

Mn(OAc)₃-Mediated C-H-Sulfonylation of 1,4-Dimethoxybenzenes with Sodium and Lithium Sulfinates

Shuai Liang, Yueling Ren and Georg Manolikakes*

Dedicated to Prof. Herbert Mayr on the occasion of his 70th birthday

Abstract: A simple and mild Mn(OAc)₃-promoted oxidative coupling of 1,4-dimethoxybenzenes with sodium and lithium sulfinates has been developed. The reaction proceeds readily at room temperature in air and various sulfones were synthesized in moderate to high yields. In addition, a straightforward approach for the conversion of organolithium reagents and sulfur dioxide into sulfonylated 1,4-dimethoxybenzenes is reported.

Introduction

Sulfones are important synthetic intermediates in organic chemistry and have found widespread application in the pharmaceutical and agrochemical industry and in material science.^[1] The sulfone moiety is of particular importance for medicinal chemistry. Various drugs, such as the non-steroidal antiandorgen casodex^[2] or the antibiotic dapsone,^[3] contain a sulfone group.

Traditional methods for the synthesis of sulfones are the oxidation of sulfides, Friedel-crafts-type reactions with sulfonyl chlorides and the addition of sulfonyl-based radicals to double or triple bonds.^[1,4] More recently, methods based on sulfinic acid salts have become an attractive alternative.^[5,6] Various three-component reactions based on the in situ formation of sulfinates using sulfur dioxide or suitable surrogates^[7] have been reported in the last five years.^[8] Concurrently, the sustainable synthesis of sulfones via the selective functionalization of C-H-bonds has gained more attention.^[9,10]

Sulfonylated benzoquinone and hydroquinone derivatives display a variety of interesting biological properties, e.g. *c*-jun-N-terminal kinase-1 (JNK-1) inhibition^[11] or marked cyctotoxic activity (Figure 1).^[12]



Figure 1. Selected biologically active 1,4-dimethoxybenzenes containing a sulfone moiety.

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Common approaches for the synthesis of these compounds are the oxidation of the corresponding sulfides,^[13] the addition of sulfinic acids or sulfinates to benzoquinones^[14] or the reactions of hydroquinone derivatives with sulfonyl chlorides.^[15] Recently, the groups of Wang and Wei reported different procedures for the direct C-H-functionalization of benzoquinones with sulfonyl chlorides or hydrazides.^[16] Herein, we wish to report a complementary approach, a Mn(OAc)₃-promoted crossdehydrogenative coupling of 1,4-dimethoxybenzene with sodium and lithium sulfinates.

Results and Discussion

In the course of our efforts towards highly modular and sustainable procedures for the synthesis of sulfones^[8d,h] and sulfonamides,^[17] we could identify the combination of a copper catalyst with Mn(OAc)₃ in 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) as highly efficient reaction system for the cross-oxidative C-H-sulfonylation of 8-aminoquinolines or anilines.^[18] We envisioned, that this system should be able to promote similar cross-dehydrogenative coupling reaction of sulfinic acid salts with other oxidation-prone substrates.

Indeed, the reaction of 1,4-dimethoxybenzene (1a) with sulfinate 2a in the 20 mol% Cu(OAc)₂ and stoichiometric amounts of Mn(OAc)₃H₂O in HFIP furnished the desired sulfone **3a** in 69% yield (Table 1, entry 1). Interestingly, the reaction proceeded more efficiently in the absence of a copper catalyst, delivering the product 3a in 78% yield (entry 2). HFIP is crucial for an efficient reaction.^[19] No product formation was observed in any other solvent, such as trifluoroethanol (TFE), acetic acid (AcOH) or CH₂Cl₂ (entries 3-6). In a similar manner, the choice of Mn(OAc)₃²H₂O is essential for a successful transformation.^[20] Various other oxidants, 2,3-dichloro-5,6e.g. dicyanobenzoquinone (DDQ), Cu(OAc)₂, FeCl₃, tert-butyl hydroperoxide (TBHP) or $K_2S_2O_8$ did not furnish the desired product at all (entries 7-11). Only in the case of the PhI(OAc)₂, a hypervalent iodine reagent which has been utilized in the oxidative functionalization of phenol ethers,^[21] minor amounts of sulfone 3a were formed (entry 12). In general, the use of other oxidants led to a fast decomposition of the sulfinate 2a. The reason for the specific reactivity of Mn(OAc)₃ remains unclear and is currently under investigation in our laboratory.

With the optimized reaction conditions at hand, we explored the reaction of 1,4-dimethoxybenzene (1a) with different sodium sulfinates 2 (Scheme 1). Aryl sulfinates bearing electron-withdrawing or electron-donating groups reacted smoothly, providing the diarylsulfones **3a-3i** in 52-90% yield. Halogen-substituted sulfinic acid salts were well tolerated, and furnished the sulfones **3d-3f**, bearing potential handles for further manipulations, in 77-90% yield. Contrary to our previous copper-catalyzed reactions,^[18] the heterocyclic 2-pyridine sulfinate

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proved to be a suitable substrate, affording the heteroarylsulfone **3j** in 57% yield. The reactions of sodium naphthylsulfinate (**2k**) and sodium methyl sulfinate (**2j**) furnished the corresponding naphthyl sulfone **3k** in 72% yield and the methyl sulfone **3j** in 55% yield, respectively.

Table 1. Optimization of the reaction parameters.^[a]

OMe	.H NaO ₂ S	kidant	o S
OMe	Me 2	5 °C MeO	Me
1a	2a		3a
entry	Oxidant	Solvent	Yield $[\%]^{[b]}$
1	$Cu(OAc)_2$ and $Mn(OAc)_3^{[c]}$	HFIP	69
2	Mn(OAc) ₃	HFIP	78
3	Mn(OAc) ₃	TFE	-
4	Mn(OAc) ₃	CH₃CN	-
5	Mn(OAc) ₃	AcOH	-
6	Mn(OAc) ₃	CH_2CI_2	-
7	DDQ	HFIP	-
8	Cu(OAc)	HFIP	-
9	FeCl₃	HFIP	-
10	TBHP	HFIP	-
11	$K_2S_2O_8$	HFIP	
12	PhI(OAc) ₂	HFIP	11

[a] Reactions conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), oxidant (0.6 mmol), HFIP (2 mL), 25 °C, 2 h; [b] Isolated yield of analytical pure product; [c] with 0.04 mmol of $Cu(OAc)_2$ and 0.6 mmol $Mn(OAc)_3$ ·H₂O.







Scheme 1. Substrate scope of sodium sulfinates. Yields of isolated products are given.

Next, we investigated reactions with the two unsymmetrical 1,4dihydroquinone derivatives **1b** and **1c** (Scheme 2). Unfortunately no regioselectivity was observed. The reaction of 1,4-dimethoxy-2-methylbenzene (**1b**) with sodium *para*-chlorophenylsulfinate (**2e**) led to the formation of the two regioisomeric sulfones **3m** and **3n** in 37% and 51% yield. In the case of dihydroquinone **1c** bearing two different protecting groups the two regioisomers **3o** and **3p** were obtained in 37% and 58% yield.

So far, the Mn(OAc)₃-mediated oxidative C-H-sulfonylation is limited to 1,4-dimethoxybenzene derivatives. Reactions with other electron-rich arenes such as anisol (1d), 4-methylanisole (1e), 1,2-dimethoxybenzene (1f), 1,3-dimethoxybenzene (1g), 1,3,5-trimethoxybenzene (1h) or *para*-Methoxyphenol (1i) did not afford the desired product (Figure 2).^[22]



Figure 2. Substrates not suitable for the ${\sf Mn}({\sf OAc})_{3}\text{-}{\sf mediated}$ oxidative sulfonylation.

For the purpose of increasing the synthetic utility of our method, we examined the coupling of lithium sulfinates, easily accesible from the reaction of the corresponding organolithium compounds with sulfur dioxide.^[1,7] Thus, lithium benzene- and *n*-butanesulfinates **4a** and **4b** were prepared from sulfur dioxide and phenyllithium **5a** or *n*-butyllithium **5b** in quantitative yields

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(Scheme 3a). To our delight, the crude sulfinates undergo an efficient coupling with 1,4-dimethoxybenzene (1a) in the presence of Mn(OAc)₃ affording the desired sulfones 3c and 3q in 72% and 78% yield. Reaction of para-toluene lithium sulfinate (5c), prepared in a two-step sequence from 4-iodotoluene using a lithium-halide exchange and subsequent trapping with sulfur dioxide, furnished sulfone 3a in 92% yield (Scheme 3b). Lithium sulfinate 5d was synthesized starting from 1.3dimethoxybenzene via deprotonation, followed by reaction of the formed organolithium compound with sulfur dioxide (Scheme 3c). The Mn(OAc)₃-mediated coupling of sulfinate 5d with 1,4dimethoxybenzene yielded diarylsulfone 3r in 66% yield. These results demonstrate, that interesting sulfone scaffolds are directly accessible from simple starting materials and sulfur dioxide by merging classical organolithium chemistry with the herein reported cross-dehydrogenative coupling.



Scheme 3. Synthesis and oxidative coupling of lithium sulfinates. Yields of isolated products are given.

Conclusions

In summary, we have developed a facile $Mn(OAc)_3$ -promoted cross-dehydrogenative coupling of sodium and lithium sulfinates with 1,4-dimethoybenzenes. The reaction is simple to perform and proceeds readily at room temperature. Various functional groups are tolerated and the products are obtained in good to excellent yields. This novel method represents the first example of a purely manganese-promoted oxidative coupling of sulfinic acid salts and could offer a new, promising approach for the C-H-functionalization of arenes or heteroarenes. In addition, the combination with organolithium chemistry allows a rapid synthesis of complex sulfones from two simple building blocks and sulfur dioxide. The unique role of $Mn(OAc)_3$ in this reaction and further applications of $Mn(OAc)_3$ in oxidative coupling reactions are currently under investigation in our laboratory.

Experimental Section

Typical procedure:

An oven dried 10 mL tube was charged with a magnetic stirring bar, 1,4dimethoxybenzene derivative **1** (1.0 equiv, 0.2 mmol), sodium sulfinate **2** (2.0 equiv, 0.4 mmol), Mn(OAc)₃·2H₂O (160.8 mg, 3.0 equiv, 0.6 mmol) and HFIP (0.1 M referring to 1,4-dimethoxybenzene derivative, 2 mL). The tube was closed with a rubber septum and the resulting reaction mixture was stirred at room temperature for 2h. After completion of the reaction, the mixture was diluted with ethyl acetate and filtered through a short plug of celite and silica gel. The filter pad was rinsed with additional ethyl acetate and the combined filtrates were concentrated under reduced pressure. Purification of the crude residue by flash column chromatography afforded the analytically pure product.

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Keywords: sulfone • C-H-functionalization • manganese • crossdehydrogenative coupling • sulfinic acid

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- [22] In most cases no reaction (except slow decomposition of the sulfinates) was observed and the arene 1 was recovered completely. For 1h and 1i decomposition of the arene and a complex mixture of products was observed.

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COMMUNICATION

A cross-dehyrogenative coupling of 1,4-dimethoxybenzenes with sodium and lithium sulfinates is reported. The reaction is mediated by Mn(OAc)₃ and provides various arylsulfones in high yields.



Mn-mediated C-H-functionalization > 15 examples, 52-92% yield

C-H-Functionalization*

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