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Generation of ArS-substituted Flavone Derivatives Using Aryl Thiols as Sulfenylation Agents

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The regioselective and metal-free sulfenylation of flavones was achieved under aerobic conditions with ammonium iodide salt as an inducer instead of traditional iodine/oxidant combinations. This method enables the generation of various ArS-substituted flavone derivatives in good to excellent yields under environmentally friendly conditions, which significantly enriches current flavone chemistry.

The construction of C-S bond is a very important transformation in organic synthesis, because C-S bond is widely present in natural products and drug molecules. Therefore, many researchers have devoted their efforts on developing highly efficient, regioselective, and environmentally friendly C-S bond formation methods. Traditionally, C(sp^3)-S bond can be constructed easily by the condensation of an alkyl halide with a metal thiolate. Recently, transition metal catalyzed C(sp^3)-S bond formation were successfully developed via cross couplings between aryl halides and various sulfenylation reagents such as thiols (Scheme 1), sulfonil chlorides, disulfides, sodium sulfinites, and sulfonil hydrazides. However, these processes require the use of prefunctionalized halides and expensive catalysts.

Recently, transition metal-catalyzed C-S bond formation via direct C-H bond functionalization has risen as an efficient alternative method, which allows direct conversion of C-H into C-S bonds. Although this method is highly efficient and atom-economic, these reactions still suffer from the high loading of transition metal catalysts, additives and harsh reaction conditions sometimes.

Very recently, metal-free iodine-induced sulfenylation method to construct C(sp^3)-S bond was successfully developed (Scheme 1). This method doesn’t need the use of any toxic and transitional metal catalysts, and proceeded well under environmentally friendly reaction conditions, generating thioesters in good yields. Despite this significant progress, the development of a new metal-free sulfenylation method is still highly desirable.

Herein, we developed a new and regioselective sulfenylation method in which a clean and colorless ammonium iodide salt was used as a reaction inducer instead of direct usage of purple iodine. In this study, air was used as the oxidant instead of pure oxygen and some oxidants (Scheme 1); and cheap aryl thiols were used as sulfenylation agents. To the best of our knowledge, there are no such reports to date. In this paper, this ammonium iodide-induced sulfenylation method was directly applied to electron-rich flavones to generate flavone derivatives which may be potentially valuable in drug discovery.

Scheme 1 Previously reported sulfenylation methods with aryl thiols as sulfenylation agents.

To find the suitable reaction conditions for the ammonium iodide-induced sulfenylation between flavones and aryl thiols, flavone 1a and thiol 2a were used as the representative reactants. Different catalysts/inducers, oxidants, and solvents were screened.
under different reaction temperature (Table 1). First, CuCl₂ and FeCl₃ were used as catalysts, and TBHP (tert-butyl hydroperoxide, 70 wt % in water) was employed as an oxidant. Both reactions gave a less than 5% yield or trace amount of expected product 3a (entries 1 and 2) at 80 °C in CH₂CN. Using CuI as a catalyst with TBHP also provided a less than 5% yield of 3a (entry 3) in CH₂CN. The combination of KI and TBHP only produced a 20% yield of 3a (entry 4). When I₂ was employed with TBHP in CH₂CN, 45% of 3a was observed (entry 5). The TBAI/TBHP combination in CH₂CN didn’t afford 3a at all (entry 6), while the combination of NH₄I/TBHP in CH₂CN afforded a 53% yield of 3a (entry 7). The combination of I₂/TBHP or I₂/DTBP afforded 3a in 70% and 65% yields, respectively (entries 8 and 9). When the reaction temperature was raised to 135 °C, the combination of NH₄I/TBHP in CH₂CN gave a 78% yield (entry 10). By converting NH₄I into I₂, the reaction afforded 75% yield of 3a (entry 11). Using DMF instead of CH₂CN afforded 83% yield of 3a (entry 12). Surprisingly, when NH₄I was used without TBHP, the reaction also gave an 86% yield of 3a (entry 13). Decreasing the amount of NH₄I from 2.0 to 1.2 equivalents led to 64% yield (entry 14). Using CH₃CN or THF as a solvent generated 55% yield or trace amount of product (entries 15 and 16). When toluene was used as a solvent, 73% yield of 3a (entry 17) was obtained. No presence of NH₄I in DMF didn’t produce any product (entry 18). Using H₂O₂ instead of TBHP as an oxidant in the presence of NH₄I afforded 3a in a 65% yield (entry 19). While the combination of I₂/H₂O₂ gave a 70% yield of 3a (entry 20). After the above screening, the suitable conditions selected for the coupling of flavone and aryl thiol were: flavone (1.0 equiv.), thiols (1.2 equiv.), NH₄I (2.0 equiv.), DMF is used as a solvent and temperature: 135°C.

After suitable reaction conditions have been obtained, different aryl thiols were reacted with different flavones which were synthesized based on existing literature. From Table 2, it can be found that all flavones with electron-donating functions gave better yields, while flavones with electron-deficient functions gave a little bit lower yields. Based on ¹H and ¹³C-NMR spectra of all products, it was found that -SAr was regioselectively added to the α-position of flavone.
<table>
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<th>Reaction</th>
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<tr>
<td>4</td>
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*Reaction conditions: flavone (1.0 equiv.), aryl thiol (1.2 equiv.), NH₄I (2.0 equiv.).* 

The ketone function of flavones, and no β-substituted products were isolated.

To further explore how the substituents on α and β-position of flavones influence the regioselective sulfonylation, two methyl-substituted flavones were synthesized with methyl function on α and β-position of the flavone (see Scheme 2, entries 1 and 2). When the α-position reaction site was blocked, no any expected product was isolated, indicating that the regioselectivity of this sulfonylation is very good, and the reaction only happened on the α-position of flavone. When the methyl group on the β-position of flavone, a decreased sulfonylation yield was observed, possibly due to the steric effects caused by neighbouring methyl function.

To determine if a radical process is involved in this sulfonylation protocol, TEMPO (2,2,6,6-tetramethylpiperidine) and BHT (butylated hydroxytoluene) were used as radical scavengers in the reaction of producing 3a. In the presence of TEMPO or BHT, 3a was still produced in good yields (Scheme 2). This fact indicated that radical intermediate is not involved in the sulfonylation process. Based on the above results and existing literature, a plausible nucleophilic substitution reaction mechanism is proposed below. At

**Scheme 2** Control reactions and radical trapping experiments.

135 ºC, NH₄I was split into NH₃ and HI, and the resulting HI was further oxidized by air to generate iodine. Thiophenol was then reacted with iodine to form electrophilic species ArS⁺I⁺, which reacted further with electron-rich flavone 1 to give reaction intermediate A. After the loss of a proton from intermediate A, final product 3 was obtained.

**Scheme 3** Proposed reaction mechanism

**Conclusion**

In summary, an efficient and regioselective ammonium iodide-induced sulfonylation of flavones is herein reported with different thiophenols as sulfonylating agents, generating various ArS⁺ substituted flavone derivatives in good to excellent yields under metal-free conditions. This method has improved the current reported protocol represented by using iodine as a catalyst. This method enriches current flavone chemistry, making it a highly valuable and practical approach in pharmaceutical industry. Investigation on biological activities of flavone derivatives currently underway. The method is also quite suitable for compound library production.

**Acknowledgment**

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Notes and references
Graphic abstract:

The regioselective and metal-free sulfenylation of flavones was achieved under aerobic conditions with ammonium iodide as an inducer.