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Metal-Free Radical Annulation of Oxygen-Containing 1,7-Enynes: Configuration-Selective Synthesis of (*E*)-3-((Arylsulfonyl)methyl)-4-Substituted Arylidenechromene Derivatives

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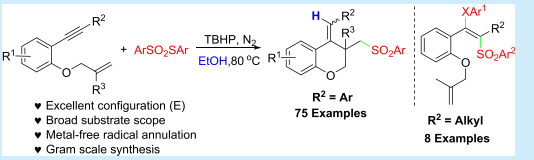
ABSTRACT: A novel strategy for the synthesis of (*E*)-3-((arylsulfonyl)-methyl)-4-substituted benzylidenechromene derivatives via a metal-free radical annulation reaction of oxygen-containing 1,7-enynes with thiosulfonates has been developed. The reaction shows broad substrate scope, wide functional group tolerance, and moderate to excellent yields. Moreover, thiosulfonates were well driven to achieve the bifunctionalization reaction of oxo-1,7-enynes which derived from aliphatic alkynes. In addition, the (*E*)-configuration of the products was highly controlled by the structure of 1,7-enyne.



Chromene and its derivatives are the privileged scaffolds widely present in many natural products[1] (Figure 1,

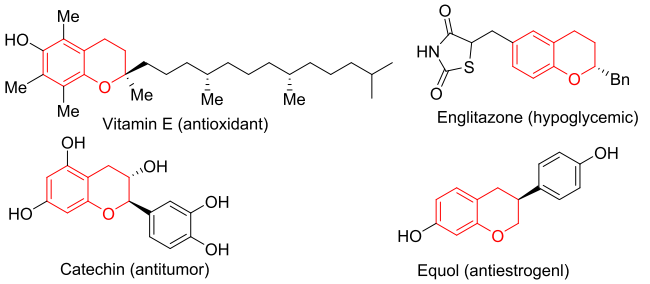
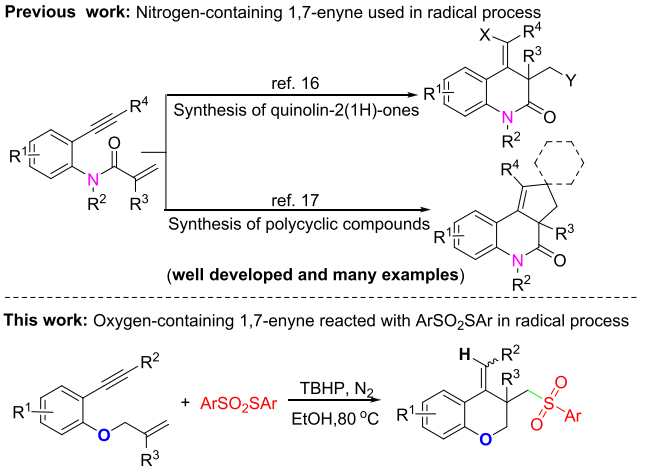


Figure 1. Bioactive molecule bearing chromene motif.

vitamin E[2]) and significant bioactive molecules (Figure 1, englitazone,[3] catechin,[4] equol[5]) with a range of biological activities, including antimicrobial,[6] antiviral,[7] mutagenicity,[8] antiproliferative,[9] sex hormone,[10] antitubercular,[11] anti-cancer,[12] anti-HIV,[13] etc. Because of their widespread applications and important biological activities, many synthetic routes of chromene derivatives have been reported over the past decades.[14] Although numerous synthetic methods have been well developed, exploring a novel strategy for construction of chromene derivative which remains in high demand.

The 1,*n*-enyne annulation reaction is one of the most important and efficient methodologies for the synthesis of small molecules with structural diversity and complexity[15] in which the nitrogen-containing 1,7-enyne radical cascade reaction is one of the most widely studied precursors for constructing diverse organic compounds with many different structures. For example, nitrogen-containing 1,7-enynes were efficient substrates for obtaining quinolin-2(1*H*)-ones[16] and azo-heterocyclic polycyclic compounds[17] (Scheme 1, previous work). In contrast, the radical reaction of oxygen-containing

Scheme 1. Radical Annulation Strategies of 1,7-Enyne



1,7-enyne was relatively less studied, although sporadic reactions could be found in the study of nitrogen-containing 1,7-enyne, which is merely a supplementary reaction of the reported work. Therefore, the study of oxygen-containing 1,7-enynes is an interesting work.

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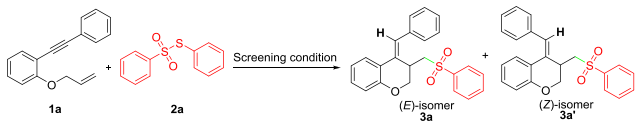
Synthesis of organic sulfone derivatives is a hot topic in organic chemistry because of their obvious bioactivities, such as anticancer, anti-HIV, and antibacterial[18] and their application in therapy for some diseases.[19] Herein, we report a radical-based tandem annulation of oxygen-containing 1,7-enynes and thiosulfonates to afford chromene derivatives bearing a sulfone skeleton (Scheme 1, this work).

At the beginning of this study, we attempted to apply the successful radical reaction cases of different sulfur reagents (such as $PhSO_2H$,[20] $PhSO_2Na$,[21] $PhSO_2NHNH_2$,[22] $PhSO_2Cl$,[23] PhSSPh,[24] and PHSH[25]) with nitrogen-containing 1,7-enyne to achieve this synthetic strategy; however, to our disappointment, the reaction results were very inferior and none of products were obtained. This may be due to the different electronic properties of the alkene in the two kinds of 1,7-enynes. The double bond in nitrogen-containing 1,7-enyne is electrophilic, while that in oxygen-containing 1,7-enyne is nucleophilic.

Recently, thiosulfonate has been proven as an effective radical precursor and successfully used in radical reactions.[26] Herein, the 1-(allyloxy)-2-(phenylethynyl)benzene **1a** and *S*-phenyl benzenesulfonothioate **2a** were chosen as the starting materials to screen the optimized reaction conditions (Table 1). Gratifyingly, when **1a** was treated with an equivalent amount **2a** in the presence of 3 equiv of *tert*-butyl hydroperoxide (TBHP) as oxidant in dimethyl formamide (DMF) at 80 °C under N_2 environment for 10 h, the desired product 4-benzylidene-3-((phenylsulfonyl)methyl)chromene **3a** was obtained in a moderate yield 51% along with excellent *E*/*Z* ratios (the ratio of *E*/*Z* (**3a**/**3a′**, > 20:1) isomers was detected by ^{1}H NMR) (Table1, entry 1). Encouraged by this result, we next screened other solvents such as ethyl acetate (EA), MeCN, dichloromethane (DCM), dichloroethane (DCE), 1,4-dioxane, and EtOH (Table 1, entries 2−7), which revealed that EtOH could give the best yield (entry 7). Subsequently, we investigated the different oxidants (Table 1, entries 8−12), which depicted that their activities were lower than that of TBHP. The temperature was evaluated in the model reaction, and it was found that the yields were not improved by elevating the temperature (entry 14), while lower temperature (entry 13) inevitably reduced the reaction yield. Then, the loading of TBHP was also carefully tested in model reaction. The results showed that the yield remained unchanged when the loading of TBHP decreased from 3 to 1 equiv (entries 15 and 16). However, when the loading of TBHP was 0.5 equiv of **1a**, the yield of the reaction decreased significantly. Thus, 1 equiv of TBHP was sufficient to ensure a successful reaction. Finally, we found that TBHP was essential to the reaction, and without it the reaction did not proceed at all (entry 18). The optimal reaction conditions was pointed out as follows: the mixture of 1-((2-methylallyl)oxy)-2-(arylethynyl)benzene (0.2 mmol), thiosulfonates (0.2 mmol), and TBHP (1 equiv, 0.2 mmol) was stirred in EtOH (2.5 mL) at 80 °C (oil bath temperature) under a nitrogen atmosphere for 10 h.

Table 1. Screening of the Reaction Conditions[a]

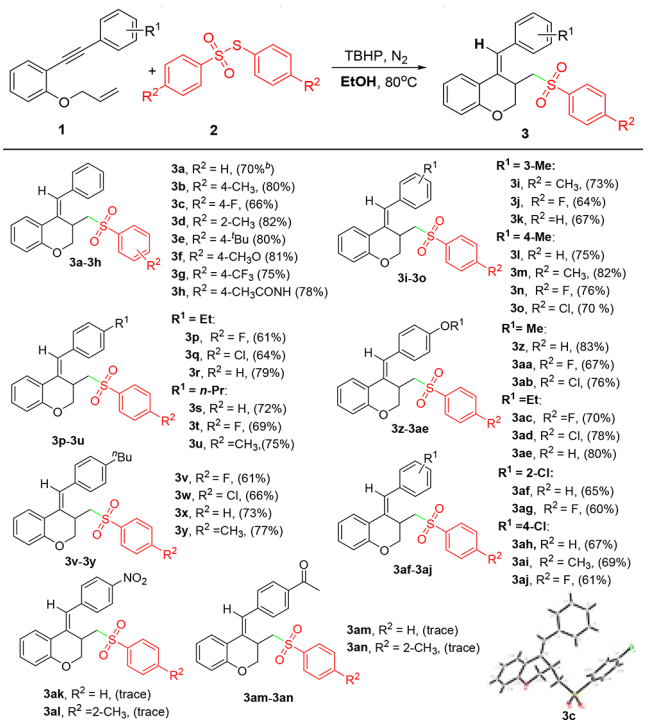


entry	oxidant (equiv)	solvent	ratio[b] (3a/3a')	3a (yield[c])
1	TBHP (3)	DMF	>20:1	51
2	TBHP (3)	EA		NR[d]
3	TBHP (3)	CH_3CN		NR
4	TBHP (3)	DCM		trace
5	TBHP (3)	DCE		trace
6	TBHP (3)	1,4-dioxane	>20:1	52
7	TBHP (3)	EtOH	>20:1	70
8	H_2O_2 (3)	EtOH	>20:1	26
9	DTBP (3)	EtOH	>20:1	43
10	TBPB (3)	EtOH	>20:1	40
11	$K_2S_2O_8$ (3)	EtOH	>20:1	34
12	BPO (3)	EtOH	>20:1	25
13	TBHP (3)	EtOH	>20:1	55[e]
14	TBHP (3)	EtOH	>20:1	70[f]
15	TBHP (2)	EtOH	>20:1	69
16	TBHP (1)	EtOH	>20:1	70
17	TBHP (0.5)	EtOH	>20:1	53
18		EtOH		NR

[a]Reaction conditions: Unless otherwise noted, **1a** (0.2 mmol), **2a** (0.2 mmol), and oxidant in solvent (2.5 mL), reaction at 80 °C for 10 h (monitored by TLC) under nitrogen atmosphere. [b]Ratio of *E*/*Z* (3*a*/3a') isomers was detected by ^{1}H NMR. [c]Isolated yields. [d]No reaction. [e]Under 60 °C. [f]Under 90 °C.

Under establishing the optimal reaction conditions, we began to survey this radical-based tandem cyclization of 1-(allyloxy)-2-(arylethynyl)benzene and thiosulfonate (Scheme 2). First, the reaction of 1-(allyloxy)-2-(phenylethynyl)-benzene and thiosulfonate **2** with different substituent groups was investigated, and all of the reactions were carried out to give compounds **3a**−**3h** in moderate to good yields, which indicated that the substituent properties of thiosulfonate have

Scheme 2. Scope for the Synthesis of Compound 3[a]



[a]Conditions: **1** (0.2 mmol), **2** (0.2 mmol), TBHP (1 equiv, 0.2 mmol), EtOH (2.5 mL), 80 °C (oil bath temperature), under a nitrogen atmosphere for 10 h. [b]Isolated yield.

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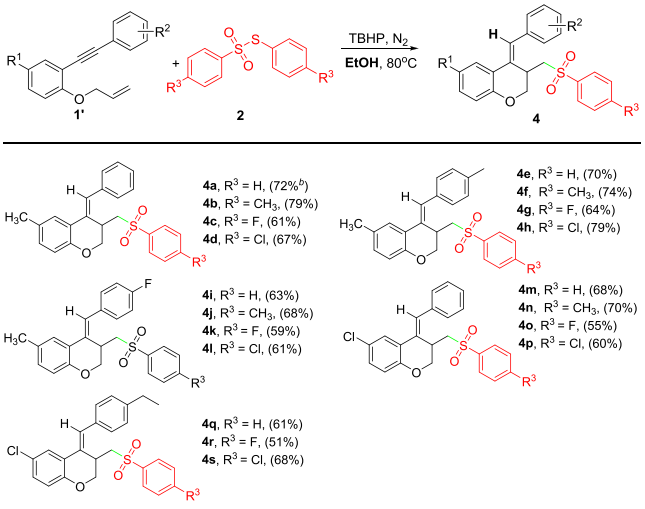
little influence on the reaction. Second, we inspected different alkyls (such as methyl, ethyl, *n*-propyl, and *n*-butyl) on the aromatic ring at the terminal alkyne (R^2), and the reactions were also performed successfully with corresponding products **3i**−**3y** in good yields. In addition, the reaction revealed that 1,7-enyne with a methoxy or ethoxy group was more suitable for this synthesis process and the higher yields could be obtained (**3z**, **3aa**−**3ae**). However, when a halogen atom (Cl−) was present on the aromatic ring of 1,7-enyne, the yields of the products were lower than those of alkyl and alkoxy (**3f**−**3aj**). While 1,7-enyne has a stronger electron-withdrawing group, the reaction failed completely (**3ak**−**3an**), which indicates that the substituent properties on 1,7-enyne had a greater influence on the reaction. Due to the steric hindrance, the products are mainly (*E*)-isomer, indicating that the reaction has excellent configurational selectivity. The X-crystal diffraction analysis of **3c** further confirmed this conclusion.

Subsequently, we investigated the substitution effect on the aromatic ring at phenol (R^1) (Scheme 3). When R^1 was a

Scheme 3. Scope for the Synthesis of Compound 4[a]

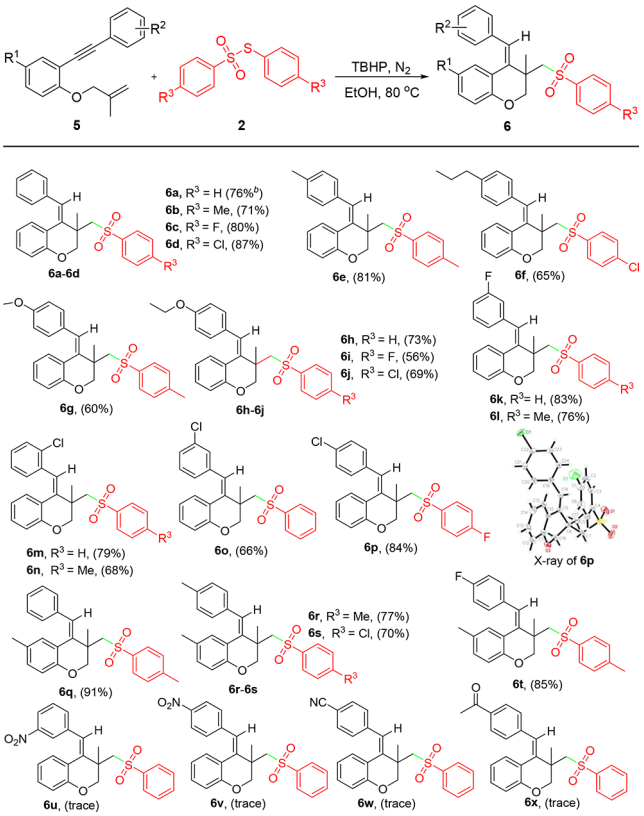


[a]Conditions: **1′** (0.2 mmol), **2** (0.2 mmol), TBHP (1 equiv, 0.2 mmol), EtOH (2.5 mL), 80 °C (oil bath temperature), under a nitrogen atmosphere for 10 h. [b]Isolated yield.

methyl, the 1,7-enyne could effectively react with thiosulfonate bearing different groups (Me−, F−, Cl−) to give the corresponding products (**4a**−**4d**) in good yield. We further found that R^2 was an electron-donating group (Me−, Et−) or a weak electron-donating group (F−), the reactions were all carried out smoothly to afford compounds (**4e**−**4l**) with satisfactory yields. When R^1 was a chlorine group (Cl−), the yield of the reaction decreased significantly (**4m**−**4s**), indicating that the substituents on 1,7-enyne had a great influence on the reaction.

Next, a series of oxygen-containing 1,7-enyne 1-((2-methylallyl)oxy)-2-(arylethynyl)benzene **5** was also studied with thiosulfonate **2** to investigate the scope of the annulation reaction (Scheme 4). At first, 1-((2-methylallyl)oxy)-2-(phenylethynyl)benzene could react well with different thiosulfonates to give **6a**−**6d** in good yields. When R^2 was a electron-donating group (Me−, Et−, Pr−, MeO−, and EtO−), which all could tolerate the screened conditions, providing the corresponding compounds with high yields (**6e**−**6j**). In addition, when R^2 was a halogen atom (F−, Cl−), the

Scheme 4. Scope for the Synthesis of Compound 6[a]



[a]Condition: **5** (0.2 mmol), **2** (0.2 mmol), TBHP (1 equiv, 0.2 mmol), EtOH (2.5 mL), 80 °C (oil bath temperature), under a nitrogen atmosphere for 10 h. [b]Isolated yield.

reported reactions proceeded well, which given the corresponding products with favorable yields (**6k**−**6p**). In addition, when R^1 was a methyl, the explored reactions were afforded the corresponding products in excellent yields (**6q**−**6t**) (up to 91%). Consistent with the result of product 3, the reaction failed when R^2 was a strongly electron-withdrawing group (NO_2−, −CN, and MeCO−) (**6u**−**6x**). Interestingly, because of the steric hindrance effect of methyl, the structure **6** was confirmed as an (*E*)-isomer by the X-ray crystal diffraction of **6p**. Therefore, this indicated that the configuration of the products was highly controlled by the structure of 1,7-enyne.

Strangely, when substrate **7** is derived from aliphatic alkynes, the obtained product **8** is only the vicinal thiosulfonylation[27] of **7** and thiosulfonate (Scheme 5), which may be due to the difference in the electronic effects of the alkyl group from the aryl group. This can be demonstrated by **8g**, indicating that allyl is not involved in the reaction. In addition, the selenosulfonate can also be used in this reaction to give product **8h** with good yield.

The gram scale reaction was also verified. When **1a** (1.0 g, 4.3 mmol) reacted with **2a** (1.07 g, 4.3 mmol) under standard conditions, the desired product **3a** could be obtained with 73% yield (1.18 g). Moreover, the obtained compound **3** can be further applied to the Julia−Kosinski-type reaction to give *β*-alcohol derivatives (Scheme 6).

In order to understand the mechanism of the reaction, the control reaction of **1a** and **2a** was investigated under the standard conditions with the typical radical scavengers TEMPO (3 equiv) and BHT (3 equiv), respectively, and the

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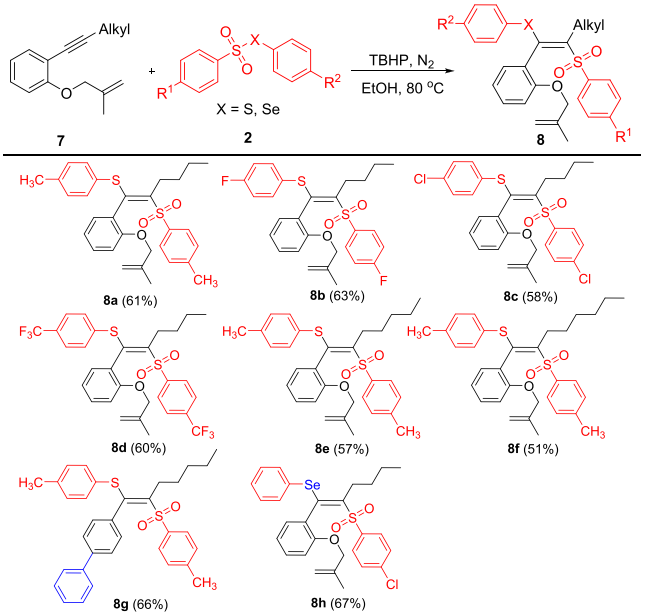
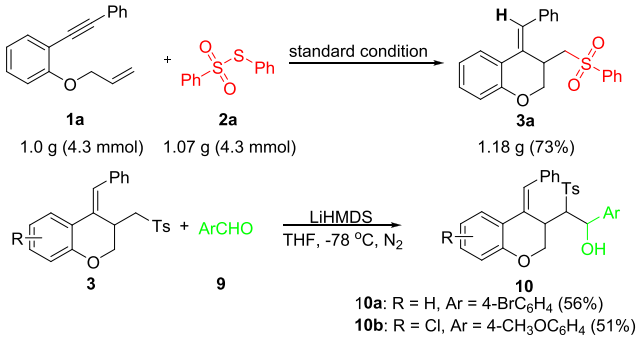
Scheme 5. Reactions of Compound 7[a]



[a]Condition: **7** (0.2 mmol), **2** (0.2 mmol), TBHP (1 equiv, 0.2 mmol), EtOH (2.5 mL), 80 °C (oil bath temperature), under a nitrogen atmosphere for 10 h. [b]Isolated yield.

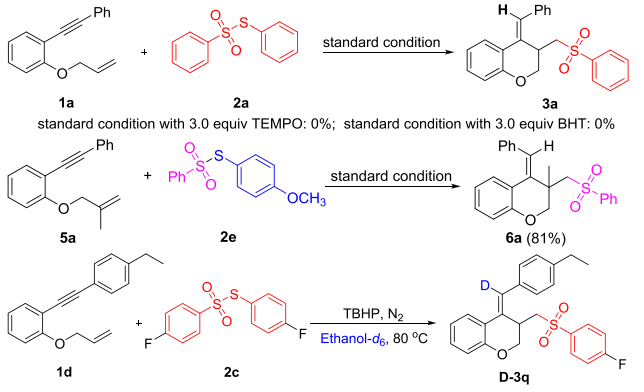
Scheme 6. Gram-Scale Reaction and Further Transformation



reaction was strictly inhibited, which indicated this reaction was a radical process. In order to further confirm the reaction mode of thiosulfonates, the reaction of **5a** and **2e** was investigated. It was found that only the **6a** was obtained, while the phenylthio group did not participate in the reaction. In addition, under the reaction of **1d** and **2c** in ethanol-d_6, the source of hydrogen on the olefinic bond was confirmed from the solvent ethanol (see the Supporting Information). The results are shown in Scheme 7.

On the basis of the above experimental results and literature,[28] a possible mechanism was proposed in Figure 2. First, TBHP produced the hydroxyl radical (OH•) and tert-butoxy radical (^{t}BuO•) by a homolysis reaction. Then, induced by these two radicals, the ethoxy radical (EtO•) was generated alongwith the release of a water and a tertiary butanol molecule. Under the initiation of radical EtO•, a sulfonyl radical **B** was formed with release of the **A** molecule.[29] Second, with the radical addition reaction between **1** and radical **B**, the intermediate **C** was obtained. Subsequently, the preferred intermediate **D** was formed by intramolecular radical addition reaction of intermediate **C**. Finally, **D** combined with a

Scheme 7. Control Experiments



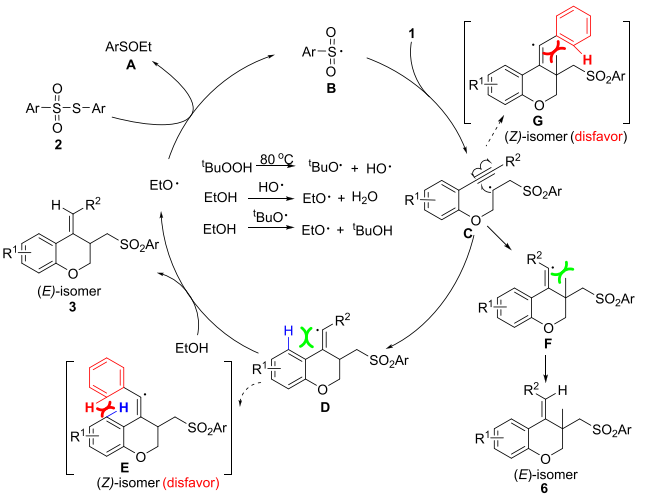


Figure 2. Proposed mechanism of the reaction.

hydrogen radical generated from EtOH to afford product **3** and simultaneously generated the radical EtO•, which reparticipated in a new radical reaction process. However, because of the steric hindrance, the intermediate **E** is not easy to form, so the (*Z*)-isomer is not easy to be obtained. When **5** was involved in the reaction, the preferred intermediates **F** could be effectively obtained so that it finally yielded the product **6** with (*E*)-configuration. Similar to intermediate **E**, the intermediate G is not easy to be generated, and its corresponding (*Z*)-isomer is also difficult to be obtained.

In conclusion, we have successfully developed a metal-free protocol for the preparation of chromene derivatives with sulfone skeleton via a radical annulation reaction of oxygen-containing 1,7-enynes with thiosulfonates. The 1,7-enynes and thiosulfonates bearing a wide range of substituted groups were well tolerated the screening condition to afford corresponding products in moderate to good yields. In addition, the bifunctionalization product was obtained from the reaction of thiosulfonates and oxo-1,7-enynes which derived from aliphatic alkynes. Moreover, the obtained products were (*E*)-isomer, indicating that the reaction had an excellent configuration selectivity. The obtained product **3** could further apply to the Julia−Kosinski reaction.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03946.

Experimental procedure, characterization data, NMR spectra and X-ray crystallographic data (PDF)

Accession Codes

CCDC 2012313 and 2012315 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Author Contributions

K.M. and M.B. contributed equally to this work.

Notes

The authors declare no competing financial interest.

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