An Efficient and Facile Synthesis of Vinyl Sulfones via Microwave-Assisted Copper Triflate Catalyzed Hydrosulfonylation of Alkynes

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Abstract: An efficient method has been described for the synthesis of vinyl sulfones via hydrosulfonylation of alkynes using sodium arene sulfinates catalyzed by $Cu(OTf)_2$ under microwave irradiation. A variety of vinyl sulfones was obtained in good to excellent (71–89%) yields and with high regio- and stereoselectivity. Shortened reaction times, simple reaction conditions and low catalyst loading are the salient features of this protocol.

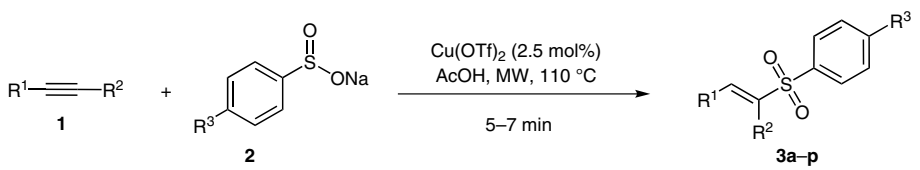
Key words: microwave, vinyl sulfones, copper triflate, alkynes, sodium arene sulfinates

Vinyl sulfones and their derivatives have been extensively used as versatile building blocks and valuable intermediates in organic synthesis[1] and medicinal chemistry.[2] They are excellent Michael acceptors[3] and 2π-partners in cycloaddition reactions.[4] Vinyl sulfones are well known to act as irreversible inhibitors of many types of cysteine proteases[5] through conjugate addition of the thiol of the active site cysteine residue. In addition to cysteine protease inhibition, vinyl sulfones also serve as key structural motifs in several other biologically active molecules possessing anticancer,[6] carcinogenesis suppression[7] and antitrypanosomal activity.[8]

In view of the importance of vinyl sulfones in synthetic chemistry and medicinal chemistry, various methods have been developed for their synthesis.[2e,f] Classical protocols for the synthesis of vinyl sulfones include olefination reactions,[9] manipulation of acetylenic sulfones,[10] and addition of sulfonyl halides to alkenes followed by elimination reactions.[11] Recent methods for synthesizing vinyl sulfones include hydrozirconation of 1-alkynyl sulfones,[12] cerium(IV) ammonium nitrate mediated oxidative addition of sodium arene sulfinate and sodium iodide with alkenes,[13] boron trifluoride or AIBN-catalyzed addition of polystyrene-supported selenosulfonates to alkenes,[14] reaction of sulfinate salts with dibromides,[15] and palladium- or copper-catalyzed cross-coupling and addition reactions of sulfinate salts.[16] Despite this range of available methodologies, these methods suffer from one or more drawbacks in terms of sensitive functional group tolerance, formation of isomer mixtures and side products, or need for inaccessible starting materials, relatively harsh reaction conditions or tedious procedures. Therefore, there remains the need to develop facile, highly selective and resource-efficient protocols to construct vinyl sulfones.

Owing to our interest in developing simple and efficient synthetic methods using metal triflates;[17] we report herein an efficient copper triflate catalyzed hydrosulfonylation of alkynes using sodium arene sulfinates under microwave irradiation to give β-vinyl sulfones in good to excellent yields with high regio- and stereoselectivity (Scheme 1). To the best of our knowledge this is first report on the synthesis of vinyl sulfones under microwave irradiation in the presence of copper triflate.[18]

Initially, we investigated the catalytic activity of various metal salts in acetic acid at 110 °C under microwave irradiation (Table 1, entries 1–9) for the addition of sodium benzene sulfinate (**2a**) to phenylacetylene (**1a**) to give [2-(phenylsulfonyl)vinyl]benzene (**3a**). Among all the screened catalysts, copper salts were found to be more effective for this reaction. Notably, $Cu(OTf)_2$ was found to be the best catalyst to afford **3a** in 80% yield. Other catalysts such as $Pd(OAc)_2$, $Yb(OTf)_3$, and $Zn(OTf)_2$ either did not promote or sluggishly promoted this reaction. We further proceeded to optimize the catalyst loading and solvent screening. It was found that there was no significant change in the yield of **3a** on increasing the amount of $Cu(OTf)_2$ from 5 mol% to 10 mol% (Table 1, entries 9 and 10) but a slight increase in yield was observed when the amount of $Cu(OTf)_2$ was reduced to 2.5 mol% (Table 1, entries 9 and 11). In the absence of $Cu(OTf)_2$, **3a** was not formed (Table 1, entry 18). Subsequently it was estab-



Scheme 1 Synthesis of vinyl sulfones

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lished that solvent has a significant role (Table 1, entries 11–17). Very poor yields of **3a** were observed in THF, water and methanol while only a trace was observed in dimethoxyethane and no product was formed in acetonitrile.

Lowering the reaction temperature to 80 °C and 60 °C under microwave irradiation decreased the yield of **3a** to 40% and 25%, respectively. Thus, the optimum conditions for this transformation were established to be microwave heating at 110 °C in the presence of $Cu(OTf)_2$ (2.5 mol%) in acetic acid.

Table 1 Optimization of the Reaction Condition[a]

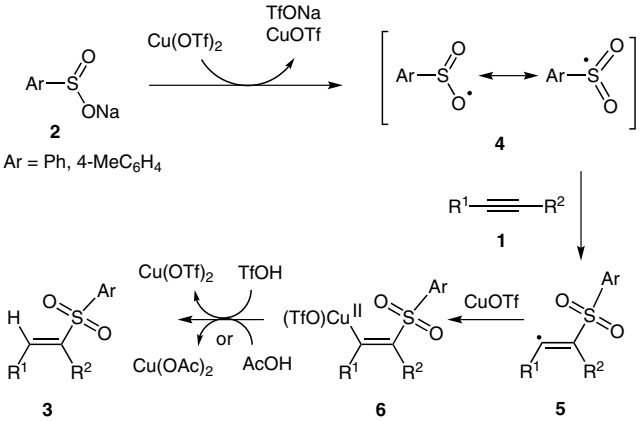
Entry	Catalyst (mol%)	Solvent	Yield (%) of **3a**[a]
1	$Pd(OAc)_2$ (5)	AcOH	0
2	$Yb(OTf)_3$ (5)	AcOH	trace
3	$Zn(OTf)_2$ (5)	AcOH	trace
4	CuI (5)	AcOH	18
5	$CuCl_2 \cdot H_2O$ (5)	AcOH	62
6	$CuBr_2$ (5)	AcOH	60
7	$CuSO_4 \cdot 5H_2O$ (5)	AcOH	74
8	$Cu(OAc)_2 \cdot H_2O$ (5)	AcOH	68
9	$Cu(OTf)_2$ (5)	AcOH	80
10	$Cu(OTf)_2$ (10)	AcOH	76
11	**$Cu(OTf)_2$ (2.5)**	**AcOH**	**82**
12	$Cu(OTf)_2$ (5)	HCOOH	64
13	$Cu(OTf)_2$ (5)	THF	25
14	$Cu(OTf)_2$ (5)	H_2O	18
15	$Cu(OTf)_2$ (5)	MeOH	16
16	$Cu(OTf)_2$ (5)	MeCN	0
17	$Cu(OTf)_2$ (5)	DME	Trace
18	–	AcOH	0

[a] Reaction conditions: **1a** (1.0 mmol), **2a** (1.0 mmol), catalyst (2.5–10 mol%), solvent (2 mL), at 110 °C under microwave irradiation, 5 min.

With the optimized reaction conditions in hand, we explored the substrate scope of the reaction using various arylacetylenes with sodium arene sulfinates. The results are shown in Table 2. Phenylacetylenes bearing either an electron-donating substituent or an electron-withdrawing substituent afforded the corresponding vinyl sulfones in good to excellent yields under the optimized conditions. Not only terminal alkynes but also internal alkynes reacted to give the corresponding vinyl sulfones (**3m** and **3n**) in good yield (Table 2, entries 13 and 14). Moreover, heteroaromatic alkynes such as 2-ethynylpyridine reacted efficiently with both sodium *p*-toluene sulfinate and sodium benzene sulfinate providing the corresponding vinyl sulfones (**3o** and **3p**) in excellent yields (Table 2, entries 15 and 16). The structures of all the synthesized vinyl sulfones were elucidated by IR and NMR analysis (see supplementary data). Based on the spectroscopic analysis it can be concluded that the reaction is regio- and stereoselective giving (*E*)-vinyl sulfones. Furthermore it is worthy of note that β-keto sulfones, which have been reported to be formed by oxidative addition of sulfinic acids to alkynes in the presence of copper catalysts,[16f,19] were not detected under these conditions.

To gain insight into the reaction mechanism, **1a** and **2a** were reacted in the presence of one equivalent of TEMPO as a radical scavenger when only a 15% yield of **3a** was observed, suggesting that the reaction might involve a radical process. Based on the literature reports[18] and our own experimental observations, a plausible mechanism is proposed as shown in Scheme 2. It is believed that initially radical **4** is generated from sulfinyl anion **2** via single electron transfer involving Cu(II).[20] The radical **4** adds to alkyne **1** affording vinyl radical **5** which further reacts with the Cu(I) species to yield vinyl sulfone copper(II) complex **6**. Finally, demetallation–protonation of **6** results in the formation of adduct **3a**.[21]

In conclusion, we have developed a very efficient method for the synthesis of vinyl sulfones via hydrosulfonylation of alkynes using sodium arene sulfinates catalyzed by $Cu(OTf)_2$ under microwave irradiation.[22] The method provides a variety of vinyl sulfones in good to excellent yields and high regio- and stereoselectivity. In addition, this method exploits the use of microwaves and is faster than the conventional heating process. The advantages of this methodology include its experimental simplicity, short reaction time, simple conditions, low catalyst loading and ready availability of the starting materials.



Scheme 2 Proposed mechanism for the synthesis of vinyl sulfones

Table 2 Vinyl Sulfones Derivatives **3a**–**p** Produced via Reaction of Arene Sulfinates and Alkynes in the Presence of $Cu(OTf)_2$ under Microwave Irradiation[a]

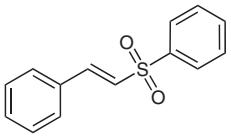
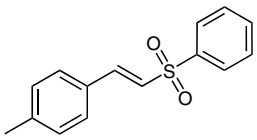
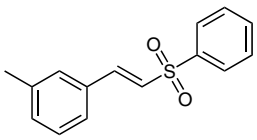
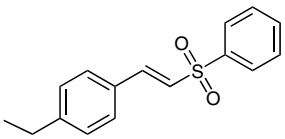
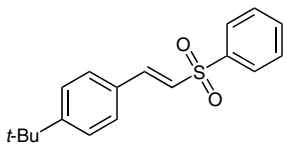
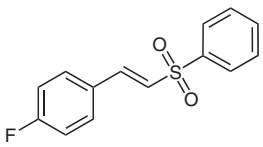
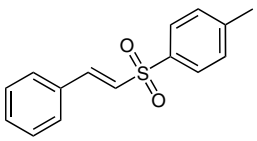
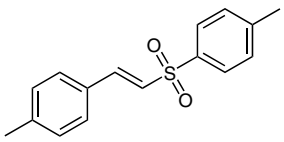
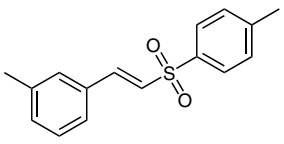
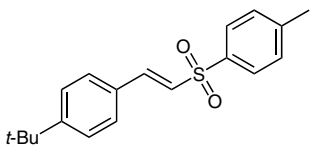
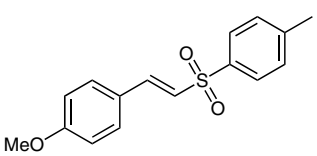
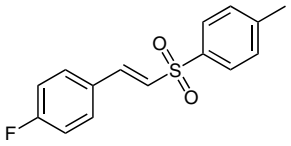
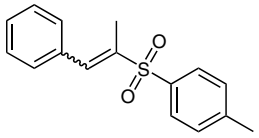
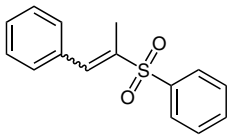
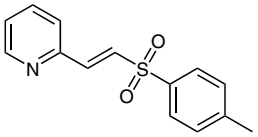
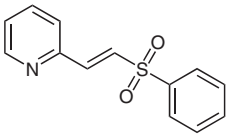
Entry	R^1	R^2	R^3	Product		Time (min)	Yield (%)[b]
1	Ph	H	H	**3a**		5	82
2	4-MeC_6H_4	H	H	**3b**		5	84
3	3-MeC_6H_4	H	H	**3c**		5	77
4	4-EtC_6H_4	H	H	**3d**		5	74
5	4-*t*-BuC_6H_4	H	H	**3e**		5	79
6	4-FC_6H_4	H	H	**3f**		5.30	71
7	Ph	H	Me	**3g**		5	84
8	4-MeC_6H_4	H	Me	**3h**		5	86
9	3-MeC_6H_4	H	Me	**3i**		5	81
10	4-*t*-BuC_6H_4	H	Me	**3j**		5	82
11	4-$MeOC_6H_4$	H	Me	**3k**		5	87

Table 2 Vinyl Sulfones Derivatives **3a–p** Produced via Reaction of Arene Sulfinates and Alkynes in the Presence of $Cu(OTf)_2$ under Microwave Irradiation[a] (continued)

Entry	R^1	R^2	R^3	Product		Time (min)	Yield (%)[b]
12	4-FC_6H_4	H	Me	**3l**		5.30	74
13	Ph	Me	Me	**3m**		6.30	89
14	Ph	Me	H	**3n**		6.30	81
15	C_5H_4N	H	Me	**3o**		5	79
16	C_5H_4N	H	H	**3p**		5	74

[a] Reaction conditions: **1** (1.0 mmol), **2** (1.0 mmol), $Cu(OTf)_2$ (2.5 mol%), AcOH (2 mL), MW irradiation (at 110 °C, 250 psi, 200 W).
[b] Isolated yield.

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(22) **Representative Procedure**: Phenylacetylene (102 mg, 1 mmol), sodium benzene sulfinate (164 mg, 1 mmol), and $Cu(OTf)_2$ (16 mg, 2.5 mol%) were added to a 10-mL microwave tube containing AcOH (2 mL) and a magnetic stirrer bar. The reaction mixture was placed in a CEM Discover BenchMate. The reaction parameters were set to 200 W, 250 psi, 110 °C for 5 min with stirring. After completion of the reaction, the reaction mixture was diluted with H_2O (10 mL) and extracted with EtOAc (2 × 10 mL). The organic layer was dried with anhyd Na_2SO_4, filtered and the solvent evaporated on a rotary evaporator to give the crude product which was purified by passing through a silica column to give pure **3a** (200 mg, 82%) as a white solid.

Selected Spectroscopic Data:

(*E*)-1-Methyl-3-[2-(phenylsulfonyl)vinyl]benzene (**3c**): yellow solid; mp 74–76 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.95–7.99 (m, 2 H), 7.68 (d, *J* = 15.4 Hz, 1 H), 7.61–7.65 (m, 1 H), 7.54–7.60 (m, 2 H), 7.29–7.33 (m, 3 H), 7.23–7.26 (m, 1 H), 6.87 (d, *J* = 15.4 Hz, 1 H), 2.37 (s, 3 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 142.71, 140.81, 138.87, 133.35, 132.31, 132.08, 129.34, 129.16, 128.99, 127.65, 127.00, 125.85, 21.28. IR (KBr): 3047, 2916, 1612, 1443, 1296, 1142 cm^{-1}. HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{15}O_2S$: 259.0787; found: 259.0765.

(*E*)-1-Ethyl-4-[2-(phenylsulfonyl)vinyl]benzene (**3d**): yellow solid; mp 95–96 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.95–7.99 (m, 2 H), 7.69 (d, *J* = 15.4 Hz, 1 H), 7.61–7.66 (m, 1 H), 7.54–7.59 (m, 2 H), 7.43 (d, *J* = 8.2 Hz, 2 H), 7.24 (d, *J* = 8.1 Hz, 2 H), 6.84 (d, *J* = 15.4 Hz, 1 H), 2.68 (q, *J* = 7.6 Hz, 2 H), 1.25 (t, *J* = 7.6 Hz, 3 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 148.19, 142.63, 140.94, 133.31, 129.85, 129.33, 128.74, 128.67, 127.61, 126.10, 28.86, 15.31. IR (KBr): 3055, 2962, 1612, 1512, 1450, 1311, 1149 cm^{-1}. HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{17}O_2S$: 273.0944; found: 273.0958.

(*E*)-1-Fluoro-4-(2-tosylvinyl)benzene (**3l**): white solid; mp 95–96 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.84 (d, *J* = 8.3 Hz, 2 H), 7.64 (d, *J* = 15.4 Hz, 1 H), 7.46–7.52 (m, 2 H), 7.36 (d, *J* = 8.0 Hz, 2 H), 7.09 (t, *J* = 8.6 Hz, 2 H), 6.81 (d, *J* = 15.4 Hz, 1 H), 2.45 (s, 3 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 164.30 (d, $J_{C–F}$ = 252.8 Hz), 144.49, 140.61, 137.65, 130.56 (d, $J_{C–F}$ = 8.7 Hz), 130.02, 128.72 (d, $J_{C–F}$ = 3.4 Hz), 127.72, 127.41 (d, $J_{C–F}$ = 2.4 Hz), 116.31 (d, $J_{C–F}$ = 22.1 Hz), 21.64. IR (KBr): 3055, 1597, 1504, 1450, 1304, 1234, 1142 cm^{-1}. HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{14}FO_2S$: 277.0693; found: 277.0685.

(*E*)-2-(2-Tosylvinyl)pyridine (**3o**): yellow solid; mp 98–99 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.62 (d, *J* = 3.9 Hz, 1 H), 7.85 (d, *J* = 8.3 Hz, 2 H), 7.74 (td, *J* = 7.7, 1.8 Hz, 1 H), 7.64 (d, *J* = 14.9 Hz, 1 H), 7.43 (dd, *J* = 13.5, 11.4 Hz, 2 H), 7.35 (d, *J* = 8.0 Hz, 2 H), 7.28–7.32 (m, 1 H), 2.44 (s, 3 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 151.11, 150.29, 144.61, 140.03, 137.25, 137.04, 132.15, 130.00, 127.94, 125.39, 124.94, 21.65. IR (KBr): 3040, 1620, 1589, 1435, 1311, 1142 cm^{-1}. HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{14}NO_2S$: 260.0740; found: 260.0725.