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tetra-n-Butylammonium iodide mediated reaction of indoles with Bunte salts: efficient 3-sulfenylation of indoles under metal-free and oxidant-free conditions[†]

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A highly efficient *tetra-n*-butylammonium iodide (TBAI) triggered procedure for 3-sulfenylation of indoles with Bunte salts is demonstrated. This protocol provides a simple strategy to prepare 3-alkylthioindole and 3-arylthioindoles from the corresponding indoles under metal-free and oxidant-free conditions.

Indole-containing organic molecules are important structural motifs in a variety of natural products and biologically active compounds.¹ Indole thioethers are currently attracting considerable attention due to their therapeutic value, including obesity, cancer ² and allergies.³ For example, MCF-7 I (Figure 1) can be used as breast cancer inhibitor; ⁴ 5-chloro-3-(phenylthio)-1*H*-indole-2-carboxamide II (Figure 1) can be used as HIV inhibitor.⁵ Recently, many methodologies have been developed for the 3-sulfenylation of indoles to prepare 3-sulfenylindoles.



. Fig. 1 Examples of thiolated indoles with biological actives.

Sulfenylation agents such as disulfides,⁶ sulfonium salts,⁷ sulfenyl halides,⁸ *N*-thioimides,⁹ thiols,¹⁰ quinone mono-*O*, *S*-acetals,¹¹*p*-toluenesulfonyl hydrazide,¹² sulfinic acids,¹³ arylsulfonyl chlorides,¹⁴ *p*-tolylsulfinate¹⁵ and α -acylthiones ¹⁶ have been applied to the 3-sulfenylation of indoles. Nevertheless, most of these

reactions have the limitations such as expensive reagents, lower reaction yields, unpleasant odors, unstable to air, and difficult to handle. Moreover, many of these sulfenylating agents can only prepare aryl-sulfenylindoles.

Bunte salts has been developed and well applied in organic synthesis due to their easy preparation and stabilities without unpleasant smell.¹⁷ In 2014, Senanayake's group reported a new method for the synthesis of sulfide by Bunte salts and Grignard reagent, avoiding the use of a thiol.¹⁸ Luo's group have designed and successfully developed an efficient catalytic method for the synthesis of 3-thioindoles.¹⁹ This protocol used iodine as the non-metallic catalyst, and employed DMSO as the oxidant and the solvent. Herein, we report a TBAI promoted sulfenylation of indoles with Bunte salts. This protocol provides a simple strategy to prepare 3-(benzylthio)-1*H*-indole from the corresponding indoles under metal-free and oxidant-free conditions.



Scheme 1 TBAI mediated reaction of indoles with Bunte salts.

Initially, we tried the reaction of indole **1a** (0.5 mmol) with sodium *S*-benzyl sulfothioate **2a** (0.7 mmol) as the test substrates in the presence of TBAI (0.75 mmol) in DCE at 80 °C. To our delight, the reaction proceeded smoothly for 10 h to afford the expected 3-(benzylthio)-1*H*-indole **3a** in 72% yield (Table 1, entry 1). It should be noted that no sulfenylation product was detected when iodine and other catalysts such as NIS (N-Iodosuccinimide), NaI, PIDA

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((Diacetoxyiodo) benzene) and CuI were added instead of TBAI (Table 1, entries 2-6). Screening of solvents, showed that DCE was the best of choice. (Table 1 entries 7-13). Next, we explored the influence of reaction temperature. Increasing the temperature from room temperature to reflux temperature, the reflux temperature led to the best result and **3a** was obtained in 86% yield (Table 1, entries 14-18). Therefore, the optimized reaction conditions were following: indole (**1a**, 1 equiv.), Bunte salts (**2a**, 1.4 equiv.), TBAI (1.5 equiv.), in DCE at reflux temperature for 10 h (Table 1, entry 18). **Table 1** Optimization of the reaction conditions ^{*a*}

	+ SO ₃ Na	<i>n-</i> Bu₄NI (1.5 eq DCE, T	uiv)	
1a 2a				3a
Entr	y Catalyst	Solvent	T (° C)	Yied $^{b}(\%)$
1	TBAI	DCE	80	72
2	I_2	DCE	80	0
3	NIS	DCE	80	0
4	NaI	DCE	80	0
5	PIDA	DCE	80	0
6	CuI	DCE	80	0
7	TBAI	H_2O	80	0
8	TBAI	MeCN	80	0
9	TBAI	EtOH	80	0
10	TBAI	DMF	80	0
11	TBAI	DMSO	80	49
12	TBAI	Dioxane	80	0
13	TBAI	CH_2Cl_2	80	0
14	TBAI	DCE	r.t.	0
15	TBAI	DCE	40	0
16	TBAI	DCE	60	36
17	TBAI	DCE	80	72
18	TBAI	DCE	reflux	86

^{*a*} General conditions: **1a** (0.5 mmol), **2a** (0.7 mmol), TBAI (0.75 mmol). ^{*b*} GC yield

With the optimized conditions in hand, we investigated the substrate scope of indoles and the results were summarized in Table 2. It was gratifying to find that a variety of indoles with methyl groups could react well with Bunte salts to give the desired products (Table 2, **3b-f**) in up to 94% yields. Indoles having electron-donating groups such as 5-methoxy and 2-phenyl gave the respective sulfenylated products (Table 2, **3g-h**). Indole with electron-withdrawing group such as bromo group also exhibited high reactivity (Table 2, **3i**).

Next, we evaluated the scope of Bunte salts. The benzyl Bunte salts with *ortho-*, *meta-* and *para-*chloro groups on the aromatic rings were tested, and all of them reacted smoothly with indoles, yielding the desired 3-arylthioindoles with high efficiency (Table 3, **5a-c**). Bunte salts possessing electron-withdrawing substituents resulted in the respective products in 69-94% yields (Table 3, **5d-f**). Furthermore, we

Table 2 Reaction of different indoles with sodium S-benzylsulfothioate a, b



^{*a*} General conditions : **1a** (0.5 mmol), **2a** (0.7 mmol), TBAI (0.75 mmol). ^{*b*} Isolated yield

examined the reactivity of various aryl-Bunte salts, which showed that aryl-Bunte salts bearing electron-withdrawing groups reacted well with indoles in good yields (Table 3, **5g-h**). It should be mentioned that when a CF₃ group was employed, the respective product was obtained in high yield too (Table 3, **5i-j**). Further attention was turned to a 5 mmol scaled reaction. It was found that when 5 mmol indole **1a** was used to react with 7 mmol sodium *S*-2-bromobenzyl sulfothioate **4k**, the expected product 3-((2-bromobenzyl)thio)-1*H*-indole **5k** could be obtained in 47% yield. Bunte salts without aromatic rings such as sodium *S*-(2-(*tert*-butoxy)-2-oxoethyl) sulfothioate **4l** and

Table 3. Reaction of 1*H*-indole with different Bunte salts ^{*a*, *b*}



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^{*a*} General conditions : **1a** (0.5 mmol), **2a** (0.7 mmol), TBAI (0.75 mmol). ^{*b*} Isolated yield. ^{*c*} **1a** (5 mmol), **2a** (7 mmol), TBAI (7.5 mmol).

sodium *S*-(cyanomethyl) sulfothioate **4m** also reacted with indoles under optimized reaction conditions in DCE to produce the corresponding 3-selenylated indoles in 50% and 85% yield (Table 3, **5l-m**). Bunte salts with electron-donating groups such as sodium S-(2-methylbenzyl) sulfurothioate (Table 3, **5n**), sodium S-(4methylbenzyl) sulfurothioate (Table 3, **5o**) and sodium S-(4methoxybenzyl) sulfurothioate (Table 3, **5p**) with indole, repectively. Unfortunately, no desired products were observed under the identical contions.

Next, we treated the sodium S,S'-(1,4-phenylenebis(methylene)) disulforhioate **6** with 2 equiv indoles **1** under standard conditions, the corresponding 1,4-bis(((1*H*-indol-3-yl)thio)methyl)benzene **7** was also prepared in 20% yield (Scheme 2).



Scheme 2 Reaction of 1*H*-indole with sodium *S*,*S*¹-(1,4-phenylenebis(methylene)) disulforthioate.

Furthermore, the versatile synthetic utility of the 3-(benzylthio)-1*H*-indolewas **5a** was studied (Scheme 3). It should be noted that 3-(benzylsulfonyl)-1*H*-indole **8** can be obtained in 96% yield through the simple oxidation of **5a** by *m*-CPBA.



Scheme 3 Oxidation of 3-(benzylthio)-1H-indole.

In order to extend the application of our reaction, we tried the Pd-catalyzed intramolecular annulation reaction²⁰ of 3-((2-bromobenzyl)thio)-1*H*-indole **5**I. To our delight, the C–H functionalization product 11-dihydroisothiochromeno[4,3-*b*]indole **9** was delivered in 79% yield (Scheme 4).





Based on the above results and the literature reports, ^{6a, 13, 17, 21, 22} a plausible mechanism was proposed in Scheme 5. Bunte salt **2** reacts with water (from Bunte salt and undried solvent) to give the thiol or thiol anion **10** and bisulfate anion in the presence of TBAI.^{17, 21} Γ is further oxidized by bisulfate anion to furnish I₂.¹³ Another Bunte salt **2** undergoes nucleophilic attack by **10** to give disulfide **11**, ²² which can be detected by GC-MS (For details, please see supporting information). Disulfide **11** reacts with I₂ to form an electrophilic species RSI **12**.^{6b, 13} Following the reaction of **12** with indole **1a** and deprotonation, the desired product **3** and Γ are observed.^{6b}



Scheme 5 proposed mechanism.

In summary, we developed a highly efficient TBAI mediated 3sulfenylation of indoles with Bunte salts under metal-free and oxidant conditions. This protocol provides a simple strategy for the efficient synthesis of 3-alkylthioindoles and 3-arylthioindoles under mild conditions.

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Notes and references

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