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Metal-Free Synthesis of Diaryl Sulfones from Arylsulfinic Acid Salts and Diaryliodonium Salts

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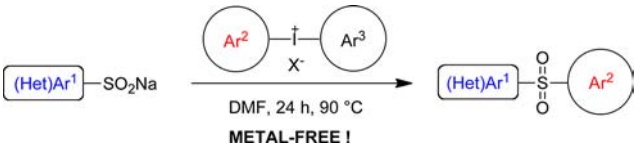
ABSTRACT



An efficient, high-yielding, and transition-metal-free synthesis of diaryl sulfones from arylsulfinic acid salts and diaryliodonium salts has been developed. The mild reaction conditions tolerate a range of functional groups, and unsymmetrical diaryliodonium salts show high chemoselectivity.

Diaryl sulfones are useful synthetic intermediates[1] and exhibit interesting biological properties.[2] For example, diaryl sulfones have been shown to possess antifungal, antibacterial, or antitumor activities or to inhibit HIV-1 reverse transcriptase.[3]

Numerous approaches for their preparation have been reported. Traditional procedures such as the oxidation of sulfides or the sulfonylation of arenes in the presence of strong acids typically require harsh reaction conditions.[1] Recently, Pd- or Cu-catalyzed coupling reactions between arylsulfinic acid salts and aryl halides or aryl boronic acids have been developed as a milder alternative.[4−6] However, the use of toxic and expensive transition metals significantly limits the applicability of these processes.

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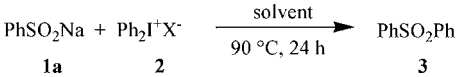
In recent years diaryliodonium salts have attracted considerable attention as powerful electrophilic arylation reagents.[7,8] They have been employed in metal-catalyzed[9] and, more importantly, in metal-free arylation reactions,[10] such as the metal-free arylation of oxygen nucleophiles recently reported by the group of Olofsson.[11]

In the course of our investigations toward new synthetic methods for the synthesis of sulfonyl-group containing molecules, we became interested in the use of diaryliodonium salts as possible arylating agents for sulfur nucleophiles. Herein, we present our results on the metal-free arylation of sulfinic acid sodium salts **1** with diaryliodonium salts **2**.

In preliminary studies, we investigated the reaction of benzenesulfinic acid sodium salt (**1a**) with diphenyliodonium triflate (**2a**). To our delight this reaction takes place in the absence of any metal catalyst or additional base. While a variety of solvents can be used for this reaction (Table 1, entries 1−7), the best results were obtained with polar aprotic solvents such as *N*,*N*-dimethylformamide (DMF), dimethyl sulfoxide (DMSO), or *N*-methyl-2-pyrrolidone (NMP).[12,13]

Interestingly, this reaction is quite insensitive to air and moisture. When the reaction was set up and run without an inert atmosphere using commercial grade DMF (entry 7), **3a** was isolated in almost equally good yield. The nature of the counterion had no influence on the yield, and different diphenyliodonium salts worked as efficiently (entries 8−11).

Table 1. Survey of Solvents and Influence of the Counterion[a]



entry	solvent	salt	X^-	yield (%)[b]
1	THF	**2a**	OTf	77[c]
2	1,4-dioxane	**2a**	OTf	65
3	toluene	**2a**	OTf	59
4	DMSO	**2a**	OTf	94
5	NMP	**2a**	OTf	96
6	DMF	**2a**	OTf	94
7	DMF	**2a**	OTf	90[d]
8	DMF	**2b**	Cl	95
9	DMF	**2c**	PF_6	96
10	DMF	**2d**	BF_4	96
11	DMF	**2e**	OTs	96

[a] Reaction conditions: 1.0 equiv of **1a** and 1.1 equiv of **2** in 1.0 mL of solvent at 90 °C for 24 h. [b] Isolated yield. [c] Reaction performed at 80 °C. [d] Reaction run without exclusion of air or moisture.

With the optimized conditions in hand, we next explored the scope of this reaction. As shown in Table 2, various arylsulfinic acid sodium salts are suitable substrates regardless of their electronic or steric properties. Both electron-rich and -poor sulfinic acid sodium salts **1c** and **1g** lead to the desired diarylsulfones **3c** and **3g** in excellent yields (entries 3 and 7). Reaction of the bromo-substituted substrate **1d** delivered diarylsulfone **3d** (entry 4) that could be easily further modified using cross-coupling chemistry. Steric hindrance, often problematic in metal-catalyzed coupling reactions,[14] does not pose a problem. The sterically very hindered (1,3,5-triisopropyl)benzenesulfinic acid sodium salt (**1j**) was phenylated in 61% yield (entry 10). This method can be extended to heteroarylsulfinic acid sodium salts **1k**−**m** to synthesize arylheteroaryl sulfones **3k**−**m**, which are of particular interest for the development of new drugs[3a,c,d] (entries 12−14). Only alkylsulfinic acid salts, such as methanesulfinic acid sodium salt (**1n**), did not react under these conditions.

We next examined the reactivity of other symmetrical and unsymmetrical diaryliodonium salts. The reaction of benzenesulfinic acid sodium salt (**1a**) with various symmetrical diaryliodonium salts **2** furnished the phenylarylsulfones of type **3** in moderate to excellent yields (Table 3, entries 1−7). Halogen-substituted substrates **2j**−**l** efficiently arylated **1a** (entries 5−7). Steric hindrance in the diaryliodonium salt was not a problem. Reaction of ortho- or bis(ortho)-substituted salts **2g** and **2h** delivered the diarylsulfones **3n** and **3o** in very high yields (entries 2 and 3). Unsymmetrical salts **2m** and **2n** selectively transferred

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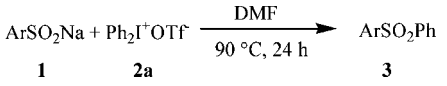
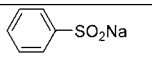
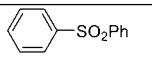
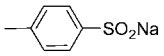
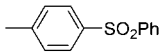
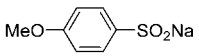
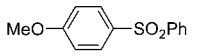
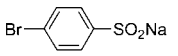
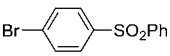
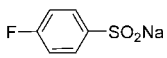
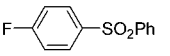
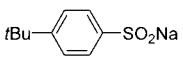
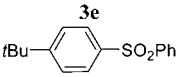
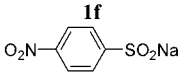
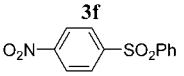
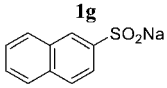
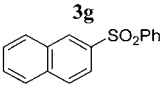
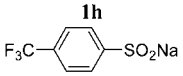
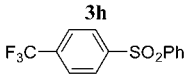
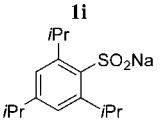
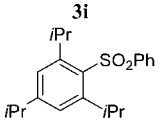
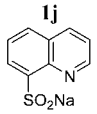
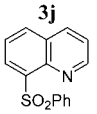
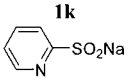
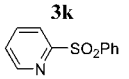
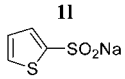
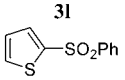
(12) This might be due to the improved solubility of the sulfinic acid sodium salts in polar solvents.

(13) While slightly higher yields were obtained in NMP and DMSO, the removal of DMF from the reaction is considerably easier.

(14) *Transition Metals for Organic Synthesis*, 2nd ed.; Beller, M., Bolm, C.; Wiley VCH: Weinheim, 2004.

Table 2. Phenylation of (Hetero)arylsulfinic Acid Salts[a]

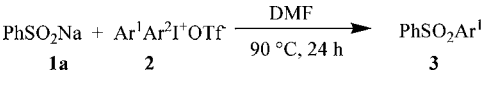


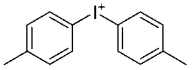
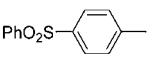
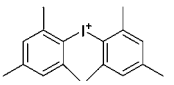
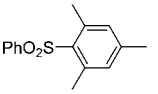
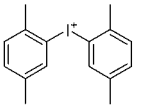
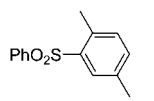
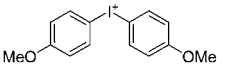
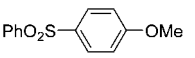
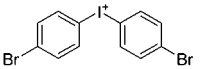
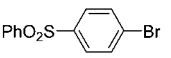
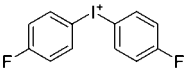
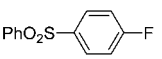
entry	$ArSO_2Na$	product	yield (%)[b]
1	 **1a**	 **3a**	94
2	 **1b**	 **3b**	96
3	 **1c**	 **3c**	90
4	 **1d**	 **3d**	90
5	 **1e**	 **3e**	83
6	 **1f**	 **3f**	54[c]
7	 **1g**	 **3g**	81
8	 **1h**	 **3h**	63
9	 **1i**	 **3i**	83
10	 **1j**	 **3j**	61
11	 **1k**	 **3k**	90
12	 **1l**	 **3l**	40
13	 **1m**	 **3m**	83[d]
14	$MeSO_2Na$ **1n**	-	no rct

[a] 1.0 equiv of **1** and 1.1 equiv of **2a** in 1.0 mL of DMF at 90 °C for 24 h. [b] Isolated yields of analytically pure product. [c] Reaction performed with 1.1 equiv of **1** and 1.0 equiv of **2a**. [d] Reaction run with 1.1 equiv of **1** and 1.0 equiv of **2a** in DMSO.

the bulky ortho-substituted aryl moiety, furnishing products **3n** and **3j** (entries 8 and 9). In the case of the unsymmetrical diaryliodonium salt **2o**, the electron-poor trifluoromethylphenyl moiety was transferred with excellent chemoselectivity (entry 10). Thus, unsymmetrical diaryliodonium salts could be used as an alternative in cases where the symmetric salt is expensive or difficult to prepare.

Table 3. Arylation of Benzenesulfinic Acid Sodium Salt (**1a**)[a]

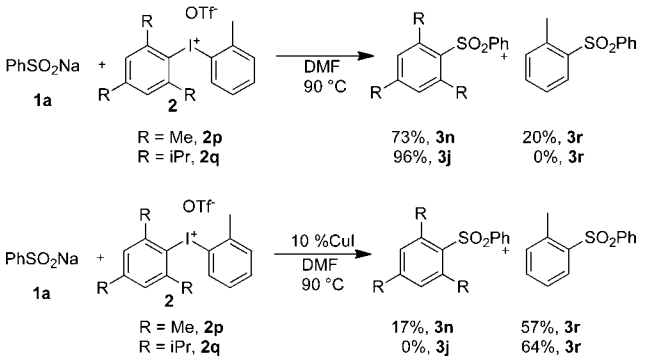


entry	$Ar^1Ar^2I^+$	product	yield (%)[b]
1	 **2f**	 **3b**	92
2	 **2g**	 **3n**	91
3	 **2h**	 **3o**	89
4[c]	 **2i**	 **3c**	87
5	 **2j**	 **3d**	61[d]
6	 **2k**	 **3e**	47[d]
7	**2l**	**3p**	96
8	**2m**	**3n**	88
9	**2n**	**3j**	94
10[c]	**2o**	**3q**	78

[a] 1.0 equiv of **1a** and 1.1 equiv of **2** in 1.0 mL of DMF for 24 h at 90 °C. [b] Isolated yield. [c] Tosylate as counterion. [d] Reaction run in NMP.

The chemoselectivity of unsymmetrical diaryliodonium salts was further investigated using (2-methylphenyl)(2,4,6-trimethylphenyl)iodonium triflate (**2p**) and (2-methylphenyl)(2,4,6-triisopropylphenyl)iodonium triflate (**2q**) as model substrates (Scheme 1). In the reaction of **2p** with benezenesulfinic acid sodium salt (**1a**) a mixture of the two diarylsulfones **3n** and **3r** was obtained, with the sterically more demanding mesityl group being transferred preferentially (ratio **3n** to **3r**: 3.6:1). Excellent selectivity was observed with unsymmetric salt **2q**, which transferred only the tri(isopropyl)phenyl group (TRIP). Interestingly, we observed contrasting chemoselectivity trends in the presence of catalytic amounts of CuI. Transfer of the less

Scheme 1. Selectivity Studies[a]



[a] Reaction conditions: 1.0 equiv of **1a** and 1.1 equiv of **2** in 1.0 mL of DMF at 90 °C for 24 h.

bulky aryl group is favored. Reaction of **2p** furnished a mixture of **3n** and **3r** with the less sterically demanding aryl group being transferred more readily (ratio **3n** to **3r**: 1:3.4). In the case of diaryliodonium salt **2q**, only product **3r** was observed.

The observed chemoselectivity trends are in agreement with previous reported selectivities. In metal-free reactions electron-poor aryl groups are transferred prefentially over electron-rich aryl groups and the transfer of a bulky, ortho-substituted aryl group is favored over the transfer of less bulky aryl groups.[10g,11,15] In the presence of a transition metal catalyst contrasting selectivities are observed.[9a,b,g,j] Transfer of more electron-rich or less bulky aryl groups is preferred, and the bulky TRIP group is often introduced as a nontransferable dummy ligand.

In summary, we have developed an efficient, transition-metal-free synthesis of diarylsulfones starting from readily available arylsulfinic acid salts and diaryliodonium salts. The reaction conditions are mild and robust and avoid the use of excess reagents or additives. The scope of this reaction is quite broad and includes the synthesis of halogen-substituted or sterically hindered diarylsulfones as well as heteroarylsulfones.

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Supporting Information Available. Experimental procedures and characterization of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(15) (a) Ochiai, M.; Kitagawa, Y.; Takayama, N.; Takaoka, Y.; Shiro, M. *J. Am. Chem. Soc.* **1999**, *121*, 9233–923. (b) Oh, C. H.; Kim, J. S.; Jung, H. H. *J. Org. Chem.* **1999**, *64*, 1338–1340.

The authors declare no competing financial interest.