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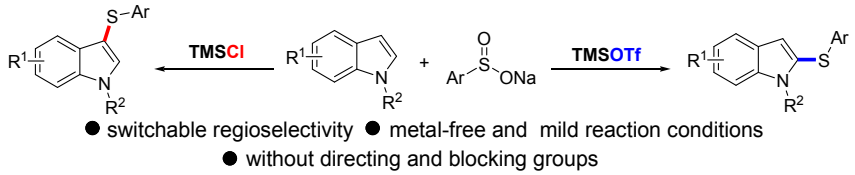
Graphical Abstract

Switchable regioselection of C-H thiolation of indoles using different TMS counterions

Yuan-Zhao Ji, Hui-Jing Li, Jin-Yu Zhang, and Yan-Chao Wu



Simply swapping the counteranions of TMS leads to a switchable regioselectivity in C2– and C3–H thiolation of indoles.

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Switchable regioselection of C-H thiolation of indoles using different TMS counterions

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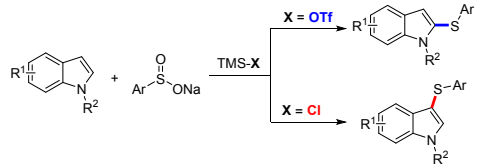
Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

A switchable regioselectivity in C–H thiolation reaction by simply swapping the counteranions of TMS is reported here for the first time. An exclusive C3–H thiolation of indoles with sodium arylsulfinates was achieved in the presence of TMSCl as promoter. In contrast, with the use of TMSOTf instead of TMSCl under otherwise identical conditions, a regiospecific C2–H thiolation of indoles was realized with the same set of substrates.

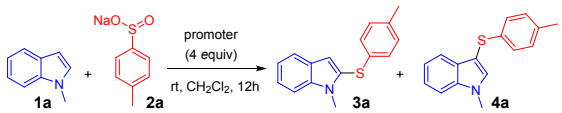
Because of the synthetic versatility of organosulfur compounds in organic synthesis,[1] C–H thiolation has become one of the most important C–H functionalization transformations and attracted considerable attention in the past decade.[2] The C–H thiolation of aromatic compounds with sulfur-based reagents could be achieved in the presence of certain transition metals such as palladium,[3] copper,[4] iron[5] and others.[6] Metal-free C–H thiolation of arenes and heteroarenes has also been developed with the use of thiols,[7] sulfonyl hydrazides[8] and sulfinate salts[9] etc[10] as the sulfenylating reagents. Usually, C–H thiolation of indoles proceeds at the C3 position. In contrast, C2–H thiolation of indoles is difficult, which has been accomplished by using special strategies such as blocking the C3 position,[11] introducing a directing group at the N1 position,[12] removing the proton at the C2 position[13], and using a *N*-(thio)succinimide/TFA reaction system.[14] Despite these advances, switchable reaction to assemble 2-thioindoles and 3-thioindoles with the same set of simple and readily accessible starting materials is still one of the most challenging tasks for synthetic chemists. It is worth noting that sodium arylsulfinates are still not used for the C2–H thiolation of indoles to date. However, sodium arylsulfinates are stable, odorless and easy-to-handle sulfur compounds, and thus are the desirable sulfur sources for the construction of C–S bonds.[2c,15] In this context, we would like to report here a regioselectivity-switchable C–H thiolation of indoles with sodium arylsulfinates just by simply swapping the counteranions of TMS (Scheme 1). Herein, indoles appeared to serve the dual role of the substrates and reduction agents.



Scheme 1. Switchable C–H thiolation of indoles with sodium arylsulfinates.

Reaction of 1-methyl-1*H*-indole (**1a**) with sodium 4-methylbenzenesulfinate (**2a**) was used as a probe for evaluating the reaction conditions, and the representative results (for details, please see ESI, Tables S1–S2) are summarized in Table 1. The C–H thiolation of indole **1a** with sodium arylsulfinate **2a** went smoothly in the presence of TMSOTf to afford exclusively

Table 1. Optimization of the reaction conditions[a]



Entry	Promoter	Yield **3a** (%)[b]	Yield **4a** (%)[b]
1	TMSOTf	80 (78[c])	N.D.
2	TMSCl	N.D.	83 (80[c])
3	Me_2SiHCl	N.D.	75
4	$TMSCF_3$	N.R.	N.R.
5	Et_3SiH	N.R.	N.R.
6	Ph_3SiH	N.R.	N.R.
7	TfOH	60	N.D.
8	*p*-TsOH	N.D.	48

[a] General conditions: **1a** (0.5 mmol), **2a** (0.2 mmol), and promoter (0.8 mmol) in CH_2Cl_2 (1.0 mL) at 25 °C for 12 h. [b] The yield was determined by ^1H NMR spectroscopy using 0.2 mmol of CH_2Br_2 as a standard. [c] Isolated yield. N.D. = no detection. N.R. = no reaction.

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† Footnotes relating to the title and/or authors should appear here.
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

C2-thioindole **3a** in a good yield (entry 1). However, a regiospecific C–H thiolation reaction took place to give C3-thioindole **4a** in 83% and 75% yields, respectively with the use of TMSCl and Me_2SiHCl instead of TMSOTf (entries 2–3). With the use of other silica promoters such as $TMSCF_3$, Et_3SiH and Ph_3SiH, no reaction take place and the starting materials could be recovered (entries 4–6). Other promoters such as TfOH and *p*-TsOH could also execute this reaction but with lower efficiencies (entries 7–8). Finally, the optimal C2–H thiolation reaction conditions to obtain C2-thioindole **3a** as follows: indole **1a** (2.5 equiv), sodium arylsulfinate **2a** (1.0 equiv), and TMSOTf (4.0 equiv) in CH_2Cl_2 at 25 °C for 12 h and the optimal C3–H thiolation reaction conditions to obtain C3-thioindole **4a** as follows: indole **1a** (2.5 equiv), sodium arylsulfinate **2a** (1.0 equiv), and TMSCl (4.0 equiv) in CH_2Cl_2 at 25 °C for 12 h.

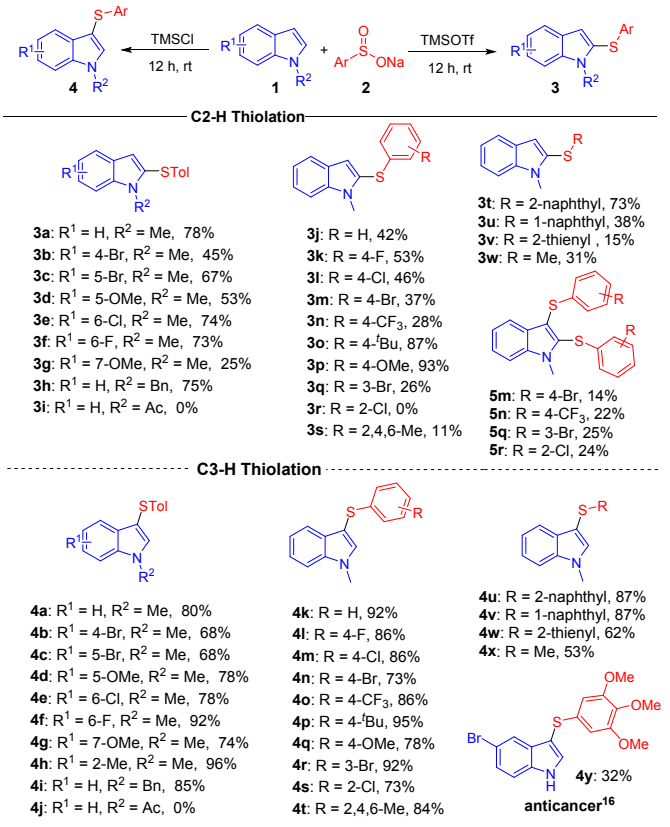
With the optimized reaction conditions in hand, the substrate scope for the C2- and C3-H thiolation reactions was investigated with a series of indoles and sodium arylsulfinates (Scheme 2). In the C2-H thiolation reaction (Scheme 2), indoles with electron-donating and electron-withdrawing substituents at their 4-, 5-, 6- and 7-positions as well as *N*-substituted indoles were all suitable substrates, and the desired C2-thioindoles **3a–g** and **3h** were obtained in moderate to good yields. Treatment of *N*-acetylindole with sodium arylsulfinate **2a** failed to give C2-thioindole **3i**. Sodium arylsulfinates **2**, with their aromatic rings bearing hydrogen atoms, electron-withdrawing and electron-donating groups, reacted smoothly with sodium arylsulfinate **2a** to afford C2-thioindoles **3j–q** and **3s** in moderate to excellent yields. 2,3-Bis-thioindoles **5m–n** and **5q–r** were observed as the reaction intermediates in some of the above C2-thiolation reactions. 2-naphthyl-, 1-naphthyl-, 2-thienyl- and methyl-substituted sodium sulfinates reacted smoothly with indole **1a** to afford C2-thioindoles **3t–w** in moderate to good yields.

In the C3-H thiolation reaction (Scheme 2), indoles **1**, with substituent groups such as methoxy, halogen and methyl at their 2-, 4-, 5-, 6- and 7-positions, reacted smoothly with sodium arylsulfinate **2a** to give C3-thioindoles **4a–i** in good to excellent yields. Treatment of *N*-acetylindole with sodium arylsulfinate **2a** failed to give C3-thioindole **4j**. Sodium arylsulfinates **2**, with their aromatic rings bearing hydrogen atoms, electron-donating and electron-withdrawing groups, reacted well with indole **1a** to afford C3-thioindoles **4k–t** in good to excellent yields. 2-naphthyl-, 1-naphthyl-, 2-thienyl- and methyl- substituted sodium sulfinates reacted well with indole **1a** to afford C3-thioindoles **4u–x** in good yields.

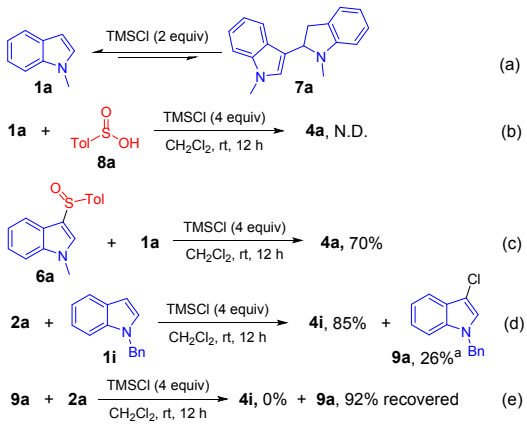
To demonstrate the practicability of this reaction, 5-bromo-3-((3,4,5-trimethoxyphenyl)thio)-1*H*-indole (**4y**), a known lead anticancer compound,[16] was synthesized from sodium 3,4,5-trimethoxybenzenesulfinate and 5-bromo-1*H*-indole in 32% yield under the standard C3-H thiolation conditions(Scheme 2).

To understand the mechanism of C3–H thiolation, reaction of indole **1a** with sodium arylsulfinate **2a** was monitored by ^1H NMR spectroscopy using CH_2Br_2 as an internal standard. During the 12 h reaction process, three peaks including those for sulfoxide **6a** (δ = 2.44 ppm), C3-thioindole **4a** (δ = 2.31 ppm) and indole dimer **7a** (δ = 2.73 ppm) were observed (see ESI, Scheme S1 and Table S3). The results indicated that sulfoxide **6a** should be a reaction intermediate in the synthesis of C3-thioindole **4a**.

To gain more mechanistic information for the C3-H thiolation, several control experiments were performed (Scheme 3). In the presence of TMSCl, indole dimer **7a** underwent tautomerization to generate indole **1a**. (Scheme 3a).[17] Reaction of indole **1a** with *p*-toluenesulfinic acid (**8a**) conditions is complex under the standard C3-H thiolation and the expected C3-thioindole was not observed (Scheme 3b). Reaction of sulfoxide **6a** with indole **1a** (1 equiv) went smoothly under the standard C3-H thiolation conditions to give C3-thioindole **4a** in 70% yield (Scheme 3c), confirming that sulfoxide **6a** was a reaction intermediate in the



Scheme 2. Substrate scopes. General conditions (for **3**): **1a** (0.5 mmol), **2a** (0.2 mmol), and TMSOTf (0.8 mmol) in CH_2Cl_2 (1.0 mL) at 25 °C for 12 h. General conditions (for **4**): **1a** (0.5 mmol), **2a** (0.2 mmol), and TMSCl (0.8 mmol) in CH_2Cl_2 (1.0 mL) at 25 °C for 12 h.

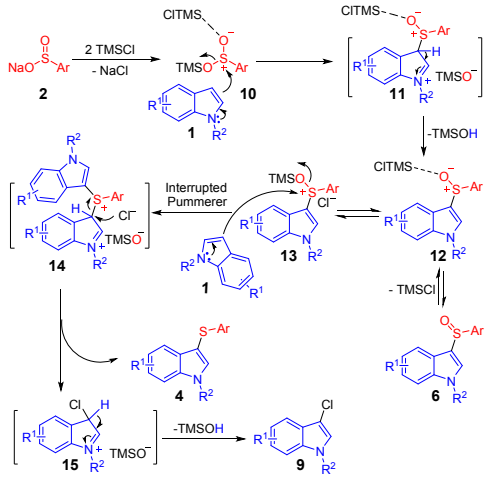


Scheme 3. Control experiments for C3–H thiolation. [a] The yield was based on indole **1i**.

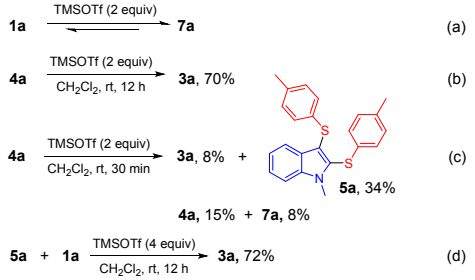
synthesis of C3-thioindole **4a**. Treatment of sodium arylsulfinate **2a** with 1-benzyl-1*H*-indole (**1i**, 2.5 equiv) gave C3-thioindole **4i** in 85% yield, in which chlorinated indole **9a** was obtained in 26% yield (Scheme 3d). Treatment of 3-chloroindole **9a** with sodium arylsulfinate **2a** failed to give C3-thioindole **4i** and the starting material **9a** was recovered in 92% yield (Scheme 3e). 3-Chloroindole **9a** displays relatively weaker electron-donating ability in comparison with the corresponding non-chlorinated indole, which might be a disadvantageous factor for the reaction of 3-chloroindole **9a** with sodium arylsulfinate **2a**.

Based on the above results and related reports in the literature,[18,19] a possible reaction mechanism for the C3-H thiolation was illustrated in Scheme 4. TMSCl reacted with sodium arylsulfinates **2** to form trimethylsilyl sulfinates **10**. Electrophilic substitution reaction of indoles **1** at the C-3 position with trimethylsilyl sulfinates **10** formed intermediates **11**, which underwent in situ a TMSOH remove to generate intermediates **12**. Detachment of TMSCl from **12** afforded sulfoxides **6**. The reversible process could be terminated by aqueous work-up with the consumption of one equivalent of TMSCl. On the other hand, tautomerization of intermediates **12** formed intermediates **13**. Nucleophilic substitution reaction of intermediates **13** with indoles **1** to form sulfonium salts **14**, which underwent in situ an intramolecular nucleophilic substitution reaction to afford C3-thioindoles **4** (Scheme 4). In the latter process, intermediates **15** were also formed, which underwent in situ a TMSOH remove to generate byproducts **9**.

To gain more mechanistic information for the C2-H thiolation, several control experiments were also performed (Scheme 5).



Scheme 4. Proposed mechanism for the C3–H thiolation.



Scheme 5. Control experiments for the C2–H thiolation.

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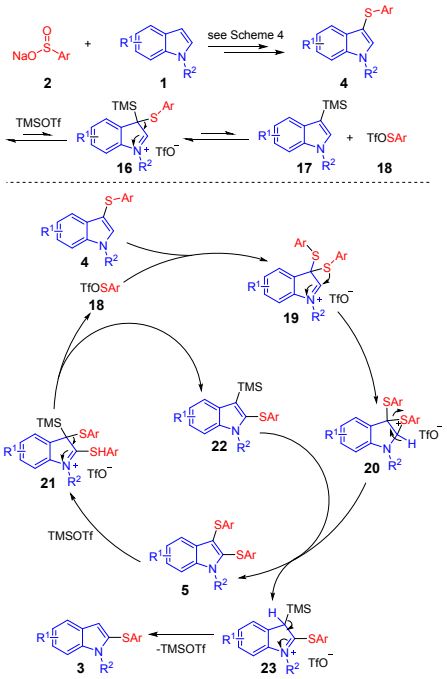
In the presence of TMSOTf, indole **1a** underwent tautomerization to form indole dimer **7a**. (Scheme 5a).[17] Treatment of C3-thioindole **4a** with the 2.0 equivalents of TMSOTf for 12 h, C2-thioindole **3a** was gained in 70% yield (Scheme 5b). This reaction afforded C2-thioindole **3a**, 2,3-bis-thioindole **5a** and indole dimer **7a** in 8%, 34% and 8% yields, respectively under the identical conditions, albeit with a shorter reaction time (*i.e.*, 30 min *versus* 12 h), in which 15% amount of C3-thioindole **4a** was recovered (Scheme 5c). Treatment of 2,3-bis-thioindole **5a** with indole **1a** (1.2 equiv) under the standard C2-thiolation reaction conditions afforded C2-thioindole **3a** in 72% yield, indicating that 2,3-bis-thioindole **5a** should be a key intermediate in the formation of C2-thioindole **3a** (Scheme 5d).

Based on the above results and related reports in the literature,[14,20] a possible reaction mechanism for the C2-H thiolation was shown in Scheme 6. Firstly, reaction of indoles **1** with sodium arylsulfinates **2** in the presence of TMSOTf formed the C3-thioindole intermediates **4** via the simlar processes shown in Scheme 4. Subsequently, electrophilic substitution reaction of C3-thioindoles **4** at the C-3 position with TMSOTf formed trace of indolenium intermediates **16** thanks to the superior leaving ablility of a triflate anion compared to a chloride anion. Indolenium intermediate **16** underwent an aromatization reaction to generate trace of TfOSAr (**18**) and compounds **17**. The trace of TfOSAr chould be the key catalyst for the conversion of C3-thioindoles **4** to C2-thioindoles **3**. C3-thiolation of C3-thioindoles **4** by TfOSAr (**18**) formed 3,3-bis-sulfide indoleniums **19**. The migration of one of the sulfide groups to the C2 position, via the formation of the episulfonium species **20**, afforded 2,3-bisubstituted indoles **5**. Electrophilic substitution reaction of 2,3-bisubstituted indoles **5** at the C-3 position with TMSOTf formed indolenium intermediates **21**, which underwent an aromatization reaction to regenerate the



Scheme 6. Proposed mechanism for the C2–H thiolation.

catalyst TfOSAr with the formation of 2-thioindole derivatives **22**. The 2-thioindole derivatives **22** were protonated by episulfonium species **20** to form 2-thioindole intermediates **23**, which underwent an aromatization reaction to afford C2-thioindoles **3** with the release of TMSOTf (Scheme 6).

In summary, we have developed a regioselectivity-switchable C-H thiolation reaction of indoles with sodium arylsulfinates, which provided a convenient and highly regioselective approach for the synthesis of both C2- and C3-thioindoles. The reaction took place at room temperature under metal-free reaction conditions, and displayed excellent functional group compatibility. The essential roles of the TMS reagents (TMSCl and TMSOTf) lies in their capacity to significantly enhance both the reactivity and regioselectivity in C2- and C3-H thiolation of indoles as well as the unexpected finding that a simple swap of the counteranions of TMS from triflate to chloride leads to a regioselective shift between C2- and C3-H thiolation of indoles. The results underline the potential importance of counteranions in tuning the regioselectivity of the related reactions. Further mechanistic investigations as well as applications of this method are in progress.

We thank the Natural Science Foundation of Shandong Province (ZR2019MB009), the Key Research and Development Program of Shandong Province (2019GSF108089), the National Natural Science Foundation of China (21672046, 21372054), and the Found from the Huancui District of Weihai City.

Conflicts of interest

There are no conflicts to declare.

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