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## Graphical Abstract

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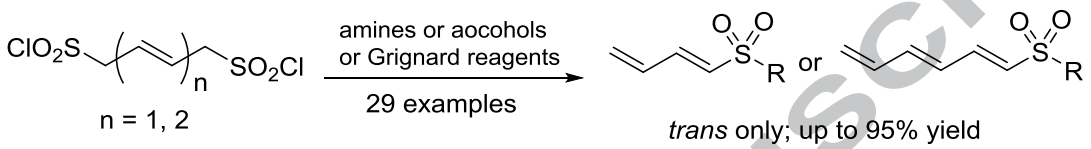

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# A convenient synthesis of (*E*)-conjugated polyene sulfonyl derivatives with excellent stereospecificity

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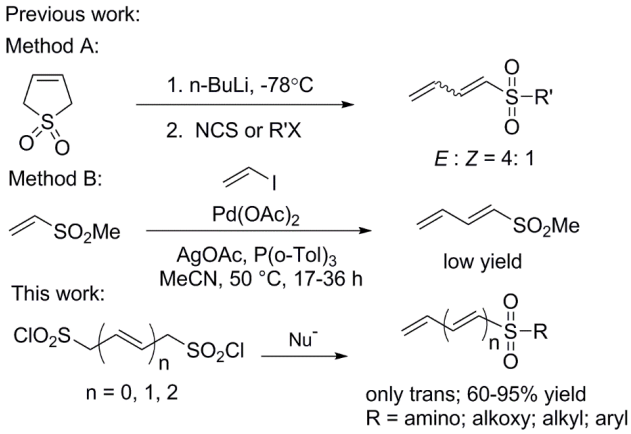
ABSTRACT

A highly selective synthesis of conjugated polyene sulfonyl derivatives is described via the elimination of disulfonyl chloride with readily accessible raw material dihaloalkane. The protocol offers a convenient way to form sulfonamides, sulfonates and even sulfones. Furthermore, this method was manipulated under mild condition with simple operation in high yield to afford only *trans* products.






**Scheme 1**. Synthetic routes of conjugated polyene-sulfonyl compounds

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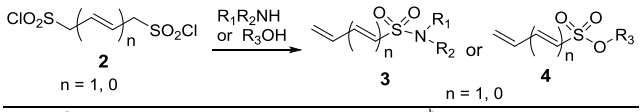
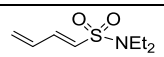
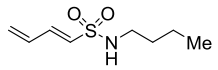
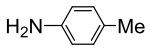
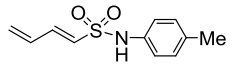
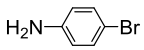
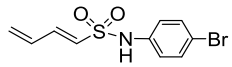
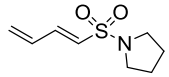
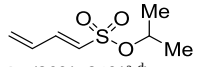
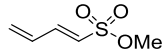
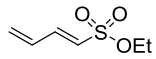
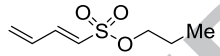
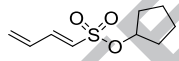
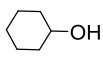
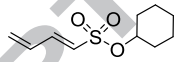
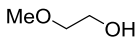
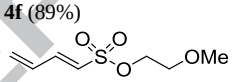
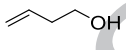
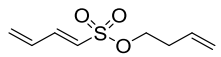
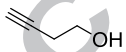
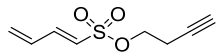
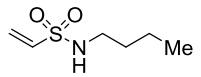
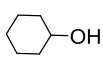
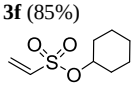
Alkene sulfonyl compounds bearing unique bifunctional moiety have been reported to exhibit a diverse range of biological and pharmaceutical activities[1], serve as important synthetic intermediates and building block in organic and medicinal chemistry[2], and represent click function in Click chemistry[3]. For instance, Cruz etc. recently reported vinyl sulfonates were utilized as efficient tools for "coupling-and-decoupling" (CAD) chemistry, in which the coupling step relied on Michael addition of various nucleophiles to vinyl sulfonates and decoupling step based on cleavage of the resulting sulfonates adducts[4]. The antimigraine drug Naratriptan was synthesized industrially by the Heck reaction of vinyl sulfonamide with substituted 5-bromoindole as a key step[5]. Vinyl- and 1,3-butadiene-sulfonyl compounds represents an important class of dienophile or diene in Diels-Alder reaction[6], Liang etc. reported the Himandrine core was synthesized through the intramolecular Diels-Alder reaction of dienic sulfonamide as diene with dienone[6c]. In addition, divinyl sulfones have been explored as thiol-terminated acrylate polymers' catchers to generate semitelechelic vinyl sulfone polymers capable of reacting with free cysteines[7a]. Very recently, the utilization of butadiene sulfonyl compound as a novel ligand was successfully applied in Ru based complex to catalyzed benzophenone hydrogenation[8].

Prior research has thoroughly investigated the synthesis of vinyl sulfonyl compounds[9], however, the convenient formation of conjugated diene- and triene-sulfonyl compounds has been much less recognized[10]. As depicted in Scheme 1, the conversion of 3-sulfolene into 1,3-butadiene-1-sulfonyl compound in the presenc--e of n-BuLi and NCS or haloalkane has a good yield, but this method generally obtains multiple products due to poor regio- and stereo-selectivity (Method A)[10a]. Then Madden etc. developed a Pd-catalyzed Matsuda-Heck reaction to give 1,3-butadiene mesylate with a poor yield (18% yield, Method B)[11].

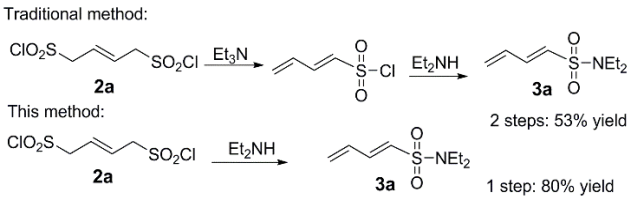

**Scheme 2**. Synthetic routes of substrates

**Table 1**. Preparation of monoene- and (*E*)-conjugated diene-sulfonamide and -sulfonate




| Entry[a] | NuH | Product[b] |
|---|---|---|
| 1 | $Et_2NH$ |  **3a** (80%) |
| 2 | n-$BuNH_2$ |  **3b** (90%) |
| 3 |  |  **3c** (93%) |
| 4 |  |  **3d** (89%) |
| 5 |  |  **3e** (82%) |
| 6[c] | i-PrOH |  **4a** (90%, 91%[a,d]) |
| 7[c] | MeOH |  **4b** (65%) |
| 8[c] | EtOH |  **4c** (76%) |
| 9[c] | n-PrOH |  **4d** (82%) |
| 10[c] |  |  **4e** (88%) |
| 11[c] |  |  **4f** (89%) |
| 12[c] |  |  **4g** (80%) |
| 13[c] |  |  **4h** (73%) |
| 14[c] |  |  **4i** (72%) |
| 15[c] | n-$BuNH_2$ |  **3f** (85%) |
| 16[c] |  |  **4j** (81%) |

[a]Reaction condition: 1.0 mmol compound **2a** or **2b** as substrate, 2.0 equiv amine or 5-10 mL alcohol, 10-20 mL DCM as solvent, room temperature, 5-15 min. [b]Isolated yield. [c]solvent-free, 35°C, 3-10 h. [d]1.0 equiv TEA and 1.0 equiv isopropanol.




**Scheme 3**. Direct comparison of two methods

In hence, considering the broad applications of the conjugated polyene sulfonyl compounds in organic chemistry, it is highly desirable to develop a general strategy to synthesize this class of building blocks with high yields in stereroselective manner.

It has been reported that the sulfonyl functionality could act as a leaving group in organic synthsis[12], Furthermore, taking advantage of the molecule's symmetry into consideration, the disulfonyl chloride (**2**) can be easily synthesized by sulfonation of dihaloalkane (**1**) with anhydrous sodium sulfite followed by chlorination with $PCl_5$, $SOCl_2$ or oxalyl chloride (Scheme 2)[13]. Herein, we employ compounds **2** as the starting material, one sulfonyl chloride could act as a leaving group to form a double bond and the other sulfonyl chloride could react with the nucleophile to offer a functional moiety such as sulfonamide, sulfonate and sulfone. Comparing with the previously reported methods, this strategy provides a general method for the syntheses of conjugated polyene-sulfonyl derivatives including monoene, diene and triene. It is noteworthy that the reaction featured with excellent stereospecificity (Scheme 1).

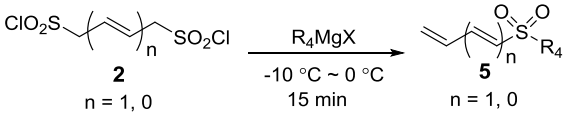
The reaction optimization commended with the treatment of 2-butene-1,4-disulfonyl chloride (**2a**) as the model substrate with various nucleophilic reagent. Firstly, our synthetic strategy was examined for the formation of alkene sulfonamide and sulfonate. As expected, N,N-diethyl-1,3-butadiene-1-sulfonamide (**3a**) and isopropyl-1,3-butadiene-1-sulfonate (**4a**) were successfully synthesized from *E*-**2a** with $Et_2NH$ and isopropanol, and moreover, only *E*-**3a** and *E*-**4a** were obtained (Table 1, entry 1 and entry 6). It was found that the use of two equivalents $Et_2NH$ maximized the yield of compound **3a**. With increasing the amount of $Et_2NH$, the yield of polyene-sulfonamide **3a** decreased since the excess $Et_2NH$ would further undergo the undesired Michael addition reaction with the product **3a**[2b,9]. It is worth noting that the formation of polyene-sulfonate was not affected even the alcoholic nucleophile was used as the solvent, no Michael addition side reaction was observed in the reaction mixture. In addition, compound **4a** could be synthesized regardless of the addition of base (Table 1, entry 6).

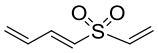
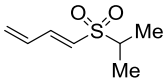
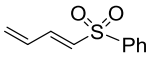
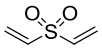
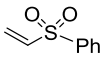
With this simple procedure in hand, the scopes of amines and alcohols were investigated carefully. As shown in Table 1, both anilines containing electron-withdrawing or electron-donating group (entries 3 and 4), cyclic amine (entry 5) and linear amines (entries 1 and 2) all generated corresponding *E*-conjugated diene sulfonamides with 80-93% yields although the yield of secondary amines were slightly lower than that of primary amines. The saturated linear alcohols (entries 6-9), cyclic alcohols (entries 10 and 11) even alcohols containing the alkene and terminal alkyne functionalities (entries 13 and 14) are suitable for this method, affording the corresponding sulfonate with 65-90% yield. Unfortunately, *tert*-Butanol was failed to add into the sulfonyl chloride group probably due to the disfavored steric hindrance. Subsequently, the monoene-sulfonamide and -sulfonate (compounds **3f** and **4j**) were given under similarly reaction condition with satisfactory yield (entries 15 and 16).

For the purpose of comparison with this method, we attempted to synthesize compound **3a** used traditional method that corresponding 1,3-butadiene-1-sulfonyl chloride reacted with $Et_2NH$ (Scheme 3). Actually, the 53% yield of latter method was far lower than that of one-pot procedure. These results clearly demonstrate the current method has unique advantages over the known strategy.

Encouraged by above results and inspired the extensive applications of sulfone in organic chemistry[14], we tried to investigate the synthesis of conjugated alkene sulfones

**Table 2**. Preparation of monoene- and (*E*)-conjugated diene-sulfone




| Entry[a] | $R_4MgX$ | Product[b] |
|---|---|---|
| 1 |  |  **5a** (78%) |
| 2 | i-PrMgBr |  **5b** (81%) |
| 3 | PhMgBr |  **5c** (75%) |
| 4 |  |  **5d** (83%) |
| 5 | PhMgBr |  **5e** (85%) |

[a]Reaction condition: 1 mmol of compound **2a** or **2b**, 2.0 equiv Grignard reagent and 10-20 mL anhydrous THF under an Ar atmosphere in ice bath. [b]Isolated yield.

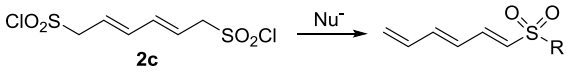
(compound **5**) to establish the generality and versatility of this protocol. The Grignard reagent was easily accessible and widely applied in modern organic synthesis, we next studied the feasibility of formation the conjugated polyene sulfone using the Grignard reagent as a nucleophile, though it may undergo the competing addition way[15]. To our delight, the (*E*)-conjugated olefin sulfones were successfully obtained from compound **2** in high efficiency without any undesired side adducts formation (Table 2). In this protocol, three representative Grignard reagents containing alkenyl, alkyl and aryl group were selected to synthesize monoene, (*E*)-conjugated diene-sulfone with 75-85% yield. It is particularly to point out, bilateral polyene sulfones (**5a**, **5d**) were furnished when vinyl Grignard reagent was used (entries 1 and 4). It's reasonable to predict that the diversity of Grignard reagents could provide more variability with this methodology. Eventually, the generality of this protocol was further approved through the application of the synthesis of various sulfones.

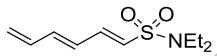
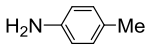
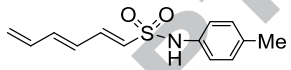
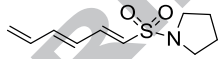
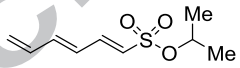
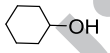
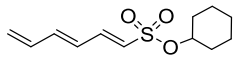
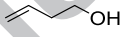
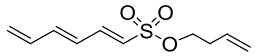
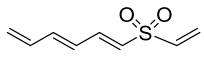
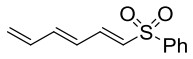
Subsequently, this strategy was used to synthesize a series of (*E*)-conjugated triene sulfonyl compounds under this similar reaction conditions. As excepted, conjugated triene sulfonyl derivatives were successfully obtained with a sole stereospecificity, and the results were shown in Table 3. Notably, the bi-polyene sulfone **5f** could also be prepared through this methodology.

The results that all above products were *trans* suggested that this method should have excellent stereoselectivity, then the *E*/*Z*-**2a** were exploited as substrates for further study. As shown in Scheme 4, only *E*-product were obtained as the sole product regardless of *E*/*Z*-**2a** was used as the starting material, suggesting the strategy has an excellent stereospecificity.

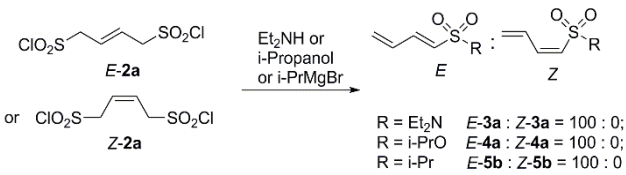
The plausible reaction mechanism was deduced through E1cb elimination mechanism by an example of compound **2a** (Scheme 5)[16]. Initially, the α-H was attacked by the nucleophile and a carbon anion was generated, then the lone pair of electrons on the carbon anion resonated to the neighboring atom, thus sulfonyl

**Table 3**. Preparation of (*E*, *E*)-conjugated triene-sulfonyl derivatives

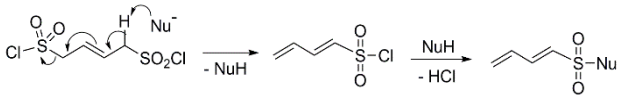



| Entry[a] | NuH | Product[b] |
|---|---|---|
| 1 | $Et_2NH$ |  **3g** (67%) |
| 2 |  |  **3h** (89%) |
| 3 |  |  **3i** ( 64%) |
| 4[c] | i-PrOH |  **4k** (80%) |
| 5[c] |  |  **4l** (71%) |
| 6[c] |  |  **4m** (75%) |
| 7[d] |  |  **5f** (60%) |
| 8[d] | PhMgBr |  **5g** (62%) |

[a]Reaction condition: 1.0 mmol compound **2c**, 2.0 equiv amine or Grignard reagent, 10-20 mL DCM as solvent, room temperature, 5-15 min. [b]Isolated yield. [c]solvent-free, 5-10 mL alcohol, 35°C, 3-8 h. [d]10-20 mL anhydrous THF as solvent.




**Scheme 4**. Stereo-selectivity of the reaction




**Scheme 5.** Proposed reaction mechanism

chloride group was expelled as the leaving group and new double bond was formed. Finally, nucleophiles attacked the intermediate again to afford target conjugated alkene sulfonyl compound.

## Conclusion

In summary, we have developed a convenient and general method for the synthesis of conjugated polyene-sulfonyl compounds including sulfonamides, sulfonates and sulfones from cheap and simple starting materials dihaloalkane under mild conditions with great yield and excellent stereospecificity. In particular, the synthesis of the conjugated triene products and the successful applications of Grignard reagents demonstrated the universality of this strategy, and the application of those

important building blocks is currently undergoing in our laboratory.

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## References and notes

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17. A gram scale experiment can also be performed: **2a** (2.0g) reacted with isopropanol (30 mL) at 35°C and stirred overnight, **4a** was isolated by by flash column chromatography with 84% yield.

## Supplementary Material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/

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- A highly selective synthesis of (*E*)-conjugated polyene sulfonyl derivatives.
- The convenient protocol has a great generality.
- The reaction was manipulated under mild condition with high yield.