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Iodine-catalyzed sulfuration of isoquinolin-1(2*H*)-ones applying ethyl sulfinates†

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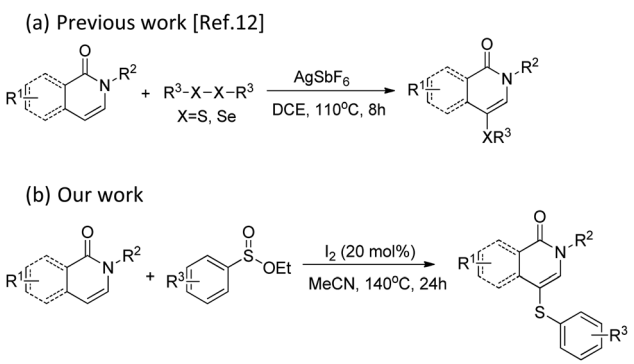
An efficient sulfuration of isoquinolin-1(2*H*)-ones at the C-4 position is reported by employing ethyl sulfinates, and the corresponding products are obtained in moderate to excellent yields in the presence of iodine. This synthetic strategy provides a range of thioether-isoquinolin-1(2*H*)-ones while tolerating a number of functional groups on the isoquinoline nitrogen atom and benzene ring. In addition, pyridin-2(1*H*)-one is also reacted smoothly and afforded the corresponding thioether product in moderate yield. A plausible mechanism is suggested based on the preliminary mechanistic studies.

The construction of carbon–sulfur bonds has gained considerable attention in organic chemistry owing to the prevalence of nitrogen-containing motifs in natural products, pharmaceuticals, agrochemicals, and functional materials.[1] Consequently, many useful and efficient synthetic methods have been developed for the formation of carbon–sulfur bonds. In this regard, many sulfur sources, such as thiol,[2] sulfenyl chloride,[3] disulfide,[4] sulfonylhydrazide,[5] sulfinic acid,[6] sodium sulfinates,[7] *S*-phenyl sulfonothioate[8] and sulfur,[9] have been used to achieve this goal. Although the classical approaches furnished efficient methods, diverse strategies and sulfur sources are still under development, culminating in more useful, economic and environmentally benign synthetic design.

Isoquinolines as a very important class of heterocycles are ubiquitously implicated in a large number of bioactive compounds and natural products.[10] Generally, the introduction of functional groups to the core skeleton is a useful approach for controlling the properties of target molecules, and selective C–H functionalization of isoquinolines developed has provided powerful synthetic access to abundant isoquinolin-1(2*H*)-one derivatives. Recently, the C3, C4 and C8-selective functionalization of isoquinolines was well documented in the literature. For instance, Samanta and co-workers[11] described the catalyst controlled C3 and C8-selective amidation of isoquinolone derivatives. Despite great progress having been achieved, the development of efficient methodologies to generate functional isoquinoline derivatives is still highly desirable and a formidable challenge. Recently, Zhu's group[12] successfully developed a $AgSbF_6$-mediated selective thiolation of isoquinolin-1(2*H*)-ones at the C-4 position (Scheme 1a). Following continuous study of our group on the formation of carbon–sulfur bonds,[13] we herein report the iodine-catalyzed reaction for the formation of C-4 thio isoquinolin-1(2*H*)-ones by employing arylsulfinates.

We commenced our study with 2-methylisoquinolin-1(2*H*)-one **1a** and ethyl 4-methyl benzenesulfinate **2a** as the model substrates to optimize the reaction conditions (Table 1). We were pleased to obtain **3aa** in 22% yield (Table 1, entry 1) when trifluoromethanesulfonic anhydride (Tf_2O) was used as a catalyst in 1,2-dichloroethane (DCE) after 12 h at 25 °C. Then, the reaction was tested under the conditions reported in the previous literature reports,[14] and only disappointing results



Scheme 1 Sulfuration of isoquinolin-1(2*H*)-ones at the C4 position.

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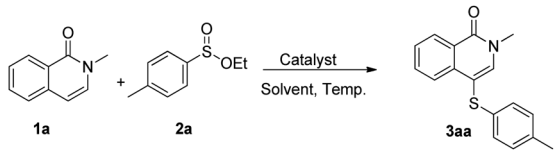
Table 1 Optimization of the reaction conditions[a]



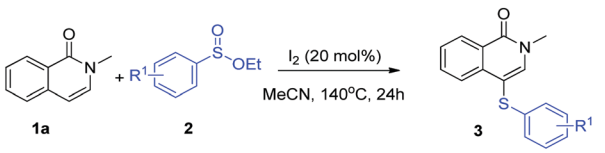
Entry	Catalyst	Solvent	Temp. (°C)	Yield[b] (%)
1	Tf_2O	DCE	25	22
2	NH_4I	DCE	25	NR
3	I_2	DCE	25	Trace
4		EtOH	90	NR
5[c]	NH_4I/1,10-Phen	Dioxane	100	NR
6	I_2	CH_3CN	120	25
7	I_2	DMSO	120	Trace
8	I_2	Dioxane	120	Trace
9	I_2	DMF	120	Trace
10	I_2	Toluene	120	17
11	I_2	CH_3CN	140	38
12[d]	I_2	CH_3CN	140	55
13[d,e]	I_2	CH_3CN	140	75
14[d,f]	I_2	CH_3CN	140	93

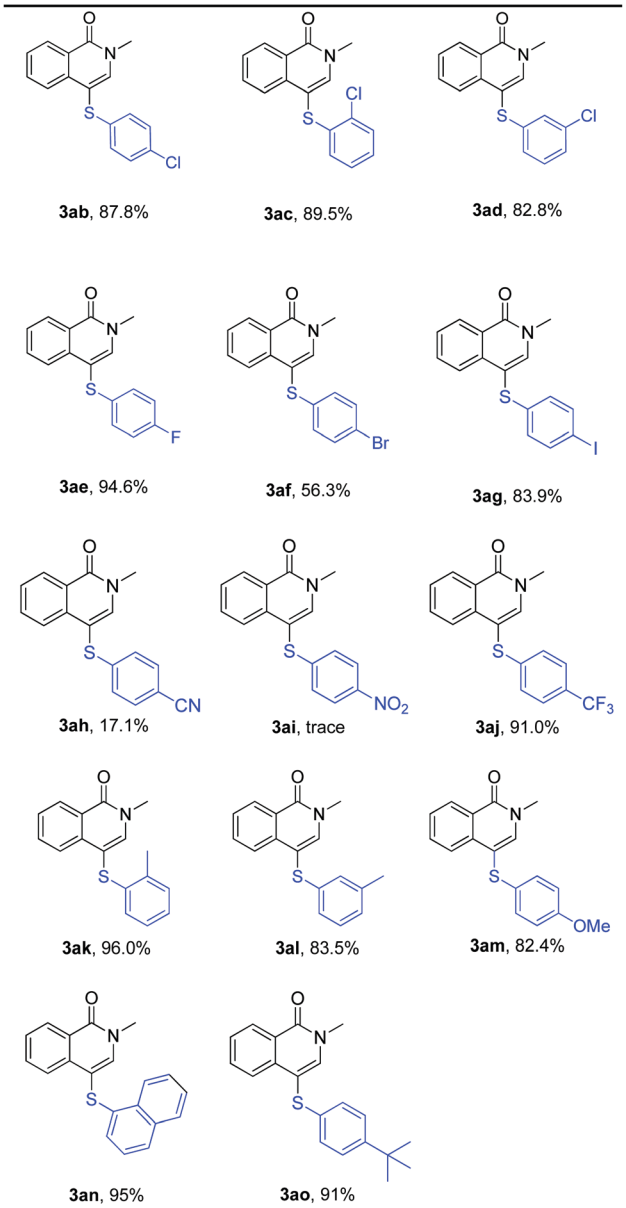
[a] **1a** (0.20 mmol), **2a** (0.20 mmol), catalyst (20 mol%), solvent (2 mL). [b] Isolated yield based on **1a**. [c] For 6 h. [d] **2a** (0.40 mmol). [e] For 16 h. [f] For 24 h.

were observed (Table 1, entries 2–4). To our delight, the reaction performed in CH_3CN afforded the target product **3aa** in 25% yield at 120 °C in the presence of I_2 (Table 1, entry 6). Evaluation of solvents revealed that CH_3CN was superior to dimethylsulfoxide (DMSO), 1,4-dioxane, dimethyl formamide (DMF), and toluene (Table 1, entries 7–10). Furthermore, the yield of **3aa** further improved to 38% by increasing the temperature to 140 °C (Table 1, entry 11), which shows that the temperature has a remarkable influence on the reaction. Increasing the stoichiometric ratio of **2a** to 2 equivalents increased the reaction yield to 55%. However, the substrate **1a** was still observed when the model reaction was performed for 12 hours, and prolonging the reaction time to 16 and 24 hours resulted in yields of 75% and 93%, respectively (Table 1, entries 13 and 14), indicating the influence of reaction time on the progress of the reaction.

With the optimized reaction conditions in hand (Table 1, entry 14), the scope of **2** was then explored by employing various ethyl arylsulfinates to react with isoquinolin-1(2*H*)-one (**1a**) (Table 2). Generally, the aryls with electron-withdrawing and electron-donating groups, such as halogen, trifluoromethyl, methoxy, methyl and naphthyl, reacted smoothly affording the corresponding products in good to excellent yield (Table 2, **3ab–g** and **3aj–o**), and the position of the substituent had no remarkable influence on the reaction (Table 2, **3ab**, **3ac** and **3ad**). A substrate with a *p*-cyano group provided a remarkably low yield of 17%, and the substrate containing a *p*-nitro substituent on the benzene ring did not participate in this protocol. It's worth noting that the bulky substituents, such as naphthyl and tertiary butyl, were well-tolerated affording the corresponding products in 95% and 91%, respectively. The results indicated that the steric hindrance had no obvious effect on this transformation.

Table 2 Synthesis of 2-methyl-4-(phenylthio)isoquinolin-1(2*H*)-one by using different ethyl sulfinates[a,b]

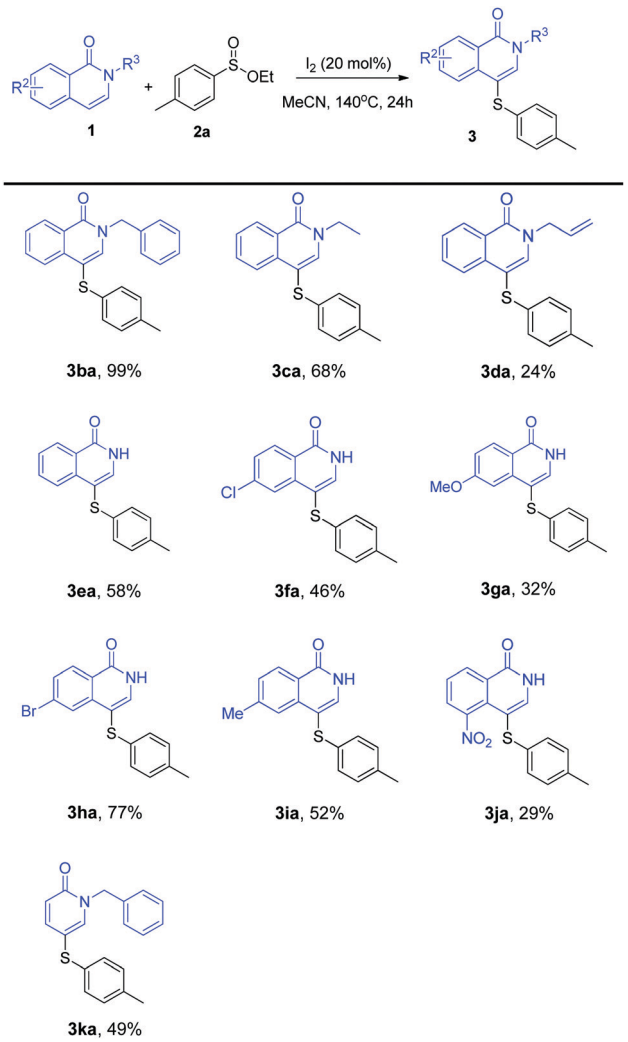




[a] Reaction conditions: **1a** (0.2 mmol), **2** (0.4 mmol), I_2 (20 mol%) and MeCN (2 mL) at 140 °C for 24 hours. [b] Isolated yield based on **1a**.

With respect to the scope of isoquinolin-1(2*H*)-ones, we also evaluated the reaction under standard conditions and the results are summarized in Table 3. First, isoquinolin-1(2*H*)-ones with substituents such as benzyl and ethyl on the N atom were found to be compatible with the reaction conditions, furnishing the desired products in 99% and 68% yields, respectively (Table 3, **3ba** and **3ca**). The substrate with an allyl group

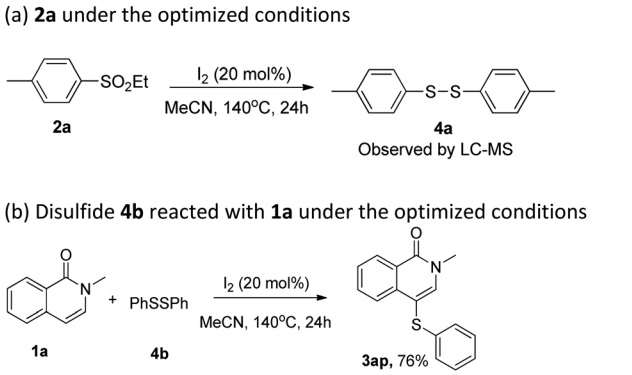
Table 3 Synthesis of 2-methyl-4-(phenylthio)isoquinolin-1(2*H*)-one by using different substituents of isoquinolin-1(2*H*)-one[a,b]



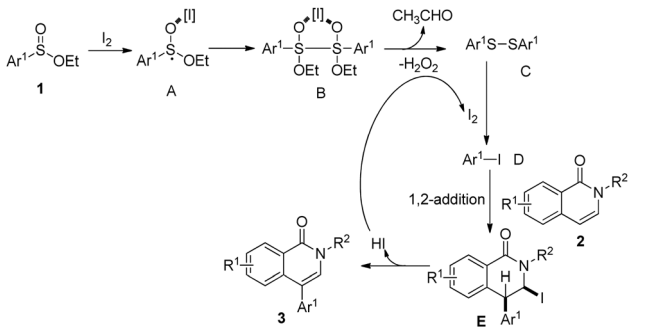
[a] Reaction conditions: **1** (0.2 mmol), **2a** (0.4 mmol), I_2 (20 mol%) and MeCN (2 mL) at 140 °C for 24 h. [b] Isolated yield based on **1**.

at the N atom afforded the corresponding product **3da** in 24% yield. Moreover, the substances devoid of substituents on the N atom were also tolerated under standard conditions, and isoquinolin-1(2*H*)-one gave the product **3ia** in 58% yield. Substrates carrying methyl, chloro, bromo, or methoxy substitution on the benzene ring were also compatible, giving moderate to good yields (Table 3, **3fa**, **3ga**, **3ha** and **3ia**). However, the nitro-substituted isoquinolin-1(2*H*)-one transformed into the corresponding products **3ja** in lower yield. Gratifyingly, a pyridin-2(1*H*)-one such as 1-benzylpyridin-2(1*H*)-one was successfully converted to the product **3ga** in satisfactory yield of 49%.

In order to understand the reaction mechanism, some control experiments were performed (Scheme 2). When **2a** was performed under optimized reaction conditions, the intermediate product **4a** was observed by liquid chromatography–mass spectrometry (LC–MS). The formation of **4a** in a similar kind of reaction had been reported in the previous literature.[15]



Scheme 2 Primary mechanism studies.



Scheme 3 Plausible mechanism.

Furthermore, 2-methylisoquinolin-1(2*H*)-one (**1a**) was treated with 1,2-diphenyldisulfane **4b** giving the product **3ap** in 76% yield. These results suggest that the disulfide is the key intermediate in this catalytic process.

On the basis of our experimental results and previous studies, a plausible mechanism is proposed and illustrated in Scheme 3. Initially, ethyl sulfinate is activated by iodine to give complex **A** which is then transformed into dimer intermediate **B** through free radical polymerization. The dimer **B** then undergoes reductive elimination to afford disulfide **C** by releasing acetaldehyde and hydrogen peroxide.[16] In the next step, the intermediate **C** splits into the active iodide species **D** in the presence of I_2,[17] leading to the formation of intermediate **E** through regioselective electrophilic attack by **2**. Finally, the desired product **3** is afforded by elimination of HI from the intermediate **E**.

Conclusions

In summary, we developed a direct and efficient I_2-mediated sulfuration of isoquinolin-1(2*H*)-ones at the C4-position by using ethyl sulfinates. This reaction has a broad scope of substrates and affords the target products in good to excellent yields. Furthermore, a plausible mechanism was proposed based on our experimental results as well as previous reports. The protocol provides a method to access sulfuration of isoquinolin-1(2*H*)-ones, and ethyl sulfinates proved to be an alternate sulfuration reagent in synthetic organic chemistry.

Experimental section

General procedure for the sulfuration of isoquinolin-1(2*H*)-ones

A mixture of isoquinolin-1(2*H*)-ones (0.2 mmol), ethyl sulfinate (0.4 mmol) and I_2 (20 mol%) in MeCN (2 mL) was taken in a sealed tube, and the reaction mixture was stirred for 24 h at 140 °C. After completion, the reaction mixture was cooled, the solvent was evaporated and the crude product was purified by column chromatography with PE/EA = 3/1 as the eluent on silica gel to afford product **3**.

Conflicts of interest

There are no conflicts to declare.

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