



Hydrosiloxane–Ti(OiPr)₄: an efficient system for the reduction of primary amides into primary amines as their hydrochloride salts

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ABSTRACT

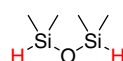
A simple and useful method for the reduction of primary amides into the corresponding amines using a polymethylhydrosiloxane (PMHS)–Ti(OiPr)₄ reducing system is described. Aromatic as well as aliphatic primary amides are reduced in high selectivity and excellent yields. The reduction could proceed via dehydration of the primary amide group into the corresponding nitrile which is then reduced into the corresponding primary amine.

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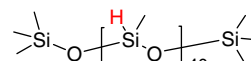
Amines are widespread functional groups found in numerous natural products, pharmaceuticals, and biologically valuable fine chemicals.¹ Among the different procedures for their synthesis, reduction of primary amides is acknowledged to be the most difficult. Traditional methods use stoichiometric amount of boron hydrides, such as BH₃·THF complex, LiBH₄, and NaBH₄.² NaBH₄ is known not to be a strong source of hydride and needs prior activation by a transition metal (TiCl₄ or CuCl₂), CF₃COOH, or ethanedithiol. In addition to air and water sensitivity, exothermic work-up and formation of stoichiometric amount of salts as by-products, harsh reaction conditions such as high temperature are commonly employed. Hydrogenation reactions using copper-chromite-based catalysts have also been studied for the reduction of primary amides. Despite their efficiency, the use of severe reaction conditions (a minimum of 200 bars H₂, 250 °C) and the presence of chromite (20 wt % loading) make this method difficult for many applications.³ Recently, Rh/Mo and Ru/Mo ‘bimetallic’ catalysts have been developed for the reduction of primary amides under milder reaction conditions (20–100 bars H₂ and 160–200 °C).⁴

During the last decade, hydrosilanes and hydrosiloxanes have emerged as good alternative methods to the existing hydride

sources since they are generally air and water stable, easy to handle, and less toxic. Since over 30 years now, they have been widely studied for the reduction of carbonyl group.^{5,6} Recently, more attention has been given for the reduction of amides. Particularly, reduction of tertiary amides into amines was applied using hydrosilanes activated by Rh,^{7a} Ru,^{7b,c} Pt,^{7d,e} Ti,^{7f} In,^{7g} Ir,^{7h} Mn,⁷ⁱ Re,^{7j} Os,^{7k} Pd,^{7l} Fe,^{7m} and Zn⁷ⁿ catalysts. Reduction of less reactive secondary amides was also studied using a ruthenium cluster catalyst for the synthesis of secondary amines or tertiary amines by judicious choice of hydrosiloxane.⁸ For primary amides, only three attempts have been reported in the literature using hydrosilanes as hydride sources. Nagashima et al.^{9a} and Beller et al.^{9b,c} have tried but failed to reduce primary amides into the corresponding amines using ruthenium cluster,^{9a} ammonium salt,^{9b} or iron^{9c} catalysts. In all cases, they observed the formation of the corresponding nitrile as the main product obtained from a dehydration reaction. Thus, find-



1,1,3,3-tetramethyldisiloxane (TMDS)

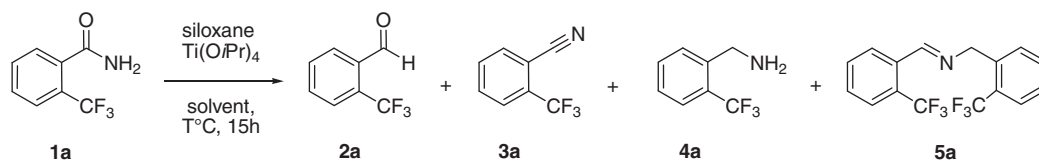


polymethylhydrosiloxane (PMHS)

Scheme 1. Structure of 1,1,3,3-tetramethyldisiloxane (TMDS) and polymethylhydrosiloxane (PMHS).

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Table 1Reduction of 2-(trifluoromethyl)-benzamide **1a** under various hydrosiloxane-Ti(OiPr)₄ reaction conditions

Entry	Siloxanes	SiH/amide	Ti(OiPr) ₄ (equiv)	Solvent	T (°C)	1a ^a (%)	2a:3a:4a:5a ^a (%)
1	TMDS	2.0	1.0	THF	60	37	0:63:0:0
2		4.0				14	1:2:70:12
3		6.0				14	1:2:44:39
4	PMHS	2.0	1.0	THF	60	<5	0:66:28:3
5		4.0	1.0	THF	60	18	2:0:60:20
6		4.0	1.0	Toluene	60	28	0:3:45:24
7		4.0	1.0	Toluene	100	00	0:0:78(89%) ^b :22
8		4.0	0.5	Toluene	100	01	3:7:43:46
9		4.0	0.1	Toluene	100	06	3:80:0:11
10	PMHS	4.0	/	Toluene	100	100	/
11	/	/	1.0	THF	60	100	/

^a % of **1a**, **2a**, **3a**, **4a**, and **5a** compounds was determined by GC–MS analysis of the organic layer after a first acidic treatment (aq 1 M HCl) followed by basification using NaOH until pH >11.

^b Amine **4a** was isolated as the hydrochloride salt after acidic treatment with a 2 M etheral-HCl solution.

ing a reducing system using hydrosilanes for the reduction of primary amides into amines is still a challenging goal.

For several years now, our group has been studying the behavior of two hydrosiloxanes, 1,1,3,3-tetramethyldisiloxane (TMDS) and polymethylhydrosiloxane (PMHS) (Scheme 1) as sources of hydride since they are safer than hydrosilanes and even more than other hydride sources.¹⁰

Activated by an environmentally benign iron(acac)₃ catalyst, they reduce nitro compounds to amines.^{11a,b} Used jointly with Pd/C and CSA as the promoter, they convert acetals into ethers.^{11c} In addition, when associated with a relatively inexpensive titanium(IV) isopropoxide, they are able to reduce tertiary and secondary amides to aldehydes,^{11d} nitriles to amines,^{11e} and phosphine oxides to phosphines.^{11f,g} Herein we report an efficient system using PMHS–Ti(OiPr)₄ for the reduction of primary amides into primary amines in high selectivity and excellent yields. The reduction may occur via the formation of the corresponding nitrile (by dehydration) which is finally reduced into the corresponding amine and isolated as the hydrochloride salt.

In a previous work, we have described the reduction of tertiary and secondary amides to aldehydes using a TMDS (2.0 SiH per amide)–Ti(OiPr)₄ (1.0 equiv) reducing system, in methylcyclohexane at rt.^{11d} Under these conditions, reduction of primary amides showed difficulties; in addition to the slight conversion of starting material, the formation of a primary amine was observed rather than aldehyde. This unprecedented result led us to concentrate our efforts for the reduction of primary amides to primary amines.

The reduction of 2-(trifluoromethyl)-benzamide **1a** was used as a model reaction to identify and optimize critical reaction parameters. Depending on reaction conditions, different products were detected by GC–MS analysis: the 2-(trifluoromethyl)-benzaldehyde **2a**, the 2-(trifluoromethyl)-benzonitrile **3a**, 2-(trifluoromethyl)-benzylamine **4a**, and the imine **5a** that might result from the condensation of the amine **4a** with the aldehyde **2a** after acidic treatment followed by a basic treatment (Table 1).

First reactions were conducted in tetrahydrofuran (THF) (due to the solubility of the starting material **1a**) at 60 °C using TMDS and a stoichiometric amount of Ti(OiPr)₄ (Table 1).¹² It appeared that the number of hydrides used plays an important role in the selectivity of the reaction (Table 1, entries 1, 2, and 3). With 2.0 SiH per amide, nitrile **3a** was obtained in 63% GC–MS yield without formation of the desired amine **4a**. Increasing the amount to 4.0 SiH per amide,

Table 2Reduction of primary amides into primary amines^a

Amide 1	Amine·HCl 4	Isolated yield ^b
		93
		87
		89
		90
		95
		33 ^c
		40 ^d

^a Reaction conditions: amide (1.0 equiv), PMHS (4.0 equiv), Ti(OiPr)₄ (1.0 equiv), toluene, 100 °C, 24 h unless differently stated.

^b Amines **4** were isolated as the hydrochloride salts after acidic treatment.

^c After acidic treatment and concentration, due to the reduction of secondary amines into aldehydes, ¹H NMR analysis revealed that the crude solid contained a mixture of the amine-HCl **4g** and benzylamine-HCl with a ratio 33:66.

^d After acidic treatment and concentration, due to the reduction of tertiary amines into aldehydes, ¹H NMR analysis revealed that the crude solid contained a mixture of the amine-HCl **4h** and diethylamine-HCl with a ratio 40:60.

a better selectivity was observed for amine **4a** (70% GC–MS yield). Surprisingly, the selectivity for amine **4a** slightly decreased when using 6.0 SiH per amide. In all cases, the conversion of **1a** was not complete.

TMDS was then substituted by PMHS. In these cases no specific improvement was observed (Table 1, entries 4 and 5). Using 2.0 SiH per amide of PMHS, the reduction of **1a** was almost complete. In this case, nitrile compound **3a** was obtained as the main product (66% GC–MS yield) and the presence of amine **4a** (28% GC–MS yield) was also observed. In the case of TMDS, no amine was observed (Table 1, entry 1). That implies that PMHS is more reactive than TMDS. Using 4.0 SiH per amide, amine **4a** was obtained with better selectivity (60% GC–MS yield).

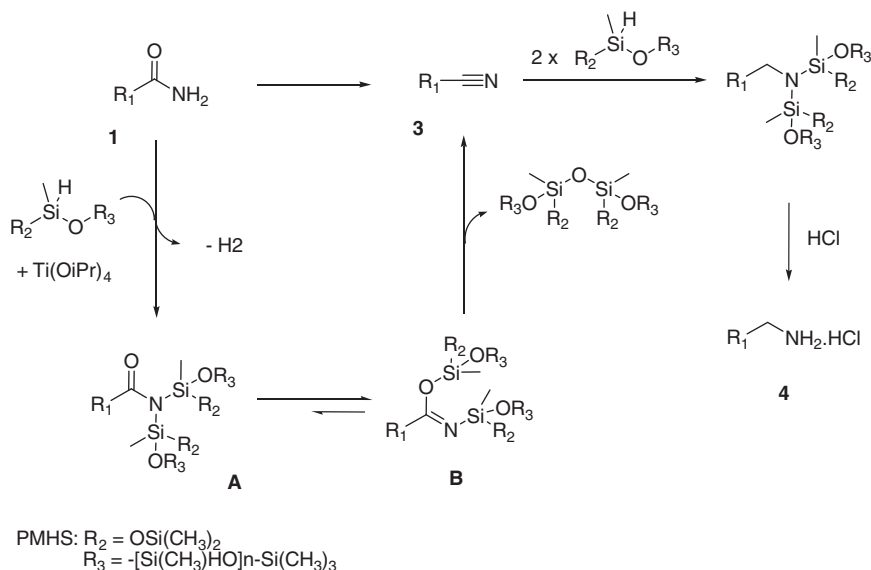
Since the previous reaction conditions did not give a total conversion of the primary amide, a different solvent than THF was tested in order to allow us to increase the reaction temperature and thus reach full conversion. Indeed, reduction of **1a** performed in toluene at 100 °C gave complete conversion and high selectivity for amine **4a** (Table 1, entry 7). Then, acidic treatment with ethereal-HCl afforded the hydrochloride salt of the amine in 89% isolated yield. A decrease of Ti(OiPr)₄ loading from 1.0 to 0.5 equiv caused a decrease in the selectivity. With 0.1 equiv (10 mol %) of Ti(OiPr)₄, reduction of **1a** was complete and produced nitrile **3a** in 80% GC–MS yield without further-reduction to amine **4a** (Table 1, entry 9). Finally control experiments showed that both Ti(OiPr)₄ and hydrosiloxane were necessary for reduction to occur (Table 1, entries 10 and 11).

Consequently, it appeared that a reducing system composed of PMHS (4.0 SiH per amide) and Ti(OiPr)₄ (1.0 equiv) in toluene at 100 °C would be efficient to transform primary amides into primary amines (Table 1, entry 7). Under these reaction conditions, we extended the reduction to other aromatic as well as aliphatic primary amides (Table 2).^{13,14} The aromatic benzamide **1b** was reduced into benzylamine **4b** in 93% isolated yield as the hydrochloride salt. Aromatic primary amides substituted by trifluoromethyl group (**1a**) and fluoride (**1c**) at the *ortho* position were also reduced into amines **4a** and **4c**, respectively, in excellent yields. Aliphatic primary amides bearing a naphthyl moiety **1d** or a long alkyl-chain **1e** were also reduced into the corresponding amines in 90% isolated yields. In addition, the perfluorinated compound **1f** was reduced into the corresponding perfluorinated amine **4f** in 95% isolated yield without affecting the fluorinated alkyl chain.

Reduction of secondary and tertiary amides has also been tested under these reaction conditions. At 100 °C, using PMHS (4.0 SiH per amide) activated by Ti(OiPr)₄ (1.0 equiv) secondary *N*-benzylbenzamide **1g** and tertiary *N,N*-diethyl-*m*-toluamide **1h** were reduced completely after 24 h. After acidic treatment and concentration under vacuum, it was possible to analyze the crude solid of the two compounds. Reduction of *N*-benzylbenzamide **1g** gave 64 wt % yield of a mixture of the desired amine **4g** and benzylamine as their hydrochloride salts with a ¹H NMR ratio 1:2. Reduction of *N,N*-diethyl-*m*-toluamide **1h** produced 72 wt % yield of a mixture of the desired tertiary amine **4h** and *N,N*-diethylamine as their hydrochloride salts with a ¹H NMR ratio 2:3. In both cases, benzylamine and *N,N*-diethylamine are released in the medium from a deprotection reaction. That implies a competition between the reduction into amine and into aldehyde which is in accordance with our previous Letter.^{11d}

The difference of reactivity between primary amides on one hand and secondary and tertiary amides on the other hand might be explained by the nature of the hydrosiloxane but especially by the mechanistic pathway. Judging from our results and the different products observed during the reduction reaction (Table 1), we assume a two step mechanism (Scheme 2): (1) dehydration of primary amide into nitrile. We believe that the PMHS–Ti(OiPr)₄ reducing system proceeds first as a dehydrating agent in a similar manner than the [HMe₂SiCH₂]₂-Ru cluster system reported by Nagashima and co-workers.^{9a} Reaction of the hydrosiloxane with titanium should generate an active species that reacts twice with the primary amide to form the bis(silyl)amide **A**. This bis(silyl)amide **A** is in equilibrium with the *N,O*-bis(silyl)imidate **B** which is more stable¹⁵ and allows the elimination of disiloxane to produce the corresponding nitrile **3**; (2) reduction of nitrile into amine. Since we have already published the reduction of nitriles into amines with a hydrosiloxane-Ti(OiPr)₄ reducing system, we assume that the excess hydrosiloxane activated by Ti(OiPr)₄ reacts with the nitrile to produce a *N,N*-bis(silyl)amine **C** which is finally hydrolyzed into amine **4**. In accordance with our results, reduction of nitrile into amine (step 2) requires more titanium than dehydration reaction (step 1).

In summary, we reported the first reducing system employing the hydrosiloxane PMHS activated by Ti(OiPr)₄ that is able to reduce primary amides into the corresponding primary amines. Aromatic as well as aliphatic primary amides were first dehydrated



Scheme 2. Supposed mechanism for the reduction of primary amide **1** into amine **4** using a PMHS-Ti(OiPr)₄ reducing system.

into the corresponding nitriles which were then reduced into the corresponding amines in high selectivity and excellent yields.

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- It should be noticed that reaction temperature of 60 °C is dictated by the use of THF (bp = 66 °C) and TMDS that also has a low boiling point (bp = 71 °C). At higher temperature, TMDS risks to get evaporated out of the reaction medium.
- Polymethylhydrosiloxane (PMHS, n = 40) and titanium(IV) isopropoxide 95% were purchased from Alfa Aesar; extra dry toluene from Acros Organics; primary amides from Alfa Aesar, Acros Organics, Maybridge, and sigma Aldrich. All reagents, reactants and solvents were used in the state without further purification.
- General procedure for the reduction of primary amides into amines*: 2-(trifluoromethyl)-benzamide **1a**. To a nitrogen purged screw-cap vial containing **1a** (250 mg, 1.3 mmol, 1.0 equiv) and 2.0 ml of anhydrous toluene were added PMHS (320 μl, 5.4 mmol, 4.2 equiv) and Ti(OiPr)₄ (400 μl, 1.3 mmol, 1.0 equiv) at rt. The mixture was stirred and heated at 100 °C until analysis by tlc showed complete consumption of the starting material (ca. overnight). The mixture was then diluted with Et₂O (30.0 ml) and acidified using 2 M Et₂O–HCl solution (2.0 ml, 3.0 equiv). The ammonium salt **4a** was precipitated, filtered, and washed first with Et₂O and then with pentane. The primary amine **4a** was isolated as the hydrochloride salt in 89% yield.
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