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Selective Reduction of Nitro-Compounds to Primary Amines by Nickel-Catalyzed Hydrosilylative reduction

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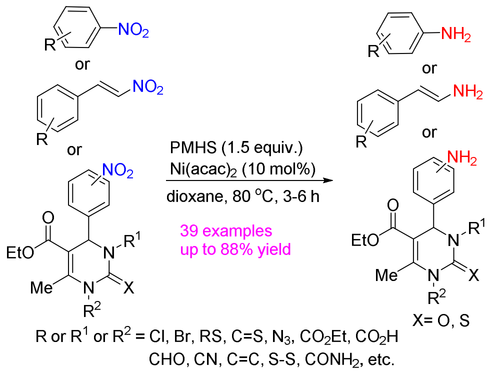
Unprecedentedly high Chemoselectivity: The tolerance of many kinds of functional groups such as aryl-chloride, aryl-bromide, alkene, alkynyl, ester, ether, oxhydryl, carboxylic acid, cyanogroup, nitrine, carbonyl, acyl, thioether and some heterocycle groups was studied for the reduction of nitro-compounds.



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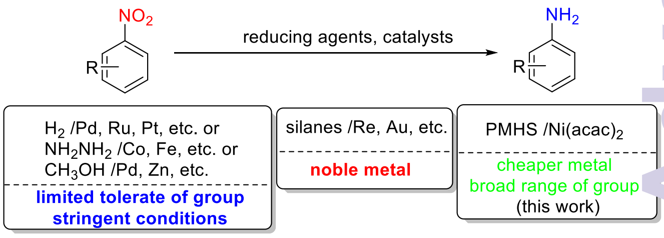
$Ni(acac)_2$ and PMHS were found to be excellent catalytic system for the chemoselective transfer hydrogenation of nitro-compounds to primary amines. Under mild conditions. A series of nitro-compounds containing a variety of sensitive functional groups including aldehydes, esters, cyano, and nitrine were reduced to their corresponding amines in good to excellent yields with no byproduct.

Amines are useful intermediates in the preparation of dyes, pharmaceuticals, and agricultural chemicals and can be easily obtained by the reduction of aromatic nitro-compounds.[1] Among the numerous available methodologies, reductions via hydrogenation with noble metal-based catalysts (Pd,[2] Ru,[3] Pt,[4] etc.), hydrazine hydrate/catalysts (Co,[5] Fe,[6] etc.), methanol/catalysts (Pd,[7] Zn,[8] etc.) or under transfer hydrogenation conditions are largely employed (Scheme 1). However, these conventional methods for nitro reduction not only involve environmentally harmful stoichiometric reducing agents and stringent conditions such as high pressure and temperature but also may suffer from the use of hazardous reagents (e.g., hydrazine). Significantly, most of these methods lack the desired chemoselectivity over other functional groups that are often present in the substrates such as alkene, halide and nitrile. In addition, reduction of nitro-compounds often stops at an intermediate stage, yielding hydroxylamine, hydrazines, and azoarenes. Due to the high importance of selective reduction of nitro-compounds, the search for alternative efficient and highly chemo- and regioselective methods remains an important target in organic synthesis.

Over the last decades, silanes have appeared to be new potential reducing agents because of their special advantages (mild conditions, high chemoselectivity and easy workup) when associated with metals. Unfortunately, several silanes have been demonstrated harmful since they generate a dangerous and toxic SiH_4 gas. As a consequence, siloxanes having Si-O-Si bridge are considered as being a good alternative to silanes. Indeed, PMHS (polymethylhydrosiloxane), a 40 units polymer, and TMDS (tetramethyldisiloxane) are safer since they are not known to release this dangerous gas. Besides, Nagashima has reported that siloxanes having Si-O-Si bridge like PMHS and TMDS could show greater efficiency with their "dual Si-H effect", in which two proximate Si-H groups cooperatively could accelerate the reaction.[9] When associated with different metals, silanes and siloxanes can selectively reduce many reducible functional groups including nitro group. For example, Fernandes has reported a catalytic systems $PhMe_2SiH/ReIO_2(PPh_3)_2$ (5 mol %) and $PhMe_2SiH/ReOCl_3(PPh_3)_2$ (5 mol %) selectively reduced a series of aromatic nitro-compounds at refluxing temperature.[10] Lykakis has described a nitro-reduction method using Au nanoparticles catalysts with silanes at low catalyst loading (0.5-1 mol %).[11] Lemaire has also reported a hydrosilation system using iron catalysts. Although iron is a good alternative to noble metals, the chemoselectivity was not very good, and the tedious reaction time (24-48 h) was hard to accept.[12] Herein, we reported a convenient and efficient reduction of nitro-compounds with PMHS. After the exploratory study on the choice of the metal catalysts, nickel emerged as an ideal candidate. And we also tried many kinds of substrates with different functional groups to prove its chemoselectivity (scheme 1).



Scheme 1. Different Processes for the Reduction of Nitro-Compounds

Initially, we studied the reduction of the test substrate nitrobenzene **1a** catalyzed by metal catalysts in the presence of PMHS as the reductant in DMF at 100 °C for 12 h (Table 1). Among

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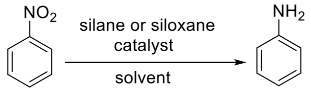
the tested metal catalysts, the active catalysts were Fe(acac)$_3$ and Ni(acac)$_2$, however, no reaction was found with Zn(OAc)$_2$, NiCl$_2$, NiCl$_2$(PPh$_3$)$_2$, FeCl$_3$ or Fe(OAc)$_2$ (Table 1, entries 1-7). Other silanes were examined in combination with PMHS but resulted in lower yields of the reduction product **2a**. TMDS as an "dual Si-H effect" siloxane was tested with Ni(acac)$_2$, but the reaction occurred with lower yield of **2a** (Table 1, entry 8). Besides, the inefficiency of EtO$_3$SiH (single "Si-H") was proved when it was used as the reductant in this reaction (Table 1, entry 9).

We then tried to control reaction time and the amount of PMHS in order to find out the best reaction condition. Interestingly, by adjusting the amount of PMHS to 1.5 and 2 equiv, respectively, full conversion of nitrobenzene **1a** was achieved affording aniline **2a** in both 72% yield (Table 1, entries 10 and 11). Decreasing the reaction time markedly to 3 h, the yield could still be 71% (Table 1, entry 12). As expected, in the absence of any metal-catalyst, none **2a** was formed (Table 1, entry 13).

In consideration of the importance and influence of solvents and temperature, the searches for the appropriate solvent and temperature were also summarized (Table 1, entries 14-23). When the reaction was conducted in MeOH, EtOH, toluene, CHCl$_3$, CH$_2$Cl$_2$, THF or DMSO, xylene at refluxing or 100 °C led to lower reactivity (Table 1, entries 14-21). Gratefully, by using dioxane, full conversion of **1a** was achieved affording **2a** in 84% or 81% yield at 100 or 80 °C, respectively (Table 1, entries 22 and 23).

Table 1. Screening of the Conditions for the Catalyzed Reduction of Nitrobenzene to Aniline[a]



1a

2a

Entry	Catalyst (10 mol/%)	Reductant (equiv.)	Solvent	Temp. °C	Time (h)	Yield[b] (%)
1	FeCl$_3$	PMHS (1)	DMF	100	12	N.R.[c]
2	Fe(OAc)$_2$	PMHS (1)	DMF	100	12	N.R.
3	Fe(acac)$_3$	PMHS (1)	DMF	100	12	48
4	Zn(OAc)$_2$	PMHS (1)	DMF	100	12	N.R.
5	NiCl$_2$	PMHS (1)	DMF	100	12	N.R.
6	NiCl$_2$(PPh$_3$)$_2$	PMHS (1)	DMF	100	12	N.R.
7	Ni(acac)$_2$	PMHS (1)	DMF	100	12	65
8	Ni(acac)$_2$	TMDS (1.5)	DMF	100	3	66
9	Ni(acac)$_2$	EtO$_3$SiH (3)	DMF	100	3	trace
10	Ni(acac)$_2$	PMHS (1.5)	DMF	100	12	72
11	Ni(acac)$_2$	PMHS (2)	DMF	100	12	72
12	Ni(acac)$_2$	PMHS (1.5)	DMF	100	3	71
13	-	PMHS (1.5)	DMF	100	3	N.R.
14	Ni(acac)$_2$	PMHS (1.5)	methanol	60	3	32
15	Ni(acac)$_2$	PMHS (1.5)	ethanol	60	3	36
16	Ni(acac)$_2$	PMHS (1.5)	THF	60	3	46
17	Ni(acac)$_2$	PMHS (1.5)	CH$_2$Cl$_2$	40	3	< 20
18	Ni(acac)$_2$	PMHS (1.5)	CHCl$_3$	40	3	< 20
19	Ni(acac)$_2$	PMHS (1.5)	toluene	100	3	48
20	Ni(acac)$_2$	PMHS (1.5)	xylene	100	3	54
21	Ni(acac)$_2$	PMHS (1.5)	DMSO	100	3	68
22	Ni(acac)$_2$	PMHS (1.5)	dioxane	100	3	84
23	Ni(acac)$_2$	PMHS (1.5)	dioxane	80	3	81

[a] Reaction conditions: nitrobenzene (1.0 mmol), solvent (3 mL). [b] Isolated yield (all of the products were purified by column chromatography). [c] No reaction.

After these studies on the nitrobenzene **1a**, the best conditions (Table 1, entry 23) were applied on different nitro-compounds (Scheme 2). As depicted in Scheme 2, the reduction of aromatic nitro-compounds was selective and efficient. When nitroarenes were substituted with bromine or chlorine (Scheme 2, **2b**-**2e**), no dehalogenated product was observed in comparison to hydrogenation in classical conditions with palladium on charcoal.[13] Moreover, when it with other functionalities such as ether (Scheme 2, **2n** and **2o**), hydroxy (Scheme 2, **2j** and **2k**), carboxylic group (Scheme 2, **2i** and **2m**), alkenyl (Scheme 2, **2s**), amide (Scheme 2, **2** or disulfide (Scheme 2, **2u**), the reaction showed high selectivity and only the nitro group was reduced to the corresponding amines in moderate yield with no byproduct.

Although Fe(acac)$_3$[12] and ReIO$_2$(PPh$_3$)$_2$[10] have been proved as effective catalysts, the chemoselectivity of carbonyl group did not realize. To our surprise, herein, we found the atalytic system from

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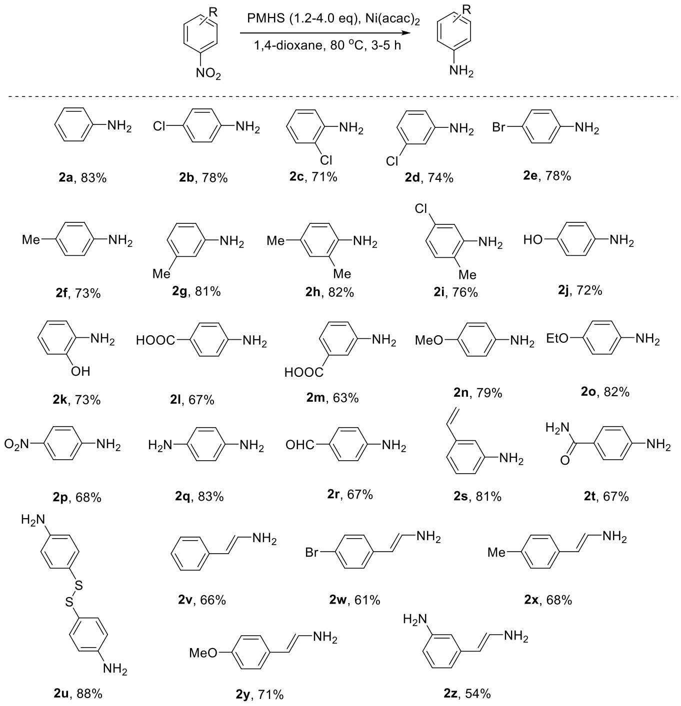
$Ni(acac)_2$ and PMHS is a more efficient catalysts with high chemoselectivity of several kinds of functional groups besides carbonyl group (Scheme 2, **2r**). Nevertheless the reaction time was very important for the reduction of *p*-nitrobenzaldehyde, or it would form a series of amines in extending time.

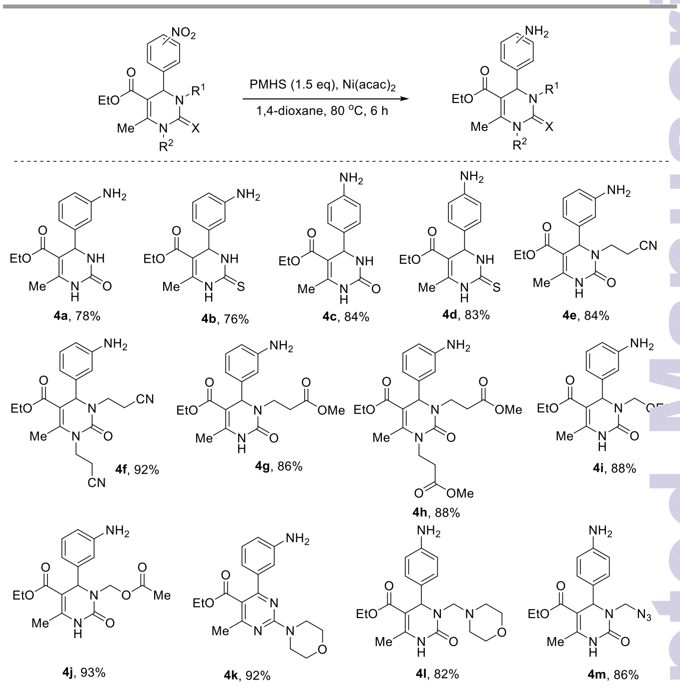
According to the high utility of this protocol as mentioned above, we considered applying it to the reduction of nitroalkene derivatives. Thankfully, it could be reduced to the corresponding enamines with no byproduct (Scheme 2, **2v**-**2z**). In this way, strong reducing agents, noble catalysts and tedious procedures were avoided as well, and it might be a good alternative to some non-reducing methods such as the dehydration of hydroxylamines.

After that, we were interested to test the reduction with two nitro groups. In the case of the 1,4-dinitrobenzene, only one nitro was reduced to amine with 1.2 eq PMHS in 3 h (Scheme 2, **2p**). If the amount of PMHS was elevated to 4 equivalent, diamine was obtained in 83% yield within 5 h (Scheme 2, **2q**). However, we could only obtain the double nitro reduced product when uses 1,2-bis(4-nitrophenyl)disulfane and 1-nitro-3-(2-nitrovinyl)benzene as substrates, no matter how much the reductant was used (Scheme 2, **2u** and **2z**).



Scheme 2. Chemoselective Reduction of Nitro-Compounds with PMHS Catalyzed by $Ni(acac)_2$

Based on the wide ranging biological activity of 3,4-dihydropyrimidinones and its utilization as an important precursor in the synthesis of pyrimidine bases,[14] as well as our continuous interest in the synthesis of novel pyrimidine derivatives,[15] we would like to further explore this protocol to the reduction of the derivatives of 3,4-dihydropyrimidin-2(1H)-one (DHPM) (Scheme 3). It was also efficiency (higher isolate yield in 6 hours), and high chemoselectivity of several functional groups performed unexpectedly. As depicted in Scheme 3, only the nitro group in different functionalized DHPMs were reduced under the optimal reaction conditions. According to this work, the tolerance of thiocarbonyl, cyano, ester, ether, nitrine, and heterocycle groups such as morpholine, pyrimidone was very fine.



Scheme 3. Chemoselective reduction of DHPMs with PMHS catalyzed by $Ni(acac)_2$

Conclusions

In summary, we have demonstrated that the catalytic system PMHS/$Ni(acac)_2$ is an efficient and convenient protocol for the reduction of nitro-compounds. Compared with the conventional methods, this reduction protocol provides an unprecedentedly high chemoselectivity toward aryl-chloride, aryl-bromide, alkene, alkynyl, ester, ether, oxhydryl, carboxylic acid, cyanogroup, nitrine, carbonyl, acyl, thioether and some heterocycle groups. Besides, no reduction byproduct was detected during the reaction process.

In addition, the high stability of $Ni(acac)_2$ and PMHS toward air and moisture makes the reaction be conducted under air atmosphere. Other outstanding advantages of this protocol include the use of PMHS, given that PMHS is produced as a byproduct in silicone industry on a large scale. Ni(acac)2 is commercially available and the reaction only requires a couple of hours to go to completion, and all of these features make this newly developed conditions attractive for synthetic chemists.

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