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Arylation of Lithium Sulfinates with Diaryliodonium Salts: A Direct and Versatile Access to Arylsulfones

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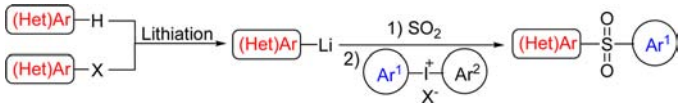
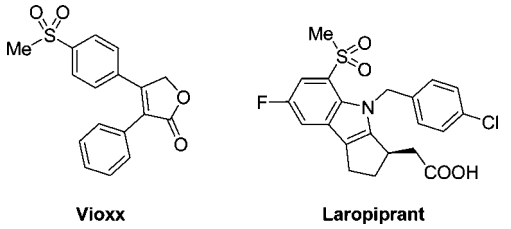
ABSTRACT



An efficient, transition-metal-free arylation of lithium sulfinates, which are readily accessible from reactions of organolithium reagents with sulfur dioxide, is described. Based on this method, a practical protocol for the direct transformation of (hetero)arenes and (hetero)aromatic halides into diarylsulfones was developed.

Arylsulfones are important building blocks in organic chemistry[1] and especially in medicinal chemistry.[2] The arylsulfone fragment is found in various drugs, such as the COX-2 inhibitor Vioxx[3] or the prostaglandin D_2 antagonist Laropiprant (Figure 1).[4] Diarylsulfones have been shown to exhibit antitumor activities[5] or to inhibit HIV-1 reverse transcriptase.[6]



Vioxx Laropiprant

Figure 1. Biologically active arylsulfones.

Because of their importance, numerous procedures for the synthesis of arylsulfones have been reported, such as the oxidation of sulfides,[1] the sulfonylation of arenes,[1] or Pd- and Cu-catalyzed coupling reactions.[7] Recently, we reported a mild, transition-metal-free synthesis of diarylsulfones from arylsulfinic acid sodium salts and diaryliodonium salts (Scheme 1).[8,9]

(1) (a) Patai, S., Rappoport, Z., Stirling, C. J. M., Eds. *The Chemistry of Sulfones and Sulfoxides*; Wiley: New York, 1988. (b) Simpkins, N. S. *Sulfones in Organic Synthesis*; Pergamon Press: Oxford, 1993.

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(5) (a) Dinsmore, C. J.; Williams, T. M.; O'Neill, T. J.; Liu, D.; Rands, E.; Culberson, J. C.; Lobell, R. B.; Koblan, K. S.; Kohl, N. E.; Gibbs, J. B.; Oliff, A. I.; Graham, S. L.; Hartman, G. D. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 3301–3306. (b) Jones, T. R.; Webber, S. E.; Varney, M. D.; Reddy, M. R.; Lewis, K. K.; Kathardekar, V.; Mazdiyasni, H.; Deal, J.; Nguyen, D.; Welsh, K. M.; Webber, S.; Johnson, A.; Matthews, D. A.; Smith, W. W.; Janson, C. A.; Bacquet, R. J.; Howland, E. F.; Booth, C. L. J.; Ward, R. W.; Herrmann, S. M.; White, J.; Bartlett, C. A.; Morse, C. A. *J. Med. Chem.* **1997**, *40*, 677.

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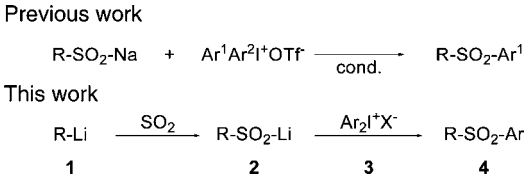
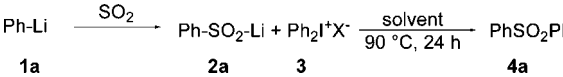
While a wide variety of different diaryliodonium salts are readily available or can be prepared efficiently,[10−12] the availability of sulfinic acid sodium salts is rather limited.[13] In order to expand the scope of our method, we were interested in the use of other, more easily accessible sulfinic acid salts. We envisioned that the corresponding sulfinic acid lithium salts **2** should display a similar reactivity (Scheme 1). These lithium sulfinates can be prepared in a very straightforward manner from the reaction of organolithium compounds **1** with sulfur dioxide.[14] Considering the huge variety of well-known organolithium reagents,[15] this approach would allow a modular synthesis of arylsulfones using sulfur dioxide[16] as the source for the sulfonyl moiety. Herein, we wish to report a one-pot synthesis of arylsulfones based on this concept.

Scheme 1. Routes to Arylsulfones Based on Diaryliodonium Salts



We started our initial studies with benzene sulfinic acid lithium salt (**2a**), which could be easily prepared in quantitative yield from the reaction of phenyllithium (**1a**) and sulfur dioxide and subsequent removal of the solvents.[17] As expected the reaction between the lithium salt **2a** and diphenyliodonium triflate (**3a**) proceeded efficiently and furnished diphenylsulfone (**4a**). The best results were obtained in the polar aprotic solvents DMF, DMSO, and NMP (Table 1, entries 1−3). Other solvents, such as THF or dioxane, led to lower yields (entries 4 and 5). As with sodium sulfinic acid salts, this reaction is insensitive to air and moisture. Performing the reaction without the exclusion of air and moisture, using commercial grade DMF or DMSO, **4a** was isolated in identical yields (entries 6 and 7). In the case of sulfinic acid lithium salts, the nature of the diphenyliodonium counterion X^- has a pronounced effect on the yield of the reaction. While reactions with non-nucleophilic counterions, such as OTf^-, BF_4^-, or PF_6^-, furnished the product **4a** in >80%

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



entry	solvent	salt	X^-	yield (%)[b]
1	DMF	**3a**	OTf	84
2	DMSO	**3a**	OTf	80
3	NMP	**3a**	OTf	83
4	1,4-dioxane	**3a**	OTf	47
5	THF	**3a**	OTf	26
6	DMSO	**3a**	OTf	79[c]
7	DMF	**3a**	OTf	86[c]
8	DMF	**3b**	Cl	60
9	DMF	**3c**	PF_6	86
10	DMF	**3d**	BF_4	91
11	DMF	**3e**	OTs	65
12[d]	DMF	**3a**	OTf	83

[a] Reaction conditions: 1.5 equiv of **2a** and 1.0 equiv of **3** in 1.0 mL of solvent at 90 °C for 24 h. [b] Isolated yield. [c] Reaction run without exclusion of air or moisture. [d] Performed as one-pot reaction/without isolating the salt **2a**.

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(8) Umierski, N.; Manolikakes, G. *Org. Lett.* **2013**, *15*, 188–191.

(9) Shortly after our communication, Kumar et. al reported an almost identical procedure: Kumar, D.; Arun, V.; Pilania, M.; Shekar, K. P. C. *Synlett* **2013**, *24*, 831–836.

(10) For reviews on diaryliodonium salts, see: (a) Merritt, E. A.; Olofsson, B. *Angew. Chem., Int. Ed.* **2009**, *48*, 9052–9070. (b) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2008**, *108*, 5299–5358. (c) Yusubov, M. S.; Maskaev, A. V.; Zhdankin, V. V. *ARKIVOC* **2011**, 370–409.

(11) For efficient routes to diaryliodonium salts, see: (a) Bielawski, M.; Olofsson, B. *Org. Synth.* **2009**, *86*, 308–314. (b) Bielawski, M.; Aili, D.; Olofsson, B. J. *Org. Chem.* **2008**, *73*, 4602–4607. (c) Zhu, M.; Jalalian, N.; Olofsson, B. *Synlett* **2008**, *4*, 592–596. (d) Bielawski, M.; Zhu, M.; Olofsson, B. *Adv. Synth. Catal.* **2007**, *349*, 2610–2618. (e) Hossain, M. D.; Kitamura, T. *Bull. Chem. Soc. Jpn.* **2007**, *80*, 2213. (f) Hossain, M. D.; Ikegami, Y.; Kitamura, T. *J. Org. Chem.* **2006**, *71*, 9903–9905. (g) Carroll, M. A.; Pike, V. W.; Widdowson, D. A. *Tetrahedron Lett.* **2000**, *41*, 5393. (h) Kitamura, T.; Matsuyuki, J.; Taniguchi, H. *Synthesis* **1994**, 147. (i) Stang, P. J.; Zhdankin, V. V.; Tykwinski, R.; Zefirov, N. S. *Tetrahedron Lett.* **1991**, *32*, 7497–7498.

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(13) Only a few sulfinic acid sodium salts are commercially available. Most commonly the sodium salts have to be prepared from the corresponding sulfonyl chlorides. See also ref 14.

(14) Truce, W. E.; Murphy, A. M. *Chem. Rev.* **1951**, *48*, 69–124.

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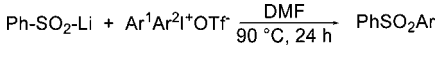
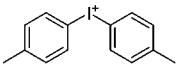
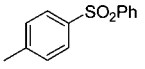
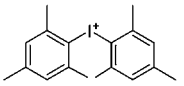
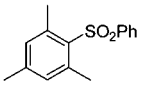
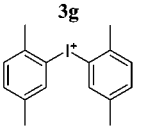
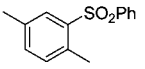
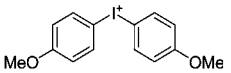
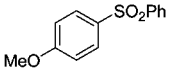
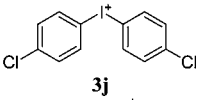
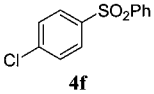
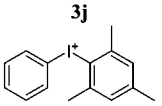
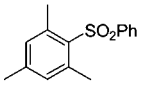
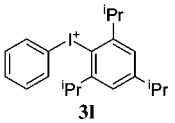
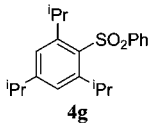
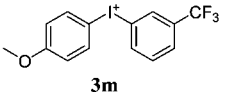
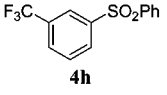
(16) For some recent examples of reactions with SO_2, see: (a) Woolven, H.; González-Rodríguez, C.; Marco, I.; Thompson, A. L.; Willis, M. C. *Org. Lett.* **2011**, *13*, 4876–4878. (b) Nguyen, B.; Emmet, E. J.; Willis, M. C. *J. Am. Chem. Soc.* **2010**, *132*, 16372–16373. (c) Markovic, D.; Volla, C. M. R.; Vogel, P.; Varela-Alvarez, A.; Sordo, J. A. *Chem.—Eur. J.* **2010**, *16*, 5969–5975. (d) Pandya, R.; Murashima, T.; Tedeschi, L.; Barrett, A. G. M. *J. Org. Chem.* **2003**, *68*, 8274–8276.

(17) See Supporting Information for experimental details.

Table 2. Arylation of Benzenesulfinic Acid Lithium Salt (**2a**)[a]



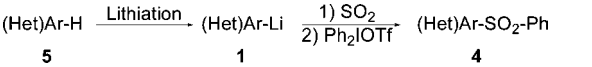
entry	$Ar^1Ar^2I^+$	product	yield (%)[b]
1	 **3f**	 **4b**	80
2	 **3g**	 **4c**	67
3	 **3h**	 **4d**	76
4[c]	 **3i**	 **4e**	74
5	 **3j**	 **4f**	78
6	 **3k**	 **4c**	73
7	 **3l**	 **4g**	81
8[c]	 **3m**	 **4h**	76[d]

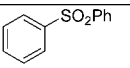
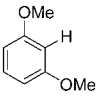
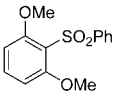
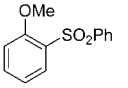
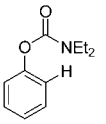
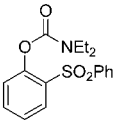
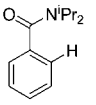
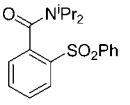
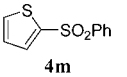
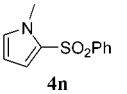
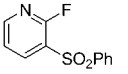
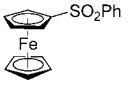
[a] Reaction conditions: 1.5 equiv of **2a** and 1.0 equiv of **3** in 1.0 mL of DMF for 24 h at 90 °C. [b] Isolated yield. [c] Tosylate as counterion. [d] Together with 6% **4e**.

yield (entries 1, 9, and 10), the yield decreased significantly if the more nucleophilic counterions Cl^- and OTs^- were employed (entries 8 and 11).[18,19] Since we were also interested in developing a practical protocol for the direct transformation of organolithium reagents into sulfones, we merged the single steps into a one-pot sequence. Reaction of PhLi (**1a**) with sulfur dioxide (typically 10 equiv),[17] followed by removal of solvents and excess SO_2 and subsequent treatment of the obtained crude lithium sulfinate with Ph_2IOTf (**3a**) in DMF, furnished diphenylsulfone (**4a**) in 83% yield (entry 12).[20]

With the optimized reaction conditions at hand, we investigated the reaction of benzenesulfinic acid lithium salt (**2a**) with different diaryliodonium salts (table 2).

Table 3. Direct Lithiation Approach to Diarylsulfones[a]



entry	(Het)Ar-H	lithiation reagent	product	yield (%)[b]
1	 **5a**	*n*BuLi, TMEDA	 **4a**	52
2	 **5b**	*n*BuLi	 **4i**	79
3	 **5c**	*n*BuLi, TMEDA	 **4j**	61
4	 **5d**	*s*BuLi, TMEDA	 **4k**	47
5	 **5e**	*s*BuLi, TMEDA	 **4l**	68
6	 **5f**	*n*BuLi	 **4m**	85 (82)[c]
7	 **5g**	*n*BuLi, TMEDA	 **4n**	51 (51)[c]
8	 **5h**	LDA	 **4o**	55
9	 **5i**	*t*BuLi	 **4p**	42

[a] Reaction conditions: Sulfinate **2** (prepared from 1.5 equiv **5**) and 1.0 equiv of **3a** in 1.0 mL of DMF for 24 h at 90 °C. [b] Isolated yield. [c] 2.0 mmol of **3a** used.

Various symmetrical diaryliodonium salts arylated **2a** in good to excellent yields (entries 1–5). Unsymmetrical iodonium salts **3k** and **3l** selectively transferred the sterically more demanding aryl moiety (entries 6 and 7).[21] In the case of the unsymmetrical iodonium reagent **3m**, a preferential transfer of the electron-poor trifluoromethylphenyl group was observed (entry 8).

One of the most atom-economical[22] routes to organolithium reagents is the direct lithiation/deprotonation of acidic C–H functionalities.[15] In combination with our method, it allows the direct transformation of simple, readily available arenes or heteroarenes into the corresponding sulfones. This four-step, one-pot reaction sequence

(18) More nucleophilic counterions can undergo a competing S_NAr reaction with the diphenyliodonium reagent. For examples, see ref 12b and: Merritt, E. A.; Olofsson, B. *Eur. J. Org. Chem.* **2011**, 3690–3694.

(19) In the case of diphenyliodonium chloride **3b**, 1-chloro-4-iodobenzene could be detected by GC/MS.

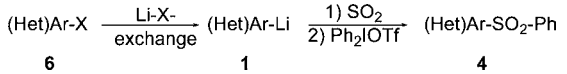
(20) For a similar alkylation of magnesium sulfinates, see: Wu, J.-P.; Emeigh, J.; Su, X.-P. *Org. Lett.* **2005**, *7*, 1223–1225.

(21) For a detailed mechanistic investigation of this effect, see: Malmgren, J.; Santoro, S.; Jalalian, N.; Himo, F.; Olofsson, B. *Chem.—Eur. J.* **2013**, *19*, 10334–10342.

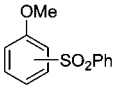
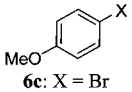
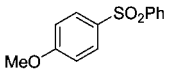
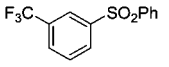
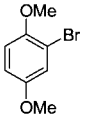
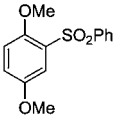
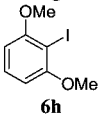
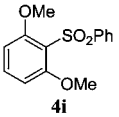
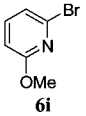
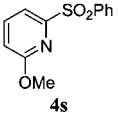
(22) Trost, B. M. *Science* **1991**, *254*, 1471–1477.

consists of (1) generation of the organolithium reagent from the corresponding arene or heteroarene using the appropriate lithiation reagents and conditions;[17] (2) reaction of the lithium reagent with SO_2; (3) removal of solvents and excess SO_2; and (4) reaction of the sulfinate with the diaryliodonium salt (Table 3). Using this procedure diphenylsulfone (**4a**) was obtained in 52% yield starting from benzene (entry 1). More importantly, different arenes bearing "directed metallation groups" (DMG),[23] e.g. carbamate **5d** or benzamide **5e**, could be transformed directly into the diarylsulfones **4k** and **4l** (entries 4 and 5). Different heteroarenes, such as thiophene (**5f**), *N*-methylpyrrol (**5g**), pyridine **5h**, or ferrocene (**5i**), could be functionalized in a similar manner (entries 6–9).

Table 4. Li/X-Exchange Approach to Diarylsulfones[a]



6 **1** **4**

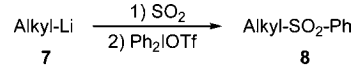
entry	(Het)Ar-X	exchange reagent	product	yield (%)[b]
1	 **6a**: *o*-Br	*n*BuLi	 **4j**	97
2	**6b**: *m*-Br		**4q**	92
3	 **6c**: X = Br	*n*BuLi	 **4e**	78
4	**6d**: X = I	*t*BuLi		53
5	 **6e**: X = Br	*n*BuLi	 **4h**	74
6	**6f**: X = I			83
7	 **6g**	*n*BuLi	 **4r**	42 (53)[c]
8	 **6h**	*n*BuLi	 **4i**	74
9	 **6i**	*t*BuLi	 **4s**	36

[a] Reaction conditions: sulfinate **2** (prepared from 1.5 equiv **6**) and 1.0 equiv of **3a** in 1.0 mL of DMF for 24 h at 90 °C. [b] Isolated yield. [c] 2.0 mmol of **3a** used.

The halogen–lithium exchange is another efficient method for the preparation of organolithium reagents.[15] This method is also compatible with our four-step one-pot approach. Thus, aryllithium reagent **1c**, prepared from 2-bromoanisol (**6a**), is treated with SO_2, followed by the removal of solvents and excess SO_2. Reaction of the remaining crude lithium sulfinate with diphenyliodonium triflate (**3a**) furnished diarylsulfone **4j** in 97% yield (Table 4, entry 1). In a similar manner, other bromo- or iodobenzene derivatives **6b**–**h** as well as heterocycles, such as bromopyridine **6i**, could be transformed directly into the corresponding diarylsulfones (entries 2–9).

To our delight, this method is not limited to (hetero)-aryllithium reagents. Starting from primary, secondary, or tertiary alkyllithium reagents **7a**–**d**, the desired alkylarylsulfones **8a**–**d** were obtained in 76–93% yield (Scheme 2).

Scheme 2. Synthesis of Aryl Alkyl Sulfones



7 **8**

7a: MeLi **8a:** 84%
7b: *n*BuLi **8b:** 89%
7c: *t*BuLi **8c:** 76%
7d: *s*BuLi **8d:** 93%

To summarize, we have developed a convenient synthesis of arylsulfones from sulfinic acid lithium salts and diaryliodonium salts. This reaction has a very broad scope, and both aryl and alkyl sulfinates were arylated efficiently. Based on this method, we were able to develop a practical protocol for the direct one-pot transformation of hetero(aromatic) halides or (hetero)arenes into arylsulfones. This protocol consists of (1) generation of the organolithium reagent via exchange or deprotonation; (2) reaction of the lithium reagent with SO_2; (3) removal of excess SO_2; and (4) treatment of the obtained crude sulfinate with the diaryliodonium salt. Various aryl- and heteroarylsulfones were synthesized using this straightforward procedure.

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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.

(23) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879–933.

The authors declare no competing financial interest.