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Title: Sulfur-Promoted Aminative Aromatization of 1,2,3,4-Tetrahydrophenazines with Amines: Flexible Access to 1-Aminophenazines

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Sulfur-Promoted Aminative Aromatization of 1,2,3,4-Tetrahydrophenazines with Amines: Flexible Access to 1-Aminophenazines

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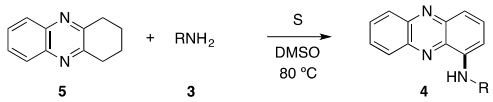
Abstract. Elemental sulfur was found to be an excellent reagent for promoting the aminative aromatization of 1,2,3,4-tetrahydrophenazines with amines to provide a wide range of functionalized 1-aminophenazines.

Keywords: elemental sulfur; C-H amination; aromatization; C-H functionalization; phenazine

The formation of C_{Arom}-N bonds occupies a significant place in chemistry for the synthesis of secondary and tertiary aromatic amines, which are important structural scaffolds in numerous functional molecules and biologically active compounds. Traditionally, these aromatic amines are conveniently synthesized via Pd- or Cu-catalyzed cross-couplings of amines and aryl halides.[1] These strategies require however the use of expensive catalysts/ligands, drastic conditions, and pre-functionalized aromatics. In this context, simple and inexpensive methods for the direct amination of readily available C-H bonds with amine nucleophiles are very desirable but far from being general.

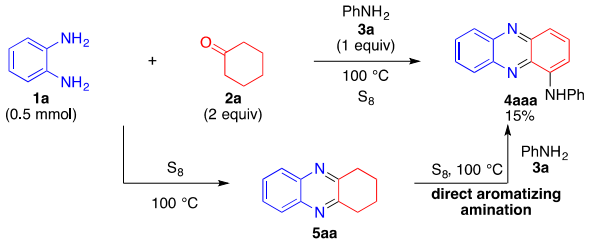
Functionalized phenazines are important structural motif in naturally occurring compounds[2] as well as artificial bioactive molecules.[3] Moreover, as redox-active scaffold, phenazine core is a potential candidate for the development of organic batteries.[4] Although many synthetic methods have been reported, the syntheses of such molecules required generally multistep sequences and employed starting materials with preinstalled functional groups necessary for the reactions.[2] In this regard, development of strategy involving simple starting materials/reagents with many transformations in a single pot provides several will provide excellent solutions for saving time, energy, resources and avoiding purification between reaction steps.

This communication describes an unexpected oxidative amination of 1,2,3,4-tetrahydrophenazine **5** with amine **3** to provide phenazine **4** in the presence of elemental sulfur under mild thermal conditions without any transition metal catalyst/ligand (Scheme 1).



Scheme 1. Aminative Aromatization of **5** with Amine

In connection with our research program aimed at exploiting the diverse reactivities of sulfur,[5] we reported the oxidative coupling promoted by this element between *o*-phenylenediamine **1a** with cyclohexanone **2a** to provide tetrahydrophenazine **5aa**.[6] The screening of sulfur activators showed that most of nitrogen-containing basic additives that were known to be capable of activating elemental sulfur (*N*-methylmorpholine, *N*-methylpiperidine, DMF) were found to be unsuitable to accelerate the expected oxidative coupling due to the degradation of cyclohexanone promoted by these basic amines. When aniline was used as an additive, because of its lower basicity, the observed activating effect was negligible. To our surprise, we obtained the unexpected 1-anilinophenazine **4aaa** as a red crystalline compound in low yield (Scheme 2).



Scheme 2. Formation of 1-anilinophenazine **4aaa**

As the ratio **4aaa**:**5aa** increased with prolonged heating, **4aaa** was obviously generated by an

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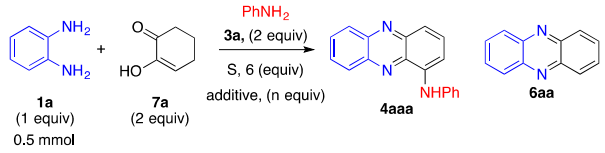
aromatizing anilination of **5aa**. This interesting initial observation prompted us to initiate an in-depth investigation for this original aromatizing amination reaction promoted by sulfur. In the first instance, to avoid complication with side reactions involving cyclohexanone **2a**, we replaced it by cyclohexane-1,2-dione **7a**,[7] which we found to react rapidly and quantitatively with *o*-phenylenediamine **1a** to provide **5aa**. As expected, the yield of **4aaa** was improved (entry 1). The conversion into **4aaa** was further improved by lower the reaction temperature to 80 °C (entry 2). The influence of different sulfur activating additive was further inspected (entries 3-8). Among them, *N*-methylpiperidine (NMP), which was the strongest base among the tested additives, appeared to be unsuitable to provide **4aaa** (entry 3). Indeed, **4aaa** was formed in trace quantity along with significant amount of phenazine **6aa** and extensive degradation. Other less basic additives such as *N*-methylmorpholine (NMM), 3-picoline (entries 4-5) or weakly basic one such as DMF, 1,4-dioxane (entries 6-7) led to better yields of **4aaa**. The best result was obtained when DMSO was used as an additive (entry 8). The amount of DMSO used was found to be important to the reaction yields, which culminated with 3 equiv (entry 8 *vs* entries 9-10). Finally, we found that while increasing the reaction temperature led to degradation and lower the yield of **4aaa** (entry 11), performing the reaction at lower temperature resulted in incomplete conversion (entry 12).

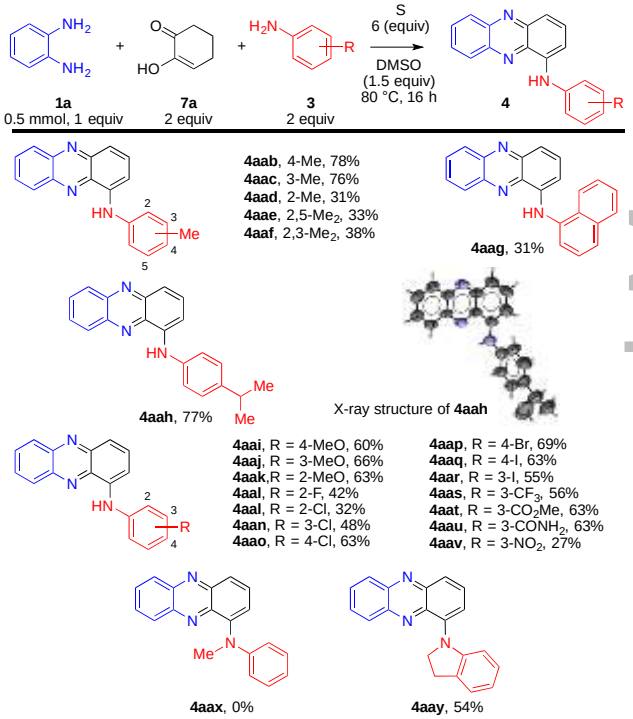
Table 1. Optimization of the Reaction Conditions



Entry[a)]	additive	n	t (°C)	yield of **4aaa** (%)[b)]
1	-	-	100	25
2	-	-	80	30
3	NMP[c)]	2	80	-[d)]
4	NMM[e)]	2	80	31
5	3-picoline	2	80	50
6	DMF	2	80	55
7	dioxane	2	80	35
8	**DMSO**	**3**	**80**	**78**
9	DMSO	1	80	62
10	DMSO	6	80	71
11	DMSO	3	100	48
12	DMSO	3	60	44

[a)] Reaction conditions: **1a** (0.5 mmol, 54 mg), **7a** (1 mmol, 112 mg), **3a** (1 mmol, 93 mg), S (3 mmol, 96 mg), additive (0.1 mL), t °C, 16 h. [b)] Isolated yield. [c)] *N*-Methylpiperidine. [d)] Not isolated. [e)] *N*-Methylmorpholine.

With the optimized reaction conditions in hand, a preliminary study was performed to determine the substrate scope of this reaction. We first explored the behavior of anilines with *o*-phenylenediamine **1a** and cyclohexane-1,2-dione **7a** (Scheme 3). Among the toluidines **3b-d**, *meta*- and *para*-isomers **3b-c** reacted smoothly, leading to the expected phenazines **4aab** and **4aac** in 76-78% yields. On the contrary, *o*-toluidine **3d** as well as other *o*-methylated anilines **3e**,**f** or 1-naphthylamine **3g** exhibited lower reactivity. Their reactions resulted in the expected product **3aae**-**3aag** in lower yields. Among our very first examples, 1-(*p*-isopropylanilino)phenazine **4aah** was obtained in high yield and its structure determined by X-ray crystallography confirmed unambiguously the 1-anilinophenazine scaffold of the family.[8] The reactions with all three anisidines **3i-k** proceeded without any difficulty even with *o*-isomer **3k**. On the contrary, *o*-halo anilines **3l**,**m** displayed reduced reactivity even with small halogen atoms such as fluorine or chlorine (phenazines **4aal** and **4aam**). Apart from this steric hindrance of the *o*-haloanilines, the reaction conditions tolerated all four halogens, including bromine **4aap** and iodine derivatives **4aaq**-**4aar**. Anilines bearing strong electron withdrawing groups such as CF_3, ester, amide or nitro **3s-3v** were shown to be less reactive although these functional groups remained intact under the present reaction conditions.



Reaction conditions: **1a** (0.5 mmol), **2b** (1 mmol), **3a** (1 mmol), S (3 mmol, 96 mg), DMSO (0.1 mL), 80 °C, 16 h.

Scheme 3. Scope of anilines **3**

It should be noted that although the reaction generate hydrogen sulfide as a by-product that was known as a strong reducing agent for nitro group, the nitro-substituted phenazine **4aav** was obtained without formation of the products in which the nitro group was reduced. The reaction was found to be sensitive to the steric hindrance on the nitrogen atom of aniline. Only trace of the expected phenazine **4aax**

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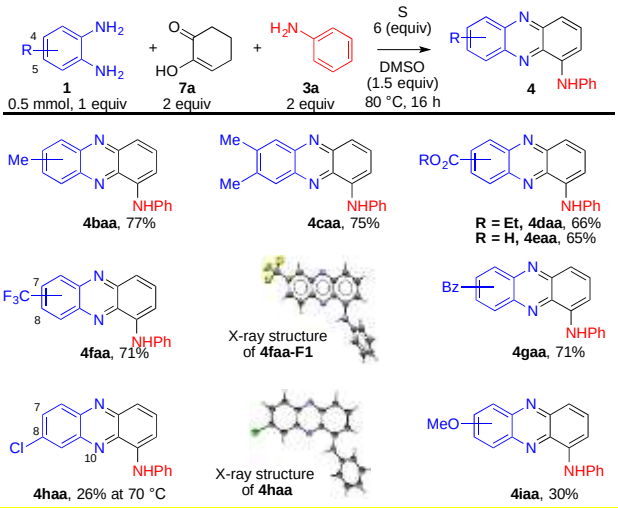
observed when *N*-methylaniline was used **3x**. On the other hand, phenazine **4aay** derived from indoline could be obtained in moderate yield, undoubtedly due to the more accessible nitrogen of indoline **3y**.To further evaluate the scope of this reaction, a variety of analogues of *o*-phenylenediamine were employed (Scheme 4). *o*-Phenylenediamines 4-substituted by a methyl, an ethyl ester, a carboxylic acid, a trifluoromethyl or a benzoyl group gave nearly equimolar mixtures of both regioisomers **4baa**, **4daa**, **4eaa**, **4faa** or **4gaa**, respectively. The reactivity of these *o*-phenylenediamines as well as of 4,5-dimethyl-*o*-phenylenediamine was found to be similar to unsubstituted *o*-phenylenediamine. It should be emphasized that the reaction was compatible with free carboxylic acid group (**4eaa**). The regioisomers of phenazine products bearing an electron-withdrawing group such as ester (**4daa**), free carboxylic acid (**4eaa**), trifluoromethyl (**4faa**) or benzoyl (**4gaa**) could be separated by column chromatography. The structure of the less polar regioisomer **4faa-F1** was determined by X-ray crystallography.[8]



Reaction conditions: **1a** (0.5 mmol), **2b** (1 mmol), **3a** (1 mmol), S (3 mmol, 96 mg), DMSO (0.1 mL), 80 °C, 16 h

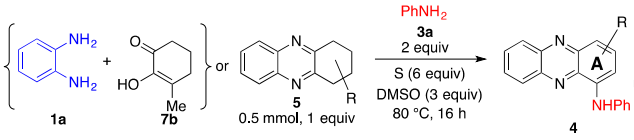
Scheme 4. Scope of *o*-phenylenediamines **1**

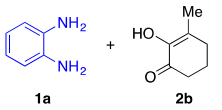
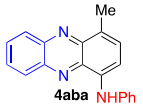
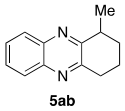
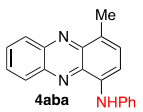
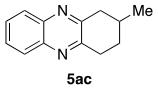
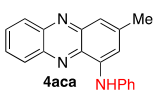
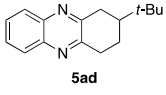
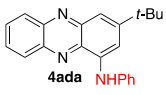
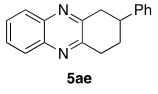
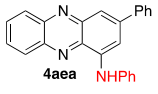
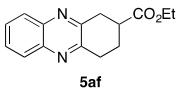
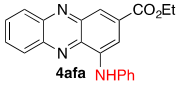
4-Chloro-*o*-phenylenediamine **1h** was found to be sensitive to the reaction conditions and its reaction was performed at lower temperature (70 °C) to yield the phenazine product **4haa**. Surprisingly, only 8-chloro regioisomer was detected in the crude reaction mixture and was isolated. [8] The low yield and the obtention of a unique regioisomer could be explained by the instability of 7-chloro regioisomer, which was supposed to be initially formed in the reaction mixture but further decomposed. Such instability would be a direct result of an intramolecular hydrogen bond between the aniline group and N-10 atom, which is at the *para* position to C-7 atom.

Readily oxidizable 4-methoxy-*o*-phenylenediamine was also competent substrate, providing the product **4iaa** as a 2:1 mixture of the two possible regioisomers.

Subsequently, we investigated the formation of phenazines **4** bearing different functional groups on the ring A (Table 2). For this purpose, tetrahydrophenazines **5** could be formed by in situ condensation between *o*-phenylenediamine **1a** with cyclohexane-1,2-dione **2b** (entry 1) or could be used directly (entries 2-6). When 1-methyltetrahydrophenazine was used (entry 2) instead of a mixture of *o*-phenylenediamine **1a** and dione **2b** (entry 1), the yield was significantly improved.

Table 2. Scope of Tetrahydrophenazines **5**



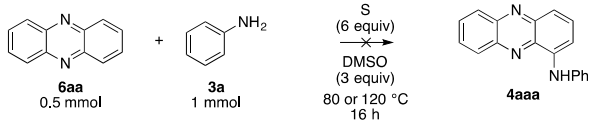
Entry[a]	(**1a** + **2**) or quinoxaline **5**	product	yield (%)
1			28
2			68
3			67
4			69
5			54
6			52

[a] Reaction conditions: **1a** (0.5 mmol), **2b** (1 mmol), **3a** (1 mmol), S (3 mmol, 96 mg), DMSO (0.1 mL), 80 °C, 16 h for entry 1; **5ab**-**5ac** (0.5 mmol) for entries 2-6.

Other tetrahydrophenazines **5ac**-**5af** bearing a substituent of different steric and electronic natures (methyl, *t*-butyl, phenyl, and ethyl ester) reacted smoothly at 80 °C, leading to the corresponding phenazines (**4aca**-**4afa**) in moderate to good yields (entries 2-6). The reaction was found to be highly regioselective as only one regioisomer could be isolated with 2-substituted tetrahydrophenazines (**5ac**-**5af**) (entries 3-6). As noted previously, the formation of C-N bond between aniline and phenazine moieties depends on the steric hindrance of both of them.

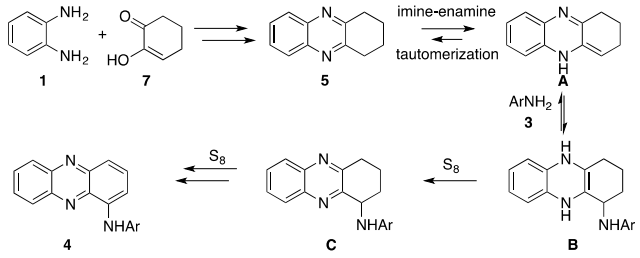
As traces of phenazine **6aa** was detected in the reaction mixtures, it was possible that anilinophenazine **4aaa** could be formed by an oxidative anilination of phenazine **6aa** in the presence of sulfur. As the control experiment shown in Scheme

5 did not lead to any trace of anilinophenazine **4aaa**, this possibility was ruled out.



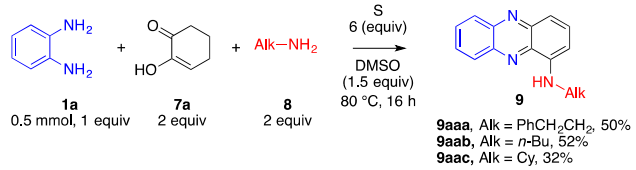
Scheme 5. Control experiment

In the present stage, our observations are consistent with the reaction pathway presented in Scheme 6. As previously described, the first step would be the formation tetrahydrophenazine **5**. The next step could be a dearomatizing tautomerization of **5** into **A**. As a Michael acceptor, **A** would subject to a nucleophilic attack by aniline **3**, leading to adduct **B**. Subsequent sequential aromatization of **B** and **C** would provide 1-anilinophenazine **4**. The determining step is obviously the Michael addition of **3** to **A**, which depends on steric hindrance of both aniline and **A**.[8]



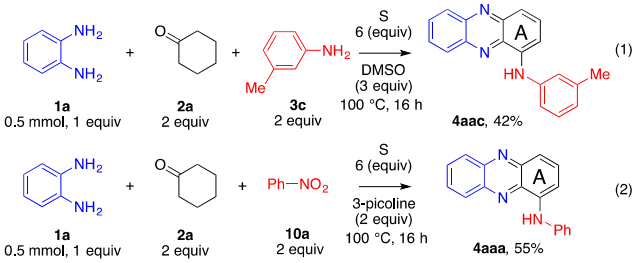
Scheme 6. Proposed mechanism

The versatility of our approach was further demonstrated with aliphatic amines **8a**-**8c** (Scheme 7). To our delight, the expected products **9aaa**-**9aac** were obtained under the standard reaction conditions, with better yields for less hindered primary amines.



Scheme 7. Reactions with selected aliphatic amines **8**

To complete our investigation, we applied cyclohexanone as an inexpensive precursor for the ring A of phenazine **4** (Scheme 8, eq. 1). Its reaction with *o*-phenylenediamine **1a** and *m*-toluidine **3c** at 100 °C provided the expected phenazine **4aac** in 42% yield. Moreover, because hydrogen sulfide is a by-product of the reaction, it is desirable to limit its formation. By using nitrobenzene **10a** as a less expensive surrogate of aniline **1a**, we could obtain the phenazine product **4aaa** while lowering the formation of H_2S from 5 equiv to only 2 equiv as 3 equiv was used for reduction of the nitro group (eq. 2). Additionally, from practical standpoint, this approach is highly advantageous as some nitro derivatives are less expensive and more readily available than their aniline analogs. Although sulfur could act as a catalyst in this reaction, its catalytic activity is far from efficient to be used in catalytic amount.



Scheme 8. Reactions with **2a** and $ArNH_2$/$ArNO_2$

In conclusion, we have described a conceptually simple but highly unusual strategy that allows a rapid assembly of a new class of functionalized 1-anilinophenazines. This reaction was achieved through the formation of three C-N bonds and the sequential double aromatization in a single operation. The method represents a rare example of multicomponent process for one-step construction of complex structures starting from very simple starting materials such as cyclohexane-1,2-diones/cyclohexanones, *o*-phenylenediamines and anilines/nitrobenzenes. Once again, the method highlights the usefulness of elemental sulfur as an excellent synthetic tool for organic chemistry. Further developments of such strategy with sulfur are ongoing in our laboratory and the results will be reported in due course.

Acknowledgements

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[2] For an excellent review on recent developments in the isolation, biological function, biosynthesis and synthesis of natural products bearing a phenazine motif, see: N. Guttenberger, W. Blankenfeldt R. Breinbauer, *Bioorg. Med. Chem*. **2017**, *25*, 6149.

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[5] a) T. B. Nguyen, *Adv. Synth. Catal*. **2017**, *359*, 1106; b) T. B. Nguyen, *Asian J. Org. Chem.* **2017**, *6*, 477.

[6] T. B. Nguyen, P. Retailleau, *Adv. Synth. Catal*. **2017**, *359*, 3843.

[7] Although cyclohexane-1,2-dione **7a** is frequently described as 1,2-dione form, its ^{1}H NMR spectrum shows that one of its ketone group is under enol form in $CDCl_3$.

[8] The crystallographic coordinates have been deposited with the Cambridge Crystallographic Data Centre; deposition no. CCDC 1544067 (**4aah**), CCDC 1584933 (**4faa-F1**), and CCDC 1811702 (**4haa**).

[9] For an example of heteroaromatization promoted by sulfur in DMSO, see: F. Shibahara, R. Sugiura, E. Yamaguchi, A. Kitagawa, T. Murai, *J. Org. Chem.* **2009**, *74*, 3566.

[10] Trace amount of **4aaa** was formed when S was used in 10 mol %.

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UPDATE

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