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Graphical Abstract

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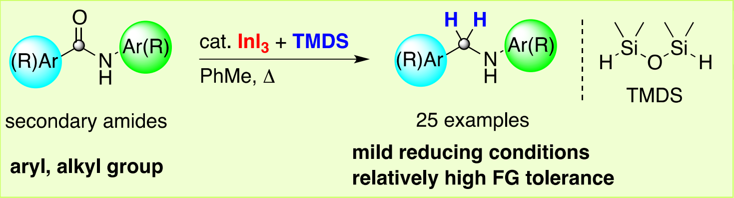

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Indium-Catalyzed Reduction of Secondary Amides with a Hydrosiloxane Leading to Secondary Amines

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ABSTRACT

Described herein is that the selective reduction of aromatic/aliphatic secondary amides using a combination of InI_3 and TMDS (1,1,3,3-tetramethyldisiloxane), which led to the production of the corresponding secondary amines. This reducing system showed a relatively high tolerance to a variety of functional groups, such as an alkyl, an alkoxy, a halogen, a cyano, an ether, a thioether, a heterocyclic ring, and a terminal alkene group.

1. Introduction

The approach to secondary amines through a catalytic reduction of the corresponding secondary amides is a central and important functional group transformation in organic synthesis, because this transformation is a simple and straightforward procedure in a laboratory-scale experiment, and the basic frameworks of secondary amines are widely found in naturally occurring products and biologically active substances.[1] Traditionally, to achieve the reduction of a secondary amide with one hydrogen on the nitrogen atom, the use of relatively strong hydride reagents that are derived from group 13 metalloids or metals, such as $(BH_3)_2$, BH_3•THF, $LiAlH_4$, and DIBAL, has been required.[2] However, these reagents directly influence undesirable functional groups, which leads to the production of unnecessary side-products, and produces large amounts of aluminum residue, which makes it difficult to isolate the desired product. Thus, to solve these problems, the combination of a transition metal catalyst with an easier-handling and mild reducing reagent, a hydrosilane has been recently utilized.[3,4]

For example, Fuchikami reported that the reduction of secondary amides with a hydrosilane was catalyzed by a Ru complex either with or without EtI as a cocatalyst.[5] Ohta described the Rh(I)-catalyzed reduction of secondary amides, but this catalytic system produced a mixture of secondary amines and imines.[6] Also, Nagashima *et al*. found that transition metal complexes containing Ru or Pt, effectively catalyzed the hydrosilylation of secondary amides, producing corresponding secondary amines.[7] Beller and co-workers found that a combination of either $Cu(OTf)_2$ or $Zn(OTf)_2$ and TMDS, or a combination of a heterocyclic boronic acid and $PhSiH_3$ catalyzed the reduction of secondary amides.[8] Moreover, Brookhart reported that an Ir(I) complex effectively catalyzed the hydrosilylation of secondary amides.[9] In this context, by using the Hantzsch ester and triethylsilane, a metal-free reduction of secondary amides has been developed.[10] Quite recently, Cantat and Adronov independently reported the $B(C_6F_5)_3$-catalyzed hydrosilylation of secondary amides.[11]

Compared with the catalytic reduction of tertiary amides with a metal catalyst,[5-7,12] that of secondary amides using a main group catalyst has not been studied systematically with the exception of examples using zinc and boron catalysts. We also found that a reducing system consisting of an indium(III) compound and a hydrosilane showed chemoselective activation to nitrogen-containing functional groups, such as an amide and a nitro group.[13,14] However, for secondary amides, the substrate employed under our reducing conditions (5 mol % of $InBr_3$, 4 equiv (*Si-H*) of Et_3SiH and $CHCl_3$ reflux) was limited to two examples (acetanilide and benzanilide), and the application of the reducing system to secondary amides with a variety of functional groups remained still unclear.[13c] Thus, after re-examinations of the reaction conditions, we found that a novel reducing system composed of InI_3 and TMDS successfully promoted the selective reduction of a variety of secondary amides, which led to the production of the corresponding secondary amines. In this letter, we report the results.

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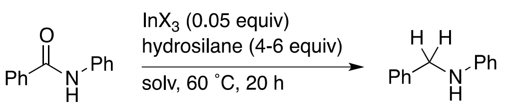
2. Results and Discussion

On the basis of the results shown in an indium-catalyzed deoxygenation of esters and tertiary amides in the presence of triethylsilane,[13c,d] when reduction of benzanilide was initially conducted with $InBr_3$ (0.05 equiv) and Et_3SiH (*Si-H*: 4 equiv) under $CHCl_3$ reflux conditions, the expected *N*-benzylaniline (**1**) was obtained in only a 21% yield (entry 1 in Table 1). Therefore, a solvent effect was then examined using several solvents including THF, CH_3CN and DMF, but these solvents showed no effect for this reduction (entries 2-4). Among several hydrosilanes examined, TMDS showed the highest reduction effect (entries 5-9). The use of $InCl_3$, $In(OAc)_3$ and $In(OTf)_3$ resulted in the recovery of the starting amide, but the use of InI_3 caused an outstanding activation of the amide to produce the secondary amine in a good yield (entries 10-13). Finally, two conditions composed of InI_3 and TMDS (*Si-H*: 6 equiv) in $CHCl_3$ at 60 ˚C or in toluene at 100˚C gave the best result (entries 14 and 15).

Table 1. Examination of reaction conditions with an secondary aromatic amide



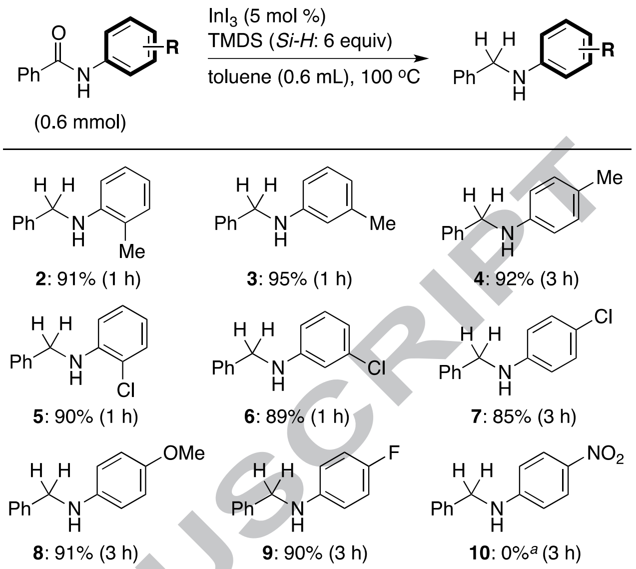
1

Entry	InX_3	Hydrosilane (*Si-H*: equiv)	Solvent	Yield (%)[a]
1	$InBr_3$	Et_3SiH (4)	$CHCl_3$	21
2	$InBr_3$	Et_3SiH (4)	THF	trace
3	$InBr_3$	Et_3SiH (4)	CH_3CN	trace
4	$InBr_3$	Et_3SiH (4)	DMF	trace
5	$InBr_3$	$PhSiH_3$ (4)	$CHCl_3$	23
6	$InBr_3$	Me_2PhSiH (4)	$CHCl_3$	24
7	$InBr_3$	$(EtO)_3SiH$ (4)	$CHCl_3$	trace
8	$InBr_3$	PMHS (4)	$CHCl_3$	trace
9	$InBr_3$	TMDS (4)	$CHCl_3$	40
10	$InCl_3$	TMDS (4)	$CHCl_3$	trace
11	$In(OAc)_3$	TMDS (4)	$CHCl_3$	trace
12	$In(OTf)_3$	TMDS (4)	$CHCl_3$	trace
13	InI_3	TMDS (4)	$CHCl_3$	87
14	InI_3	TMDS (6)	$CHCl_3$	99 (60)[c]
15	InI_3	TMDS (6)	PhMe[b]	(95)

[a] GC (Isolated) yield based on the sample after quenching with H_2O. [b] Bath temperature at 100 ˚C for 1 h. [c] TMDS (*Si-H*: 2 equiv).

Then, the scope and limitations to this reduction of secondary amides that derived from benzoic acid and a variety of aniline derivatives with the optimal conditions were examined (Table 2).[15] In most amides with either electron-donating or electron-withdrawing groups, such as a methyl group, a methoxy group and halogens, on an aniline moiety, the expected reduction proceeded smoothly to produce the corresponding secondary amines **2-9** in good to excellent yields. Also, the location of a substituent on the benzene ring had no direct effect on the chemical yield. When the amide with a nitro group on the benzene ring was treated with the InI_3-TMDS system, the consumption of the starting amide was observed, and finally resulted in the formation of a complicating mixture.[16]

Table 2. Reduction of benzanilide derivatives leading to *N*-arylbenzylamine derivatives

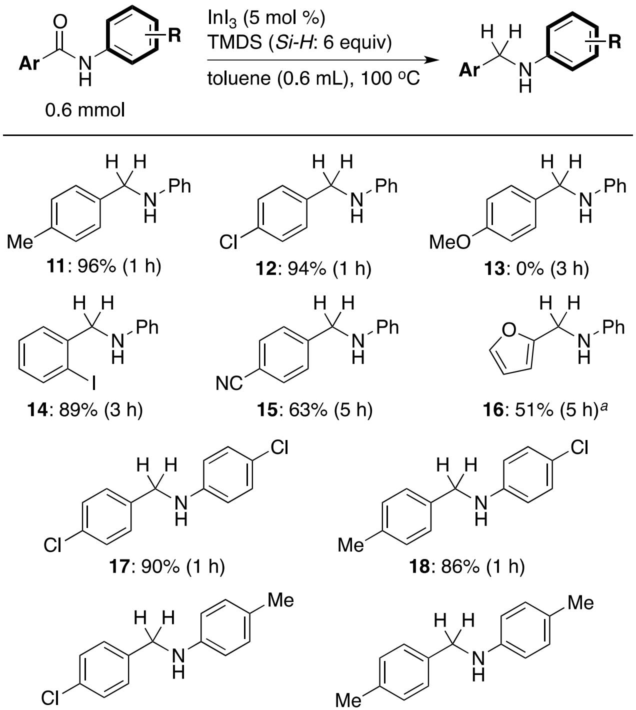


2: 91% (1 h)
3: 95% (1 h)
4: 92% (3 h)
5: 90% (1 h)
6: 89% (1 h)
7: 85% (3 h)
8: 91% (3 h)
9: 90% (3 h)
10: 0%[a] (3 h)

[a] A complex mixture was formed.

Next, the reduction of secondary amides with some type of substituent either on the benzoyl moiety or on both benzene rings was examined (Table 3). With a substituent, such as a methyl or a chloro group, the expected deoxygenation was smoothly completed within 1 h to produce secondary amines **11** and **12** in excellent yields. In sharp contrast to the result from compound **8**, the amide with a 4-methoxy substituted benzene ring next to the carbonyl group did not undertake the reduction, resulting in the formation of unidentified compounds without the recovery of the starting amides.[16] There was no clear reason for this result at this stage, probably due to the low electrophilicity of the carbonyl

Table 3. Reduction of various secondary amides leading to secondary amines



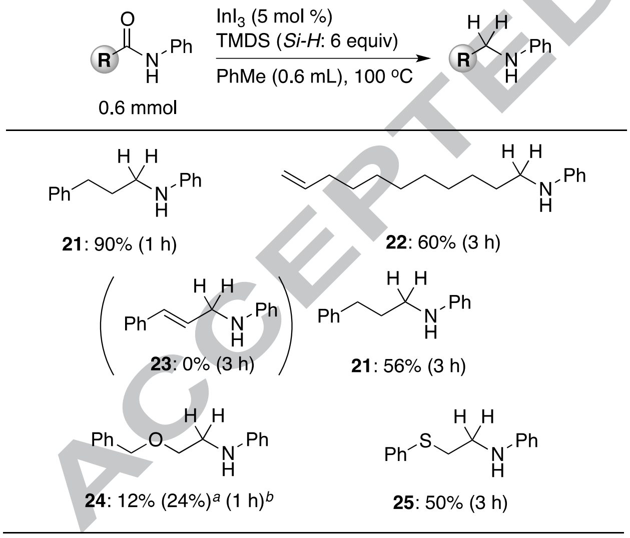
11: 96% (1 h)
12: 94% (1 h)
13: 0% (3 h)
14: 89% (3 h)
15: 63% (5 h)
16: 51% (5 h)[a]
17: 90% (1 h)
18: 86% (1 h)
19: 80% (1 h)
20: 78% (1 h)

[a] Temp = 60 ˚C.

group. An iodide substituent on the benzene ring remained after reduction, and the corresponding secondary amine **14** was obtained in a good yield. On the other hand, unlike the result with a $B(C_6F_5)_3$-TMDS system,[11b] when the reaction was carried out using an amide with a cyano group, the desired amine **15**, in which the cyano group remained after reduction, was produced in a relatively good yield. As extension of the substrate, when using the secondary amide with a furan ring, the reaction proceeded to produce the corresponding amine **16** in a moderate yield. Four types of amides with an electron-donating and/or electron-withdrawing group on two benzene rings produced the corresponding secondary amine derivatives **17**-**20** in good yields.

Then, to show the utility of the reducing system, *N*-phenylated secondary amides with an aliphatic group on the acyl group side were reduced under optimal conditions, as summarized in Table 4. In most cases, the alkyl chain on the acyl moiety had no influence on the chemical yield. Interestingly, a terminal alkene moiety on the amide showed a high tolerance, and the expected amine **22** was obtained. By contrast, the amide with a conjugated double bond was totally reduced by this reducing system to produce saturated secondary amine **21** without the expected amine **23**. The result agreed with the results from a $B(C_6F_5)_3$-TMDS system reported by Cantat *et al.*[11a] On the other hand, a reductive conversion of the secondary amide with an ether moiety was rather low, producing the amine **24** in a low yield. When the reduction of the secondary amide with a thioether unit was carried out, the corresponding amine **25** was produced in a moderate yield.

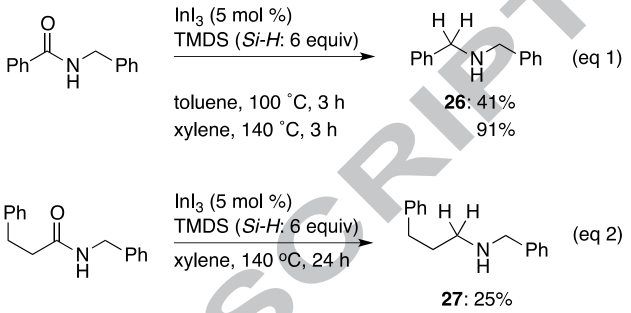
Table 4. Reduction of several *N*-arylated secondary amides leading to secondary amines



[a] GC yield. [b] Temp = 60 °C.

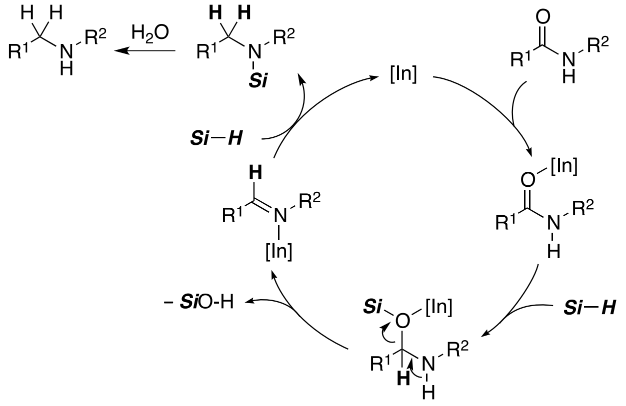
Moreover, to confirm whether this reducing system activates an *N*-alkyl substituted amide or not, we attempted the reduction of several secondary amides with an aliphatic substituent (Scheme 1). Contrary to our expectations, under the toluene reflux conditions, product **26** derived from *N*-benzylbenzamide was obtained in a low yield (41%) and the recovery of the starting amide. Thus, when the reaction temperature was raised to the xylene reflux conditions (140 °C), this problem was successfully solved, producing **26** in a 91% yield (eq 1 in Scheme 1).[17] On the other hand, when the reaction of the *N*-alkylated secondary amide, which was prepared from both an aliphatic amine and acid chloride, was conducted with the InI_3-TMDS reducing system under the xylene reflux conditions, the conversion of the amide was rather low to give the corresponding amine **27** in only a 25% isolated yield with the recovery of the starting amide (eq 2 in Scheme 2). It seemed that the stability of an imine intermediate with both aliphatic groups would be rather lower than that of an imine with only one aromatic group, which hinders the forward drive of the reaction.

Scheme 1. Application to the reduction of *N*-alkylated secondary amides



We proposed a plausible reaction path for the reduction of secondary amines as well as that suggested by a $Fe_3(CO)_{12}$-catalyzed reduction of tertiary amides with a hydrosilane (Scheme 2).[12e] First, hydrosilylation of an amide activated by InI_3 occurs to give an *N*,*O*-acetal intermediate. Then, the generated acetal would be converted to a thermodynamically stable imine intermediate by liberation of a silanol. Finally, the imine is reduced again by a further hydrosilane to produce the corresponding secondary amine after a common work-up.

Scheme 2. A plausible reaction path for the reduction of secondary amides



3. Conclusions

We have demonstrated the direct conversion of a variety of secondary amides to the corresponding secondary amines with an InI_3-TMDS reducing system, and have found that the present reducing system tolerates a variety of functional groups: an alkyl, a cyano, halogens, a heterocyclic ring, an ether chain, a sulfide unit and a terminal alkene. Also, via an increase in the reaction temperature the present method could be applied to the reduction of *N*-alkylated secondary amide to a certain extent.

Acknowledgments

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15. General procedure for the indium-catalyzed reductive preparation of secondary amines: To a 5 mL screw-capped vial containing a freshly distilled toluene (0.6 mL) were successively added under N_2 secondary amide (0.6 mmol), InI_3 (0.030 mmol, 15 mg) and 1,1,3,3-tetramethyldisiloxane (1.80 mmol, 318 μL). After the vial was sealed with a cap that contained a PTFE septum, the mixture was stirred at 100 ˚C (bath temperature), and monitored by GC analysis. After completion of the reaction, the reaction was quenched with H_2O. The aqueous layer was extracted with $CHCl_3$ (6 mL x 3), the organic phases were dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure. The crude product was purified by silica gel chromatography (hexane/AcOEt = 9/1) to give the corresponding secondary amine. If necessary, the isolated product was subjected to a gel permeation chromatography with chloroform as an eluent. All secondary amine prepared by this procedure were known compounds, and the characterization was confirmed by NMR spectra shown in the literature. For detailed procedure and spectra, see supporting information.
16. See supporting information.
17. Although Cantat's group reported the formation of dibenzylamine from *N*-benzylbenzamide, Adronov *et al* confirmed no formation of the same secondary amine under almost the same conditions. Both opposite results confused us to discuss our result, see ref 11a and 11b.

Supplementary Material

Copies of the ^{1}H and ^{13}C NMR spectra of the secondary amines that were produced by this procedure were supplied.