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The involvement of the trisulfur radical anion in electron-catalyzed sulfur insertion reactions: facile synthesis of benzothiazine derivatives under transition metal-free conditions[†]

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An efficient and practical synthesis of benzothiazine by K_2S initiated sulfur insertion reaction with enaminones *via* electron catalysis is developed. This protocol provides a new, environment-friendly and simple strategy to construct benzothiazine derivatives *via* formation of two C–S bonds under transition metal-free, additive-free and oxidant-free conditions. K_2S not only provides the sulfur insertion source, but also ignites the reaction through the formation of a trisulfur radical anion and electrons in DMF.

Organosulfur heterocycles have been widely used as functional materials, pharmaceuticals, and synthetic intermediates. 1,4-Benzothiazine derivatives are present in natural products, biologically relevant compounds, and other functional molecules (Fig. 1).¹ During the past decade, a number of new synthetic protocols for 1,4-benzothiazine construction based on transition metal-catalyzed reactions have been well developed.² The

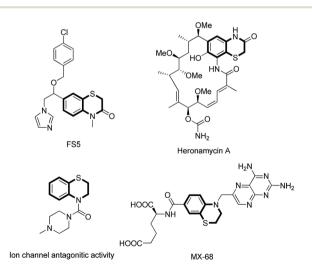


Fig. 1 Representative bioactive 1,4-benzothiazine derivatives.

[†] Electronic supplementary information (ESI) available. CCDC 1043637. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c6sc00240d development of new methods to construct 1,4-benzothiazine derivatives *via* C–S bonds formation under transition metal-free conditions is highly desirable.

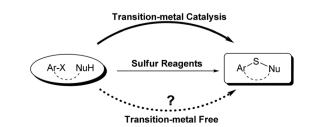
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Sulfur-centered radicals such as thiyl radicals and sulfonyl radicals (RSO₂[•]) have gained much interest for their special activities and applications in organic synthesis.³ However, other sulfur-centered radicals such as pentafluorosulfanyl radicals (F₅S[•]),^{4a} thiocyanato (NCS[•]),^{4b} and trisulfur radical anion (S₃^{•-})^{4c} gained less attention for their few applications in organic reactions.⁴ S₃^{•-} can be easily formed by the reaction of elemental sulfur with KOH in DMF at room temperature.⁵ Although S₃^{•-} species has been known for more than 40 years,⁵ applications for the synthesis of organosulfur compounds have been very limited.⁶ The development of new reactions involving S₃^{•-} and its further applications are still great challenges.

Sulfur reagents such as K_2S have been widely used in transition-metal catalyzed sulfur insertion reactions.⁷ However, there are no reports utilizing K_2S to initiate aryl radicals or radical anions from aryl halides under transition-metal free conditions (Scheme 1). Herein, we report a K_2S initiated sulfur insertion reaction with enaminones to construct benzothiazine derivatives *via* formation of two C–S bonds and C–X bond cleavage under transition metal-free conditions. As such, the



Scheme 1 Approaches for aryl sulfide.

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present reaction enables the synthesis of the benzothiazine derivatives under mild conditions and also attracts more attention for trisulfur radical anion $(S_3^{\cdot-})$ involved reactions under transition metal-free conditions.

Initially, the model reaction of 3-((2-iodophenyl)amino)-5,5dimethylcyclohex-2-enone **1a** and K₂S **2a** was performed in DMF at 110 °C for 12 h catalyzed by 10 mol% CuI in the presence of 20 mol% of I₂ under Ar atmosphere. The [5 + 1] cyclization product 4*H*-benzo[*b*][1,4]thiazine derivative **3a** was obtained in 65% liquid chromatography yield (LC-yield). The structure of **3a** was confirmed by NMR, IR, HRMS and X-ray analysis (Fig. 2).

We further screened the reaction conditions and found that the reaction also proceeded even without the copper salt and iodine (for details see ESI[†]). Then different solvents such as CH₃CN, 1,4-dioxene, 1,2-dichloroethane (DCE), toluene, tetrahydrofuran (THF), dimethyl sulfoxide (DMSO), *N*,*N*-dimethylformamide (DMF) and H₂O were tested for the reaction of **1a** and **2a** at 130 °C for 12 h under Ar atmosphere. As shown in Fig. 3, CH₃CN, 1,4-dioxene could give moderate yields of **3a**. Trace product **3a** could be detected when the reaction was carried out in DCE, toluene, THF and H₂O, respectively. Gratifyingly, the LC-yield of **3a** was dramatically increased to 75% by using DMSO as solvent. It should be noted that the reaction proceeded smoothly to give **3a** in 90% LC-yield when DMF was used.

Then other sulfur reagents such as cyclo-S₈, Na₂S·9H₂O, NaHS·H₂O, Na₂S₂O₃ were applied in this reaction under transition metal-free conditions (Table 1). The reaction of **1a** with Na₂S·9H₂O occurred smoothly to give **3a** in 80% LC-yield. NaHS·H₂O also showed a moderate activation with **1a** in this reaction to give **3a** 60% LC-yield. **3a** could also be obtained in 27% LC-yield when the sulfur was used. Only trace amount of **3a** was detected when **1a** reacted with Na₂S₂O₃ under the identical conditions.

To explore the potential applications of this method, a variety of enaminones **1** were examined (Table 2). Electrondonating substituents on the phenyl ring of enaminone such as –Me, –OMe, promoted the cross-coupling product **3b** and **3c** in excellent yield (95, 88%). The substitution pattern of the chlorine group made some difference to the reaction outcome (**3d**, **3e** and **3f**). The reaction of 3-(4-fluorophenylamino)-5,5-dimethylcyclohex-2-enone **1g** with **2a** also led to the desired product **3g** in 85% yield. Electron-withdrawing groups, such as NO₂, CF₃, also worked well and the desired products (**3h**, **3i**) were isolated in excellent yields, too. The reactions of other substituted enaminones **1i–l** with **2a** furnished the products **3i–l**

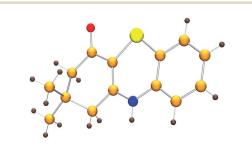


Fig. 2 Crystal structure of 3a

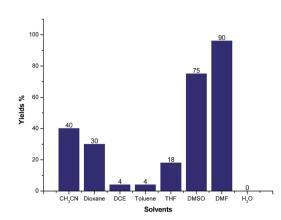
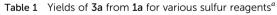
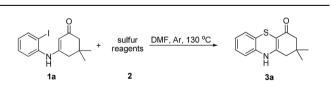


Fig. 3 The effect of different solvents. Reaction conditions: 1a (0.5 mmol), 2a (0.6 mmol), solvent (3 mL) at 130 $^{\circ}$ C, 12 h under Ar atmosphere. The yields were determined by LC analysis using biphenyl as the internal standard.

in moderate to excellent yields (47–96%). Unfortunately, when the unstable enaminone (E)-4-(phenylamino)pent-3-en-2-one **1n** was applied to the reaction, trace product **3n** could be detected.

Subsequently, enaminones 3-((2-chlorophenyl)amino)-6,6dimethylcyclohex-2-enone 1a-Cl and 3-((2-bromophenyl)amino)-6,6-dimethylcyclohex-2-enone 1a-Br instead of 1a-I were applied to reaction with 2a. The results indicated that chlorofunctionalized enaminone 1a-Cl showed poor reactivity but bromo-functionalized enaminone 1a-Br showed competitive reactivity compared to iodo-functionalized enaminone 1a-I and resulted in 3a in 94% yield (Scheme 2). Some other bromofunctionalized enaminones reacted with 2a also has been investigated (Table 3). The reactions of 3-((2,5-dibromophenyl)amino)-5,5-dimethylcyclohex-2-enone and 3-((2,6-dibromophenyl)amino)-5,5-dimethylcyclohex-2-enone with K2S were explored, and the desired products 30 and 3p were observed in 80% and 68% yields, respectively, leaving one bromide and another bromide substituents untouched. However, the reaction of 5,5-dimethyl-3-((2,4,6-tribromophenyl)amino)cyclohex-2-enone failed to isolate the corresponding product 3q. The





Reagent	Yield (%)
K ₂ S	80
Cyclo-S ₈	27
$Na_2S \cdot 9H_2O$	80
NaHS·H ₂ O	60
Na ₂ S ₂ O ₃	Trace

 a Reaction conditions: 1a (0.5 mmol), 2 (0.6 mmol), DMF (3 mL) at 130 $^\circ C$, 12 h under Ar atmosphere.

 Table 2
 Synthesis of 4H-benzo[b][1,4]thiazine derivatives^a

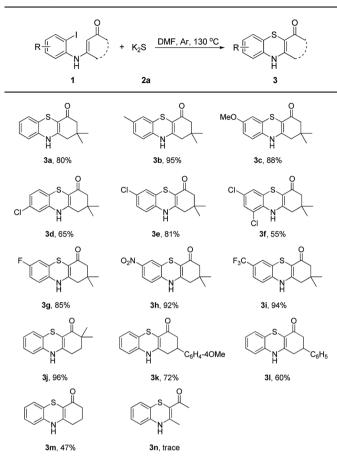
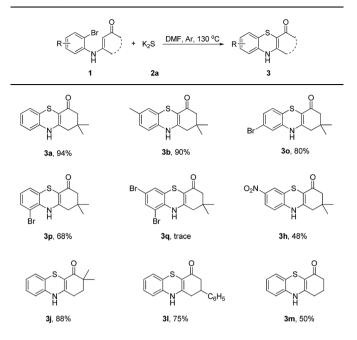


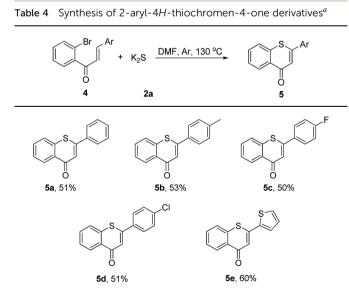
Table 3 Synthesis of 4H-benzo[b][1,4]thiazine derivatives^a



 a Reaction conditions: 1 (0.5 mmol), 2a (0.6 mmol), DMF (3 mL) at 130 $^\circ C$, 12 h under Ar atmosphere.

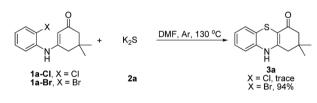
group **4e** was also found to be appropriate for this reaction, and the corresponding product **5e** was obtained in 60% yield.

To explore the plausible mechanism of this reaction, we first analyzed K_2S using inductively coupled plasma atomic absorption spectroscopy (ICP-AAS). Indeed, 2–10 ppm of Cu, Pd, Fe species were detected in K_2S although its purity is >99.99%. It was found that adding 1000 times amounts of these metal salts



 a Reaction conditions: 4 (0.5 mmol), 2a (0.6 mmol), DMF (3 mL) at 130 $^\circ \rm C$, 12 h under Ar atmosphere.

 a Reaction conditions: 1 (0.5 mmol), 2a (0.6 mmol), DMF (3 mL) at 130 $^\circ \rm C$, 12 h under Ar atmosphere.



Scheme 2 The reaction with 2a

3-(2-iodo-4-nitrophenylamino)-5,5-dimethylcyclohex-2-enone **1h-Br** promoted the cross-coupling product **3h** in 48% yield. Other substituted enaminones (**1j-Br** to **1m-Br**) reacted with **2a** also furnished the desired products **3j-m** in moderate yields (50% to 88%).

Then, an attempt was made to achieve the efficient synthesis of 2-phenyl-4*H*-thiochromen-4-one derivatives with 2'-bromochalcones **4** as the starting materials (Table 4). The reaction of 2'-bromochalcone **4a** progressed well and gave the corresponding product **5a** in 51% yield. The 2'-bromochalcones with methyl, chloro and fluoro substituents, which could be useful for further derivatization, were found to be suitable for this reaction (**5b–d**). Besides aryl groups, substrates with thienyl

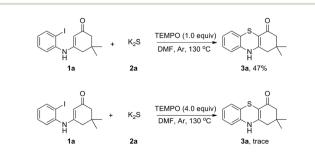
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to the reaction system did not obviously enhance the reaction rate, which indicated that this reaction was not transition-metal catalyzed and the radical addition pathway was an apparent consideration to the mechanism. Therefore, radical-trapping experiments were performed as shown in Scheme 3. When 1.0 equiv. of TEMPO was added to the reaction the yield of **3a** was reduced to 47%. As the amount of TEMPO was increased to 4.0 equiv., the reaction was almost fully suppressed. This observation indicated that a radical pathway might be involved in the reaction.

To gain some insight into the interaction between K_2S and DMF or other solvents, an electron paramagnetic resonance (EPR) experiment was carried out (Fig. 4). A strong single EPR signal was observed in DMF solution of K_2S at room temperature (deep blue line). When the solvent was changed to DMSO, the EPR signal was significantly attenuated (purple line). As for the other solvents, almost no EPR signal was observed. Lelieur found similar EPR signals in liquid ammonia solution of sulfur, and identified it as the trisulfur radical anion (S_3^{-}) .⁸ Gratifyingly, our EPR parameter (g = 2.02) is very similar with the reported one detected by the DMF solution of $Na_2S \cdot 9H_2O$ and elemental sulfur at room temperature.^{6b} So we suspected that a free radical S_3^{-} might be generated from the solution of K_2S in DMF.

We further confirmed the presence of trisulfur radical anion $(S_3^{\cdot-})$ by the UV-visible spectra and Raman spectra studies (Fig. 5). From the UV-visible spectra, we could detect a characteristic absorption peak at about 550–700 nm wavelength in the DMF solutions of K₂S or Na₂S·9H₂O and elemental sulfur. In addition, the Raman spectra results also gave us some strong evidence of the trisulfur radical anion $(S_3^{\cdot-})$.⁹ The 531 cm⁻¹ peak (ν_1) corresponds to the symmetric S–S stretching. The resonance phenomenon is induced *via* the absorption of S₃^{•-} by the laser radiation, which results in the high-order overtones $(2\nu_1 \approx 1068 \text{ cm}^{-1}, 3\nu_1 \approx 1597 \text{ cm}^{-1}, 4\nu_1 \approx 2124 \text{ cm}^{-1})$ for the enhancement effects.¹⁰

We also found that the reaction takes place to give similar results under an argon atmosphere or in air. This observation indicated that DMF might be the oxidant for this reaction instead of oxygen or other oxidants. In order to prove this proposal, we tried the reaction of **1a** with **2a** in d⁷-DMF (Fig. 6). From the crude ¹H NMR spectrum of this reaction, it was found that d⁷-DMF was reduced to give G' (for further details see ESI†). This result indicates that S_3 .⁻ was formed *via* the oxidation of S^{2-} by DMF, which is different with the one in Lei's work (S_3 .⁻



Scheme 3 Radical-trapping experiments.

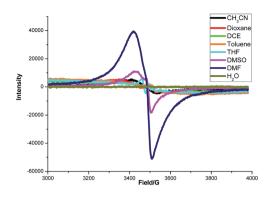


Fig. 4 EPR spectra of solutions of K_2S (0.6 mmol) in various solvents (3 mL) at 298 K.

was obtained by the disproportionation reaction of sulfur with Na₂S·9H₂O).^{6b}

Based on the reported literatures and above results, a S_{RN1} type electron catalysis mechanism¹¹ is proposed in Scheme 4. DMF activates the electron-donating agent K_2S to give S_3 .⁻ radical anion, radical anion **A** and electrons. An aryl halide radical anion **B** is generated from enaminone **1a** by single electron transfer (SET).¹² The elimination of I⁻ leads to an aryl radical **C** (the protonated species could be detected by LC-MS¹³), the radical **C** reacts with S_3 .⁻ to form the intermediate **D**. The homolysis of intermediate **D** gives S_2 .⁻ and a thiyl radical **E**, which subsequently undergoes intramolecular radical addition to afford the radical **F**. We propose that there are two possible pathways for the oxidation of S_2 .⁻ to give S_3 .⁻. One possibility is

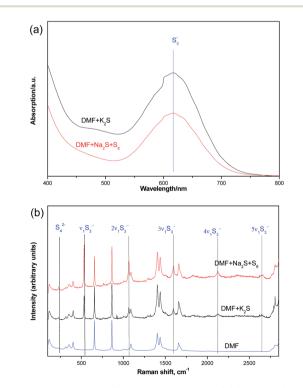


Fig. 5 UV-visible spectra (a) and Raman spectra (b) (632.8 nm) studies of interaction between K_2S and DMF.

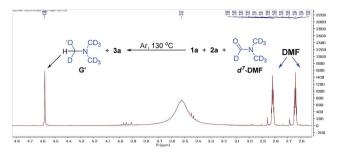
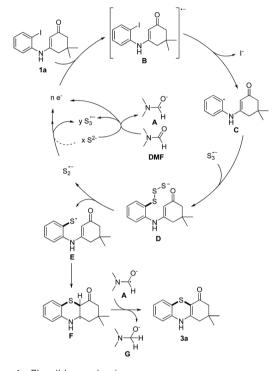


Fig. 6 ¹H NMR spectrum of the reaction of **1a** with **2a** in d^7 -DMF.



Scheme 4 Plausible mechanism.

that S_2 ^{•-} dimerizes to afford the dianion S_4^{2-} , which then disproportionates to give blue S_3 ^{•-}.¹⁴ The other possibility is that S_2 ^{•-} reacts with S^{2-} to afford S_3 ^{•-} and the electrons. Following the electron transfer of **F** with **A**, anion **G** and **3a** are formed.

In summary, we have developed a K_2S initiated and electroncatalyzed sulfur insertion reaction with enaminones to construct the [5 + 1] cyclization product 4H-benzo[b][1,4]thiazine and 2-aryl-4H-thiochromen-4-one derivatives. This protocol provides a new, environment-friendly and simple strategy to the synthesis of the 4H-benzo[b][1,4]thiazine and 2-aryl-4H-thiochromen-4-one derivatives under transition metal-free, additive-free and oxidant-free conditions. The presence of the trisulfur radical anion was proven by EPR spectroscopy, and reasonable mechanisms have been proposed. Further investigations of the trisulfur radical anion triggered electron-catalyzed reactions under transition metal-free conditions are currently under study in our laboratory.

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$$4S_2^{2} \longrightarrow 2S_4^{2-} \xrightarrow{2S_4^{-}} 2S_4^{-} \xrightarrow{S_8^{2-}} 2S_6^{2-} \longrightarrow 4S_3^{-}$$