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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.

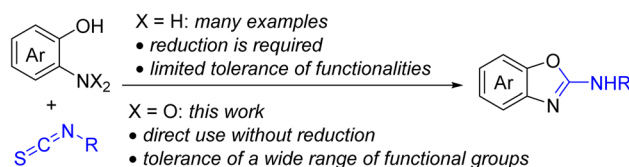
Introduction

The replacement of 2-aminophenols by 2-nitrophenols in annulations has attracted prominent attention over the last decade.¹ 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.² 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).³ Given the importance of the aforesaid N,O-heterocycles in bio-related studies,⁴ substantial studies have been devoted to extension of substrate scope.⁵ 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 nitro-arenes to replace the related anilines in synthesis of 2-aminobenzoxazoles (Scheme 1).

Results and discussion

Encouraged by the previous reports,^{2,df} 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^a

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

^a **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. ^b Fe(acac)₃ (0.01 mmol). ^c 100 °C. ^d Elemental sulfur (0.1 mmol). ^e DMF (0.5 mL) instead of DMSO.

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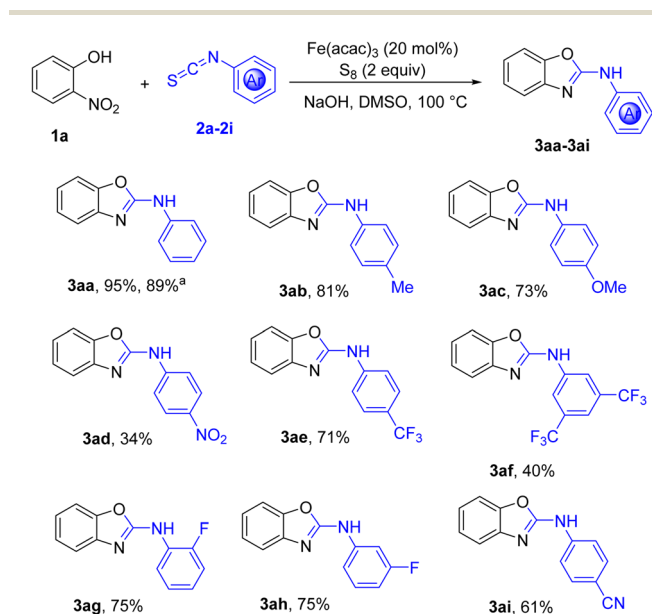


isothiocyanate **2a** facilitated by Fe/S cluster. Effects of reaction conditions on the yield of the target product **3aa** were thoroughly studied,⁶ and some of the notable results are shown in Table 1. While the use of iron powder did not furnish **3aa**, a 28% yield of **3aa** was obtained in the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

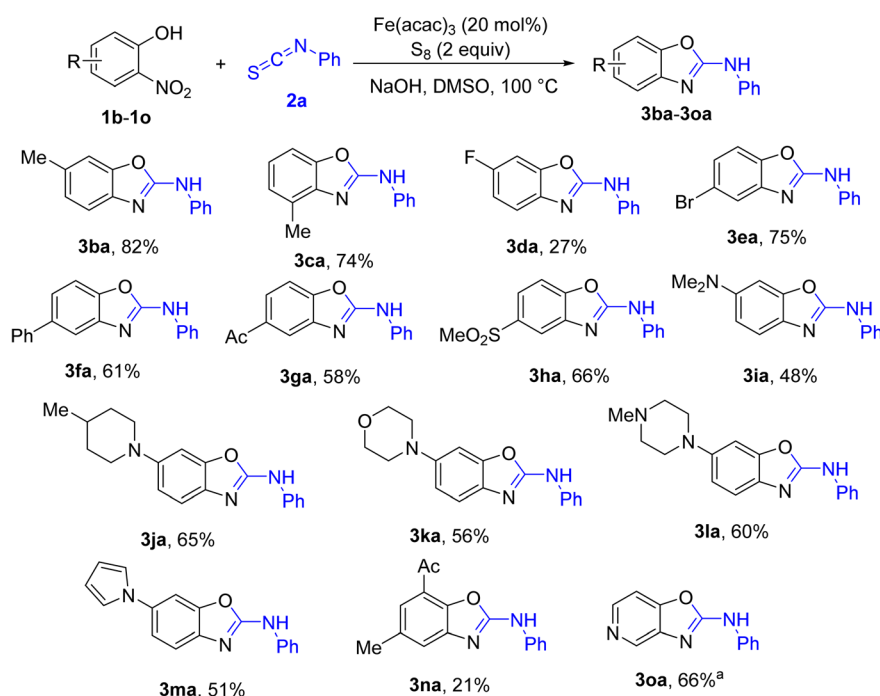
when anhydrous FeCl_3 was used (entry 3). Among the tested iron salts, $\text{Fe}(\text{acac})_3$ was the superior (entry 4).⁶ Decreasing the amount of $\text{Fe}(\text{acac})_3$ slowed down the annulation (entry 5). The reaction did not progress in the absence of $\text{Fe}(\text{acac})_3$. The yield of **3aa** was slightly improved if the temperature was boosted to 100 °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).

Scope of aryl isothiocyanates was next studied. The results are shown in Scheme 2. In comparison with a related report from our group,^{5g} 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.^{5g} 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.⁵ 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,^{3f} 5-fluoro-2-nitrophenol was not compatible with reaction conditions (**3da**). Meanwhile, 2-



Scheme 2 Scope of aryl isothiocyanates. Reaction conditions: **2a** (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 °C, 3 h. Yields are isolated yields. ^a1 mmol scale.

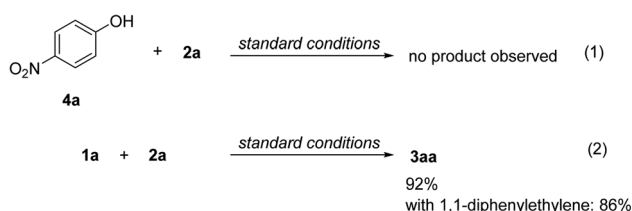


Scheme 3 Scope of 2-nitrophenols. Reaction conditions: **1b-1o** (0.1 mmol), **2a** (0.2 mmol), $\text{Fe}(\text{acac})_3$ (0.02 mmol), elemental sulfur (0.2 mmol), NaOH (0.2 mmol), DMSO (0.5 mL), 100 °C, 3 h. Yields are isolated yields. Abbreviation: Ac = acetyl. ^aPurity: 90%.

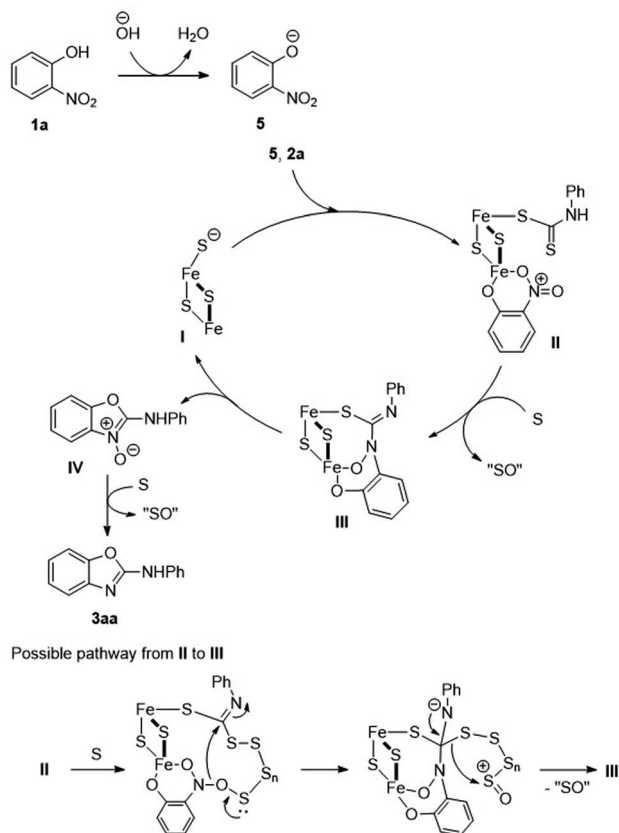


nitrophenols bearing acetyl and methylsulfonyl substituents were competent substrates (**3ga**, **3ha**). As substitution of fluorine by amines was feasible,⁷ 2-nitrophenols attached with secondary amines and pyrrole were prepared (**1i–1m**), then treated with the standard conditions. The ensuing annulations were somewhat successful (**3ia–3ma**). These molecules were hardly obtained from methods starting with 2-aminophenols.⁵ 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)₃ (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.^{2df} 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.^{2df} 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**.⁸ Intramolecular addition followed by an extrusion of nitrene **IV** would regenerate the active cluster **I**.^{2d} 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)₃ 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.

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