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Iodine-catalyzed Direct Thiolation of Indoles with Thiols Leading to 3-Thioindoles Using Air as the Oxidant

Xiaoxia Liu[1] · Huanhuan Cui[1] · Daoshan Yang[1] · Shicui Dai[1] · Guoqin Zhang[1] · Wei Wei[1] · Hua Wang[1]

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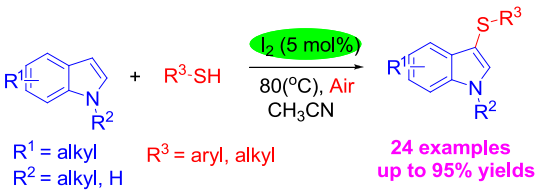
Abstract A simple and convenient method has been developed for the construction of 3-thioindoles via molecular iodine-catalyzed direct thiolation of indoles with thiols. The present protocol, which employs thiols as the thiolating agents, inexpensive molecular iodine as the catalyst, and environmentally benign air as the oxidant, allows the regioselective generation of 3-thioindoles in good to excellent yields.

Graphical Abstract



Keywords Molecular iodine · Thiolation · 3-Thioindoles · Indoles · Thiols

1 Introduction

Indole represents an important class of structural scaffold omnipresent in various natural products, pharmaceutically active compounds and materials [1–8]. In particular, 3-thioindoles constitute a permanent focus of scientific interest since they have a broad spectrum of biological and pharmaceutical activities, such as anti-cancer activity [9], anti-HIV activity [10], anti-bacterial infection [11], anti-obesity [12, 13], and inhibitory activity against tubulin polymerization [14]. For example, compound **I** can be used as inhibitor against 5-lipoxygenase, which may increase the antitumor activity of celecoxib in colorectal cancer [16]; compound **II** is a powerful and selective CRTh2 antagonist [17]; compound **III** is a potent inhibitor of tubulin polymerization, inhibiting the growth of breast cancer cells (Fig. 1) [14, 15, 18].

Because of the importance of such compounds, numerous synthetic methods have been successfully established. Among them, the C3-thiolation of indoles has been exhibited to be the most efficient and extensively explored one. So far, a variety of thiolating agents such as arylsulfenyl halides [19, 20], arylsulfonyl chlorides [21–23], sulfonyl hydrazides [24, 25], diaryl disulfides [26–33], *N*-thiophthalimides [34–37], *O*,*S*-acetals [38, 39], arylsulfonium salts [40, 41], sulfinic acids [42] and Bunte Salts [43] have been employed for C3-thiolation of indoles. Despite the merits of these methods, most of these reactions require an additional step for the synthesis of thiolating reagents. From a synthetic standpoint, the direct use of thiols as thiolating reagents is an effective strategy for constructing 3-thioindoles because of its advantages of low cost, easy availability, and high atom economy. Up to date, a few methods have been reported to synthesize 3-thioindoles from thiols [44–50]. Nevertheless, most of these methods suffer from some limitations such as the need for toxic

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✉ Wei Wei
weiweiqfnu@163.com

✉ Hua Wang
huawang_qfnu@126.com

[1] The Key Laboratory of Life-Organic Analysis and Key Laboratory of Pharmaceutical Intermediates and Analysis of Natural Medicine, School of Chemistry and Chemical Engineering, Qufu Normal University, Qufu 273165, Shandong, China

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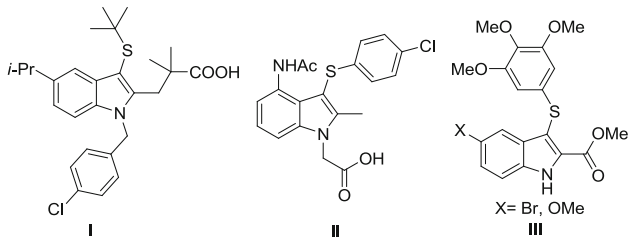
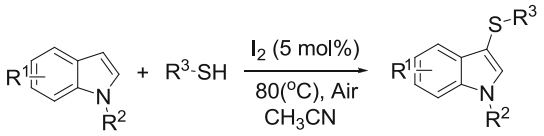


Fig. 1 Biologically active 3-thioindoles



Scheme 1 Molecular iodine-catalyzed regioselective synthesis of 3-thioindoles

metal catalysts, relatively harsh reaction conditions, poor substrate scope, and the use of stoichiometric amounts of base or potentially dangerous oxidants. Therefore, it is still a highly desirable task to develop a convenient and efficient approach to 3-thioindoles directly from thiols.

With our continuous interests in the synthesis of sulfur-containing compounds [51–61], here, we wish to present a simple and efficient synthesis method for the direct thiolation of indoles with various thiols in the presence of inexpensive and environmentally friendly iodine under air conditions (Scheme 1). The present protocol provides a convenient and highly attractive approach to a variety of 3-thioindoles in good to excellent yields, and does not require any metal catalyst, base, or peroxide oxidants.

2 Experimental

2.1 General Information

All commercially available reagents and chemicals were purchased from chemical suppliers and used as received without further purification. All reactions were carried out under air. Column chromatography was performed on silica gel (200–300 mesh). ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra were recorded of samples dissolved in $CDCl_3$ with TMS as internal standard at room temperature. Mass analyses and HRMS were obtained on a Finnigan-LCQDECA mass spectrometer and a Bruker Daltonics Bio-TOF-Q mass spectrometer by the ESI method, respectively.

2.2 General Procedure for Regioselective Synthesis of 3-Thioindoles Under Air

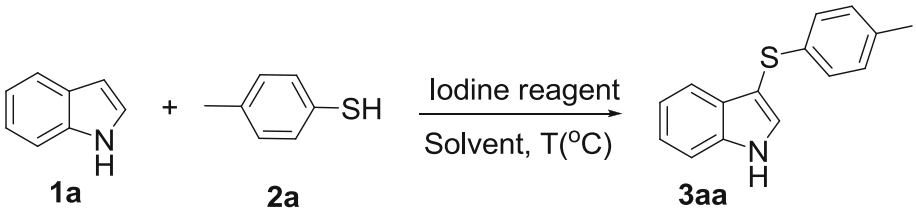
Acetonitrile (2 mL) was added into a mixture of indoles **1** (0.25 mmol), thiols **2** (0.375 mmol) and I_2 (5 mol %) in a 25 mL round-bottomed flack at room temperature under air. The reaction vessel was allowed to stir at 80 °C for 16 h. After the reaction, the solvent was then removed under vacuum. The residue was purified by flash column chromatography using a mixture of petroleum ether and ethyl acetate as eluent to give the desired 3-thioindoles **3**. The characterization of the corresponding products was shown in Supporting Materials.

3 Results and Discussions

In an initial experiment, indole **1a** and 4-methylbenzenethiol **2a** were chosen as the model substrates to optimize the reaction conditions in the presence of various iodine reagents (Table 1, entries 1–4). Among the iodide-containing reagents (20 mol%) examined, molecular iodine was found to be the most efficient catalyst for mediating the formation of product **3aa** in 65 % yield (Table 1, entry 4), others such as NaI, KI, and TBAI did not promote this reaction (Table 1, entries 1–3). Further optimization of catalyst loading showed that 5 mol % of iodide was the best choice, giving the corresponding product **3aa** in 87 % yield (Table 1, entry 8). Moreover, none of product was detected when the reaction was conducted in the absence of molecular iodine (Table 1, entry 10). The screening of various solvents found that CH_3CN was the optimal reaction medium (Table 1, entries 8, 11–17). In contrast, only a trace amount of product **3aa** was detected when reaction was performed in THF, EtOH, or DMF (Table 1, entries 15–17). In addition, the reaction efficiency was obviously low with the decreasing of reaction temperature (Table 1, entries 18–19), and only 17 % yield was obtained when reaction was conducted at room temperature. The appropriate proportion of the indole **1a** and 4-methylbenzenethiol **2a** was 1:1.5 (Table 1, entries 20–22).

Under the optimized conditions, we then examined the scope of the thiolation reactions. As shown in Table 2, generally, aryl thiols bearing an electron-donating group or an electron-withdrawing group on the aryl rings could react smoothly to give the corresponding products in good to excellent yields (**3aa**–**3an**). It should be noted the steric effect of aryl thiols did not affect the yields significantly. The ortho- or meta-substituted aryl thiols were effectively reacted with indole to deliver the desired products (**3ac**–**3aj**) in good yields. Moreover, functionalities such as amino and halogen groups were compatible with this reaction leading to the products **3ag**–**3am**, which are the potential substrates for further transformations. As expected, 2-naphthalenethiol was also tolerated in this process to afford desired product **3ao** obtained in 82 % yield. Notably, various alkyl thiols such as thiophen-3-ylmethanethiol, phenylmethanethiol and 2-phenylethanethiol were

Table 1 Screening of the reaction conditions



Entry	Catalyst (mol%)	Solvent	T (°C)	Yield (%)[a]
1	NaI (20)	CH_3CN	80	0
2	KI (20)	CH_3CN	80	0
3	TBAI(20)	CH_3CN	80	0
4	I_2(20)	CH_3CN	80	65
5	I_2(30)	CH_3CN	80	40
6	I_2(40)	CH_3CN	80	38
7	I_2(10)	CH_3CN	80	68
8	I_2(5)	CH_3CN	80	87
9	I_2(2)	CH_3CN	80	72
10	I_2(0)	CH_3CN	80	0
11	I_2(5)	1,4-Dioxane	80	29
12	I_2(5)	DMSO	80	77
13	I_2(5)	Toluene	80	14
14	I_2(5)	DME	80	10
15	I_2(5)	THF	Reflux	Trace
16	I_2(5)	EtOH	Reflux	Trace
17	I_2(5)	DMF	80	Trace
18	I_2(5)	CH_3CN	25	17
19	I_2(5)	CH_3CN	60	66
20	I_2(5)	CH_3CN	80	73[b]
21	I_2(5)	CH_3CN	80	83[c]
22	I_2(5)	CH_3CN	80	55[d]

Reaction conditions **1a** (0.25 mmol), **2a** (0.375 mmol), Iodine reagent (0–40 mol%), solvent (2 mL), 25–80 °C, 16 h, under air

[a] Isolated yields based on **2a**

[b] **1a** (0.5 mmol), **2a** (0.5 mmol)

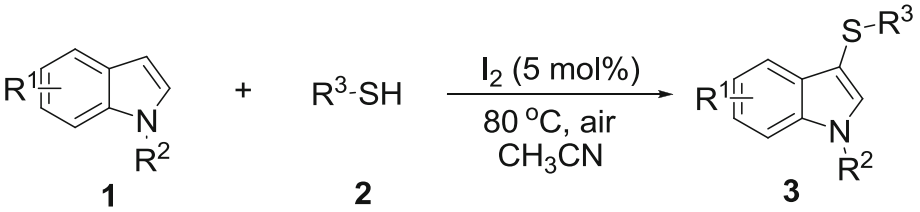
[c] **1a** (0.5 mmol), **2a** (0.6 mmol)

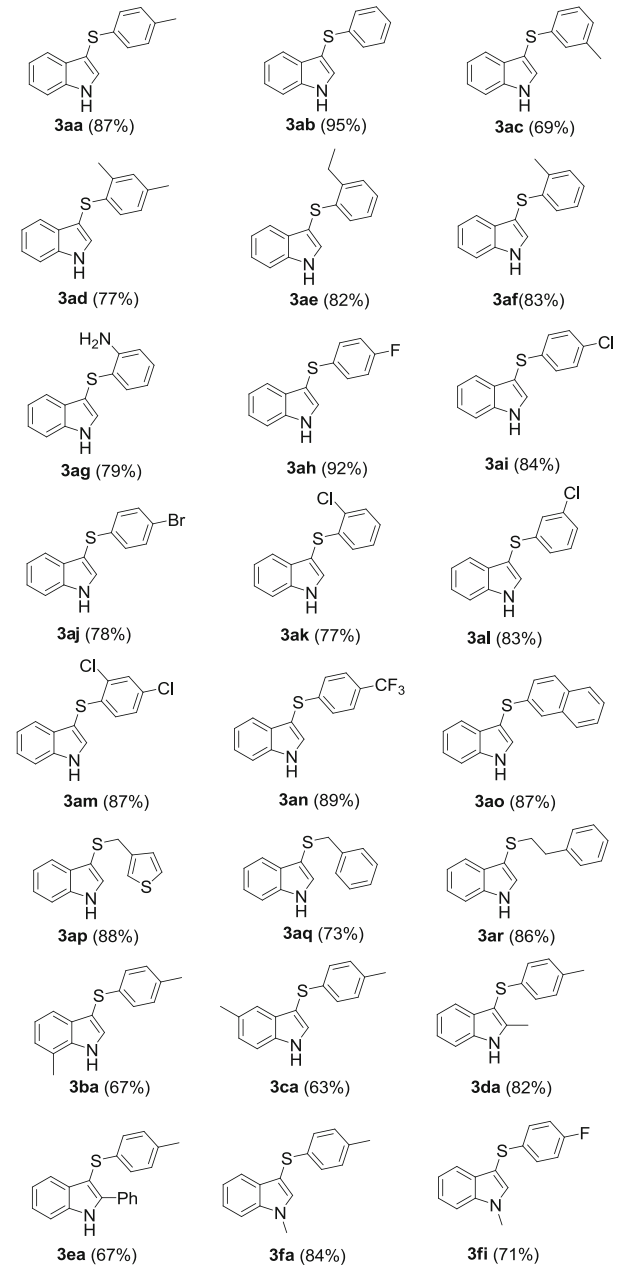
[d] **1a** (0.5 mmol), **2a** (1 mmol)

suitable for this reaction, with the desired products obtained in good yields (**3ap**–**3ar**). With respect to indoles, in addition to 1-H indole, some substituted indoles such as N-methylindole, 2-methylindole, 2-phenylindole, 5-methylindole, and 7-methylindole worked well with this thiolation reaction to generate the corresponding products in good yields (**3ba**–**3ei**).

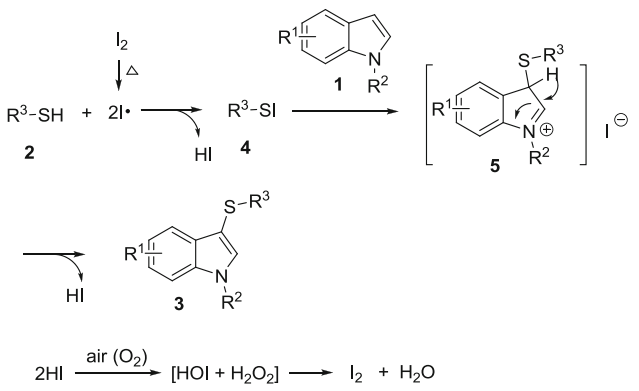
Although the detailed reaction mechanism is still unclear at the present stage, based on the above experiments and previous studies [44–51, 62–71], a possible reaction pathway was proposed as shown in Scheme 2. Initially, the interaction of thiol **2** with molecular iodine would give electrophilic species R3-SI **4** with the concomitant generation of HI [66–71]. Subsequently, the intermediate **5** could be produced by a direct electrophilic substitution of indole **2** with R_3-SI at the C-3 position. Next, the loss of HI from **5** led to the formation of desired product **3**. Finally, the formed two equivalents of HI would be oxidized by air oxygen into molecular iodine to accomplish the catalytic cycle.

Table 2 Results for iodine-catalyzed regioselective synthesis of 3-thioindoles





Reaction conditions **1** (0.25 mmol), **2** (0.375 mmol), I2 (5mol%), CH3CN(2 mL), 80 °C, 16 h
Isolated yields based on **1**



Scheme 2 Postulated reaction pathway

4 Conclusions

In conclusion, a simple and efficient method has been successfully developed for the synthesis of 3-thioindoles via molecular iodine-catalyzed direct thiolation of indoles with thiols using air as the oxidant. In comparison with previous methods, the present protocol, which possesses some advantages of cheap and metal-free catalysts, readily-available starting materials, mild and environmentally friendly reaction conditions. Further studies on the scope and application of this reaction are underway.

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