



One-step conversion to tertiary amines: InBr₃/Et₃SiH-mediated reductive deoxygenation of tertiary amides

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ABSTRACT

We have developed a simple and practical procedure for a direct reductive conversion from a variety of tertiary amides to the corresponding tertiary amines using an InBr₃/Et₃SiH reducing system. This reducing system can be applied to the reduction of a secondary amide and provides a more efficient alternative to conventional methods that use aluminum and boron hydrides.

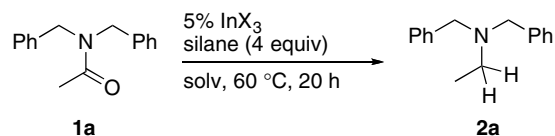
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The reductive transformation of an amide to an amine has occupied a central and important position in organic syntheses.¹ Conventionally, aluminum hydride reagents such as LiAlH₄ and DIBAL,² boron hydrides such as NaBH₄ and (BH₃)₂,³ or a reducing system that combines hydrides with an additive⁴ has been utilized to achieve this objective. Generally, these relatively strong reducing reagents have several disadvantages that often restrict the utility of the synthetic procedure: the undesirable reduction of substituted groups other than the carbonyl group, the production of several byproducts, the removal of the aluminum residue from the crude product, and laborious handling in an usual laboratory. Recently, a convenient and selective procedure using either a Lewis acid or a transition metal and a milder and an easier-handling hydrogen source, a hydrosilane, has been demonstrated.⁵ In this context, during the last decade several groups have reported that a reducing system comprises an indium salt and a milder reducing reagent, a hydrosilane, functions as a highly effective tool for the reductive conversion of a functional group involving the dehalogenation of organic halides, the reduction of alcohols, the 1,4-reduction of enones, and reductive aldol reactions.⁶ We also found that an InBr₃-Et₃SiH reducing system effectively promotes direct and selective reduction of a carbonyl group on esters to produce the corresponding ethers.⁷ Herein, we report that this InBr₃-Et₃SiH reducing system can be adapted to successfully complete a selective reduction of the carbonyl group of tertiary amides, which leads

to the production of the corresponding tertiary amines. Also, the reducing reagents accommodated the reductive transformation of a secondary amide to a secondary amine.

Initially, reduction of *N,N*-dibenzylacetamide (**1a**) with an indium catalyst and a hydrosilane was examined as a model reaction.⁸ Based on our previous study,⁷ when the reaction was conducted with 5% InBr₃ and 4 equiv of Et₃SiH in chloroform at 60°C, the expected reduction proceeded cleanly to produce the desired tertiary amine **2a** in 90% yield (run 1 in Table 1). However, when a similar reaction was carried out with InCl₃ and In(OTf)₃,

Table 1
Examination of reaction conditions



Run	InX ₃	Silane	Solvent	Yield ^a (%)
1	InBr ₃	Et ₃ SiH	CHCl ₃	(90)
2	InCl ₃	Et ₃ SiH	CHCl ₃	Trace
3	In(OTf) ₃	Et ₃ SiH	CHCl ₃	48
4	InBr ₃	PhMe ₂ SiH	CHCl ₃	65
5	InBr ₃	Ph ₂ SiH ₂	CHCl ₃	46
6	InBr ₃	(Me ₂ SiH) ₂ O	CHCl ₃	51
7	InBr ₃	Et ₃ SiH	CH ₃ CN	Trace
8	InBr ₃	Et ₃ SiH	PhH	Trace

^a GC yield (isolated yield).

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a recovery of the starting material and a drastic decline of product yield was observed (runs 2 and 3). Thus, it was found that only InBr_3 was highly effective for reduction of the tertiary amide and showed outstanding catalytic activity. Running this reaction with PhMe_2SiH , Ph_2SiH_2 , and $(\text{Me}_2\text{SiH})_2\text{O}$, instead of Et_3SiH , resulted in a reduced product yield (runs 4–6). Interestingly, use of CH_3CN , a solvent that is widely used in reductive functional group conversions in the presence of an indium halide and a silane compound, did not give the desired product. Instead, it led to the recovery of the starting material (run 7). Also, when the reaction was conducted in PhH , the reaction did not proceed (run 8). Consequently, a reducing system composed of 5% InBr_3 and 4 equiv of Et_3SiH in CHCl_3 proved to give the best results.

With the optimized conditions shown in Table 1, the generality of this reduction was examined using a variety of tertiary amides (Table 2). In all cases using a tertiary amide derived from benzamide, the reductive deoxygenation proceeded cleanly, producing the corresponding benzylamine derivatives **2b–d** in moderate to good yields (runs 2–4). The substrates comprises an acetanilide moiety also converted to the expected aniline derivatives **2f–i** in practical yields (runs 5–9). In particular, this InBr_3 – Et_3SiH reducing system was also applicable to the reduction of amide **1f** involving a heterocyclic skeleton such as indoline (run 6). In addition, it was found that a cyano group on the benzene ring, which is sensitive to a common reducing reagent, such as BH_3 and LiAlH_4 , is tolerant of our reducing system (run 7). Similarly, aliphatic groups, such as a *t*-butyl group and a cyclopropane ring, on the carbonyl group did not influence the reducing system (runs 10 and 11).⁹ Interestingly, for an aliphatic amide having a benzyl moiety or a benzene ring somewhere in the substrate, although the reduction of the aliphatic amide required quite long reaction times to complete, the corresponding amines **2l,m** were obtained in relatively good yields (runs 12 and 13). It was found that a bromide substituent on the benzene ring would not reduce with the present reducing agent. In contrast, the use of the aliphatic amide without a benzene ring gave the aliphatic amine derivatives **2n,o** in low yields with the recovery of the starting materials after 72 h (runs 14 and 15).

On attempted reaction of *N*-methyl-*N*-phenylformamide (**3**), the expected *N,N*-dimethylaniline (**4**) was obtained in 47% yield with 23% yield of unexpected dimerized product **5** (Scheme 1).¹⁰

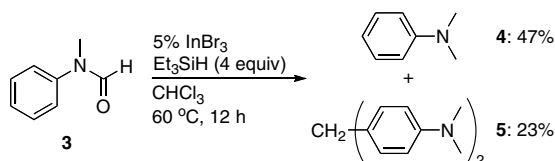
To extend the application of the present reducing agent, the reaction using a secondary amide was examined under our standard conditions (Scheme 2). Thus far, success in the reduction of a secondary amide using a silane has been limited to several transition-metal complexes besides a highly reactive reducing reagent, such as aluminum and boron hydrides.^{5d,5g,5h} Thus, when reduction using acetanilide (**6a**) and benzanilide (**6b**), which was derived from aniline, was performed with the InBr_3 – Et_3SiH reducing system, the expected reaction proceeded to produce *N*-ethyl-aniline (**7a**) and *N*-benzylaniline (**7b**) in 45% and 72% yields, respectively.¹¹

For the reaction mechanism of the present reducing system, we assume that the reduction proceeds via the following path shown in Scheme 3: (i) first, hydroindation of a starting amide with HInBr_2 and an exchange reaction of the formed indium intermediate with Et_3SiBr consecutively occur to generate an *N,O*-acetal intermediate;¹² (ii) the intermediate further transforms to an iminium (imine) intermediate through InBr_3 -promoted desoxygenation; and (iii) reduction of the iminium ion occurs, finally leading to the corresponding amine with regeneration of InBr_3 . In addition, no ring-opening product was obtained during the reduction of an amide having a cyclopropane ring (run 11 in Table 1),¹³ and neither was there a corresponding ring product from a substrate having a cyano group through 5-*exo*-zig cyclization (run 7 in Table 1).¹⁴ These results strongly imply that the reduction proceeds via not a radical path, but an ionic mechanism.

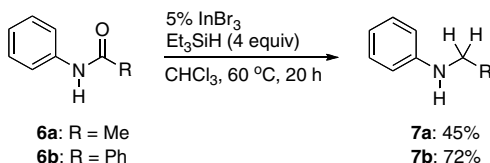
Table 2
Reduction of amides to amines

Run	Amide	Time (h)	Amine	Yield ^a (%)
1		20		(2a) 90
2		20		(2b) 66
3		20		(2c) 64
4		20		(2d) 94
5		20		(2e) 86
6		20		(2f) 81
7		20		(2g) 85
8		15		(2h) 81
9		15		(2i) 80
10		12		(2j) 84
11		30		(2k) 56
12		72		(2l) 65
13		48		(2m) 73
14		72		(2n) 34
15		72		(2o) 27

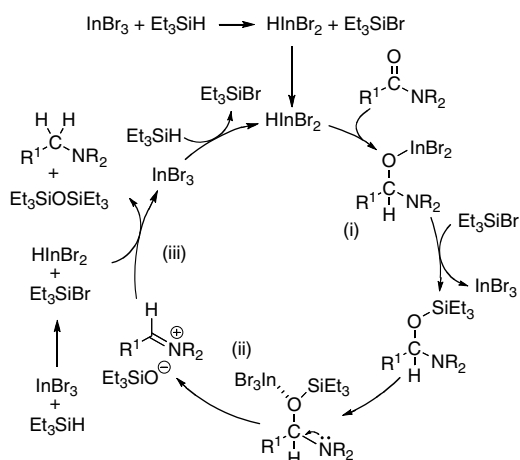
^a Isolated yield.



Scheme 1.



Scheme 2.



Scheme 3. Plausible mechanism for reduction of amides.

In summary, we have developed a highly efficient reduction procedure for the direct conversion of a variety of amides to the corresponding tertiary and secondary amines. Also, we found that the present reducing system can be applied to the reduction of a secondary amide. The present method using the InBr_3 – Et_3SiH system provides a simpler and more convenient alternative to traditional methods.

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- General procedure for reduction of amides to amines: To a CHCl_3 solution (0.6 mL) in a screw-capped vial under a N_2 atmosphere, amide **1a** (142 mg, 0.593 mmol), InBr_3 (10.5 mg, 0.0300 mmol), and Et_3SiH (380 μL , 2.40 mmol) were successively added. During the stirring of the reaction mixture at 60 °C (bath temperature), the solution turned from colorless to yellow, then to orange. After the reaction, 1 N HCl aq (5 mL) was added to the resulting mixture. The aqueous layer was basified with 1 N NaOH aq, and was extracted with CH_2Cl_2 (5 mL \times 3). The combined organic layer was dried over anhydrous Na_2SO_4 , which was filtered, then evaporated under reduced pressure to give tertiary amine **2a** (120 mg, 90%), which is almost pure. Spectral data for selected compound: dibenzylethylamine (**2a**); yellow oil; $^1\text{H NMR}$ (500 MHz, CDCl_3): δ = 1.06 (t, 3H, J = 7.0 Hz), 2.50 (q, 2H, J = 7.0 Hz), 3.56 (s, 4H), 7.22 (m, 2H), 7.30 (m, 4H), 7.37 (m, 4H); $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ = 11.9, 47.1, 57.7, 126.7, 128.1, 128.7, 140.0; MS(FAB): m/z 226 (M^+H , 100%).
- Starting amide **1k** was recovered in 37% yield.
- We confirmed the formation of compound **5** in comparison with spectral data of the identical compound, which was made via another route; however, we have not been able to rationalize the formation of the side product. This result implies the existence of another route for the reduction of formamide derivatives. Spectral data for bis[4-(*N,N*-dimethylamino)phenyl]methane (**5**): $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 2.89 (s, 12H), 3.80 (s, 2H), 6.68 (d, 4H, J = 9.0 Hz), 7.05 (d, 4H, J = 9.0 Hz); $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 39.9, 40.9, 113.0, 129.4, 130.3, 149.1; MS(FAB): m/z 255 (M^+H).
- Reduction with an *N*-alkylacetamide type of secondary amine did not proceed, see Ref. 7.
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