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Fe-catalysed oxidative C–H functionalization/C–S bond formation†

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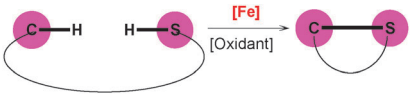
Iron was used as the catalyst for the direct C–H functionalization/C–S bond formation under mild conditions. Various substrates could afford benzothiazoles in moderate to excellent yields. Preliminary mechanistic studies revealed that pyridine played a crucial role for the high yields and selectivities.

Direct C–H bond functionalization towards C–C and C–heteroatom (N, O and S *etc.*) bond formation promoted by transition metals has attracted extensive attention in the past decades.[1] However, most efforts were focused on noble metal catalysts, such as Ru,[2] Rh,[3] Pd,[4] *etc*. Due to the wide existence and low toxicity of iron compounds, more and more attention have been paid to the iron-catalysed reaction for organic synthesis.[5] Remarkable results have been reported on iron promoted "traditional" cross couplings between R^1X and R^2M.[6] Recently, Fe-catalysed direct C–H arylation of unactivated arenes with aryl halides has also been demonstrated simultaneously by Charette *et al.* and our group.[7] To the willing of greener and more atom-economic C–C and C–heteroatom bond formations, the Fe-catalysed direct oxidative cross-coupling between two C–H bonds or C–H and X–H bonds would be an ideal approach to realize this goal. However, few examples have been reported regarding Fe-catalysed direct oxidative C–H functionalizations.[8]

Benzothiazoles are a very important class of heterocycles in the pharmaceutical area.[9] Generally, oxidative cyclization is an efficient approach for the synthesis of thiobenzanilides by using various oxidants,[10] such as quinone,[10a] bromine,[10b] and hypervalent iodine,[10d] or metal salt.[10c,e] Meanwhile, Pd-catalyzed C–S bond formation from thioamides *via* C–H functionalization has also been realized.[11] Alternatively, cyclization of 2-halophenylthiobenzamides using Pd or Cu as a catalyst provided another approach to benzothiazoles.[12] However, the pre-functionalization of the starting materials in this protocol limited its application. It is no doubt that the direct oxidative intramolecular C–S bonds formation *via* C–H functionalization would be an attractive approach to synthesize benzothiazole. Herein, we report our progress on iron-salts-catalysed intramolecular C(Ar)–H/X–H activation/C–S bond formation under mild conditions (Scheme 1).



Scheme 1 Intramolecular C–S bond formation *via* C–H and S–H activation.

Aiming at highly efficient iron-catalysed oxidative coupling, we chose 4-chloro-*N*-phenylbenzothioamide **1a** as the model reaction for initial investigations. Condition optimization (see details in Tables S1, S2 and S3 of ESI†) showed that using $Na_2S_2O_8$ as the oxidant in DMSO with 10% $FeCl_3$ as the catalyst at 80 °C produced 68% of **2a** in 4 h (Table 1, entry 2). In the absence of Fe catalyst, only 16% of **2a** was obtained (Table 1, entry 1). Additives such as HOAc or Na_2CO_3 showed no obvious effect on improving the reaction selectivity. The breakthrough was achieved when 2 eq. of pyridine was employed as the additive. Up to 87% of the desired product **2a** was obtained with higher selectivity (**2a** : **3a** was 87 : 10) (Table 1, entry 5). Further optimization of catalyst precursors in the presence of pyridine gave no obvious improvement (Table 1, entry 6–8). Even using super pure $FeCl_3$ (99.99%) as the catalyst, the result showed no significant difference from commercial $FeCl_3$ (98%) (Table 1, entry 9). By elongating the reaction time, the reaction could also undergo smoothly at 40 °C (Table 1, entry 10) with the slightly decreased selectivity of **2a**.

Substrate scope of this transformation was further investigated under the optimal conditions (Table 2). The influence of the substituent on the aryl group of the thiobenzoyl part (Ar^2, Table 2, substrate **1b–1f**) was not the crucial factor for this transformation. Either with the electronic or steric property good to excellent yields (72–95%) can be achieved. Halo substituents (Br, I) can be well tolerated under the reaction conditions (Table 2, substrates **1e** and **1f**). Then, the effect of the substituents on Ar^1 was examined (Table 2, substrate **1g–1m**). When the substituent group was the electron-donating group, either *ortho* or *para*-position did not influence the reaction. Excellent yields (84–93%) were obtained (Table 2, substrates **1g**, **1h** and **1l**). The reaction of *N*-naphthalene substituted benzothioamide gave excellent yields (97%) of the cyclization product (Table 2, substrate **1m**). However, electron-withdrawing groups decreased the yields dramatically, only moderate yield was obtained when the NO_2 substituent was introduced

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† Electronic supplementary information (ESI) available: General procedures, spectral data and other supplementary information. See DOI: 10.1039/c1cc16184a

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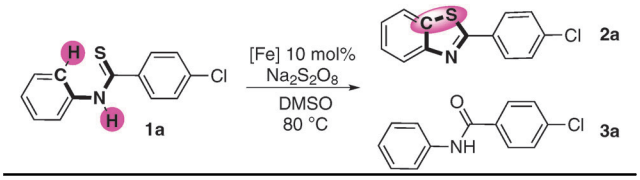
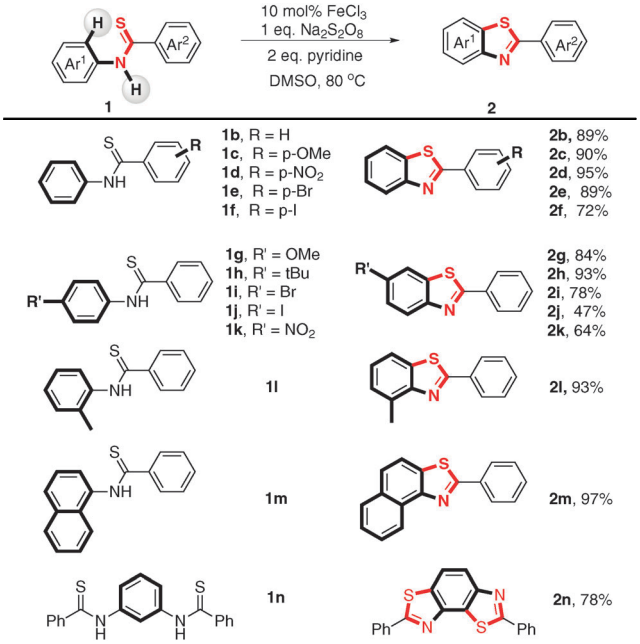
Table 1 Reaction parameters of **1a**[a]



Entry	Cat.	Additive	Conversion **1a** [%]	Yield [%] **2a**	**3a**
1	No	—	100	16	81
2	$FeCl_3$	—	100	68	28
3	$FeCl_3$	HOAc (2 eq)	100	65	30
4	$FeCl_3$	Na_2CO_3 (2 eq)	99	64	34
5	**$FeCl_3$**	**Pyridine (2 eq)**	**100**	**87**	**10**
6	$FeCl_2$	Pyridine (2 eq)	100	82	15
7	$FeBr_2$	Pyridine (2 eq)	100	46	33
8	$Fe(acac)_3$	Pyridine (2 eq)	90	30	32
9[b]	$FeCl_3$	Pyridine (2 eq)	100	85	15
10[c]	$FeCl_3$	Pyridine (2 eq)	100	83	13

[a] Reaction conditions: **1a** (0.5 mmol), $Na_2S_2O_8$ (0.5 mmol) and catalyst (0.05 mmol) in 2 mL of DMSO at 80 °C for 4 h. The purity of $FeCl_3$ is 98% unless otherwise indicated. Yields were determined by HPLC with an internal standard. [b] 99.99% $FeCl_3$. [c] 40 °C for 10 h.

Table 2 Synthesis of substituted 2-arylbenzothiazoles[a]

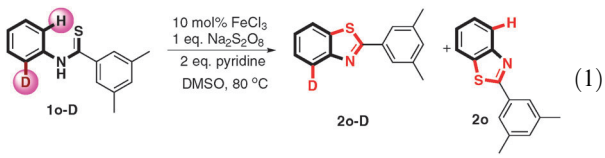


[a] Reaction conditions: **1** (0.5 mmol), $Na_2S_2O_8$ (0.5 mmol), pyridine (1 mmol) and $FeCl_3$ (0.05 mmol) in 2 mL of DMSO at 80 °C for 4 h. All yields are isolated yields.

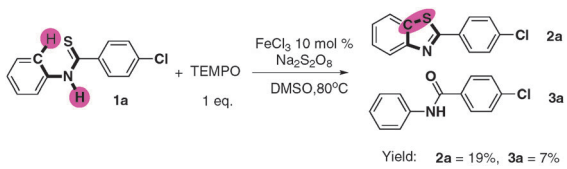
(Table 2, substrate **1k**). C–Br and C–I could also be well tolerated (Table 2, substrates **1i** and **1j**). Interestingly, the reaction of **1n** proceeded smoothly to give **2n** with high selectivity.

Furthermore, *N*-aryl alkylthioamides and thioureas were also employed as substrates (Table 3). *N*-Aryl *tert*-pentanethioamide bearing both electron-donating and withdrawing groups could undergo the C–H activation/C–S bond formation smoothly in moderate to excellent yields (71–92%) (Table 3, product **5a–5c**). However, when *N*-phenyl alkylthioamide bore a less hindered substituted group, only low yields were obtained. For instance, only 21% desired product **5d** and even no **5e** were obtained. When thioureas were employed as substrates, the reaction of 1,1-dibutyl-3-phenylthiourea (**4f**) and 1,1-diethyl-3-phenylthiourea (**4g**) gave corresponding products in good (**5f**, 70%) and moderate (**5g**, 57%) yields. When **R** was NHPh and NHBn, 50% of **5h** and 22% of **5i** were obtained, respectively.

To gain preliminary mechanistic information about this transformation, isotopic effect experiments have been carried out. The reaction of deuterium-**1o** (**1o-D**) under the standard condition provided a mixture of the products deuterium-**2o** (**2o-D**) and **2o** in 93% combined yields, in which the ratio of **2o-D** : **2o** was 1.3 (eqn (1)). The KIE values revealed that the C–H bond cleavage is not the rate-determining-step. When running the reaction in the presence of a radical scavenger (TEMPO) at the same condition, only 19% product was obtained (as shown in eqn (2)) indicating that the reaction might proceed *via* a radical process.



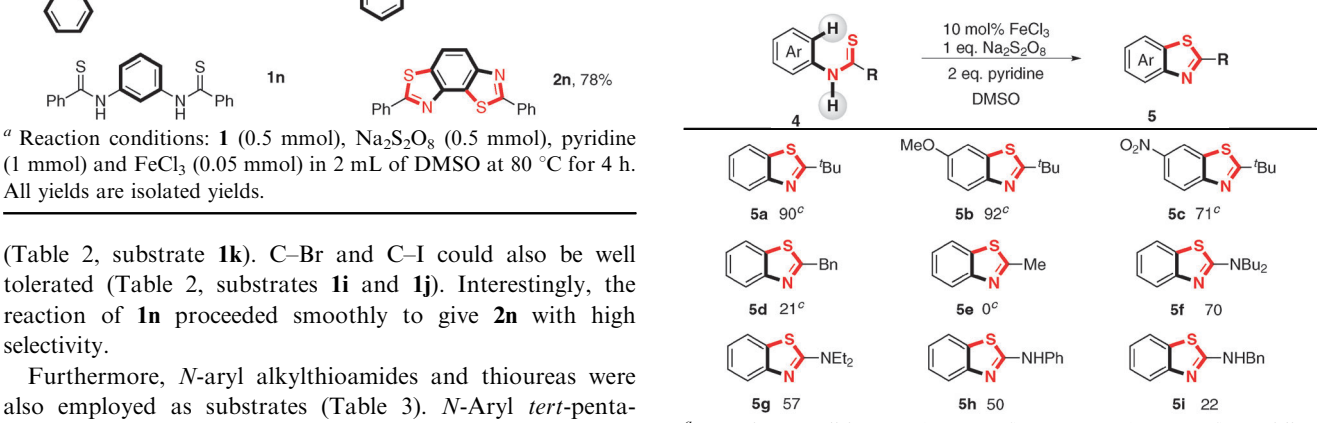
(1)



(2)

Furthermore, a series of stoichiometric reactions were carried out monitored by *in situ* IR. The profiles of ConcIRT *vs.* time shown in Fig. 1 represent the relative concentrations *vs.* time for individual species. Clearly, no reaction occurred when $Na_2S_2O_8$, pyridine and $FeCl_3$ were sequentially added. However, as soon as **1a** was added, we could see the consumption of $Na_2S_2O_8$, **1a** and the formation of **2a** was in accordance

Table 3 Synthesis of 2-substituted benzothiazoles[a]



[a] Reaction conditions: **4** (0.5 mmol), $Na_2S_2O_8$ (0.5 mmol), pyridine (1 mmol) and $FeCl_3$ (0.05 mmol) in 2 mL of DMSO at 80 °C for 4 h. All yields are isolated yields. [c] 40 °C for 10 h.

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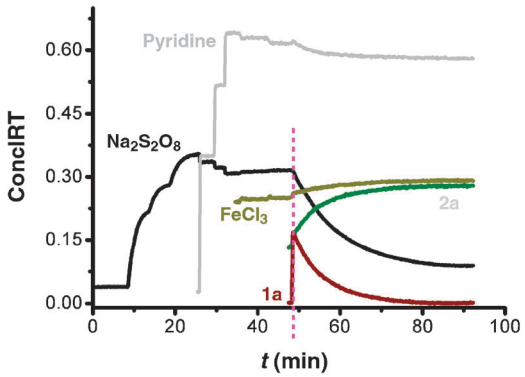

Fig. 1 The 2D-kinetic profiles of the stoichiometric reaction of $Na_2S_2O_8$ (0.2 M), pyridine (4 M), $FeCl_3$ (0.02 M) and **1a** (0.2 M) added to 5 mL DMSO at 40 °C one by one; the reaction was monitored by *in situ* IR.

obviously. Other stoichiometric reactions varying the addition sequences of these species (see Fig. S8 and S9 in ESI†) also indicated that the C–H activation and C–S bond formation required the co-existence of oxidant, $FeCl_3$ and the substrates.

Further kinetic investigation showed that the reaction was first order in [**1a**], and zero order in the oxidant [$Na_2S_2O_8$] (see Table S4 and Fig. S10–S17 in ESI†).

Finally, in order to clarify the role of $FeCl_3$ and pyridine in the reaction, comparison experiments were carried out and monitored by *in situ* IR. We found that pyridine is crucial for the high selectivity of C–H activation/C–S bond formation (for detailed information see Fig. S18–S20 in ESI†).

According to all above results, we proposed a mechanism shown in Scheme 2. The substrate *N*-phenyl benzothioamide was oxidized by Fe(III) through path A and lost an electron and H^+ to form the thioyl radical intermediate, in the meantime Fe(III) was reduced to Fe(II). Fe(II) species was re-oxidized by $Na_2S_2O_8$ to regenerate Fe(III). Then, the cyclization of the thioyl radical intermediate followed by oxidation in the presence of $Na_2S_2O_8$ gave the product 2-phenyl benzothiazole.

In conclusion, we have developed an efficient iron-catalysed C–H functionalization/C–S bond formation under mild conditions. This transformation could be conveniently carried out affording various benzothiazoles in moderate to excellent yields. Preliminary mechanistic studies revealed that the reaction required the co-existence of substrate, oxidant, $FeCl_3$ and pyridine. Kinetic studies indicated that pyridine was crucial for the high selectivity of this transformation and the reaction was first order in the substrate and zero-order in oxidant $Na_2S_2O_8$.

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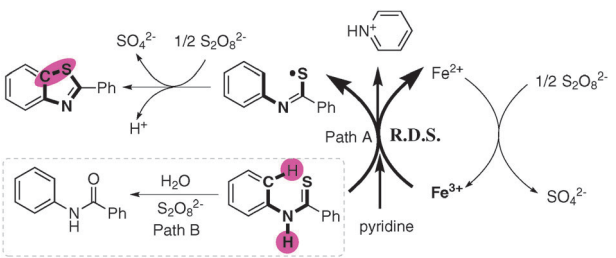

Scheme 2 Proposed mechanism.

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