## <u>Cramic</u> LETTERS

# Iodine-Catalyzed Facile Approach to Sulfones Employing TosMIC as a Sulfonylating Agent

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**Supporting Information** 

**ABSTRACT:** A novel iodine-catalyzed functionalization of a variety of olefins and alkynes and direct decarboxylative functionalization of cinnamic and propiolic acids with TosMIC to provide access to various vinyl, allyl, and  $\beta$ -iodo vinylsulfones is described. This simple, efficient, and environmentally benign approach employing inexpensive molecular iodine as a catalyst demonstrates a versatile protocol for the synthesis of highly valuable sulfones, rendering it attractive to both synthetic and medicinal chemistry.

he widespread popularity of sulfur-containing compounds can be attributed to their potential biological activity, pharmaceutical significance, and synthetic utility.<sup>1</sup> Among them, organosulfone compounds are an important class of functionalities and have drawn considerable interest of chemists owing to their versatility as intermediates in organic synthesis and ability to serve as building blocks in the construction of biologically active molecules or functional materials.<sup>2</sup> The sulfone functionality can serve as an activating, an electron-withdrawing, or a good leaving group and can be employed as a temporary modulator of chemical reactivity. Therefore, a variety of different transformations are feasible with this functional group, so aptly been described as a chemical chameleon by Trost.<sup>3</sup> Traditionally, sulfones are synthesized by the oxidation of corresponding sulfides or sulfoxides, alkylation of sulfinate salts, Friedel-Craftstype sulfonylation of arenes, and addition reactions to alkenes and alkynes.<sup>4</sup> Because of their distinctive electronic and structural features, the development of efficient approaches for the synthesis of these molecules is an appealing and valuable task in synthetic community.

*p*-Toluenesulfonylmethyl isocyanide (TosMIC), a unique isocyanide, is the most versatile synthon in organic chemistry.<sup>5</sup> It could be used to prepare quite different products from the same substrates by changing the reaction conditions. Therefore, it has long been renowned for its diversity in numerous synthetic transformations. In general, TosMIC undergoes base-mediated 1,3-dipolar cycloadditions with activated alkenes to provide pyrroles as products (Scheme 1).<sup>6</sup> We previously reported the first examples of synthesis of oxazoles and pyrroles C-nucleosides using TosMIC.<sup>7</sup> This report details the synthesis of sulfones from the same substrate molecules in the presence of iodine, demonstrating the diversity of TosMIC.



Scheme 1. Diversity of Reaction of TosMIC with Unsaturated Compounds



Over the past decade, our group has been working to expand the synthetic applications of TosMIC chemistry.<sup>8</sup> In continuation of that work, a novel access to various vinyl, allyl, and  $\beta$ -iodo vinyl sulfones employing TosMIC as a sulfonyl source is described herein (Scheme 2). In this newly developed protocol,







the addition of sulfonyl radical to unsaturated carbon takes place, which is the most popular approach for synthesis of sulfones in which sulfonyl halides,<sup>9</sup> sulfonyl hydrazides,<sup>10</sup> sulfinic acid,<sup>11</sup> and sodium sulfinate<sup>12</sup> are generally used as precursors of sulfonyl radicals. However, the notable advantages of the present reaction such as TosMIC as a rapid sulfonyl source, simple, cheap, and readily available iodine as an efficient catalyst, common and nontoxic DMSO as a solvent medium, wide applicability, and mild reaction conditions could make it as an effective complement for current methods.

Based on the recent development of iodine mediated reactions, we initiated our investigation with the reaction of styrene **1aa** and TosMIC **2** in the presence of 1 equiv of molecular iodine using DMSO as a solvent. To our delight, the corresponding vinyl sulfone **3aa** was observed with 90% yield. This promising result prompted us to optimize the reaction conditions. The screening of various iodine sources (NIS, PhI(OAc)<sub>2</sub>, CuI) and solvents (CH<sub>3</sub>CN, DCE, THF) shows no product formation except with NIS, albeit in low yield. Thus, the I<sub>2</sub>/DMSO system was found to be irreplaceable for sulfonylation of olefins. Pleasingly, the transformation worked well even with a catalytic amount of iodine (40 mol %) without a significant effect on reaction time and yield. The increase in amount of TosMIC did not improve the yield of **3aa**.

With the optimized reaction conditions in hand, a series of styrenes were applied in the reaction to establish the scope and generality of this protocol (Scheme 3). The results indicated that



<sup>*a*</sup>Reaction conditions: **1aa** (1.0 equiv), TosMIC (1.0 equiv), and  $I_2$  (0.4 equiv) in DMSO solvent at rt. <sup>*b*</sup>Yields refer to isolated products purified by column chromatography.

a wide range of substituted groups, such as methyl, chloro, fluoro, bromo, methoxy, nitro, cyano, and ester (1ab-ak), were well tolerated under the present conditions and afforded the corresponding vinyl sulfones (3ab-ak) in good yields. The 2vinyl naphthalene 1al and  $\alpha$ -phenyl styrene 1am were also applied in the reaction successfully to provide the corresponding vinyl sulfones 3al and 3am in 95 and 93% yields, respectively. The heterocycle-derived alkene, 2-vinyl thiophene 1an, is well tolerated and afforded 3an in 87% yield. However, the reactions of 4-hydroxy styrene and *N*,*N*-dimethyl-4-vinylaniline failed to give the corresponding products.

Interestingly, the reaction of  $\alpha$ -methylstyrene **1ba** provided the corresponding allylic sulfone **3ba** as the sole product instead

of the expected vinyl sulfone (Scheme 4). The formation of allylic sulfone could be rationalized by the sulfonylation at the

Scheme 4. Synthesis of Ally	yl Sulfones from Methy	yl Styrenes <sup>a, ø</sup>
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"Reaction conditions: **1ba** (1.0 equiv), TosMIC (1.0 equiv) and  $I_2$  (0.4 equiv) in DMSO solvent at rt. <sup>b</sup>Yields refer to isolated products purified by column chromatography.

terminal double bond with the migration of the double bond.  $^{10\mathrm{b}}$ The versatility of allylic sulfones to form C–C bonds via sulfonyl carbanions motivated us to test a series of substituted  $\alpha$ methylstyrenes (1bb-bi) under the standard conditions. Gratifyingly, the reactions proceeded smoothly with high regioselectivity, leading to the formation of the corresponding allylic sulfones (3bb-bi) exclusively. Moreover, the reaction shows high stereoselectivity. Thus, the  $\alpha$ -ethylstyrenes 1bj gave rise to the allyl sulfone 3bj as a single Z-isomer in 91% vield.<sup>10b,11g</sup> The reaction of 3-chloro- $\alpha$ -ethylstyrenes 1bk afforded 3bk in 88% yield. Similarly, when 1-cyclopropylvinylbenzene 1bl was used as the substrate 3bl was obtained as product. This result demonstrates the sulfonylation at terminal double bond with migration of the double bond followed by cyclopropyl ring opening with iodine. The configuration of 3bk and **3bl** was established as "Z" on the basis of the same analogy.

Next, the present approach, i.e., sulfono functionalization using TosMIC, was extended to acetylene functionality. The iodine-catalyzed reaction of phenyl acetylene with TosMIC resulted in the formation of the corresponding (E)- $\beta$ -iodo vinyl sulfone in 92% yield (Scheme 5). The recent report by Tiwari and co-workers revealed nanocopper-catalyzed synthesis of (E)vinyl sulfones from the same substrates, i.e., terminal acetylenes and TosMIC.<sup>13</sup> However, the current approach provides a good illustration of the diversity of TosMIC. A range of alkynes (4abai) bearing electronically varied groups (e.g., Me, Et, OMe, Cl, Br, OMe, Ph, CN,  $CO_2Me$ ) on the phenyl ring were found to be tolerant in these transformations, and the corresponding products (5ab-ai) were obtained in good yields. The sulfonylation of sterically hindered substrate 1-ethynylnaphthalene 4aj with TosMIC also afforded the desired sulfone 5aj effectively. (E)-But-1-en-3-yn-1-yl benzene 4ak could also be successfully employed to afford the desired iodosulfonylation product 5ak in 90% yield. However, the reaction of hex-1-yne did not afford the desired product. Pleasingly, 3-ethynylthiophene 4al could be employed in the reaction to furnish the desired product 5al in 82% yield. Notably, the internal alkynes 4ba-bc could be converted to the corresponding products 5ba-bc, although they are less reactive than others.

Scheme 5. Synthesis of Iodo Vinyl Sulfones from Acetylenes $^{a,b}$ 



<sup>*a*</sup>Reaction conditions: 4aa (1.0 equiv), TosMIC (1.0 equiv) and I<sub>2</sub> (0.5 equiv) in DMSO solvent at rt. <sup>*b*</sup>Yields refer to isolated products purified by column chromatography. <sup>*c*</sup>No significant improvement in the yield of the product was observed with further increase of the amount of catalyst. <sup>*d*</sup>The yield in parentheses refer to the yield obtained with 0.4 equiv of iodine.

In general, the decarboxylative sulfonylation of cinnamic acid requires harsh conditions and long reaction time. Intrigued by the above results, we envisioned TosMIC-mediated decarboxylative sulfono functionalization of cinnamic acid **1ca** under the standard conditions. Nonetheless, we did not obtain any product in the absence of base. To our delight, the desired (*E*)-1-methyl-4-(styrylsulfonyl)benzene **3aa** was obtained in the presence of K<sub>2</sub>CO<sub>3</sub>, while the other bases (DBU, Cs<sub>2</sub>CO<sub>3</sub>) failed to furnish the product. The optimum amount of K<sub>2</sub>CO<sub>3</sub> was found to be 1 equiv. Next, the scope of substrates was investigated, and the results are summarized in Scheme 6. Various cinnamic acid





<sup>*a*</sup>Reaction conditions: **4ca** (1.0 equiv), TosMIC (1.0 equiv), and  $I_2$  (0.4 equiv) in DMSO solvent at 80 °C. <sup>*b*</sup>Yields refer to isolated products purified by column chromatography

derivatives **1cb**–**ch**, which have substituents on the phenyl ring  $(CH_3, Cl, F, Br, OMe, NO_2, CN)$ , could proceed smoothly to afford the corresponding products **3ab**–**ah** in good yields. Moreover, (*E*)-3-(thiophene-2-yl)acrylic acid **1cn**, was also good substrate for this transformation, affording the corresponding product **3an** in 84% yield.

The synthetic utility of the present protocol was further extended to the decarboxylative coupling of phenyl propiolic acid **4ca**. The reaction resulted in the formation of **5aa** in 65% yield

(Scheme 7). To the best of our knowledge, this is the first example of direct synthesis of halogenated vinyl sulfones from

Scheme 7. Synthesis of Iodo Vinyl Sulfones from Phenyl Propiolic  ${\rm Acid}^{a,b}$ 



<sup>*a*</sup>Reaction conditions: **4ca** (1.0 equiv), TosMIC (1.0 equiv) and I<sub>2</sub> (0.4 equiv) in DMSO solvent at 80 °C. <sup>*b*</sup>Yields refer to isolated products purified by column chromatography. <sup>*c*</sup>No significant improvement in the yield of the product was observed with further increase of the amount of catalyst.

arylacetylenic acid. The previous related work shows synthesis of either vinyl or acetylenic sulfones as the products.<sup>12e,14</sup> The phenyl propiolic acids bearing substituents on the aromatic ring such as CH<sub>3</sub>, Cl and OMe participated in the reaction to deliver the products **Sab**-af in 61–69% yields. It is worth mentioning that the reactions were performed on each set of model substrates, i.e., on a 1.0 g scale, to afford the corresponding sulfones without significant effect on the yield, indicating that the present reaction is scalable and practical.

To explore the mechanism for TosMIC-mediated sulfono functionalization, we carried out some control experiments (Scheme 8). In the presence of TEMPO, a common radical

Scheme 8. Control Experiments



scavenger the reaction of styrene and TosMIC under standard conditions was almost ceased. This result suggests that the reaction have proceeded through a radical mechanism. It is worth pointing out that, during the optimization studies, the reaction of styrene and TosMIC mediated by NIS (instead of iodine) resulted in the formation of **3aa**, attesting the generation of sulfonyl radical from TosMIC. The reaction of styrene with 4-methylbenzene 1-sulfonyl iodide  $(A)^{15}$  without TosMIC and iodine furnished **3aa** in 78% yield. The result suggested that A might be the possible intermediate in this transformation.

On the basis of the control experiments, we propose a possible mechanism as shown in Scheme 9. Initially, the interaction of iodine with TosMIC generates *p*-toluenesulfonyl iodide **A** with the concomitant formation of iodine radical. Thus, formed *p*-toluenesulfonyl iodide underwent homolytic clevage to generate sulfonyl radical **B**, which then reacted with styrene **1aa** to generate the reactive alkyl radical **C**. Subsequently, the radical **C** is combined with iodine radical to give the intermediate **D**. Finally, the intermediate **D** undergoes elimination of HI to

#### Scheme 9. Proposed Mechanism



restore the unsaturation to afford the desired vinyl sulfone **3aa**. The regeneration of molecular iodine takes place by the oxidation of HI into molecular iodine along with the generation of dimethyl sulfide and water.

In summary, we have demonstrated TosMIC-mediated novel protocol that offers a convenient synthetic route to sulfones under metal-free conditions. Mechanistically the formation of sulfone is suggested to proceed via a radical mechanism. The protocol exhibited experimental simplicity, short reaction time, and high regio- and stereoselectivity with a broad substrate scope, which suggests that this approach has potential applications in organic synthesis. Further efforts to expand the substrate scope and applications are currently underway in our laboratory.

#### ASSOCIATED CONTENT

### **Supporting Information**

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00896.

Typical experimental procedures, detailed screening the reaction conditions, preparation and characterization of compounds, and spectroscopic data (PDF)

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The authors declare no competing financial interest.

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