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# Regioselective Synthesis of 1-Alkyl- or 1-Aryl-1*H*-indazoles via Copper-Catalyzed Cyclizations of 2-Haloarylcarbonylic Compounds

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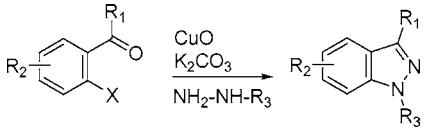
## ABSTRACT




**A general method for the one-step regioselective synthesis of 1-alkyl- or 1-aryl-1*H*-indazoles from ortho-halogenated alkanoylphenones, benzophenones, and arylcarboxylic acids, via copper-catalyzed amination, was developed by using 0.2% mol of CuO in the presence of $K_2CO_3$. The reaction involves amination followed by intramolecular dehydration. Different functionalized alkyl aryl ketones, diaryl ketones, and benzoic acid derivatives were efficiently coupled with several hydrazines. Ligands commonly employed as catalysts for intermolecular amination were shown to be ineffective for this cyclization.**

Indazoles constitute an important class of organic compounds which have found various biomedical applications in the anti-inflamatory, antitumor, anti-HIV, antidepressant, and contraceptive therapeutic areas.[1] The most widely employed method for the construction *N*-substituted indazoles involves the creation of the $N^1-N^2$ bond by intramolecular reduction of *o*-nitrobenzylamines with Sn, Zn, or Fe in acidic medium[2] and, most recently, by Pd-catalyzed cyclization of arylhydrazones or arylhydrazines of 2-halobenzaldehyde.[3] However, the formation of hydrazones from alkyl aryl ketones is difficult. This requires a very long reaction time, and often a low conversion rate is attained.[4] Despite significant improvements in the Pd-catalyzed *N*-arylation of amines,[5] some limitations still remain. These include the reactivity of some functional groups in presence of the amine and base required in C−N coupling protocols.[6] Moreover, the high cost of palladium invites the search toward less expensive alternatives.

Both the Ullmann reaction (copper-catalyzed *N*-arylation of amines)[7] and the Goldberg reaction (copper-catalyzed *N*-arylation of amides)[8] predate the Pd-catalyzed amination methodology by several decades. However, the use of high temperatures, poor substrate scope, and the need for stoi-

(1) (a) Picciola, G.; Ravenna, F.; Carenini, G.; Gentili, P.; Riva, M. *Farmaco* **1981**, *36*, 1037. (b) Keppler, B. K.; Hartmann, M. *Met. Based Drugs* **1994**, *1*, 145. (c) Rodgers, J. D.; Johnson, B. L.; Wang, H.; Greenberg, R. A.; Erickson-Viitanen, S.; Klabe, R. M.; Cordova, B. C.; Rayner, M. M.; Lam, G. N.; Chang, C.-H. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 2919. (d) Ykeda, Y.; Takano, N.; Matsushita, H.; Shiraki, Y.; Koide, T.; Nagashima, R.; Fujimura, Y.; Shindo, M.; Suzuki, S.; Iwasaki, T. *Arzneimittel.-Forsch.* **1979**, *29*, 511. (e) Corsi, G.; Palazzo, G.; Germani, C.; Barcellona, P. S.; Silvestrini, B. *J. Med. Chem.* **1976**, *19*, 778.

(2) (a) Paal, C.; Krecke, F. *Chem. Ber*. **1980**, *23*, 2640. (b) Paal, C. *Chem. Ber*. **1891**, *24*, 959. (c) Busch, V.; Hartman, P. *J. Prakt Chem.* **1895**, *2*, 404. (d) Campi, E. M.; Habsuda, J.; Jackson, W. R.; Jonasson, C. A. M.; McCubbin, Q. *J. Aust. J. Chem.* **1995**, *48*, 2023.

(3) (a) Song, J. J.; Yee, N. K. *Org. Lett*. **2000**, *2*, 519. (b) Song, J. J.; Yee, N. K. *Tetrahedron Lett.* **2001**, *42*, 2937.

(4) Lebedev, A. Y.; Khartulyari, A. S.; Voskoboynikov, A. Z. *J. Org. Chem.* **2005**, *70*, 596.

(5) (a) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805. (b) Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2046. (c) Yang, B. H.; Buchwald, S. L. *J. Organomet. Chem.* **1999**, *576*, 125. (d) Muci, A. R.; Buchwald, S. L. *Top. Curr. Chem*. **2002**, *219*, 133.

(6) (a) Batch, A.; Dodd, R. H. *J. Org. Chem.* **1998**, *63*, 872. (b) Deng, B.-L.; Lepoivre, J. A.; Lemière, G. *Eur. J. Org. Chem.* **1999**, 2638.

(7) Ullmann, F. *Ber. Dtsch. Chem. Ges.* **1903**, *36*, 2382.

(8) Goldberg, I. *Ber. Dtsch. Chem. Ges.* **1906**, *39*, 1691.

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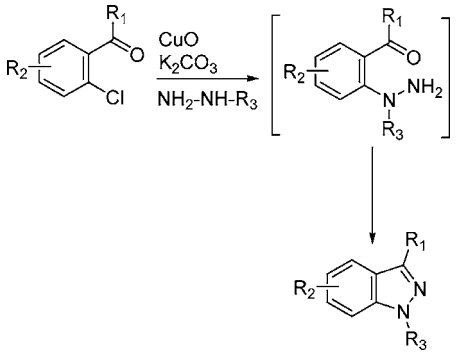
chiometric amounts of the copper reagent have limited the usefulness of these reactions. In recent years, a milder Ullmann-type methodology (CuI, 1,10-phenanthroline, and $Cs_2CO_3$) for the *N*-arylation of hydrazides has been reported. Although C−N coupling of *N*-Boc hydrazine with *para*- and *meta*-substituted aryl iodides usually yields regioselectively the desired *N*-arylated products, a reversal in regioselectivity has been observed for the arylation of benzoic acid hydrazide with *ortho*-substituted aryl iodides, providing the *N*′-arylated products.[9]

In view of these antecedents, aiming to develop an easier and less expensive route to a library of potential antimicrobial indazoles, we became interested into searching whether a strategy based on arylation of alkyl (aryl) hydrazines with *ortho*-carbonylated aryl halides, followed by intramolecular cyclization, would be effective in obtaining the desired indazoles.

In this study, we describe our preliminary results in developing a new regioselective procedure leading, through a convenient one-step route, to a range of 1-alkyl- or 1-aryl-1*H*-indazoles displaying varied functionalizations. This methodology is based on the CuO-catalyzed reaction between *N*-alkyl- or *N*-arylhydrazine with 2-haloaryl ketones and 2-halobenzoic acids, followed by intramolecular dehydration (Scheme 1).

**Scheme 1**




The effect of the base on the coupling reaction was also examined. In general, the use of $K_2CO_3$ gave yields superior to those achieved with $Cs_2CO_3$. Further optimization of the reaction conditions revealed that the use of ligands as 1,10-phenantroline and *N*,*N*′-dimethylethylenediamine, commonly employed for intermolecular amination,[10] were shown to be ineffective for cyclization.

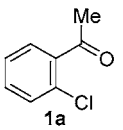
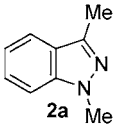
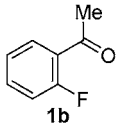
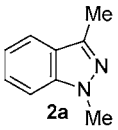
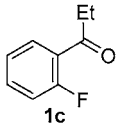
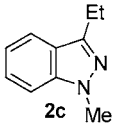
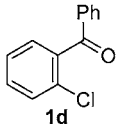
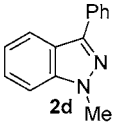
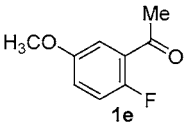
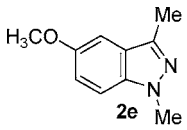
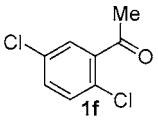
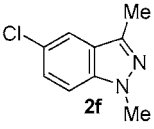
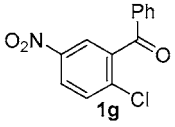
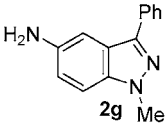
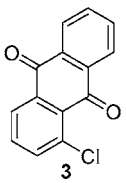
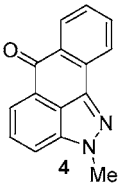
In preliminary experiments, we observed that the reaction of 2-chloroacetophenone with methylhydrazine could be performed in the presence of CuO and anhydrous $K_2CO_3$, affording 1,3-dimethyl-1*H*-indazole (**2a**) in 54% yield, after 20 h at 110 °C in a sealed tube. Attempts to carry out the reaction in a conventional flask were unsuccessful, leading only to the corresponding unstable hydrazone.

Changing CuO to the more expensive $Cu_2O$ or Cu/CuO[11] as catalysts gave similar results. Then, the above-mentioned conditions [substrate/hydrazine derivative/CuO/$K_2CO_3$],[12] with control of the reaction temperature (110−200 °C), were subsequently applied in all of the reactions.

To explore the scope of this methodology, first, the reaction of a number of haloaryl ketones with methylhydrazine was assayed (Table 1).

In all of the examined cases, the desired 1-methyl-1*H*-indazoles (**2a**−**g**) were readily obtained in moderate to good yields. Reaction yields were not too different for chloro- and fluoroacetophenones (**1a**/**1b**). Acetophenones and benzophenones bearing electron-donating (methoxy, amino) substituents at the *para* position relative to the halogen gave

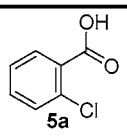
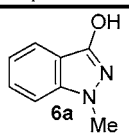
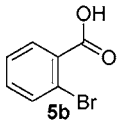
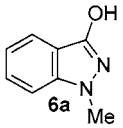
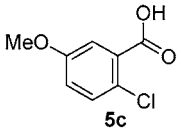
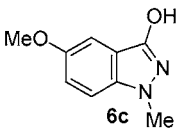
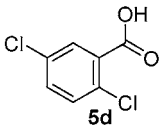
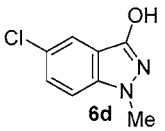
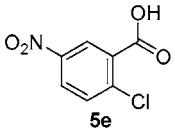
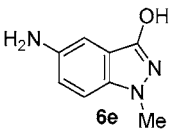
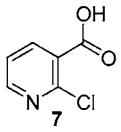
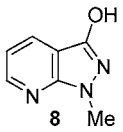
**Table 1.** CuO-Catalyzed Coupling of 2-Haloarylketones with Methylhydrazine

| substrate | product[a] | yield[b] |
|---|---|---|
|  **1a** |  **2a** | 54% |
|  **1b** |  **2a** | 50% |
|  **1c** |  **2c** | 63% |
|  **1d** |  **2d** | 43% |
|  **1e** |  **2e** | 83% |
|  **1f** |  **2f** | 30% |
|  **1g** |  **2g** | 80% |
|  **3** |  **4** | 83%[c] |

[a] All new compounds were characterized by $^1H/^{13}C$ NMR and HRMS data. [b] After chromatography. [c] Modified reactions conditions: DMA/THF.

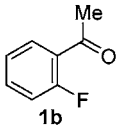
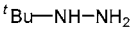
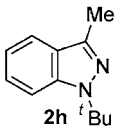
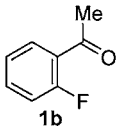
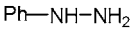
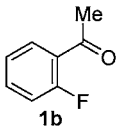
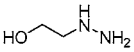
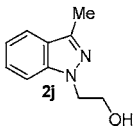
(9) Wolter, M.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2001**, *3*, 3803.
(10) Klapars, A.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 7421.

**Table 2.** CuO-Catalyzed Coupling of 2-Haloarylcarboxylic Acids with Methylhydrazine

| substrate | product[a] | yield[b] |
|---|---|---|
|  |  | 20%[c] |
|  |  | 22% |
|  |  | 22% |
|  |  | 16% |
|  |  | 26% |
|  |  | 54% |

[a] All new compounds were characterized by $^1H/^{13}C$ NMR and HRMS data. [b] After chromatography. [c] Benzene was used as solvent.

**Table 3.** CuO-Catalyzed Coupling of 2-Fluoroarylketones with Alkyl- and Arylhydrazines

| substrate | hydrazine | product[a] | yield[b] |
|---|---|---|---|
|  |  |  | 22% |
|  |  |  | 40% |
|  |  |  | 30% |

[a] All new compounds were characterized by $^1H/^{13}C$ NMR andHRMS data. [b] After chromatography.

higher indazole yields than that provided by the *p*-chloro-substituted compound **1f**. The high yield observed in the conversion of the nitro derivative **1g** into the corresponding the amine **2g** would be explained by the reduction of the nitro group, prior to the condensation, due to hydrazine excess. In the cases of **1a**, **1d**, and **1f**, the starting substrate was recovered unchanged and further refluxing resulted in a decrease of the yield due to the formation of byproducts. In the case of compound **3**, under the above-mentioned conditions, a complex crude mixture was obtained. However, in the absence of catalyst and using DMA/THF as solvent,[13] a fairly high yield of compound **4** was achieved (Table 1).

We then attempted to extend the method to 2-haloaryl acids (Table 2). Under the above-mentioned conditions, 2-chlorobenzoic acid or 2-bromobenzoic acid was not soluble enough in methylhydrazine; therefore, we used other solvents (benzene, THF, *n*-butyl alcohol) for improving the reaction rate. The best results were achieved in benzene. The presence of 1,10-phenanthroline, often used as ligand in this type of reactions, failed to yield the desired product. The best result for the series of 2-haloarylcarboxylic acids was obtained with nicotinic acid, easily soluble in methylhydrazine. In the presence of enough $K_2CO_3$, salt formation occurred and the yield of the desired compound decreased, whereas lowering the amount of the base led to improved yields. Additionally, dehalogenation of the starting material ocurred in several cases (**5a**,**c**).

To explore further the generality of this practical approach, condensations of *o*-halobenzoic acids **5a**−**e** and that of 2-chloronicotinic acid (**7**) with methylhydrazine were performed, using the best conditions found (Table 2). The starting halobenzoic acids included in Table 2 were selected for evaluating the influence of the electrostatic nature of additional substituents on the reaction.

Similar to those results found for acetophenones, in comparison with 2-chlorobenzoic acid itself, the additional presence of the electron-withdrawing 5-chloro group (**5d**) led to a reduced indazole yield, whereas the electron-donating 5-methoxy substituent (**5c**) and the 5-nitro group (**5e**), being reduced to the corresponding amine (**6e**), increased the indazole formation. It is worthy to note that the presence of the nitrogen atom at the α position of the chlorine atom to be substituted, practically doubled the conversion rate and yield.

Finally, we turned our attention to the influence of the hydrazine used in the reaction. We carried out the condensation with representative alkyl and arylhydrazines. The results (Table 3), showed that this method can be extended to other

(11) Wolf, C.; Liu, S.; Mei, X.; August, A. T.; Cusinur, K. D. *J. Org. Chem.* **2006**, *71*, 3270.

(12) **Representative Procedure for the Synthesis of 1-Alkyl-1*H*-indazoles: 1,3-Dimethyl-1*H*-indazole (2a).** An oven-dried reseable Schlenk tube was charged with CuO (4 mg, 2 mol %) and $K_2CO_3$ (150 mg, 1.5 mmol), evacuated, and back-filled with argon. 2-Chloroacetophenone (154 mg, 0.13 mL, 1 mmol) and methylhydrazine (0.35 mL, 6.4 mmol) were added under argon. The Schlenk tube was sealed, and the reaction was stirred magnetically at 110 °C for 20 h. The resulting suspension was cooled to room temperature, filtered, diluted with ethyl acetate, and washed with water. The organic phase was concentrated. Purification of the residue by flash cromatography on silica gel (hexane/EtOAc, 95:5) gave the desired product.

(13) Zhang, L.; Meier, W. E.; Watson, E. J.; Gibson, E. P. *Tetrahedron Lett.* **1994**, *35*, 3675.

hydrazines, with similar yields, by changing only the reaction temperature.

In summary, we have developed a general methodology for synthesis of indazoles, based on the *N*-arylation of alkyl- and arylhydrazines, followed by intramolecular dehydration in the presence of a common and cheap catalyst. It results as an efficient strategy for the easy synthesis of a variety 1-alkyl- or 1-aryl-1*H*-indazoles, that can be extended as well to the preparation of pyrazolo[3,4-*b*]pyridines and presumably to that of other pyrazolo-fused polyheterocyclic systems. This method applies to a variety scope of substrates and is tolerant with a range of functional groups. Efforts to expand the scope of the method to other aryl halides (esters, amides) are in progress in our laboratory.

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**Supporting Information Available:** Detailed experimental procedures and characterization data for the reaction products included in this paper. This material is available free of charge via the Internet at http://pubs.acs.org.

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