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A Simple and Straightforward Approach to Quinoxalines by Iron/Sulfur-Catalyzed Redox Condensation of *o*-Nitroanilines and Phenethylamines

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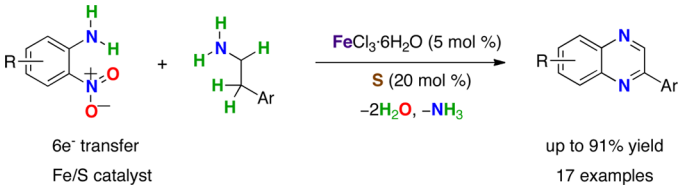
ABSTRACT



In situ **generated iron sulfide from elemental sulfur and ferric chloride was found to be a highly efficient catalyst for the redox condensation cascade reaction between *o*-nitroanilines and 2-arylethylamines. This method constitutes a new atom-, step-, and redox-economical route to 2-arylquinoxalines.**

Development of methods to transform functional groups efficiently which respect the concept of atom, step, and redox economy plays a crucial role in modern sustainable organic synthesis.[1] In this context, unnecessary energy consuming steps might be avoided by the judicious choice of catalytic chemical processes. Because of the unique electrochemical properties of iron, its highest natural abundance, which results in low cost and ready accessibility on a large scale, and its low toxicity compared to other transition metals, iron seems to be a highly promising catalyst for redox transformations.[2]

Iron–sulfur clusters, a subgroup of iron catalysts in the active sites of redox proteins of all living forms, play an important role in the electron transfer between functional groups. Thanks to their property of storing and releasing electrons during metabolic reactions, iron–sulfur clusters behave as molecular capacitors and are capable of accelerating the redox tranformations.[3] Despite the ubiquity and the essential roles of iron–sulfur clusters in living systems, only a few examples of the application of Fe/S clusters as redox catalysts in organic synthesis have been reported.[4,5] Compared to other ligands which are expensive, with high molecular weights and/or sensitivity to oxygen and moisture, elemental sulfur is obviously very cheap, toxicologically benign, and potentially efficient even under physiological systems.

Our recent investigation demonstrated that Fe/S was catalytically active for achieving a redox condensation between *o*-nitroanilines/phenols and 2- or 4-picolines and related compounds, yielding the corresponding 2-hetaryl benzimidazoles and benzoxazoles with the formation of water as the only byproduct.[5] In continuing our effort in developing new applications of an Fe/S catalyst, here we report a redox condensation between *o*-nitroanilines

(1) For a recent review, see: Wender, P. A. *Tetrahedron* **2013**, *69*, 7529.

(2) For selective reviews on iron-catalyzed reactions in organic synthesis, see: (a) Bolm, C.; Legros, J.; Le Paih, J.; Zani, L. *Chem. Rev.* **2004**, *104*, 6217. (b) Sun, C.; Li, B.; Shi, Z. *Chem. Rev.* **2011**, *111*, 1293. (c) Jana, R.; Pathak, T. P.; Sigman, M. S. *Chem. Rev.* **2011**, *111*, 1417. (d) Sarhan, A. A. O.; Bolm, C. *Chem. Soc. Rev.* **2009**, *38*, 2730. (e) Correa, A.; Mancheño, O. G.; Bolm, C. *Chem. Soc. Rev.* **2008**, *37*, 1108.

(3) (a) Johnson, M. K.; Smith, A. D. Iron–Sulfur Proteins. In *Encyclopedia of Inorganic Chemistry*, 2nd ed.; King, R. B., Ed.; John Wiley & Sons: Chichester, 2005. (b) Beinert, H.; Holm, R. H.; Münck, E. *Science* **1997**, *277*, 653.

(4) Wang, J.; Wang, S.; Wang, G.; Zhang, J.; Yu, X. Q. *Chem. Commun.* **2012**, *48*, 11769.

(5) Nguyen, T. B.; Ermolenko, L.; Al-Mourabit, A. *J. Am. Chem. Soc.* **2013**, *135*, 118.

10.1021/ol402435c

and 2-phenethylamines as a straightforward access to 2-phenylquinoxalines.[6]

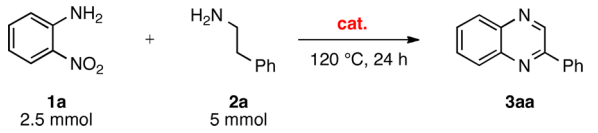
While an oxidizing agent is generally necessary for functionalization of sp^3 C−H bonds,[7] the use of a nitro group as a nitrogen synthon inevitably requires a reducing agent.[8] Alternatively, when the nitro group plays the role of an oxidizing agent for functionalization of sp^3 C−H bonds, no additional oxidizing or reducing agent is needed. Such an atom-, step-, and redox-economical transformation is highly desirable. Based on this principle, we studied a model reaction between 2-phenethylamine and *o*-nitroaniline. This six-electron transfer process would occur with the formation of two molecules of water and one molecule of ammonia as the only byproducts.

At the beginning of our study, *o*-nitroaniline **1a** and 2-phenethylamine **2a** (2 equiv) were chosen as model substrates for redox condensation (Table 1). When the reaction was carried out in the absence of catalysts, both starting materials were recovered unchanged (entry 1). Except for $MnCl_2$, $NiCl_2 \cdot 6H_2O$, and CuCl which were catalytically inactive (entries 2,8 and 9), we observed a low conversion into product with iron (entries 3−6) and cobalt salts (entry 7). Gratifyingly, the addition of elemental sulfur (20 mol %, entries 10−15) provided an improved conversion in most cases (except for $CoCl_2 \cdot 6H_2O$, entry 13). Most significantly, a high conversion into product was observed with the $FeCl_3 \cdot 6H_2O$/S system (entry 12). The use of sulfur (entry 16) as the catalyst without ferric chloride as well as the ferric chloride without elemental sulfur (entry 4) gave only low formation of product, 7% and 10% respectively. The almost 10-fold decrease of the C−H/NO_2 electron transfer clearly indicates the key role of the ensemble Fe/S clusters. The conditions identified in Table 1 (entry 12) were therefore used for further reactions.

To explore the application of this method, the scope of the redox condensation reaction was examined under the optimized conditions (Tables 2 and 3).

A range of 2-arylethylamines (2 equiv) were allowed to react with *o*-nitroaniline in the presence of $FeCl_3 \cdot 6H_2O$ (5 mol %) and sulfur (20 mol %) under solvent-free conditions (Table 2). 2-Phenethyalmines bearing differing substitution patterns and electronic properties were proven to be suitable substrates, providing products in good yields. While electron-poor 2-phenethylamine **2c** was particularly reactive (Table 2, entry 3), electron-rich substrates **2f**, **2h**, and **2j** (Table 2, entries 6, 8, and 10) gave products in lower yields. An *ortho* substituent of the 2-phenethylamines

Table 1. Optimization of Reaction Conditions[a]



1a 2.5 mmol + **2a** 5 mmol → **3aa**

entry	metal salt (5 mol %)	S (mol %)[b]	conversion (%)[c]
1	–	0	0
2	$MnCl_2$	0	0
3	$FeCl_2 \cdot 4H_2O$	0	20
4	$FeCl_3 \cdot 6H_2O$	0	10
5	$FeSO_4 \cdot 7H_2O$	0	7
6	$Fe(NO_3)_3 \cdot 9H_2O$	0	18
7	$CoCl_2 \cdot 6H_2O$	0	10
8	$NiCl_2 \cdot 6H_2O$	0	0
9	CuCl	0	0
10	$MnCl_2$	20	29
11	$FeCl_2 \cdot 4H_2O$	20	75
12	**$FeCl_3 \cdot 6H_2O$**	**20**	**93**
13	$CoCl_2 \cdot 6H_2O$	20	5
14	$NiCl_2 \cdot 6H_2O$	20	8
15	CuCl	20	5
16	–	20	7

[a] Reaction conditions: **1a** (2.5 mmol), **2a** (5 mmol). [b] 32.1 g mol^{-1}. [c] Determined by ^1H NMR.

Table 2. Substrate Scope of the Fe/S-Catalyzed Redox Condensation Reaction of Ethylamines **2** with *o*-Nitroaniline **1a**[a]

1a 2.5 mmol + **2** 2 equiv → **3**

entry	**2**	R	**3**	yield (%)[b]
1	**2a**	Ph	**3aa**	75
2	**2b**	3-MeC_6H_4	**3ab**	78
3	**2c**	4-FC_6H_4	**3ac**	94
4	**2d**	4-ClC_6H_4	**3ad**	73
5	**2e**	4-BrC_6H_4	**3ae**	75
6	**2f**	4-$MeOC_6H_4$	**3af**	56
7	**2g**	3-$MeOC_6H_4$	**3ag**	78
8	**2h**	2-$MeOC_6H_4$	**3ah**	58
9	**2i**	2-FC_6H_4	**3ai**	63
10	**2j**	3,4-$(MeO)_2C_6H_3$	**3aj**	56
11	**2k**	*n*-hexyl	**3ak**	48

[a] Reaction conditions: **1a** (2.5 mmol), **2** (5 mmol), $FeCl_3 \cdot 6H_2O$ (0.125 mmol, 34 mg), S (0.5 mmol, 16 mg). [b] Isolated yield.

(6) For representative examples of synthesis of quinoxalines, see: from *o*-phenylenediamines: (a) Martin, L. J.; Marzinzik, A. L.; Ley, S. V.; Baxendale, I. R. *Org. Lett.* **2011**, *13*, 320. (b) Chen, Y.; Li, K.; Zhao, M.; Li, Y.; Chen, B. *Tetrahedron Lett.* **2013**, *54*, 1627. (c) Padmavathy, K.; Nagendrappa, G.; Geetha, K. V. *Tetrahedron Lett.* **2011**, *52*, 544. (d) Lian, M.; Li, G.; Zhu, Y.; Yin, G.; Wu, A. *Tetrahedron* **2012**, *68*, 9598. (e) Wang, W.; Shen, Y.; Meng, X.; Zhao, M.; Chen, Y.; Chen, B. *Org. Lett.* **2011**, *13*, 4514. (f) Song, J.; Li, X.; Chen, Y.; Zhao, M.; Dou, Y.; Chen, B. *Synlett* **2012**, 2416. (g) Zhang, C.; Xu, Z.; Zhang, L.; Jiao, N. *Tetrahedron* **2012**, *68*, 5258. From *o*-nitroanilines in the presence of an external reducing agent: (h) Wallace, J. M.; Soederberg, B. C. G.; Tamariz, J.; Akhmedov, N. G.; Hurley, M. T. *Tetrahedron* **2008**, *64*, 9675. (i) Blaikley, D. C. W.; Currie, D. W; Smith, D. M.; Watson, S. A.; McNab, H. *J. Chem. Soc., Perkin Trans. 1* **1984**, 367. (j) Cho, C. S.; Ren, W. X.; Shim, S. C. *Tetrahedron Lett.* **2007**, *48*, 4665. (k) Neochoritis, C.; Stephanidou-Stephanatou, J.; Tsoleridis, C. A. *Synlett* **2009**, 302. (l) Cho, C. S.; Oh, S. G. *Tetrahedron Lett.* **2006**, *47*, 5633. (m) Meshram, H. M.; Santosh Kumar, G.; Ramesh, P.; Chennakesava Reddy, B. *Tetrahedron Lett.* **2010**, *51*, 2580.

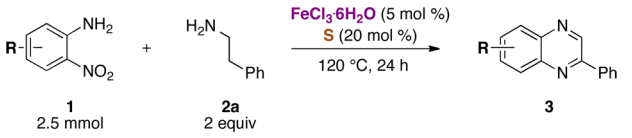
(7) Zhang, S.; Zhang, F.; Tu, Y. *Chem. Soc. Rev.* **2011**, *40*, 1937.

(8) (a) Ono, N. *The Nitro Group in Organic Synthesis*; Wiley-VCH: New York, 2001. (b) Yan, G.; Yang, M. *Org. Biomol. Chem.* **2013**, *11*, 2554.

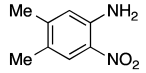
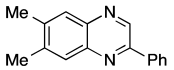
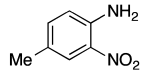
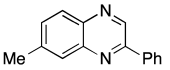
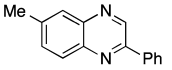
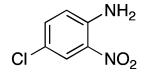
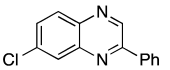
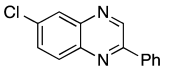
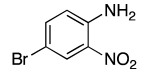
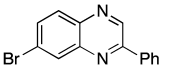
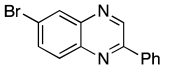
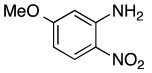
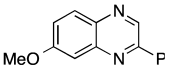
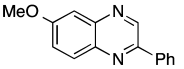
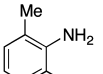
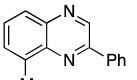
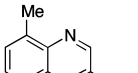
was well-tolerated (Table 2, entries 8, 9), although the yield was slightly lower. A long chain aliphatic amine such as *n*-octylamine only gave a moderate yield (Table 2, entry 11).

We then applied these reaction conditions to the conversion of 2-phenethylamine **2a** with various *o*-nitroanilines into 2-phenylquinoxalines (Table 3). The reaction of monosubstituted *o*-nitroanilines **1c**–**g** resulted in a mixture of two possible regioisomers in good yields. These regioisomers were readily separable by column chromatography in most cases (entries 3–6).

Table 3. Substrate Scope of the Fe/S-Catalyzed Redox Condensation Reaction of Phenethylamine **2a** with Various *o*-Nitroanilines **1**[a]



1, 2.5 mmol — **2a**, 2 equiv — **3**

entry	1	3, yield (%)[b]	ratio[c]
1	 **1b**	 **3ba**, 80	-
2	 **1c**	 **3ca-7**  **3ca-6** 80[d]	1:1.3
3	 **1d**	 **3da-7**, 48  **3da-6**, 34	1.4:1
4	 **1e**	 **3ea-7**, 32  **3ea-6**, 34	1:1
5	 **1f**	 **3fa-7**, 30  **3fa-6**,[e] 56	1:1.7
6	 **1g**	 **3fa-8**,[e] 32  **3fa-5**, 32	1:1

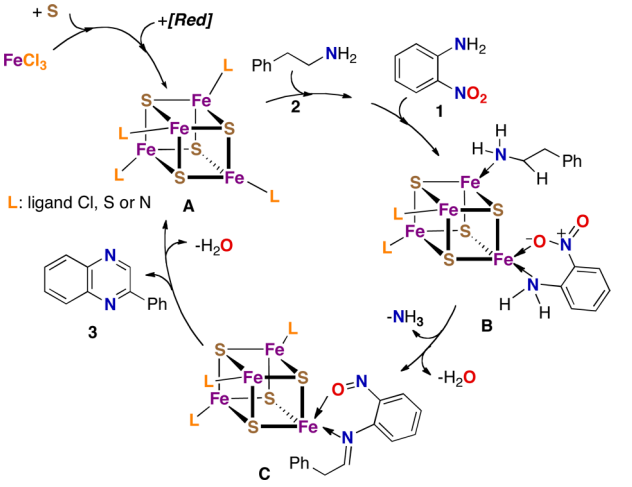
[a] Reaction conditions: **1** (2.5 mmol), **2a** (5 mmol), $FeCl_3 \cdot 6H_2O$ (0.125 mmol, 34 mg), S (0.5 mmol, 16 mg). [b] Isolated yield. [c] Determined by ^1H NMR. [d] Yield of the mixture of both regioisomers. [e] Structure determined by X-ray crystallography.

Although the details regarding the nature of the clusters involved in the present method are not yet known, we propose a possible reaction mechanism in Scheme 1. The formation of iron–sulfur cluster **A** can occur spontaneously when sufficient amounts of soluble iron and sulfur are available in the presence of a reducing agent (2-phenethylamine in this case).[9] Iron–sulfur cluster **A** is presented arbitrarily as cube **A**. The next step could be the fixation of *o*-nitroaniline **1** on **A** by chelation and 2-phenthylamine **2** by coordination.

(9) Berg, J. M.; Holm, R. H. In *Iron-Sulfur Proteins*; Spiro, T. G., Ed.: John Wiley and Sons: 1981; pp 1–66.

A subsequent two-electron transfer process would occur intramolecularly via complex imine-nitroso **C** with removal of one molecule of water and ammonia. Further four-electron transfer and dehydration would furnish quinoxaline **3** and regenerate the starting complex **A** to complete the catalytic cycle.

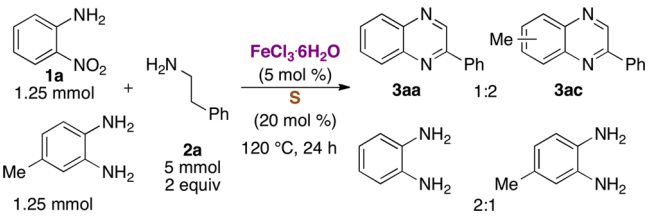
Scheme 1. Proposed Mechanism



The formation in variable ratios of both possible regioisomers of **3** from 2-nitroanilines **1c**–**g** monosubstitued at the 4, 5, or 6 position of the aromatic ring (entries 2–6, Table 3) could suggest that *o*-phenylenediamines corresponding to the reduced products of **1** as the intermediate were generated prior to the cyclization into quinoxaline **3**. Indeed, minor amounts of the *o*-phenylenediamines corresponding reduced products of **1** were isolated in some instances.

To confirm this hypothesis, we carried out a control experiment using *o*-nitroaniline **1a** (0.5 equiv), 4-methyl-*o*-phenylenediamine (0.5 equiv), and 2-phenethylamine (2 equiv) under standard conditions (Scheme 2). We observed a full conversion of **1**, the formation of a mixture of 2-phenylquinoxaline **3aa**, 6- and 7-methyl-2-phenylquinoxaline **3ca** (**3aa**:**3ca** = 1:2), and a mixture of *o*-phenylenediamine and 4-methyl-*o*-phenylenediamine (2:1).

Scheme 2. Control Experiment



In summary, the above developed method of redox condensation of *o*-nitroanilines and 2-arylethylamines to 2-arylquinoxalines provides a beautiful example of atom-, step-, and redox-economical transformation. The use of a catalytic amount of iron sulfide generated *in situ* from

nontoxic $FeCl_3 \cdot 6H_2O$ and elemental sulfur under solvent-free conditions makes the method very interesting for preparative purposes and sustainable development. Mechanistic studies aimed at identifying the reaction intermediates, expansion of the scope, and exploration of the related reactions are in progress.

Supporting Information Available. Experimental procedures, product characterization, and copies of the ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.