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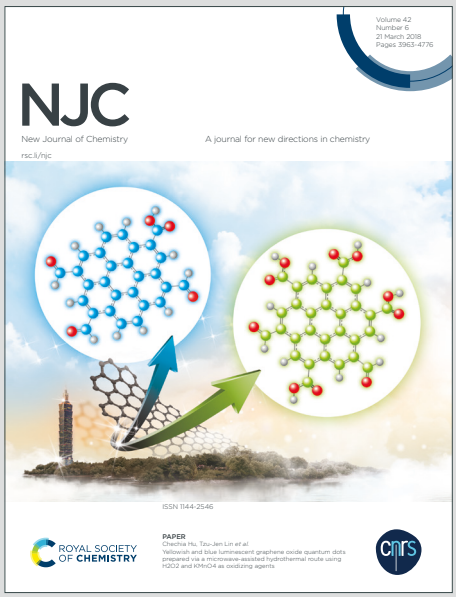

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COMMUNICATION

Transition-Metal-Free Sulfonylation of Methylthiolated Alkynones to Synthesize 3-Sulfonylated Thioflavones

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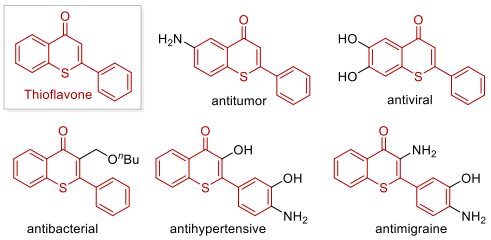
A transition-metal-free NaI/TBHP-mediated sulfonylation cyclization reaction of methylthiolated alkynones with sulfonyl hydrazides was developed, by which various 3-sulfonylated thioflavones were prepared under mild reactions. The features of this procedure include metal-free reaction conditions, the ease of reagent handling, short reaction time, and a broad functional group tolerance.

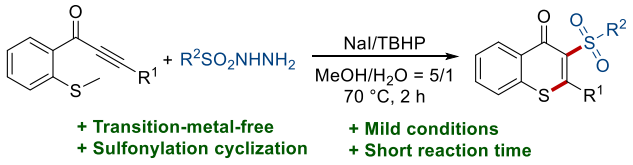
Thioflavone is one of the most important frameworks that widely spread in numerous natural products, pharmaceuticals and functional materials.[1] In the past decades, thioflavones have gained tremendous attention because of their intriguing bioactivities in antibacterial, antitumor as well as anti-malarial, *etc* (Scheme 1).[2] Furthermore, thioflavones and their oxidized sulfone derivatives exhibit extraordinary promising applications in medicinally relevant molecules and advanced materials, such as anti-infective agents and photolabile protecting groups.[3] Nowadays, the development of novel and straightforward synthetic methods to access structurally diverse thioflavones is highly desirable.

Due to the importance of organic sulfur compounds, the development of efficient methods for the construction of C-S bond has gained huge attention.[4] Particularly, it is well known that sulfones display various unique biological and pharmaceutical activities and are therefore of great importance in the development of drugs and agrochemicals.[5] Moreover, sulfones are versatile synthetic intermediates in organic synthesis, which can undergo interesting conversions, such as Julia olefination and Ramberg-Bäcklund reaction.[6] Therefore, enormous efforts have been devoted to the development of novel and facile methods to introduce the sulfonyl group into organic frameworks in recent years.[7]



Scheme 1. Examples of thioflavones

Over the past decades, sulfonyl hydrazides, as readily accessible compounds, have been employed as sulfonyl radical precursors to access a number of sulfonyl-substituted heterocycles and carbocycles *via* sulfonyl radical-initiated reactions.[8] As our ongoing interest in radical reaction and sustainable chemistry,[9] we herein disclosed a transition-metal-free NaI/TBHP-mediated sulfonylation of methylthiolated alkynones with sulfonyl hydrazides to access 3-sulfonylated thioflavones under mild reaction conditions (Scheme 2). It should be noted that although the cascade cyclization reaction of methylthiolated alkynones has been realized recently,[10] the development of efficient protocols for the transformation of methylthiolated alkynones in a short time is still desired.



Scheme 2. Preparation of 3-sulfonylated thioflavones

The exploratory study was initiated by using methylthiolated alkynone (**1a**) and $TsNHNH_2$ (**2a**) as model substrates to optimize the reaction conditions (Table 1). Fortunately, when the model reaction was treated with KI (1 equiv) and TBHP (3 equiv) in MeOH, the desired product **3a** was obtained in an isolated yield of 43% (entry 1). Encouraged by this exciting result, other iodide reagents, including NH_4I, TBAI, NaI, and I_2, were also tested to improve the reaction efficiency (entries 2-5). It was pleased to see that when NaI was employed, the product **3a** was obtained in highest yield (69%, entry 5). Then the NaI loading was screened, suggested that the stoichiometric amount of NaI was necessary (entries 5-7). Afterward, various

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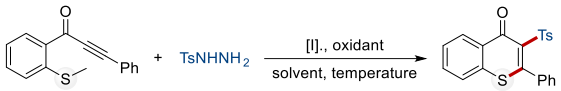
oxidants like $K_2S_2O_8$, H_2O_2, DTBP, and BPO were further investigated for the model reaction, and the results showed that TBHP was still the best choice for this transformation (entries 8-11). Subsequently, the amount of TBHP as an oxidant was examined. As it can be seen, the yield of **3a** increased from 66% to 77% as the amount of TBHP increased from 1 to 2 equiv (entries 12 and 13), and decreased from 77% to 69% as the amount continuously increased from 2 to 3 equiv. (entries 13 *vs* 5). For further optimization, a range of solvents, including DMSO, CH_3CN, EtOH, DMF, DCE, 1,4-dioxane, THF, H_2O, and methanol aqueous solution were evaluated (entries 14-24). The results showed that the mixed solvent MeOH/H_2O (v/v = 5/1) was the most efficient and provide the desired product **3a** in 79% yield (entry 24). Furthermore, when the amount of **2a** was increased to 3 equiv, we were delighted to obtain the product **3a** in yield of 85% (entry 25). When the reaction was conducted in the absence of NaI or TBHP, no desired product was observed (entries 26-27), demonstrating that this reaction is initiated by the NaI/TBHP system. Overall, the optimal reaction conditions were thus established as follows: **1a** (0.2 mmol), **2a** (3 equiv), NaI (1 equiv) and TBHP (2 equiv) were stirred in mixed solvent of MeOH/H_2O (v/v = 5/1) at 70 °C for 2 h.

With the optimized reaction conditions established, the substrate scope of this transition-metal-free sulfonylation reaction was further evaluated by using various methylthiolated alkynones **1** and sulfonyl hydrazides **2**. As it can be seen in Table 2, numerous methylthiolated alkynones **1**, including those attached with electron-donating and electron-withdrawing groups at different position of the phenyl ring, reacted smoothly with $TsNHNH_2$ (**2a**) to afford the desired products **3a-m** in good to excellent yields. The presence of electron-withdrawing and electron-donating groups has no significant impact on the reaction efficiency under the optimal conditions. Notably, the trifluoromethyl group (CF_3), as versatile structural units widespread in pharmaceuticals and

Table 1. Optimization of reaction conditions [a]

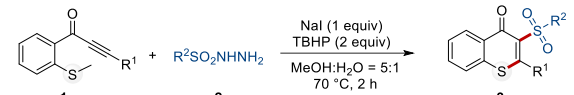


1a 2a 3a

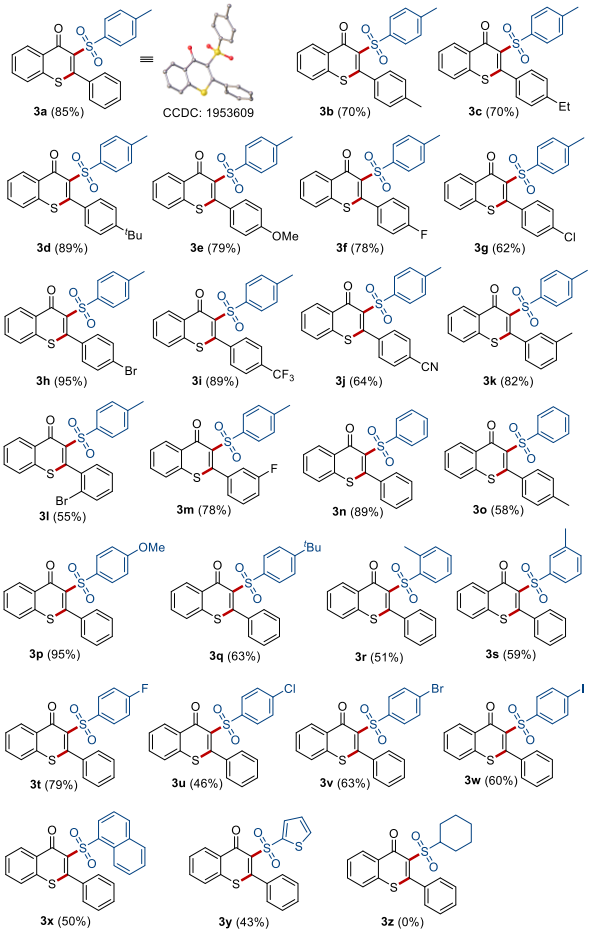
Entry	[I] (equiv)	Oxidant (equiv)	Solvent	Yield (%)
1	KI (1)	TBHP (3)	MeOH	43
2	NH_4I (1)	TBHP (3)	MeOH	59
3	TBAI (1)	TBHP (3)	MeOH	63
4	I_2 (1)	TBHP (3)	MeOH	35
5	NaI (1)	TBHP (3)	MeOH	69
6	NaI (0.25)	TBHP (3)	MeOH	41
7	NaI (0.1)	TBHP (3)	MeOH	25
8	NaI (1)	$K_2S_2O_8$ (3)	MeOH	65
9	NaI (1)	H_2O_2 (3)	MeOH	23
10	NaI (1)	DTBP (3)	MeOH	N.D.
11	NaI (1)	BPO (3)	MeOH	45
12	NaI (1)	TBHP (1)	MeOH	66
13	NaI (1)	TBHP (2)	MeOH	77
14	NaI (1)	TBHP (2)	DMSO	6
15	NaI (1)	TBHP (2)	CH_3CN	36
16	NaI (1)	TBHP (2)	EtOH	62
17	NaI (1)	TBHP (2)	DMF	N.D.
18	NaI (1)	TBHP (2)	DCE	N.D.
19	NaI (1)	TBHP (2)	1,4-Dioxane	39
20	NaI (1)	TBHP (2)	THF	57
21	NaI (1)	TBHP (2)	H_2O	44
22	NaI (1)	TBHP (2)	MeOH/H_2O = 1/1	54
23	NaI (1)	TBHP (2)	MeOH/H_2O = 3/1	63
24	NaI (1)	TBHP (2)	MeOH/H_2O = 5/1	79
25[b]	NaI (1)	TBHP (2)	MeOH/H_2O = 5/1	85
26[b]	---	TBHP (2)	MeOH/H_2O = 5/1	N.D.
27[b]	NaI (1)	---	MeOH/H_2O = 5/1	N.D.

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (2 equiv), catalyst, oxidant, solvent (2 mL), 70 °C, 2 h. TBHP = *tert*-butyl hydroperoxide (70% aqueous solution), DTBP = di-*tert*-butyl peroxide, BPO = benzoyl peroxide, DCE = 1,2-dichloroethane. Isolated yields were given based on **1a**. [b] **2a** (3 equiv) was employed.

Table 2. Substrate scope for 3-sulfonylated thioflavones



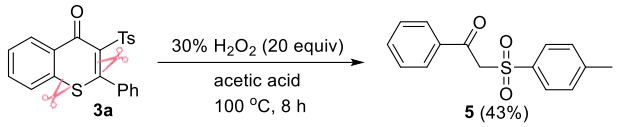
1 2 3



[a] Reaction conditions: **1** (0.2 mmol), **2** (3 equiv), NaI (1 equiv), TBHP (2 equiv), MeOH/H_2O (v/v = 5/1, 2 mL), 70 °C, 2 h. Isolated yields were given based on **1**.

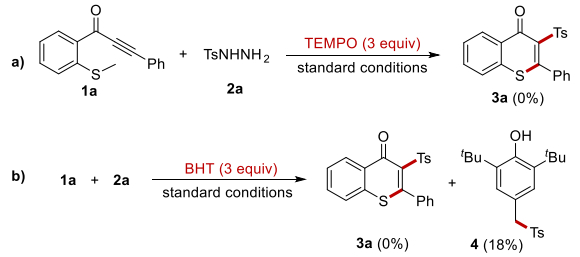
agrochemicals,[11] can also be well tolerated in this reaction system, offering the products **3i** in excellent yield (89%). Afterward, a variety of sulfonyl hydrazides **2** were investigated to further explore the limitations of the reactions (**3n-y**). Different sulfonyl hydrazides bearing various groups, such as alkyl (–Me and –^{t}Bu), methoxyl as well as halide (–F, –Cl, –Br and –I), exhibited good reactivities for the cyclization reaction producing the desired products **3o-x** in moderate to good yields (46%–95%). 1-Naphthyl and 2-thienyl-based sulfonyl hydrazides were also applicable for this transformation, and the corresponding products **3x** and **3y** were isolated in 50% and 43% yield, respectively. Unfortunately, the reaction using alkyl sulfonyl hydrazide as substrate did not generate the corresponding product (**3z**). Notably, the structure of **3a** was further confirmed by X-ray crystallography (CCDC 1953609).

The gram-scale reaction was also conducted based on the model reaction (see the Supporting Information for details). Unfortunately, only 33% yield of **3a** was obtained, probably due to the limitation of mass transfer. Furthermore, the synthesized 3-sulfonylated thioflavone **3a** could be converted into β-carbonyl sulfone **5** in an isolated yield of 43% under oxidative reaction conditions (Scheme 3, see the Supporting Information for details).



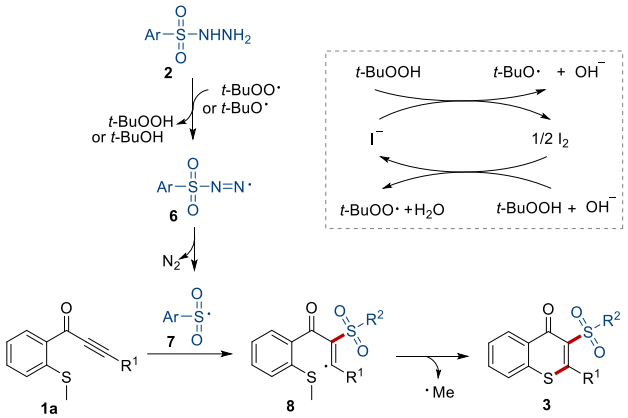
Scheme 3. Transformation of **3a**

To gain deep mechanistic insights into this transition-metal-free sulfonylation of methylthiolated alkynones, several control experiments were carried out. As it can be seen in Scheme 4, the treatment of **1a** with $TsNHNH_2$ (**2a**) in the presence of TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) or BHT (2,6-di-*tert*-butyl-4-methylphenol), two well-known radical scavengers, the reactions were severely inhibited, suggesting that a radical pathway should be involved in the reaction. Furthermore, when BHT was subjected to the reaction system under standard conditions, the adduct **4** was successfully separated with 18% yield, demonstrating that a sulfonyl radical was produced and participated in this reaction.



Scheme 4. Control experiments

Based on the results of control experiments and previous reports,[12] a plausible mechanism involved radical process is proposed as shown in Scheme 5. Initially, the radicals *t*-BuO· and *t*-BuOO· are generated from TBHP in the presence of iodide anion under 70 °C. Then, the resultant radicals react with sulfonyl hydrazide **2** produce the sulfonyl diazene radical **6**, which is rapidly converted into sulfonyl radical **7** by releasing N_2. Subsequently, the addition of radical **7** to the C≡C bond of **1a** leads to the vinyl radical intermediate **8**, which undergoes a 6-*exo*-trig cyclization with the SMe moiety to generate the aromatic ring, affording the final product **3** along with methyl radical. The methyl radical is further converted to methane *via* H-abstraction.[13]



Scheme 5. Proposed mechanism

Conclusions

In conclusion, we have disclosed a NaI/TBHP-mediated transition-metal-free strategy for the synthesis of 3-sulfonylated thioflavones from easily accessible methylthiolated alkynones and sulfonyl hydrazides. The features of this methodology include metal-free reaction conditions, the ease of reagent handling, short reaction time, and a broad functional group tolerance. The transformation of the synthesized 3-sulfonylated thioflavone into β-carbonyl sulfone suggested that 3-sulfonylated thioflavones could be employed as useful building blocks in organic synthesis. Further applications of this synthetic strategy and the biological activities of 3-sulfonylated thioflavones are currently ongoing in our laboratory.

Conflicts of interest

There are no conflicts to declare.

Acknowledgment

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Transition-Metal-Free Sulfonylation of Methylthiolated Alkynones to Synthesize 3-Sulfonylated Thioflavones

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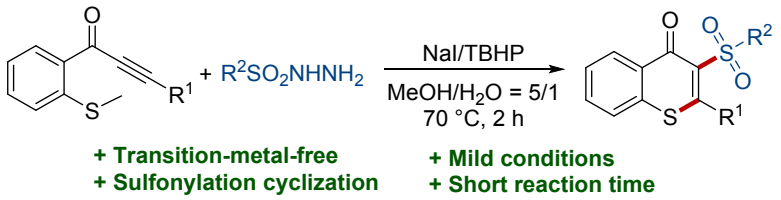

A transition-metal-free NaI/TBHP-mediated sulfonylation cyclization reaction of methylthiolated alkynones with sulfonyl hydrazides was developed, by which various 3-sulfonylated thioflavones were prepared under mild reactions. The features of this procedure include metal-free reaction conditions, the ease of reagent handling, short reaction time, and a broad functional group tolerance.