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Highly Regioselective C–N Bond Formation through C–H Azolation of Indoles Promoted by Iodine in Aqueous Media

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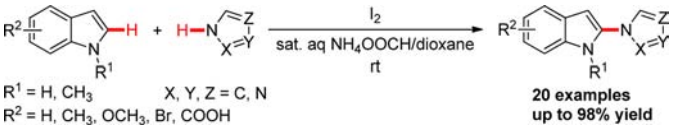
ABSTRACT



An efficient and metal-free method for the direct C–N coupling of indoles with azoles to produce 2-(azol-1-yl)indoles in aqueous solution has been developed. This reaction proceeded highly regioselectively to provide a variety of indole derivatives with good to excellent yields.

The substituted indole core, which is present in numerous biologically active products,[1] has attracted the extensive attention of synthetic chemists to explore methods for indole C–C and C–N functionalization.[2] Compared with a large number of reports on C–C functionalization, the general method of C–N derivatization of indoles is still limited, especially for the direct C–N bond formation at the C2 position. It is rare due to the poor control of both the chemo- and regioselectivities. Recently, Li and co-workers reported a copper-catalyzed regioselective amidation of 1-methylindole at the C2 position with acetanilide.[3] Liu and co-workers reported a Pd/Cu-catalyzed C2 regioselective amination of N-protected indole derivatives with chlorosulfonamides.[4] Liang and co-workers described the reactions of N-protected indoles with morpholine and *N*-tosylbenzenamines in the presence of iodine.[5,6]

2-(Azol-1-yl)indoles, which represent another group of N-linked indoles at the C2 position, were found in some biologically active compounds, such as 11*H*-1,5,11,11*b*-tetraaza-benzo[*a*]trindene-4,6-dione (**I**),[7] indolo[3,2-*e*]-[1,2,3]triazolo[1,5-*a*]pyrimidine (**II**),[8] and the celogentin and moroidin family of compounds[9] (Figure 1). Some groups had reported the synthesis of the 2-(azol-1-yl)indoles

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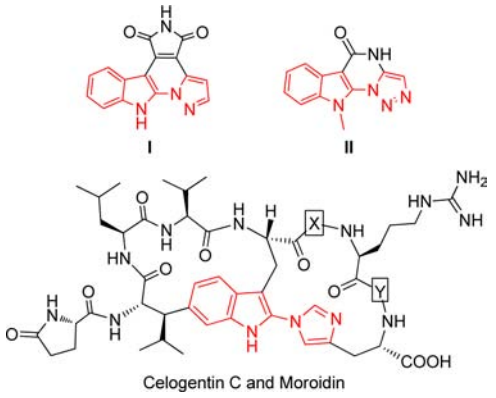


Figure 1. Structure of compounds **I**, **II**, celogentin C (X = Pro, Y = bond) and moroidin (X = bond, Y = Gly).

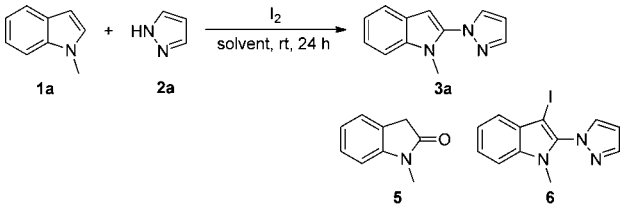
from indole derivatives with an electron-withdrawing group at the C3 position.[10] And recently, Poirier and Beaulieu reported a general method of a thermal or microwave-mediated reaction of haloindoles with azoles to afford novel 2-(azol-1-yl)indoles.[11] Since some of the haloindoles are not readily accessible and some are not stable, exploring new methods of direct C−H amination of nonactivated indoles with azoles is highly desirable, even though an intramolecular oxidative coupling method has been applied in the total synthesis to build up the 2-(imidazole-1-yl)indole core.[12]

In recent years, organic reactions in aqueous media have attracted a great deal of attention, because of environmental concerns and the unique reactivity and selectivity observed in aqueous reactions.[13] In connection with our interests in aqueous medium reactions,[14] herein we report a metal-free selective C−N bond formation of inactive indoles with azoles in aqueous media.

Initial studies were performed with the reaction of 1-methylindole (**1a**) with 2.5 equiv of pyrazole (**2a**) in the presence of 2.0 equiv of iodine (I_2) in H_2O/dioxane (1:1) at room temperature. After 24 h, the desired product **3a** was obtained in 30% yield, and a 32% yield of 1-methyl-1,3-dihydro-indol-2-one (**5**) was observed (Table 1, entry 1). Optimization studies were then performed to improve the yield of the desired product. When water was replaced with a saturated NH_4OOCH solution, the yield was significantly increased to 96% (Table 1, entry 2), and a saturated NaOOCH solution gave a slightly lower yield of 90% (Table 1, entry 3). However, a saturated NH_4Cl and a saturated NH_4OAc solution led to drastic reductions in yields (Table 1, entries 4 and 5). Studies on the influence of different organic cosolvents showed that CH_3CN gave an almost identical yield with dioxane (Table 1, entry 7), but other solvents such as THF, DMF, DMSO, CH_3OH, and sulfolane were inferior to dioxane (Table 1, entries 8−12). Furthermore, an attempt to reduce the iodine loading showed that lowering the amount of I_2 to 1.5 equiv decreased the yield sharply (Table 1, entry 13). Hence, our optimized reaction conditions are illustrated in entry 2, Table 1.

Next, a wide variety of indole derivatives were examined to react with pyrazole under the optimized conditions, and the results are summarized in Scheme 1. It showed that free indoles afforded comparable yields with 1-methylindoles. The new method revealed a tolerance toward functional groups for both 1-methylindole derivatives and indole

Table 1. Optimization of the I_2-Promoted C−N Bond Formation of 1-Methylindole with Pyrazole[a]



entry	solvent	yield (**3a/5/6/1a**, %)[b]
1[c]	H_2O/dioxane (1:1)	30/32/0/0
2	sat. aq NH_4OOCH/dioxane (1:1)	**96**/2/1/0
3	sat. aq NaOOCH/dioxane (1:1)	90/2/5/0
4	sat. aq NH_4Cl/dioxane (1:1)	45/50/0/0
5	sat. aq NH_4OAc/dioxane (1:1)	15/0/65/15
6	NaOAc−HOAc buffer (pH 5.5)[d]/ dioxane (1:1)	47/0/50/0
7	sat. aq NH_4OOCH/CH_3CN (1:1)	**95**/2/2/0
8	sat. aq NH_4OOCH/THF (1:1)	72/2/1/24
9	sat. aq NH_4OOCH/DMF (1:1)	74/2/2/20
10	sat. aq NH_4OOCH/DMSO (1:1)	76/2/10/10
11	sat. aq NH_4OOCH/CH_3OH (1:1)	62/2/10/25
12	sat. aq NH_4OOCH/sulfolane (1:1)	52/0/23/23
13[e]	sat. aq NH_4OOCH/dioxane (1:1)	80/1/1/16

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (1.25 mmol), I_2 (1.0 mmol), solvent (sat. aq NH_4OOCH/dioxane (1:1), 0.6 mL), rt, 24 h. [b] Yield based on ^1H NMR using CH_3NO_2 as an internal standard. [c] With some other unidentified compounds. [d] Prepared from saturated aqueous NaOAc solution (250 μL) and HOAc (50 μL). [e] I_2 (0.75 mmol, 1.5 equiv).

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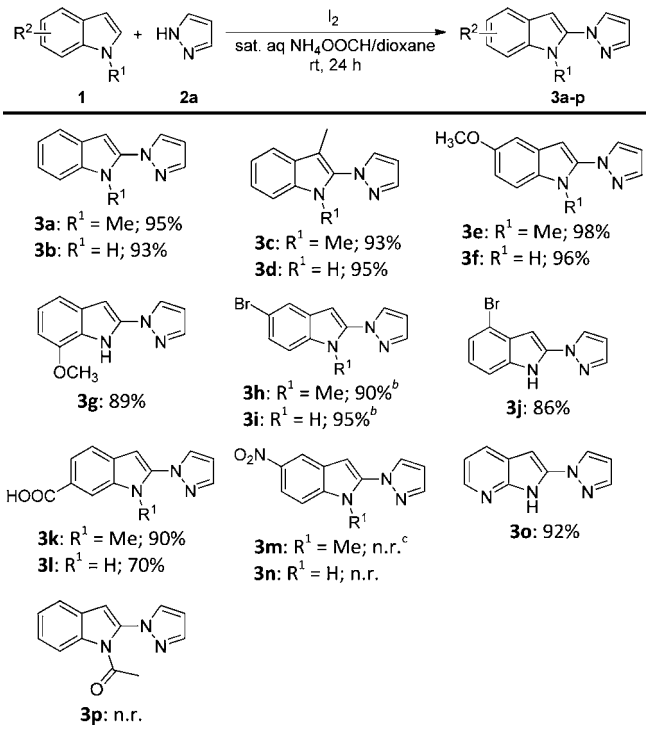
Scheme 1. Reaction of 1-Methylindoles and Indoles with Pyrazole[a]



[a] Unless otherwise specified, all reactions were carried out using **1** (0.5 mmol), **2a** (1.25 mmol), and I_2 (1.0 mmol) in sat. aq NH_4OOCH/dioxane (1:1, 0.6 mL), rt, 24 h. Isolated yield. [b] I_2 (1.5 mmol), 30 h. [c] n.r. = no reaction.

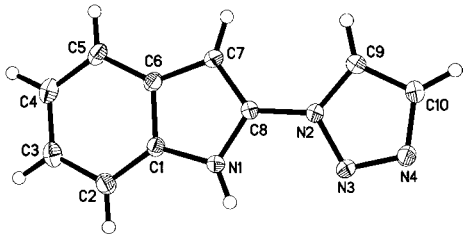
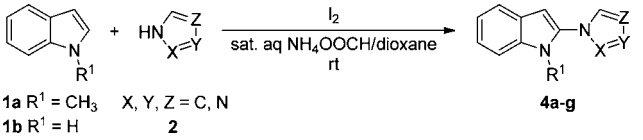


Figure 2. ORTEP drawing of compound **4e**.

derivatives (**3a**–**l**), and in most cases, excellent yields were obtained. It is noteworthy that the functional group of carboxylic acid can be utilized in this method (**3k** and **3l**), whereas 5-nitro-indoles (**3m** and **3n**) and 1-acetylindole (**3p**) were not active in this procedure. The 1,3-dimethylindole and 3-methylindole, which are more sterically hindered with a methyl group at the C3 position, led to excellent yields too (**3c** and **3d**). This method also worked

(15) Crystallographic data for the structures of **3b**, **4a**, **4d**, and **4e** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 891118 (**3b**), CCDC 900318 (**4a**), CCDC 891119 (**4b**), and CCDC 900319 (**4e**). Data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, U.K. [fax: +44 (0) 1223-336033; e-mail: deposit@ccdc.cam.ac.uk].

Table 2. Reaction of Azoles with 1-Methylindole and Indole[a]



entry	azole	R^1	I_2 (equiv)	time (h)	**4**	yield (%)[b]
1	1,2,3-triazole	Me	3	30	**4a**	81[c]
2	1,2,4-triazole	Me	3	30	**4b**	81
3	imidazole	Me	2	48	**4c**	64
4	2-methylimidazole[d]	Me	4	48	**4d**	61
5	1,2,3-triazole	H	3	30	**4e**	93[e]
6	1,2,4-triazole	H	3	30	**4f**	80
7	imidazole[f]	H	4	48	**4g**	90

[a] Standard conditions: **1a** or **1b** (0.5 mmol), **2** (1.25 mmol), sat. aq NH_4OOCH/dioxane (1:1, 0.6 mL), rt. [b] Isolated yield. [c] Only the 1-triazolyl isomer observed. [d] 2-Methylimidazole (4.0 mmol). [e] Only the 1-triazolyl isomer observed. [f] Imidazole (4.0 mmol), HOAc (0.5 mmol).

for 7-azaindole, and the desired product was obtained in 92% yield (**3o**). The structure of **3b** was confirmed by X-ray diffraction analysis.[15]

Encouraged by the above results, we applied this reaction system to other azoles to synthesize various 2-(azol-1-yl)-indole derivatives (**4a**–**g**) in aqueous solution (Table 2). The reactions of 1-methylindole and indole with different azoles proceeded smoothly with good to excellent yields. It was found that, for the 1,2,3-triazole, only the 2-(1-triazolyl)indole isomer **4a** was observed in 81% yield (Table 2, entry 1) when it was treated with 1-methylindole. And only 2-(1-triazolyl)indole isomer **4e** was collected in 93% yield in the case of free indole (Table 2, entry 5). The structure of **4a**, **4b**, and **4e** (Figure 2) had been determined by X-ray diffraction analysis.[15]

To investigate further the effect of the salts in the solvent mixtures, the pH values of some of the reaction mixtures (Table 1, entries 1–6) were carefully monitored during the process of the reaction. The results obtained were shown in Figure 3. It was found that, under the optimized conditions (Table 1, entry 2), the pH value dropped rapidly from 7.0 to 4.7 within 30 min after the I_2 was added, and a slow decline from 4.7 to 3.8 was observed during the remaining reaction time. A control study showed that the pH variation of the solvent was mainly caused by I_2. Similar processes were seen when the solute was changed to pure water, NaOOCH, NH_4Cl, and NH_4OAc, while the pH values were different (Table 1, entries 1 and 3–5). When the reactions proceeded in a saturated NH_4Cl solution or pure water, both pH values were maintained near 1.0 during the reaction, and an oxidation product **5** was observed (Table 1, entries 1 and 4). When the reaction proceeded in saturated NaOOCH and NH_4OAc solutions, after 30 min, the pH values slowly changed from 4.3 to 3.5, and 6.1 to 5.2, respectively, and an iodination product **6** was detected in both conditions (Table 1, entries 3 and 5). These results

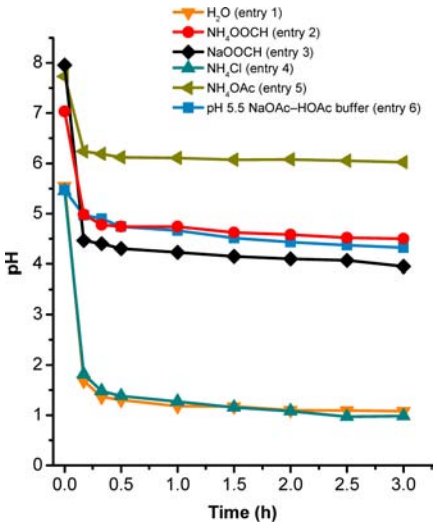


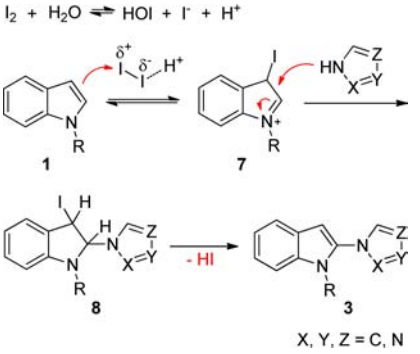
Figure 3. Monitoring the pH values of the reaction mixtures in different solutions for the first 3 h. For a full display over 24 h, see the Supporting Information.

suggested that the direct coupling reaction of indoles with azoles was sensitive to the pH of the reaction mixture. Also, the NH_4OOCH solution might work as a buffer system, which provided an appropriate pH environment for this reaction. A lower or higher pH value accounted for the lower yields. Although buffer NaOAc–HOAc (pH 5.5) gave a similar pH curve with the NH_4OOCH solution during the reaction time from 10 min to 24 h, only a 47% yield of desired product was observed (Table 1, entry 6). This result showed that the two ions, NH_4^+ and $HCOO^-$, were also important for this reaction.

A mechanism for the reaction was proposed (Scheme 2). The reaction was promoted by the H^+ which was produced from a slow reaction between iodine and water.[16]

(16) For example, see: Lengyel, I.; Epstein, I. R.; Kustin, K. *Inorg. Chem.* **1993**, *32*, 5880 and references cited therein.

Scheme 2. Proposed Mechanism



Iodination on C3 produces reactive iminium intermediate **7**. Then the intermediate **7** was trapped by azoles, and the subsequent elimination generated the product **3**.[11,12a]

In conclusion, an efficient and metal-free method for a direct C–N bond formation from indoles and azoles to produce 2-(azol-1-yl)indoles in aqueous solution was developed. The reaction worked on free and alkyl-protected indoles, and a series of novel indole derivatives were prepared by this method. The reaction is highly selective, mild, and environmentally friendly. Application of this method to the synthesis of more complex indole compounds is currently under investigation.

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Supporting Information Available. Experimental procedures, characterization data, NMR spectra for all compounds, and crystallographic data for **3b**, **4a**, **4b**, and **4e** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.