Advanced Synthesis & Catalysis

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To be cited as: *Adv. Synth. Catal.* 10.1002/adsc.201801258

Link to VoR: http://dx.doi.org/10.1002/adsc.201801258

DOI: 10.1002/adsc.201((will be filled in by the editorial staff))

Solvent Controlled Transformation between Sulfonyl Hydrazides and Alkynes: Divergent Synthesis of Benzo[*b*]thiophene-1,1-dioxides and (E)-β-iodo Vinylsulfones

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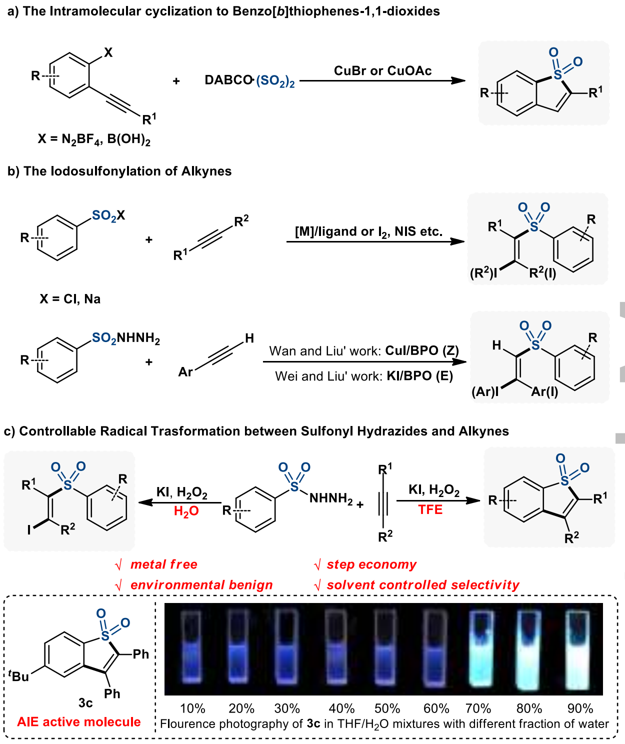
Received: ((will be filled in by the editorial staff))

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201######.((Please delete if not appropriate))

Abstract. A green, efficient and controllable transformation between sulfonyl hydrazides and alkynes leading to benzo[*b*]thiophene-1,1-dioxides and (E)-β-iodo vinylsulfones via radical pathway has been developed. The reaction occurs rapidly in the presence of simply H_2O_2 and KI without the help of any transition metal. The chemoselectivity of the reaction is determined by the solvent in which the process is performed: TFE favors the cyclic product, while H_2O medium generates the iodosulfonylative product. Notably, this protocol also represents the first direct approach to the aggregation-induced-emmision (AIE) active benzo[*b*]thiophene-1,1-dioxides from readily available sulfonyl hydrazides and alkynes in one step.

Keywords: Solvent; Metal-free; Benzo[*b*]thiophene-1,1-dioxides; iodo vinylsulfones; AIE



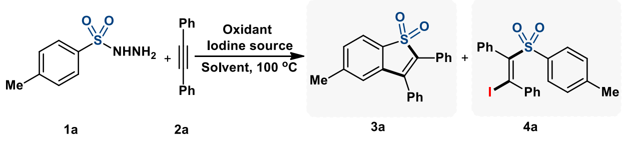
Scheme 1. The existing approaches to construct benzo[*b*]thiophene-1,1-dioxides and β-iodo vinylsulfones.

In the last few decades, radical based reactions have become one of the most powerful instruments for the synthetic community.[1,2] Even significant progress has been made in this field, switchable radical based reactions to obtain skeletal divergent products in controllable manners remain relatively unexplored and challenging due to the highly reactive nature of free radicals.[3] These reactions are of great value for green chemistry and organic synthesis. Benzo[*b*]thiophene-1,1-dioxides represent a class of interesting organosulfur compounds which exhibit wide applications in pharmaceuticals,[4] organic synthesis[5], and optoelectronic materials.[6] The most frequent approach to prepare benzo[*b*]thiophene-1,1-dioxides rely on the oxidation of the pre-synthesized benzo[*b*]thiophenes,[7] which suffer from tedious steps, poor yield and limited functional group tolerance. Recently, two Cu-catalyzed insertion/cyclization reactions of 2-alkynylaryldiazonium[8] and (2-alkynylaryl)boronic Acids[9] with DABCO-bis(sulfur dioxide) offering 2-substituted benzo[*b*]thiophene -1,1-dioxides were developed by Wu and coworkers (Scheme 1a). As we know, a straightforward synthetic route to benzo[*b*]thiophene-1,1-dioxides from readily available organosulfur species and simple alkynes remain unexplored. The iodosulfonylation of alkynes employing sulfonic acid derivatives have been well established as efficient methodologies to obtain iodo vinylsulfones (Scheme 1b).[10] Among these elegant examples, Wan and Liu reported a Cu-mediated stereoselective Z-iodosulfonylation of terminal alkynes employing sulfonyl hydrazides in 2016.[11]

Next, a KI/BPO mediated E-iodosulfonylation of terminal alkynes were achieved by Wei and Liu in 2017.[12] Despite these successes, their study was focused on the iodosulfonylation of internal alkynes. The iodosulfonylation of internal alkynes, especially diphenyl-alkynes, using sulfonyl hydrazides remain rarely reported. Herein, we disclose a controllable radical reaction between sulfonyl hydrazides and alkynes offering benzo[*b*]thiophene-1,1-dioxides and (E)-β-iodo vinylsulfones. This protocol exhibits excellent selectivity, operational simplicity, scalability, and good yields. Only environmentaly benign KI and H_2O_2 were necessary to generate the two precious products without the use of toxic transition metal. Additionally, the photo-physical properties of the selected product **3c** were studied to confirm the AIE nature of the skeleton.

We began our investigations employing 4-methylbenzenesulfonohydrazide, **1a**, and 1,2-diphenylethyne, **2a**, as the model substrates. To our delight, 11% of **3a** was obtained when the reaction was conducted with of 0.5 equivalents of KI, and 4.0 equivalents of TBHP in 2,2,2-trifluoroethanol (TFE) (Table 1, Entry 1). Peroxide oxidants, such as DTBP, and H_2O_2, were examined to increase the yield to 79% (Table 1, Entries 2-3). The screening of other oxidants such as Iodobenzene diacetate (PIDA), $K_2S_2O_8$ and Oxone did not improve the yield of **3a**, yet, iodosulfonylative product, **4a**, was produced in yields of no more than 20% (Table 1, Entries 4-6).

Table 1. Optimization of conditions. [a, b]



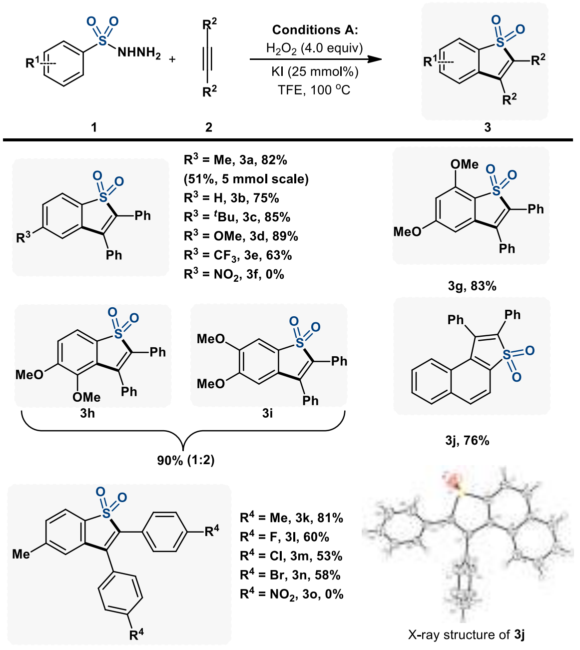
Entry	Oxidant	Solvent	Iodine source	Yield (3a)	Yield (4a)
1	TBHP	TFE	KI	11%	Nd.
2	DTBP	TFE	KI	20%	23%
3	H_2O_2	TFE	KI	79%	Nd.
4	PIDA	TFE	KI	Nd.	Nd.
5	$K_2S_2O_8$	TFE	KI	35%	17%
6	Oxone	TFE	KI	30%	19%
7	H_2O_2	TFE	I_2	77%	Nd.
8	H_2O_2	TFE	TBAI	19%	10%
9[c]	H_2O_2	TFE	KI	82%	Nd.
10[d]	H_2O_2	TFE	KI	60%	Nd.
11	H_2O_2	TFE	/	Nd.	Nd.
12[e]	H_2O_2	THF	KI	Nd.	47%
13[e]	H_2O_2	CH_3CN	KI	Nd.	15%
14[e]	H_2O_2	Toluene	KI	Nd.	55%
15[e]	H_2O_2	DMF	KI	Nd.	Nd.
16[e]	H_2O_2	H_2O	KI	Nd.	85%

[a] Reaction conditions: **1a** (0.4 mmol, 2.0 equiv), **2a** (0.2 mmol, 1.0 equiv), oxidant (0.8 mmol, 4.0 equiv), iodine source (0.1 mmol, 0.5 equiv), solvent (2 mL), 100 °C, 2 hours under air atmosphere. [b] Isolated yield. [c] 0.05 mmol KI was used. [d] 0.02 mmol KI was used. [e] 0.3 mmol iodine source was used.

When 0.1 mmol of iodine was loaded to the reaction system, 77% of **3a** was obtained (Table 1, Entry 7). Iodine was also examined in H_2O to offer **4a** as the single product (see Surpporting Information Table 1, Entry 1). **3a** and **4a** were obtained in 19%, and 10% yields respectively when TBAI was applied (Table 1, Entry 8). Later, the amounts of KI were also tested and the yield of **3a** increased to 82% with a reduction of KI to 0.05 mmol (Table 1, Entries 9-11). To improve the yield of **4a**, we increased the amount of KI to 1.5 equivalents and screened a variety of solvents (comprehensive screening was provided in Supporting Information). The use of THF increased the yield of **4a** to 47% (Table 1, Entry 12). When H_2O was used as solvent, **4a** was obtained with a yield of 85% (Table 1, Entry 16).

With the optimized conditions in hand, the substrate scope of the addition/cyclization reaction was studied as shown in Table 2. First of all, a series of sulfonyl hydrazides was investigated. When benzenesulfonyl hydrazide (**1b**) was tested in conditions A, 75% of **3b** was produced. Substrate which are with sterically bulky tert-butyl at the para-position performed smoothly to give 85% yield (**3c**). An excellent yield of 89% was obtained when a strong electron-donating methoxyl group substituted benzenesulfonyl hydrazide was examined (**3d**). A trifluoromethyl group at the para-position did not influence the process, and the corresponding product **3e** was prepared in the yield of 63%. Substrate with a strong electronic-withdrawing nitro group failed to produce **3f**. These results indicated that the electron density of the benzene ring is of great importance for

Table 2. Substrate scope of the addition/cyclization reaction.[a, b]

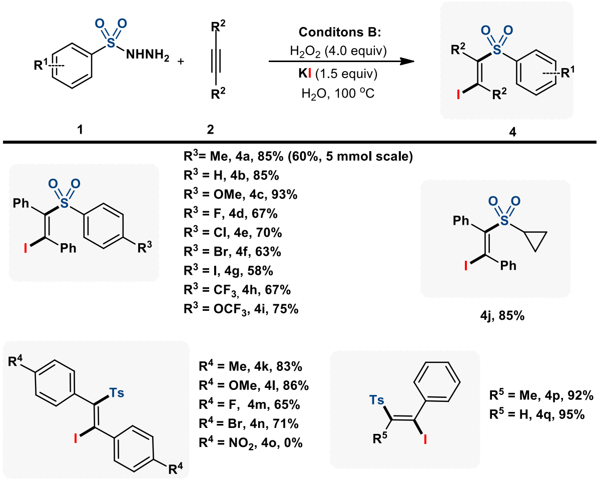


[a] Reaction conditions A: **1a** (0.4 mmol, 2.0 equiv), **2a** (0.2 mmol, 1.0 equiv), H_2O_2 (0.8 mmol, 4.0 equiv), KI (0.1 mmol, 0.5 equiv), TFE (2 mL), 100 °C, 2 hours under air atmosphere. [b] Isolated yield.

the product generation. Multi-substituted product **3g** was also obtained in 83% yield. When 3,4-dimethoxy substrate was examined in the system, **3h** and **3l** were generated in the ratio of 1:2 and totally 90% yield. **3j** was also synthesized through our method with a yield of 76%, and its structure was identified by single-crystal X-ray analysis.[13] Next, various symmetric internal alkynes were examined to generate corresponding products in yields of 0% to 81% (**3k-3o**). In particular, bromo- and chloro-substituted products were prepared smoothly, which provides the possibility for further functionalizations. Terminal alkynes such as phenylacetylene and ethyl propiolate were also examined, but failed to yield desired cyclic products.

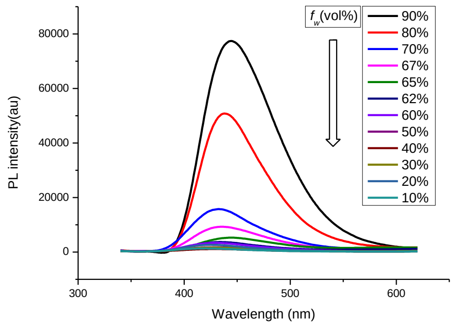
Next, the scope of the iodosulfonylation reaction was expanded and summarized in Table 3. Firstly, alkyl, alkoxyl substituted benzenesulfonyl hydrazides were examined to give corresponding products in the yield of 85% to 93% (**4a-4c**). Halo-substituted products **4d-4g** were synthesized in 67%, 70%, 63%, 58% yields respectively. Benzenesulfonyl hydrazides bearing trifluoromethyl and trifluoromethoyl in the para-position offered correponding products **4h** and **4i** in the yields of 67% and 75%. Alkylsulfonyl hydrazide was also examined to offer **4j** in 85% yield. Apart from the substrate with a strong electronic-withdrawing nitro group, diphenylalkynes performed smoothly in the optimized conditions B to generate corresponding products in the yields of 65% to 86%. **4p** and **4q** were also obtained in the yield of 92% and 95%. To expand the application of our method, the generated iodo vinylsulfone product **4a** was also functionalized via Pd-catalyzed phenylation. The structure of the product was identified by single-crystal X-ray analysis (for details, see Supporting Information).

Table 3. Substrate scope of the iodosulfonylation reaction.[a, b]



[a] Reaction conditions B: **1a** (0.4 mmol, 2.0 equiv), **2a** (0.2 mmol, 1.0 equiv), H_2O_2 (0.8 mmol, 4.0 equiv), KI (0.3 mmol, 1.5 equiv), H_2O (2 mL), 100 °C, 2 hours under air atmosphere. [b] Isolated yield.

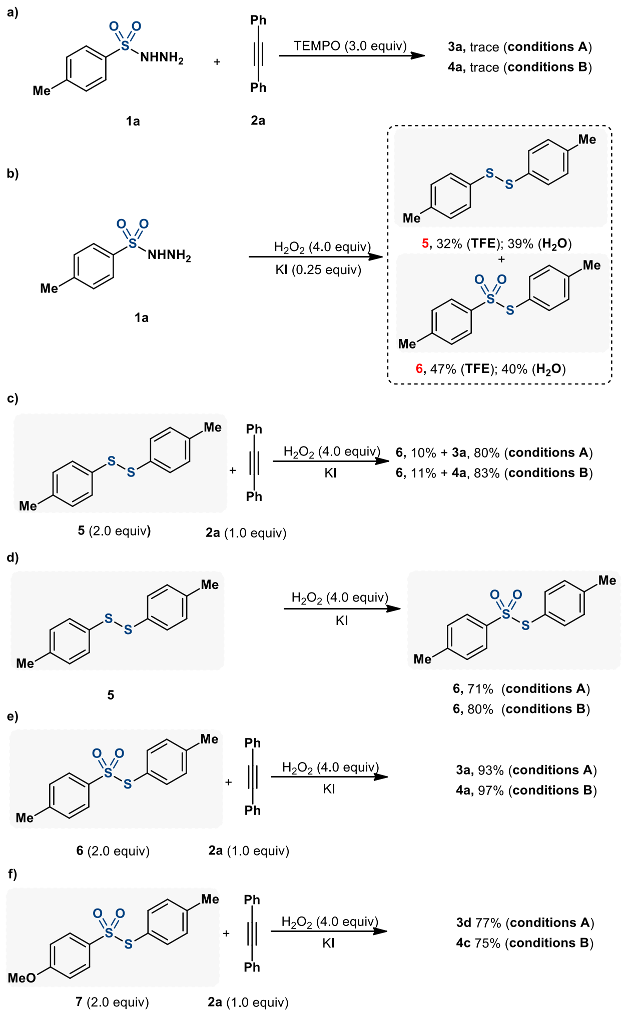
In the past decade, the developments of novel organic luminescent materials with AIE properties have attracted considerable attention.[14] To confirm the AIE nature of the benzo[*b*]thiophene-1,1-dioxides generated herein, **3c** was picked as a representative example and its photoluminescent (PL) spectra of solid powder (for PL spectra of solid powder of **3c,** see Supproting Information) and in mixtures of THF/water (scheme 2) with different fractions of water (f_w) were investigated. When the f_w was no more than 60%, the PL emission remained very weak. After increasing the f_w to 65%, an emission peak appeared. A dramatic enhancement in luminescence was observed when the water fraction was increased to 80%. These observation clearly identified the AIE nature of **3c**.



Scheme 2. PL spectra of **3c** in THF-water mixtures with different water fractions (f_w).

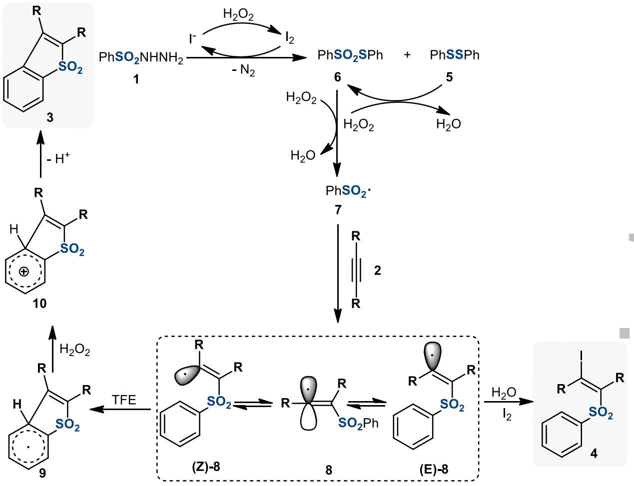
Next, experiments were performed to get some insight into the possible mechanism of the reaction, as shown in Scheme 3. When 3.0 equivalents of free radical scavenger TEMPO were added to the reaction system, the reaction was completely inhibited, which indicated that our protocol should involve a radical pathway (Scheme 3a). To identify the intermediates of the reactions, control experiments were carried out to generate **5** and **6** in the two standard conditions (Scheme 3b). When **5** and **2a** were treated with the standard conditions, **3a** and **4a** were obtained in over 80% yields. Moreover, **6** was also isolated in the yields of about 10% (Scheme 3c). When **5** was subjected to the standard conditions, **6** was generated in the yields of 71% and 80% (Scheme 3d). The examinations of **6** in the standard conditions generated **3a** and **4a** in the yields of 93% and 97% respectively (Scheme 3e). The results of these experiments indicated that the **5** and **6** generated from the substrate **1** were the intermediates of the transformations. Unsymmetrical thiosulfonate **7** was also tested in standard conditions to offer **3d** and **4c** (Scheme 3f). It has been reported that the strong H-bond donor (HBD) solvents, such as hexafluoro-2-propanol, and TFE might prove useful for the cyclizations of radicals reactions.[15] To confirm the role of TFE in the regulation of the reaction selectivity, experiments were performed in the mixture of TFE/water with different fractions of TFE

(f_{T}) (for details, see Supporting Information). The yield of **3a** decreased significantly with the reduction of f_{T}. When f_{T} was decreased to 40%, **3a** was not detected in the reaction system, while **4a** was obtained as the single product. Moreover, other solvents with similar properties, such as HFIP, and 4-(CF$_3$)-PhCH$_2$OH were also examined to offer **3a**.



Scheme 3. Mechanism study.

Based on the experiments above and previous reports,[16] the mechanism of the reaction was proposed as shown in Scheme 4. Firstly, iodine was generated from the oxidization of the KI, which later mediated the transformation from sulfonyl hydrazides substrates **1** to the intermediates **5** and **6**.[17] The intermediate **5** could be further oxidized to intermediate **6** in the presence of H_2O_2. Subsequently, the free radical intermediate **7** was produced from the intermediate **6**. Next, the addition of **7** to alkyne substrate **2** yielded the vinyl radicals **8** which has Z and E two isomers.[18] TFE could serve as a strong HBD to increase the persistence of the vinyl radical **8** and decrease its ability to react with I_2. Meanwhile, the solvation of both reactants and transition states in TFE medium could decrease the activation energy of the cyclization reaction. When the reaction was performed in TFE, intra-molecular cyclization of **Z-(8)** happened to produce **9.** Further oxidization and deprotonation processes gave the cyclic product **3.** However, when the reaction was conducted in H_2O, **E-(8)** was captured by generated I_2 to deliver **4.**



Scheme 4. Plausible reaction pathway.

In conclusion, a green, efficient and solvent-controlled strategy has been developed for the divergent synthesis of benzo[*b*]thiophene-1,1-dioxides and (E)-β-iodovinylsulfones from readily available sulfonyl hydrazides and alkynes *via* radical pathway for the first time. Remarkably, the AIE properties of the generated benzo[*b*]thiophene-1,1-dioxides were confirmed and a series of novel AIE-active molecules were obtained *via* our method. Further applications of the method in medicinal and other fields are under investigation.

Experimental Section

Conditions A: A sealed tube was charged with alkynes (0.2 mmol, 1.0 equiv), sulfonyl hydrazides (0.4 mmol, 2.0 equiv), KI (0.05 mmol, 25 mmol%), 30% H_2O_2 (0.8 mmol, 4.0 equiv) and 2.0 mL TFE. The reaction mixture was vigorously stirred at 100 ºC (oil temperature) for 2 hours. After cooling to room temperature, the reaction mixture was quenched with 10 mL saturated ammonium chloride solution and then diluted with ethyl acetate (20 mL). The organic layer was washed with distilled water and brine successively. After the solvent been removed under reduced pressure, the rude product was purified by flash chromatography on silica gel to afford the desired benzo[*b*]thiophene-1,1- dioxides.

Conditions B：A sealed tube was charged with alkynes (0.2 mmol, 1.0 equiv), sulfonyl hydrazides (0.4 mmol, 2.0 equiv), KI (0.3 mmol, 1.5 equiv), 30% H_2O_2 (0.8 mmol, 4.0 equiv) and 2.0 mL H_2O. The reaction mixture was vigorously stirred at 100 ºC (oil temperature) for 2 hour. After cooling to room temperature, the reaction mixture was quenched with 10 mL saturated ammonium chloride solution and then diluted with ethyl acetate (20 mL). The organic layer was washed with distilled water and brine successively. After the solvent been removed under reduced pressure, the rude product was purified by flash chromatography on silica gel to afford the desired (E)-β-iodo vinylsulfones.

Acknowledgements

Generous financial support from the National Natural Science Foundation of China (21702235, 81641002), the Fundamental Research Funds for the Central Public Welfare Research Institutes (ZZ10-024, ZXKT17053), Major National Science and Technology Program of China for Innovative Drug (2017ZX09101002-001-001). We also thank Mr. Sean Spurlin at Auburn University for the help of preparing the manuscript.

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UPDATE

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