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# Utilization of 2-nitrophenols in annulations with aryl isothiocyanates towards the synthesis of 2-aminobenzoxazoles†

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A method for the annulation of 2-nitrophenols with aryl isothiocyanates is reported. The reactions proceeded in the presence of an iron(III) acetylacetonate catalyst, elemental sulfur, NaOH as a base, and DMSO as a solvent. Derivatives of 2-aminobenzoxazoles bearing nitro, cyano, acetyl, sulfone, secondary amine, and pyrrolyl groups were successfully isolated.

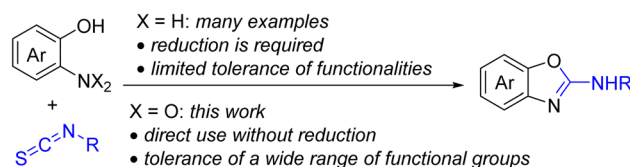
## Introduction

The replacement of 2-aminophenols by 2-nitrophenols in annulations has attracted prominent attention over the last decade.<sup>1</sup> Since anilines are typically obtained from the reduction of their nitro upstreams, the direct utilization of 2-nitrophenols would arguably help avoid this extra step, thus increasing the atom efficiency. Yet precedent methods for the utilization of 2-nitrophenols have exorbitantly focused on furnishing carbon-based C2-substituted benzoxazoles.<sup>2</sup> As such, diversification by using 2-nitrophenols in annulations still requires more examples.

2-Aminophenols are excellent substrates to couple with aryl isothiocyanates, affording 2-aminobenzoxazoles (Scheme 1).<sup>3</sup> Given the importance of the aforesaid N,O-heterocycles in bio-related studies,<sup>4</sup> substantial studies have been devoted to extension of substrate scope.<sup>5</sup> Notably, 2-aminophenols attached with varied functionalities are neither commercially available nor viably prepared. Herein we would like to report a method for synthesis of 2-aminobenzoxazoles from annulation of 2-nitrophenols and aryl isothiocyanates. Tolerance of an array of functionalities on 2-nitrophenols including acetyl, methylsulfonyl, cyano, amines, and pyrrolyl groups was observed. Our method marks a rare example for using nitroarenes to replace the related anilines in synthesis of 2-aminobenzoxazoles (Scheme 1).

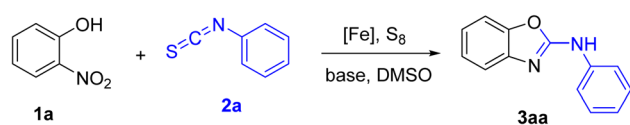
## Results and discussion

Encouraged by the previous reports,<sup>2d,f</sup> we started our investigation on the annulation of 2-nitrophenol **1a** and phenyl



**Scheme 1** Methods for annulation of 2-aminophenols/2-nitrophenols to yield 2-aminobenzoxazoles.

**Table 1** Optimization of reaction conditions<sup>a</sup>



Entry	[Fe]	Base	Yield of <b>3aa</b> (%)
1	Fe powder	DABCO	0
2	FeCl <sub>3</sub> ·6H <sub>2</sub> O	DABCO	28
3	FeCl <sub>3</sub>	DABCO	30
4	Fe(acac) <sub>3</sub>	DABCO	73
5 <sup>b</sup>	Fe(acac) <sub>3</sub>	DABCO	57
6 <sup>c</sup>	Fe(acac) <sub>3</sub>	DABCO	81
7 <sup>c,d</sup>	Fe(acac) <sub>3</sub>	DABCO	67
8 <sup>c</sup>	Fe(acac) <sub>3</sub>	DMAP	85
9 <sup>c</sup>	<b>Fe(acac)<sub>3</sub></b>	<b>NaOH</b>	<b>92</b>
10 <sup>c</sup>	Fe(acac) <sub>3</sub>	—	55
11 <sup>c,e</sup>	Fe(acac) <sub>3</sub>	NaOH	79

<sup>a</sup> **1a** (0.1 mmol), **2a** (0.2 mmol), [Fe] (0.02 mmol), elemental sulfur (0.2 mmol), base (0.2 mmol), DMSO (0.5 mL), 80 °C, 3 h. Yields are GC yields. <sup>b</sup> Fe(acac)<sub>3</sub> (0.01 mmol). <sup>c</sup> 100 °C. <sup>d</sup> Elemental sulfur (0.1 mmol). <sup>e</sup> DMF (0.5 mL) instead of DMSO.

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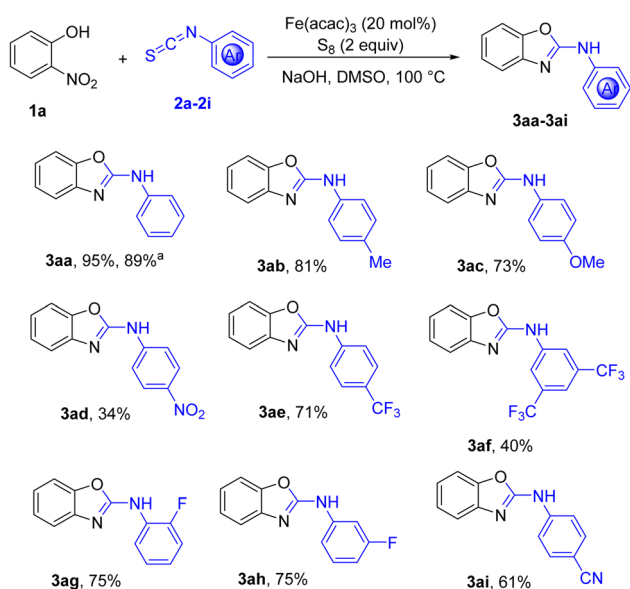
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isothiocyanate **2a** facilitated by Fe/S cluster. Effects of reaction conditions on the yield of the target product **3aa** were thoroughly studied,<sup>6</sup> and some of the notable results are shown in Table 1. While the use of iron powder did not furnish **3aa**, a 28% yield of **3aa** was obtained in the presence of catalytic amount of  $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$  (entry 2). A nearly identical yield was obtained

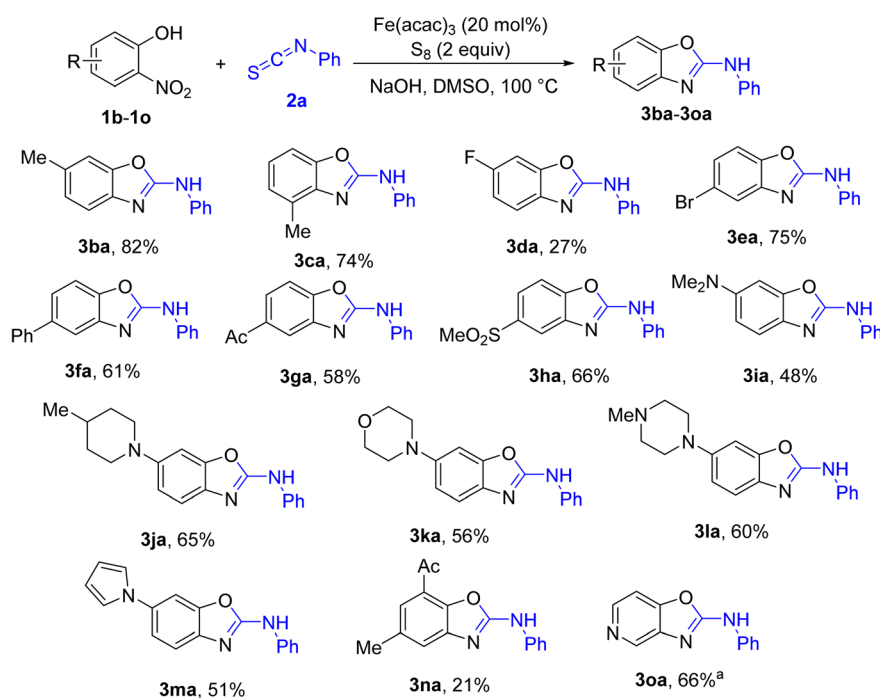
when anhydrous  $\text{FeCl}_3$  was used (entry 3). Among the tested iron salts,  $\text{Fe}(\text{acac})_3$  was the superior (entry 4).<sup>6</sup> Decreasing the amount of  $\text{Fe}(\text{acac})_3$  slowed down the annulation (entry 5). The reaction did not progress in the absence of  $\text{Fe}(\text{acac})_3$ . The yield of **3aa** was slightly improved if the temperature was boosted to  $100^\circ\text{C}$  (entry 6). The amount of elemental sulfur was pivotal to affording a reasonable yield of **3aa** (entry 7). The choice of base should also be considered. While the use of DMAP did not improve the yield of **3aa** (entry 8), a nearly quantitative yield of **3aa** was obtained in the presence of NaOH (entry 9). It should be noted that omitting base still afforded **3aa**, albeit in a moderate yield (entry 10). The reaction could be tolerated in DMF solvent (entry 11).



**Scheme 2** Scope of aryl isothiocyanates. Reaction conditions: 2-nitrophenol **1a** (0.1 mmol), **2a-2i** (0.2 mmol),  $\text{Fe}(\text{acac})_3$  (0.02 mmol), elemental sulfur (0.2 mmol), NaOH (0.2 mmol), DMSO (0.5 mL),  $100^\circ\text{C}$ , 3 h. Yields are isolated yields. <sup>a</sup>1 mmol scale.

Scope of aryl isothiocyanates was next studied. The results are shown in Scheme 2. In comparison with a related report from our group,<sup>5g</sup> significant differences regarding electronic properties of aryl isothiocyanates were observed. Low to moderate yields of the annulation products were obtained in case very electron-poor aryl isothiocyanates were attempted (**3ad**, **3af**). Such effect was not detected if 2-aminophenol was used to couple with aryl isothiocyanates.<sup>5g</sup> The reaction conditions were tolerant of cyano functionality (**3ai**).

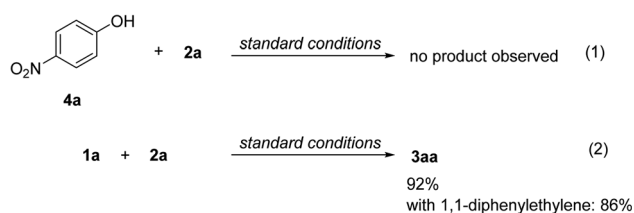
We then turned our attention to extending the scope of 2-nitrophenols, as this is the major improvement compared with previous methods.<sup>5</sup> The results are shown in Scheme 3. To our expectation, an array of 2-aminobenzoxazoles bearing useful functionalities has been successfully isolated. Steric effect on the nitrogen atom of 2-nitrophenol was somewhat minor (**3ca**). In contrast to the previous report,<sup>5f</sup> 5-fluoro-2-nitrophenol was not compatible with reaction conditions (**3da**). Meanwhile, 2-



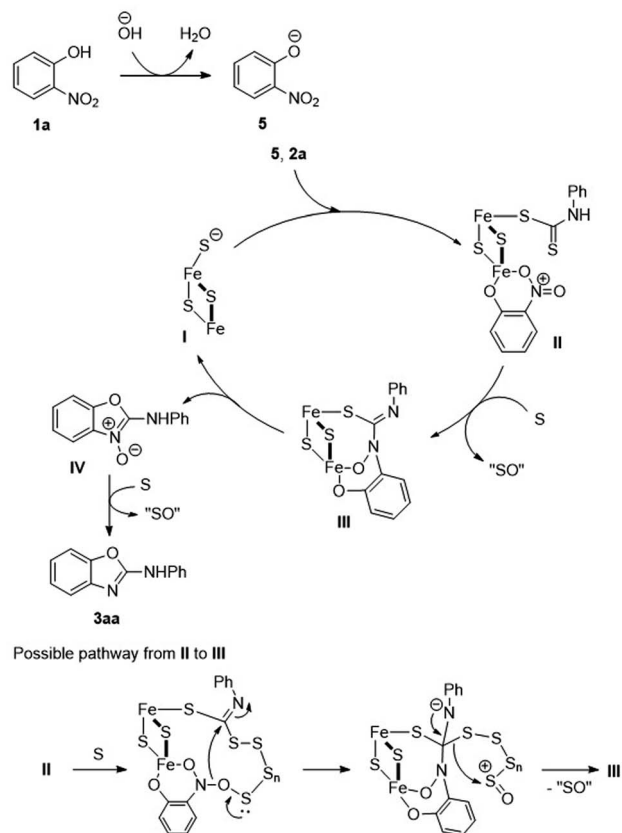
**Scheme 3** Scope of 2-nitrophenols. Reaction conditions: **1b-1o** (0.1 mmol), **2a** (0.2 mmol),  $\text{Fe}(\text{acac})_3$  (0.02 mmol), elemental sulfur (0.2 mmol), NaOH (0.2 mmol), DMSO (0.5 mL),  $100^\circ\text{C}$ , 3 h. Yields are isolated yields. Abbreviation: Ac = acetyl. <sup>a</sup>Purity: 90%.

nitrophenols bearing acetyl and methylsulfonyl substituents were competent substrates (**3ga**, **3ha**). As substitution of fluorine by amines was feasible,<sup>7</sup> 2-nitrophenols attached with secondary amines and pyrrole were prepared (**1i–1m**), then treated with the standard conditions. The ensuing annulations were somewhat successful (**3ia–3ma**). These molecules were hardly obtained from methods starting with 2-aminophenols.<sup>5</sup> 2-Aminobenzoxazole derived from 4-hydroxy-3-nitropyridine was obtained in moderate yield (**3oa**), somewhat indicating that heteroaryl-based 2-nitrophenols were also competent substrates. Attempt to use 2-nitroaniline to couple with phenyl isothiocyanate was not successful at this moment.

Some control experiments were then performed (Scheme 4). An attempt to couple 4-nitrophenol **4a** with **2a** was unsuccessful



**Scheme 4** Mechanistic considerations. Standard conditions: **1a** (0.1 mmol), **2a** (0.2 mmol), Fe(acac)<sub>3</sub> (0.02 mmol), elemental sulfur (0.2 mmol), NaOH (0.2 mmol), DMSO (0.5 mL), 100 °C, 3 h. In eqn (1), 4-nitrophenol (**4a**, 0.1 mmol) was used. In eqn (2), 1,1-diphenylethylene (0.1 mmol) was added. Yields are GC yields.



**Scheme 5** Possible mechanism.

(eqn (1)). The result implied the importance of *ortho* effect if somehow a Fe/S cluster is formed.<sup>2d,f</sup> The addition of a radical quencher such as 1,1-diphenylethylene did not inhibit the main annulation (eqn (2)), suggesting that a radical-based mechanism was unlikely. Based on these results, a possible mechanism is proposed (Scheme 5). The formation of the Fe/S cluster **I** would be crucial for the mechanism.<sup>2d,f</sup> Complexation of phenoxide **5** (obtained from deprotonation of **1a**), **2a**, and **I** would yield **II**, followed by elimination of oxygenated sulfur compounds to afford **III**.<sup>8</sup> Intramolecular addition followed by an extrusion of nitrene **IV** would regenerate the active cluster **I**.<sup>2d</sup> Reduction of **IV** in the presence of elemental sulfur would yield the target **3aa**.

## Conclusion

In conclusion, we have developed a method for annulation of 2-nitrophenols and aryl isothiocyanates to yield 2-aminobenzoxazoles. The successes relied on the generation of Fe/S cluster by using Fe(acac)<sub>3</sub> catalyst and elemental sulfur. Tolerance of a wide range of useful functionalities is presented. Our method would offer a unique, direct tactic to obtain complex 2-aminobenzoxazoles for relevant studies.

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

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