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# Cooperative Activating Effect of Tertiary Amine/DMSO on Elemental Sulfur: Direct Access to Thioaurones from 2′-Nitrochalcones under Mild Conditions

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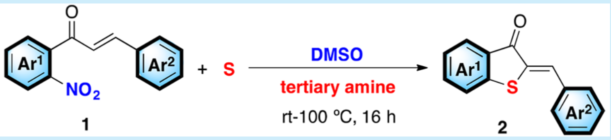
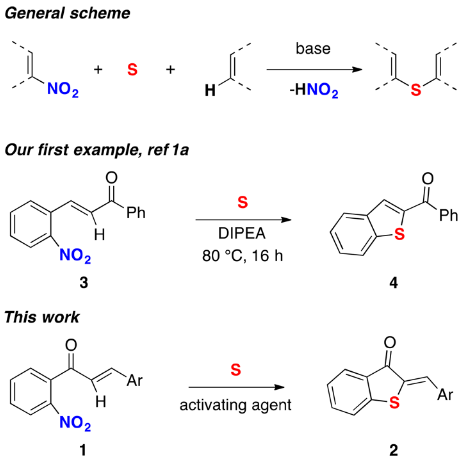
Supporting Information

**ABSTRACT:** A new mode for the activation of elemental sulfur is reported. In the presence of both DMSO and a tertiary aliphatic amine (triethylamine or *N*-methylpiperidine), this element reacts directly with a wide range of 2′-nitrochalcones **1** to provide the corresponding thioaurones **2** in high yields even at room temperature and in the absence of transition metal catalyst.



The ready availability of compounds bearing $C(sp^2)-NO_2$ and $C(sp^2)-H$ bonds and the synthetic versatility of elemental sulfur have prompted us to focus our efforts on exploiting their synthetic utility together.[1] For such purposes, we initiated a project aimed at constructing two C−S bonds from a direct combination of these three fragments (Scheme 1).

**Scheme 1. Construction of Two C−S Bonds from a $C(sp^2)-H$ Bond, a $C(sp^2)-NO_2$ Bond, and Sulfur**



Very recently, we reported an example of the synthesis of 2-benzoylbenzothiophenes **4** starting from 2-nitrochalcone substrates **3** using elemental sulfur activated by diisopropylethylamine (DIPEA) at 80 °C.[1a] Lowering the reaction temperature is a challenging task, especially in the absence of a transition metal catalyst, and will broaden the scope of substrates.

As a part of our ongoing project, we considered whether the same strategy could be extended to 2′-nitrochalcones **1**. Such a transformation would allow the direct synthesis of thioaurones or hemithioindigos **2**, which are important scaffolds in dyes, cosmetics, and photoswitches.[2] They can also be used as synthetic intermediates for other bioactive sulfur-containing molecules.[3] Although many synthetic methods for **2** have been developed,[4] they are all based on organosulfur starting materials, the syntheses of which require additional steps involving malodorous sulfides or thiols. Using elemental sulfur as the sulfur precursor would be an excellent solution for this drawback, which is also frequently encountered in sulfur chemistry.

Accordingly, we set up a screening of conditions for the reaction between elemental sulfur and 2′-nitrochalcone **1a** by varying different activators (Table 1). At 80 °C, *N*-methylpiperidine (NMP) was shown to be an excellent sulfur activator, leading to the clean and total conversion of **1a** into thioaurone **2a** (Table 1, entry 1). Other aliphatic amines such as *N*-methylmorpholine (NMM) and DIPEA were also found to be capable of promoting the transformation, although their efficiencies were lower than that of *N*-methylpiperidine (Table 1, entries 2 and 3). Chalcone **1a** remained totally unaffected by sulfur with weakly or non basic additives such as 3-picoline, DMF, or DMSO (Table 1, entries 3−6). At room temperature, the activating effect of *N*-methylpiperidine was not observed (Table 1, entry 7). Pleasingly, we serendipitously found that when both *N*-methylpiperidine and DMSO were present in the reaction medium, a noticeable color change was observed even at rt, and thioaurone product **2a** was consequently obtained in excellent yield (Table 1, entry 8).

At this stage, we wondered whether this double activation could be extended to other amines. Unsurprisingly, $Et_3N$ ($pK_a = 10.65$) and DIPEA ($pK_a = 10.61$), which are as basic as NMP ($pK_a = 10.08$), exhibited the same activating effect (Table 1, entries 9 and 10). Weaker bases such as NMM ($pK_a = 7.41$) and 3-picoline ($pK_a = 5.68$) were much less efficient (Table 1,

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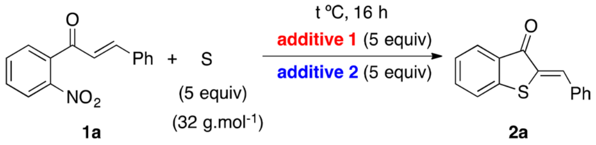
### Table 1. Optimization of the Reaction Conditions



| entry[a] | additive 1 | additive 2 | temp (°C) | conv (%)[b] |
|---|---|---|---|---|
| 1 | NMP | - | 80 | 100 |
| 2 | NMM | - | 80 | 10 |
| 3 | DIPEA | - | 80 | 57 |
| 4 | DMF | - | 80 | 0 |
| 5 | DMSO | - | 80 | 0 |
| 6 | 3-picoline | - | 80 | 0 |
| 7 | NMP | - | rt | 0 |
| 8 | NMP | DMSO | rt | >95 (86)[c] |
| 9 | $Et_3N$ | DMSO | rt | >95 (88)[c,d] |
| 10 | DIPEA | DMSO | rt | >95 (82)[c] |
| 11 | NMM | DMSO | rt | 15 |
| 12 | 3-picoline | DMSO | rt | 0 |
| 13 | $Et_3N$ | DMF | rt | 61 |

[a] Reaction conditions: **1a** (0.2 mmol), S (1 mmol, 32 mg), base (1 mmol, 5 equiv). [b] Determined by $^1$H NMR analysis of the crude mixtures. [c] Isolated yield. [d] 86% on a 1 mmol scale.

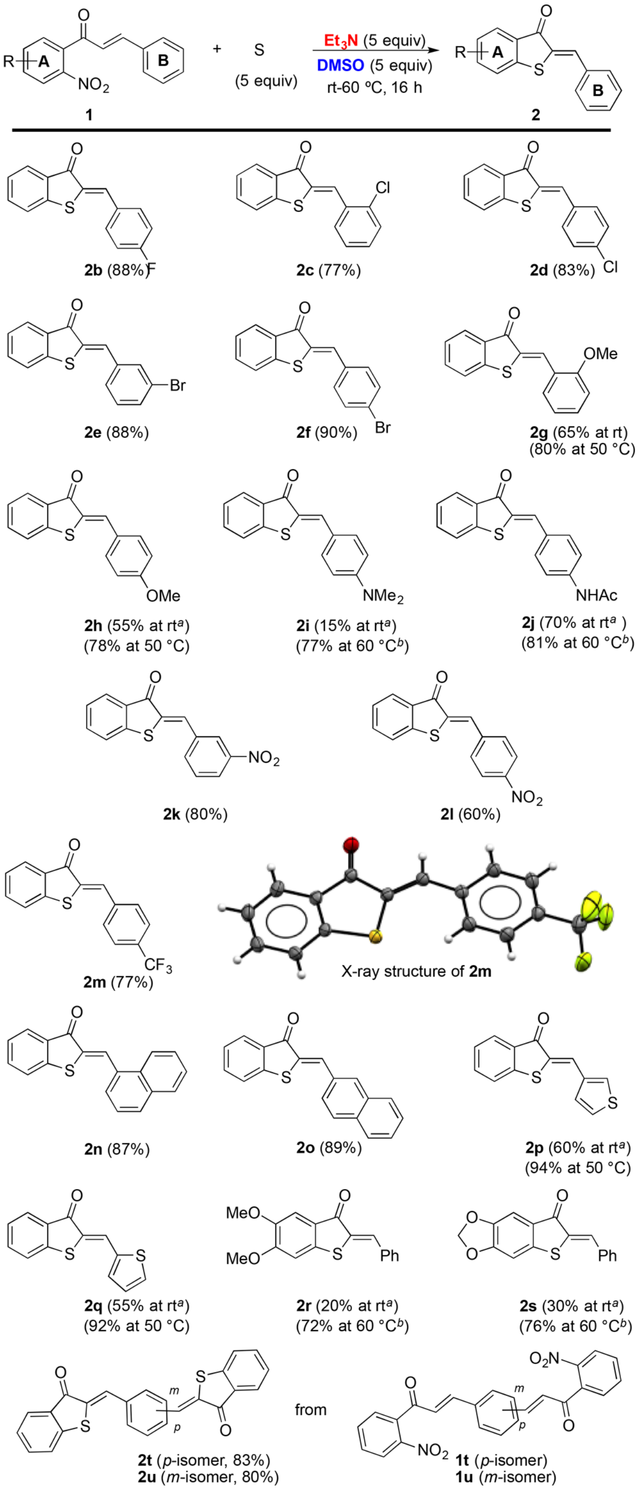
entry 11) or totally inefficient (Table 1, entry 12). Finally, we found that as a second additive, DMSO is better than DMF. In fact, the reaction activated by $Et_3N$/DMF was incomplete and less clean than those with $Et_3N$/DMSO and NMP/DMSO.

The optimized conditions with the $Et_3N$/DMSO activator pair were chosen for the investigation of the scope of 2′-nitrochalcones substrates **1** (Scheme 2). Reaction of halogenated chalcones **1b**–**f**, including a fluorine, chlorine, or bromine atom at different positions of the aromatic ring B, proceeded well, delivering products **2b**–**f** in good yields. Substrates bearing an electron-donating group such as methoxy, dimethylamino, or acetamido (**1g**–**j**) were less reactive. Their reactions at rt were incomplete, and the conversion was proven to depend on the electron-donating capacities of these substituents. While the conversion at rt was low for the substrate bearing a strongly donating *p*-*N*,*N*-dimethylamino group (**2i**), the reactivity was improved significantly with *p*-acetamido substituent (**2j**). The conversions at rt with methoxy-substituted substrates **1g** and **1h** remained moderate and depended on the substituent position. Gratifyingly, all of these electron-enriched substrates **1g**–**j** were fully transformed into the expected thioaurones **2g**–**j** upon heating at 50–60 °C.[5]

In contrast, the rt conditions were successfully applied to other chalcones bearing an electron-withdrawing substituent such as nitro or trifluoromethyl (**1k**–**m**). It should be noted that between the two nitro groups of chalcones **1k** and **1l**, only the 2′-nitro group was reactive. The structure of **2m** was confirmed by X-ray crystallography. The reaction worked well also with both naphthyl (**1n**, **1o**) and thienyl (**1p**, **1q**) substrates, although gentle heating at 50 °C was required to achieve high yields for the latter cases.

The scope of 2′-nitrochalcones with different functional groups on ring A was next examined. When ring A was substituted with oxygen-containing substituents as in substrates **1r** and **1s**, the reactivity was low at rt. This phenomenon is consistent with an $S_NAr$ mechanism. Via an addition—elimination pathway of the nitro group by a sulfur moiety, the negatively charged intermediate adduct **D** is generated and destabilized by electron-donating groups (see Scheme 4). Interestingly, high yields of the corresponding thioaurones **2r** and **2s** could be achieved at 60 °C.

### Scheme 2. Formation of Thioaurones 2b–u from 2′-Nitrochalcones 1b–u

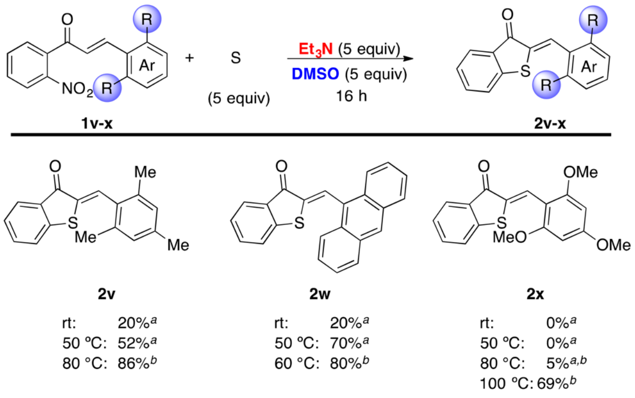


[a] Yield determined by $^1$H NMR analysis of the crude reaction mixture. [b] NMP was used instead of $Et_3N$.

The efficiency of the present conditions was further evaluated on a twofold reaction with substrates **1t** and **1u**. In these cases, because of the low solubilities of the products (including mono- and bisthioaurones), gentle heating at 60 °C was applied to facilitate the stirring. Accordingly, bisthioaurones **2t** and **2u** were isolated in high yields as orange (**2t**) and bright-yellow (**2u**) precipitates by simple filtration followed by washing with common laboratory solvents (toluene, $CH_2Cl_2$, MeOH), even on a small scale. Their solubilities were found to be extremely low even in DMSO, especially when they were pure.[6]

We further interrogated the mechanism of the reaction. Because the reactivities were lower with substrates bearing electron-donating substituents on ring B, a possible initiating step could be a Michael addition of the amine to the alkene moiety of the 2′-nitrochalcone substrate. Moreover, if this were the case, any steric factors that could impede this initiating step would further hamper the reactivity. To confirm this hypothesis, we first investigated the reaction of 2′-nitrochalcone substrates **1v** and **1w** bearing sterically demanding but electronically neutral groups at both *ortho* positions of ring B (Scheme 3). Both of them were transformed slowly at rt, although full conversions could be achieved cleanly upon heating at 60 °C.

**Scheme 3. Reactions with Sterically Demanding 2′-Chalcones 1v−x**

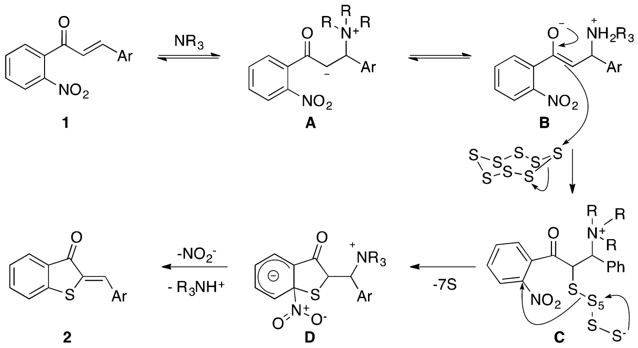


[a] Yield determined by $^1$H NMR analysis of the crude reaction mixture. [b] NMP was used instead of $Et_3N$.

As an extreme case, we evaluated the reactivity of trimethoxychalcone **1x**, which is at the same time electronically enriched and sterically hindered. As expected, **1x** remained intact at rt to 50 °C and nearly unchanged even at 80 °C. However, at 100 °C **1x** was fully transformed into the corresponding thioaurone **2x**.

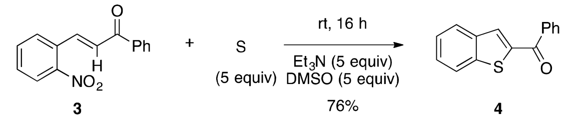
On the basis of the above observations, a possible mechanistic pathway is outlined in Scheme 4. Michael addition of the tertiary amine to 2′-nitrochalcone **1** would provide 1,3-ammoniumketone **A**, which could exist as its enol tautomer **B**, stabilized by the proximal positive charge of the quaternary ammonium group. Enol **B** (or its deprotonated zwitterion ammonium enolate) could attack elemental sulfur to provide polysulfide **C**. Subsequent fragmentation of $S_7$ with simultaneous cyclization via nucleophilic aromatic attack would deliver zwitterion **D**. The negative charge on ring A of intermediate **D** is stabilized by the adjacent electron-withdrawing carbonyl group, which is in turn activated further by the nearby quaternary ammonium moiety. Finally, elimination of tertiary amine would lead to thioaurone **2**. Although the activating role of DMSO remains unclear at the moment, it is possible that it stabilizes some polar intermediates and accelerates the transformation.

**Scheme 4. Proposed Mechanism for the Formation of Thioaurones 2 from 2′-Nitrochalcones 1**



Finally, to demonstrate the cooperative effect of DMSO and tertiary amine, we employed this activating system to the reaction of 2-nitrochalcone **3**. This reaction was reported previously by our group to provide 2-benzoylbenzothiophene **4** using DIPEA at 80 °C.[1a] In the presence of DMSO as a second additive, the expected product **4** was obtained in good yield even at rt (Scheme 5).

**Scheme 5. 2-Benzoylbenzothiazole 4 from 2-Nitrochalcone 3 at Room Temperature**



In conclusion, we have developed a direct method for the incorporation of one sulfur atom into 2′-nitrochalcones **1** through direct C−H bond functionalization and aromatic nucleophilic substitution of the nitro group. The corresponding thioaurones **2** are smoothly formed under mild and metal-free conditions. The synergy of a tertiary amine (triethylamine or *N*-methylpiperidine) and DMSO was shown to be extremely powerful to activate elemental sulfur, leading to clean and total conversions even at rt for substrates bearing electronically neutral or poor substituents. Further development and applications of this cascade of direct construction of two C−S bonds from a C($sp^2$)−H bond, a C($sp^2$)−$NO_2$ bond, and elemental sulfur are ongoing in our laboratory. We hope that new reactivities of elemental sulfur will find their applications in organic chemistry, especially in green and sustainable syntheses of high-added-value molecules.

## ■ ASSOCIATED CONTENT

### Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03547.

Experimental procedures, characterizations of new compounds, and copies of their NMR spectra (PDF)

### Accession Codes

CCDC 1584932 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by e-mailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: +44 1223 336033.

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### Notes

The authors declare no competing financial interest.

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(5) In view of the higher volatility of $Et_3N$ (bp 89 °C) and lower stability with sulfur upon heating compared with NMP (bp 107 °C), $Et_3N$ was systematically replaced by NMP for the reactions performed at 60 °C or higher. For the reaction of elemental sulfur with $Et_3N$, see: (a) Nguyen, T. B.; Ermolenko, L.; Dean, W. A.; Al-Mourabit, A. *Org. Lett.* **2012**, *14*, 5948. For reactions using elemental sulfur and promoted by *N*-methylpiperidine upon heating, see: (b) Nguyen, T. B.; Pasturaud, K.; Ermolenko, L.; Al-Mourabit, A. *Org. Lett.* **2015**, *17*, 2562. (c) Nguyen, T. B.; Ermolenko, L.; Corbin, M.; Al-Mourabit, A. *Org. Chem. Front.* **2014**, *1*, 1157. (d) Nguyen, T. B.; Retailleau, P. *Org. Lett.* **2017**, *19*, 3887.

(6) We were unable to record even the $^1H$ NMR spectrum of **2u**, but the microanalysis result of its sulfur content corresponded to the expected structure (sulfur content calculated for $C_{24}H_{16}N_2O_6$, 16.09%; found, 16.03%).

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