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Synthesis of *N*-aryl-3-(arylimino)-3*H*-indol-2-amines via hypervalent iodine promoted oxidative diamination of indoles

Xinpeng Jiang [a], Guizhou Li [b], Chuanming Yu [a,b,*]

[a] College of Pharmaceutical Sciences, Zhejiang University of Technology, Hangzhou, PR China
[b] Collaborative Innovation Center of Yangtze River Delta Region Green Pharmaceuticals, Zhejiang University of Technology, Hangzhou, PR China

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ABSTRACT

A direct and fast oxidative diamination of substituted indoles with anilines was realized by using 1-fluoro-1,2-benziodoxol-3(1*H*)-one under mild conditions. This protocol could provide a wide range of synthetically valuable *N*-aryl-3-(arylimino)-3*H*-indol-2-amine derivatives under peroxide-free conditions within 30 min in up to 91% yields.

Introduction

Functionalized indoles[1–4] are important synthetic building blocks used in many pharmaceuticals,[5] pesticides,[6] and natural products.[7,8] They also serve as useful structural components in medicinal chemistry due to their high receptor binding affinity.[9,10] Among them, *N*-aryl-3-(arylimino)-3*H*-indol-2-amine derivatives have recently attracted much attention owing to their application in the synthesis of bioactive polymeric indole alkaloids[11] and nitric oxide synthase inhibitors.[12] A few procedures have been established for their synthesis, but most of them involve multi-step transformation, noble transition-metal catalyzed functionalization, or potential dangerous peroxides.[8–12]

Grimshaw reported a two-step synthesis that starting from chlorination of indole-2,3-diones, the product then reacted with excess aniline to afford *N*-aryl-3-(arylimino)-3*H*-indol-2-amines (Scheme 1, Eq. (1)).[13] Tedious operation and environmentally unfriendly reagent are main limitation of this reaction. In 2015, Jiang revealed a palladium catalyzed isocyanides insertion-cyclization strategy. However, the requirement of expensive catalysts, highly toxic isocyanides[14] and harsh reaction conditions restricted its application (Scheme 1, Eq. (2)).[15] Although direct diamination of indoles is an atom-economic approach to synthesize *N*-aryl-3-(arylimino)-3*H*-indol-2-amines, efficient methodologies for oxidative diamination at C2 and C3 position of indoles remain rare.[16–19] As far as we know, the pioneering direct diamination was realized by using iodine and excess peroxides, nevertheless the reaction gave low yields with halogen-substituted anilines (Scheme 1, Eq. (3)).[20] Therefore, developing versatile and mild methods to synthesize *N*-aryl-3-(arylimino)-3*H*-indol-2-amines directly from commercially available indoles are highly valuable.

Hypervalent iodine compounds have been widely applied in organic synthesis as mild and environmentally benign oxidants.[21] Enlightened by $PhI(OAc)_2$ promoted C-2,3 diacetoxylation of *N*-substituted indoles[22] and applications of Togni's reagents,[23–25] we expected that cyclic hypervalent iodine(III) could be used to synthesize *N*-aryl-3-(arylimino)-3*H*-indol-2-amines via oxidative diamination at the C2 and C3 positions of indoles (Scheme 1, Eq. (4)).

Results and discussion

Since the 4-halogen substituted aniline gave low yields in I_2/TBHP system,[20] our initial effort commenced with the reaction of 1*H*-indole **1a** and 4-chloroaniline **2a** under air conditions (Table 1). When $PhI(OAc)_2$ was used, only trace amount of desired product was detected (Table 1, entry 1). To our delight, the use of 1-chloro-1,2-benziodoxol-3-(1*H*)-one gave the desired product (*E*)-*N*-(4-chlorophenyl)-3-((4-chloromophenyl)imino)-3*H*-indol-2-amine **3a** in 60% yield (Table 1, entry 2). However, further improvement of the yield turned out to be very difficult due to the formation of 3-chloro-1*H*-indole. We reasoned that it might be

* Corresponding author at: College of Pharmaceutical Sciences, Zhejiang University of Technology, Hangzhou, PR China.
E-mail address: ycm@zjut.edu.cn (C. Yu).

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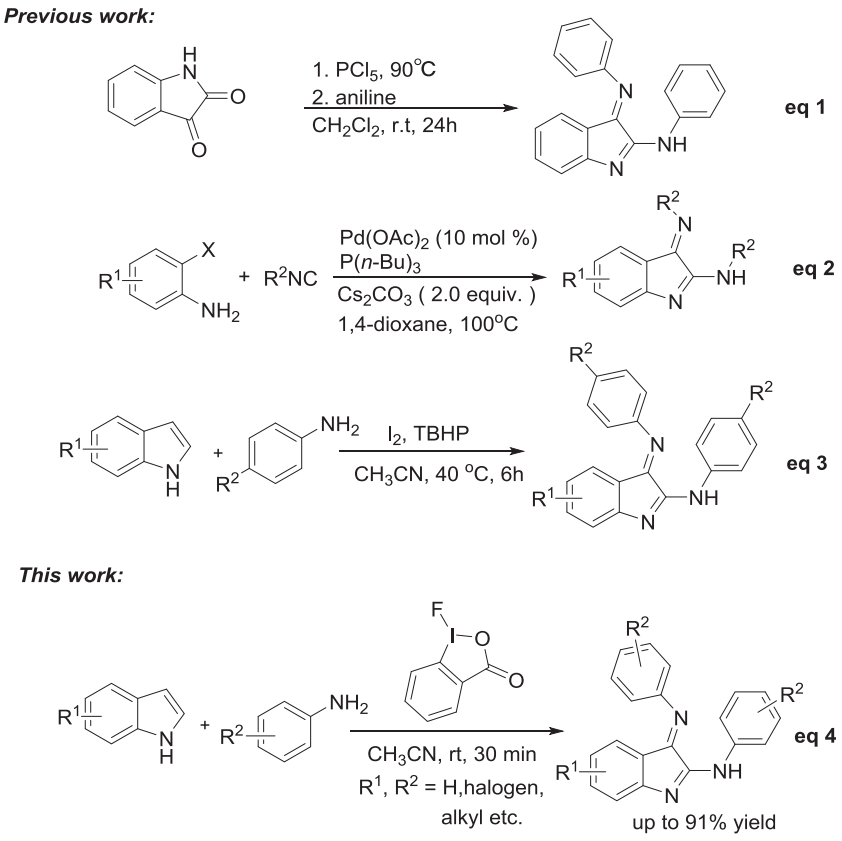

Scheme 1. Design of synthesis of *N*-aryl-3-(arylimino)-3*H*-indol-2-amines.

caused by the chlorine's strong nucleophilicity, which could be solved by replacing chlorine to fluorine. To our delight, the use of 1-fluoro-1,2-benziodoxol-3-(1*H*)-one gave **3a** in 85% yield, without incorporating any fluorine into the final products (Table 1, entry 3). Subsequently, solvent effect was also explored, ethanol, *N*, *N*-dimethylformamide, and nitro methane were evaluated under identical conditions, but led to lower yields (Table 1, entries 4–6). Then we investigated the dosage of hypervalent iodine and **2a**, either increasing or reducing the amount of 1-fluoro-1,2-benziodoxol-3-(1*H*)-one gives inferior result (Table 1, entries 7–9). To further improve the yield of this reaction, extra additives such as K_2CO_3, $NaHCO_3$, Et_3N, or *p*-TsOH·H_2O were added to the reaction system, but gave product **3a** in lower yields (Table 1, entries 10–13). Thus, our optimal reaction conditions were determined as indoles and substituted anilines (2 eq) were reacted with 1-fluoro-1,2-benziodoxol-3-(1*H*)-one (3.5 eq) in CH_3CN under air conditions at room temperature for 30 min.

With optimized reaction conditions in hand, we next investigated the substrate scope of this reaction. As summarized in Table 2, a variety of anilines bearing different substituent were reacted with indole **1a** to give *N*-phenyl-3-(phenylimino)-3*H*-indol-2-amines in good yields. The reaction with aniline proceeded smoothly to give the corresponding product **3b** in 66% yield. Halogen substituent such as —Br was tolerated under the current conditions, which allowed further elaborations of product **3c**. For precursors with electron withdrawing substituent, such as —F and —CN group, the reaction proceeded smoothly gave **3d** and **3e** in excellent yields. Aniline with electron donating methyl group gave **3f** in 67% yield. Compared to *meta*-Cl aniline **2g**, reaction of *ortho*-Cl aniline **2h** require higher temperature and longer time owing to deactivated amino group caused by intramolecular hydrogen bond with *ortho*-Cl. Furthermore, alkyl amines, such as cyclohexanamine and octan-1-amine were also tested, but did not afford desired products under standard conditions.

Encouraged by these results, we further explored the scope of this reaction by evaluating a range of substituted indoles under standard conditions (Table 3). The substituent on indole rings showed significant influence to the yields. For example, when C5 or C7 position of the indole ring was substituted by halogen, the corresponding products could be obtained in good yields (**3j–k** and **3n–o**). Whereas indoles substituted with halogen at C4 or C6 position only gave diamination products in 60–81% yields (**3l**, **3m**, and **3p**). Indoles bearing methyl group at C4 and C5 position gave **3i** and **3s** in moderate yields, while 4- and 5-benzyloxyindole only gave trace amount of corresponding products on account of strong electron donating property and steric hindrance of benzyl group. Furthermore, *N*-methyl substituted indole could also react with aniline and gave **3t** in 62% yield.

To gain an insight of possible reaction mechanism, a control experiment was carried out. As shown in Scheme 2, when radical scavenger TEMPO (2 eq) was added to the reaction mixture, its slightly lower yield ruled out the possibility of radical mechanism. On the basis of our results, a plausible mechanism was outlined in Scheme 3. Initially, intermediate **A**, which was derived from indole **1a** and 1-fluoro-1,2-benziodoxol-3-(1*H*)-one, captured aniline via nucleophilic addition to access intermediate **B**. After elimination of *o*-iodobenzoic acid, 2-amino indole **C** was formed. Next, nucleophilic attack of **C** to 1-fluoro-1,2-benziodoxol-3-(1*H*)-one afforded intermediate **D**, which was then attacked by aniline to form 2,3-diamine indole **E**. Finally, nitrogen atom at C3 position of **E** underwent nucleophilic attack to 1-fluoro-1,2-benziodoxol-3-(1*H*)-one forming intermediate **F**, which would easily afforded the final product **3** after subsequent elimination.