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# Umpolung Strategy for $\alpha,\alpha'$ -Functionalization of Ketones with 2-Aminothiophenols: Stereoselective Access to Spirobis(1,4-Benzothiazines)

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**Abstract.** In the presence of TFA as a strong acid catalyst in DMSO,  $\alpha,\alpha'$ -enolizable ketones were found to be stereoselectively  $\alpha,\alpha'$ -functionalized with 2-aminothiophenols to provide spirobis(1,4-benzothiazine) derivatives.

**Keywords:** sulfur; 1,4-benzothiazines; DMSO

1,4-Benzothiazine derivatives<sup>[1]</sup> have been reported to be present in a variety of natural products<sup>[2]</sup> and to exhibit a wide range of pharmacological properties including immunomodulating, antifungal, anti-rheumatic, anti-aldoso-reductase, anti-arrhythmic, vasorelaxant, anti-allergic, anti-hypertensive, neuroprotective and cytotoxic activities.<sup>[3]</sup>

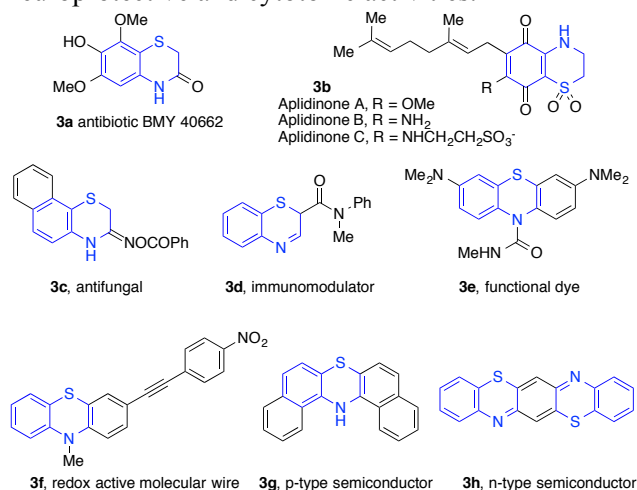


Figure 1. Selected useful 1,4-benzothiazine derivatives

For example, antibiotic **3a** designated BMY 40662 was discovered during a large scale fermentation of the anticancer agent esperamicin A<sub>1</sub>,<sup>[2a,b]</sup> whereas aplidinones A-C **3b** were isolated from the

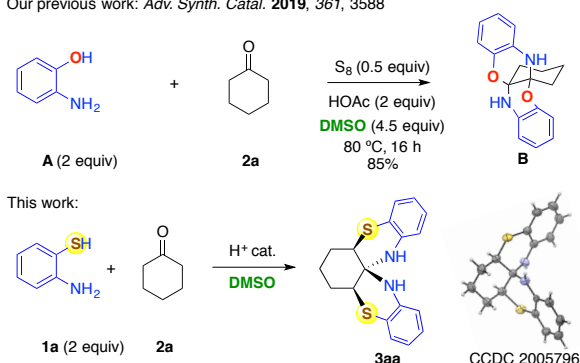
Mediterranean ascidian *Aplidium conicum* (Figure 1).<sup>[2d]</sup> While carbamate 1,4-benzothiazine **3c** displays a good antifungal activity,<sup>[4]</sup> amide **3d** is an immunomodulator.<sup>[5]</sup> Compound **3e** was found to be a functional dye capable of decomposing in biological systems to methylene blue and was used in diagnostics.<sup>[6]</sup> 1,4-Benzothiazine-substituted acetylene **3f** could be used as models for redox-active molecular wires.<sup>[7]</sup> Interestingly, 1,4-benzothiazine derivatives **3g,h** were found to exhibit either p-type or n-type semiconductivity depending on their angular or linear arrangement of the fused pentacyclic system.<sup>[8]</sup>

One of the most important objectives of organic chemistry is to develop straightforward and selective access to complex molecules using simple and readily available starting materials. Such a strategy becomes more attractive, especially for large scale production if the reactions could proceed under simple conditions without using expensive reagents or catalysts. Following this direction, we have been focusing our efforts on using elemental sulfur as a versatile tool to achieve a wide range of redox transformation as either stoichiometric or catalytic component.<sup>[9]</sup> The rich chemistry of elemental sulfur relies heavily on the ready scission of its S-S bonds under thermal, photochemical or catalytic conditions. In a broader extent, the study of any compounds bearing S-S bond or capable of forming this linkage during the course of the reaction could benefit from the organic chemistry of this element thanks to the facile interconversion between SH and S-S species. Herein, we disclose an unusual approach to novel spirobis(1,4-benzothiazines) based on an acid-catalyzed oxidative condensation of two molecules of 2-aminothiophenols with one molecule of  $\alpha,\alpha'$ -enolizable ketones. The strategy meets most of the above-mentioned expectations.

We have previously reported an oxidative functionalization of cyclohexanones with 2-aminophenols in DMSO catalyzed by elemental sulfur.

Via this reaction, a wide range of heteropropellanes were regio- and stereoselectively formed in high yields (Scheme 1).<sup>[10]</sup>

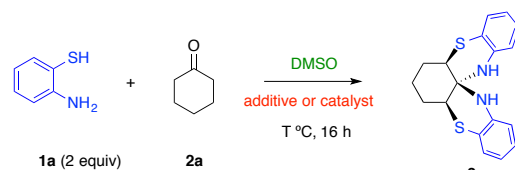
Our previous work: *Adv. Synth. Catal.* **2019**, *361*, 3588



Scheme 1. Difference in reactivity between *o*-aminophenol **A** and *o*-aminothiophenol **1a** with cyclohexanone **2a**

Extrapolating from this, we wondered if the same reactivity could be observed with 2-aminothiophenols.<sup>[11]</sup> For this purpose, the same reaction conditions were applied to 2-aminothiophenol **1a** and cyclohexanone **2a** (Scheme 1 and Table 1, entry 1).

Table 1. Screening of the reaction conditions

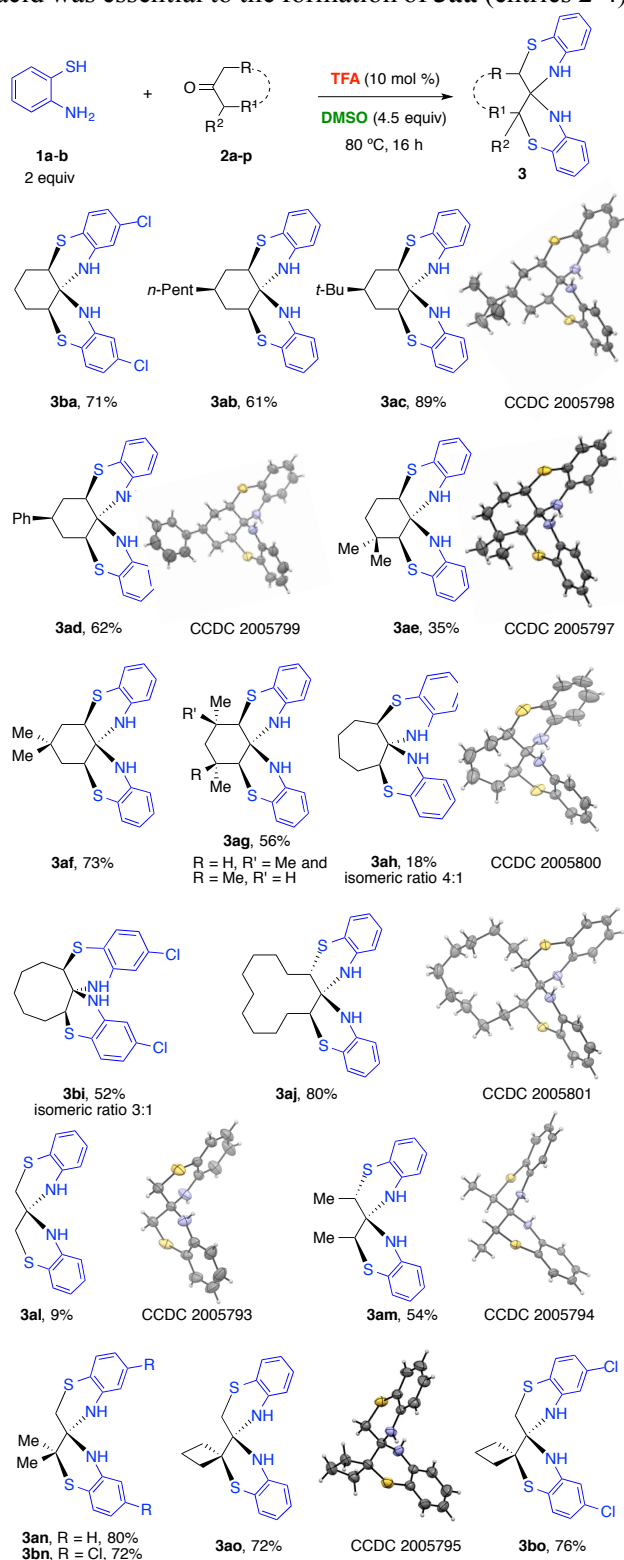


Entry <sup>[a]</sup>	Additive/catalyst (x equiv)	Temp (°C)	Yield (%) <sup>[b]</sup>
1	HOAc (2)/S (0.5)	100	46
2	S (0.5)	100	57
3	HOAc (2)	100	40
4	-	100	35
5	TFA (0.1)	100	67
6	TFA (0.1)	80	70
7	PTSA (0.1)	80	69
8 <sup>[c]</sup>	TFA (0.1)	80	65
9 <sup>[d]</sup>	TFA (0.1)	60	0
10 <sup>[e]</sup>	<b>TFA (0.1)</b>	<b>80</b>	<b>71</b>

<sup>[a]</sup> Reaction conditions: **1a** (2 mmol, 250 mg), cyclohexanone (1 mmol, 98 mg), DMSO (0.3 mL, 4.5 mmol), additive or catalyst (x equiv) under an argon atmosphere. <sup>[b]</sup> Isolated yield. <sup>[c]</sup> Reaction performed in the absence of DMSO. <sup>[d]</sup> Reaction performed in *N,N*-dimethylacetamide (DMAc) (0.3 mL) instead of DMSO. <sup>[e]</sup> Reaction performed under air.

To our delight, a 2:1 solid adduct with a similar empirical formula was obtained. To our surprise, the X-ray crystallographic study revealed its molecular structure as a unique racemic stereoisomer with two equatorial C-S bonds issued from the sulfuration of C-1 and C-6 of **2a** and the two geminal C-N bonds resulting from condensation of two amino groups with the carbonyl function. Further optimization of the

reaction conditions proved that neither sulfur nor acetic acid was essential to the formation of **3aa** (entries 2-4).



Scheme 2. Reaction scope

More strikingly, we subsequently found that the reaction could be performed in better yields in the presence of TFA or PTSA as a strong acid catalyst (entries 5-7). When DMSO was replaced by a dipolar aprotic solvent such as DMAc, only trace of **3aa** was

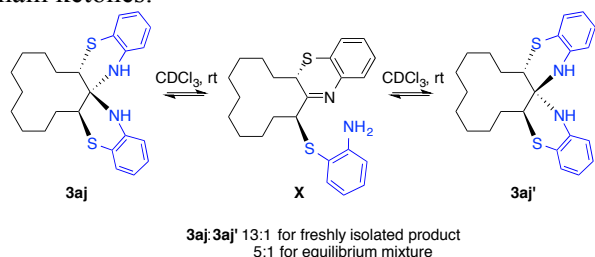
formed, suggesting the essential role of DMSO (entry 8). The reaction was found also to stagnate at temperature as low as 60 °C (entry 9). Additionally, no significant difference was observed if the reaction was performed under air or an inert atmosphere (entries 10 vs 6).

With this set of optimized conditions in hand (entry 10), we went on to investigate the scope of the reaction. Similar reactivity was observed with 2-amino-4-chlorothiophenol **2b**, leading to high yield of spiro compound **3ba**. To confirm the regiochemistry, the reaction with three 4-substituted cyclohexanones **2b-d** were evaluated (Scheme 2).

To our delight, in all cases, the reactions resulted in the products as expected regioisomers **3ab**, **3ac** and **3ad**. More interestingly, only one stereoisomer was formed. X-ray structural analyses showed that two newly formed C-S bonds and the existing C-C bond between the cyclohexane ring and the 4-substituent were all equatorial. The reaction conditions were next applied to 3,3- and 4,4-dimethylcyclohexanones **2e-f**. In both cases, the products were obtained as single isomers with two equatorial C-S bonds. On the other hand, the reaction of 3,3,5-trimethylcyclohexanone **2g** with **1a** resulted in a 2:1 mixture of two isomers **3ag**.

At this stage, we were eager to extend our method to other cycloalkanones. Gratifyingly, the reaction with cycloheptanone **2h** and cyclooctanone **2i** gave the major products **3ah** and **3bi** with the same stereochemistry, i.e. two newly formed C-S bonds are in a *cis* geometry. A better reactivity was observed with cyclooctanone than with cycloheptanone.

The ratio of these isomer and the other minor ones were found to be 4:1 and 3:1 for cycloheptanone **2h** and cyclooctanone **2i**, respectively. In opposition, the reaction of cyclododecanone provided the C<sub>2</sub> symmetric product **3aj**. The structure of which was determined once again by X-ray. The presence of another minor isomer **3aj'** was also detected by <sup>1</sup>H NMR (**3aj**:**3aj'** ratio 13:1). Upon leaving the solution in CDCl<sub>3</sub> of the freshly isolated in an NMR tube at rt, the major isomer **3aj** was found to convert to the minor isomer **3aj'** and an equilibrium was attained with a new ratio **3aj**:**3aj'** 5:1. It was possible that this isomerization proceeded via ring opening-ring closing mechanism as suggested in Scheme 3. The difference in stereochemistry outcome between six-to-eight membered cycloalkanones and cyclododecanone could be explained based on ring constraints (*vide infra*). We investigated further the chemical behavior of open chain ketones.<sup>[12]</sup>



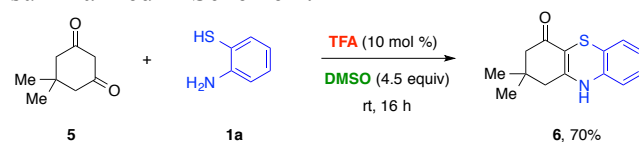
Scheme 3.

As the simplest member of this series, acetone reacted without any surprise, leading to C<sub>2</sub> symmetric product **3al** in a low yield, possibly due to its low boiling point (bp 56 °C) whereas the reaction was performed at 80 °C. In the case of diethyl ketone, product **3am** was formed along with a minor epimer at the *gem* N,N-disubstituted carbon **3am'** in a 1.4:1 ratio. Since both **3am** and **3am'** were C<sub>2</sub>-symmetric, their <sup>1</sup>H and <sup>13</sup>C NMR spectra corresponded to half of the molecule (see Supporting Information).

The relative configuration of **3am** determined by X-ray crystallography was shown to be the same as that of cyclododecanone. This similarity suggested that the twelve-membered ring ketone substrate behaved in the same manner as an open chain dialkyl ketone. Subsequently, non-symmetrical ketones were tested. Isopropyl methyl ketone **2n** and cyclobutyl methyl ketone **2o** were found to react efficiently, providing the corresponding spiro product in good to excellent yields. The dispiro structure of **3ao** was verified by X-ray structural determination.

Our conditions however failed with 4-heptanone, diisopropyl ketone and cyclopropyl methyl ketone. This can be explained by steric hindrance for the two first cases and ring constraint for the third case.

Finally, we applied our conditions to dimedone **5**. In this case, regardless excess use of **1a** (up to 4 equiv), the corresponding 1:1 adduct **6**<sup>[13]</sup> was formed exclusively as orange solid in high yields, even at rt temperature. The result of the reaction involving equimolar amounts of both starting materials was summarized in Scheme 4.



Scheme 4. Reaction with 1,3-dicarbonyl compounds **5a-c**

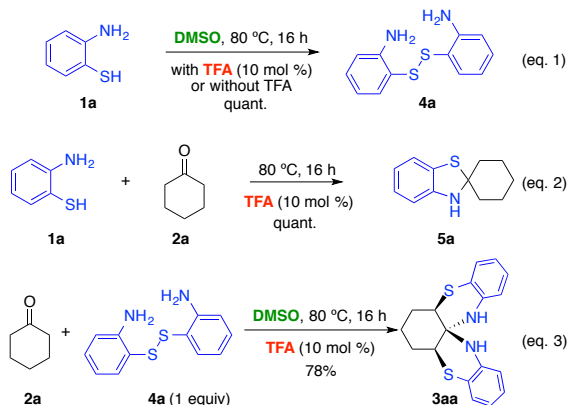
To gain a mechanistic insight into these oxidative C-S bond formation reactions, some control experiments were carried out (Scheme 5). First, 2-aminothiophenols **1a** was found to readily undergo oxidative dimerization to disulfide **4a** upon heating with DMSO in the presence or even in the absence of TFA catalyst (eq. 1).

Second, heating an equimolar mixture of **1a** and **2a** with TFA catalyst in the absence of DMSO yielded only in benzothiazoline **5a** as a result of a non-redox condensation. Third, when disulfide **4a** was used in place of 2-aminothiophenol **1a** under the standard conditions, spiro **3aa** was formed in a comparable yield.<sup>[14]</sup>

On the basis of previous reports and our results, a proposed reaction mechanism is shown in Schemes 6 and 7. Two different reaction pathways are hypothesized for the formation of spiro compounds derived from either cyclohexanone **2a** (Scheme 6) or diethyl ketone **2m** (Scheme 7).

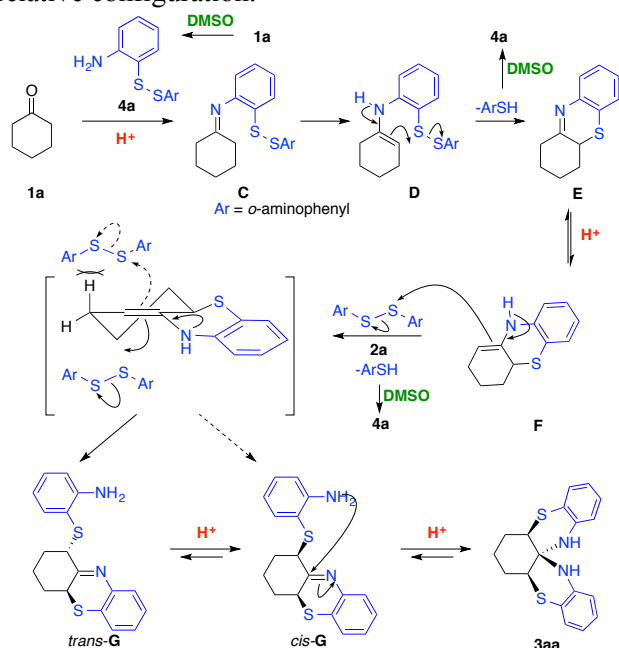
As demonstrated in eq 1. Scheme 5, since 2-aminothiophenol **1a** is readily oxidized into dimer **4a**,

the nucleophilicity of the thiol group in **1a** is masked and replaced by electrophilicity of disulfide linkage in **4a**. In another word, the sulfur atom was subjected to a polarity inversion or umpolung by oxidation promoted by DMSO.<sup>[15]</sup>



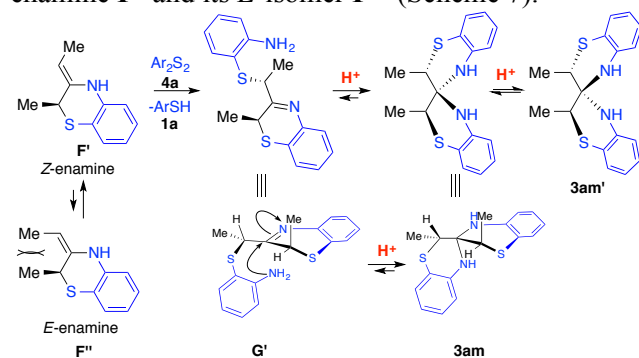
Scheme 5. Control experiments

Consequently, a similar reactivity as for 2-aminophenol **A** to form disulfide analog of heteropropellane **B** (Scheme 2) could not be observed. The reaction was initiated by an acid-catalyzed condensation of cyclohexanone **1a** and aniline **4a** to form imine **C**, which underwent an electrophilic sulfurative cyclization into tetrahydrophenothiazine **E** via enamine **D** (Scheme 6). Enamine **F** issued from imine **D** could experience another electrophilic sulfurative with disulfide **4a** to generate *cis*-**G**. Although the isomer *trans*-**G** could be initially formed, it could undergo an acid-catalyzed isomerization into *cis*-**G** which is thermodynamically more stable. Final acid-catalyzed cyclization of *cis*-**G** would provide **3aa**. It should be noted that attack from either upper or lower side would result in the products with the same relative configuration.



Scheme 6. Proposed reaction pathway for cyclohexanone

In the cases of acyclic ketones or large ring such as cyclododecanone, the initial steps of formation of 1:1 adduct proceeded in the same manner to give *Z*-enamine **F'** and its *E*-isomer **F''** (Scheme 7).



Scheme 7. Proposed reaction pathway for diethyl ketone

While the *E*-configuration of the double bond of enamine **F** is determined by the ring constraint for six-membered ring, in the present cases, *Z*-enamine **F'** is more stable than its *E* isomer **F''**. Subsequent oxidative sulfuration of **F'** with **4a** via lower face attack would lead to **G'** which finally cyclized to spiro compounds **3am** and **3am'**. It should be noted that while both *S*-substituted chiral carbons are configurationally relatively stable, the configuration of *gem* *N,N*-disubstituted carbon is much more flexible. **3am** and **3am'** are thus interconvertible.

In conclusion, we have explored an umpolung reactivity of 2-aminothiophenols in the  $\alpha,\alpha'$ -functionalization of ketones. A wide range of acyclic and alicyclic ketones could be used as carbonyl substrates, leading to the corresponding spirobis(1,4-benzothiazines) in moderate to good yields and excellent stereoselectivity in most cases. More strikingly, the reaction required only TFA as an acid catalyst and DMSO as oxidant. The stereochemical outcome was found to be strongly controlled by ring constraint. The results presented here confirm once again the fact that complex structures could be achieved from simple starting materials under simple reaction conditions. Further experiments on the mechanism as well as synthetic application are currently ongoing in our laboratory.

## Experimental Section

A mixture of 2-aminothiophenol **1** (2 mmol), ketone **2** (1 mmol), TFA (0.1 mmol, 10 mg) in DMSO (4 mmol, 0.3 mL) was stirred in a 7-mL tube closed with a rubber septum equipped with a deflated rubber balloon at 70 °C for 16 h. After being cooled to room temperature, the crude reaction mixture was purified as indicated for each compound, by trituration with methanol or column chromatography on silica gel column (eluent heptane:EtOAc 99:1 to 95:5). For experimental details, full characterization, and copies of NMR spectra of all compounds, see Supporting Information.

CCDC 2005793-2005801 contain the supplementary crystallographic data for **3ai**, **3am**, **3ao**, **3aa**, **3ae**, **3ac**, **3ad**, **3ah**, **3aj** respectively in this paper. These data can be

obtained free of charge from The Cambridge Crystallographic Data Centre via [www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif)

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