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$K_2S_2O_8$/Arenesulfinate: an Unprecedented Thiolating System Enabling Selective Sulfenylation of Indoles under Metal-Free Conditions†

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An unprecedented thiolating system $K_2S_2O_8$/arenesulfinate is described for selective sulfenylation of indoles in CH_3CN/H_2O. This metal-free strategy enables a simple, efficient and environment-benign approach to the pharmaceutically important candidates, 3-arylthioindoles. Catalytically reactive halogen and aryl groups are well tolerated.

Indole scaffold is a prominent and privileged functionality occurring in many biologically important compounds,[1] and consequently, it has been attracting considerable attentions from synthetic chemists to develop strategies for the construction and chemical modification of the indole ring.[2] Among these strategies, the sulfenylation of indoles is particularly attractive owing to the promising therapeutic applications of the resulting thiolated indoles, in which the 3-sulfanylindoles could serve as potential candidates for the treatment of cancer,[3] HIV,[4] allergies,[5] and heart disease (Figure 1).[6]

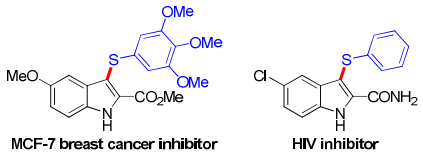
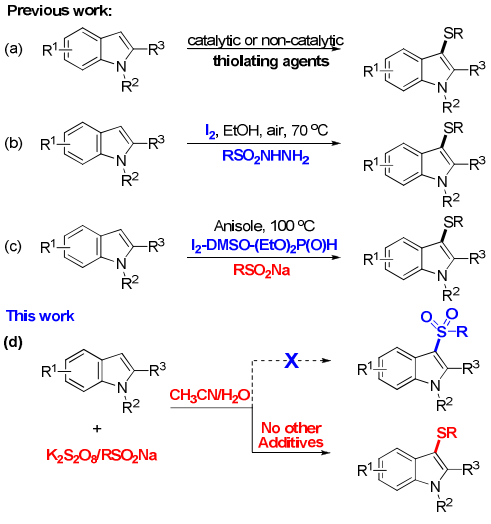


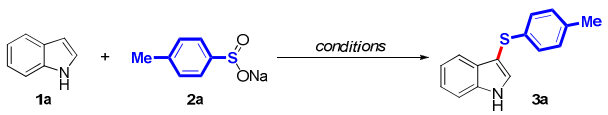
Figure 1. Examples of thiolated indoles with biological activities

Conventional methods for the syntheses of 3-sulfanylindoles rely on the transition-metal-catalyzed cross-couplings between 3-(pseudo)halogenated indoles and thiols.[7] Given the electron-rich nature of indole rings, direct C-H sulfenylation of indoles with electrophiles has aroused much more interests in recent years due to their advantages from both step- and atom-economy points of view in industrial and green chemistry. In this regard, a variety of thiolating agents such as thiols, disulfides and activated sulphur reagents were employed with the C-H sulfenylation occurring smoothly catalyzed by vanadium,[8] magnesium,[9] iron,[10] cerium,[11] copper,[12] palladium[13] and ruthenium catalysts.[14] Some intriguing achievements *via* direct C-H sulfenylations to 3-thioindoles were further developed under metal-free conditions (Scheme 1a).[15] For instance, disulfides as the thiolating agents promoted by *N*-bromosuccinimides,[16] carbonates,[17] persulfate[18] and I_2[19] displayed efficient reactivities in the absence of any transition metals. Very recently, sulfonyl hyrazide has been proved to be a successful sulfenylation agent with catalytic amount of I_2 molecule (Scheme 1b).[20] Besides, Deng[21] and other groups[22] found that arenesulfinates can also undergo sulfenylation reactions with indoles using molecule I_2 as the organocatalyst similarly (Scheme 1c). But it should be noted that DMSO and phosphite or phosphine are crucial for the deoxygenation of arylsulfonyl to arylthio group when using arenesulfinate as the thiolating agent, and thus might give off unpleasant odors (for dimethyl sulfide was generated from DMSO). Therefore, it is still desirable to explore cheaper, simpler and more environment-friendly sulfenylation systems for the syntheses of 3-sulfanylindoles. It is well known that $K_2S_2O_8$ can play as a radical initiator to generate sulfonyl radicals from sulfinates,[23] however, to the best of our knowledge, no examples were given that $K_2S_2O_8$ acted as promoters for deoxygenation reactions. *Herein, we disclose an unprecedented thiolating system, $K_2S_2O_8$/arenesulfinate, for the direct selective sulfenylation of indoles, affording 3-arylthioindoles in moderate to excellent yields in CH_3CN/H_2O (v/v ratio 10:1) without any other additives (Scheme 1d).*



Scheme 1. C3-sulfenylation of indoles with various thiolating systems

Table 1. Optimization of reaction conditions.[a]



Entry	Cat. (mol%)	[Ox] (equiv.)	Solvent	Temp. (°C)	Yield[b] (%)
1	TBAB (10)	$TBHP^{dec}$ (2.0)	CH_3CN	100	0
2	TBAI (10)	$TBHP^{dec}$ (2.0)	CH_3CN	100	Trace
3	TBAI (10)	$TBHP^{aq}$ (2.0)	CH_3CN	100	<10
4	TBAI (10)	$K_2S_2O_8$ (2.0)	CH_3CN	100	20
5	-	$K_2S_2O_8$ (2.0)	CH_3CN	100	32
6	-	$K_2S_2O_8$ (1.0)	CH_3CN	100	46
7	-	$(NH_4)_2S_2O_8$ (1.0)	CH_3CN	100	37
8	-	$Na_2S_2O_8$ (1.0)	CH_3CN	100	41
9	-	Oxone (1.0)	CH_3CN	100	41
10	-	$K_2S_2O_8$ (1.0)	EtOAc	100	<10
11	-	$K_2S_2O_8$ (1.0)	DMF	100	35
12	-	$K_2S_2O_8$ (1.0)	*p*-dioxane	100	0
13[c]	-	**$K_2S_2O_8$ (1.0)**	**CH_3CN/H_2O**	**100**	**89**
14[c]	-	$K_2S_2O_8$ (1.0)	CH_3CN/H_2O	120	81
15[c]	-	$K_2S_2O_8$ (1.0)	CH_3CN/H_2O	80	74
16[c,d]	-	$K_2S_2O_8$ (1.0)	CH_3CN/H_2O	100	70
17[e]	-	$K_2S_2O_8$ (1.0)	CH_3CN/H_2O	100	71
18[c]	-	$K_2S_2O_8$ (0.5)	CH_3CN/H_2O	100	65
19[c]	-	$K_2S_2O_8$ (1.0)	CH_3CN/H_2O	100	88[f], 76[g]

[a] Reaction conditions: indole (0.2 mmol), *p*-tolylsulfinate (0.3 mmol, 1.5 equiv.), solvent (1.0 mL), reaction time (24 h), under N_2. [b] Isolated yield. [c] CH_3CN/H_2O 10:1 (*v/v* ratio). [d] Under air. [e] CH_3CN/H_2O 1:1 (*v/v* ratio). [f] *p*-Tolylsulfinate (0.4 mmol, 2.0 equiv.). [g] *p*-Tolylsulfinate (0.1 mmol, 0.5 equiv.). cat. = catalyst, [Ox] = oxidant, Temp. = temperature, TBAB = tetra-*n*-butylammonium bromide, TBAI = tetra-*n*-butylammonium iodide, $TBHP^{dec}$ = *tert*-butyl hydroperoxide (5.0-6.0 M in decane), $TBHP^{aq}$ = *tert*-butyl hydroperoxide (70% aqueous solution).

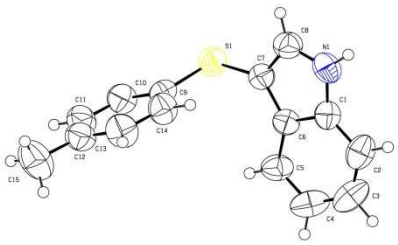
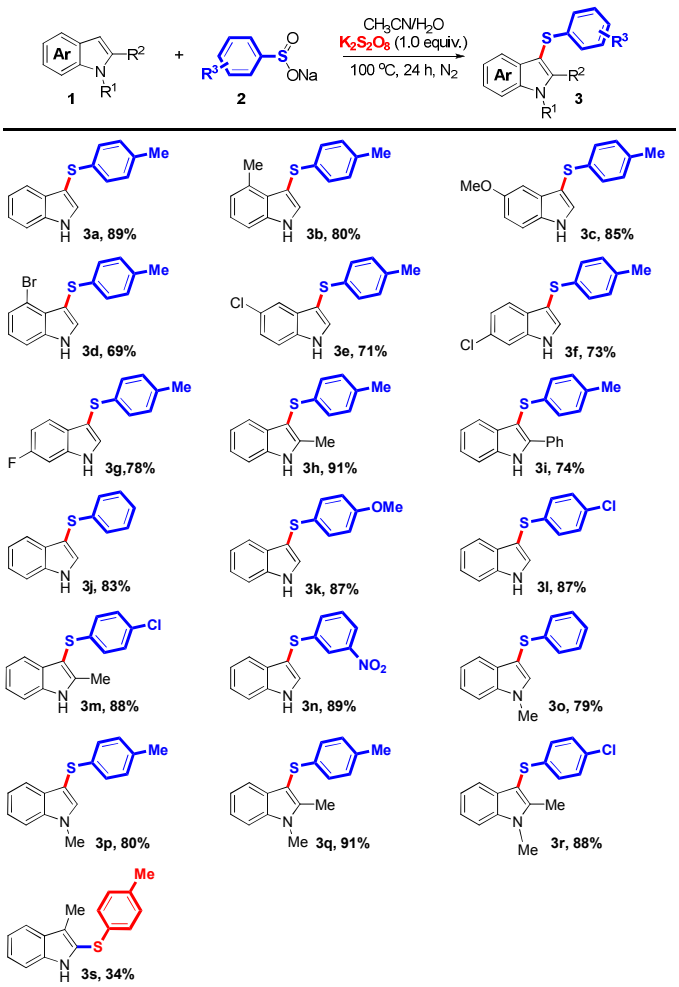


Figure 2. Structure of compound **3a** determined by X-Ray diffraction.

Since ammonium halide/TBHP organocatalytic system has already been proved to be efficient for C-H functionalizations by our group,[24] the direct C-H sulfenylation of indole (1.0 equiv.) was commenced by testing different ammonium halides at 100 °C under inert atmosphere, with TBHP as the oxidant, *p*-tolylsulfinate (1.5 equiv.) as the sulfenylation (or sulfonylation) agent, and CH_3CN (1.0 mL) as the solvent. As screened in Table 1, either TBAB/TBHP or TBAI/TBHP as the organocatalytic system afforded nearly full recovery of indole (Table 1, entries 1-3), while the unexpected product **3a**, 3-*p*-tolylthioindole (Figure 2), was obtained in 20% isolated yield if replacing TBHP with $K_2S_2O_8$ (2.0 equiv.) (entry 4). Inspiringly, the reaction efficiency increased to 46% when only subjecting $K_2S_2O_8$ (1.0 equiv.) to the reaction system (entries 5-6).

Table 2. Direct C-H sulfenylation of indoles to 3-sulfanylindoles with $K_2S_2O_8$/arenesulfinates as the thiolating system.[a]

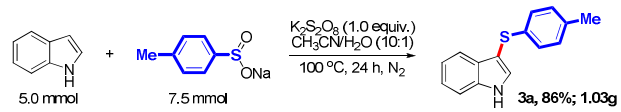


[a] Reaction conditions: indole (0.2 mmol), arenesulfinate (0.3 mmol, 1.5 equiv.), $K_2S_2O_8$ (0.2 mmol, 1.0 equiv.), CH_3CN/H_2O (1.0 mL, *v/v* ratio 10:1), reaction temperature (100 °C), reaction time (24 h), under N_2. Isolated yields were given unless otherwise noted.

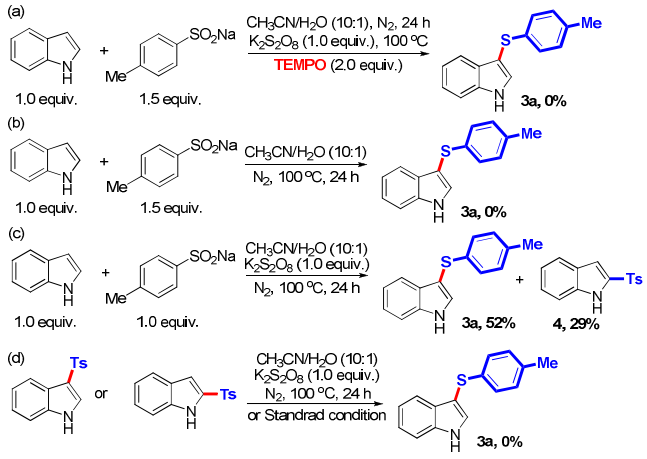
Since persulfate could greatly improve the direct C-H sulfenylation of indole, several persulfates such as $(NH_4)_2S_2O_8$, $Na_2S_2O_8$ and oxone were tested and particularly $K_2S_2O_8$ gave the highest (46%) yield of product **3a** (entries 6-9). In the meanwhile, the efficiency of the direct sulfenylation shows a strong dependence on solvents. For example, a sharp decrease was observed when using EtOAc or DMF as the solvent (entries 10-11). Moreover, even no sulfenylation product was observed when conducting the reaction in *p*-dioxane (entry 12). Fortunately, a small amount of water (*v/v* ratio to CH_3CN 1:10) enhanced the reaction efficiency dramatically, giving **3a** in the highest yield of 89% among all the solvents examined (entry 13). Other endeavours to improve the yield of **3a** were attempted, such as altering the reaction temperature, reducing the loading of $K_2S_2O_8$, running the reaction in air atmosphere or loading different amounts of reagent *p*-tolylsulfinate, but none of them could lead to higher sulfenylation reactivity (entries 14-19).

With the optimized reaction conditions in hand, the substrate scope was explored at 100 °C for 24 h under N_2 atmosphere, using $K_2S_2O_8$/arenesulfinate as the thiolating system and CH_3CN/H_2O (*v/v* ratio 10:1) as the solvent. As summarized in Table 2, free NH-

indoles that might exhibit site-selectivity challenges were reacted with *p*-tolylsulfinate to the corresponding 3-arylthioindoles exclusively in good to excellent yields (Table 2, *cf.* **3a-g**). Indoles with electron-donating substituents such as methyl and methoxyl groups (*cf.* **3b-c**) exhibited higher reactivities over that with electron-withdrawing groups such as fluoro, chloro and bromo groups (*cf.* **3d-g**). To some extent, the sulfenylation efficiency is affected by steric hindrance, for example, 4-methylindole as the substrate afforded slightly lower yield than indole did (*cf.* **3a-b**). Other arylsulfinates bearing electron-donating group (e.g. methoxy group) or electron-withdrawing groups (e.g. chloro and nitro group) were also tested, and all of them reacted smoothly with indoles, yielding the desired 3-arylthioindoles highly efficiently (*cf.* **3j-n**). Besides, *N*-protected indoles could couple with arenesulfinates effectively as well (*cf.* **3o-r**). The availability of 3-substitued indoles for this sulfenylation strategy was also explored, and the desired 3-methyl-2-(*p*-tolylthio)indole product from 3-methylindole was obtained, albeit in a much lower yield (*cf.* **3s**).[25] Particularly, it is noteworthy that the tolerance of catalytically reactive substituents such as halides and phenyl groups enables further chemical modifications of the desired 3-arylthioindoles (*cf.* **3d-g**, **3i**, **3k-n** and **3r**), and thus promises the discovery of various 3-sulfanylindoles with important therapeutic value. To investigate the practical application of this transformation in organic synthesis, we conducted gram-scale synthesis of **3a**. The desired product was produced without any significant decrease in efficiency (86% versus 89% for the reaction on a 0.2 mmol scale for **3a**; Scheme 2).



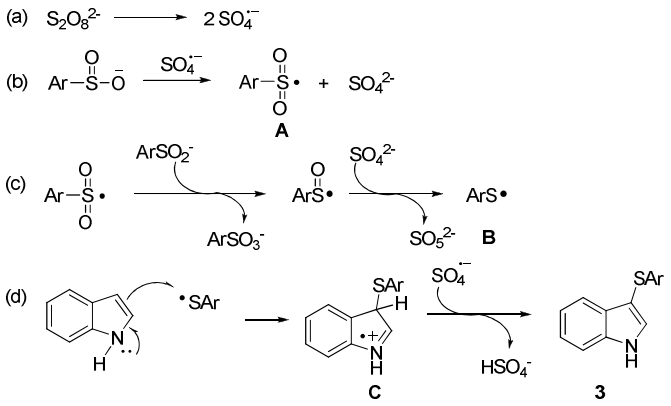
Scheme 2. Gram-scale synthesis of **3a**



Scheme 3. Control experiments

To gain some insights into the sulfenylation pathway with this unprecedented thiolating system, some control experiments were conducted under various reaction conditions. As $S_2O_8^{2-}$ usually serves as a radical initiator at elevated temperature,[26] the radical process is a preferred consideration. Therefore, a radical-trapping experiment was carried out by introducing TEMPO into the standard conditions (Scheme 3a). And indeed, the desired sulfenylation reaction did not occur, thus indicating that this transformation is likely to involve a radical intermediate. Meanwhile, the reaction also did not take place in the absence of $K_2S_2O_8$ (Scheme 3b), whereas it afforded only 52% of the desired product **3a** and 29% of the undesired product 2-*p*-tosylindole **4** when employing only 1.0 equivalent of *p*-tolylsulfinate (Scheme 3c). These observations suggest that both $K_2S_2O_8$ and excess amount of arenesulfinates are necessary for the radical sulfenylation reaction, and most importantly, arylsulfonyl radical is involved in this process. Furthermore, deoxygenation of 3-*p*-tosylindole (or 2-*p*-tosylindole) with $K_2S_2O_8$ (1.0 equiv.) in CH_3CN/H_2O (*v*/*v* ratio 10:1) or under standard reaction conditions was conducted to explore that whether 3-arylsulfonylindole (or 2-arylsulfonylindole) is the key intermediate for this sulfenylation strategy, but unfortunately, full recovery of the starting material was observed (Scheme 3d). This result indicates that the tosylated indole is unlikely to serve as the key intermediate in the sulfenylation pathway, and arylsulfonyl radical most probably undergoes deoxygenation to arylthio radical (or cation) before finally introduced to indole ring.

Based on previous work[23,27] and the above results, a tentative mechanism for this unprecedented sulfenylation reaction is proposed in Scheme 4. The reaction is initiated via the homolysis of $K_2S_2O_8$ to radical anion $SO_4^{\bullet-}$ (scheme 4a), which could promote the formation of arylsulfonyl radical **A** upon reaction with arenesulfinate (Scheme 4b), and the resulting radical A undergoes deoxygenation with excess amount of arylsulfinate and SO_4^{2-} to afford arylthio radical **B** (Scheme 4c). The radical addition of **B** to indole ring gives intermediate **C**, which is believed to undergo the direct deprotonation to release the final product **3** (Scheme 4d). (However, multiple pathways may be involved in this transformation. A thorough mechanistic study is needed to unravel the mechanistic intricacies of this process, especially for the generation of arylthio radical **B**.)



Scheme 4. Proposed mechanism

In conclusion, we have developed a cheap, simple and efficient strategy for direct C3-sulfenylation of indoles. This strategy employs $K_2S_2O_8$/arenesulfinate as the unprecedented thiolating system and CH_3CN/H_2O as the solvent without any other additives. It shows good tolerance towards carbon-halogen and aryl functionalities, thus promises further modifications of the desired 3-arylthioindoles. As such, the simplicity, high efficiency and environment-friendliness associated with this protocol suggest its potential for widespread use in the construction of pharmaceutically important molecules 3-arylthioindols. Further investigations to elucidate the detailed mechanism and synthetic applications of this efficient and practical sulfenylation protocol are currently underway in our lab.

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Notes and references

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†Electronic Supplementary Information (ESI) available: General procedure for synthesis, characterization data, and ^{1}H and ^{13}C NMR spectra of compounds. See DOI: 10.1039/c000000x/

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25 A reaction mixture of 2-methylindole (0.2 mmol), 3-methylindole (0.2 mmol), $K_2S_2O_8$ (0.2 mmol, 1.0 equiv.) and *p*-tolylsulfinate (0.3 mmol, 1.5 equiv.) in CH_3CN/H_2O (1.0 mL, *v/v* ratio 10:1) was stirred at 100 °C under N_2 atmosphere. In 24 h, product 2-methyl-3-*p*-tolylthioindole (**3h**) was isolated in 87%, while product 3-methyl-2-*p*-tolylthioindole (**3q**) in less than 5%.
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One Sentence:

Direct selective sulfenylation of indoles is disclosed via an unprecedented deoxygenation of arylsulfonyl radical only under $K_2S_2O_8$/arenesulfinate system in CH_3CN/H_2O.

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