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Iron-catalyzed selective reduction of nitro compounds to amines

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ABSTRACT

An efficient reduction of the nitro group with a catalytic amount of $Fe(acac)_3$ and TMDS in THF at 60 °C affording the corresponding amine is described.

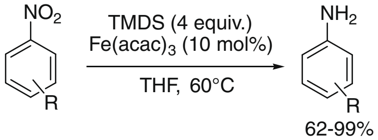
Amines can be prepared by the reduction of the nitro precursor by hydrogenation, electron-transfer, electrochemical, and hydride-transfer conditions.[1] The reduction of nitro functions to amines by iron was first described in 1854 by Bechamp.[2] Despite the efficiency of this reaction, the low cost and toxicity of iron, this technology presents two major drawbacks. The first one concerns the utilization of more than a stoichiometric amount of iron powder and the second one is the acidic medium which is not compatible with many organic functions. Other metals have been used including cobalt,[3] zinc,[4] tin,[5] and molybdenum.[6]

Over the last decade, silanes or siloxanes have been associated with metals in order to perform nitro compound reductions under milder conditions. However metals used in these cases are very expensive Pd,[7] Pt,[8] Rh,[9] or Re.[10] In the literature, only few articles relate the reduction of organic functionality in the presence of environmentally benign iron. Aldehydes[11] and ketones[12] can be reduced to alcohols or alkanes[13] with silanes or siloxanes. Iron complexes allowed the hydrogenation of double or triple bonds.[14] Recently, Nagashima[15] reported the reduction of amides to amines. He pointed out the high reactivity for the nitro group in the presence of an amide by the use of a catalytic system involving iron carbonyl and TMDS in toluene at 100 °C. The drawback associated with the methodology is the release of carbon monoxide and the high temperature leading to excess pressure in the reaction vessel. This work prompted us to report our preliminary results that benefit of a lower temperature and environmentally benign conditions.

In our laboratory, we previously described the reduction of phosphine oxides to phosphines[16] and more recently the reduction of the cyano group to amine[17] in the presence of $Ti(OiPr)_4$ and TMDS (1,1,3,3-tetramethyldisiloxane). In order to eliminate the risk of generating pyrophoric gases from silanes,[18] only siloxanes (PMHS and TMDS) were used. In this Letter, we described the reduction of the nitro group to amine with a catalytic quantity of $Fe(acac)_3$ and 4 equiv of TMDS in THF at 60 °C (Scheme 1).

We started our investigation by testing different sources of iron, using PMHS as the reducing agent (Table 1).

The formation of the desired product was observed with $Fe(OAc)_2$, $Fe(acac)_3$, and $Fe(acac)_2$ (Table 1, entries 1, 3, 4, 5, 6). However, when catalytic quantities of iron were used only $Fe(acac)_3$ and $Fe(acac)_2$ displayed interesting results (Table 1, entries 5 and 6). No conversion was observed with other iron sources.



Scheme 1. Reduction of the nitro function to amine.

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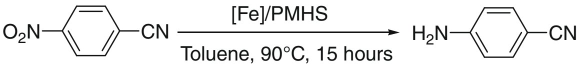
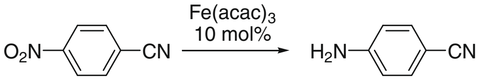
Table 1
Reduction of 4-nitrobenzonitrile with different iron sources



Entry	Iron Source	Quantity (mol/mol)	PMHS (SiH equiv)	Conv.[a] (%)
1	$Fe(OAc)_2$	1	2	44
2		0.1	4	–
3	$Fe(acac)_3$	1	2	90
4		0.2	4	85
5		0.1	4	55
6	$Fe(acac)_2$	0.1	4	51
7	$FeCl_3$	1	2	–
8	$FeCl_2$	1	2	–
9	$K_3Fe(CN)_6$	1	2	–

[a] Conversions were determined with ^1H NMR.

Table 2
Conditions study



Entry	Solvent	Siloxane	*T* (°C)	*C*	Time	Conv. (%)
1	Toluene	PMHS	90	0.5	17 h	55
2		TMDS	60	1	48 h	>98
3	THF	PMHS	70	0.5	17 h	93
4		TMDS	60	1	24 h	>98
5	MeTHF	TMDS	60	1	24 h	>98
6	DEC[a]	TMDS	60	0.6	24 h	50
7	*t*-BuOH	TMDS	60	0.6	4 d	>98

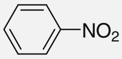
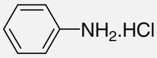
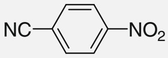
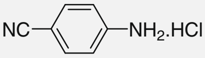
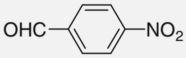
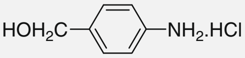
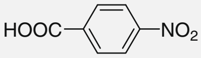
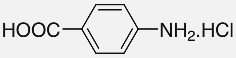
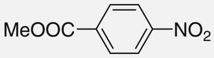
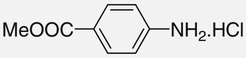
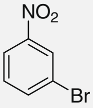
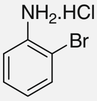
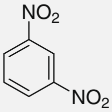
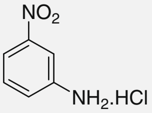
Conversions were determined with ^1H NMR.
[a] DEC: diethylcarbonate.

Moreover when reaction occurred, the formation of a gel was observed and may prevent complete conversion after 48 h. This is the major drawback of PMHS. Thus, studies were carried out with TMDS and different solvents were evaluated.

Based on the known activated effect of fluorides,[7b,19] some tests were realized in the presence of fluoride sources CeF_3, TBAF, and KF. No significant improvement was observed. Because of the low boiling point of TMDS (71 °C), tests were realized at lower temperature in order to avoid the use of sealed tubes. At room temperature, after 36 h the conversion was less than 5%, but at 60 °C in 24 h good results were obtained. When the experiments were performed in toluene (Table 2, entry 2), DEC (Table 2, entry 6), or *t*-BuOH (Table 2, entry 7) the reactions were slower. Without the solvent, the reaction mixture was heterogeneous and conversion was not complete after 36 h. A solvent screening indicated that the best results were obtained in THF or MeTHF. MeTHF is more expensive than THF but is environmentally more friendly. $Fe(acac)_2$ and $Fe(acac)_3$ have shown similar reactivity but from an economical point of view only cheaper Fe^{III} was employed. Best conditions[20] (Table 2, entry 4) were applied on different nitroarenes.

As depicted in Table 3, the reduction of aromatic nitro compounds is selective and efficient except when the nitro compound is *para* substituted by an aldehyde (Table 3, entry 3). In this particular case, the aldehyde, substituted by a withdrawing group, is probably reduced first followed by the conversion of the nitro group into amine. Moreover Beller[11] previously reported that $Fe(acac)_3$ was not a good catalyst for the reduction of aldehyde to alcohol. Only 5% conversion of benzaldehyde to alcohol was detected. When nitroarenes are substituted by other functionalities, carboxylic acids (Table 3, entry 4), nitriles (Table 3, entry 2), or esters (Table 3, entry 5), this method is selective, only nitro groups are reduced to amines. The nitro arene substituted by an ester function has shown, surprisingly, a low reactivity in comparison with the nitrile derivative. In order to obtain complete conversion, the reaction was performed in toluene at 90 °C (Table 3, entry 5). In the

Table 3
Reduction of different nitro compounds to amines

Entry	Substrates	Amines	Conversion (%)	Time (h)	Isolated yield (%)
1			100	24	>99
2			100	24	92
3			100	24	80
4			87	24	62
5			100	48	95[a]
6			100	24	>99%
7			44 85	24 48	nd 66
8			100	24	98

Conditions: nitro compounds (2 mmol), $Fe(acac)_3$ (0.2 mmol), TMDS (8 mmol), THF, 60 °C. Conversions were determined with ^1H NMR. Isolated as hydrochlorides salts with >99% purity.
[a] Reaction was performed in toluene at 90 °C.

presence of a bromide substituent (Table 3, entries 6 and 7), no dehalogenated product was observed. However, a difference in reactivity between *ortho*- and *meta*- substituted nitroarene was noticed. From the 1,4-dinitrobenzene (Table 3, entry 8) under this condition only one nitro function was reduced. The reaction was performed on 3 g (20.2 mmol) of *p*-nitrobenzonitrile. Same isolated yield was obtained (Table 3, entry 2). Analytical data of the prepared compound were compared to those of the literature.[21]

In conclusion, we have developed a mild, safe, and efficient reduction procedure of the nitro function to amine. This method can constitute an alternative to the Bechamp procedure which presented several drawbacks detailed above. Scope and limitations as well as mechanistic investigations are currently underway in our laboratory.

Acknowledgment

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20. *Typical procedure for the reduction of nitro compounds*: In a solution of nitro compound (2 mmol) in 0.6 mL of THF were added Fe(acac)$_3$ (10 mmol %, 70 mg) and TMDS (4 equiv or 8 Si-H, 1.4 mL). After 24 h under heating the reaction mixture was diluted with Et$_2$O 5 mL, stirred for 5 min, and filtered through a plug of Celite (top layer) and neutral alumina (bottom layer) in a 1 cm diameter column by flushing with EtOAc. The filtrate was concentrated, diluted with a minimum of toluene, and mixed with 1 M HCl. The aqueous layer was washed with toluene, and concentrated to afford the desired product.
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