

Catalyst- and Additive-Free Hydrosulfonylation of 1, 3-Dienes for Allylic Sulfones Synthesis

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Abstract

The demand for environmentally-friendly processes in organic synthesis has spurred interest in developing catalyst- and additive-free reactions for the synthesis of valuable organic compounds. Among these, allylic sulfones are a crucial structural motif used in drug development and organic synthesis. Despite several catalytic protocols have been established for the synthesis of allylic sulfones in recent years, the catalyst- and additive-free process has yet to be explored. In this study, we report a highly efficient and green pro-protocol for the synthesis of allylic sulfones from aryl-1, 3-dienes and sulfinic acids. The reaction was conducted under mild conditions using an aerobic atmosphere at room temperature without any catalyst or additive. The procedure demonstrated excellent atom economy, good regio- and chemo-selectivity, simple operation, and scalability. Overall, this method provides a promising strategy for the synthesis of allylic sulfones in a sustainable and cost-effective manner.

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Catalyst- and Additive-Free Hydrosulfonylation of 1, 3-Dienes for Allylic Sulfones Synthesis

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Keywords

Catalyst-free, Hydrosulfonylation, 1,3-Diene, Allylic sulfones, Green chemistry

Comprehensive Summary

The demand for environmentally-friendly processes in organic synthesis has spurred interest in developing catalyst- and add

Background and Originality Content

As increasing pollution and waste generated during chemical processes, catalyst- and additive-free organic synthesis is attracting more and more attention.^[1-4] This strategy provides an economic and environment-friendly route for synthesizing useful organic compounds, with processes that are less sensitive to air/moisture and operationally simple.^[1, 2, 5-9] Allylic sulfones are widely used in the synthesis of pharmaceuticals, bi-

logically active molecules, and organic materials due to their modifiable alkene moiety and stereogenic center.^[10-13] Therefore, the development of feasible synthetic methods for allylic sulfones is of great interest.^[14-17] While transition-metal-catalysed cross-coupling reactions and hydrosulfonation reactions have been established for the preparation of allylic sulfones,^[12, 18] their application in pharmaceutical and industrial manufacturing is limited in some extent due to the expensive and toxic catalysts employed,^[19-27] which generates significant amounts of waste and poses safety concerns. To address these issues, there is a need to develop more efficient and environmentally benign protocols. 1, 3-Dienes are a kind of readily available bulk materials that have been extensively studied as allylic source in synthetic chemistry. The hydro-functionalization of 1, 3-dienes offers convenient approaches to complex allylic compounds.^[28-33] In 2019, Chatterjee's group reported a hydrothiolation of 1, 3-dienes that yielded 1, 2-Markovnikov sulfide products. These products could be oxidized to produce branched allylic sulfones (Scheme 1a).^[29] In 2020, Zhou^[19] and Zi^[23] reported palladium-catalyzed hydrosulfonylation of 1,3-dienes with sulfonyl hydrazides and sulfonic acid, respectively (Scheme 1b), producing a series of chiral allylic sulfones with excellent regio- and stereo-selectivity. Our group have recently explored a boron-catalyzed hydrosulfonylation of 1,3-dienes with sulfonic acids to construct branched allylic sulfones (Scheme 1c).^[34] With our ongoing commitment to green chemistry,^[9, 35-37] we present a catalyst-free hydrosulfonylation approach that utilizes electron-rich 1,3-dienes and sulfonic acids at room temperature (Scheme 1d). The process has the potential to provide a straightforward and environmentally friendly route to allylic sulfones with excellent atom economy and regioselectivity.

Scheme 1. Hydrosulfonylation of 1, 3-Dienes for the Synthesis of Allylic Sulfones.

Results and Discussion

Results

At first, the reaction was conducted between 1-(buta-1, 3-dien-1-yl)4-methoxybenzene (**1a**) and 4-methylbenzenesulfonic acid (**2a**) (Table 1). After the considerable screening, the allylic sulfone (**3aa**) could be obtained in 94% yield with excellent regioselectivity using dichloromethane (DCM) as solvent at room temperature for 8 hours (Table 1, entry 1). When Boron-trifluoride-etherate was added, the yield decreased significantly which may be ascribed to the decomposition of the electron rich diene substrate under the conditions of strong Lewis' acid (Table 1, entry 2). A series of solvents were examined and the results indicated that DCM was the proper choice (Table 1, entries 3-11). When the reaction was performed at higher temperature, only 69% and 56% product were generated (Table 1, entry 12-13). When the ration of the substrates was changed to 1:1.2 and 1:1.5 (Table 1, entry 14-15), the product was obtained in the yield of less than 90%. There was no obvious promotion of the yield with a prolonged reaction time to 12 hours.

Table 1. Optimization of the conditions.

| Entry | Variation from the standard conditions ^a | Yield ^b |
|-------|---|------------------------|
| 1 | None | 94% (93%) ^c |
| 2 | Added 10 mol% BF ₃ ·OEt ₂ | 35% |
| 3 | with petroleum ether instead of DCM | 32% |
| 4 | with CYH instead of DCM | 25% |
| 5 | with toluene instead of DCM | 30% |
| 6 | with THF instead of DCM | 0 |
| 7 | with EA instead of DCM | 0 |
| 8 | with acetone instead of DCM | 0 |
| 9 | with MeOH instead of DCM | 0 |
| 10 | with MeCN instead of DCM | 0 |
| 11 | with MTBE instead of DCM | 0 |
| 12 | 40 °C | 69% |
| 13 | 70 °C | 56% |
| 14 | 1a/2a = 1.2 | 67% |

^a Standard reaction conditions: **1a** (0.20 mmol, 2 equiv), **2a** (0.10 mmol, 1 equiv), DCM (3 mL), 25 °C, 8 h.
^b Isolated yield. ^c 12 h.

^a Standard reaction conditions: **1** (0.20 mmol, 2 equiv), **2** (0.10 mmol, 1 equiv), DCM (3 mL), 25 °C, 8 h.
^b Isolated yield.

With the optimized reaction conditions established, we investigated the scope and generality of the present process (Table 2). Initially, we explored the scope of the sulfinic acids, starting with phenyl sulfinic acid, which afforded **3ab** in 90% yield. We then evaluated phenyl sulfinic acids with substituents at the C4 position of the phenyl ring, with chloro and bromo substituents offering the desired products in 76% (**3ad**) and 94% (**3ae**) yields, respectively. Even electron-withdrawing groups (-CN, -CF₃, -NO₂) at the C4 position of the phenyl ring were tolerated under the standard conditions, giving the desired allylic sulfones (**3ac**, **3af**, **3ag**) in 62%-81% yields. A product with multiple halogen groups, **3ah**, was also synthesized in 79% yield. We also examined phenyl sulfinic acids with methyl or trifluoromethyl groups at the C3 and C2 positions of the phenyl ring, which gave **3ai** to **3al** in 64% to 83% yields. Replacing the phenyl group with 2-naphthyl led to the synthesis of **3am** in 81% yield. Additionally, aliphatic sulfinic acid also proved to be an efficient sulfonylation reagent, affording **3an** in 68% yield. We then investigated the limitation of 1,3-dienes. Firstly, we examined the substituent effect at the C4 position of the phenyl group of **1a**, which yielded **3bain** 54% yield when the C4 position of the phenyl ring was substituted with methyl. However, removing the substitution at the benzene ring resulted in a yield of only 10% (**3ca**). Meanwhile, products with substitutions at the C3 and C2 positions of the phenyl group were only generated in yields of 24%-27% (**3da**, **3ea**). The 1,3- diene bearing a naphthalene group was well-tolerated and afforded the corresponding product **3fa** in 67% yield. Notably, substrates with electron-rich aromatic rings such as thiophene, furan, and their derivatives offered corresponding products **3ha** -**3ja** in the yields of 61%-72%. To showcase the effectiveness of this approach, the reaction was scaled up to 10 mmol, and **3aa** was successfully synthesized at a gram scale with a yield of 71%.

Scheme 2. Scale-up experiment.

A series of calculated green metrics have been employed as a measurable tool for evaluating the eco-friendliness of reactions in the chemical and pharmaceutical industries. Herein, the atom efficiency (AE), and environmental factor (E factor) of the processes were calculated to assess the green features of the process as shown in Table 3. Compared with the previous two methods developed by Zhou and Zi, this protocol exhibits superior atom economy and E factor, which indicate this is a more fascinating solution to prepare allylic sulfones from the view point of green chemistry.

Table 3. Green chemistry metrics of the previous reports and our method

| Scope of the reaction Conditions | Atom Economy (AE) | Environmental Factor (E factor) |
|----------------------------------|-------------------|---------------------------------|
| Zhou's work ¹⁹ | 0.83 | 1.28 |
| Zi's work ²³ | 0.91 | 0.65 |
| Our work | 0.95 | 0.60 |

Based on previous reports and initial experimental findings,^[38-41] a proposed mechanism for this reaction is presented in Scheme 3. The hydrosulfonylation of 1,3-dienes **1** with sulfinic acids **2** is proposed to proceed through the following steps: (1) Proton migration from the **2** to the terminal of 1,3-diene generates an allyl carbocation intermediate; (2) The benzenesulfonic acid anion acts as a nucleophile and attacks the allyl carbocation, leading to the formation of product **3** via C-S bond formation.

Scheme 3. Proposed reaction pathway.

Conclusions

We have successfully developed a highly regioselective hydrosulfonylation method for 1,3-dienes using sulfinic acids, without the need for any catalyst or additive, under mild conditions at room temperature. This approach offers excellent atom economy and good functional group compatibility, making it a promising strategy for synthetic applications. Our ongoing research aims to further elucidate the mechanistic details and expand the methodology to enable its application in a broader range of organic transformations.

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