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Redox-Neutral Access to Sultams from 2-Nitrochalcones and Sulfur with Complete Atom Economy

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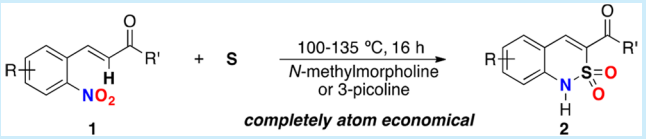
Supporting Information

ABSTRACT: A catalyst-free, redox-neutral, and completely atom-economical synthesis of sultams by simply heating 2-nitrochalcones with elemental sulfur in 3-picoline or *N*-methylmorpholine is described. The S−N, C−S, and S═O bonds of the sulfonamide are efficiently formed between the nitrogen atom of the 2-nitro group and the α-carbon of the chalcones and elemental sulfur with the migration of two oxygen atoms from the 2-nitro group to the sulfur atom.



Sulfonamides,[1] including their cyclic derivatives sultams, are important scaffolds in medicinal chemistry. In particular, 2,1-benzothiazine 2,2-dioxide[2] analogues have potent biological uses such as antibacterial activity (**I**),[3] lipoxygenase inhibition, and drugs for heart disease (**II**)[4] (Figure 1).

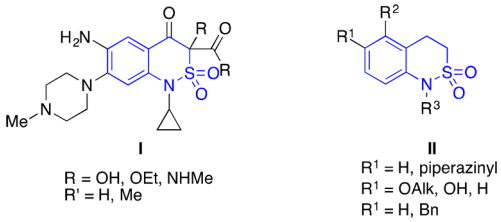
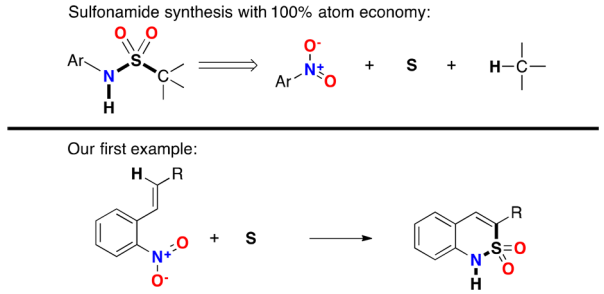


Figure 1. Bioactive 2,1-benzothiazine 2,2-dioxides.

Classical approaches to sulfonamide function can be roughly classified as non-redox and redox on the sulfur atom. In the first category, the majority of reports used an amine group to condense with an activated sulfonyl group.[5] Another widely developed strategy is to *N*-functionalize the parent sulfonamides.[6] In the second category, sulfonamide derivatives with lower oxidation states such as sulfenylamides,[7] sufinylamides[8] were oxidized.[9] Recently, Luo et al. reported an iron-catalyzed redox coupling between nitroarenes and sodium sulfinate in the presence of $NaHSO_3$ in excess quantities as external reductant.[10] In both cases of redox or non-redox strategies, even when water is formed as the only byproduct, the atom economy of the reaction can hardly attain 100%.[11]

During the course of our research focused on the use of elemental sulfur as an inexpensive but versatile synthetic tool in organic synthesis,[12] we reasoned that the involvement of elemental sulfur as a building block in a given reaction would provide an excellent strategy to sulfur-containing compounds.[13] This approach is even more advantageous if the organic starting substrates are readily available and the reaction does not lead to any byproduct. In this context, using nitro groups[14] and C−H moieties as the nitrogen and carbon precursors, respectively, would provide an ideal access to the expected sulfonamide group with complete atom economy (Scheme 1).

Scheme 1. 100% Atom-Economical Synthesis of Sulfonamide



Indeed, the nitro groups are easily, directly, and selectively introduced to the carbon skeleton thanks to a wide arsenal of nitrating agents, ranging from cheap nitric acid/nitrates salts to powerful nitronium salts (NO_2BF_4, for example) and dinitrogen pentoxide N_2O_5.[15]

The nitro group would act as oxidant to oxidize elemental sulfur and the C−H moiety to the required oxidation states in the sulfonamide group. Consequently, neither added oxidant nor external reductant would be necessary.

We first intended to apply this transformation to the case in which the reacting nitro and C−H moieties are on the same molecules. To examine our concept, we chose 2-nitrochalcone **1a** as a model substrate to investigate the sulfur incorporation conditions (Table 1). We initially tried several aza-heterocycles that have been demonstrated to be suitable for reactions involving elemental sulfur (*N*-methylmorpholine, *N*-methylpiperidine, pyridine, 3-picoline).

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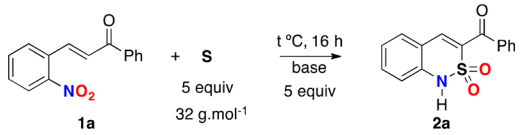
Table 1. Optimization of the Reaction Conditions



entry[a]	base	temp (°C)	yield[b] (%)
1	*N*-methylpiperidine	100	52
2	*N*-methylmorpholine	100	75
3	pyridine	100	30
4	pyridine	120	54
5	3-picoline	135	86 (89)[d]
6	3-picoline	135[c]	65
7	quinoline	135	75
8	DMF	135	45
9	dimethyl sulfoxide	135	56

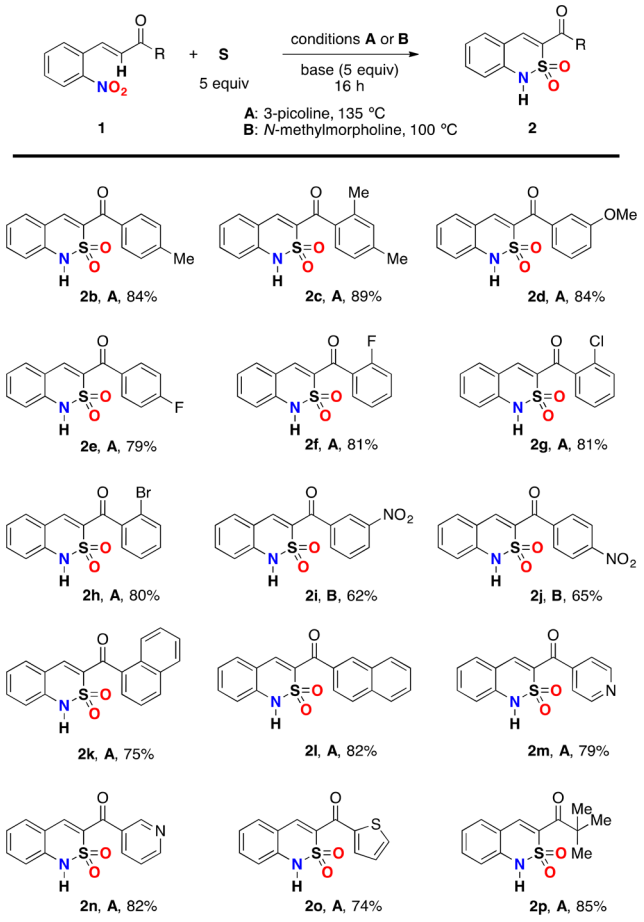
[a]Reaction conditions: **1a** (0.2 mmol), S (1 mmol, 32 mg), base (1 mmol, 5 equiv). [b]Isolated yield. [c]S (0.5 mmol, 2.5 equiv) was used. [d]Yield of 1 mmol scale reaction.

The desired 2,1-benzothiazine 2,2-dioxide **2a** was obtained, albeit in moderate yield (52%), when *N*-methylpiperidine was used (entry 1). A better yield was obtained with *N*-methylmorpholine (entry 2). Since some degradation was observed in both of these cases, we decided to use pyridine bases. The reaction in pyridine proceeded more slowly, but the reaction mixture is cleaner than the previous cases (entry 3 vs entries 1 and 2). Accordingly, increasing the reaction temperature accelerated the conversion into lactam **2a** (entries 4 and 5), and this product was obtained in excellent yield in 3-picoline at 135 °C (entry 5).

Further survey of the reaction conditions indicated that the reaction yield was dependent on the quantity of sulfur. Lower loading of S_8 led to a diminished yield of **2a** (entry 6). While quinoline was found to be a good solvent for this reaction (entry 7), reactions in DMF or DMSO resulted in lower yields, possibly due to the degradation of **1a** in these solvents. After screening experiments, 3-picoline and/or *N*-methylmorpholine were identified as suitable additives for this reaction (conditions A and B, respectively).

With the optimal conditions in hand, substrate scope was investigated. First, various chalcones bearing different substituents on the benzoyl moiety were tested (Scheme 2). Various methylated chalcones **1b-c** including *ortho*-substituted one (**1c**) provided the corresponding sultams in good yields. Chalcones bearing an electron-donating methoxy group **1d** gave methoxy sultam **2d** in excellent yield. In the case of halogenated chalcones (**1e−h**), no significant difference in reactivities was observed. The corresponding sultams were formed in good to excellent yields. The bromo substituent in **2h** is particularly useful for further functionalization. When dinitrochalcones **1i,j** were subjected to reaction in 3-picoline (conditions A), the expected nitrosultams **2i,j** were formed in low yields with significant degradation. To our delight, these nitrosultams **2i,j** were obtained in improved yields in *N*-methylmorpholine (conditions B). This strategy furnished efficiently both regioisomeric naphthone sultams **2k,l**. Heteroaromatic chalcones bearing a thienyl or pyridyl moieties were also competent substrates (**1m−o** to **2m−o**). Similar behavior was found for nitrochalcone **1p** derived from pinacolone. The reaction furnished sultam **2p** in high yield.

Scheme 2. Formation of Aroyl Sultams 2b−p



The connectivity of **2d** was supported by an X-ray diffraction study (Figure 2; see also the Supporting Information).

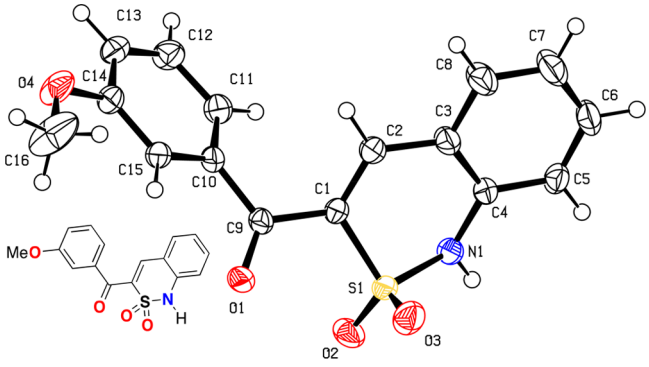


Figure 2. X-ray crystal structure of **2d**.

Next, the reactions were investigated with substrates bearing different substituents on the nitrobenzene ring (Scheme 3). When 3-picoline was used as the basic additive, while the electron-donating methoxy group substituted chalcone **1q** gave good yield of **2q**, halogen-substituted chalcones **1r,s** exhibited slightly reduced activity. Gratifyingly, good reactivities were observed in *N*-methylmorpholine for these two halogenated chalcones.

It should be noted that the starting 2-nitrochalcones **1** were conveniently prepared via Claisen−Schmidt condensation reaction between the parent 2-nitrobenzaldehyde and aceto-

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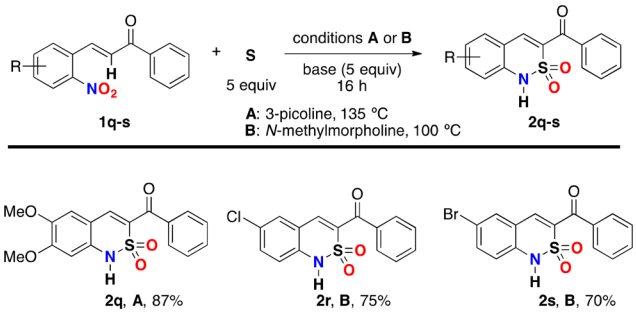
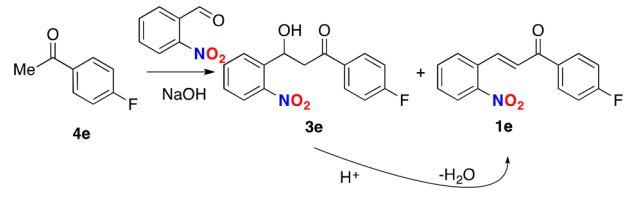
Scheme 3. Formation of Benzoyl Sultams 2q–s



phenones in the presence of NaOH as the catalyst. Although the chalcones **1** were obtained in high yields in most cases, we noticed that the dehydration step of the intermediately yielded *β*-hydroxy ketones **3** proceeded partially in some cases (example of synthesis of **1e**, Scheme 4). The yield of chalcone

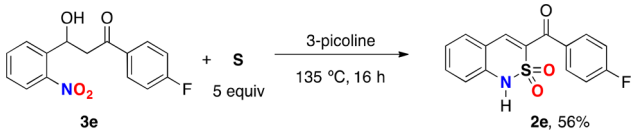
Scheme 4. Claisen–Schmidt Condensation with Incomplete Dehydration Step



1e was thus low. Moreover, if **1e** is isolated by filtration, it is contaminated by various amounts of **3e**. In order to ensure a complete dehydration, further refluxing of the crude mixture of the Claisen–Schmidt reaction under acidic conditions is needed to afford high yields of chalcones **1e**.

We wondered if the reaction of *β*-hydroxy ketone **3e** with elemental sulfur under standard conditions would lead to the same product **2e** as for chalcone **1e**. The experimental result presented in Scheme 5 confirmed our hypothesis. Although the

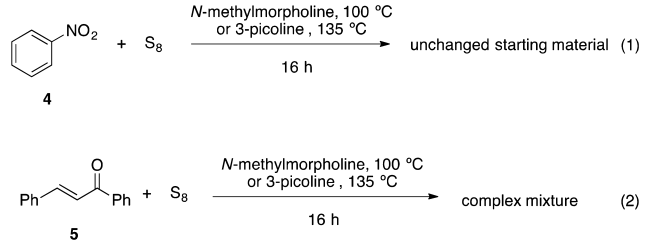
Scheme 5. Similar Reaction Outcome with *β*-Hydroxy Ketones 3e



yield with *β*-hydroxy ketone **3e** was slightly lower, this observation allowed the use of *β*-hydroxy ketones **3e** or even chalcones **1e** contaminated with **3e** due to their convergent transformation into **2e**, respectively.

While the mechanism is not clear at this moment, it is important to point out that the choice of basic additive is of vital importance to the success of the reaction. Two significant comparative observations may be discussed. First, although the combination of sulfur and a base (even a weak base such as $NaHCO_3$ in DMF) was known to reduce nitroarenes to anilines,[16] under our conditions (S_8/3-picoline at 135 °C or S_8/*N*-methylmorpholine at 100 °C), nitrobenzene **4** remained unchanged even after 16 h of heating (Scheme 6, eq 1). Second, a conjugated enone moiety is reactive to base, and a relatively

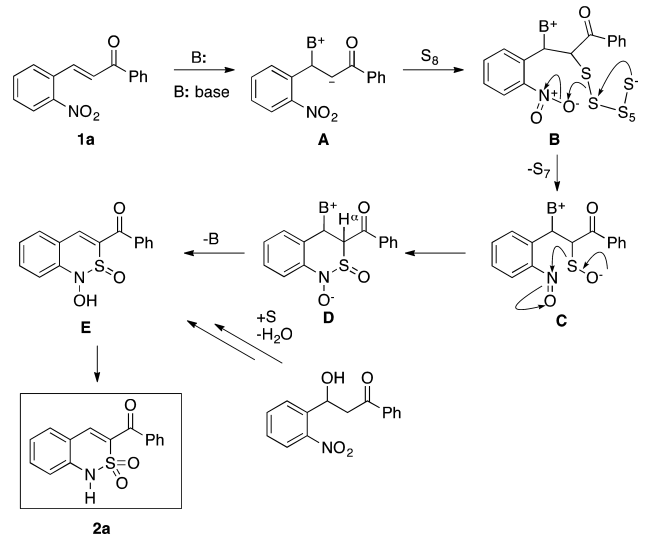
Scheme 6. Investigation of the Reaction Mechanism



complex mixture could be observed by heating unsubstituted chalcone **5** under similar conditions (Scheme 6, eq 2).

Consequently, although it is still too early to present detailed mechanistic evidence, the transformation is thought to be initiated at the 1,3-enone moiety of **1**. Michael addition of the nitrogen base would form a stabilized nucleophilic anion **A** (Scheme 7). This in situ generated nucleophile then attacks

Scheme 7. Possible Reaction Pathway



sulfur to provide polysulfide **B**. Subsequent fragmentation of polysulfide **B** with simultaneous attack of the remaining sulfide on the nitro group would lead to nitroso sulfenate **C**. The proximity of electrophile nitroso group and nucleophile sulfenate group would favor the cyclization to provide *N*-hydroxysulfinamide **D**. Because of the presence of both benzoyl and sulfinyl groups, the H *α* of **D** becomes acidic. This would facilitate the *β* elimination of pyridine to provide **E**. Further migration of another oxygen atom from nitrogen to the sulfur atom would furnish the final cyclic sulfonamide **2**. When *β*-hydroxy ketone **3** was used as the starting substrate as described in Scheme 5, the reaction occurred in a similar manner in which the base substituent B of intermediates **A–D** was simply replaced by an OH group.

In conclusion, we demonstrated for the first time that sultams could be conveniently synthesized via an unconventional redox-neutral reaction of 2-nitrochalcones with elemental sulfur in the presence of 3-picoline or *N*-methylmorpholine under catalyst-free conditions. Since both the nitro group and chalcone skeleton are readily constructed or introduced, the disclosed strategy to sultams is highly versatile and has great potential as a synthetic tool. Moreover, this completely atom-economical, redox-neutral, and operatively simple method

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using elemental sulfur as the best sulfur source will provide a more environmentally friendly method for sulfonamide bond formation. Further development of this strategy, especially in a multicomponent version in which the nitro substituent and the alkene moiety are in different molecules, is underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01766.

Experimental procedures, characterization of new compounds, and NMR spectra (PDF)

X-ray crystallographic data for compound **2d** (CIF)

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Notes

The authors declare no competing financial interest.

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