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Microwave-assisted synthesis of 1-aryl-1*H*-indazoles via one-pot two-step Cu-catalyzed intramolecular *N*-arylation of arylhydrazones

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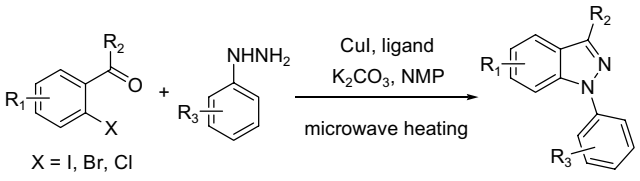
Abstract—A highly efficient one-pot two-step microwave procedure was developed for the synthesis of 1-aryl-1*H*-indazoles. Microwave heating of 2-halobenzaldehydes or 2-haloacetophenones with phenylhydrazines at 160 °C for 10 min quantitatively yielded the arylhydrazones, which were further cyclized to give 1-aryl-1*H*-indazoles via CuI/diamine-catalyzed *N*-arylation under microwave heating (160 °C, 10 min). Good to excellent yields were observed for 2-iodo, 2-bromo, and 2-chloro benzaldehydes or acetophenones.

The indazole ring is an important pharmacophore in medicinal chemistry. Indazole derivatives have shown different levels of activity as MAPKAP kinase modulators,[1a] PPARs agonists,[1b] potassium channel blockers,[1c] 5-HT_4 receptor antagonists,[1d] CCK-A agonists,[1e] and inhibitors of protein kinase C-β,[1f] SAH/MTA nucleosidase,[1g] and DNA gyrase.[1h] Indazoles have been synthesized in many ways.[2] Several groups have recently reported the synthesis of indazoles via palladium-catalyzed intramolecular *N*-arylation of *N*-aryl-*N*-(*o*-bromobenzyl)hydrazines,[3a] *N*-aryl-*N*′-(*o*-bromobenzyl)-hydrazines,[3b] [*N*-aryl-*N*′-(*o*-bromobenzyl)-hydrazinato-*N*′]-triphenylphosphonium bromides,[3b] or hydrazones of 2-halobenzaldehydes or 2-haloacetophenones.[3c–e] The developed conditions are limited with either 2-bromo or activated 2-chloro substrates. A more efficient and general *N*-arylation procedure for the synthesis of indazoles remains desirable.

Cu-mediated systems have proven equally effective in *N*-arylation of anilines,[4] amides,[5] hydrazides,[6] alkylamines,[7] and nitrogen heterocycles.[8] Mild conditions have been developed using ligands such as diamines,[8] diols,[7a] diethylsalicylamide,[7b] amino alcohols,[9] and amino acids.[10] Fukuyama and co-workers have reported mild intramolecular *N*-arylation using a stoichiometric amount of CuI.[11] The success of these studies prompted us to examine the Cu-catalyzed *N*-arylation in the indazole synthesis, especially for unactivated chloro substrates. Herein, we report an efficient microwave-assisted synthesis of 1-aryl-1*H*-indazole via CuI-catalyzed *N*-arylation of hydrazones of 2-haloaldehydes or 2-haloacetophenones.



Microwave irradiation has been widely applied in organic synthesis.[12] Many organic transformations, including *N*-arylation,[13] have been accelerated by subjecting them to microwave irradiation. As part of our

Keywords: 1*H*-Indazole; Hydrazone; Copper; Cyclization; Arylation; Microwave irradiation.
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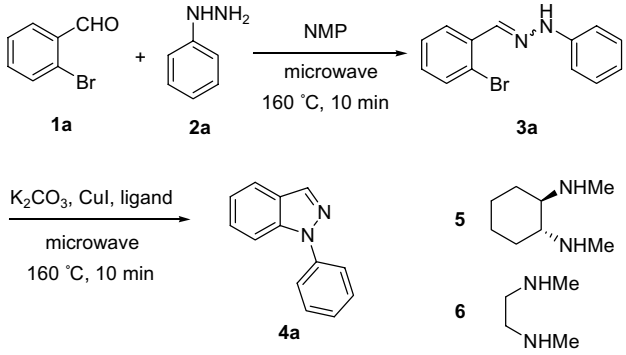
continuing interest in the application of this technology,[14] microwave heating was used to speed up the reaction optimization.

As illustrated in Table 1, a Buchwald Cu–diamine system was found effective in the cyclization of 2-bromobenzaldehyde and phenylhydrazine. After a few tests, we noticed that better yields could be achieved by stepwise cyclization. Thus, a one-pot two-step intramolecular Cu-catalyzed *N*-arylation procedure was developed. In a recent study on Pd-catalyzed indazole synthesis, preformed hydrazones were similarly found to give better yields.[3e] The hydrazone **3** was easily prepared in quantitative yield by microwave heating a mixture of 2-bromobenzaldehyde and phenylhydrazine in NMP at 160 °C for 10 min. Next, K_2CO_3, CuI and diamine ligand were added, and the mixture was again microwave heated to facilitate the cyclization. The best condition for the second step *N*-arylation was 160 °C for 10 min with 2 equiv of K_2CO_3, 5 mol % of CuI and 10 mol % of diamine **5** (entry 1). When diamine **6** was used as the ligand, the conversion dropped to 82% (entry 2). Without a ligand, only trace amount of product was formed and the conversion was <5% (entry 3). As compared to K_2CO_3, no difference was observed when Cs_2CO_3 was used as the base (entry 4). Heating at 195 °C generated 5% of uncharacterized side product, while heating at 100 and 140 °C caused incomplete conversion (entries 5–7). Using other substrates, we also found that solvents such as toluene, dioxane, and DMF were not as effective as NMP. Notably, longer reaction time was required to drive the reaction to completion when a regular heating source was used. The microwave reactions were carried out without nitrogen atmosphere.

With an optimized procedure in hand, a list of 2-halobenzaldehydes or 2-haloacetophenones were examined to explore the scope of the Cu-catalyzed one-pot two-step transformation (Table 2).[15] Good to excellent yields were observed for 2-bromobezaldehydes bearing electron-donating or electron-withdrawing substituents (entries a–d). For 2-bromo-5-nitrobenzaldehyde, heating at lower temperature gave better yield (entry d). When 2-bromonicotinic aldehyde was used, the observed yield was 95% (entry e). While under $Pd(dba)_2$/DPEphos catalysis, no cyclization product was formed for the same substrate due to possible catalyst inhibition.[3e] The yield using 2-chlorophenylhydrazine was essentially the same as using the nonsubstituted phenylhydrazine (entries c and f). In comparison with 2-bromobenzaldehyde (entry a), 2-iodobenzaldehyde gave a slightly higher yield (94%) (entry g). It was reported that the reaction of 2-chlorobenzaldehyde with phenylhydrazine using palladium catalysis yielded less than 1% of indazole product.[3e] In contrast, a remarkable yield of 87% was achieved using the microwave conditions we described (entry h). For the less reactive 2-bromo and 2-chloro acetophenone substrates, the CuI/diamine microwave condition was also effective with good yields achieved (entries i–k). While using palladium catalysis, only 2-bromoacetophenone substrates were studied with lower yields being reported.[3e]

In conclusion, a highly efficient one-pot two-step microwave procedure was developed for the synthesis of 1-aryl-1*H*-indazoles. Microwave heating of 2-halobenzaldehydes or 2-haloacetophenones with phenylhydrazines at 160 °C for 10 min quantitatively yielded the arylhydrazones, which were further cyclized to give

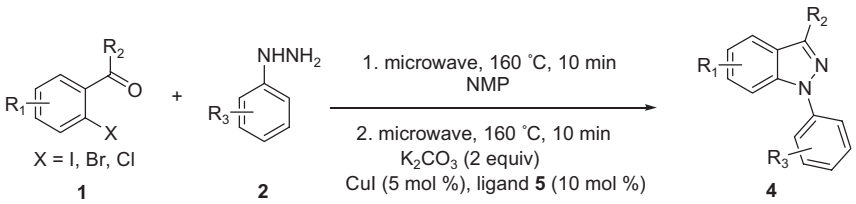
Table 1. Optimization of Cu-catalyzed one-pot two-step intramolecular cyclization

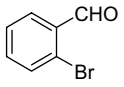
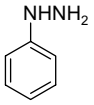
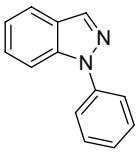
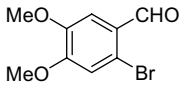
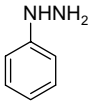
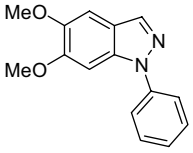
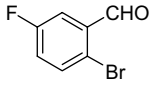
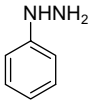
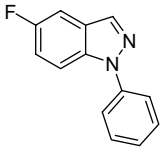
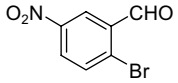
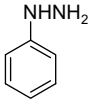
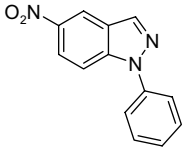
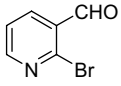
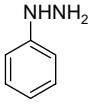
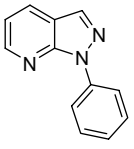
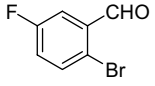
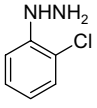
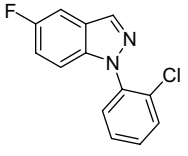
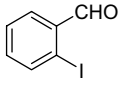
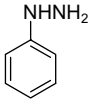
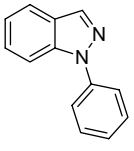
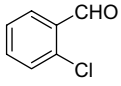
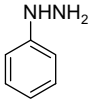
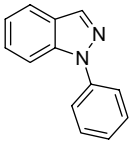
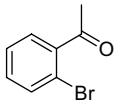
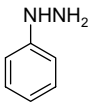
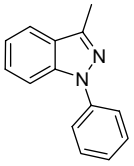


Entry	Ligand[a]	Base[b]	Microwave conditions	Conversion (%)
1	**5**	K_2CO_3	160 °C, 10 min	100[c]
2	**6**	K_2CO_3	160 °C, 10 min	82[c]
3	No ligand	K_2CO_3	160 °C, 10 min	<5[d]
4	**5**	Cs_2CO_3	160 °C, 10 min	100[c]
5	**5**	K_2CO_3	195 °C, 10 min	94[c,e]
6	**5**	K_2CO_3	100 °C, 10 min	40[c,d]
7	**5**	K_2CO_3	140 °C, 10 min	83[d]

[a] 5 mol % of CuI and 10 mol % of diamine ligand were used.
[b] 2 equiv of base was used.
[c] Based on ^{1}H NMR analysis.
[d] Based on LC–MS analysis.
[e] 5% of uncharacterized side product was observed.

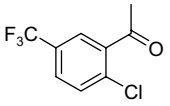
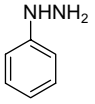
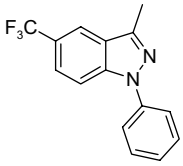
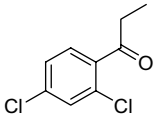
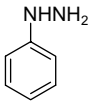
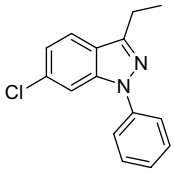
Table 2. Synthesis of 1-aryl-1*H*-indazoles **4** via CuI/diamine-catalyzed intramolecular cyclization



Entry	Substrate	Hydrazine	Product[a]	Isolated yield (%)
a				91
b				82
c				84
d				65, 95[b]
e				95
f				82
g				94
h				87
i				75

(*continued on next page*)

Table 2 (*continued*)

Entry	Substrate	Hydrazine	Product[a]	Isolated yield (%)
j				78
k				69

[a] Final compounds were characterized by MS, ^{1}H NMR, and ^{13}C NMR analyses.
[b] The second step *N*-arylation was carried out at 120 °C for 10 min.

1-aryl-1*H*-indazoles via CuI/diamine-catalyzed *N*-arylation under microwave heating (160 °C, 10 min). Good to excellent yields were observed for hydrazones of 2-iodo, 2-bromo, and 2-chloro benzaldehydes. Notably, a yield of 87% was achieved for a hydrazone of unactivated 2-chlorobezaldehyde, while using the reported palladium catalysis, the yield was less than 1% for the same substrate. Furthermore, for the less reactive hydrazones of 2-bromo and 2-chloroacetophenones, good yields were achieved using the same Cu-catalyzed microwave procedure.

Acknowledgements

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References and notes

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15. **Typical procedure for the microwave-assisted synthesis of 1-aryl-1*H*-indazole**: A 0.5–2 mL Smith Process vial containing a magnetic stir bar was charged with the 2-halobenzaldehyde (or 2-haloacetophenone) (0.5 mmol, 1.0 equiv), phenylhydrazine (0.5 mmol, 1.0 equiv) and NMP (0.5 mL). The vial was sealed without degassing, and the solution was heated at 160 °C for 10 min (fixed hold time) in the Smithcreator. Next, the reaction vial was unsealed, and to the preformed hydrazone solution was added base (1.0 mmol, 2.0 equiv), CuI (0.025 mmol, 0.05 equiv), and ligand (0.05 mmol, 0.1 equiv). The reaction vial was again sealed without degassing, and the suspension was heated at 160 °C for 10 min (fixed hold time). The reaction mixture was filtered through Celite and purified by flash chromatography (ethyl acetate/hexanes). Characterization of compound **4e**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.64 (dd, $J = 4.5$, 1.5 Hz, 1H), 8.27 (d, $J = 8.4$ Hz, 2H), 8.20 (s, 1H), 8.13 (d, $J = 8.4$ Hz, 1H), 7.54 (t, $J = 8.4$ Hz, 2H), 7.32 (t, $J = 7.5$ Hz, 1H), 7.21 (dd, $J = 8.1$, 4.5 Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 150.5, 149.5, 139.9, 134.3, 130.6, 129.5, 126.5, 121.7, 118.0, 117.6 ppm.