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Metal-free synthesis of sulfonylated amides through radical aryl migration-desulfonylation

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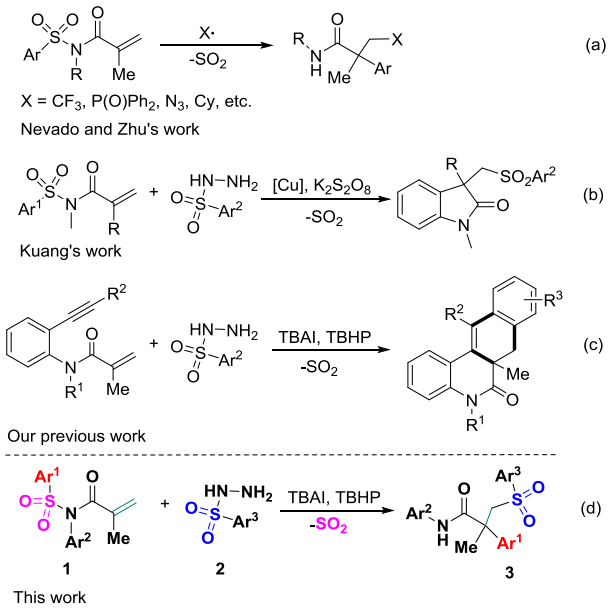
ABSTRACT

A metal-free arylsulfonyl radical-triggered desulfonylation of *N*-aryl-*N*-arylsulfonyl-acrylamides under mild conditions for the facile synthesis of a series of sulfonylated amides has been described. The radical transformation simultaneously installs C-S and C-C bonds with concomitant cleavage of N-S and C-S bonds through continuous 5-*exo*-*trig* cyclization, desulfonylation and aryl migration sequence.

Desulfonylation reactions have taken an important position in the total synthesis of many natural products and in medicinal chemistry, because these reactions could realize direct functionalization of the desired bioactive molecules by functional group transformations (FGTs).[1] Traditional desulfonylations demand a two-step process including i) introduction of sulfone functionality into reagents to modify molecular polarity and activate reaction site; ii) after the completion of the required operation, the sulfone moiety has to be removed by using reductive, alkylative and oxidative desulfonylation, etc.[2] However, these desulfonylations suffer from the shortcomings such as the use of strong bases, transition-metal catalysts and toxic metal salts peroxides. Recently, Nevado, Zhu and co-workers independently reported radical-triggered aryl migration and desulfonylation reactions of *N*-arylsulfonyl-acrylamides, leading to C-C and/or C-N bond formation (Schemes 1a).[3,4] Later, Kuang et al. developed a similar radical protocol toward sulfonated oxindoles from copper-catalyzed reaction of *N*-methyl-*N*-arylsulfonyl-acrylamides with sulfonyl hydrazides using $K_2S_2O_8$ as an oxidant (Scheme 1b).[5] Very recently, we presented a new tetrabutylammonium iodide (TBAI)/*t*-butyl hydroperoxide (TBHP)-mediated 1,7-enyne-bicyclization, providing densely functionalized benzo[*j*]phenanthridines. In this reaction, metal-free radical desulfonylation was successfully realized (Scheme 1c).[6] Based on aforementioned studies and our interest in radical chemistry[7] and considering the difference of *N*-nucleophilicity between alkylamines and arylamines, we reasoned that with replacement of methyl group with aryl counterpart at the *N*-substituent (Scheme 1b), a metal-free desulfonylation of *N*-aryl-*N*-arylsulfonyl-acrylamides with aryl



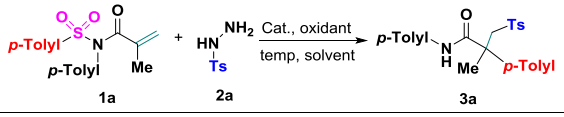
Scheme 1. Desulfonylation-involved radical reactions

sulfonhydrazides could be achieved under TBAI/TBHP-mediated conditions, delivering a wide range of sulfonylated amides with structural diversity, (Scheme 1d). The success of this reaction is based on the factors that in the presence of TBAI/TBHP, aryl sulfonhydrazides could be converted into the arylsulfonyl radicals,[8] which is quickly intercepted by radical acceptors such as activated olefins.[9] Herein, we would like to report this metal-free radical method for the synthesis of sulfonylated amides.

We began our study with *N*-aryl-*N*-arylsulfonyl-acrylamides **1a** and *p*-toluenesulfonyl hydrazide (**2a**) by using TBAI/TBHP

system in CH_3CN at room temperature under air conditions for 12 h (Table1, entry1). The reaction proceeded to give the desired sulfonylated amides **3a**, albeit with a relatively low 23% yield. An increase of the reaction temperature resulted in the remarkable improvement of the reaction efficiency (entries 2-3). A higher 78% chemical yield was obtained when the reaction temperature was increased to 70 °C. However, the higher reaction temperature (90 °C) is not beneficial to the chemical yield (entry 4). Next, different solvents, such as DMSO, DMF, EtOH, CH_2Cl_2, 1,2-dichloroethane (DCE), toluene and water, were conducted to examine the solvent effects (entries 5-11). It was found that the reaction in DMSO did not work at all and the starting materials remained completely unconsumed (entry 5), whereas the use of other solvents, including DMF, EtOH, CH_2Cl_2, 1,2-dichloroethane (DCE), toluene and water, all led to the formation of product **3a**, but gave inferior results compared with CH_3CN (entries 6-12). Afterword, the loading of TBAI was evaluated. Increasing or decreasing the loading of TBAI did not improve the reaction efficiency (entries 13-14). Then, we adjusted other reaction parameters including catalysts and oxidants. Replacing TBAI with iodine or potassium iodide, the reaction resulted in slightly lower yield of **3a** (entries 15-16), whereas the reaction completed suppressed in copper catalysis (entries 17-18). Without TBAI, no product **3a** was observed (entry 19). Screening followed by various oxidants showed that the oxidants like benzoyl peroxide (BPO), *tert*-butyl peroxybenzoate (TBPB) and H_2O_2 as well as *m*-chloroperoxybenzoic acid (m-CPBA) all gave unsatisfactory outcomes compared with TBHP in terms of

Table 1. Optimization of conditions for the product **3a**[a]

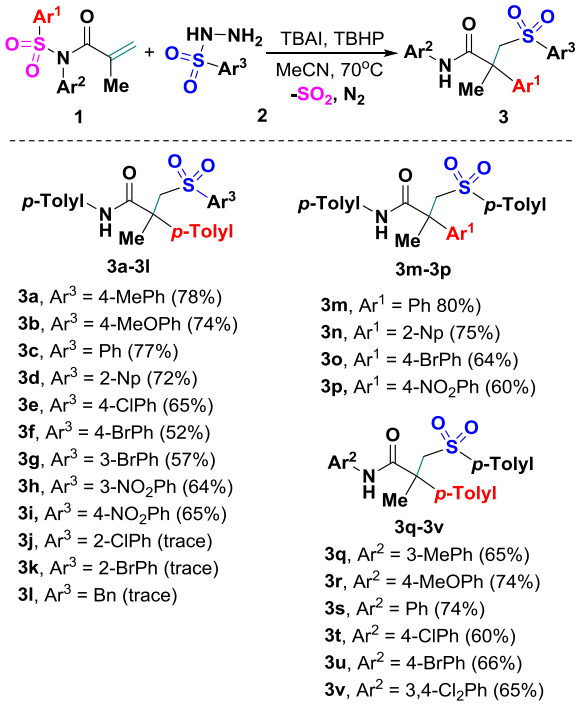


Entry	Oxidant	Cat. (mol %)	Solvent	T / °C	Yield / %[b]
1	TBHP	TBAI (20)	CH_3CN	rt	23
2	TBHP	TBAI (20)	CH_3CN	40	36
3	TBHP	TBAI (20)	CH_3CN	70	78
4	TBHP	TBAI (20)	CH_3CN	90	50
5	TBHP	TBAI (20)	DMSO	70	ND[c]
6	TBHP	TBAI (20)	DMF	70	37
7	TBHP	TBAI (20)	EtOH	70	46
8	TBHP	TBAI (20)	CH_2Cl_2	70	52
9	TBHP	TBAI (20)	DCE	70	64
10	TBHP	TBAI (20)	toluene	70	37
11	TBHP	TBAI (20)	1,4-dioxane	70	57
12	TBHP	TBAI (20)	H_2O	70	62
13	TBHP	TBAI (10)	CH_3CN	70	71
14	TBHP	TBAI (50)	CH_3CN	70	76
15	TBHP	I_2 (20)	CH_3CN	70	70
16	TBHP	KI (20)	CH_3CN	70	66
17	TBHP	CuI (20)	CH_3CN	70	ND[c]
18	TBHP	CuBr (20)	CH_3CN	70	ND[c]
19	TBHP	-	CH_3CN	70	ND[c]
20	BPO	TBAI (20)	CH_3CN	70	60
21	TBPB	TBAI (20)	CH_3CN	70	42
22	H_2O_2	TBAI (20)	CH_3CN	70	65
23	*m*-CPBA	TBAI (20)	CH_3CN	70	27
24	DTBP	TBAI (20)	CH_3CN	70	trace
25	O_2	TBAI (20)	CH_3CN	70	ND[c]

[a] Reaction conditions: **1a** (0.25 mmol), **2a** (0.50 mmol), catalyst, oxidant (2 equiv.), solvent (2.5 mL), 70 °C, 12 h, under air conditions. [b]Isolated yield based on **1a**. [c]Not detected (ND). TBHP (70% solution in water).

reaction yields (entries 19-23). The reaction did not proceed in the presence of di-*tert*-butyl peroxide (DTBP) or O_2 (entries 24-25).

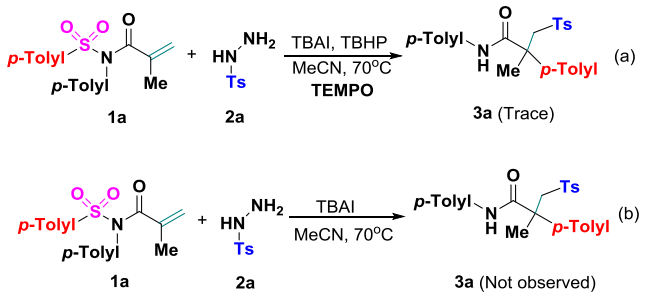
With the optimized reaction conditions in hand, the scope of this metal-free radical desulfonylation was examined by treating *N*-aryl-*N*-arylsulfonyl-acrylamides with aryl sulfonhydrazides. As shown in Scheme 2, we firstly used *N*-(p-tolyl)-*N*-tosylmethacrylamide (**1a**) to react with a wide range of sulfonyl hydrazides **2** under the oxidative conditions. It was found that the sulfonyl hydrazides with substituents at *meta* or *para*-position on the phenyl group were all successfully engaged in the transformation and gave the corresponding sulfonylated amides **3a-3i** in 52%-78% yields. The electronic nature of substituents exerted a slight influence on the reaction efficiency and the obtainable yields. For instance, electron-donating groups on the phenyl ring, such as CH_3, and OCH_3, showed higher reactivity and gave higher yields than those with electron-withdrawing substituents like Cl, Br or NO_2 (**3a** and **3b** vs. **3e-3i**). Similarly, phenyl and 2-naphthyl counterparts were also proved to be effective substrates, resulting in the corresponding products **3c** and **3d** in 77% and 72% yields, respectively. Unluckily, sulfonyl hydrazides with *ortho* substituents on the phenyl ring gave a complex mixture and a trace amount of product **3j** (or **3k**) was observed (Scheme 2), which may be caused by their large steric effect. The similar result was observed when benzyl counterpart was used (Scheme 2, **3l**), which may be ascribed to the relative instability of the benzyl sulfonyl radical generated in situ. In view of these results, we then varied substituents of methacrylamides **1** to further expand their synthetic utility of this methodology. As we had expected, methacrylamides **1** bearing electron-donating, -neutral, or -withdrawing groups on the arylsulfonyl (Ar^1) moiety were successfully engaged in the current TBAI/TBHP-mediated reactions with **2a**, affording the desired sulfonylated amides **3m-3p** with yields ranging from 60% to 80% yields. With the tosyl group (Ar^1) on the amine anchor, the variant of substituents on the aryl (Ar^2) moiety was compatible with the catalytic oxidation system. Functional groups like methyl, methoxy, chloro and bromo could be accommodated, thus confirming the reaction efficiency, as **3q-3v** was generated in 60%-74% yields.



Scheme 2. The scope of metal-free cascade reaction. Reaction conditions: **1** (0.25 mmol), **2** (0.50 mmol), catalyst (20 mol%), oxidant (2 equiv.), CH_3CN (2.5 mL), 70 °C, 12 h, under air conditions. Isolated yield based on **1**.

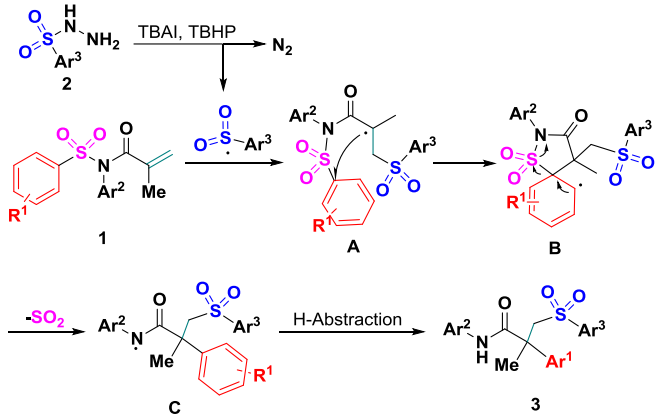
To understand the mechanism, the following control reactions were conducted. Firstly, methacrylamides **1a** was subjected to reaction with **2a** in the presence of 2,2,6,6-tetramethylpiperidine

oxide (TEMPO)[10] radical inhibitor under the standard conditions, and a trace amount of **3a** was detected (Scheme 3a). Without TBHP, no conversion to the desired product **3a** was observed and starting materials **1a** and **2a** were recovered (Scheme **3b**) these experimental results supported the present reaction involving a radical pathway under TBAI/TBHP system.



Scheme 3. Control Experiments

Based on the above experiments and literature reports,[11] a plausible mechanism is proposed in Scheme 4. Acrylamides **1** first capture sulfonyl radicals, generated *in situ* from the oxidative decomposition of sulfonyl hydrazides mediated by TBAI and TBHP,[12] to give **A** *via* radical addition. Intermediates **A** undergo 5-*exo-trig* cyclization and desulfonylation to access amide radicals **C**, which are converted into sulfonylated amides **3** through hydrogen abstraction with TBHP.



Scheme 4. The proposed mechanism

In summary, we have reported a metal-free sulfonylation reaction of *N*-aryl-*N*-arylsulfonyl-acrylamides under catalytic oxidation conditions. The addition of sulfonyl radicals to the double bond of acrylamides can trigger a domino 5-*exo-trig* cyclization, desulfonylation and aryl migration sequence, giving access to a series of sulfonylated amides in C–S/C–C bond-forming process with concomitant cleavage of N-S and C-S bonds. We hope this protocol will find applications in the synthesis of functionalized sulfones of potential usefulness.

Acknowledgments

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Supplementary Material

Supplementary data (experimental details and spectroscopic characterization of all compounds along with ^{1}H NMR, IR and mass spectra) associated with this article can be found, in the online version, at doi:

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(13) General procedure for the synthesis of compounds **3a**: To a stirred mixture of *N*-aryl-*N*-arylsulfonyl-acrylamides **1a** (82.2mg, 0.25 mmol) and *p*-toluenesulfonyl hydrazide **2a** (93 mg, 0.5 mmol) in CH_3CN (2.5 ml) and then the TBAI (18.5 mg, 0.05 mmol) TBHP (70% solution in water) (64.2 mg, 0.5mmol) were successively added. Then the reaction mixture was immersed in a 70 °C oil bath and stirred overnight. The mixture was cooled to room temperature, and then quenched by water and extracted with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated. After

purification by flash column chromatography on silica gel (Hexane/EtOAc = 50/1-20/1 as eluent), compound **3a** was obtained as a white solid. 2-methyl-*N*,2-di-*p*-tolyl-3-tosylpropanamide (3a): White solid; mp 176-177 °C; IR (KBr, v, cm^{-1}): 3368, 2920, 2360, 1910, 1676, 1597, 1521, 1453, 1400, 1312, 1298, 1239, 1208, 1146, 1128, 1084, 1058, 921, 867, 818, 750, 710, 627, 553, 512. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, J = 8.0 Hz, 2H), 7.20 (m, 6H), 7.13 – 7.02 (m, 4H), 6.86 (s, 1H), 4.15 (d, J = 14.8 Hz, 1H), 3.85 (d, J = 14.8 Hz, 1H), 2.41 (s, 3H), 2.34 (s, 3H), 2.30 (s, 3H), 2.12 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8, 143.9, 138.2, 137.9, 136.3, 134.8, 134.3, 129.6, 129.5, 129.4, 127.6, 127.0, 120.2, 64.1, 50.0, 22.7, 21.6, 21.0, 20.9. HRMS (ESI) m/z: calcd for $C_{25}H_{27}NO_3S$: 406.1471[M-H]$^-$; found: 406.1479.

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Metal-free synthesis of sulfonylated amides through radical aryl migration-desulfonylation

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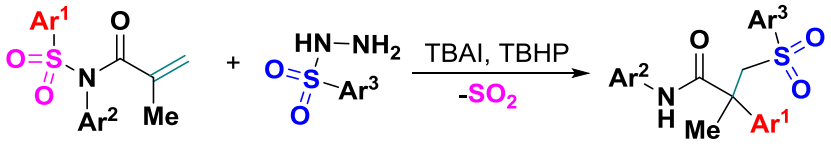

1. A metal-free desulfonylation of *N*-aryl-*N*-arylsulfonyl-acrylamides is developed
2. The mechanism involves 5-*exo*-*trig* cyclization, desulfonylation and aryl migration.
3. This method installs C-S and C-C bonds with cleavage of N-S and C-S bonds.