Organic LETTERS

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Regioselective Synthesis of Substituted Arenes via Aerobic Oxidative [3 + 3] Benzannulation Reactions of α,β-Unsaturated Aldehydes and Ketones

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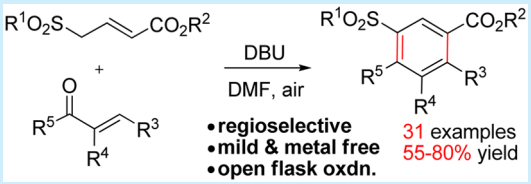
Supporting Information

ABSTRACT: Facile conversion of α,β-unsaturated aldehydes and ketones into highly substituted arenes via a base-mediated, completely regioselective, air-oxidative [3 + 3] benzannulation reaction with readily available 4-sulfonylcrotonates or 1,3-bisphenylsulfonylpropene is reported. The reaction can also be carried out as a one-pot, three-component operation using 4-bromocrotonates, aryl sulfinates, and cinnamaldehyde. This open-flask, metal-free reaction does not require anhydrous solvents, proceeds under mild conditions, and uses atmospheric oxygen as the oxidant to afford high yields of the 3-(arylsulfonyl)benzoic acid esters.



Chemists routinely encounter substituted arenes either as the core unit of a number of important natural products, pharmaceuticals, and functional materials or as building blocks for the synthesis of such molecules.[1] Substituted arenes are generally prepared by the selective introduction of functional groups onto simpler benzenoid systems via classical aromatic electrophilic substitution reactions (and nucleophilic aromatic substitution to a lesser extent).[2] Synthesis of polysubstituted arenes by electrophilic substitution reactions, however, becomes challenging when the inherent electronic nature of the arene and the directing effects of the substituents do not allow the desired substitution patterns to be achieved. Modern methods of aromatic functionalization such as the directed metalation[3] and catalytic coupling reactions[4] address this issue to some extent. These methods require arenes with preinstalled directing/functional groups that are in-turn introduced mostly by means of aromatic substitution reactions. Construction of arenes from acyclic precursors, commonly referred to as benzannulation, on the other hand, permits a greater degree of control of the regiochemical outcome.[5] Benzannulation reactions may be classified into various types depending upon the number of components and the number of carbons that each of them contribute to the final product, such as [5 + 1],[6] [4 + 2],[7] [3 + 3],[8] [2 + 2 + 2],[5f,9] [3 + 2 + 1],[8a,10] etc. The variety available for benzannulation reactions in terms of precursors, reaction conditions, catalysts, and mechanistic pathways vis-à-vis electrophilic substitution reactions makes the former an excellent method for the synthesis of polysubstituted arenes.[11]

A number of aryl sulfones, designed and synthesized for drug discovery programs, exhibit inhibitory activities against various enzymes (such as cyclooxygenase-2 (COX-2),[12] HIV-I reverse transcriptase,[13] sodium-proton exchanger-1 (NHE1),[14] etc.). In addition, the chromophoric activity[15] and coordinating properties[16] of aryl sulfones make them valuable synthetic targets (Figure 1).

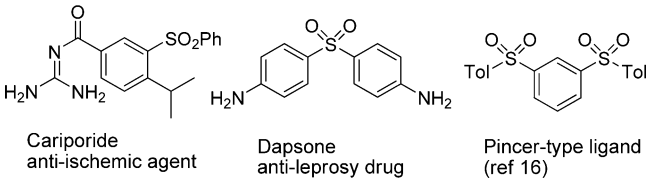


Figure 1. Some important aryl sulfones.

Sulfonylation of arenes,[17] oxidation of aryl sulfides,[18] and coupling of aryl halides with sulfinates[19] are the commonly used methods for synthesizing aryl sulfones. These methods are limited by the availability of the suitable arene precursors and their innate reactivity patterns. Therefore, it is evident that a benzannulation strategy, in view of its advantages, would constitute a superior protocol for the synthesis of substituted aryl sulfones.

We have been interested in exploring the synthetic potential of the readily available 4-sulfonyl crotonates **1** (Scheme 1) in annulation reactions. Our investigations along this direction resulted in the discovery of a facile, base-mediated oxidative benzannulation reactions for the regioselective synthesis of substituted 3-sulfonyl benzoates and 1,3-bissulfonylarenes, and the preliminary results are presented in the following passages.

Received: February 2, 2015
Published: February 27, 2015

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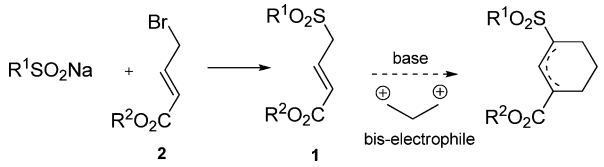
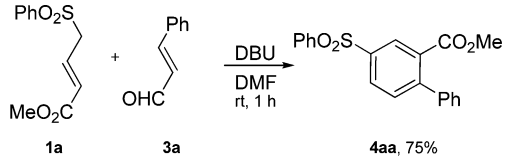
DOI: 10.1021/acs.orglett.5b00318
Org. Lett. 2015, 17, 1449−1452

Scheme 1. Preparation and Proposed Annulation Reaction of Sulfonyl Crotonate 1



4-Sulfonyl crotonates **1** can be readily prepared from the commercially available 4-bromocrotonates **2** and sulfinate salts via a nucleophilic displacement reaction, as depicted in Scheme 1.[20] We surmised that under basic conditions, and in the presence of a suitable bis-electrophile, **1** can function as a 1,3-bisnucleophile[20] leading to annulation reactions. To test our hypothesis, **1a** was treated with a base and a commercially available 1,3-biselectrophile, viz., *trans*-cinnamaldehyde **3a** (Scheme 2). It may be noted that, in the event of an annulation

Scheme 2. DBU-Mediated Benzannulation Reaction



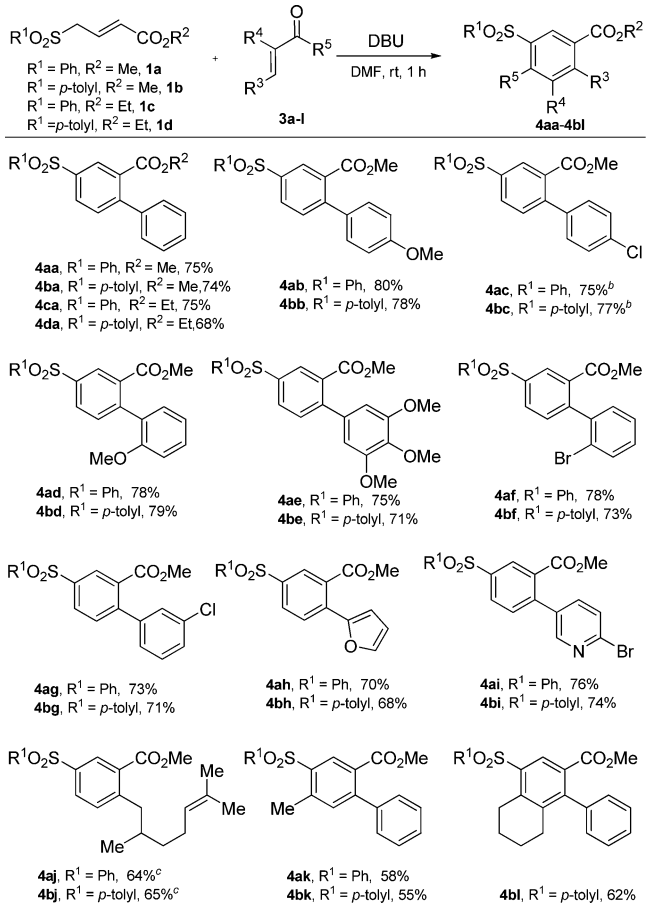
reaction of **1a** and **3a**, two regioisomeric outcomes are possible and each of the initially formed products could potentially aromatize by the base-mediated elimination of the phenylsulfinate group.[21] Under optimized conditions (2 equiv of DBU, DMF, rt; see Supporting Information (SI) for details), however, a benzannulated product retaining the phenylsulfonyl group was obtained that was tentatively assigned the structure **4aa** (Scheme 2).

This pleasing outcome prompted us to explore the scope of the regioselective benzannulation reaction with different 4-sulfonyl-crotonates **1a−d** and *α,β*-unsaturated aldehydes and ketones **3a−l**. The results are summarized in Scheme 3. A wide variety of highly substituted biphenyl derivatives are obtained in high yields from readily available starting materials. Heteroarene-bearing *α,β*-unsaturated aldehydes **3h−i** afforded the corresponding benzannulated products **4ah−bi**. The bromine-containing biphenyls **4af** and **4bf** can potentially serve as building blocks for the synthesis of important terphenyls[22] and other related analogues via palladium mediated coupling reactions. The presence of the ester functionality in the products also offers avenues for further synthetic manipulations (*vide infra*). The *α,β*-unsaturated aldehyde **3j** derived from (±)-citronellal, however, afforded an inseparable 2:1 mixture of regioisomeric products (**4aj−bj**). Importantly, representative *α,β*-unsaturated ketones [**3k**, R_3 = Ph, R_4 = H, R_5 = Me and **3l**; R_3 = Ph, R_4 = R_5 = $(CH_2)_4$] also underwent the benzannulation reaction to afford highly substituted 3-sulfonyl benzoates **4ak−4bl**.

The structures assigned for the products were confirmed by detailed ID and 2D NMR experiments (see SI) on representative product **4bd**. The NOE cross-correlations depicted in Figure 2 clearly demonstrate that the methoxyphenyl ring is closer to the ester functionality.

Additionally, this benzannulation reaction can be carried out conveniently as a one-pot procedure from commercially available materials as depicted in Scheme 4. The required sulfinate salt was allowed to react with the selected 4-bromocrotonate overnight,

Scheme 3. Scope of the Benzannulation Reaction[a]



[a]Reaction conditions: **1** (0.5 mmol), **3** (0.25 mmol), DBU (1 mmol), LR DMF (1 mL), 1 h, rt. Yields of isolated products. [b]Reaction run at 0 °C. [c]2:1 mixture of regioisomers.

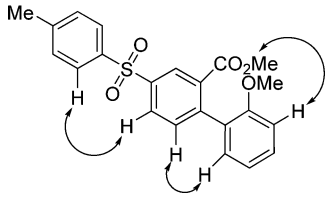
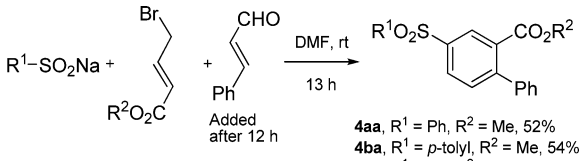


Figure 2. Important NOE cross-correlations in **4bd**.

Scheme 4. One-Pot, Three-Component Synthesis of Substituted Biphenyls 4aa−da



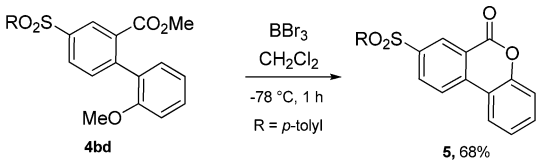
and then cinnamaldehyde was introduced into the reaction mixture. This one-pot, three-component protocol afforded biphenyl derivatives **4aa−da** that are identical to those obtained in the corresponding two-component reaction, albeit in lesser yields. It is noteworthy that this protocol combines the well-known advantages of multicomponent reactions (MCRs)[23] with

DOI: 10.1021/acs.orglett.5b00318
Org. Lett. 2015, 17, 1449−1452

that of benzannulation reactions (vide supra). Interestingly, one of the components (sulfinate salt) ends up as the substituent on the newly formed aromatic ring. The present method constitutes a unique addition to the thin list of three-component benzannulation reactions that are known to date.[7g,8a,10a]

As stated above, the multifunctional nature of the benzannulated products provide opportunities for further synthetic maneuvers. For example, treatment of the benzannulation product **4bd** with boron tribromide resulted in the formation of the benzocoumarin derivative **5** via sequential demethylation and lactone formation (Scheme 5). The benzocoumarin moiety

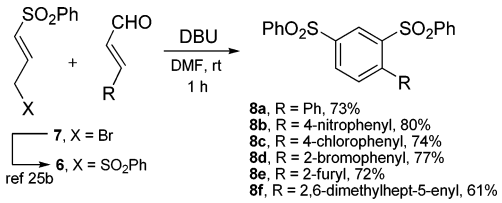
Scheme 5. Conversion of the Benzannulation Product 4bd to Benzocoumarin 5



is an important structural unit that imparts desirable properties in a number of (natural and man-made) anticancer agents, antithrombotic agents, and even laser dyes.[24] Moreover, the reaction depicted in Scheme 5 clearly establishes the proximity of the ester unit and the 2-methoxyphenyl ring in **4bd** and independently confirms the regiochemical outcome of the benzannulation reaction.

It was observed that the symmetric 1,3-bisphenylsulfonylpropene **6** also partakes as the three-atom nucleophilic component in the benzannulation reaction of α,β-unsaturated aldehydes. The former is easily prepared from the known bromide **7** by nucleophilic substitution.[25] Reaction of cinnamaldehyde **3a** with **6**[26] under the optimized conditions afforded the 2,4-bis(phenylsulfonyl)biphenyl **8a** in 73% yield (Scheme 6). A quick exploration of the scope of this reaction

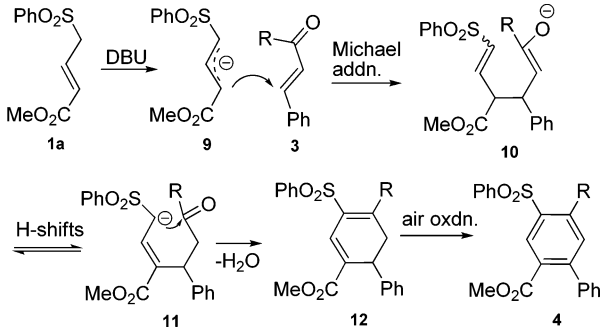
Scheme 6. Benzannulation Reaction of 6 with α,β-Unsaturated Aldehydes



revealed that both aromatic and aliphatic enals participate efficiently in this benzannulation reaction (Scheme 6). It is noteworthy that directed lithiation and utility as a pincer-type ligand of a structurally similar 1,3-bissulfonyl benzene was reported recently (Figure 1).[16]

A plausible mechanistic rationalization for the benzannulation reaction is presented in Scheme 7. 4-Sulfonylcrotonate **1a** is readily deprotonated by DBU, and the resulting allylic carbanion **9** may undergo a Michael addition with the enal/enone **3** via either of its terminal carbons. Steric repulsion between the bulky arylsulfonyl group of **9** and the β-aryl substituent of **3** presumably prevents the Michael addition of the α-sulfonyl anion. Thus, the reaction of **3** with the carbanion **9** proceeds via the sterically less demanding α-carbonyl end of the latter resulting in the formation of the enolate **10** (note that a regiosiomeric mixture of products

Scheme 7. Mechanistic Rationalization of the Benzannulation Reaction



4aj–bj were formed from the enal **3j** with a less bulky β-substituent). Base-mediated prototropy generates the carbonyl compound **11**, and subsequent intramolecular condensation produces the cyclohexadiene derivative **12**. Facile oxidation of the latter by atmospheric oxygen furnishes the aromatic product **4**. The cyclohexadiene **12** can, in principle, aromatize by base mediated proton shifts and elimination of the phenylsulfinate anion, which is a good leaving group. Evidently, air oxidation is the preferred pathway for aromatization over the loss of the sulfonyl group and this leads to the formation of a more functionalized product. An alternate mechanism involving a sequential Knoevenagel condensation (of the α-sulfonyl anion of **9** and **3**), 6π-electrocyclization, and air oxidation is deemed less probable because of the following reasons: (a) Knoevenagel condensation is usually sluggish with enones, (b) condensation of **9** with enals is expected to be nonregioselective, and (c) 6π-electrocyclizations generally require thermal activation.

In conclusion, a regioselective, oxidative [3 + 3] benzannulation reaction of 4-sulfonylcrotonates (or 1,3-bissulfonylpropene) with α,β-unsaturated aldehydes and ketones has been developed. Highly substituted 3-sulfonyl benzoic ester derivatives can be prepared from readily available starting materials in an open flask procedure. The reaction can also be carried out as a one-pot, three-component process. The protocol is notable for its scope, efficiency, mild, and metal-free conditions and the use of atmospheric oxygen as the oxidizing agent. It is presumable that the method will find applications in the targeted synthesis of designed biphenyl and terphenyl derivatives of importance. Studies along this direction as well as explorations of new reactions of 4-sulfonylcrotonates are currently underway.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures and characterization data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The Department of Science and Technology (DST), India is acknowledged for the award of Ramanujan fellowships to both R.S.M. and K.K.S. DST is thanked for the award of a Start-up

DOI: 10.1021/acs.orglett.5b00318
Org. Lett. 2015, 17, 1449–1452

Research Grant (young scientists) to R.S.M. Financial support in part from the XIIth five year plan project "Affordable Cancer Therapeutics (ACT)" and Research Fellowships for P.R.J. and S.U. from the Council of Scientific and Industrial Research (CSIR), India are also acknowledged. The authors also thank Mrs. Viji S. (CSIR-NIIST, Trivandrum, India) for HRMS analysis.

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DOI: 10.1021/acs.orglett.5b00318
Org. Lett. 2015, 17, 1449−1452