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Easy Access To Allylic Sulfones Through Transition Metal-Free Hydrosulfonylation Of Allenes.

Lucas Pagès,[†] Sébastien Lemouzy,[†] Marc Taillefer,^{†*} and Florian Monnier^{†, ‡*}

[†]ICGM, Univ Montpellier, CNRS, ENSCM, Montpellier, France, 240 Avenue du Professeur Emile JEANBRAU - 34296 Montpellier (France)

[‡]Institut Universitaire de France (IUF), 1 Rue DESCARTES, Paris 75231 Cedex 5, France.

Supporting Information Placeholder

ABSTRACT: A Brønsted acid-mediated addition of (hetero)aryl and (cyclo)alkyl sodium sulfinates to *N*-allenyl derivatives, which proceeds in water, is described under very smooth conditions. This reaction provided a practical and efficient protocol for the regio- and stereoselective synthesis of allylic sulfones in an atom- and step-economic fashion.

Allylic sulfones are highly valuable structures commonly found in bioactive molecules for pharmaceutical or agrochemical use.¹⁻⁷ They can also be useful intermediates to variously functionalized compounds, either through the C(sp²)-C(sp²) bond or the carbon atom adjacent to the sulfone group.⁸⁻¹⁰ The SO₂ moiety is classically introduced either through in situ oxidation of sulfides (S^{II}) or sulfoxides (S^{IV}) or the use of pre-oxidized sulfur-based reagents (S^{VI}) i.e. sulfinic acid derivatives and their salts, in substitution or cross-coupling reactions (Scheme 1, A).

Allenenes are interesting precursors of these allylic structures via hydrofunctionalization¹¹ with hydrothiolation followed by in situ oxidation or with direct hydrosulfonylation. The first allene hydrosulfonylation strategies were based on the use of sulfonylhydrazines as a source of sulfone. They can be catalyzed by a palladium/diphosphine system (Yamamoto,¹² Scheme 1, eq 1) or by a Rhodium/DPEPhos system (Breit,¹³ Scheme 1, eq 2), occurring respectively on the distal and the proximal carbon of the allene. These methods require the presence of a Brønsted acid in at least stoichiometric quantity, and the use of an organic solvent under moderately high temperature (70°C-80°C). Breit's group also developed an asymmetric rhodium-catalyzed hydrothiolation of terminal allenenes followed by oxidation to afford the chiral

branched allylic sulfones in a two-step process (Scheme 1, eq 3).¹⁴ Over the last years, two transition metal-free allene hydrosulfonylation methods have been described. In 2016, Miao, Ren and coworkers reported a transition metal-free tunable hydrosulfonylation of 3-cyclopropylideneprop-2-en-1-ones using sodium sulfinates in the presence of acetic acid affording the corresponding allylic sulfone (γ-adduct) in DMSO¹⁵ (Scheme 1, eq 4). Very recently, the group of Loh reported a transition-metal catalyst-free regioselective Michael addition of sulfinic acids to α-ketoallenenes in a mixture of water and ethanol as a solvent, affording the corresponding vinylic sulfone¹⁶ (Scheme 1, eq 5). This method requires the synthesis of sulfinic acids in one to two steps, either from sodium sulfinate or sulfonyl chloride.¹⁷

Scheme 1. Metal-catalyzed or metal-free hydrosulfonylation of allenes: known methods and novel pathway described herein with TFA.

In our course to build new original allylic structures, we started to investigate the C-S bond formation *via* copper-catalyzed hydrofunctionalization of allenes. After starting with usual conditions described in our previous work for the C-C,^{18–20} C-N^{21–24} and C-O²⁵ bonds formation, we quickly realized that the reaction could occur without a transition metal, in the presence of a Brønsted acid and under very smooth and easy-to-handle conditions. We herein describe an efficient synthesis of allylic sulfones and 1,3-disulfones through regio- and stereoselective mono and double addition of various (hetero)aryl and (cyclo)alkyl sodium sulfinates to *N*-allenyl derivatives in aqueous conditions and at room temperature in the presence of trifluoroacetic acid (TFA).

Based on our previous works, we began to study the model reaction between *N*-allenyl-2-pyrrolidinone **1a** and benzene sulfinic acid sodium salt **2a** under our Cu(CH₃CN)₄PF₆-catalyzed system (Table 1). With an acid source we showed that the presence of catalytic amount of copper allows the formation of 50% of **3aa** (entry 2, Table 1). Different ligands were associated to copper but no real improvement was detected (entries 3–5, Table 1). In the next set of experiments we tested different sources of acid (entries 6–8, Table 1) and we defined trifluoroacetic acid (TFA) as the best one. However in the absence of the copper system, we surprisingly observed that **3aa** could be obtained in total conversion with 90% yield (entry 9, Table 1).

Table 1. Copper-catalyzed hydrosulfonylation of **1a with **2a** : selected data for reaction parametric study.^a**

Entry	x	y	Ligand ^d	H ⁺ source	Conversion (%) ^{b,c}	Yield (%) ^c
1	0	0	-	none	-	-
2	10	0	-	<i>p</i> -toluic acid	63%	50%
3	10	10	Bpy	<i>p</i> -toluic acid	86%	57%
4	10	10	Phen	<i>p</i> -toluic acid	74%	33%
5	10	10	TMEDA	<i>p</i> -toluic acid	95%	51%
6	10	10	Bpy	TMBA	79%	39%
7	10	10	Bpy	PTSA	76%	30%
8	10	10	Bpy	TFA	>99%	58%
9	0	0	-	TFA	>99%	90%

^a Reaction conditions: **1a** (0.25 mmol), **2a** (2 equiv., 0.5 mmol), H⁺ source (1 equiv.). Catalyst and ligand were placed in a Schlenk tube under argon in 0.5 mL of THF (0.5M) for 18 hours at 55°C. ^b Based on recovered starting material **1a**. ^c Determined through ¹H NMR analysis using trichloroethylene (1 equiv., 0.25 mmol) as internal standard. ^d TMBA = 2,4,6-trimethylbenzoic acid. PTSA = *p*-toluenesulfonic acid. Bpy = 2,2'-bipyridine. Phen = 1,10-phenanthroline. TMEDA = *N,N,N',N'*-tetramethylethylenediamine.

As above mentioned in table 1, best conditions were based on the use of only 1 equivalent of TFA in the absence of the copper catalyst. Hence, we opted to explore milder conditions (Table 2) and were finally able to perform the reaction in water, under open air at room temperature. Thanks to these improved system we could reach the target product **3aa** in a better yield (from 90% up to quantitative yield).

Table 2. Acid-mediated hydrosulfonylation of **1a with **2a** : Selected data for reaction parametric study.^a**

Entry	Variations from the standard conditions	Conversion (%) ^{b,c}	Yield (%) ^c
1	THF, instead of H ₂ O	>99%	80%
2	under argon, instead of open air	>99%	90%

3	55°C, instead of 25°C	>99%	96%
4	no TFA	66%	0
5	none	>99%	>99%

^a Reaction conditions: **1a** (0.25 mmol), **2a** (2 equiv., 0.5 mmol) and TFA (1 equiv., 0.25 mmol) were placed in a tube under open air in 0.5 mL of solvent (0.5M) for 4 hours at 25°C. ^b Based on recovered starting material. ^c Determined through ¹H NMR analysis using trichloroethylene (1 equiv., 0.25 mmol) as internal standard.

With these optimized conditions in hand, we first explored the scope of the method for the hydrosulfonylation of *N*-allenyl-2-pyrrolidinone **1a** with various readily available (hetero)aryl and (cyclo)alkyl sodium sulfinates compounds **2a-o** (Scheme 2). Different *para*-substituted benzene sodium sulfinates were tested, such as sodium *p*-toluenesulfinate **2b**, 4-fluoro and 4-chlorobenzenesulfonic acid **2c** and **2d**, and afforded the corresponding products **3ab** to **3ad** in high yields (85-91%). *Meta* substituted aryl sulfinates partners, 3-chloro 4-methyl benzenesulfonic acid sodium salt **2e** and 3-(trifluoromethyl)benzenesulfonic acid sodium salt **2f** were also successfully engaged in the reaction and gave corresponding products in 80-89% yields. Finally, *N*- and *S*-heteroaromatics **2g** and **2h** provided the desired products **3ag** and **3ah** in good to high yields (60-83%). Alkyl sulfinates were then investigated, and both linear (**2i**, **2j**) and cyclic (**2k**, **2l**) derivatives yielded the hydrosulfonylation products, in good isolated yields (61-75%). Functionalized sulfinates such as sodium triflate **2m** and sodium 1-methyl 3-sulfinopropanoate **2n** were also able to provide the allylic sulfones in good yields (70-73%), showing the high tolerance of the process. To prove the robustness of the reaction, we were interested in performing it on a larger scale. The reaction between our model substrates **1a** and **2a** was then conducted on a 2 mmol scale, *i.e.* on a scale eight times larger than usual, and afforded the corresponding hydrosulfonylation product **3aa** with a 97% isolated yield.

Interestingly, we also performed a one-step double hydrosulfonylation of **1a** with **2a** to obtain the corresponding 1,3-disulfone **4aa** in high yield. It is noteworthy to mention that the same 1,3-disulfone **4aa** can also be obtained through the hydrosulfonylation of **3aa**, demonstrating that our reaction can be applied both to *N*-allenyl and *N*-alkenyl derivatives.

Scheme 2. TFA-mediated hydrosulfonylation of allenyl **1a with various sodium sulfinates **2a-n**.**

Reaction conditions: **1a** (0.25 mmol), **2a-n** (2 equiv., 0.5 mmol), TFA (1 equiv., 0.25 mmol), H₂O (0.5M, 0.5 mL), open air, 25°C, 4h. Isolated yields. ^a The reaction was performed on a 2 mmol scale. ^b The reaction was performed at 40°C over two days under open air with 4 equiv. of TFA, 4 equiv. of PhSO₂Na and H₂O/THF 1:1 (0.25M) as the solvent. ^c The reaction was performed with 2 equiv. of TFA.

We then explored the reactivity of different *N*-allenyl derivatives with several (hetero)aryl and (cyclo)alkyl sodium sulfinates (Scheme 3). The *N*-allenyl-2-oxazolidinone **1b** was successfully involved in the reaction, affording both aryl and alkyl allylic sulfones in medium to excellent yields (51-90%). The symmetrical diallene *N,N*-diallenyl-2-imidazolidinone **1c** afforded the corresponding double hydrosulfonylation product **3ca** in 60% yield when a mixture 1:1 of water and THF was used as solvent. We also investigated the reactivity of *N*-sulfonyl allenamides, and observed that these substrates and their corresponding hydrofunctionalization products are sensitive under our acidic conditions. Nevertheless, the sulfones **3da** and **3db** were obtained in moderate to good isolated yields (35-60%).

Scheme 3. TFA-mediated hydrosulfonylation of various allenyl derivatives with different sodium sulfonates.

Reaction conditions (unless otherwise mentioned): **1** (0.25 mmol), **2** (2 equiv., 0.5 mmol), TFA (1 equiv., 0.25 mmol), H₂O (0.5M, 0.5 mL), open air, 25°C, 4h. Isolated yields. ^a H₂O/THF 1:1 (0.5M) was used as the solvent.

The mechanism of the reaction could take place in two stages. The first step is the hydrocarboxylation of the allene with the TFA, leading to the formation of the corresponding allylic ester (observed in both ¹H and ¹⁹F NMR), which is in presence of water in equilibrium with the corresponding iminium/carbocation forms (observed in HRMS ESI+). The second step could be either a nucleophilic substitution on the ester by the sulfinate, with the trifluoroacetate as a leaving group, or either a conjugated addition of the sulfinate to the iminium species, which finally leads to the formation of the desired allylic sulfone. The nucleophilic addition occurred on the β position of the iminium salt, which is a classical pathway to obtain enamines. (Scheme 4, A.).²⁶ When the reaction was performed using D₂O as a solvent, while in the presence of TFA or deuterated TFA, 90% deuterium incorporation was observed at the central position of the allene, which is consistent with the mechanism proposed above. By using benzenesulfinic acid (PhSO₂H) instead of the corresponding sodium salt (PhSO₂Na), no product was formed, suggesting that the sulfinic acid is not strong enough to protonate the *N*-allenyl derivative. (Scheme 4, B).

Scheme 4. Proposed mechanism and control experiments.

To conclude, we developed a Brønsted acid-mediated allylation of S(VI)-containing nucleophiles. This transition metal-free methodology occurs in mild conditions and allows the hydrosulfonylation of a wide range of *N*-allenyl derivatives substrates with total regio- and stereoselectivity in water. Unprecedented (*E*)-allylic sulfones and a 1,3-disulfone were obtained with moderate to excellent yields in a total atom economical fashion. Further investigations and mechanistic studies for hydrofunctionalization of allenes will be reported in due course.

ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures and characterization data (NMR ¹H, ¹³C, ¹⁹F, ESI-HRMS and m.p. if solid) for all new compounds are provided in the supporting information (PDF).

The Supporting Information is available free of charge on the ACS Publications website.

AUTHOR INFORMATION

Corresponding Authors

* **Florian Monnier** Institut Charles Gerhardt Montpellier (ICGM), ENSCM, Université de Montpellier, CNRS and Institut Universitaire de France (IUF); orcid.org/0000-0002-9924-2012; email: florian.monnier@enscm.fr

* **Marc Taillefer** Institut Charles Gerhardt Montpellier (ICGM), ENSCM, Université de Montpellier, CNRS; email: marc.taillefer@enscm.fr

Authors

Lucas Pagès Institut Charles Gerhardt Montpellier (ICGM), ENSCM, Université de Montpellier, CNRS

Sébastien Lemouzy Institut Charles Gerhardt Montpellier (ICGM), ENSCM, Université de Montpellier, CNRS

Author Contributions

The manuscript was written through contributions of all authors. / All authors have given approval to the final version of the manuscript.

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