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Desulfurization and H-Migration of Secondary Thioamides Catalyzed by an Iron Complex to Yield Imines and Their Reaction Mechanism

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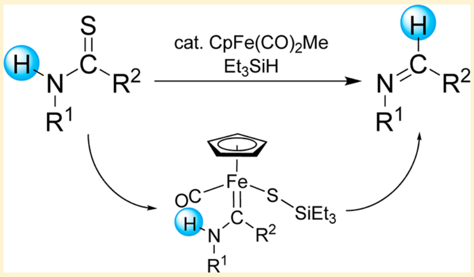
Ⓢ *Supporting Information*

ABSTRACT: Secondary thioamides were converted into imines as the major products using hydrosilane in the presence of an iron catalyst. An iron carbene complex with a silyl thiolato ligand was isolated as one of the intermediates of the catalytic cycle and was characterized by X-ray analysis.

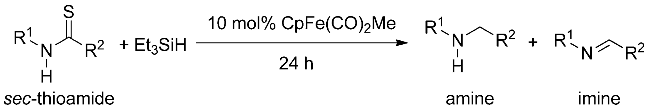


Efficient reduction of amides without the use of strong hydride reagents is of great interest in the development of medicines and drug candidates, as these compounds usually have many other fragments that are also reactive toward strong hydrides.[1] There are a number of reports concerning reduction of amides to amines by hydrosilanes with the help of a transition metal catalyst.[2] Among the many transition metals that are suitable as such catalytic centers, iron has attracted considerable attention because of its high natural abundance, low cost, and low toxicity. In 2009, Nagashima and co-workers reported that [$Fe(CO)_5$] and [$Fe_3(CO)_{12}$] were effective catalysts for thermal and photoassisted reduction of tertiary amides to tertiary amines, using bifunctional hydrosilane and polymethylhydrosiloxane (PMHS) as reducing agents.[3] Pannell et al.[4] and our group[5] recently reported that $CpFe(CO)_2Me$ (**1**) (Cp = η^5-C_5H_5) served as a catalyst for reactions of tertiary amides with R_3EH (E = Si, Ge) to give amines, and we proposed that an iron carbene complex was an intermediate.

In other work, the reduction of amides to imines has been reported,[6,7] where Schwartz's reagent (Cp_2ZrHCl) was used as a reducing agent;[5] however, under some reaction conditions this method led to the production of aldehydes.[8] In contrast, until recently, there were no reports on the reduction of thioamides. Pannell et al.[9] and we[10] reported desulfurization of thioamide (Me_2NCHS) by hydrosilane (R_3SiH) in the presence of $Mo(CO)_6$ and **1**, respectively, to give amine (NMe_3) and disilathiane ($R_3SiSSiR_3$). Herein, we describe the first example of secondary thioamides being reduced to form imines as the major or sole product, by hydrosilanes in the presence of a catalytic amount of **1**. The isolation and characterization of one of the intermediates are also reported.

Catalytic reductions of secondary thioamides were examined under conditions similar to those previously reported for tertiary thioamides.[5a] Tetrahydrofuran (THF, 0.43 mL), $CpFe(CO)_2Me$ (0.053 mmol), *N*-phenylthiobenzamide (PhNHC(S)Ph, 0.53 mmol), and triethylsilane (Et_3SiH, 2.7 mmol) were charged in a Schlenk tube, and the solution was heated at 80 °C for 24 h (Table 1, entry 1). The ^1H NMR spectra and GC-MS analysis of the products demonstrate the formation of *N*-benzylaniline ($PhNHCH_2Ph$) and *N*-benzylideneaniline (PhN═CHPh). The formation of $(Et_3Si)_2S$ was also confirmed by the ^1H NMR results, but the amount could not be estimated because of its degradation to disiloxane by the Fe complex.[11] This is the first example of desulfurization of *sec*-thioamide to give an imine by using a transition metal catalyst, although the TON was only 1.7. This catalytic reaction is notable owing to the susceptibility of transition metal catalysts

Table 1. Catalytic Desulfurization of Secondary Thioamides with a Methyl Fe Complex in Et_3SiH



entry	*sec*-thioamide	equiv of Et_3SiH	condition	TON[a] of amine	TON[a] of imine
1[b]	PhNHC(S)Ph	5	80 °C	0.6	1.7
2[b]	PhNHC(S)Ph	5	hν[d]	0	trace
3[c]	PhNHC(S)Ph	30	80 °C	1.0	7.4
4[c]	MeNHC(S)Ph	30	80 °C	trace	2.4
5[c]	PhNHC(S)Me	30	80 °C	0	0
6[c]	$PhCH_2NHC(S)Ph$	30	80 °C	2.1	6.5
7[c]	$PhCH_2NHC(S)H$	30	80 °C	0	0

[a]The value is based on the concentration of $CpFe(CO)_2Me$. [b]0.060 M THF solution. [c]In free solvent. [d]Photoirradiation at 5 °C

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to be poisoned by S-containing compounds. Desulfurization to form the imine was also observed using a photoinitiated reaction; however, only a low efficiency was achieved (entry 2). Comparison of entries 1 and 3 shows that a large excess of Et_3SiH led to high conversion efficiency. Other thioamides were also converted into the corresponding amines and imines (entries 4 and 6) via the Fe-catalyzed reaction; however, those listed as entries 5 and 7 did not react under these conditions. Therefore, it is speculated that a Ph substituent on the thioamide C is essential for successful desulfurization. The effect of the hydrosilane on desulfurization was next examined under the reaction conditions shown in entry 3 of Table 1, and it was found that the products were dependent on the particular hydrosilane used as the reducing agent (Table 2). When Et_3SiH was used, PhN═CHPh (imine) was formed as a major product, with $PhNHCH_2Ph$ (amine) as a minor product (<1/7th the yield of PhN═CHPh) (entry 1). In contrast, when Me_2PhSiH was used, the corresponding amine was exclusively formed (entry 2), and when $MePh_2SiH$ was used, only the imine was catalytically formed (entry 3). For Ph_3SiH, the imine was produced exclusively, but not catalytically (entry 4). Therefore, the results indicate that the selective formation of secondary amines or imines can be achieved by use of an appropriate hydrosilane, although the reason for the selectivity is not yet clear.

Table 2. Desulfurization with Hydrosilane under Thermal Conditions

$$\mathrm{PhNHC(S)Ph} + 30\ \text{equiv}\ \mathrm{R_3SiH} \xrightarrow[80\ ^\circ\mathrm{C},\ 24\ \mathrm{h}]{10\ \mathrm{mol\ \%\ CpFe(CO)_2Me}} \mathrm{PhNHCH_2Ph} + \mathrm{PhN{=}CHPh}$$

entry	R_3SiH	TON[a] of amine	TON[a] of imine
1	Et_3SiH	1.0	7.4
2	Me_2PhSiH	2.0	0
3	$MePh_2SiH$	0	2.6
4	Ph_3SiH	0	0.8

[a] The value is based on the concentration of $CpFe(CO)_2Me$.

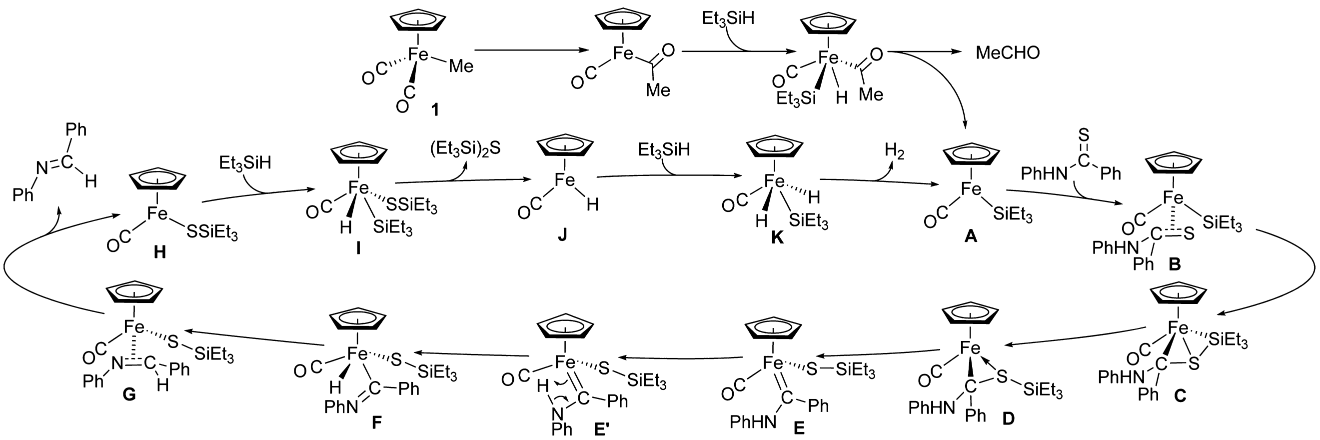
Scheme 1 shows a proposed catalytic cycle for the reaction of **1** with Et_3SiH and PhNHC(S)Ph. The 16*e* species, CpFe(CO)(C(O)Me), is formed by CO insertion under heating, followed by the oxidative addition of the Si−H bond in Et_3SiH and the reductive elimination of MeCHO to form **A**. PhNHC(S)Ph then interacts with **A** to give **B** in the η^2-CS coordination fashion. The silyl group in **B** migrates from Fe to the S atom via a pentavalent Si complex **C** to produce the Fe−C−S three-membered-ring complex **D**. Successive C−S bond cleavage in the coordination sphere gives amino-carbene complex **E**. These reaction sequences are the same as those for the desulfurization of tertiary thioamides.[10] Those are a sort of a silyl-migration-induced reaction (SiMI reaction).[10,12]

The subsequent reaction sequences for secondary thioamides are different from those for tertiary thioamides, where a Si−H bond of the hydrosilane adds to the Fe═C double bond. The N−H bond in the substituent on the carbene carbon in **E** adds to the Fe═C double bond to give **F**. This step presumably takes place intramolecularly (**E′**), although an intermolecular addition cannot be ruled out. This addition has not been reported to date; however, it has been shown that an H in an NHR group on a carbene carbon can be replaced by using an electrophile.[13] Dötz and co-workers reported the alkylation of the N in an aminocarbene complex by reaction with lithium diisopropylamide (LDA) and an alkyl halide.[13c] Complex **F** undergoes reductive elimination of the imine PhN═CHPh with formation of **H** via **G**. As **H** is a 16*e* species, an oxidative addition of the Si−H bond in Et_3SiH takes place to give **I**, followed by a reductive elimination of the $(Et_3Si)_2S$ detected in the reaction system to give **J**. A subsequent oxidative addition of Et_3SiH to give **K** and a reductive elimination of H_2 to afford **A** then complete the catalytic cycle.

According to the catalytic cycle, dihydrogen gas (H_2) was expected to be formed. In order to check it, the gas portion in the reaction of entries 1 and 3 shown in Table 1 was bubbled in a C_6D_6 solution individually, and the solutions were subjected to the ^1H NMR measurement. A singlet at 4.48 ppm assignable to H_2 was observed marginally in the former and clearly in the latter, indicating the formation of dihydrogen in the catalytic cycle.

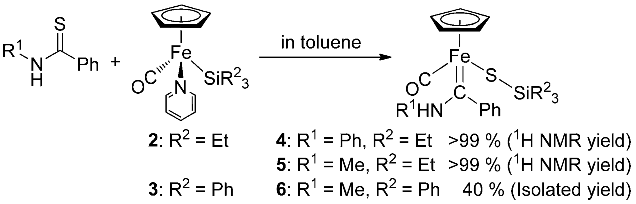
In order to obtain further experimental evidence supporting this proposed cycle, isolation of carbene Fe complex **E** was attempted. The isolation of **E** from the reaction mixture of **1**, Et_3SiH, and PhNHC(S)Ph was unsuccessful. However, reactions of $R^1NHC(S)Ph$ (R^1 = Ph, Me) with CpFe(CO)(py)(SiR^2_3) (py = pyridine; R^2 = Et (**2**), Ph (**3**)), considered as a synthon of a 16*e* complex CpFe(CO)(SiR_3),[5,12c−e] resulted in the isolation of amino-carbene complexes. Treatment of **2** with PhNHC(S)Ph in toluene for 2 h gave **4** in a high yield according to the NMR measurement, but the isolation as a solid

Scheme 1. Proposed Reaction Sequence



was not successful (Scheme 2). In contrast, **6** obtained in the reaction of **3** with MeNHC(S)Ph could be isolated as an orange powder in 40% yield.

Scheme 2. Synthesis of *sec*-Amino-carbene Iron Complexes



The unprecedented *sec*-amino-carbene Fe complex was confirmed using X-ray analysis (Figure 1). The Fe was seen to take a distorted three-legged piano-stool structure. The bond distance of Fe1−C1 (1.9036(17) Å) agrees with that of a typical Fe═C bond in a Fischer-type carbene.[14] The structures of **6** and the corresponding amino-carbene complex CpFe(CO){C(NMe$_2$)H}(SSiPh$_3$) (**7**)[10] were found to be similar: (i) the N1−C1−Fe1 angle was 123.01(15)° for **6** and 135.96(12)° for **7**, being larger by 13° presumably due to the steric repulsion between the Me group and the Fe center; (ii) the C1−N1−C2 angle was 127.5(2)° for **6** and 123.56(13)° for **7**; and (iii) the torsion angle of C2−N1−C1−Fe1 was −174.52(13)° for **6** and 169.06(12)° for **7**. As the N of **7** could be seen to have a planar geometry that indicates sp^2 hybridization, it is highly likely that N1 of **6** was also sp^2 hybridized, although the position of H1 could not be determined by the X-ray analysis. The position of H1 was obtained using calculations assuming the sp^2 hybridization of N1. The distance between N1 and Fe1 was found to be 2.8357(12) Å, which is shorter than the sum of the van der Waals radius of N (1.55 Å)[15] and the atomic radius of Fe (1.56 Å).[16] Therefore, some interaction between H1 on N1 and Fe1 or between the N1−H1 bond and Fe1 is indicated, meaning that the barrier of H1 migration to Fe1 would be lower.

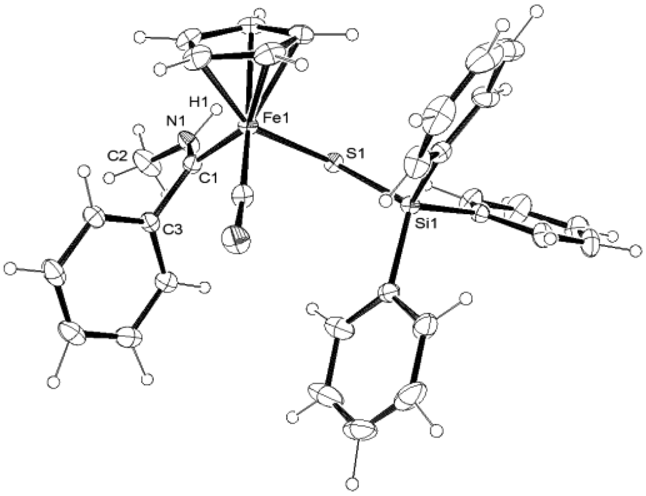


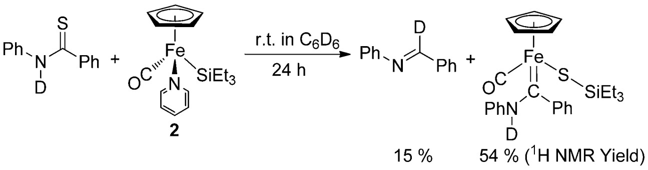
Figure 1. ORTEP drawing of carbene complex **6**.

Complex **6** was dissolved in C$_6$D$_6$ and heated at reflux temperature for 24 h, and the formation of MeN═CHPh in 9% yield was observed by ^{1}H NMR. This yield is approximately equal to the amount of MeN═CHPh in the thermal reaction of **1** with 1 equiv of Ph$_3$SiH and 1 equiv of MeNHC(S)Ph in C$_6$D$_6$ for 24 h. The catalytic activity of a *sec*-amino-carbene complex was also investigated. Complex **5**, prepared according to Scheme 2, was treated with MeNHC(S)Ph and Et$_3$SiH at 80 °C for 24 h and was found to generate MeN═CHPh with a TON of 3.2 (eq 1). These results demonstrate that a *sec*-amino-carbene complex is an intermediate in the desulfurization of MeNHC(S)Ph.

$$\mathrm{MeNHC(S)Ph} + 30\ \text{equiv}\ \mathrm{Et_3SiH} \xrightarrow[24\ \text{h}]{10\ \text{mol}\ \%\ \mathbf{5},\ 80\ °\text{C}} \underset{\text{TON 3.2}}{\mathrm{MeN{=}CHPh}} \tag{1}$$

Reaction of pyridine−Fe complex **2** with partially deuterated *sec*-thioamide PhNDC(S)Ph was also examined in C$_6$D$_6$ at room temperature for 24 h. The NMR and GC-MS spectra of the reaction mixture suggest the formation of the corresponding imine, PhN═CDPh, and a carbene complex (Scheme 3).

Scheme 3. Reaction of 2 with Deuterated Thioamide



In conclusion, this study constitutes the first example of desulfurization of a *sec*-thioamide to imine by an Fe-methyl complex. A *sec*-amino-carbene complex was isolated in the reaction of a pyridine−Fe complex with a *sec*-thioamide and characterized by X-ray analysis. The carbene complex was demonstrated to be an intermediate in the reaction pathway, enabling elucidation of the mechanism of the Fe complex-mediated transformation.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Text giving detailed experimental procedures and the characterization data for the products and a CIF file giving crystallographic data for **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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