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Vinyl Sulfones

Silver-Catalyzed Denitrative Sulfonylation of β-Nitrostyrenes: A Convenient Approach to (*E*)-Vinyl Sulfones

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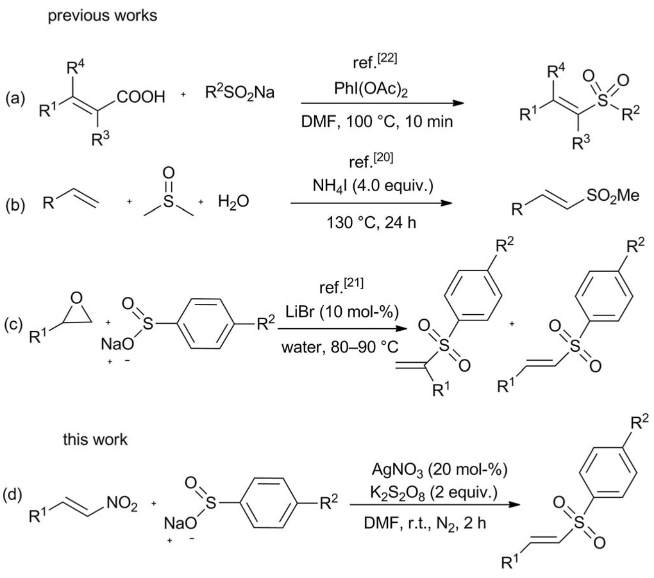
Abstract: The first utilization of β-nitrostyrenes (readily available by the Henry reaction) for a highly stereoselective, convenient, and catalytic synthesis of (*E*)-vinyl sulfones at room temperature was investigated. The protocol involves efficient silver-catalyzed denitrative radical cross-coupling of β-nitrostyrenes and sodium sulfinates by using potassium persulfate as an additive to complete the catalytic cycle.

Introduction

Vinyl sulfones constitute an important class of compounds with diversified biological activities and synthetic applications.[1–5] Substituted vinyl sulfones have received overwhelming attention in medicinal chemistry and the pharmaceutical industry owing to their wide scope of utilization as cysteine protease inhibitors,[6] antibiotic TAN-1085,[7] and HIV-1 integrase.[8] As far as a synthetic point of view is concerned, they act as efficient Michael acceptors and 2π partners in cycloaddition reactions.[9] Keeping in view the importance and further exploitation of vinyl sulfones, many approaches are available for their synthesis, and many more novel synthetic routes continue to be developed.

The literature records a number of methods for the synthesis of vinyl sulfones that involve the direct oxidation of vinyl sulfides,[10] β-elimination,[11] Knoevenagel condensation,[12] Wittig reaction,[13] and Horner–Emmons reaction.[14] These methods have been replaced by more efficient Pd- and Cu-catalyzed cross-coupling reactions of vinyl halides,[15] vinyl tosylates,[16] vinyl triflates,[17] alkenylboronic acids,[18] and alkenes.[19] Although these reactions are efficient, the use of poisonous metals and expensive ligands makes them unsuitable from a synthetic point of view. Li and co-workers developed the ammonium iodide induced sulfonylation of alkenes with DMSO.[20] However, this method is limited to the synthesis of only vinyl methyl sulfones. We also reported the regioselective synthesis of vinyl sulfones from epoxides.[21]

Very recently, decarboxylative sulfonylation reactions of cinnamic acids[22] were reported, and this led us to hypothesize that denitrative sulfonylation reactions of β-nitrostyrenes, readily available by the Henry reaction, could be a convenient way to access vinyl sulfones. In several instances, β-nitrostyrenes have been used for denitrative C–C bond formation by an addition/elimination reaction.[23] Considering the above points and our continued work on the functionalization of alkenes,[24] we report herein a convenient catalytic approach to (*E*)-vinyl sulfones from β-nitrostyrenes and sodium sulfinates (Scheme 1d). We opted to use silver catalysis so that we could efficiently generate sulfonyl radicals from sodium sulfinates.



Scheme 1. Different routes for the synthesis of vinyl sulfones.

Results and Discussion

To realize our hypothesis, we commenced the study with a model reaction of sodium *p*-toluenesulfinate (**2a**; 0.25 mmol) and β-nitrostyrene (**1a**; 0.25 mmol) in the presence of $AgNO_3$ (20 mol-%) as a catalyst and $K_2S_2O_8$ (0.50 mmol) as an additive in DMF at room temperature (Table 1). (*E*)-Vinyl sulfone **3a** was obtained in an excellent yield of 90 % in just 2 h. Encouraged by this result, we switched over to optimizing the reaction conditions, and different additives such as *tert*-butyl hydroperoxide (TBHP), di-*tert*-butyl peroxide (DTBP), and $(NH_4)_2S_2O_8$ were

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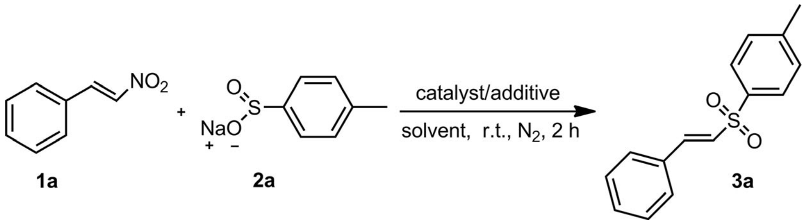
Table 1. Optimization of the reaction conditions.[a]



Entry	Solvent	Catalyst (mol-%)	Additive (equiv.)	Yield [%][b]
1	DMF	$AgNO_3$ (20)	$K_2S_2O_8$ (2)	90
2	DMF	$AgNO_3$ (20)	TBHP (2)	27
3	DMF	$AgNO_3$ (20)	DTBP (2)	38
4	DMF	$AgNO_3$ (20)	$(NH_4)_2S_2O_8$ (2)	54
5	DMF	Fe_2O_3 (20)	$K_2S_2O_8$ (2)	45
6	DMF	CuI (20)	$K_2S_2O_8$ (2)	26
7	DMF	$FeCl_3$ (20)	$K_2S_2O_8$ (2)	70
8	DMF	AgOAc (20)	$K_2S_2O_8$ (2)	40
9	DMF	CuCl (20)	$K_2S_2O_8$ (2)	20
10	DMF	$Cu(OAc)_2$ (20)	$K_2S_2O_8$ (2)	50
11	DMF	–	$K_2S_2O_8$ (2)	25
12	DMF	$AgNO_3$ (20)	$K_2S_2O_8$ (1.0)	65
13	DMF	$AgNO_3$ (20)	$K_2S_2O_8$ (3)	90
14	DMF	$AgNO_3$ (15)	$K_2S_2O_8$ (2)	75
15	DMF	$AgNO_3$ (25)	$K_2S_2O_8$ (2)	90
16	dioxane	$AgNO_3$ (20)	$K_2S_2O_8$ (2)	26
17	DMSO	$AgNO_3$ (20)	$K_2S_2O_8$ (2)	85
18	MeOH	$AgNO_3$ (20)	$K_2S_2O_8$ (2)	22
19	CH_3NO_2	$AgNO_3$ (20)	$K_2S_2O_8$ (2)	15
20	THF	$AgNO_3$ (20)	$K_2S_2O_8$ (2)	–
21	CH_3CN	$AgNO_3$ (20)	$K_2S_2O_8$ (2)	–
22	toluene	$AgNO_3$ (20)	$K_2S_2O_8$ (2)	–
23	DMF	$AgNO_3$ (20)	$K_2S_2O_8$ (2)	–[c]

[a] Reaction conditions: A mixture of β-nitrostyrene (**1a**; 0.25 mmol), sodium *p*-toluenesulfinate (**2a**; 0.25 mmol), catalyst, and additive in solvent (3 mL) was stirred for 2 h under N_2. [b] Yield of isolated product after column chromatography. [c] Reaction was performed in the presence of O_2.

tested in place of $K_2S_2O_8$, but none of them was found to be better than $K_2S_2O_8$ (Table 1, Entries 1–4). Then, we proceeded to investigate the optimum amount of the additive required, and it was found that 2 equiv. was sufficient, as upon decreasing the amount, the yield decreased, and upon increasing the amount no change in the yield was observed (Table 1, Entries 12 and 13). As shown in Table 1 (Entry 1 vs. Entries 5–10), $AgNO_3$ proved to be the best catalyst among those tested to give the desired product in a maximum yield of 90 %. In the absence of a catalyst, the yield was poor (Table 1, Entry 11). Subsequently, quantitative optimization of the catalyst showed that 20 mol-% was the optimum catalyst loading (Table 1, Entry 1 vs. Entries 14 and 15).

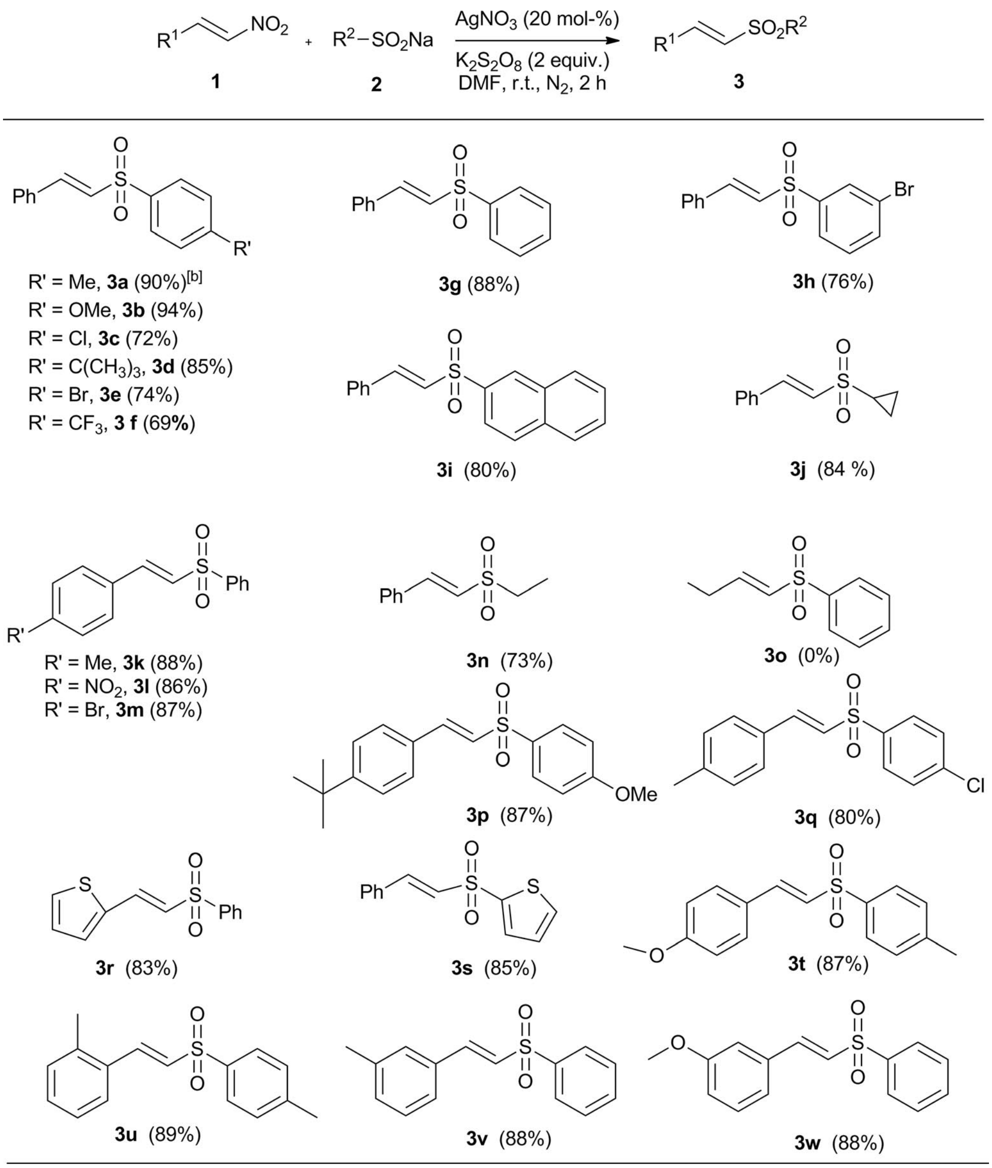
Screening of various solvents revealed DMF to be the best among dioxane, DMSO, MeOH, CH_3NO_2, THF, CH_3CN, and toluene (Table 1, Entries 16–22). The formation of product **3a** was not observed if the reaction was performed in the presence of O_2 (Table 1, Entry 23).

Under the standardized reaction conditions, a variety of β-nitrostyrenes and sodium sulfinates were explored, and the results are summarized in Table 2. Notably, sodium sulfinates **2** bearing an electron-donating group [e.g., Me, OMe, or $C(Me)_3$] on the aromatic ring were superior for the radical addition/elimination reaction than those bearing an electron-withdrawing group (e.g., CF_3, Cl, or Br; see Table 2, **3a**–**f**). Other sulfinic salts such as sodium 2-thienylsulfinate and sodium 2-naphthylsulfinate also produced the products in excellent yields (Table 2, see **3i** and **3s**). Moreover, alicyclic and aliphatic sulfinates also reacted under the conditions to afford the products in good yields (Table 2, see **3j** and **3n**).

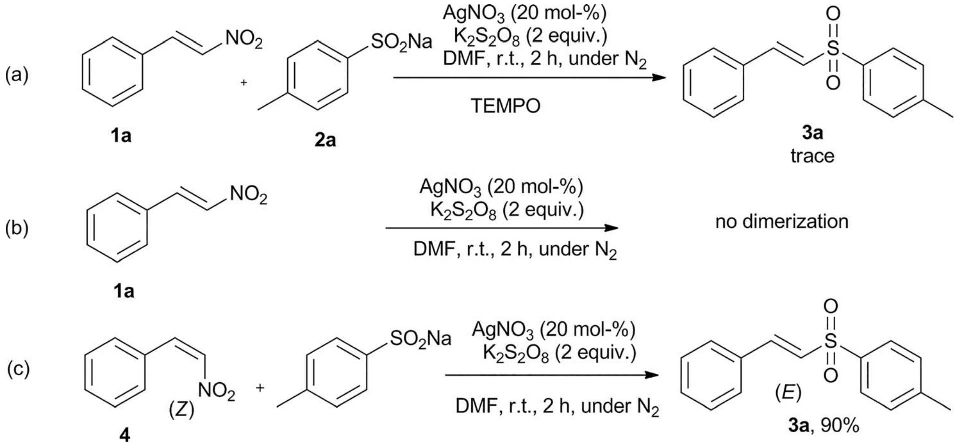
Similarly, β-nitrostyrenes bearing an electron-donating group on the aromatic ring worked better than those bearing an electron-withdrawing group. Unfortunately, the reaction did not produce the desired product in the case of an alkyl-substituted β-nitroalkene (Table 2, see **3o**). This is probably the case because for β-nitrostyrenes the formation of a resonance-stabilized radical is highly favored, contrary to alkyl-substituted β-nitroalkenes. Moreover, α- and/or β-substituted β-nitrostyrenes and nitrogen-containing heterocycles were not compatible with the reaction conditions.

Trace amounts or no products were observed if the radical scavenger 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) was added to the reaction mixture, which proves that the reaction proceeds by a radical pathway (Scheme 2a). The formation of the *p*-toluenesulfonyl–TEMPO adduct was confirmed by MS [HRMS (EI): calcd. for $C_{16}H_{25}NO_3S$ 311.1555; found 311.1552]. In the absence of the sulfinate, reactant **1a** was recovered, which implies that the self-coupling of β-nitrostyrenes does not occur

Table 2. Synthesis of vinyl sulfones.[a]



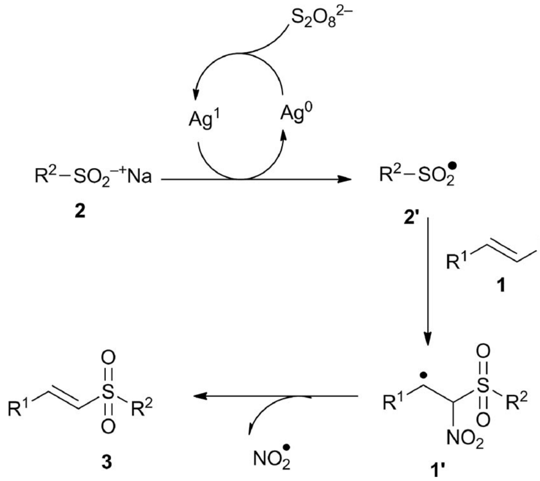
[a] Reaction conditions: A mixture of β-nitrostyrene **1** (0.25 mmol), sodium sulfinate **2** (0.25 mmol), $AgNO_3$ (20 mol-%), and $K_2S_2O_8$ (0.50 mmol) in DMF (3 mL) was stirred at room temperature under N_2 for 2 h (for details, see the Experimental Section). [b] The yields of isolated products **3** are given in parentheses.



Scheme 2. Mechanistic investigation.

by a radical pathway (Scheme 2b). Moreover, (*E*)-vinyl sulfone was selectively obtained upon using a (*Z*)-β-nitrostyrene under the standard conditions (Scheme 2c).

On the basis of the above results and literature precedent,[23a,24b,24c] a plausible radical addition/elimination mechanism is proposed in Scheme 3. At first, Ag^I triggers the formation of sulfonyl radical **2′**, and the resulting Ag^0 is oxidized to Ag^I with the persulfate anion to complete the catalytic cycle. The addition of the sulfonyl radical to the olefinic double bond of β-nitrostyrene **1** generates carbon-centered radical **1′**. Finally, **1′** eliminates NO_2 and produces the more stable (*E*)-vinyl sulfone **3**.



Scheme 3. Plausible mechanism for the formation of vinyl sulfones.

Conclusions

We developed an efficient silver-catalyzed one-pot protocol for the highly stereoselective synthesis of (*E*)-vinyl sulfones by denitrative radical cross-coupling of readily available β-nitrostyrenes and sodium sulfinates at room temperature under mild reaction conditions. The reaction involves a radical addition/elimination pathway for the formation of the product. This is the first report on the facile formation of $C(sp^2)$–S bonds leading to vinyl sulfones.

Experimental Section

General Procedure for the Denitrative Sulfonylation of β-Nitrostyrenes with Sodium Sulfinate: A mixture of (*E*)-β-nitrostyrene **1** (0.25 mmol), sodium sulfinate **2** (0.25 mmol), $AgNO_3$ (20 mol-%), $K_2S_2O_8$ (0.50 mmol), and DMF (3 mL) was stirred at room temperature under N_2 in a round-bottomed flask for 2 h. Upon completion of the reaction (monitored by TLC), water (5 mL) was added, and the mixture was extracted with EtOAc (3 × 5 mL). The combined organic phases were dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude product was purified by column chromatography (silica gel; EtOAc/*n*-hexane, 1:4) to afford an analytically pure sample of (*E*)-vinyl sulfone **3**.

Acknowledgments

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Keywords: Cross-coupling · Elimination · Radical reactions · Silver · Sulfur

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