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 | *p*-Xylene | 2 |
| 14 | CuI | TMEDA | Diglyme | 31 |
| 15 | CuI[b] | TMEDA | DMSO | 92 |
| 16 | CuI[c] | TMEDA | DMSO | 64 |

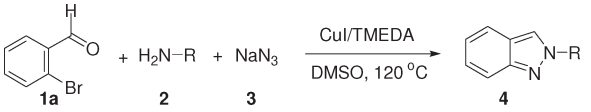
[a] Reaction conditions: **1a** (0.30 mmol), **2a** (0.36 mmol), **3** (0.60 mmol), and catalyst (0.03 mmol) in solvent (1.0 mL). [b] 0.015 mmol. [c] 0.009 mmol. [d] Determined by gas chromatography with internal standard.

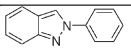
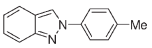
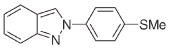
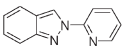
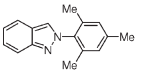
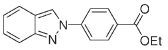
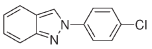
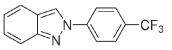
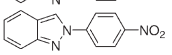
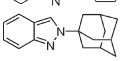
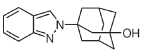
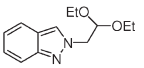
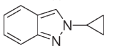
scope of the reaction using various amines. We tested aromatic, heteroaromatic, and aliphatic amines in the above reaction which yielded a series of 2*H*-indazoles (Table 2). In the case of aromatic amines bearing electron-neutral and -donating groups, such as aniline, *p*-toluidine, and 4-methylthioaniline, 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 $NaN_3$ 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).

(11) Halland, N.; Nazaré, M.; R'kyek, O.; Alonso, J.; Urmann, M.; Lindenschmidt, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 6879.
(12) Stokes, B. J.; Vogel, C. V.; Urnezis, L. K.; Pan, M.; Driver, T. G. *Org. Lett.* **2010**, *12*, 2884.
(13) Haag, B.; Peng, Z.; Knochel, P. *Org. Lett.* **2009**, *11*, 4270.
(14) Wu, C.; Fang, Y.; Larock, R. C.; Shi, F. *Org. Lett.* **2010**, *12*, 2234.
(15) Wasilke, J.-C.; Obrey, S. J.; Baker, R. T.; Bazan, G. C. *Chem. Rev.* **2005**, *105*, 1001.
(16) For selective recent examples, see: (a) Wen, L. -R.; Ji, C.; Li, M.; Xie, H.-Y. *Tetrahedron* **2009**, *65*, 1287. (b) Attanasi, O. A.; Crescentini, L. D.; Favi, G.; Filippone, P.; Giorgi, G.; Mantellini, F.; Moscatelli, G.; Behalo, M. S. *Org. Lett.* **2009**, *11*, 2265. (c) Wu, X.; Dai, X.; Nie, L.; Fang, H.; Chen, J.; Ren, Z.; Cao, W.; Zhao, G. *Chem. Commun.* **2010**, *46*, 2733. (d) Shen, Z.-L.; Xu, X.-P.; Ji, S.-J. *J. Org. Chem.* **2010**, *75*, 1162. (e) Ma, D.; Lu, X.; Shi, L.; Zhang, H.; Jiang, Y.; Liu, X. *Angew. Chem., Int. Ed.* **2011**, *50*, 1118.

**Table 2.** Synthesis of 2*H*-Indazole from 2-Bromobenzaldehyde[a]




| entry | **2** (R) | product | | yield (%) |
|---|---|---|---|---|
| 1 | Ph |  | **4aa** | 98 |
| 2 | 4-$MeC_6H_4$ |  | **4ab** | 81 |
| 3 | 4-$MeSC_6H_4$ |  | **4ac** | 84 |
| 4 | 2-Pyridyl |  | **4ad** | 82 |
| 5 | Mesityl |  | **4ae** | 46 |
| 6 | 4-$EtO_2CC_6H_4$ |  | **4af** | 64 |
| 7 | 4-$ClC_6H_4$ |  | **4ag** | 80 |
| 8 | 4-$CF_3C_6H_4$ |  | **4ah** | 46(72[b]) |
| 9 | 4-$NO_2C_6H_4$ |  | **4ai** | 20(48[b]) |
| 10 | 1-Adamantyl |  | **4aj** | 84 |
| 11 | 3-(HO)Ad |  | **4ak** | 80 |
| 12 | $CH_2CH(OEt)_2$ |  | **4al** | 76 |
| 13 | cyclopropyl |  | **4am** | 63 |
| 14 | $HCO_2NH_4$[c] |  | **4an** | 30 |

[a] Reaction conditions: 2-bromobenzaldehyde (1.5 mmol), aniline (1.8 mmol), $NaN_3$ (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. [b] 2-Bromobenzaldehyde and aniline derivative were first reacted, and then $NaN_3$, CuI, and TMEDA were added. [c] Ammonium formate.

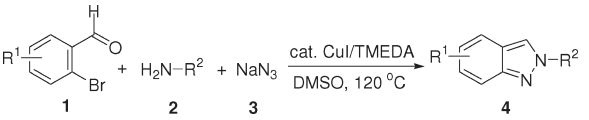
Surprisingly, ammonium formate was also coupled with 2-bromobenzaldehyde and $NaN_3$ to produce 1*H*-indazole (**4an**), which might be produced from the tautomerization of 2*H*-indazole, due to it being more thermodynamically stable than 2*H*-indazole (Table 2, entry 14).[17]

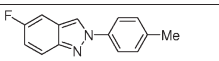
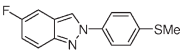
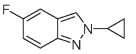
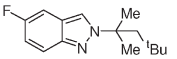
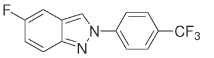
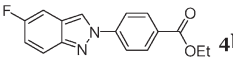
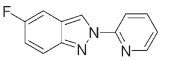
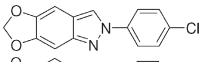
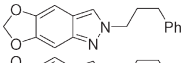
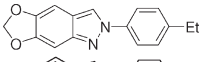
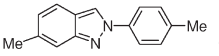
Encouraged by these results, we attempted to expand the scope of 2-bromobenzaldehydes by using substituted versions. Table 3 shows three-component coupling reactions using 2-bromo-5-fluorobenzaldehyde (**1b**), 6-bromo-1,3-benzodioxole-5-carboxaldehyde (**1c**), and 2-bromo-4-methylbenzaldehyde (**1d**).

All three reacted with amines and $NaN_3$ 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

(17) (a) Minkin, V. I.; Garnovskii, D. G.; Elguero, J.; Katritzky, A. R.; Denisko, O. V. *Adv. Heterocycl. Chem.* **2000**, *76*, 157. (b) Alkorta, I.; Elguero, J. *J. Phys. Org. Chem.* **2005**, *18*, 719.

**Table 3.** Synthesis of 2*H*-Indazole from Substituted 2-Bromobenzaldehyde[a]

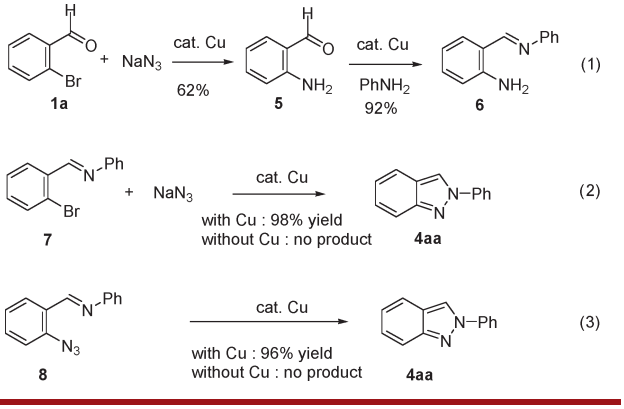



| entry | **1** ($R^1$) | product | | yield (%) |
|---|---|---|---|---|
| 1 | **1b** (5-F) |  | **4bb** | 78 |
| 2 | **1b** (5-F) |  | **4bc** | 88 |
| 3 | **1b** (5-F) |  | **4bm** | 86 |
| 4 | **1b** (5-F) |  | **4bo** | 80 |
| 5 | **1b** (5-F) |  | **4bh** | 57 |
| 6 | **1b** (5-F) |  | **4bf** | 61 |
| 7 | **1b** (5-F) |  | **4bd** | 55 |
| 8 | **1c** (4,5-$OCH_2O$) |  | **4cg** | 40 |
| 9 | **1c** (4,5-$OCH_2O$) |  | **4cp** | 65 |
| 10 | **1c** (4,5-$OCH_2O$) |  | **4cq** | 62 |
| 11 | **1d** (4-Me) |  | **4db** | 70 |

[a] Reaction conditions: 2-bromobenzaldehyde (1.5 mmol), aniline (1.8 mmol), $NaN_3$ (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



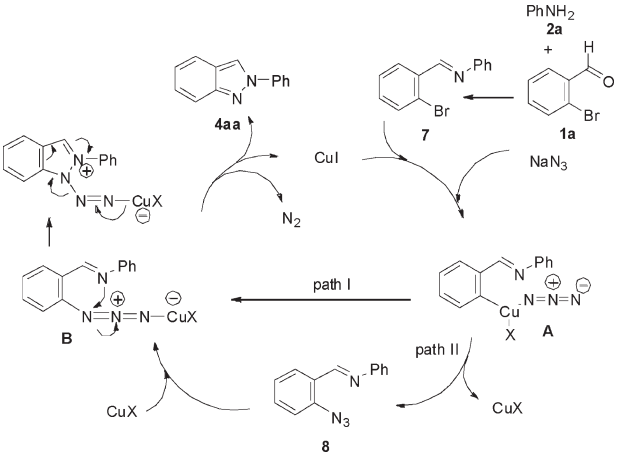
When 2-bromobenzaldehyde (**1a**) was reacted with $NaN_3$ in the presence of CuI/TMEDA, 2-aminobenzaldehdyde (**5**) was formed instead of the expected *N*-(2-azidobenzaldehyde (**8**).[18,19] The resulting product was reacted with aniline to yield 92% of *N*-(2-aminobenzylidene)aniline (**6**) (Scheme 1, eq 1); however, the desired 2*H*-indazole was not formed. *N*-(2-Bromobenzylidene)aniline (**7**) reacted with $NaN_3$ in the presence of 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 CuI/TMEDA in DMSO, the desired product was formed in 96% yield (Scheme 1, eq 3).[20] 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.[12] 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.[21]

The sequential procedure of the emission of $N_2$ and the dissociation of the copper catalyst afforded the desired 2*H*-indazole **4aa**.[22] However, we do not exclude the mechanism of path **I** because intermediate **8** was not found in the reaction mixture.[23] 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 $NaN_3$ 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 multicomponent 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.

(18) For the amination reaction of aryl halide with $NaN_3$ using a Cu catalyst, see: Goriya, Y.; Ramana, C. V. *Tetrahedron* **2010**, *66*, 7642.

(19) For the formation of aryl azide from aryl halides and $NaN_3$ using a Cu catalyst, see: (a) Andersen, J.; Madsen, U.; Björkling, F.; Liang, X. *Synlett* **2005**, 2209. (b) Zhu, W.; Ma, D. *Chem. Commun.* **2004**, 888.

(20) We found that $FeBr_2$ does not show catalytic activity in the C−N bond formation of aryl halides and $NaN_3$. However, $FeBr_2$ afforded the desired 2*H*-indazole through the N−N bond formation of *N*-(2-azidobenzylidene)aniline (**8**).

(21) Yan, X.-M.; Chen, Z.-M.; Yang, F.; Huang, Z.-Z. *Synlett* **2011**, 569.

(22) The elimination of dinitrogen has been reported in the copper catalytic system. See: (a) Chiba, S.; Zhang, L.; Lee, J.-Y. *J. Am. Chem. Soc.* **2010**, *132*, 7266. (b) Chiba, S.; Zhang, L.; Ang, G. Y.; Hui, B. W.-Q. *Org. Lett.* **2010**, *12*, 2052.

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