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Palladium-Catalyzed Sulfination of Aryl and Heteroaryl Halides: Direct Access to Sulfones and Sulfonamides

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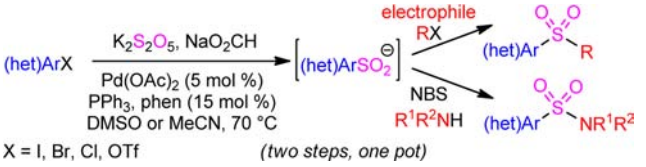
ABSTRACT



A novel palladium-catalyzed sulfination of aryl and heteroaryl halides is described. This reaction operates under mild conditions and provides access to a wide range of aryl and heteroaryl sulfinates, a useful and versatile class of synthetic intermediates. Capitalizing on this sulfination reaction, one-pot protocols allowing direct access to sulfones and sulfonamides have also been developed. The practicality of these transformations is illustrated with the parallel synthesis of analogues of the drug Viagra.

Aryl and heteroaryl [(het)Ar] sulfinate salts are useful and versatile synthetic intermediates that provide access to structural motifs of relevance to numerous fields of chemistry;[1] sulfones, sulfonamides, and structures arising from C−C bond formation, such as Ar−(het)Ar, Ar−COR, and Ar−CN, can all be accessed from a common sulfinate intermediate (Figure 1). In particular, sulfinates are among the intermediates of choice in drug discovery where analogue generation based on versatile synthetic intermediates helps promote rapid exploration of structure−activity relationships (SAR).[2] Indeed, such an approach allows for the efficient synthesis of analogues containing sulfone and sulfonamide functionalities which, as illustrated by the medicines bicalutamide (Casodex) and sildenafil (Viagra), are two pharmacophores often found in therapeutic agents (Figure 1). However, the scope for using sulfinates as intermediates in synthesis has been limited by their modest commercial availability (~200 compounds)[3] and the practicality of existing preparative methods used to access them.[1,4] As a result, there remains a need to develop novel synthetic transformations that will allow direct access to aryl and heteroaryl sulfinate salts from a large pool of readily available reactants.

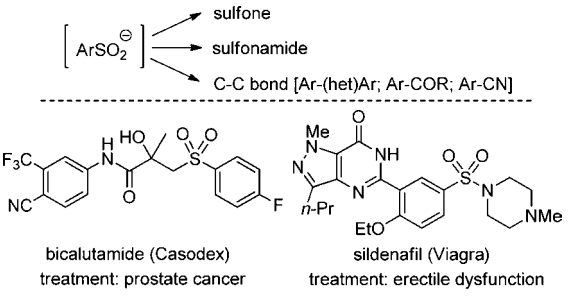


Figure 1. Aryl sulfinates as versatile synthetic intermediates and some medicines containing an arylsulfonyl motif.

(1) Schubart, R. Sulfinic Acids and Derivatives. *Ullmann's Encyclopedia of Industrial Chemistry* **2000**, 677–693.

(2) In this context, we refer to "a versatile synthetic intermediate" as one that can be diversely further functionalized and effectively reacted with another broad set of reactants.

(3) Results from a search conducted using the ACD and eMolecules databases (total of 7.9 million compounds exemplified). In comparison, a search for boronic acids/esters returned ~15 000 examples commercially available.

(4) Aryl sulfinates have been traditionally accessed by the following: (i) Reaction of organometallic reagents with SO_2 gas or a surrogate; see: Woolven, H.; Gonzalez-Rodriguez, C.; Marco, I.; Thompson, A. L.; Willis, M. C. *Org. Lett.* **2011**, *13*, 4876. (ii) Reduction of sulfonyl halides; see ref 1. (iii) Reaction of aryl halides with the SO_2^{2-} surrogate SMOPS; see: Baskin, J. M.; Wang, Z. *Tetrahedron Lett.* **2002**, *43*, 8479.

(5) (a) Wojcicki, A. *Adv. Organomet. Chem.* **1974**, *12*, 31. (b) Pelzer, G.; Herwig, J.; Keim, W.; Goddard, R. *Russ. Chem. Bull.* **1998**, *47*, 904.

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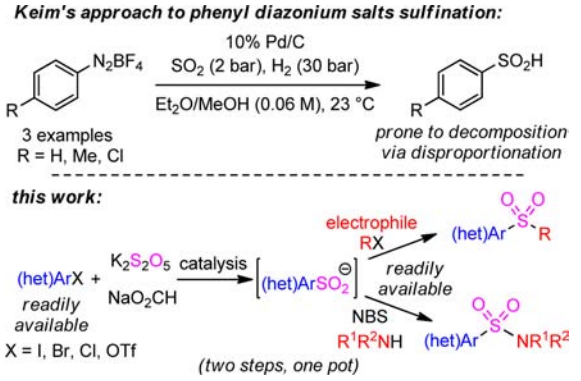


Figure 2. Approaches to metal-catalyzed sulfination reactions.

Interestingly, even though the behavior of SO_2 as a ligand and its insertion into metal−carbon bonds has been long known,[5] only one catalytic sulfination reaction has been reported to date.[6] In this approach reported by Keim, the palladium-catalyzed reaction of phenyl diazonium tetrafluoroborate salts with SO_2 and hydrogen gas under high pressure/high dilution conditions produces the corresponding phenyl sulfinic acid (Figure 2).[6] Unfortunately, the use of phenyl diazonium salts as reactants and the ready disproportionation of sulfinic acids severely limit the scope of this transformation. Concurrent with the submission of our work, Willis also reported a method that allows indirect access to aryl sulfinates by capitalizing on a palladium-catalyzed *N*-aminosulfonylation of aryl iodides previously developed in his laboratories.[7,8] However, under these conditions, sulfinates are not directly obtained from the catalytic reaction but instead are generated in situ by subsequent treatment of the *N*-aminosulfonamides (products from the catalytic reaction) with an excess of an alkylating agent under basic conditions. Thus, in contrast to the plethora of metal-catalyzed methods available for carbonylation there is still a notable lack of mild, catalytic, and general methods for effecting sulfination reactions.

Herein we report the first palladium-catalyzed reaction of aryl and heteroaryl halides and triflates in the presence of potassium metabisulfite ($K_2S_2O_5$) and sodium formate (NaO_2CH) to directly produce sulfinate synthetic intermediates. As shown in Figure 2, these can be used without isolation to form sulfones and sulfonamides.

In the first experiment demonstrating the feasibility of our approach, 1-iodo-4-methoxybenzene was treated with $K_2S_2O_5$ and NaO_2CH (SO_2 and hydrogen donors respectively)[9,10] in the presence of $Pd(OAc)_2$ and PPh_3 in DMF at 70 °C. As desired, this reaction led to the formation of the corresponding sulfinate, which was converted to sulfone **1** (38% yield) by in situ alkylation with iodomethane (Table 1, entry 1). Our choice of $Pd(OAc)_2$ was based on its excellent bench and air stability; thus, based on the success of this initial experiment, subsequent optimization was conducted retaining this palladium source. This effort focused on identification of various ligands and additives that could stabilize the palladium-derived catalytic species and prevent their possible premature decomposition.[11] From this work, we found that addition of 15 mol % of the bidentate ligand 1,10-phenanthroline (phen) led to the isolation of **1** in 66% yield (entry 2). Addition of tetrabutyl ammonium bromide (TBAB) further increased the yield slightly (entry 3). DMSO and MeCN also proved to be effective solvents for this transformation providing **1** in 71% and 61% yield respectively (entries 4−5). Interestingly, the one-pot conversion of the crude sulfinate intermediate formed in situ led to similar yields of **1** compared to when the crude sulfinate was isolated as a solid and subsequently reacted with iodomethane (61% vs 55%, entry 5); the same trend was observed when benzyl bromide was used as the alkylating agent (benzyl sulfone obtained in 79% and 71% yield respectively). In contrast, when 1-bromo-4-methoxybenzene was used, DMSO emerged as the solvent of choice giving **1** in 56% yield (entries 6−8). The reaction did not proceed in the absence of a catalyst or hydrogen donor source, and among the ones we tested, sodium formate gave the best results. We used potassium metabisulfite as a source of SO_2, as it offers the advantage of buffering the pH of the reaction mixture, thus minimizing any risk of decomposition of the sulfinate by disproportionation of

Table 1. Summary of Reaction Optimization[a]

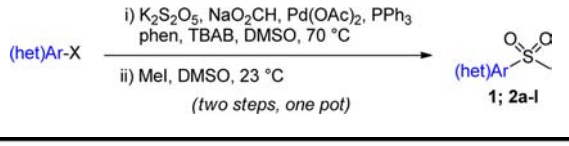
entry	X	ligand(s)	additive	solvent	yield[b]
1	I	PPh_3	–	DMF	38%
2	I	PPh_3; phen	–	DMF	66%
3	I	PPh_3; phen	TBAB	DMF	69%
4	**I**	**PPh_3; phen**	**TBAB**	**DMSO**	**71%**
5	I	PPh_3; phen	TBAB	MeCN	61%
					55%[c]
6	Br	PPh_3; phen	TBAB	DMF	21%
7	**Br**	**PPh_3; phen**	**TBAB**	**DMSO**	**56%**
8	Br	PPh_3; phen	TBAB	MeCN	3%

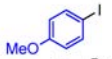
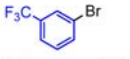
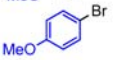
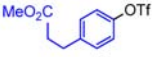
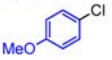
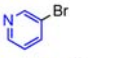
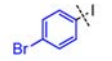
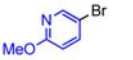
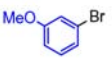
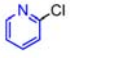
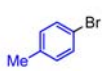
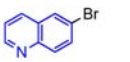
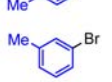
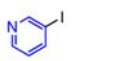
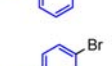
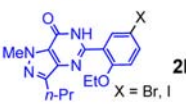
[a] ArX (0.58 mmol), $K_2S_2O_5$ (2 equiv), TBAB (1.1 equiv), NaO_2CH (2.2 equiv), solvent (2 mL), 70 °C then MeI (1.5 equiv), solvent (2 mL), 23 °C. [b] Isolated yield of sulfone **1**. [c] Sulfinate isolated as a solid was used in alkylation step.

(6) Pelzer, G.; Keim, W. *J. Mol. Catal. A.: Chem.* **1999**, *139*, 235.
(7) Richards-Taylor, C. S.; Blakemore, D. C.; Willis, M. C. *Chem. Sci.* **2013**, DOI:10.1039/c3sc52332b.
(8) Nguyen, B.; Emmett, E. J.; Willis, M. C. *J. Am. Chem. Soc.* **2010**, *132*, 16372.
(9) For a recent example of application of $K_2S_2O_5$ in a catalytic process, see: Ye, S.; Wu, J. *Chem. Commun.* **2012**, *48*, 10037.
(10) Pri-Bar, I.; Buchman, O. *J. Org. Chem.* **1984**, *49*, 4009.
(11) For a postulated catalytic cycle operating in the palladium-mediated sulfination of aryldiazonium salts, see ref 5b.

the corresponding sulfinic acid.[1] Based on all of the above observations, we selected $Pd(OAc)_2/PPh_3$/phen in the presence of $K_2S_2O_5$, NaO_2CH, and TBAB in DMSO at 70 °C as general conditions to use in further evaluating the scope of the transformation.

Table 2. Representative Set of (het)Aryl Halides/Triflates[a]

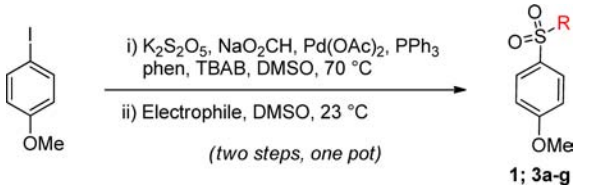


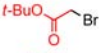
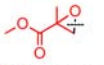
entry	(het)Ar-X	1-2	yield[b]	entry	(het)Ar-X	2	yield[b]
1		1	71%[c]	9		2f	69%
2		1	56%	10		2g	57%
3		-	0%[d]	11		2h	40%
4		2a	67%[e]	12		2i	58%
5		2b	56%	13		2j	41%
6		2c	53%	14		2k	68%
7		2d	55%	15		2h	64%
8		2e	72%	16		2l	54%[f] (X = Br) 68%[c,f] (X = I)

[a] Reaction conditions: (het)ArX, $K_2S_2O_5$ (2 equiv), TBAB (1.1 equiv), NaO_2CH (2.2 equiv), $Pd(OAc)_2$ (5 mol %), PPh_3 (15 mol %), phen (15 mol %), DMSO, 70 °C, 3 h; then MeI (1.5 equiv), 23 °C, 18 h. [b] Isolated yield. [c] Step 1 was run for 2 h. [d] Step 1 was run for 20 h. [e] Each step was run in MeCN for 20 h. [f] TEAB used instead of TBAB.

In further exploration of our methodology, we decided to focus on the synthesis of sulfones and sulfonamides in view of the importance of these functionalities in chemistry. The scope of the sulfination reaction as it relates to aryl and heteroaryl halides and triflates is illustrated in Table 2. As noted previously with 1-bromo-4-methoxybenzene (Table 1, entry 7), aryl bromides are competent substrates for the reaction. This is beneficial for future applications, as the bromides are more widely commercially available than the iodides by an order of magnitude (~500 000 vs 50 000 compounds).[3] Mindful of this observation, emphasis was placed on bromides in the evaluation of the reaction scope. When submitted to a two-step, one-pot protocol (i.e., alkylating agent added directly to the reaction mixture arising from the sulfination step), electron-rich, -neutral, and -deficient aryl bromides produced the corresponding sulfone **1**, **2a**–**f** in 53–72% yield (entries 2 and 4–9). Unless activated, aryl chlorides did not react (entry 3 vs 13). Taking advantage of the difference in reactivity between 1-iodo-4-methoxybenzene and its bromo analogue (Table 1, entry 5 vs 8) in MeCN, treatment of 1-bromo-4-iodobenzene in this solvent led to the chemoselective reaction of the aryl iodide functionality to provide **2a**, leaving the bromide unreacted and available for subsequent cross-coupling if desired. Also of note, an aryl triflate provided sulfone **2g** in 57% yield (entry 10) whereas an aryl tosylate or mesylate proved unreactive. Of particular interest to medicinal chemistry, where control of the lipophilicity is critical during optimization of drug-like properties, the method is compatible with heteroaryl halides (entries 11–14). Thus, heteroaryl bromides and chlorides produced the corresponding sulfones **2h**–**k** in yields ranging from 40% to 68%. As is the case for aryl halides (entry 2 vs 1), the yields of sulfones produced from these substrates can be conveniently increased by using the corresponding heteroaryl iodide (entry 11 vs 15, and 16). The compatibility with heterocycles of medicinal chemistry relevance was nicely demonstrated by the preparation of sildenafil sulfone analogue **2l** from the corresponding bromoaryl and iodoaryl pyrazolopyrimidones (entry 16).[12] Substrates containing functional groups that are prone to reduction (entry 10) or oxidation (entries 11–15) are compatible with the reaction conditions thereby allowing for the rapid synthesis of sulfones that otherwise may have been difficult to directly access using currently available methods.

Table 3. Representative Set of Electrophiles[a]



entry	electrophile	1-3	yield[b]	entry	electrophile	3	yield[b]
1	MeI	1	71%	6		3c	56%
2	*n*-PrI	3a	55%[c,d]	7	BnBr	3d	79%[c]
3	*n*-PrBr	3a	40%	8	*i*-PrI	3e	31%[c,d]
4	*n*-PrOTs	3a	45%	9		3f	41%[e]
5	$Ph(CH_2)_2Br$	3b	56%	10	H_2NOSO_3H	3g	37%[f]

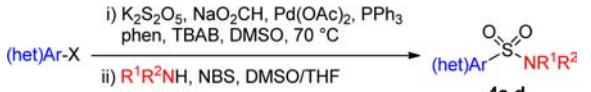
[a] Reaction conditions: see Table 2 and Supporting Information. [b] Isolated yield. [c] Each step run in MeCN for 20 h. [d] Step 2 run at 50 °C. [e] Step 2 was run at 60 °C for 48 h. [f] For step 2: sulfinate isolated as a solid was employed, and water was used as solvent; H_2NOSO_3H (4 equiv).

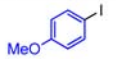
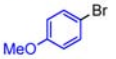
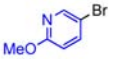
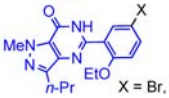
As described in Table 3, the crude sulfinates could be used without isolation and treated in situ with a wide range of electrophiles to provide the corresponding sulfones or sulfonamides in yields similar to those reported in literature for equivalent transformations.[13] Primary alkyl halides and tosylates, secondary alkyl iodides, and benzyl

(12) TEAB used instead of TBAB to facilitate the purification of **2l**.

(13) For representative examples of reactions of sulfinate anions with electrophiles, see: Meek, J. S.; Fowler, J. S. *J. Org. Chem.* **1968**, *33*, 3422 and ref 7 (alkylation). Culvenor, C. C. J.; Davies, W.; Heath, N. S. *J. Chem. Soc.* **1949**, 278 (epoxide opening).

Table 4. Two-Step, One-Pot Sulfonamide Synthesis[a]



entry	(het)Ar-X	amine	4	yield[b]
1			**4a**	52% 53%[c]
2			**4a**	32%
3			**4b**	36%
4			**4c**	65%
5			**4d (sildenafil)**	37%[d] (X = Br) 50%[d] (X = I)

[a] Reaction conditions: see Table 2 and Supporting Information. [b] Isolated yield of **4**. [c] DMF used as solvent, and NCS used instead of NBS. [d] TEAB used instead of TBAB; 10 and 30 mol % of catalyst and ligands used.

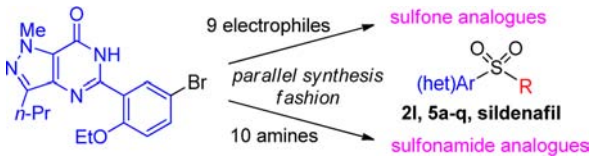
bromide provided (alkylsulfonyl)benzene derivatives **1**, **3a**–**e** in 31–79% yield (entries 1–8). When methyl glycidate was used as the electrophile, epoxide opening led to the formation of the corresponding 3-phenylsulfonylpropanoate derivative **3f** (entry 9), offering direct access to the carbon framework found in the drug bicalutamide (Figure 1). Lastly, upon treatment with hydroxylamine-*O*-sulfonic acid, primary sulfonamide **3g** was obtained in 37% yield (entry 10).

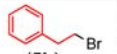
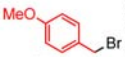
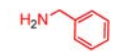
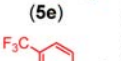
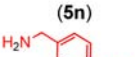
We next sought to identify a two-step, one-pot protocol that would provide access to *N*-substituted sulfonamides. Thus, when an amine was added to the precooled (0 °C) reaction mixture from the sulfination step, followed by a solution of *N*-bromosuccinimide (NBS) in THF, the corresponding sulfonamide **4a** was isolated in 52% yield (Table 4, entry 1). The same yield of **4a** was obtained when DMF and *N*-chlorosuccinimide (NCS) were used instead of DMSO and NBS respectively. Additional examples are presented in Table 4.[14] Notably, heteroaryl bromides again proved to be suitable substrates, in this case affording the corresponding sulfonamides in useful yields. The transformation also provides a convenient way to rapidly synthesize sildenafil and, by inference, sulfonamide analogues of this drug as well (entry 5). The overall yields could be increased by using the corresponding heteroaryl iodide as the substrate (entry 5 and also 2 vs 1).

Finally, reflecting their robustness and scope, all these protocols could be carried out in a parallel synthesis format

(14) Novel transformations have also been recently reported that allow access to *N*-aminosulfonamides from aryl iodides (refs 8, 9) and to sulfonamides from arylboronic acids (DeBergh, J. R.; Niljianskul, N.; Buchwald, S. L. *J. Am. Chem. Soc.* **2013**, *135*, 10638).

Table 5. Rapid Synthesis of Analogues of Sildenafil



electrophile (sulfone product: **2-5**)			amine (sulfonamide product: **5**)			
 **(2l)**	 **(5a)**	 **(5b)**	 **(sildenafil)**	 **(5i)**	 **(5j)**	 **(5k)**
 **(5c)**	 **(5d)**	 **(5e)**	 **(5l)**	 **(5m)**	 **(5n)**	
 **(5f)**	 **(5g)**	 **(5h)**	 **(5o)**	 **(5p)**	 **(5q)**	

as demonstrated by the synthesis of sulfone and sulfonamide analogues of sildenafil using a representative set of alkylating agents and amines (Table 5). Beyond medicinal chemistry, this example highlights the potential offered by these two-step, one-pot protocols for future application in any field where the rapid synthesis of sulfone and sulfonamide derivatives is needed.

In conclusion, we have developed a novel palladium-catalyzed sulfination of aryl and heteroaryl halides and triflates. The sulfinate synthetic intermediates thus formed can be used without isolation and converted to the corresponding sulfones and sulfonamides in situ, providing unprecedented direct and practical access to these derivatives from aryl and heteroaryl halides. The method has a broad scope, is well suited for parallel chemical synthesis, and is compatible with nitrogen-containing aromatic heterocycles of medicinal chemistry relevance.

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

The authors declare no competing financial interest.