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Iron Sulfide Catalyzed Redox/Condensation Cascade Reaction between 2-Amino/Hydroxy Nitrobenzenes and Activated Methyl Groups: A Straightforward Atom Economical Approach to 2-Hetaryl-benzimidazoles and -benzoxazoles

Thanh Binh Nguyen,* Ludmila Ermolenko, and Ali Al-Mourabit

Centre de Recherche de Gif-sur-Yvette, Institut de Chimie des Substances Naturelles, CNRS, 91198 Gif-sur-Yvette Cedex, France

Supporting Information

ABSTRACT: Iron sulfide generated *in situ* from elemental sulfur and iron was found to be highly efficient in catalyzing a redox/condensation cascade reaction between 2-amino/hydroxy nitrobenzenes and activated methyl groups. This method represents a straightforward and highly atom economical approach to 2-hetaryl-benzimidazoles and -benzoxazoles.

Development of new efficient functional group transformations in organic synthesis plays a crucial role in modern sustainable chemistry. For this purpose, application of catalytic chemical processes might avoid unnecessary steps, thus reducing material and energy waste. The Fe−S redox system is considered among the most interesting catalysts involving electron transfer in active centers of redox catalytic proteins. Many types of Fe−S clusters are based on the coordination of elemental sulfur and usually bridged to their proteins by cysteine thiolates.[1] The chemistry of redox reactions involving organic compounds and the sulfur/iron interaction is consequently very interesting to investigate. Iron sulfide clusters are found in all living forms, ranging from bacteria to man and are present at the active sites of a wide variety of redox proteins.[2] In many of these proteins, the main role of the cluster is to accelerate electron transfer, to act as capacitors, storing and releasing electrons to metabolic reactions.[3] Fe−S cluster formation can occur spontaneously when sufficient amounts of reduced and soluble iron and sulfur are available.[4] The prevalence of such conditions early in the history of the earth could account for the presence of these groups in a wide variety of proteins.[5] Based on these literature reports, we reasoned that iron sulfide could be a promising, contributing candidate in both oxidation and reduction.

Benzimidazoles and benzoxazoles are important building blocks for the construction of pharmaceuticals, natural products, functional materials, and agrochemical compounds. In the course of our research on new strategies of C−N bond formation, we were interested in the creation of this moiety. Typically, these compounds are synthesized by condensing 2-amino/hydroxy anilines **4** with carboxylic acid derivatives **5** (Scheme 1).[6] This approach, although extensively used, cannot be considered as an atom economical transformation because both of the starting materials are usually obtained by two opposite reactions: (i) anilines **4** from the reduction of the corresponding nitrobenzenes **1** (6e$^-$ transfer); (ii) carboxylic acids **5** from the oxidation of their lower oxidation degree parent compounds **2** such as aldehydes, primary alcohols, or even methyl groups (2e$^-$, 4e$^-$, or 6e$^-$

Scheme 1. Approaches to Benzazoles

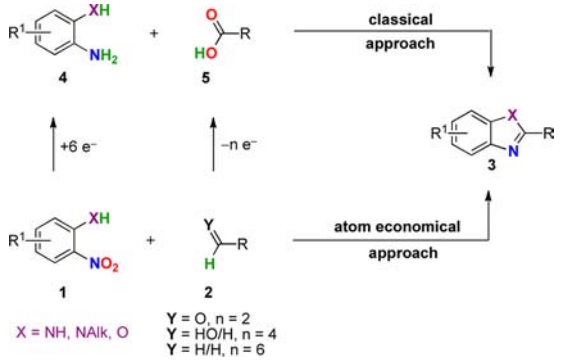
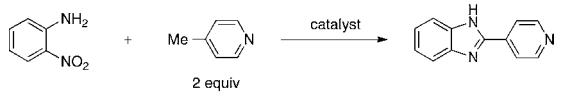


Table 1. Optimization of Reaction Conditions[a]



1a 2a 3aa

entry	catalyst (mol %)	conditions	conversion (%)[b]
1	–	150 °C, 72 h	0
2	FeS (10)	150 °C, 16 h	30
3	$FeCl_3·6H_2O$ (10)	150 °C, 16 h	<5
4	$FeCl_3$ (10)	150 °C, 16 h	<5
5	$FeSO_4·7H_2O$ (10)	150 °C, 16 h	<5
6	$Fe(NO_3)_3·9H_2O$ (10)	150 °C, 16 h	<5
7	$Fe(acac)_3$ (10)	150 °C, 16 h	<5
8	$FeSO_4·7H_2O/Na_2S$ (10/10)	150 °C, 16 h	30
9	Fe (10), S (10)	150 °C, 16 h	95
10	S (10)	150 °C, 16 h	7
11	Fe (10)	150 °C, 16 h	<5
12	S (1), Fe (1)	150 °C, 16 h	<5
13	S (10), Fe (10)	140 °C, 16 h	75

[a]Reaction conditions: *o*-nitroaniline **1a** (5 mmol), 4-picoline **2a** (10 mmol). [b]Determined by ^{1}H NMR.

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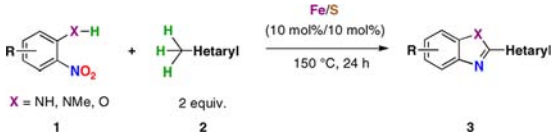
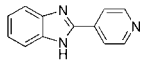
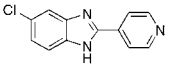
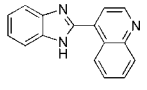
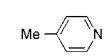
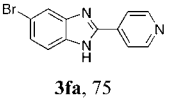
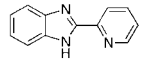
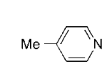
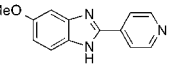
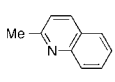
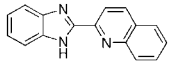
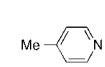
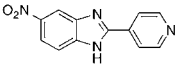
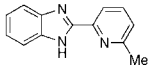
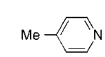
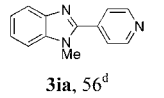
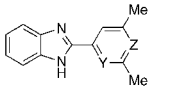
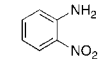
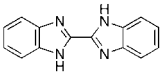
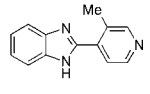
Table 2. Iron Sulfide Catalyzed Reaction between 2-Amino/Hydroxy Nitrobenzenes and Methyl Hetarenes[a]



entry	nitro, **1**	methyl-Hetarene, **2**	product, **3**, yield (%)	entry	nitro, **1**	methyl-Hetarene, **2**	product, **3**, yield (%)
1	 **1a**	 **2a**	 **3aa**, 90	12	 **1e**	 **2a**	 **3ea**, 82
2	 **1a**	 **2b**	 **3ab**, 83	13	 **1f**	 **2a**	 **3fa**, 75
3	 **1a**	 **2c**	 **3ac**, 75	14[c]	 **1g**	 **2a**	 **3ga**, 69
4	 **1a**	 **2d**	 **3ad**, 73	15	 **1h**	 **2a**	 **3ha**, 57
5	 **1a**	 **2e**	 **3ae**, 56	16	 **1i**	 **2a**	 **3ia**, 56[d]
6[b]	 **1a**	 **2f**	 **3af-2**, Y = N, Z= CH, 40 **3af-4**, Y = CH, Z= N, 22	17	 **1a**	 **2i**	 **3ai**, 85
7	 **1a**	 **2g**	 **3ag**, 91	18	**1a**	**2j**	**3aj**, 72
8	**1a**	**2h**	**3ah**, 0	19	**1i**	**2i**	**3aj**, 66
9	**1b**	**2a**	**3ba**, 75	20	**1j**	**2b**	**3jb**, 53
10	**1c**	**2a**	**3ba**, 73	21	**1j**	**2d**	**3jd**, 51
11	**1d**	**2a**	**3da**, 70				

[a]Reaction conditions: nitrobenzene **1** (5 mmol), methyl hetarene **2** (10 mmol), Fe (0.5 mmol), S (0.5 mmol), 150 °C, 24 h unless otherwise noted. [b]**3af-2:3af-4** ratio of the crude mixture determined by ^{1}H NMR = 2:1. [c]Reaction performed at 160 °C. [d]~90% purity by ^{1}H NMR.

transfer respectively). A catalyst capable of effecting a direct H-transfer from **2** to **1** would be highly desirable because three processes, oxidation, reduction, and condensation, are carried out in only one operation.

Recently, the formation of 2-arylbenzoxazoles from *o*-nitrophenols and benzylic alcohols using 1,1′-bis-(diphenylphosphino)ferrocene (dppf) as a H-transfer catalyst has been reported.[7] Although efficient in some cases, this method suffered from a major intrinsic drawback. Because benzyl alcohol can transfer only four electrons while the reduction of *o*-nitrophenols requires six electrons, the use of excess benzyl alcohol and the formation of its side products are obviously unavoidable. Moreover, the use of an expensive, high molecular weight dppf catalyst hindered practical application.

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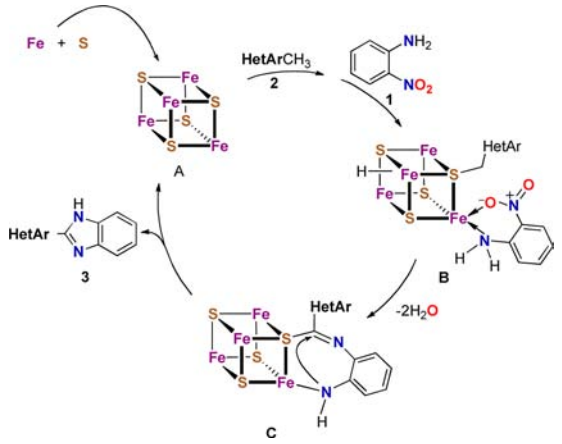
Scheme 2. Proposed Mechanism



In this context, a reaction between *o*-amino/hydroxy nitrobenzenes **1** and methylhetaryl **2** catalyzed by efficient, low-cost, readily available, and nontoxic catalysts such as iron sulfide would provide a new straightforward approach to benzazoles **3**.

Herein, we report an extremely simple iron sulfide based catalytic system for a direct condensation between 2-hydroxy/amino nitrobenzenes with a methylhetarene without any added oxidizing or reducing agent.

As an exploratory study, we chose the reaction between *o*-nitroaniline **1a** and 4-picoline **2a** as a model reaction under solvent-free conditions (Table 1). This reaction has been reported by using a large excess of elemental sulfur at high temperature (up to 185 °C) and resulting in benzimidazole **3aa** formation by ∼30%.[8] Our objective was to find milder solvent-free reaction conditions catalyzed by an Fe−S system.

Without a catalyst, no reaction occurred, and the starting substrates remained intact after heating at 150 °C for 72 h (entry 1, Table 1). Gratifyingly, commercially available iron sulfide powder (100 mesh, 99.9% trace metals basis, Sigma Aldrich) gave the desired compound in 30% yield (entry 2, Table 1). Screening other iron salts did not result in any significant conversion (entries 3−7, Table 1). When an iron sulfide catalyst generated *in situ* from ion metathesis reaction between an equimolar mixture of $FeSO_4{\cdot}7H_2O$ and Na_2S was used (entry 8, Table 1), a similar conversion was observed as for commercial FeS (entry 2, Table 1). Remarkably, adding an equimolar mixture of metallic iron powder and elemental sulfur (10 mol %) boosted the conversion up to a nearly quantitative level (entry 9, Table 1).[9] In order to confirm if iron sulfide generated *in situ* in this run or each separate element is responsible for this reactivity enhancement, two other experiments were carried out with elemental sulfur and iron powder. Addition of sulfur[10] in a 10 mol % amount resulted in 7% conversion (entry 10, Table 1). This result is however encouraging because it showed that sulfur displayed some catalytic effect (oxidation of 1 mol of 4-picoline requires in principle 3 mol of sulfur). However, metallic iron is not catalytically active for this reaction. Although the equimolar mixture Fe/S was highly active at a 10% amount, this system displayed only negligible catalytic activity at 1% (entry 12, Table 1). This result suggested that, at low concentration, the iron sulfide formation decreases strongly. Moreover, in this case, sulfur is consumed in promoting the reaction between **1a** and **2a** as in entry 10, Table 1. Finally, a lower reaction temperature resulted in lower conversion (entry 13, Table 1).

To investigate the scope and limitation of this catalytic system, we next applied the optimized conditions to different substrates (Table 2). Pyridine and quinoline derivatives possessing a methyl group at the 2- or 4-position, **2a**−**g**, were all suitable substrates in the reaction with *o*-nitroaniline providing the corresponding benzimidazole products **3aa**−**3ag** in yields ranging from 56% to 91% (entries 1−7, Table 2). In the case of 2,4,6-trimethylpyridine, no remarkable difference in reactivity of the 2- and 4-methyl groups was observed. Both regioisomers **3af-2** and **3af-4** were obtained in a 2:1 ratio. However, 3-picoline **2h** failed to react with **1a** (entry 8, Table 2) and both starting materials were recovered unchanged. This result is in agreement with earlier observed reactivities of the methyl groups of picolines in elemental sulfur-mediated oxidation.[11] This difference in reactivity was demonstrated clearly when 3,4-lutidine **2g** reacted with *o*-nitroaniline **1a** and afforded only one product, **3ag**.[12] *o*-Nitroanilines **1b**−**h** having electron-donating and -withdrawing substituents on the benzene ring were all capable of reacting with 4-picoline **2a** to afford the corresponding benzimidazoles **3ba**−**3ha** in high to excellent yields (entries 9−15, Table 2). Moreover, the reaction displayed high functional group tolerance. Chloride, bromide, and methoxy functionalities are all tolerated. Interestingly even a reaction between dinitroaniline **1h** and **2a** could be achieved, leaving the other nitro group at the *para* position to aniline intact (entry 15, Table 2). Although **1i** is a highly sterically demanding substrate, the H-transfer process was successfully carried out with **2a** (entry 16, Table 2).

In addition, 2-methylbenzimidazoles (**2i**−**j**) can be oxidized and converted to the desired product **3ai**−**aj** in 66−85% yields (entries 17−19). Finally, *o*-nitrophenol **1j** reacted successfully with 2- and 4-methylquinolines **2b,d** (entries 20−21).

While the mechanism of the transformation is not clear at this moment, three important observations may be discussed. First, the methyl group must be located at the 2- or 4-position of the pyridine ring or at the 2-position of the benzimidazole ring.[13] Second, the catalytic activity of iron sulfide depends strongly on the preparation methods.[10] Third, during the reaction process, for example between **1a** and **2a**, only starting material **1a**, **2a** and benzimidazole product **3aa** were observed as the main components (by ^{1}H NMR of the methanol soluble part of reaction mixture). All the reaction intermediates were fixed on the surface of the iron sulfide catalyst, and the entire sequence of reactions including oxidation, reduction, and condensation was carried out on the surface as well. We tentatively propose the catalytic mode of the iron sulfide cluster. For clarity purposes, iron sulfide is presented as an uncharged Fe_4S_4 cube **A** (Scheme 2). The first step could be the fixation of methylhetaryl **2** on **A** in which a C−S bond is created with the removal of one hydride from the methyl group. *o*-Nitroaniline is fixed at the vicinal iron site by coordination to yield intermediate **B**. The next step could be the redox reaction between the methylene group with the nitro group with simultaneous removal of water to provide thioacetimidate **C**. Nucleophilic attack of the vicinal amino group on the thioacetimidate function would result in benzimidazole **2** and recycle the catalyst A.

In conclusion, we have developed a new, remarkably simple, and straightforward method for the direct coupling of amino/hydroxy nitrobenzenes and the methyl group bearing a 2-, 4-picolyl or 2-benzimidazolyl substituent providing 2-hetaryl-benzimidazoles/-benzoxazoles. The reaction employs a catalytic amount of iron sulfide generated in situ from the elements under solvent-free conditions. The utilization of inexpensive, readily available starting materials and catalyst are significant advantages

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that allow for the increased usefulness of the reaction. The reaction shows high generality, excellent selectivity toward the 2- and 4-methyl group of azine and 1,3-diazole systems, and good functional group tolerance. Mechanistic, scope, and limitation studies of the reaction as well as attempts to identify reaction intermediates are in progress.

■ ASSOCIATED CONTENT

Supporting Information

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.

■ AUTHOR INFORMATION

Corresponding Author

nguyen@icsn.cnrs-gif.fr

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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■ REFERENCES

(1) 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.

(2) (a) Spiro, T. G., Ed. *Iron-Sulfur Proteins*; John Wiley and Sons: New York, 1982. (b) Amstrong, F. *Adv. Inorg. Bioinorg. Mech.* **1982**, *1*, 65. (c) Stiefel, E. I.; George, G. N. *Ferredoxins, Hydrogenases, and Nitrogenases: Metal-Sulfide Proteins in Bioinorganic Chemistry*; University Science Books: 1994; pp 365−455. (d) Herskovitz, T.; Averill, B. A.; Holm, R. H.; Ibers, J. A.; Phillips, W. D.; Weiher, J. F. *Proc. Natl. Acad. Sci. U.S.A.* **1972**, *69*, 2437.

(3) Johnson, D.; Dean, D. R.; Smith, A. D.; Johnson, M. K. *Annu. Rev. Biochem.* **2005**, *74*, 247.

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

(5) Maden, B. E. H. *Trends Biochem. Sci.* **1995**, *20*, 337.

(6) (a) Abou-Jneid, R.; Ghoulami, S.; Martin, M.-T.; Tran Huu Dau, E.; Travert, N.; Al-Mourabit, A. *Org. Lett.* **2004**, *6*, 3933. (b) Schroif-Gregoire, C.; Travert, N.; Zaparucha, A.; Al-Mourabit, A. *Org. Lett.* **2006**, *8*, 2961. (c) Vergne, C.; Appenzeller, J.; Ratinaud, C.; Martin, M.-T.; Debitus, C.; Zaparucha, A.; Al-Mourabit, A. *Org. Lett.* **2008**, *10*, 493. (d) Nguyen, T. B.; Martel, A.; Dhal, R.; Dujardin, G. *Org. Lett.* **2008**, *10*, 4493. (e) Picon, S.; Tran Huu Dau, E.; Martin, M.-T.; Retailleau, P.; Zaparucha, A.; Al-Mourabit, A. *Org. Lett.* **2009**, *11*, 2523. (f) Nguyen, T. B.; Beauseigneur, A.; Martel, A.; Dhal, R.; Laurent, M.; Dujardin, G. *J. Org. Chem.* **2010**, *75*, 611. (g) Nguyen, T. B.; Sorres, J.; Tran, M. Q.; Ermolenko, L.; Al-Mourabit, A. *Org. Lett.* **2012**, *14*, 3202. (h) Nguyen, T. B.; Ermolenko, L.; Al-Mourabit, A. *Org. Lett.* **2012**, *14*, 4274. (i) Nguyen, T. B.; Ermolenko, L.; Al-Mourabit, A. *Heterocycles* **2012**, DOI: 10.3987/COM-12-S(N)53. (j) Nguyen, T. B.; Ermolenko, L.; Al-Mourabit, A. *Org. Lett.* **2012**, *14*, 5948.

(7) From carboxylic acids: (a) Charton, J.; Girault-Mizzi, S.; Sergheraert, C. *Chem. Pharm. Bull.* **2005**, *53*, 492. (b) Seijas, J. A.; Vazquez, T.; Pilar, M.; Carballido, R.; Raquel, M.; Crecente, C. J.; Romar-Lopez, L. *Synlett* **2007**, 313. (c) Maradolla, M. B.; Allam, S. K.; Mandha, A.; Chandramouli, G. V. *ARKIVOC* **2008**, *15*, 42. (d) Sharghi, H.; Asemani, O. *Synth. Commun.* **2009**, *39*, 860. (e) Wen, X.; Bakali, J. E.; Deprez-Poulain, R.; Deprez, B. *Tetrahedron Lett.* **2012**, *53*, 2440. From acid chlorides: (f) Harrop, T. C.; Rodriguez, K.; Mascharak, K. *Synth. Commun.* **2003**, *33*, 1943. (g) Brembilla, A.; Roizard, D.; Lochon, P. *Synth. Commun.* **1990**, *20*, 3379. From anhydrides: (h) Khilya, V.; Lezenko, G. A. *Chem. Heterocycl. Compd.* **1970**, *6*, 1584. (i) Quast, H.; Ach, M.; Kindermann, M. K.; Rademacher, P.; Schindler, M. *Chem. Ber.* **1993**, *126*, 503. From nitriles: (j) Hofmann, A. W. *Chem. Ber.* **1880**, *13*, 1238. (k) Shi, D. F.; Bradshaw, T. D.; Wrigley, S.; McCall, C. J.; Lelieveld, P.; Fichtner, I.; Stevens, M. F. *J. Med. Chem.* **1996**, *39*, 3375. (l) Kourounakis, A.; Charitos, C.; Rekka, E. A.; Kourounakis, N. *J. Med. Chem.* **2008**, *51*, 5861. (m) From esters: Campagne, E.; Van Verth, J. E. *J. Org. Chem.* **1958**, *23*, 1344. (n) Chakraborti, A. K.; Rudrawar, S.; Kaur, G.; Sharm, L. *Synlett* **2004**, 1533. From ortho-esters: (o) Bastug, G.; Eviolitte, C.; Markó, I. E. *Org. Lett.* **2012**, *14*, 3502. (p) Patil, A. V.; Lee, S. H.; Bandgar, B. *Bull. Korean Chem. Soc.* **2010**, *31*, 1719. (q) Mohammadpoor-Baltork, I.; Khosropour, A. R.; Hojati, S. F. *Monatsh. Chem.* **2007**, *138*, 663. (r) Mohammadpoor-Baltork, I.; Khosropour, A. R.; Hojati, S. F. *Catal. Commun.* **2007**, *8*, 1865. From imidates: (s) Sheng, C.; Che, X.; Wang, W.; Wang, S.; Cao, Y.; Yao, J.; Miao, Z.; Zhang, W. *Eur. J. Med. Chem.* **2011**, *46*, 1706. (t) Kristinsson, H. *Synthesis* **1979**, 102. (u) Gomez, E.; Avendano, C.; McKillop, A. *Tetrahedron* **1986**, *42*, 2625. From azlactones: (v) Katritzky, A. R.; Sakizadeh, K.; Swinson, J.; Helmann, S. M.; Krepski, L. R.; Pathre, S. V.; Rasmussen, J. K. *Synth. Commun.* **1988**, *18*, 651. (w) Harb, A. F. A.; Zayed, S. E.; El-Maghraby, A. M.; Metwally, S. A. *Heterocycles* **1986**, *24*, 1873. From amides: (x) Kornilov, M. Y.; Ruban, E. M. *Zhur. Org. Khim.* **1973**, *9*, 2188. (y) Botta, A. U.S. Patent US3972890 A1, 1976.

(8) Wu, M.; Hu, X.; Liu, J.; Liao, Y.; Deng, G. J. *Org. Lett.* **2012**, *14*, 2722.

(9) (a) Wuppwetal-Elberfeld, H. A. O. DE949059, 1953. (b) Yutilov, Y. M.; Shcherbina, L. I.; Smolyar, N. N. *Russian J. Org. Chem.* **1994**, *30*, 461.

(10) For reviews on the chemistry of iron sulfides, see: (a) Rickard, D.; Luther, G. W. *Chem. Rev.* **2007**, *107*, 514. (b) Venkateswara Rao, P.; Holm, R. H. *Chem. Rev.* **2004**, *104*, 527.

(11) Elemental sulfur is known for acting as an oxidizing agent of an activated methyl group in 4-picoline and analogues: (a) Gres'ko, S. V.; Smolyar, N. N.; Yutilov, Yu. M. *Russian J. Org. Chem.* **2001**, *37*, 1026. (b) Ahlmark, M.; Bäckström, R.; Luiro, A.; Pystynen, J.; Tiainen, E. WO2007/10085 A2, 2007. (c) Yutilov, Y. M.; Shcherbina, L. I.; Efremenko, A. F. *Chem. Heterocycl. Compd.* **1989**, *25*, 783. (d) Mazzone, G.; Puglisi, G.; Marchetta, G.; Corsaro, A. *J. Heterocycl. Chem.* **1984**, *21*, 181. (e) Hisano, T.; Ichikawa, M.; Tsumoto, K.; Tasaki, M. *Chem. Pharm. Bull.* **1982**, *30*, 2996. (f) Emmert, B.; Holz, A. *Chem. Ber.* **1954**, *87*, 676. (g) Saikachi, H.; Hisano, T. *Chem. Pharm. Bull.* **1959**, *7*, 716. (h) Porter, H. D. *J. Am. Chem. Soc.* **1954**, *76*, 127. (i) Miller, P. E.; Oliver, G. L.; Dann, J. R.; Gates, J. W., Jr. *J. Org. Chem.* **1957**, *22*, 664. (j) Würzburg, B. E.; Wuppwetal-Elberfeld, H. A. O.; Köln-Mülheim, M. G.; Würzburg, A. H. DE930926, 1953. Sulfur has been shown to act as a reducing agent in basic media for an aromatic nitro group: (k) McLaughlin, M. A.; Barnes, D. M. *Tetrahedron Lett.* **2006**, *47*, 9095. (l) Niknam, K.; Kiasat, A.-R.; Kazemi, F.; Hossieni, A. *Phosphorus, Sulfur Silicon Relat. Elem.* **2003**, *178*, 1385. (m) Kas'yan, O. A.; Tarabara, I. N.; Zlenko, E. T.; Kas'yan, L. I. *Russian J. Org. Chem.* **2002**, *38*, 165. (n) Huber, D.; Andermann, G.; Leclerc, G. *Tetrahedron Lett.* **1988**, *29*, 635. (o) Sato, R.; Takizawa, S.; Oae, S. *Phosphorus, Sulfur Relat. Elem.* **1979**, *7*, 229. (p) Porter, H. K. *Org. React.* **1973**, *20*, 455. (q) Cope, O. J.; Brown, R. K. *Can. J. Chem.* **1962**, *40*, 2317. (r) Hirao, N. *J. Osaka Inst. Sci. Technol.* **1950**, *1*, 57.

(12) The lower reactivity of the 3-picoline compared to 2- and 4-picolines has been observed for reactions with aldehydes under acidic conditions. It suggests that the 2- and 4-picolines react via a nonaromatic enamine intermediate. For examples, see: (a) Hamana, H.; Sugasawa, T. *Chem. Lett.* **1983**, 333. (b) Hamana, H.; Sugasawa, T. *Chem. Lett.* **1984**, 1591. We thank one of the referees for this constructive suggestion. Moreover, xylenes and mesitylene fail to react and were recovered unchanged. We thank the Editor for this useful suggestion.

(13) (a) Pryor, W. A. *Mechanism of Sulfur Reactions*; McGraw-Hill: New York, 1962. (b) Perregaard, J.; Thomsen, I.; Lawesson, S. O. *Acta Chem. Scand. B* **1975**, *29*, 538.