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Sulfonylation of Five-Membered Heterocycles via an S_NAr Reaction

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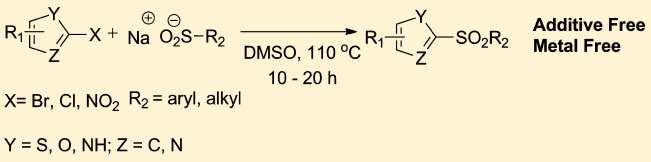
Supporting Information

ABSTRACT: An efficient, concise, and transition metal-free synthesis of functionalized sulfonylated five-membered heterocyclic compounds via an S_NAr reaction has been developed. Using commercially available sodium sulfinates as sulfonylation reagents, various five-membered heterocyclic sulfones were obtained in good yields.



INTRODUCTION

The heterocyclic sulfone moiety has been proven to be a useful building block in medicinal chemistry. It exits widely in medicinally active compounds, such as antagonists,[1−4] enzyme inhibitors,[5−9] and antimicrobial agents.[10−12] In addition to their medicinal importance, heterocyclic sulfones are useful intermediates in organic synthesis. For example, heterocyclic sulfones serve as substrates in the Julia olefination to construct double bonds[13−15] (Figure 1).

Several approaches for preparation of aryl sulfones have been reported. Traditional methods to prepare aryl sulfones include the oxidation of sulfides[16,17] and the sulfonylation of arenes in the presence of strong acids.[18,19] These traditional methods have been replaced by more efficient routes through Pd or Cu catalyzed cross-coupling reaction between sulfinate salts and aryl halides, aryl boronic acids, or special arenes.[20−32] Despite significant advances in metal-catalyzed C−S bond formation methods, only a few five-membered heteroaryl sulfones were successfully prepared through cross-coupling reactions because five-membered heteroaryl halides are notoriously poor coupling partners.[33] Furthermore, the sulfonylation of heterocycles containing multiple heteroatoms remains a challenge. Recently, metal-free protocols have attracted considerable attention. Efficient methods for the synthesis of pyridyl, phenyl, and vinyl sulfones have also been developed[34−38] (Figure 2). Herein, we describe a practical synthesis of five-membered heterocyclic sulfones via the nucleophilic substitution of halogenated or nitrated five-membered heterocycles with sulfinate salts under metal-free conditions.

RESULTS AND DISCUSSION

Compared to pyridine and benzene, five-membered heterocycles show intrinsically low reactivity toward nucleophilic reagents because of their π-excessive character. Accordingly, suitably located electron-withdrawing groups are necessary to activate these substrates. Furthermore, the substitution proceeds in general more readily at the α-position than at the β-position to the heteroatom.[39] In view of these rules, the coupling of 2-acetyl-5-bromothiophene with sodium *p*-toluenesulfinate was chosen as a model reaction for optimization studies. After stirring at 110 °C for 10 h under air atmosphere, no product was found in 1,4-dioxane, water, or toluene (Table 1, entries 1−3). In fact, the solubility of the substrate is the cause of ineffectiveness of these three solvents. Only trace amount of product was found in DMA (entry 4), and this transformation was still sluggish even after 0.3 equiv of Bu_4NBr was added (entry 5). It should be mentioned that the sulfonylation of pyridyl halides under the same condition proceeded smoothly,[34] which suggest that five-membered heteroaromatic halides are poor coupling partners. Fortunately, using DMSO as solvent, we obtained the product in 60% yield (entry 6). The addition of Bu_4NBr was not helpful for this reaction (entry 7). When the dosage of **2a** increased to 3 equiv, the reaction afforded product in 72% yield (entry 8). Further increasing **2a** to 5 equiv, we isolated the product in 93% yield (entry 9). Prolonging the reaction time to 20 h resulted in a slightly increased yield (entry 10 vs entry 9). Reducing the reaction time or lowering the reaction temperature resulted in an obviously decreased yield (entry 11 or 12 vs entry 8).

With the optimized reaction condition in hand, we next explored the scope of the reaction between various sulfinate salts and heterocylic halides. Aryl sulfinates and alkyl sulfinates afforded sulfones in excellent yields (Table 2, entries 1−7). It seemed that the reactivity was influenced by the nucleophilic ability of sulfinates. Sulfinates with electron-donating group on the benzene ring performed better than those with electron-withdrawing group (entries 1−3 vs entry 4). Interestingly, chlorothiophene provided the product with the same high yield as corresponding bromothiophene (entry 1 and entry 7). It should be noted that chlorothiophenes often give notably lower yields than bromothiophenes in a transition metal-catalyzed system. Subsequently, we applied this method to a range of five-membered heterocycles. This reaction has good compatibility with various functional groups. Acetyl, ester, and even aldehyde survived in this reaction (entries 1, 8, 9). When 2-bromothiophene **1e** was subjected to this reaction, only trace of product was observed, which may be ascribed to its lower

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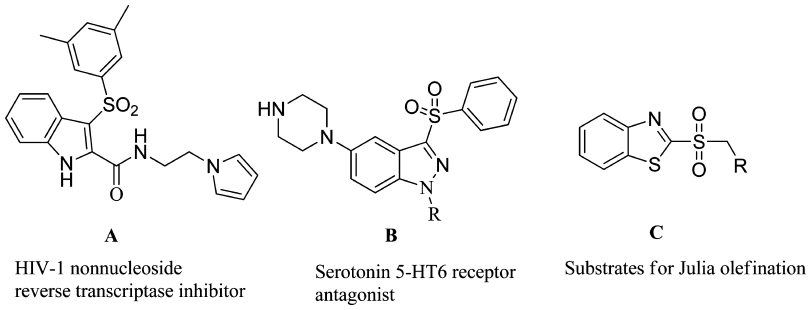


Figure 1. Examples of important five-membered heteroaryl sulfones.

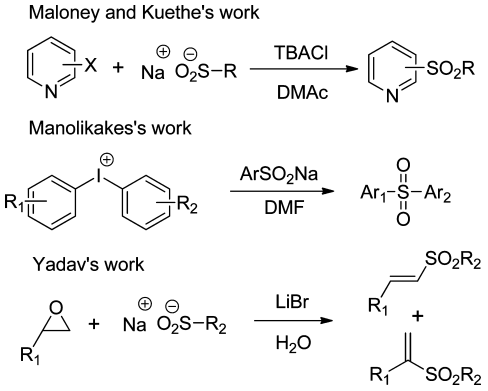


Figure 2. Recent works for the synthesis of sulfones in metal-free protocol.

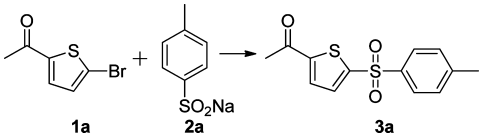
reactivity toward nucleophilic reagents (entry 10). Even 3-bromothiophene **1f** did not undergo this transformation, which may be due to the lower stability of its σ-adduct intermediate (entry 11). These experimental results are consistent with the S_NAr mechanism of five-membered heteroaromatic substrates. Furyl halides, for example, **1g**, also underwent such transformation, and afforded the product in moderate yield (entry 12). Interestingly, brominated indoles were good substrates for this reaction, which provides a convenient synthetic method for important indole derivatives (entries 13 and 14). Compound **3n** is an analogue of compound **A**, which was found to be a novel potent and highly selective HIV-1 nonnucleoside reverse transcriptase inhibitor.[5] **1h** has no electron-withdrawing group, but it performed efficiently; it may ascribe to the formation of a stable benzyl anion intermediate. We further found that an NO_2 group could serve as the leaving group. 5-Nitrothiophene-2-carboxaldehyde **1j** gave sulfone **3i** in moderate yield (entry 15). When 2-bromo-5-nitrothiophene was subjected to this reaction, disulfone **3o** and **3p** were isolated in good yield (entries 16, 17). 2-Nitrothiophene, like 2-bromothiophene, still remains problematic (entry 18).

Then, we put our focus on the transformation of heterocyclic halides containing multiple heteroatoms.[40] The reaction of 2-bromothiazole **4a** with different sulfinates performed smoothly (Table 3, entries 1−6). Other heterocycles with multiple heteroatoms were further tested. 2-Bromobenzothiazole and 2-clorobenzothiazole were efficiently transformed into sulfones in the presence of sulfinate salts (entries 7 and 8). When methyl sulfinate was used as the nucleophile, a mixture of **5i** and 2(3*H*)-benzothiazolone was obtained (entry 9). 2-Bromo-*N*-methylimidazole **4d** and 8-bromocaffeine **4f** were also good substrates for this reaction (entries 10, 12, and 13). However, 5-chloro-*N*-methylimidazole **4e** kept no change (entry 11). Only trace amount of product was isolated for oxazole **4g** (entry 14). It was transformed into 2(3*H*)-benzoxazolone.

In support of the application of this method, we conducted the reaction on a gram scale, and it also showed good performance (Table 3, entry 5). The structure of **5e** was characterized by X-ray diffraction (Figure 3), which confirms that the coupling occurs via C−S bond formation. To our knowledge, synthesis of five-membered heterocyclic sulfones containing multiple heteroatoms has hardly been studied, and several products are reported for the first time; they may be effective skeletons in medicines or organic synthesis.

Although the above experimental results are in accordance with a metal-free S_NAr mechanism, the effect of trace of metal impurities and a radical mechanism should still be considered. To study whether a metal or a radical intermediate is involved in this reaction, several control experiments were carried out. First, the reaction substrates were analyzed using inductively

Table 1. Optimization of the Reaction Conditions[a]



entry	solvent	equiv. of **2a**	yield (%)	entry	solvent	equiv. of **2a**	yield (%)
1	1,4-dioxane	1.5	N.R	7	DMSO	1.5	58[b]
2	H_2O	1.5	N.R	8	DMSO	3	72
3	Toluene	1.5	N.R	9	DMSO	5	93
4	DMA	1.5	Trace	10	DMSO	5	96[c]
5	DMA	1.5	Trace[b]	11	DMSO	5	70[d]
6	DMSO	1.5	60	12	DMSO	5	31[e]

[a]Conditions: **1a**, 0.3 mmol; **2a**, 1.5−5 equiv; solvent, 2 mL; 110 °C; under air; 10 h. [b]0.3 equiv of Bu_4NBr was added. [c]For 20 h. [d]5 h. [e]70 °C.

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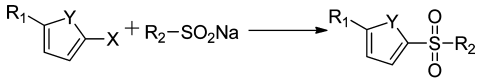
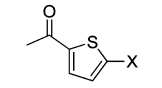
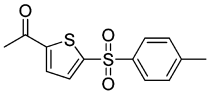
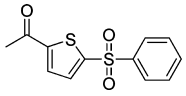
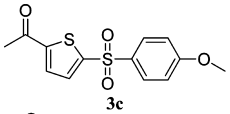
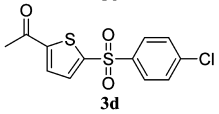
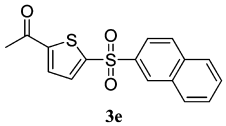
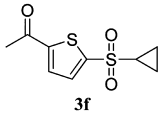
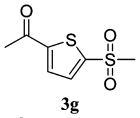
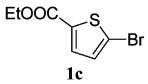
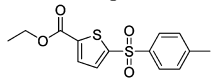
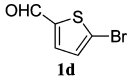
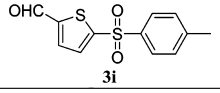
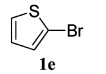
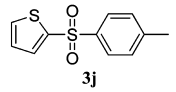
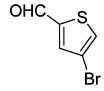
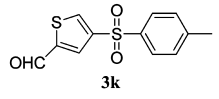
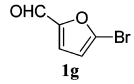
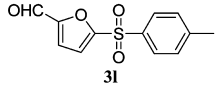
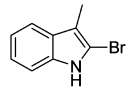
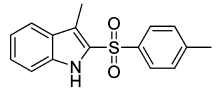
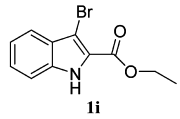
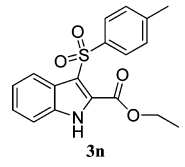
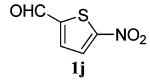
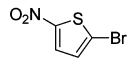
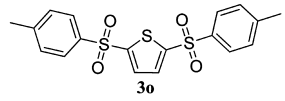
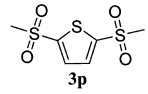
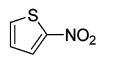
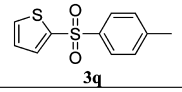
Table 2. Sulfonylation of Thiophenes, Furans, or Indoles[a]



1 **2** **3**

X= Br, Cl, NO_2
Y= S, O, NH

Entry	Substrates 1	Product	Yield (%)
1	 **1a**: X= Br, **1b**: X = Cl	 **3a**	93 (**1a**) 96 (**1b**)
2	**1a**	 **3b**	83
3	**1a**	 **3c**	96
4	**1a**	 **3d**	64[b]
5	**1a**	 **3e**	89
6	**1a**	 **3f**	82
7	**1a** **1b**	 **3g**	80 (**1a**) 84 (**1b**)
8	 **1c**	 **3h**	64[b]
9	 **1d**	 **3i**	98
10	 **1e**	 **3j**	Trace
11	 **1f**	 **3k**	N.R[c]
12	 **1g**	 **3l**	54
13	 **1h**	 **3m**	81
14	 **1i**	 **3n**	38[b]
15	 **1j**	**3i**	55[b]
16	 **1k**	 **3o**	62
17	**1k**	 **3p**	51
18	 **1l**	 **3q**	N.R

[a]Conditions: **1a**, 0.3 mmol; **2a**, 5 equiv; DMSO, 2 mL; 110 °C; under air; 10−20 h. [b]Compound **1** did not transform completely. [c]Other 3-substituted substrates gave the same results.

coupled plasma atomic emission spectroscopy (ICP-AES), 0.1 ppm of Pd, Cu, Fe, and other metal species were detected in sulfinate (Table S1). Then, the reaction was carried out in the presence of 200 ppm of $Cu(OAc)_2$ or $Pd(OAc)_2$. As shown in Scheme 1, none of them promoted the reaction rate. We further found that the yield had no change in Ar atmosphere, and the addition of 0.5 equiv of TEMPO showed no inhibition (Scheme 2). Based on these results, the effect of metal impurities and a radical mechanism should be excluded.

With the above results and proof in the literature,[39] an addition−elimination mechanism is proposed as shown in Scheme 3. First, the addition of nucleophile **2a** to the heteroaromatic electrophile **1d** generates σ-adduct intermediate **D**. The intermediate is stabilized by an electron-withdrawing group. Then, elimination of bromide gives the product **3i**. The formation of σ-adduct intermediate **E**, resulting from the addition of **2a** to 3-bromothiophene **1f**, is difficult, so it hardly undergoes such a transformation. However, if the intermediate forms, it could afford the sulfonylation product.

CONCLUSIONS

In conclusion, we have developed an efficient approach for the synthesis of five-membered heterocyclic sulfones, which have been proven to be important in series of medicinally active compounds. The reaction proceeds under mild conditions and avoids the use of metal catalysts and other additives, which make it significantly greener than current alternatives. Meanwhile, we have conducted several experiments to identify a transition metal-free S_NAr mechanism.

EXPERIMENTAL SECTION

General Description. ^1H NMR and ^{13}C NMR spectra were measured on a 400 MHz spectrometer (^1H 400 MHz, ^{13}C 100 MHz), using $CDCl_3$ as the solvent with tetramethylsilane (TMS) as the internal standard Chemical shifts (δ) are reported in ppm, and

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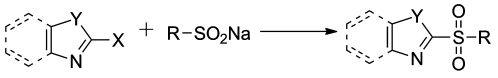
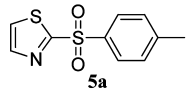
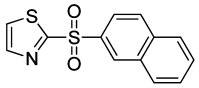
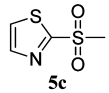
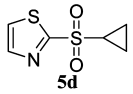
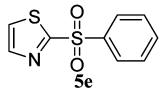
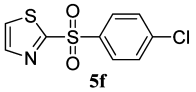
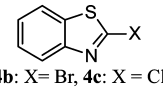
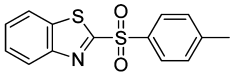
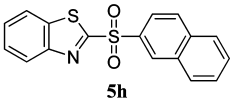
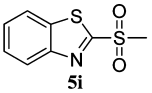
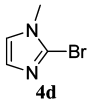
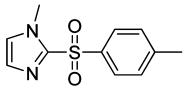
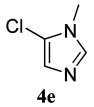
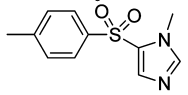
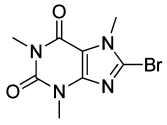
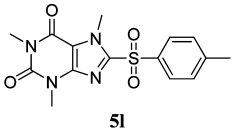
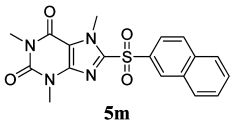
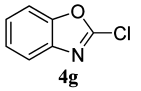
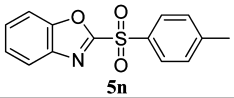
Table 3. Sulfonylation of Hetrocyclics Containing Multiple Heteroatoms[a]



4 2 5

X= Br,Cl
Y= N, S

Entry	Substrates 1	Product	Yield (%)
1	 **4a**	 **5a**	84
2	**4a**	 **5b**	73
3	**4a**	 **5c**	69
4	**4a**	 **5d**	89
5	**4a**	 **5e**	82 [b]
6	**4a**	 **5f**	40 [c]
7	 **4b**: X= Br, **4c**: X = Cl	 **5g**	70(**4b**) 82(**4c**)
8	**4b**	 **5h**	78
9	**4b**	 **5i**	55 [d]
10	 **4d**	 **5j**	68
11	 **4e**	 **5k**	N.R
12	 **4f**	 **5l**	72
13	**4f**	 **5m**	67
14	 **4g**	 **5n**	Trace

[a]Conditions: **1a**, 0.3 mmol; **2a**, 5 equiv; DMSO, 2 mL; 110 °C; under air; 10−20 h. [b]Gram scale. [c]Compound **4** did not transform completely. [d]Based on ^{1}H NMR analysis.

coupling constants (J) are in Hertz (Hz). s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Mass spectra were recorded with ESI mode. HRMS analysis was recorded on a Q-TOF mass spectrometer with ESI mode. Chemicals were purchased or prepared by literature.[41,42] Anhydrous DMSO was used for reaction.

General Procedure (3a for Example). To a 10 mL flask was added 2-acetyl-5-bromothiophene (0.3 mmol), sodium *p*-toluenesulfinate (1.5 mmol), and 2 mL anhydrous DMSO, and the reaction mixture was stirred at 110 °C for 10 h. After cooling down to room temperature, the reaction mixture was mixed with ethyl acetate (15 mL), then washed by brine (4 × 15 mL) to get rid of DMSO and excess sodium sulfinates. After drying with Na_2SO_4, the ethyl acetate extracts were concentrated in vacuum, and the residue was purified by flash column chromatography on silica gel to give the product.

3a.[31] White solid (78.0 mg, 93%). mp = 162.0−163.7 °C. Isolated by flash column chromatography (ethyl acetate/petroleum ether = 1:4). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.87 (d, J = 7.6 Hz, 2 H), 7.63 (d, J = 4.0 Hz, 1 H), 7.55 (d, J = 4.0 Hz, 1 H), 7.33 (d, J= 7.6 Hz, 2 H), 2.54 (s, 3 H), 2.41 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ 190.4, 150.2, 150.1, 145.2, 138.0, 132.6, 131.3, 130.2, 127.7, 26.9, 21.6 ppm. MS (ESI): *m*/*z* calcd. $[M+1]^+$ = 281.4; Found 281.3.

3b.[31] Light yellow solid (66.2 mg, 83%). mp = 131.6−131.9 °C. Isolated by flash column chromatography (ethyl acetate/petroleum ether = 1:4). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.99 (d, J = 8.0 Hz, 2 H), 7.66−7.52 (m, 5 H), 2.54 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ 190.3, 150.4, 149.7, 140.9, 133.9, 132.9, 131.3, 129.5, 127.6, 26.9 ppm. MS (ESI): *m*/*z* calcd. $[M+1]^+$ = 267.3; Found 267.3.

3c.[43] White solid (85.2 mg, 96%). mp = 146.4−146.8 °C. Isolated by flash column chromatography (ethyl acetate/petroleum ether = 1:4). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.93 (d, J = 8.8 Hz, 2 H), 7.62 (d, J = 4.0 Hz, 1 H), 7.55 (d, J = 4.0 Hz, 1 H), 7.00 (d, J = 9.2 Hz, 2 H), 3.87 (s, 3 H), 2.54 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ 190.3, 164.0, 150.8, 149.8, 132.3, 132.2, 131.2, 130.0, 114.8, 55.7, 26.8 ppm. HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ Calcd for $C_{13}H_{13}O_4S_2$ 297.0255; Found 297.0255.

3d.[43] Light yellow solid (57.6 mg, 64%). mp = 112.0−112.6 °C. Isolated by flash column chromatography (ethyl acetate/petroleum ether = 1:4). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.93 (d, J = 8.8 Hz, 2 H), 7.66 (d, J = 4.0 Hz, 1 H), 7.57 (d, J = 4.0 Hz, 1 H), 7.52 (d, J = 8.4 Hz, 2 H), 2.55 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ 190.2, 150.8, 149.2, 140.7, 139.5, 133.2, 131.3, 129.9, 129.1, 26.9 ppm. HRMS (ESI-TOF) *m*/*z*: $[M - H]^-$ Calcd for $C_{12}H_8ClO_3S_2$ 298.9603; Found 298.9597.

3e.[43] Light yellow solid (84.3 mg, 89%). mp = 121.9−122.0 °C. Isolated by flash column chromatography (ethyl acetate/petroleum ether = 1:4). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.60 (s, 1 H), 8.01−7.89 (m, 4H), 7.70−7.56 (m, 4 H), 2.53 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ 190.3, 150.4, 149.8, 137.7, 135.3, 132.9, 132.2, 131.3, 129.9, 129.6, 129.5, 129.4, 128.0, 127.9, 122.3, 26.8 ppm. HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ Calcd for $C_{16}H_{13}O_3S_2$ 317.0306; Found 317.0324.

3f.[31] White solid (56.5 mg, 82%). mp = 87.8−88.1 °C. Isolated by flash column chromatography (ethyl acetate/petroleum ether = 1:4). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.65 (q, J = 4.0 Hz, 2 H), 2.62−2.56 (m, 4 H), 1.44−1.42 (m, 2 H), 1.15−1.13 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ 190.4, 150.1, 148.2, 132.9, 131.1, 34.0, 27.0, 6.9 ppm. HRMS (ESI-TOF) *m*/*z*: $[M - H]^-$ Calcd for $C_9H_9O_3S_2$ 228.9993; Found 228.9994.

3g.[44] White solid (48.9 mg, 80%). mp = 136.0−136.3 °C. Isolated by flash column chromatography (ethyl acetate/petroleum ether = 1:4). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.70 (d, J = 4.0 Hz, 1 H), 7.65 (d, J = 4.0 Hz, 1 H), 3.20 (s, 3 H), 2.61 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ 190.2, 150.5, 148.1, 133.3, 131.2, 45.8, 26.9 ppm. Ms (ESI): *m*/*z* Calcd. $[M+1]^+$ = 205.3; Found 205.3.

3h.[43] White solid (59.5 mg, 64%). mp = 92.7−95.0 °C. Isolated by flash column chromatography (ethyl acetate/petroleum ether = 1:4). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.87 (d, J = 8.4 Hz, 2 H), 7.67 (d, J = 4.0 Hz, 1 H), 7.60 (d, J = 4.0 Hz, 1 H), 7.33 (d, J = 8.0 Hz, 2 H), 4.35 (q, J = 7.2 Hz, 2 H), 2.42 (s, 3 H), 1.35 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ 160.9, 149.0, 145.0, 140.6, 138.2, 132.6,

dx.doi.org/10.1021/jo401828b | J. Org. Chem. 2013, 78, 11874−11880

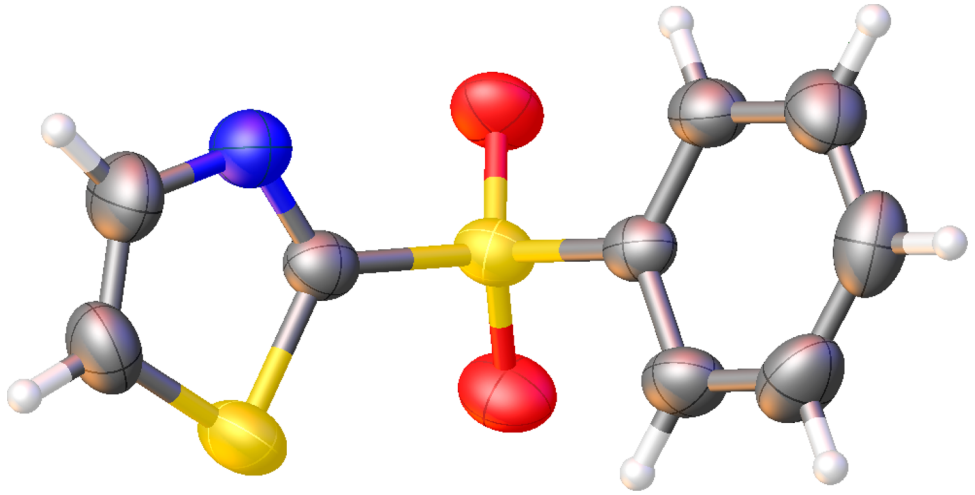
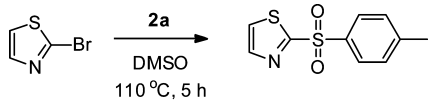


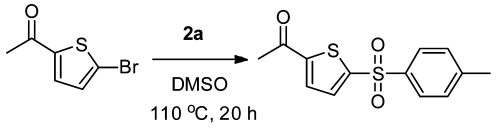
Figure 3. X-ray crystal structure of **5e**. CCDC 965064 contains the supplementary Crystallographic data for this paper. Data can be obtained free of charge from The Cambridge crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Scheme 1. Sulfonylation of 2-Bromothiazole without or with the Addition of Metals



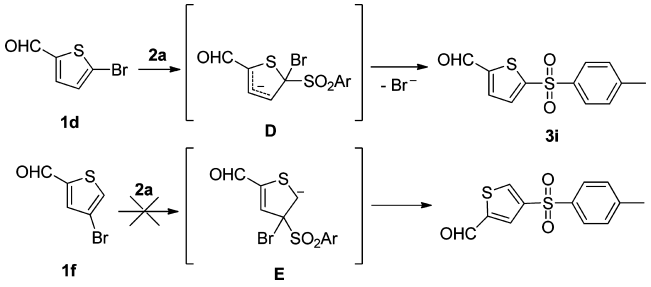
Additive	Yield
—	47%
200 ppm $Cu(OAc)_2$	45%
200 ppm $Pd(OAc)_2$	52%

Scheme 2. Experiments for Mechanism



Air atmosphere	96%
Ar atmosphere	98%
TEMPO (0.5 equiv)	96%

Scheme 3. Proposed Mechanism



132.3, 130.1, 127.6, 62.0, 21.6, 14.2 ppm. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{14}H_{15}O_4S_2$ 311.0412; Found 311.0412.

3i.[43] White solid (78.2 mg, 98%). mp = 126.9−127.6 °C. Isolated by flash column chromatography (ethyl acetate/petroleum ether = 1:4). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.93 (s, 1 H), 7.89 (d, J = 8.4 Hz, 2 H), 7.71 (d, J = 4.0 Hz, 1 H), 7.67 (d, J = 3.6 Hz, 1 H), 7.85 (d, J = 8.0 Hz, 2 H), 2.43 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ 182.8, 151.8, 148.8, 145.4, 137.7, 134.6, 132.5, 130.2, 127.8, 21.6 ppm. HRMS (ESI-TOF) m/z: $[M - H]^-$ Calcd for $C_{12}H_9O_3S_2$ 264.9993; Found 264.9987.

3l.[30] Light yellow solid (40.5 mg, 54%). mp = 114.8−116.7 °C. Isolated by flash column chromatography (ethyl acetate/petroleum ether = 1:4). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.71 (s, 1 H), 7.93 (d, J = 8.4 Hz, 2 H), 7.38 (d, J = 8.0 Hz, 2 H), 7.26 (d, J = 3.2 Hz, 1 H), 7.22 (d, J = 3.6 Hz, 1 H), 2.45 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ 178.4, 154.5, 154.4, 145.9, 135.6, 130.3, 128.4, 118.4, 117.3, 21.7 ppm. MS (ESI): m/z Calcd. $[M+1]^+$ = 251.3; Found 251.2.

3m.[43] White solid (69.6 mg, 81%). mp = 116.1−117.8 °C. Isolated by flash column chromatography (ethyl acetate/petroleum ether = 1:4). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.88 (s, 1 H), 7.86 (d, J = 8.4 Hz, 2 H), 7.60 (d, J = 8.4 Hz, 1 H), 7.40−7.28 (m, 4 H), 7.18−7.14 (m, 1 H), 2.53 (s, 3 H), 2.39 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ 144.3, 139.0, 135.8, 129.9, 129.6, 129.4, 128.3, 127.0, 126.1, 120.7, 118.4, 112.1, 21.6, 8.9 ppm. HRMS (ESI-TOF) m/z: $[M - H]^-$ Calcd for $C_{16}H_{14}NO_2S$ 284.0745; Found 284.0737.

3n.[43] Light yellow solid (39.1 mg, 38%). mp = 153.2−153.5 °C. Isolated by flash column chromatography (ethyl acetate/petroleum ether = 1:2). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.49 (s, 1 H), 8.56 (d, J = 8.0 Hz, 1 H), 7.97 (d, J = 8.0 Hz, 2 H), 7.46−7.36 (m, 3 H), 7.25 (d, J = 7.2 Hz, 2 H), 4.40 (q, J = 7.2 Hz, 2 H), 2.38 (s, 3 H), 1.37 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.0, 143.6, 140.3, 134.1, 129.2, 127.7, 127.3, 126.4, 126.3, 123.6, 122.7, 119.5, 112.1, 62.4, 21.6, 14.1 ppm. HRMS (ESI-TOF) m/z: $[M - H]^-$ Calcd for $C_{18}H_{16}NO_4S$ 342.0800; Found 342.0806.

3o.[43] White solid (72.9 mg, 62%). mp = 151.2−152.2 °C. Isolated by flash column chromatography (ethyl acetate/petroleum ether = 1:1). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.84 (d, J = 8.4 Hz, 4 H), 7.52 (s, 2 H), 7.34 (d, J = 8.4 Hz, 4 H), 2.43 (s, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ 150.7, 145.5, 137.6, 132.0, 130.3, 127.8, 21.7 ppm. HRMS (ESI-TOF) m/z: $[M - H]^-$ Calcd for $C_{18}H_{15}O_4S_3$ 391.0132; Found 391.0138.

3p.[45] White solid (36.7 mg, 51%). mp = 171.7−172.5 °C. Isolated by flash column chromatography (ethyl acetate/petroleum ether = 1:2). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.72 (s, 2 H), 3.24 (s, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ 149.2, 132.9, 45.9 ppm. HRMS (ESI-TOF) m/z: $[M - H]^-$ Calcd for $C_6H_7O_4S_3$ 238.9506; Found 238.9510.

5a.[43] White solid (60.2 mg, 84%). mp = 129.3−129.8 °C. Isolated by flash column chromatography (ethyl acetate/petroleum ether = 1:2). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.98 (d, J = 8.4 Hz, 2 H), 7.94 (d, J = 2.8 Hz, 1 H), 7.64 (d, J = 2.8 Hz, 1 H), 7.36 (d, J = 7.6 Hz, 2 H), 2.43 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.6, 145.6, 145.2, 135.8, 130.1, 128.7, 125.6, 21.7 ppm. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{10}H_{10}NO_2S_2$ 240.0153; Found 240.0142.

dx.doi.org/10.1021/jo401828b | J. Org. Chem. 2013, 78, 11874−11880

5b.[43] White solid (60.2 mg, 73%). mp = 129.4−130.2 °C. Isolated by flash column chromatography (ethyl acetate/petroleum ether = 1:2). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.72 (s, 1 H), 8.06−7.90 (m, 5 H), 7.68−7.63 (m, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ 145.3, 135.7, 135.6, 132.2, 130.7, 129.8, 129.7, 129.7, 128.0, 127.8, 125.8, 123.0 ppm. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{13}H_{10}NO_2S_2$ 276.0153; Found 276.0138.

5c.[46] Colorless oil (33.7 mg, 69%). Isolated by flash column chromatography (ethyl acetate/petroleum ether = 1:2). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.04 (d, J = 3.2 Hz, 1 H), 7.74 (d, J = 3.2 Hz, 1 H), 3.33 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ 166.2, 144.9, 125.8, 42.7 ppm. Ms (ESI): m/z Calcd. $[M+1]^+$ = 164.2; Found 164.2.

5d.[43] White solid (50.5 mg, 89%). mp = 70.8−72.5 °C. Isolated by flash column chromatography (ethyl acetate/petroleum ether = 1:2). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.06 (d, J = 3.2 Hz, 1 H), 7.72 (d, J = 3.2 Hz, 1 H), 2.82−2.75 (m, 1 H), 1.51−1.49 (m, 2 H), 1.18−1.16 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ 166.1, 145.1, 125.6, 31.8, 6.5 ppm. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_6H_8NO_2S_2$ 189.9996; Found 190.0006..

5e.[47] White solid (1.1g, 82%). mp = 122.5−124.3 °C. Isolated by flash column chromatography (ethyl acetate/petroleum ether = 1:2). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.12−8.10 (m, 2 H), 7.96 (d, J = 3.2 Hz, 1 H), 7.67−7.55 (m, 4 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.1, 145.3, 138.9, 134.3, 129.5, 128.7, 125.9 ppm. MS (ESI): m/z Calcd. $[M+1]^+$ = 226.3; Found 226.1.

5f.[48] White solid (31.1 mg, 40%). mp = 136.6−138.1 °C. Isolated by flash column chromatography (ethyl acetate/petroleum ether = 1:2). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.04 (d, J = 8.8 Hz, 2 H), 7.97 (d, J = 3.2 Hz, 1 H), 7.69 (d, J = 2.8 Hz, 1 H), 7.54 (d, J = 8.8 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ 166.7, 145.4, 141.3, 137.3, 130.1, 129.8, 126.0 ppm. MS (ESI): m/z Calcd. $[M+1]^+$ = 260.7; Found 260.7.

5g.[49] White solid (60.6 mg, 70%). mp = 129.9−131.8 °C. Isolated by flash column chromatography (ethyl acetate/petroleum ether = 1:2). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.15 (d, J = 7.6 Hz, 1 H), 8.04 (d, J = 7.6 Hz, 2 H), 7.95 (d, J = 8.0 Hz, 1 H), 7.54 (m, 2 H), 7.37 (d, J = 7.2 Hz, 2 H), 2.43 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.7, 152.9, 145.9, 137.0, 135.5, 130.2, 129.0, 127.7, 127.4, 125.5, 122.2, 21.7 ppm. MS (ESI): m/z Calcd. $[M+1]^+$ = 290.4; Found 290.3.

5h.[50] Light yellow solid (76.0 mg, 78%). mp = 154.3−156.0 °C. Isolated by flash column chromatography (ethyl acetate/petroleum ether = 1:2). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.77 (s, 1 H), 8.15−7.89 (m, 6 H), 7.67−7.51 (m, 4H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.4, 152.9, 137.0, 135.7, 135.3, 132.2, 131.1, 129.9, 129.8, 129.7, 128.0, 127.8, 127.5, 125.5, 123.1, 122.2 ppm. MS (ESI): m/z Calcd. $[M+1]^+$ = 326.4; Found 326.3.

5i.[51] White solid (it is an inseparable mixture containing **5i** and 2(3*H*)-benzothiazolone, identified by GC-MS, and a ratio of 2:1 via ^{1}H NMR. Totally 47.5 mg, the yield for only **5i** after calculation: 55%). Isolated by flash column chromatography (ethyl acetate/petroleum ether = 1:4). For only **5i**: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.21 (d, J = 7.6 Hz, 1 H), 8.01 (d, J = 8.0 Hz, 1 H), 7.62 (m, 2 H), 3.41 (s, 3 H) ppm. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_8H_8NO_2S_2$ 213.9996; Found 213.9991.

5j.[43] White solid (48.1 mg, 68%). mp = 155.6−156.5 °C. Isolated by flash column chromatography (ethyl acetate/petroleum ether = 1:1). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.92 (d, J = 8.4 Hz, 2 H), 7.35 (d, J = 8.0 Hz, 2 H), 7.09 (d, J = 1.2 Hz, 1 H), 6.94 (d, J = 1.2 Hz, 1 H), 3.97 (s, 3 H), 2.43 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ 145.2, 143.4, 136.7, 129.9, 129.4, 128.2, 125.5, 35.2, 21.7 ppm. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{11}H_{13}N_2O_2S$ 237.0698; Found 237.0680.

5l.[43] White solid (75.1 mg, 72%). mp = 208.9−209.7 °C. Isolated by flash column chromatography (ethyl acetate/petroleum ether = 1:1). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.93 (d, J = 8.4 Hz, 2 H), 7.39 (d, J = 8.4 Hz, 2 H), 4.30 (s, 3 H), 3.52 (s, 3 H), 3.37 (s, 3 H), 2.46 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ 155.5, 151.2, 146.7, 146.5, 146.3, 135.6, 130.2, 128.6, 109.8, 34.2, 30.0, 28.2, 21.8 ppm. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{15}H_{17}N_4O_4S$ 349.0971; Found 349.0961.

5m.[43] White solid (77.1 mg, 67%). mp = 221.0−223.3 °C. Isolated by flash column chromatography (ethyl acetate/petroleum ether = 1:1). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.66 (s, 1 H), 8.05−7.93 (m, 4 H), 7.74−7.65 (m, 2 H), 4.36 (s, 3 H), 3.51 (s, 3 H), 3.37 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ 155.4, 151.2, 146.6, 146.4, 135.7, 135.4, 132.0, 130.6, 130.1, 129.9, 129.7, 128.1, 122.7, 39.3, 30.0, 28.2 ppm. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{18}H_{17}N_4O_4S$ 385.0971; Found 385.0962.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^{1}H and ^{13}C NMR, MS (EI) spectra for new compounds, and ICP-AES analysis of sulfinate salt. This material is available free of charge via the Internet at http://pubs.acs.org/.

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Notes

The authors declare no competing financial interest.

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