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# Metal-free, high yielded synthesis of unsymmetrical biaryl, bi(heteroaryl), aryl vinyl, aryl alkyl sulfones *via* coupling of aryne with sulfinic acid salts

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Sravan Kumar Aithagani,[1,2] Kushalava Reddy Yempalla,[1,2] Gurunadham Munagala,[1,2] Ram A. Vishwakarma[1,2] and Parvinder Pal Singh[1,2,*]

**Here, we have reported metal-free, high yielded method for the synthesis of unsymmetrical biaryl sulfones *via* coupling of benzyne with sulfinic acid salts. The optimized condition also works efficiently for bi(heteroaryl), aryl vinyl and aryl alkyl sulfones. The present method took comparatively lesser reaction times and has good functional group compatibility.**

Organosulfones represent an important class of compounds because of their presence in many bio-active molecules[1] as well as their chemical properties.[2] Organosulfones are known for their; i) medicinal properties *viz.,* dapsone (**A,** as anti-bacterial),[1d] casodex (**B,** anti-androgen),[1e] eletriptan (**C,** anti-migraine),[1f] mesotrione (**D,** herbicide);[1g] ii) antagonist properties (**E** and **F,** serotonin 5-HT6 receptor antagonist)[1h,1i] and iii) enzyme inhibitory properties (**G,** HIV-1 non-nucleoside reverse transcriptase inhibitor).[1j] Very recently, aryl vinyl sulfones **H** were reported as potent neuroprotective agents for the treatment of Parkinson's disease.[1k] In addition to this, aryl alkyl and heteroaryl alkyl sulfones are also used as synthons[3] in the organic transformations such as Julia-olefination[4] and Ramberg-Backlund rearrangement.[5]

Traditionally organosulfones were prepared either by oxidation of sulphides[6a] or by sulfonation of arene in the presence of strong acid.[6b] Keeping in view the importance of organosulfones, several metal-catalysed methods have been developed.[7] However, emergence of metal-free synthesis is the choice of interest these days and therefore attempts have also been made to develop metal-free synthesis of organosulfones as shown in Fig 2.[8] These methods are specific to some particular class among the diverse range of organosulfones. Moreover, benzyne mediated organic synthesis has attracted the attention and have been extensively explored in last decade for the diverse range of organic synthesis.[9] In this present study, we have explored first time the use of reactive benzyne intermediates for the synthesis of unsymmetrical biaryl, bi(heteroaryl), aryl vinyl, aryl alkyl sulfones.

Initially, we have chosen 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **1a,** the benzyne precursor and benzene

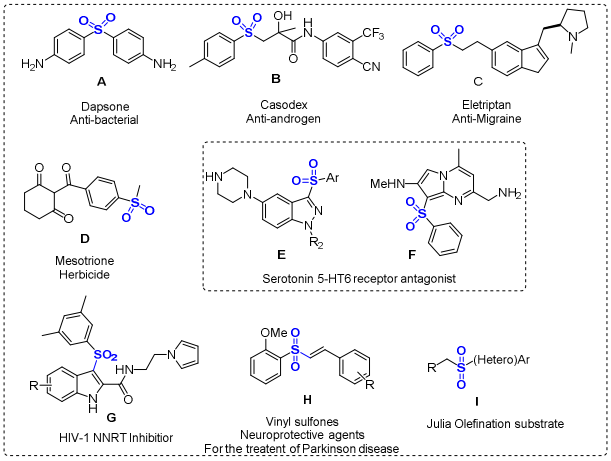


Fig 1: Examples of important sulfones

-sulfinic acid sodium salt **2a** as standard substrates to optimize suitable conditions for this reaction (Table 1). The reaction of **1a** with **2a** in the presence of CsF in $CH_3CN$ solvent at room temperature for 12 h under nitrogen atmosphere provided biaryl sulfone **3a** in 75% yield (Table 1, entry 1). The best yield (85%) was obtained upon increasing the temperature from rt to 80 °C in CsF (Table 1, entry 2), this effect may be due to the rate of reaction was enhanced by increasing the temperature. A similar result was achieved when the reaction was performed under oxygen atmosphere (Table 1, entry 3) ruled out the possibilities of involvement of radical intermediacy. Upon switching the fluoride source to KF/18-crown-6 and TBAF, comparatively slightly lesser yield of coupled product **3a** was obtained (Table 1, entry 4 and 5). Keeping the fluoride sources KF/18-crown-6 and TBAF constant and by changing the solvent CH3CN to THF, also didn't give any improvement (Table 1, entry 6 and 7).

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With the optimized reaction conditions established, we next explored the scope of the various sulfinic acid sodium salts and all the results are summarized in Table 2. Firstly, benzene sulfinic acid sodium salt when treated with benzyne precursor (**1a**) afforded the desired product in 85% yield (**3a**). Moreover, aryl sulfinates bearing

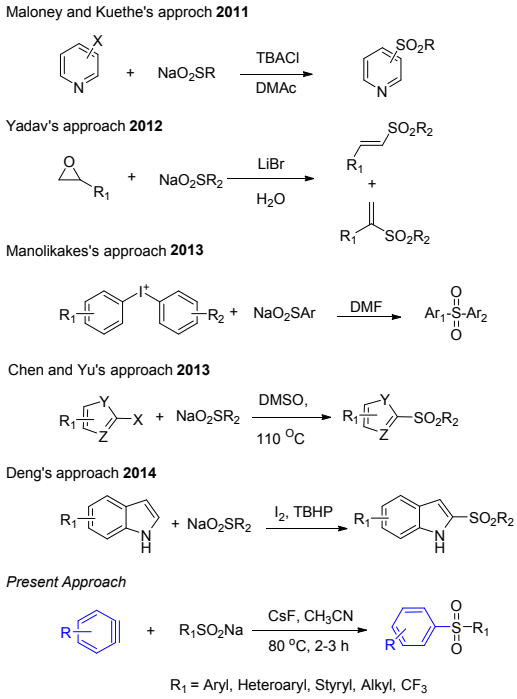
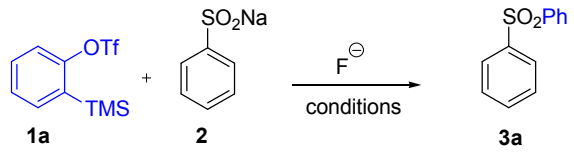



Fig 2: Previous and present approaches for the synthesis of sulfones

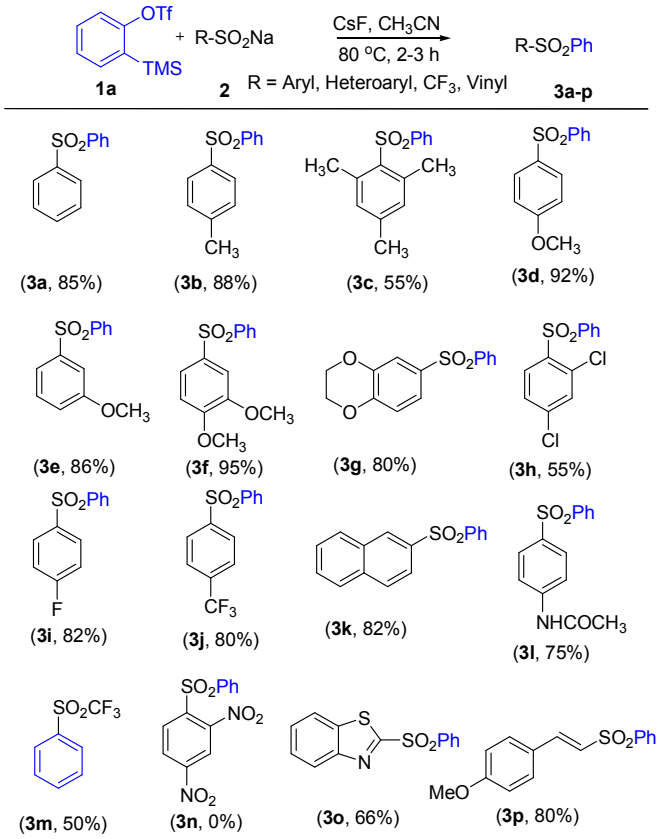



| Entry | F⁻ source | Solvent | Temp (°C), Time (h) | Yield[b] (%) |
|---|---|---|---|---|
| 1 | CsF | $CH_3CN$ | rt, 12 | 75 |
| **2** | **CsF** | **$CH_3CN$** | **80, 2** | **85** |
| 3[c] | CsF | $CH_3CN$ | 80, 3 | 82 |
| 4 | KF/18-crown-6 | $CH_3CN$ | 80, 5 | 62 |
| 5 | TBAF | $CH_3CN$ | 80, 5 | 83 |
| 6 | KF/18-crown-6 | THF | 70, 5 | 65 |
| 7 | TBAF | THF | 70, 5 | 80 |

[a] Reaction conditions (unless otherwise stated): **1a** (0.25 mmol, 1.0 equiv), **2a** (0.5 mmol, 2.0 equiv), F⁻ source (1.0 mmol, 4.0 equiv), solvent 4 ml, under $N_2$; [b] Isolated yield.
[c] Reaction was done in presence of oxygen.

Table 1: Optimization studies[a]

electron-donating groups due to their high nucleophilic nature furnished good to excellent yields of corresponding products (examples **3b-3g**, except **3c**). *p*-Methyl substituted sulfinate proceeded smoothly and gave the corresponding diarylsulfone **3b** with 88% yield. Mesitylene sulfinate gave the corresponding coupled product 3c with 55% yield, the comparatively lower yield might be due to steric hindrance. To our delight, methoxy substituted benzene sulfinates gave the corresponding products in an excellent yields of coupled products (**3d-3f**). Additionally, sodium 2,3-dihydrobenzo[b][1,4]dioxine-6-sulfinate also provided the corresponding product **3g** in 80% yield. On the other hand, electron-




[a]Reaction conditions: Aryne precursor **1a** (0.25 mmol, 1.0 equiv), arene sulfinic acid sodium salt **2** (0.5 mmol, 2.0 equiv), CsF (1.0 mmol, 4.0 equiv), solvent 4 ml, 80 °C, under $N_2$.

Table 2: Coupling of different sulfinic acid salts with benzyne[a]

-withdrawing groups containing aryl sulfinates gave corresponding coupled products with moderate to good yields. When 2,4-dichloro benzene sulfinic acid sodium salt was subjected to the reaction, 55% yield of the corresponding biaryl sulfones **3h** obtained. 4-F and 4-$CF_3$ benzene sulfinates were also proceeded well and afforded the desired products **3i and 3j** with 82%, 80% yield respectively. To verify the vast substrate scope of this method we have chosen different (naphthyl, acetamido, trifluoromethyl) sulfinates, which also gave respective coupled products **3k**-**3m** with good yields. Nevertheless, when di-nitro substituted sulfinate **3n** was used no reaction took place. The presence of two nitro groups makes respective sulfinate **3n** weak nucleophile and responsible for non-reactivity. Encouraged by the results obtained, we turned our interest to heterocyclics; sodium benzo[*d*]thiazole-2-sulfinate was also efficiently transformed to sulfone (**3o**) with a 66% yield. Additionally, it was found that

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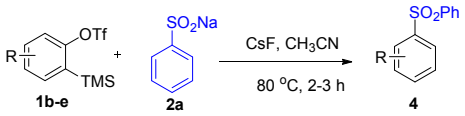
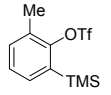
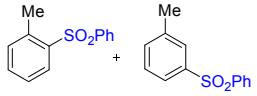
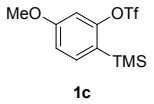
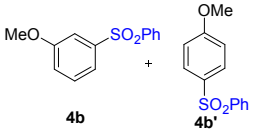
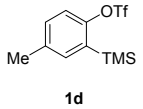
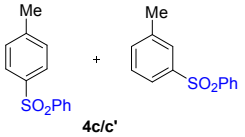
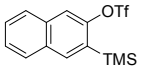
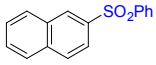
substituted styrene sulfinate also worked well and afforded the desired vinyl sulfone (**3p**) in 80% yield.

The versatility of the present reaction was also explored with substituted arynes (Table 3). Methyl (*at 6th position*) substituted benzyne precursor **1b** underwent coupling with benzene sulfinic acid sodium salt **2a** and gave an unseparable mixture of coupled products **4a/a'** with 55% yield in the ration of 37:63 (ratio was determined by GC-MS). Methoxy (*at 5th position*) substituted benzyne precursor **1c** when tried, also underwent coupling and gave 62% of coupled products **4b** and **4b'** in the ratio of 45 and 55 (determined by GC-MS) which were easily separated by column chromatography. On the other hand, methyl (*at 4th position*) benzyne precursor **1d** also gave an inseparable mixture of coupled products **4c/c'** with 58% yield. Further, napthlene containing benzyne precursor **1e** also underwent coupling smoothly and gave a 2-napthyl phenyl sulfone **4d** with 50% yield. Effect of temperature on regio-selectivity was also studied by performing all the reactions at room temperature but no improvement in the regio-selectivity was observed, however the reactions gave comparatively lower yields (Table 3).

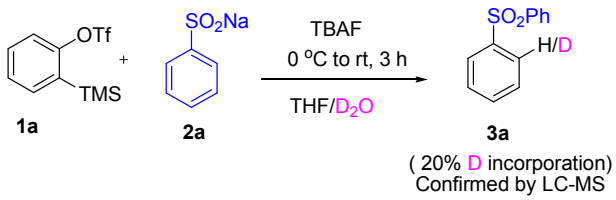



| Entry | Aryne precursor | Products | Yield(%)[b] |
|---|---|---|---|
| 1 |  1b |  4a/a' | 55/35[c] (37 : 63)[d] |
| 2 |  1c |  4b 4b' | 62/43[c] (45 : 55) |
| 3 |  1d |  4c/c' | 58/55[c] (53 : 47)[d] |
| 4 |  1e |  4d | 50 |

[a]Reaction conditions: Aryne precursor **1b-e** (0.25 mmol, 1.0 equiv), **2a** benzene sulfinic acid sodium salt (0.5 mmol, 2.0 equiv), CsF (1.0 mmol, 4.0 equiv), solvent 4 ml, 80 °C, under $N_2$; [b]Ratio was determined by GC-MS analysis; [c]Reactions were performed at rt for 18h; [d]unseparable mixtures.

Table 3: Coupling of benzenesulfinic acid salt with substituted benzynes[a]

To gain further insight into the reaction mechanism, the coupling reaction was performed in the presence of D2O (Scheme 1), wherein the corresponding coupled product **3a** was formed with 20% deuterium incorporation which was confirmed by LC-MS (Details given in SI). Based on our finding (reactions in presence of O2 and D2O) and literature precedent,[8b,9] a plausible mechanism can be described by the nucleophilic attack of aryl sulfnate[8b] on the aryne[9] derived from **2a** followed by proton capture resulting in the formation of the corresponding sulfones.




Scheme 1: Coupling in the presence of $D_2O$.

In conclusion, we have developed an efficient and general method for the synthesis of unsymmetrical sulfones under metal-free condition. The optimized method works well for the synthesis of diverse range of sulfones such as unsymmetrical biaryl, bi(heteroaryl), aryl vinyl, aryl alkyl sulfones. The present method gave good to excellent yields and also have a good functional group compatibility. Further, the efforts towards the bi-functionalization as well as sulfonation with other benzyne precursor to expand the generality are presently underway and will be published in due course.

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## Notes and references

[1]Medicinal Chemistry Division, [2]Academy of Scientific and Innovative Research, CSIR-Indian Institute of Integrative Medicine, Canal Road, Jammu 180 001, India; Tel.: +91-191-2569000-010 (ext. 292), Fax: +91-191-2569333; E-mail: ppsingh@iiim.ac.in

Electronic Supplementary Information (ESI) available: [Synthesis and characterization data]. See DOI: 10.1039/c000000x/

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**Graphical Abstract:**