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Cyanide-Mediated Synthesis of Sulfones and Sulfonamides from Vinyl Sulfones

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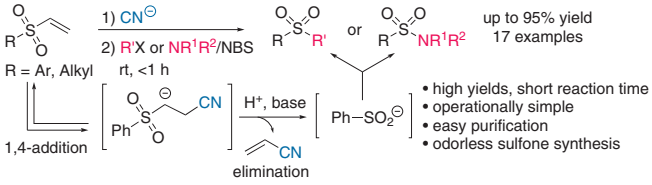

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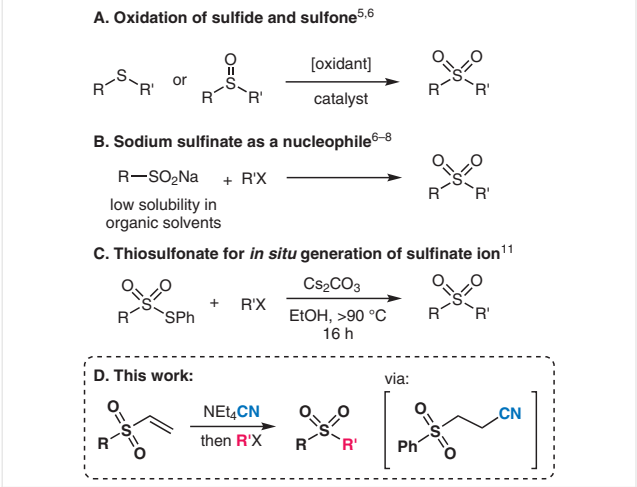
Abstract We report a facile synthesis of sulfones, β-keto sulfones, and sulfonamides from vinyl sulfones via an addition–elimination sequence where *in situ* generation of nucleophilic sulfinate ion is mediated by cyanide. The use vinyl sulfones renders high selectivity for *S*-alkylation to produce sulfones in high yields. In the presence of *N*-bromosuccinimide, primary and secondary amines underwent sulfonamide formation. A preliminary mechanistic study showed the formation of acrylonitrile as an innocent byproduct, without interfering with the desired reaction pathway while generating a sulfinate nucleophile.

Key words cyanide, sulfonate, sulfones, sulfonamides, vinyl sulfones

Compounds comprising sulfur(IV), for instance, sulfones and sulfonamides are useful synthetic targets for organic chemists attributable to their unique biological activities and utility as building blocks and catalysts in several organic transformations.[1] Typically, sulfonyl derivatives are synthesized from the oxidation of sulfides or sulfoxides (Scheme 1, A).[2] However, these routes suffer shortcomings, i.e., multiple synthetic steps, use of over-stoichiometric amount of strong oxidizing agents, elevated temperatures, extended reaction time, and unendurable odor of thiols. Sulfinated salts are an adequate alternative to access sulfone functional groups via nucleophilic substitution reactions at sulfur.[2b] Recent developments in sulfinate derivatives in sulfonylative couplings and desulfinative couplings showed promising reactivity patterns.[3] However, the intrinsic low solubility of sulfinate salts in organic solvents prohibits general applications with electrophilic reagents (R'X, Scheme 1, B). Recently, Shyam et al. reported the use of thiosulfonates to *in situ* generate the sulfinate anion, which then subsequently reacted with various alkyl halides or amines to afford sulfones or sulfonamides at elevated temperature (Scheme 1, C).[4] However, the process still requires elevated reaction temperatures (>90 °C) and longer reaction times to achieve the desired transformation.



Scheme 1 Conventional routes to access sulfones: (A) Oxidation of sulfides and sulfoxides, (B) nucleophilic substitution reaction of metal sulfinates, and (C) thiosulfonates to generate sulfinates. (D) This work represents devinylation to access nucleophilic sulfinate ions for substitution reactions.

During our investigation on the reactivity of cyanide with carbon dioxide and electrophiles,[5] we observed that commercially available vinyl sulfones were decomposed presumably to acrylonitrile and sulfinate anion. Therefore, we anticipated that the *in situ* generated sulfinate anion can be a useful intermediate for substitution reactions with electrophilic partners to access sulfones and sulfonamides (Scheme 1, D). This reaction would involve an addition–elimination sequence of vinyl sulfones, converting this common electrophilic Michael acceptor into nucleophilic

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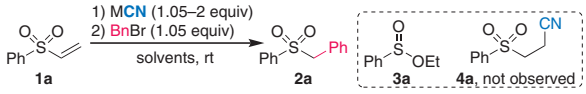
sulfinate.[6] Furthermore, the generation of sulfinates from an accessible source would be an interesting alternative for transition-metal-catalyzed C–H activation[7] and photoredox catalysis,[8] where promising reactivities are shown with sulfur(IV) derivatives.

We commenced our investigation under previously established experimental conditions[5a] using phenyl vinyl sulfone (**1a**) as a model electrophile. We observed no trace of the corresponding cyanide adduct, although complete consumption of the starting material was detected. Kiyokawa et al. reported the transformation of vinyl sulfones to 1,2-dicyanoalkanes mediated by TMSCN and tetrabutylammonium fluoride.[6] Based on our observation, the absence of cyanated product with phenyl vinyl sulfone suggested a possible concerted addition–elimination reaction. To establish our hypothesis, benzyl bromide was employed to the reaction mixture, resulting in a rapid formation of (benzylsulfonyl)benzene (**2a**) with a yield of 90% in 15 minutes (Table 1, entry 1). Without strict anhydrous atmosphere, a clean reaction profile was obtained, indicating high selectivity toward the desired product **2a** under ambient reaction conditions.

The absence of any *O*-benzylated product under the present reaction conditions is notable.[9] The use of sodium benzenesulfinate as a surrogate under the same reaction conditions afforded less than 10% yield of the desired product, highlighting the advantage of *in situ* generation of the sulfinate via de-vinylation (Table 1, entry 2). The use of sodium benzenesulfonate together with stoichiometric amount of tetrabutylammonium bromide as a phase-transfer reagent furnished **2a** in moderate yield even at higher temperatures (60% at room temperature and 76% at 80 °C, entries 3 and 4, respectively). These results indicate that the solubility of sulfinate anion is important to attain the desired reactivity of the nucleophilic sulfinate. Based on the well-established phase-transfer reaction mechanism, NaCN and KCN were employed as a cyanide source, which afforded moderate yields of the desired product **2a** in the presence of NBu_4I as a phase-transfer catalyst (54–56% yield, Table 1, entries 5 and 6). Soluble cyanide sources such as TMSCN and acetone cyanohydrin were found to be ineffective to generate product **2a**. A quick optimization of the solvents showed both DCM and THF are optimum (Table 1, entries 11 and 12). A protic solvent, ethanol, afforded the formation of ethyl sulfonate (*O*-ethylated product **3a**, 35%) as a predominant product over the *S*-benzylated product (**2a**, 22%, Table 1, entry 14). To our delight, the reaction could also be carried out in neat water but at the cost of diminished reactivity and product yield (60% yield, 2 h, Table 1, entry 15).

Under optimized conditions, several aryl alkyl sulfone derivatives were prepared (Scheme 2). Both alkyl iodides and alkyl bromides were found to be adequate choices as alkylating agent, furnishing corresponding sulfones in high

Table 1 Optimization of the Reaction Conditions[a]

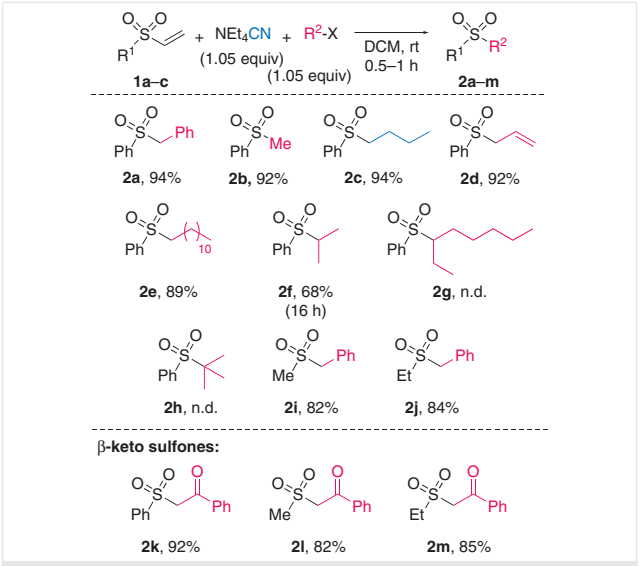


Entry	Solvent	Cyanide source	Time (min)	Yield (%)[b]
1	MeCN	NEt_4CN	15	90
2[c]	MeCN	–	30	<10
3[c,d]	MeCN	–	15	60
4[c,e,f]	MeCN	–	960	76
5[e]	MeCN	NaCN	960	56
6[e]	MeCN	KCN	120	54
7	MeCN	$Zn(CN)_2$	960	n.d.
8	MeCN	TMSCN	120	n.d.
9	MeCN	acetone cyanohydrin	960	n.d.
10	DMF	NEt_4CN	15	85
11	DCM	NEt_4CN	15	99
12	THF	NEt_4CN	30	96
13	toluene	NEt_4CN	120	20
14	EtOH	NEt_4CN	30	22
15	water	NEt_4CN	120	60

[a] Reaction conditions: phenyl vinyl sulfone (0.4 mmol), NEt_4CN (1.05 equiv)/other cyanides (2 equiv), benzyl bromide (1.05 equiv), solvent (1 mL).
[b] NMR yield using 1,3,5-trimethoxybenzene as an internal standard; n.d. = not detected.
[c] Sodium benzenesulfinate was used instead of phenyl vinyl sulfone and a cyanide source.
[d] 100 mol% of *n*-Bu_4NBr were added.
[e] 10 mol% of *n*-Bu_4NI were added.
[f] Reaction mixture was heated at 80 °C.

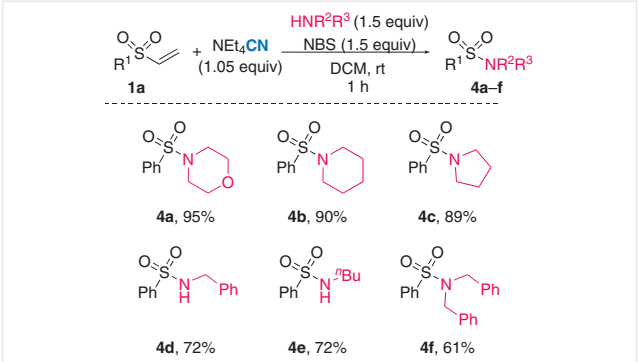
isolated yields. The alkylation using a secondary alkyl bromide, i.e., 2-bromopropane, was expectedly slower; however, we obtained moderate yield of the corresponding product **2f**, together with a small amount of *O*-alkylated product **3f**. Bulkier alkyl bromides or alkyl chlorides were found to be inefficient as an alkylating agent under current optimized conditions. We noticed slight drop in isolated yield of products **2i** (82% yield) and **2j** (84% yield), when methyl- (**1b**) and ethyl (**1c**) vinyl sulfones were used as starting materials instead of phenyl vinyl sulfone (**1a**), respectively.

β-Keto sulfones are lately drawing significant attention as synthetic targets[2b,10] due to their biological activities[11] and widespread applications as synthons in organic synthesis.[12] We extended the application of current synthetic protocol for the synthesis of β-keto sulfones using α-bromo ketones as electrophiles. To our delight, we obtained high isolated yield of β-sulfone phenyl ketone (**2k**) under optimized reaction conditions without complicated purification steps. Methyl and ethyl vinyl sulfones were also tolerant to afford the corresponding sulfones **2l** and **2m** in good isolated yields (82% and 85%, respectively).



Scheme 2 Substrate scope in the synthesis of sulfones and β-keto sulfones.

After establishing a facile and straightforward protocol to access sulfones, we turned our attention to generate sulfonamides by forming halogenated amines as electrophiles. A similar protocol was reported starting from primary and secondary amines using NBS as an oxidant, generating electrophilic nitrogen species at elevated temperatures (Scheme 3).[4] The use of vinyl sulfone as a starting material enabled us to synthesize various sulfonamides from secondary and primary amines at room temperature via the cyanide-mediated addition–elimination sequence. Under ambient reaction conditions primary and secondary amines were smoothly converted into the corresponding sulfonamides with good to excellent yields (61–95% yield).



Scheme 3 Synthesis of sulfonamides.

To probe our suggested reaction mechanism, the Michael addition reaction of cyanide to vinyl sulfone was monitored by ^{1}H NMR spectroscopy in $CDCl_3$ as a reaction solvent.[6] Our direct observation of the elimination product, acrylonitrile, manifested the suggested mechanism (Scheme 1, D). In the crude reaction mixture, we detected the formation of acrylonitrile before the addition of an alkylating agent (Figure 1, red). The elimination reaction was instantaneous and quantitative; however, we presumed that some of acrylonitrile was evaporated during the preparation for the NMR measurement due to the low boiling point of acrylonitrile. We ruled out any radical mechanisms due to the lack of negative effects with TEMPO as a radical scavenger in the alkylation reaction with benzyl bromide. The presence of sulfinate was unambiguously confirmed by ESI-MS showing quantitative conversion of the vinyl sulfone (**1a**) into the corresponding sulfinate mediated by cyanide (see Supporting Information, Figure S1).

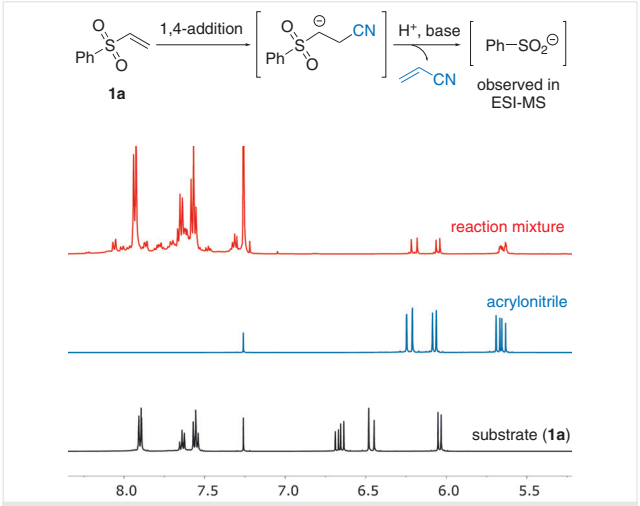


Figure 1 Mechanistic study based on ^{1}H NMR spectra of the reaction mixture (red), a pure sample of acrylonitrile (blue) and the starting material, phenyl vinyl sulfone (**1a**, black).

In conclusion, we demonstrated the *in situ* formation of sulfinate ion, which was beneficial for conducting nucleophilic substitution reactions and amination reaction to afford sulfones[13] and sulfonamides[14] under mild reaction conditions. Preliminary mechanistic studies revealed the sulfone and sulfonamide formation reactions proceeded by expelling acrylonitrile mediated by cyanide, while generating the nucleophilic sulfinate ion. Further applications of *in situ* generated sulfinate nucleophiles in olefin synthesis (Julia–Kocienski type), asymmetric catalysis[15] and CO_2 functionalization[16] are under way.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0039-1690991.

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(13) **General Procedure for the Synthesis of Sulfones 2a–m**
Vinyl sulfone (0.4 mmol) and tetraethylammonium cyanide (1.05 equiv, 0.42 mmol) were dissolved in DCM (1 mL). The reaction mixture was stirred for 5 min, and a solution of an appropriate electrophile (1.05 equiv, 0.42 mmol) in DCM (0.5 mL) was added dropwise. The resultant reaction mixture was stirred at room temperature. After completion of the reaction (checked by crude ^{1}H NMR or GC–MS), water (10 mL) was added to the reaction mixture, and the product was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum. The crude product thus obtained was purified by column chromatography using 10–20% ethyl acetate in petroleum ether.
(Benzylsulfonyl)benzene (2a)
Compound **2a** (87 mg, 94%) was synthesized using the general procedure for the synthesis of sulfones and isolated as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.66–7.56 (m, 3 H), 7.47–7.42 (m, 2 H), 7.35–7.29 (m, 1 H), 7.28–7.23 (m, 2 H), 7.13–7.04 (m, 2 H), 4.31 (s, 2 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 138.0, 133.8, 131.0, 129.0, 128.9, 128.8, 128.7, 128.3, 63.0. HRMS (EI): *m/z* calcd for $C_{13}H_{13}O_2S$ $[M + H]^+$: 233.0636; found: 233.0636.
1-Phenyl-2-(phenylsulfonyl)ethan-1-one (2k)
Compound **2k** (96 mg, 92%) was synthesized using the general procedure for the synthesis of sulfones and isolated as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.95–7.93 (m, 2 H), 7.91–7.89 (m, 2 H), 7.68–7.60 (m, 2 H), 7.60–7.54 (m, 2 H), 7.50–7.47 (m, 2 H), 4.74 (s, 2 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 188.1, 138.9, 135.9, 134.5, 134.4, 129.4, 129.4, 129.0, 128.7, 63.6. HRMS (EI): *m/z* calcd for $C_{14}H_{13}O_3S$ $[M + H]^+$: 261.0585; found: 261.0586.

(14) **General Procedure for the Synthesis of Sulfonamides 4a–f**
N-Bromosuccinimide (1.5 equiv, 0.6 mmol) was added portionwise to a vial containing a solution of an appropriate amine (1.5 equiv, 0.6 mmol) in DCM (1 mL). In another vial, vinyl sulfone (0.4 mmol) and tetraethylammonium cyanide (1.05 equiv, 0.42 mmol) were taken together with DCM (1 mL) and stirred for 5 min. The later solution was then added dropwise to the former mixture. The combined reaction mixture was allowed to stir at room temperature. After completion of the reaction (checked by crude ^{1}H NMR and TLC), water (10 mL) was added to the reaction mixture, and the product was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum. The crude product thus obtained was purified by column chromatography using 10–20% ethyl acetate in petroleum ether.
4-(Phenylsulfonyl)morpholine (4a)
Compound **4a** (86 mg, 95%) was synthesized using the general procedure for the synthesis of sulfonamides and isolated as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.78–7.74 (m, 2 H), 7.66–7.61 (m, 1 H), 7.59–7.54 (m, 2 H), 3.77–3.72 (m, 4 H), 3.03–2.98 (m, 4 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 135.3, 133.2, 129.3, 128.0, 66.2, 46.1. HRMS (EI): *m/z* calcd for $C_{10}H_{14}NO_3S$ $[M + H]^+$: 228.0694; found: 228.0693.

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