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Iron(II)-Catalyzed Direct Synthesis of NH Sulfoximines from Sulfoxides

*Hao Yu, Zhen Li, and Carsten Bolm**

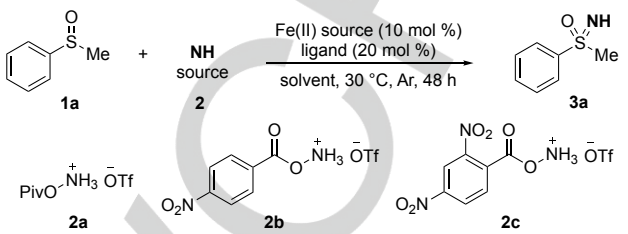
Abstract: *Free NH-sulfoximines have directly been prepared from sulfoxides by iron catalysis applying a readily available, shelf-stable hydroxylamine triflic acid salt. No additional oxidant is needed, and the substrate scope is wide including a range of heterocyclic compounds.*

Sulfoximines are of interest in various fields of research including synthetic organic chemistry,[1] crop protection,[2] and medicinal chemistry.[3] While initial protocols for preparing target compounds and relevant intermediates with sulfoximidoyl groups relied on the use of hazardous reagents such as azide/acid combinations or unstable hydroxyl amine derivatives, more recent methods predominantly involving metal catalysis allow applying safer reagents such as acid amides or dioxazolones.[4,5] Importantly, most of the latter strategies lead to N-functionalized sulfoximines, which need to be deprotected for obtaining the frequently desired free *N*H-derivatives. To avoid this additional step, Ge, Richards, and co-worker used *O*-(2,4-dinitrophenyl)-hydroxylamine (DPH) as imidating agent which under rhodium catalysis directly led to NH sulfoximines.[6] Subsequently, a remarkable breakthrough was reported by Bull, Luisi, and co-workers, who obtained such N-unprotected derivatives by treatment of sulfoxides with ammonium carbamate (as NH source) and diacetoxyiodobenzene (as oxidant).[7,8] The three goals of our study summarized here were: First, the direct preparation of NH sulfoximines, second, the avoidance of a previous metal catalyst (e. g. based on rhodium), and third, the use of a safe, bench-stable imidating agent that does not require the activation by an additional oxidant (such as a high-valent iodine reagent).

Iron catalysis in sulfoxide imidation was first described by Bach and Körber applying Boc-azide as nitrogen source.[9] We improved this approach by optimizing the iron catalyst, increasing the substrate scope, and developing asymmetric sulfur imidations.[10,11] In all cases, N-functionalized products resulted. Focusing on the three aforementioned goals and taking into account recent findings by Morandi[12] and Jiao[13] on iron-catalyzed aminohydroxylations and arene aminations, respectively, leading to products with free NH_2 groups, we wondered about the use of hydroxylamine triflic acids salts in sulfur imidations under iron catalysis. To initiate the study, phenyl methyl sulfoxide (**1a**) was chosen as representative substrate, which was combined with commercially available Fe^{II} phthalocyanine ($Fe^{II}Pc$) (10 mol %) and $PivONH_3OTf$ (**2a**) (2.5 equiv) in acetonitrile at 30 °C under argon.[14] To our delight, our hypothesis proved valid, and NH sulfoximine **3a** was obtained in 60% (NMR) yield (Table 1, entry 1). Changing the solvent from acetonitrile to 2,2,2-trifluoroethanol (TFE), hexafluoroisopropanol (HFIP), methanol, dichloromethane (DCM) or toluene had a negative effect on the yield of **3a** (Table 1, entries 2-6). A screening of iron(II) salt/ligand combinations (Table 1, entries 7-10) revealed that $FeSO_4$/phenanthroline was particularly effective in generating **3a** (72% yield). In the absence of the metal, no imidation occurred (entry 11). Changing the NH transfer agent from **2a** to arylhydroxylamine triflic acid **2b** resulted in an increase in yield of **3a**, which was now obtained in 80% yield (Table 1, entry 12).[15] With analogous **2c** as imidating agent, the yield of **3a** was only 71% (Table 1, entry 13).[15] Finally, by doubling the catalyst loading (from 10 mol % to 20 mol % of the iron salt while keeping the metal/ligand ratio the same; Table 1, entry 14) **3a** was isolated in 93% yield (with **2b** as NH source).[16]

Under the optimized conditions [20 mol % of $FeSO_4$, 40 mol % of 1,10-phenanthroline, in acetonitrile (0.5 M) at 30 °C under argon for 48 h] and with **2b** as NH source (2.5 equiv) the substrate scope was evaluated. The results are summarized in Scheme 1.[17]

Table 1: Evaluation of reaction conditions.[a]



Entry	Catalyst	Ligand[b]	Solvent	NH source[c]	Yield [%][d]
1	$Fe^{II}Pc$	–	MeCN	**2a**	60
2	$Fe^{II}Pc$	–	TFE	**2a**	43
3	$Fe^{II}Pc$	–	HFIP	**2a**	36
4	$Fe^{II}Pc$	–	MeOH	**2a**	5
5	$Fe^{II}Pc$	–	DCM	**2a**	trace
6	$Fe^{II}Pc$	–	toluene	**2a**	trace
7	$Fe(OAc)_2$	2,2'-bipy	MeCN	**2a**	trace
8	$Fe(acac)_2$	2,2'-bipy	MeCN	**2a**	trace
9	$FeSO_4$	2,2'-bipy	MeCN	**2a**	63
10	$FeSO_4$	1,10-phen	MeCN	**2a**	72
11	–	1,10-phen	MeCN	**2a**	n.r.
12	$FeSO_4$	1,10-phen	MeCN	**2b**	80
13	$FeSO_4$	1,10-phen	MeCN	**2c**	71
14[e]	$FeSO_4$	1,10-phen	MeCN	**2b**	98 (93)[f]

[a] Reaction conditions: **1a** (0.20 mmol), **2** (0.50 mmol), catalyst (0.02 mmol, 10 mol %), ligand (0.04 mmol; 20 mol %), solvent (0.5 M), 30 °C, under argon, 48 h. [b] 2,2'-bipy = 2,2'-bipyridine, 1,10-phen=1,10-phenanthroline. [c] Piv = pivalate, Tf = trifluoromethanesulfonyl. [d] As determined by ^{1}H NMR spectroscopy with dibromomethane as internal standard. [e] Use of 20 mol % of the iron salt and 40 mol % of the ligand. [f] Yield after column chromatography.

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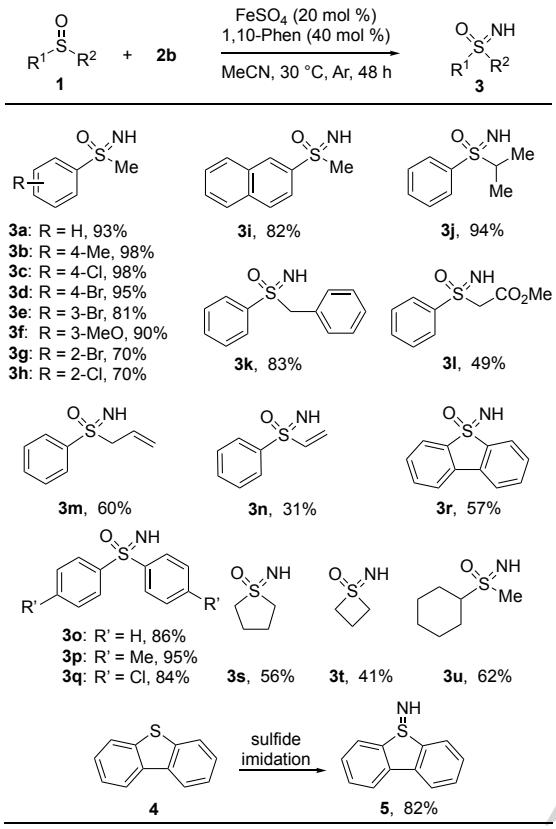
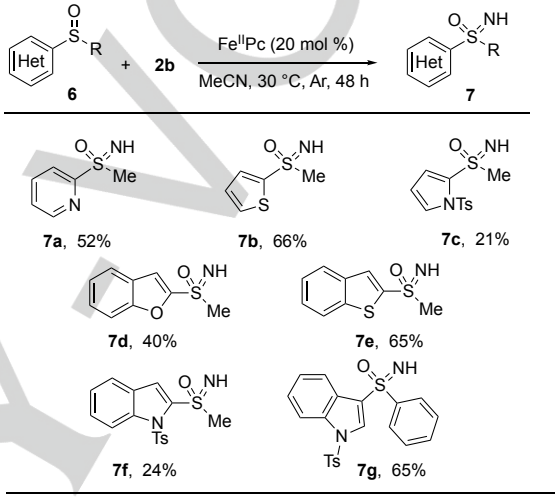


Scheme 1. Substrate scope of the iron-catalyzed sulfur imidation.

In imidations of *S*-aryl *S*-methyl sulfoxides, the process remained essentially unaffected by methyl, methoxy, halo, and aryl substituents on the arene. In all cases the yield of the corresponding NH sulfoximine **3a**-**i** was high ranging from 70% to 98%.[18] In this series, the lowest yields were obtained for *ortho*-bromo and *ortho*-chloro substituted products **3g** and **3h**, which could be attributed to steric factors affecting the catalysis. This interpretation was contrasted by the high yield of **3j** (94%) bearing a sterically more demanding *S*-isopropyl substituent (instead of an *S*-methyl group as in **3a**-**i**). NH Sulfoximines **3k** and **3l** were obtained in yields of 83% and 49%, respectively. Probably, those transformations were difficult because of the high acidities of the protons at the α-methylene groups. Unsaturation in the non-aromatic *S*-substituents was tolerated as revealed by the formations of allyl- and vinyl-containing products **3m** and **3n**. Apparently, imidation was favored over aziridination. Conversions of dibenzothiophene 5-oxide and other diaryl sulfoxides led to the corresponding NH sulfoximines in yields of 57% (for **3r**) and 84-95% (for **3o**-**q**). Finally, products **2s**-**u** were obtained in yields ranging from 41% to 61% indicating that also imidations of *S*,*S*-dialkyl-substituted sulfoxides proceeded well independent of their cyclic or acyclic nature. In the light of our interest in imidated compounds with a dibenzothiophene scaffold,[19] we also tested the formation of sulfilimine **5** starting from dibenzothiophene **4** under the given conditions (Scheme 1). To our delight, also this NH transfer to a sulfide proceeded well affording **5** in 82% yield.

Being aware that most sulfoximines with relevance for crop protection or medical applications contain heterocycles,[2,3] we decided to include such substrates in our study as well. To our disappointment the aforementioned optimized conditions proved unsuitable. Probably those compounds formed metal chelates hampering the catalysis. In light of the previous results summarized in Table 1 and hoping for an altered substrate activation path, the nature of the metal catalyst was changed and $Fe^{II}Pc$ was applied. To our delight, this approach proved successful, and with that iron(II) catalyst also sulfoxides with additional donor atoms in heterocyclic frames could be imidated. The data are shown in Scheme 2.



Scheme 2. Iron-catalyzed imidations of heterocyclic sulfoxides.

With **2b** as imidating agent, 2-pyridinyl-, 2-thienyl- and *N*-tosyl-protected 2-pyrrolyl-containing *S*-methyl sulfoxides afforded the corresponding NH sulfoximines **7a**-**c** in yields of 52%, 66%, and 21%, respectively. Furthermore, substrates with benzofuranyl, benzothienyl, and indolyl substituents including one with an *S*-phenyl group could be imidated leading to products **7d**-**g** in yields ranging from 24% to 65% (Scheme 2).

Although mechanistic interpretations of iron-catalyzed nitrogen transfer reactions have proven challenging,[20] we dare to suggest that the sulfur imidation reported here proceeds via an iron nitrene complex, which is formed by expulsion of *para*-nitro benzoic acid from salt **2b**. A subsequent direct oxidative nitrene transfer onto the substrate provides the product and regenerates the iron catalyst. We assume, also reflecting prior literature reports,[12,13] that in this reaction path triflic acid plays a significant role by triggering protonation events with importance for both the formation of relevant intermediates and a potential catalyst deactivation by the product through metal coordination.[21,22]

In summary, we discovered an iron-catalyzed direct synthesis of free NH sulfoximines from sulfoxides utilizing a readily accessible, shelf-stable aminating reagent. No additional oxidant is required, and the mild reaction conditions allow the preparation of NH sulfoximines with heteroaromatic substituents, which are difficult to access by other methods.

Experimental Section

General procedure for the sulfoximine synthesis (Scheme 1): Under argon atmosphere, a 10 mL sealed tube was charged with sulfoxides (0.2 mmol), reagent **2b** (166.0 mg, 0.5 mmol), $FeSO_4$ (6.1 mg, 0.04 mmol), phenanthroline (14.5 mg, 0.08 mmol) and MeCN (0.4 mL). Then, the reaction mixture was stirred at 30 °C for 48 h. After cooling to room temperature, the reaction mixture was quenched with a saturated $NaHCO_3$ solution (5 mL). The organic layer was separated from the aqueous one, which was extracted with CH_2Cl_2 (5 mL × 3). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The product was purified by column chromatography using silica gel as stationary phase and mixtures of pentane/ethyl acetate or ethyl acetate/methanol as eluent.
For the synthesis of heteroaromatic sulfoximines **7** (Scheme 2), the procedure was identical except that the $FeSO_4$/ligand combination was substituted by $Fe^{II}Pc$ (22.7 mg, 0.04 mmol).

Acknowledgements

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Keywords: imidation • iron catalysis • heterocycles • sulfoxides • sulfoximines

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[16] Considering that the imidating agents (used in excess) were TfOH salts with oxidation capability, we also applied $Fe(OTf)_2$ amd $Fe(OTf)_3$ as iron sources (20 mol %). Under standard conditions (with 2.5 equiv of **2b** and 40 mol % of 1,10-phen), they provided NH sulfoximine **3a** in 91% and 90% (NMR) yield, respectively. Performing the catalysis (under standard conditions) at 50 °C (instead of 30 °C) had only a minor effect on the reaction time.

[17] The transformations shown in Scheme 1 started from racemic sulfoxides. The use of enantioenriched (*S*)-**1a** (62% ee) with **2b** provided (*S*)-**3a** with retention of configuration showing that the imidation was stereospecific. Attempts to kinetically resolve racemic **1a** by substituting 1,10-phen by chiral py-Box ligands failed (for details see Supporting Information).

[18] Substrates with strongly electron-withdrawing substituents such as nitro groups proved unsuitable.

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[21] The importance of the acid being present in the reaction mixture was confirmed by the following experiments: 1. Use of the corresponding MsOH salt of **2b** gave product **3a** in 90% yield. 2. Applying the pure arylhydroxylamine (**2b** without TfOH led to **3a** in only 18% (NMR) yield. 3. In the presence of 2.5 equiv of K_2CO_3, the (NMR) yield of product **3a** was reduced to 42%.

[22] The reaction between the iron(II) salt and **2b** might also involve ET processes as suggested by Jiao and co-workers (ref. 13). Here, the presence of 2.0 equiv of TEMPO did not inhibit the catalysis but only reduced the yield of **3a** (to 72% as determined by NMR spectroscopy).

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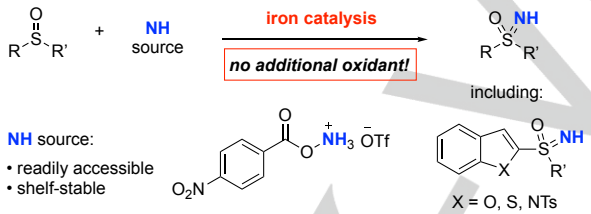

Simple iron catalysts activate a readily accessible, shelf-stable imidating agent allowing to convert sulfoxides to synthetically attractive free NH sulfoximines without the need of an additional oxidant. The substrate scope is wide including heterocyclic compounds which are difficult to imidate by other means.