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# Rongalite-promoted synthesis of β-keto sulfones *via* radical cascade reaction

**Min-xiao Xu*[a] and Kai-ming Zhang[a,b]**

[a] *Jiangsu Police Institute, 210031 Nanjing, P. R. China. E-mail: xuminxiao_88@126.com*
[b] *Nanjing Institute of Technology, 211167 Nanjing, P. R. China*

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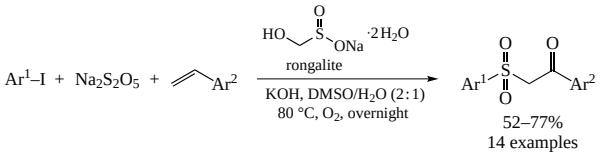
**Direct arylsulfonylation of arylethenes with aryl iodides and sodium metabisulfite to access β-keto sulfones is described. In this reaction, rongalite (sodium hydroxymethanesulfinate) and sodium metabisulfite serve as the radical promoter and the sulfur dioxide surrogate, respectively.**



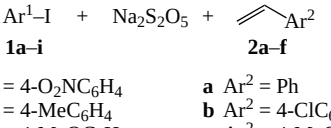

*Keywords*: rongalite, sodium metabisulfite, aryl halides, alkenes, radical cascade, β-keto sulfones.

β-Keto sulfones, the versatile intermediates in organic and medicinal chemistry,[1] possess antibacterial, antifungal and anti-hepatitis properties.[2–4] Traditionally, the synthesis of β-keto sulfones involved (i) the sulfonylation of α-halo ketones,[5] α-tosyloxy ketones[6] or silyl enol ethers;[7] (ii) oxidation of 2-oxoalkyl sulfides;[8] (iii) reactions of diazo sulfones with aldehydes[9] and (iv) acylation of sulfones.[10] These methods, however, suffer from the poorly accessible starting materials, narrow substrate scope and harsh reaction conditions.

Recently, radical-promoted sulfonylation of alkenes or alkynes with sulfonyl halides, sulfinic acids, sulfonyl hydrazines, or sodium sulfonates has provided an efficient access to β-keto sulfones.[11] However, the reported methods usually require toxic, hazard, or corrosive reagents. Alternatively, the insertion of sulfur dioxide to generation of sulfonyl compounds has been recognized as an environmentally friendly pathway.[12,13] For example, Wu and coworkers reported a three-component coupling of aryldiazonium salts with 1,4-diazabicyclo[2.2.2]-octane bis(sulfur dioxide) (DABSO) and silyl enolates.[14] Ni and coworkers developed a photocatalyzed hydrosulfonylation of alkynes with the insertion of sulfur dioxide using aryldiazonium salts and DABSO.[15]

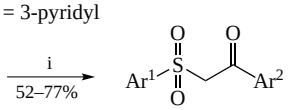
Inspired by these pioneering contributions, we envisioned that the radical cascade reaction using aryl halides, sodium metabisulfite and alkenes to access β-keto sulfones could be promising. Just recently, Wang and co-workers demonstrated that rongalite could generate aryl radical from cheap and available aryl halides.[16] Rongalite ($HOCH_2SO_2^-Na^+ \cdot 2H_2O$) is a cheap industrial material and it is also identified as the precursor of the highly reductive sulfoxylate anion ($SO_2^{2-}$). Moreover, the use of sodium metabisulfite as the sulfur dioxide surrogate is also cost-effective and environmentally friendly.

Reaction conditions were optimized using 4-iodonitrobenzene **1a**, $Na_2S_2O_5$ and styrene **2a** as the model substrates (Scheme 1, Table 1). Base nature showed significant influence on the reaction outcome. No reaction was observed when $Et_3N$ was used and only 14% yield of **3a** was obtained in the presence




**a** $Ar^1$ = 4-$O_2NC_6H_4$
**b** $Ar^1$ = 4-$MeC_6H_4$
**c** $Ar^1$ = 4-$MeOC_6H_4$
**d** $Ar^1$ = 4-$BrC_6H_4$
**e** $Ar^1$ = 4-$ClC_6H_4$
**f** $Ar^1$ = 2-$ClC_6H_4$
**g** $Ar^1$ = 3-$ClC_6H_4$
**h** $Ar^1$ = 4-$EtO_2CC_6H_4$
**i** $Ar^1$ = 3-pyridyl

**a** $Ar^2$ = Ph
**b** $Ar^2$ = 4-$ClC_6H_4$
**c** $Ar^2$ = 4-$MeC_6H_4$
**d** $Ar^2$ = 4-$MeOC_6H_4$
**e** $Ar^2$ = 3-$MeC_6H_4$
**f** $Ar^2$ = 2-thienyl




**3a–n**

**a** $Ar^1$ = 4-$O_2NC_6H_4$, $Ar^2$ = Ph
**b** $Ar^1$ = 4-$MeC_6H_4$, $Ar^2$ = Ph
**c** $Ar^1$ = 4-$MeOC_6H_4$, $Ar^2$ = Ph
**d** $Ar^1$ = 4-$BrC_6H_4$, $Ar^2$ = Ph
**e** $Ar^1$ = 4-$ClC_6H_4$, $Ar^2$ = Ph
**f** $Ar^1$ = 2-$ClC_6H_4$, $Ar^2$ = Ph
**g** $Ar^1$ = 3-$ClC_6H_4$, $Ar^2$ = Ph
**h** $Ar^1$ = 4-$EtO_2CC_6H_4$, $Ar^2$ = Ph
**i** $Ar^1$ = 3-pyridyl, $Ar^2$ = Ph
**j** $Ar^1$ = 4-$O_2NC_6H_4$, $Ar^2$ = 4-$ClC_6H_4$
**k** $Ar^1$ = 4-$O_2NC_6H_4$, $Ar^2$ = 4-$MeC_6H_4$
**l** $Ar^1$ = 4-$O_2NC_6H_4$, $Ar^2$ = 4-$MeOC_6H_4$
**m** $Ar^1$ = 4-$O_2NC_6H_4$, $Ar^2$ = 3-$MeC_6H_4$
**n** $Ar^1$ = 4-$O_2NC_6H_4$, $Ar^2$ = 2-thienyl

**Scheme 1** *Reagents and conditions*: i, aryl iodide **1** (0.3 mmol), $Na_2S_2O_5$ (0.6 mmol), alkene **2** (0.2 mmol), $HOCH_2S(O)ONa \cdot 2H_2O$ (rongalite, 0.6 mmol), KOH (0.6 mmol), DMSO/$H_2O$ (2 : 1, 2 ml), air, 80 °C, overnight.

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

| Entry | Base | Solvent | *T*/°C | Yield of **3a** (%)[b] |
|---|---|---|---|---|
| 1 | – | DMSO | 80 | 0 |
| 2 | $Et_3N$ | DMSO | 80 | 0 |
| 3 | $K_2CO_3$ | DMSO | 80 | 14 |
| 4 | KOH | DMSO | 80 | 58 |
| 5 | KOH | DMF | 80 | trace |
| 6 | KOH | MeCN | 80 | 31 |
| 7 | KOH | THF | 80 | 0 |
| 8 | KOH | $H_2O$ | 80 | 0 |
| 9 | KOH | DMSO/$H_2O$ (1 : 1) | 80 | 54 |
| 10 | KOH | DMSO/$H_2O$ (2 : 1) | 80 | 72 |
| 11 | KOH | DMSO/$H_2O$ (2 : 1) | 60 | 30 |
| 12 | KOH | DMSO/$H_2O$ (2 : 1) | 100 | 65 |
| 13 | KOH | DMSO/$H_2O$ (2 : 1) | 80 | 0[c] |
| 14 | KOH | DMSO/$H_2O$ (2 : 1) | 80 | 70,[d] 51,[e] 74[f] |

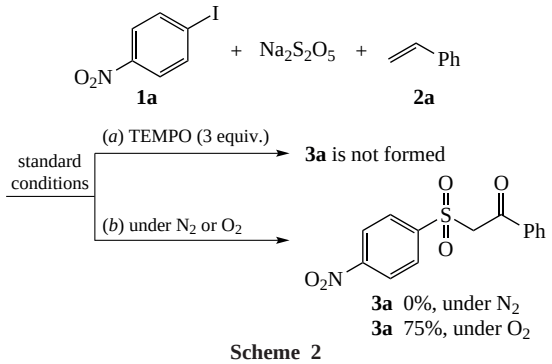
[a] *Reaction conditions*: 4-iodonitrobenzene **1a** (0.3 mmol), $Na_2S_2O_5$ (0.6 mmol), styrene **2a** (0.2 mmol), rongalite (0.6 mmol), base (0.6 mmol), solvent (2 ml), air, overnight. [b] Isolated yield. [c] Without rongalite. [d] DABSO instead of $Na_2S_2O_5$. [e] $Na_2S_2O_5$ (0.2 mmol) was used. [f] $Na_2S_2O_5$ (1 mmol) was used.

of $K_2CO_3$ (entries 1–3). Pleasingly, addition of KOH afforded the desired product **3a** in 58% yield. Reactions in other solvents such as DMF, acetonitrile and THF were not effective. The reaction in DMSO/$H_2O$ (2 : 1) gave 72% yield of **3a**. Most probably, the addition of water increases the solubility of the substrates and base in DMSO (entries 4–10). The temperature effect was then evaluated. Reaction processed at 60 °C gave relative lower yield, and further raising the temperature to 100 °C did not benefit the yield (entries 11 and 12). Control experiment showed that rongalite was essential (entry 13). Comparable yield was obtained when using DABSO as the sulfur dioxide surrogate. The reaction was also influenced by the loading of $Na_2S_2O_5$, and 3 equiv. of $Na_2S_2O_5$ was sufficient (entry 14).

With the optimized reaction conditions in hand, the scope and generality of the procedure were explored (see Scheme 1).† Both electron-rich and electron-deficient aryl iodides were compatible. Aryl iodides containing nitro, methyl, methoxyl, halogen, ester and pyridyl group reacted with sodium metabisulfite and styrene to afford the corresponding products in moderate to good yields. Steric hindrance showed some influence on the reaction. The *ortho*-, *meta*-, and *para*-chlorine substituted iodobenzene underwent this reaction to give products **3e**–**g** in 72, 52 and 58% yields, respectively. Styrenes with different substituents also reacted smoothly to provide products **3j**–**m** in good yields. Moreover, heterocyclic alkene such as 2-vinylthiophene **2f** showed good reactivity, generating the desired product **3n** in 60% yield.

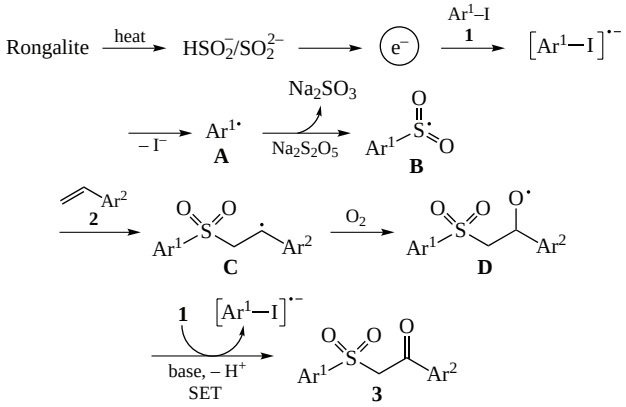
Some control experiments were carried out to gain insight into the reaction. Initially, when 3 equiv. of the radical scavenger, 2,2,6,6-tetramethylpiperidine *N*-oxyl (TEMPO) was added, no desired product **3a** was observed [Scheme 2(*a*)]. These results indicated the involvement of a radical mechanism. Moreover, when the reaction was carried out under $N_2$ or $O_2$ atmosphere, product **3a** was obtained in 0 and 75% yields, respectively [Scheme 2(*b*)], which evidenced that $O_2$ played a crucial role.

On the basis of experimental results and previous reports, a mechanism is proposed (Scheme 3). Initially, rongalite releases an electron under heating. Then aryl iodide **1** captures an electron to generate radical anion, followed by losing an iodine anion to give aryl radical **A**.[16,17] Next, the aryl radical reacts with $Na_2S_2O_5$ to generate radical **B**.[18] Then, addition of radical **B** to styrene **2** provides intermediate **C** which is attacked by oxygen followed by homolytic cleavage to result in intermediate **D**.[19,20] Finally,




**Scheme 2**

† *General procedure for the synthesis of* **3a**–**n**. A sealed tube equipped with a magnetic stirrer bar was charged with aryl iodide **1** (0.3 mmol), $Na_2S_2O_5$ (114 mg, 0.6 mmol), alkene **2** (0.2 mmol), rongalite (93 mg, 0.6 mmol), KOH (34 mg, 0.6 mmol) and DMSO/$H_2O$ (2 : 1, 2 ml). The reaction mixture was then heated to 80 °C and stirred overnight under air. Upon reaction completion, the resulting solution was quenched with water and extracted by ethyl acetate. The collected organic extracts were dried over $Na_2SO_4$. The solvent was then removed under reduced pressure and the residue was purified by silica gel column chromatography using petroleum ether/ethyl acetate (8 : 1, v/v) as eluent to afford products **3a**–**n**.




**Scheme 3**

intermediate **D** undergoes deprotonation and electron transfer with aryl iodide **1** providing the coupling product **3**.[21]

In summary, we have developed an arylsulfonylation of alkenes with aryl iodides and sodium metabisulfite to access β-keto sulfones. In this reaction, rongalite was used as a novel precursor of super electron donors to generate aryl radicals from aryl iodides. The use of sodium metabisulfite as the sulfur dioxide surrogate is also cost-effective and environmentally friendly. A broad scope of aryl iodides and alkenes survived the reaction conditions to afford β-keto sulfones in moderate to good yields.

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*Online Supplementary Materials*

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2022.09.019.

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