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Synthesis of 3-sulfenylated indoles by a simple NaOH promoted sulfenylation reaction†

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The C-3 sulfenylation reaction of indoles has been achieved under mild reaction conditions by simply employing NaOH as promoter and thiols as thiolating reagents. This simple method allows for easy and rapid synthesis of various 3-sulfenylated indoles with generally good to excellent yields. Primary attempts in scale-up synthesis give satisfactory result.

Introduction

Sulfenylated indoles consist of an important class of indole derivatives and have been discovered as scaffolds possessing versatile biological relevance. According to known results, 3-sulfenylated indoles, for example, has displayed a broad spectrum of biological and pharmaceutical activities, including anti-HIV activity,[1] inhibitory activity against tubulin polymerization,[2] anti-cancer activity,[3] anti-obesity activity,[4] to name but a few. In the known methods for synthesizing these valuable molecules, the catalytic C3-sulfenylation of indoles has been found to be the most efficient and extensively explored one. During the synthetic efforts, a variety of thiolating reagents have been discovered as reaction partners. For examples, sulfonyl hydrazides could regioselectively couple indoles to give 3-sulfenylated indoles using simply molecular iodine as catalyst.[5] Other thiol sources such as arylsulfonyl chlorides,[6] *N*-thiophthalimides,[7] *O*,*S*-acetals[8] and sodium sulfinates[9] *etc.* have also been discovered as effective thiolating reagents in the synthesis of 3-sulfenylated indoles and other related heterocycles.[10] While these thiolating reagents have all been found to be capable of efficiently provide 3-sulfenylated indoles, however, disulfides[11] and thiols[12] are still the most frequently employed thiolating reagents in the preparation of sulfenylated indoles. The main advantages of thiols and disulfides are the easy availability, low cost as well as general functional group tolerance. The main problem of disulfide-based synthesis are that disulfides need to be prepared *via* the oxidative coupling of thiols, which means additional operation step and low atom economics.[13] In this regard, directly using thiols as thiolating reagents for the transformation is more favorable. On the other hand, in those presently known thiol-based indole sulfenylation methods, either transition metal catalyst or harsh heating conditions are required. In this context, a mild and generally applicable, transition metal free protocol for the 3-sulfenylation of indoles using thiols is still highly demanding. Following our recent interests in sulfur-based coupling chemistry,[13,14] we report herein a facile NaOH promoted, thiol-based approach for the 3-sulfenylation of indoles under mild and transition metal free conditions.

Results and discussion

The investigation began from the model reaction of indole **1a** and *p*-tolyl thiol **2a**. In tentative study, K_2CO_3 was employed as the base to promote the reaction in DMSO and heating of 100 °C. The result from the entry showed the production of target sulfenylated product **3a** with moderate yield (entry 1, Table 1). Subsequently, systematic investigation has been conducted to enhance the efficiency of the reaction. As outlined in Table 1, initial attempt on increasing the amount of thiol component was found to be effective to enhance the yield of **3a**, and using 2 equivalent moles of **2a** led to significant improvement by giving **3a** with 76% yield (entries 1–4, Table 1). Further examination on reaction media of different polarity, including water, EtOH, DMF, toluene and MeCN disclosed that DMSO was amongst the best solvent (entries 5–9, Table 1). Subsequent screening on base promoters suggested that inorganic bases could generally promote the reaction, while organic base such as Et_3N failed to initiated the expect reaction. The highest yield

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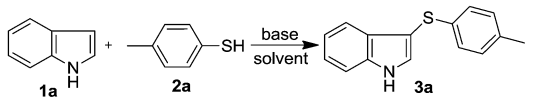
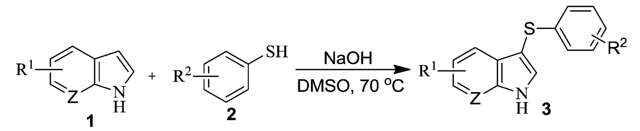
Table 1 Optimization on reactions conditions[a]



Entry	Base	Solvent	T (°C)	Yield[b] (%)
1[c]	K_2CO_3	DMSO	100	47
2[d]	K_2CO_3	DMSO	100	53
3[e]	K_2CO_3	DMSO	100	66
4	K_2CO_3	DMSO	100	76
5	K_2CO_3	H_2O	100	nr
6	K_2CO_3	EtOH	100	40
7	K_2CO_3	DMF	100	20
8	K_2CO_3	Toluene	100	nr
9	K_2CO_3	MeCN	100	50
10	no	DMSO	100	nr
11	Na_2CO_3	DMSO	100	70
12	KOH	DMSO	100	94
13	NaOH	DMSO	100	95
14	Et_3N	DMSO	100	nr
15	*t*-BuOK	DMSO	100	76
16	NaOH	DMSO	80	94
17	NaOH	DMSO	70	95
18	NaOH	DMSO	60	85
19	NaOH	DMSO	40	83

[a] General conditions: **1a** (0.25 mmol), **2a** (0.5 mmol), base (0.5 mmol), solvent (2 mL), stirred at 70 °C for 6 h. [b] Yield of isolated product. [c] 0.25 mmol **2a** was employed. [d] 0.3 mmol **2a** was employed. [e] 0.4 mmol **2a** was employed.

Table 2 Synthesis of various 3-sulfenylated indoles[a]



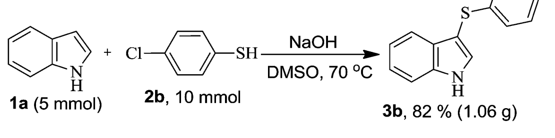
R^1	R^2	Z	Product	Yield[b] (%)
H	4-Me	CH	**3a**	95
H	4-Cl	CH	**3b**	94
H	4-Br	CH	**3c**	85
H	4-F	CH	**3d**	95
H	4-*i*-Pr	CH	**3e**	95
H	H	CH	**3f**	85
H	2-Me	CH	**3g**	92
H	2-Cl	CH	**3h**	90
H	2-NH_2	CH	**3i**	95
H	3-Me	CH	**3j**	86
H	4-Me	N	**3k**	93
2-Me	4-Me	CH	**3l**	87
2-Me	2-Me	CH	**3m**	95
2-Me	4-Cl	CH	**3n**	76
2-Me	3-Me	CH	**3o**	96
2-Me	2-Cl	CH	**3p**	75
5-Br	4-Me	CH	**3q**	78
5-Br	4-Cl	CH	**3r**	86
5-Br	4-Br	CH	**3s**	89
5-Br	3-Me	CH	**3t**	96
5-OMe	4-Me	CH	**3u**	67
5-OMe	3-Me	CH	**3v**	89
5-OMe	4-Cl	CH	**3w**	75
5-OMe	4-Br	CH	**3x**	72
5-CN	4-Me	CH	**3y**	85
5-CO_2Me	4-Me	CH	**3z**	75
5-CO_2Me	4-Cl	CH	**3aa**	71

[a] General conditions: **1** (0.25 mmol), **2** (0.5 mmol), NaOH (0.5 mmol), DMSO (2 mL), stirred at 70 °C for 6 h. [b] Yield of isolated yield.

of **3a** was obtained from the entry using NaOH (entries 10–15, Table 1). Finally, variation on the reaction temperature proved that heating at 70 °C gave equally excellent result as 100 °C, further lowering the temperature, however, led to evident decrease in the product yield (entries 16–19, Table 1).

After optimization study on the model reaction, the application scope of this facile catalytic protocol was conducted. The results from this section demonstrated that the present method was broadly applicable for the synthesis of sulfenylated indoles of type **3**. Functional groups such as alkyl, alkoxyl, halide, cyano and ester all displayed satisfactory tolerance to the protocol and provided corresponding products with good to excellent yields. Generally, electron enriched indoles, for example, 2-methyl indole and 5-methoxyl indole underwent the transformation to provide corresponding products with slightly lower yields when coupling with electron deficient thiols, which could be attributed to the hindrance effect of the electron intensity in indole component and the electron deficience in thiol component to the nucleophilicity of thiols (**3n**, **3p**, **3w**, **3n**). Most of other entries, on the other hand, provided thiolated indoles with excellent yields without showing evident impact from the substrates. Similar sulfenylation reaction using aliphatic thiols, including isobutyl thiol, benzyl mercaptan and cyclohexanethiol, however, was not successful under present catalytic conditions. In addition, *N*-methylindole and 3-methylindole failed to undergo any sulfenylation transformation either when they were employed as the heterocycle component, respectively. While no additional oxidant was employed in all these sufenylating reactions, as the case in other related indole sulfenylation process employing either thiols or disulfides,[11a,12d] it was deducible that the oxygen in the air was the main oxidant to promote this sulfenylation process in our work (Table 2).

Being inspired by the simplicity of the synthetic method, we then attempted to conduct scale-up experiments to examine the synthetic efficiency. When **5** mmol indole was subjected for the reaction with *p*-chlorothiophenol **2b**, corresponding product **3b** has been afforded with satisfactory yield of 82% (1.06 g), demonstrating the great potential of the present method for large scale synthesis of 3-sulfenylated indole products (Scheme 1).



Scheme 1 Gram scale synthesis of 3-sulfenylated indoles.

Conclusions

In conclusion, we have established a facile and atom economical synthetic method towards the synthesis of 3-sulfenylated indoles under transition metal free conditions. A variety of indoles and thiols have been efficiently transformed to structurally diverse products by mild heating in the presence of NaOH. In addition, the present protocol is advantageous for good tolerance to scale-up synthesis.

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