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A mild titanium-based system for the reduction of amides to aldehydes

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ABSTRACT

A mild method for the reduction of amides to aldehydes using 1,1,3,3-tetramethyldisiloxane/titanium(IV) isopropoxide reducing system is described. The reaction occurs under mild conditions and allows the reduction of aromatic as well as aliphatic, tertiary amides to the corresponding aldehydes, in good yields. This methodology was extended to the reduction of aromatic secondary and primary amides to the corresponding aldehydes.

1. Introduction

The amide group is a robust functionality that is fairly inert to many oxidative and reductive conditions.[1] The reduction of amides to aldehydes still represents a challenge since such a transformation is in most cases achieved by aluminum hydrides such as LAH[2], DiBAl-H[3], Red-Al,[4] and their derivatives.[5] Indeed the latter suffer from serious drawbacks such as the use of potentially hazardous water-soluble solvents, exothermic workup, handling under anhydrous conditions, production of stoichiometric amounts of salts as by-products, and selectivity problems. In addition, most of the reactions are substrate specific; they reduce either tertiary amides or primary ones. Moreover, the nature of the substituents carried on the amide nitrogen plays an important role in the outcome of the reaction. In the literature, special amide derivatives where the most common are the *N*,*O*-dimethylhydroxamic acids, also called Weinreb amides, have been studied for their reduction to aldehydes. Usually, these amides are reduced by aluminum hydrides as well.[6] Borohydride reagents have also been found to be suitable for the reduction of tertiary amides but much less than aluminum hydrides.[7] Other reducing systems have also been reported and included reduction with the association of alkyltrifluoro-methanesulfonate and L-Selectride at −78 °C,[8] a SmI_2 (at least 4 equiv)-acid system,[9] and a hydrozirconation with a stoichiometric quantity of a onerous zirconium complex.[10]

Over the past decade, silicon derivatives such as silanes and siloxanes have emerged as new potent hydride sources. Activated by transition metals, they have already proven good abilities for the reduction of organic functions.[11] However, only one reference was found in the literature for the reduction of amides to aldehydes.[12] Indeed Buchwald and co-workers have reported a procedure that utilizes diphenylsilane and titanium(IV) isopropoxide that can effectively reduce a variety of *N*,*N*-substituted amides to the corresponding aldehydes. This method was successfully applied to a variety of substrates containing sensitive functionalities. However it is limited to α-enolizable amides. This condition is explained by Buchwald and co-workers by the necessity of forming an enamine intermediate which is finally hydrolyzed into aldehyde. In addition, this methodology uses an expensive diphenylsilane known to be dangerous by generating pyrophoric gas.[13]

In our laboratory, we have developed and reported the use of 1,1,3,3-tetramethyldisiloxane (TMDS) activated by titanium(IV) isopropoxide for the reduction of phosphine oxides to phosphines,[14] and more recently nitriles to amines.[15] Compared to diphenylsilane, 1,1,3,3-tetramethyldisiloxane is cheaper and less hazardous when activated by titanium species.[13] Herein we extend the scope of the TMDS/$Ti(OiPr)_4$ reducing system to the reduction of aromatic and aliphatic tertiary amides under mild conditions as well as secondary and primary aromatic ones.

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2. Results and discussion

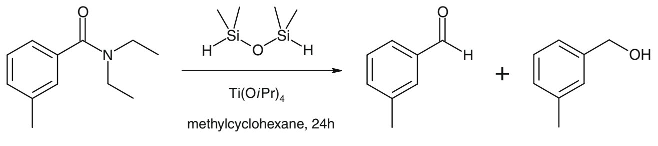
The first reduction experiments using TMDS/Ti(O*i*Pr)$_4$ system were conducted with *N*,*N*-diethyl-*m*-toluamide **1a**, in order to determine the feasibility of the reduction of tertiary aromatic amides to aldehydes (Table 1). The reactions were carried out in methylcyclohexane for 24 h at rt.[16] Using a catalytic amount of Ti(O*i*Pr)$_4$, the reduction did not proceed.[12,14,17] Thus we carried on the reactions with a stoichiometric amount of the titanium species, since the cost of the Ti(O*i*Pr)$_4$ is relatively low and the generated by-products, that is, TiO_2 are inert. The amount of TMDS appeared essential for the reduction. Increasing the proportion from 1.2 to 1.6 and 2.0 Si-H mol/mol substrate increased the conversion of the reaction from 40% to 75% and 100%, respectively (Table 1, entries 1, 2, and 4). In the latter case, after acidic workup and purification on flash column chromatography, aldehyde **2a** could be isolated in 70% yield. However, increasing the amount of Ti(O*i*Pr)$_4$ did not affect the conversion (Table 1, entries 2 and 3). In all cases, the presence of alcohol **3a** issued from an over-reduction of the aldehyde **2a** was detected in about 10% NMR estimated yield. To decrease its formation and thus increase the chemoselectivity of the reaction, two reactions were conducted at lower temperature which caused a decrease in the conversion rate (Table 1, entries 5 and 6). Consequently, it appeared that a reducing system composed of 100 mol % of TMDS and 100 mol % of Ti(O*i*Pr)$_4$ in methylcyclohexane at rt would be efficient to transform tertiary aromatic amides to the corresponding aldehydes.

With the optimized reaction conditions (Table 1, entry 4), we extended the reduction to other tertiary as well as a secondary and a primary aromatic amide (Table 2).[18–20]

Aromatic tertiary amides **1b** and **1c** bearing a *para*-chlorobenzene and a naphthyl moiety are reduced into the corresponding aldehydes **2b** and **2c** in good yields. As expected, the chlorine is not affected by the reaction conditions.[15,17,21] Aliphatic tertiary amides were not completely reduced under these reaction conditions after 24 h. Dodecanamide **1e** was partially reduced after 24 h (conversion rate of 60%). An additional amount of the TMDS/Ti(O*i*Pr)$_4$ system allowed full conversion and the resulting aldehyde **2e** was isolated in 90% yield. The formation of the corresponding alcohol was not observed which might explain the good chemoselectivity in this particular case. Diphenylacetamide **1d** was also totally reduced after adding an additional amount of TMDS and Ti(O*i*Pr)$_4$ and the corresponding aldehyde **2d** was isolated in 85% yield.

Reduction of aromatic secondary and primary amides has also been tested under these reaction conditions. For solubility reason (insoluble substrates in MCH at rt), the reaction was carried out in tetrahydrofuran (THF). *N*-Benzyl-benzamide **1f** was not completely reduced to the corresponding aldehyde **2f** after 24 h. GC–MS analysis showed a ratio **1f**:**2f** equal to 21:79. Increasing the quantities of the TMDS/Ti(O*i*Pr)$_4$ system (0.8 additional equiv) with 24 h extra stirring time allowed a complete consumption of the starting material. GC–MS analysis showed the expected aldehyde **2f** and the tertiary amine (issued from the reduction of the amide to amine) with a ratio aldehyde: amine of 86:14. The formation of a tertiary amine implies the formation of an imine intermediate. Finally, reduction of the primary amide 2-(trifluoromethyl)-benzam-

Table 1
Screening of the reaction conditions



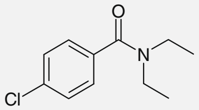
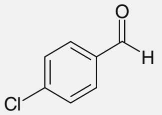
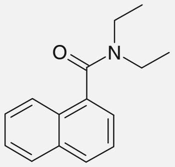
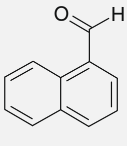
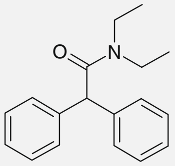
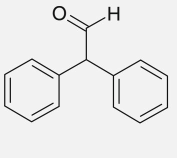
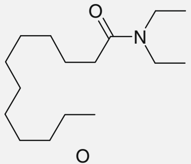
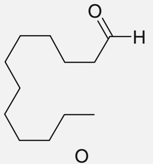
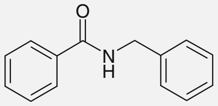
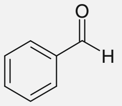
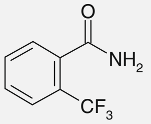
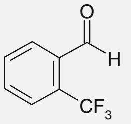
1a **2a** **3a**

Entry	TMDS (mol %)	Ti(O*i*Pr)$_4$ (mol %)	*T* (°C)	Conv.[a] (%)	**2a**:**3a**[a]
1	60	100	rt	39	31:8
2	80	100	rt	75	62:13
3	80	200	rt	75	65:10
4	100	100	rt	100	85:15[b]
5	100	100	15	19	n.d.
6	100	100	10	0	n.d.

[a] Determined by ^1H NMR after acidic workup, extraction, and concentration.

[b] The aldehyde **2a** was isolated in 70% yield after flash column chromatography.

Table 2
Reduction of amides to aldehydes[a]

Amides **1**		Aldehydes **2**		Isolated yield[b] (%)
	**1b**		**2b**	81
	**1c**		**2c**	75
	**1d**		**2d**	85[c]
	**1e**		**2e**	90[d]
	**1f**		**2f**	86[e]
	**1g**		**2g**	3[f]

[a] All the reactions were carried out in methylcyclohexane at room temperature for 24 h using 1.0 mol/mol amide TMDS and 1.0 mol/mol amide Ti(O*i*Pr)$_4$ unless differently stated.

[b] Yields were calculated after flash column chromatography unless differently indicated.

[c] Reaction conducted in toluene for solubility reason. After 24 h, additional amounts of TMDS (1.0 equiv) and Ti(O*i*Pr)$_4$ (1.0 equiv) were added and the crude mixture was stirred for additional 24 h until complete conversion.

[d] After 24 h, the conversion was 60%. Thus an additional amount of TMDS/Ti(O*i*Pr)$_4$ (1.0 equiv) was added and the crude mixture was stirred for an additional 24 h until complete conversion. Aldehyde **2e** was finally isolated in 90% yield after flash column chromatography.

[e] Reaction was conducted in THF for solubility reason. After 24 h, additional amount of TMDS/Ti(O*i*Pr)$_4$ (0.8 equiv) was added and the crude mixture was stirred for an additional 24 h until complete conversion. Aldehyde **2f** was detected by GC–MS with the over-reduced tertiary amine in a ratio 86:14, respectively.

[f] Reaction was conducted in THF for solubility reason. After 24 h, the aldehyde **2g** was detected by GC–MS with the starting material **1g** with a ratio 3:97, respectively. After an additional amount of TMDS/Ti(O*i*Pr)$_4$ (2.0 equiv) and 48 h additional stirring, GC–MS analysis showed the starting material **1g**, the alcohol and the tertiary amine with a ratio 55:3:20, respectively. Aldehyde **2g** was not present anymore in the crude.

ide **1g** was more difficult under the reduction conditions described above for **1a**. The starting material remained almost totally intact and only traces (3%) of the corresponding aldehyde **2g** were detected by GC–MS. Surprisingly, after two additional amounts of the TMDS/Ti(O*i*Pr)$_4$ system and 48 h extra stirring time, the desired aldehyde **2g** was not detected by GC–MS analysis of the crude. The only detected products were the starting material (55%), the alcohol issued from the over-reduction of the aldehyde 3% and 20% of the tertiary amine. Consequently the TMDS/Ti(O*i*Pr)$_4$ system is unsuccessful for the reduction of an aromatic primary amide to aldehyde.

At present, no detailed mechanistic studies have been undertaken yet. However, considering the mechanistic highlights published recently by Petit et al. for the reduction of phosphine oxides to phosphines using the TMDS/Ti(O*i*Pr)$_4$ reducing system, we assume the presence of Ti(III) species in the reaction medium. That suggests a mechanism via a single electron transfer (SET) rather than a titanium hydride-like complex.[14c] In view of our preliminary results we assume that the mechanism of the reduction is substrate dependent. In fact, we presume that Ti(III) species react with the amide substrate to form a hemi-aminal in first instance. Then this hemi-aminal (stabilized by coordination with Ti or Si) or the imine (resulting from hemi-aminal rearrangement) is hydrolyzed to the corresponding aldehyde. Mechanistic studies are still underway in the laboratory.

3. Conclusion

In summary we reported here a mild procedure for the reduction of amides to aldehydes that proceeds at room temperature and employs readily available and air-stable reagents. The reaction is general for aromatic and aliphatic tertiary amides and also shows good preliminary results with a secondary aromatic one. However preliminary essays with a primary aromatic amide did not give the expected results. Nevertheless, the ease of this method constitutes an alternative to existing methods. The tolerance and selectivity of the TMDS/Ti(O*i*Pr)$_4$ reducing system as well as the mechanistic pathway will be studied in due course.

Acknowledgment

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16. It is noticed that reductions of amide **1a** in MCH or toluene give similar results. Solvents are chosen in way to render the starting material soluble in the reaction medium; otherwise the reduction does not occur. MCH and toluene are suitable for tertiary amides whereas secondary and primary ones require THF.
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18. 1,1,3,3-Tetramethyldisiloxane 97% and *N*,*N*-diethyl-*m*-toluamide 98% were purchased from ACROS; titanium (IV) isopropoxide 95% and *N*,*N*-diethyldodecanamide 98% from ALFA AESAR; 2-(trifluoromethyl)-benzamide 97% from Maybridge.
19. *N*,*N*-Diethyl-4-chlorobenzamide, *N*,*N*-diethyl-1-naphtyl-benzamide, *N*,*N*-diethyl-2,2-diphenylacetamide and *N*-benzyl-benzamide were synthesized from the corresponding acid. *Typical procedure for the synthesis of N,N-diethyl-4-chlorobenzamide* **1b**: To a suspension of 4-chlorobenzoic acid (8.0 g, 51.3 mmol, 1.0 equiv) in dichloromethane (35 mL) were added at rt. Oxalyle chloride (5.4 mL, 61.7 mmol, 1.2 equiv) and dimethylformamide (one drop). [caution: exothermic reaction]. The crude mixture was stirred until gas evolution stopped. Then it was concentrated in vacuo, washed with dichloromethane and concentrated again, twice. The 4-chloro-benzoyl chloride was isolated as a yellow oil in quantitative yield. The latter was then transferred into a round-bottom flask, diluted in toluene (40 mL) and the crude heated to 50 °C. Then *N*,*N*-diethylamine (12 mL, 116.0 mmol, 2.3 equiv) was added dropwise and the mixture was stirred at 50 °C overnight. The temperature was cooled to rt, the organic layer was washed with 3 × 20 mL HCl 1 m, dried with MgSO$_4$ and concentrated in vacuo. The *N*,*N*-diethyl-4-chloro-benzamide was isolated as an orange oil in 90% yield.
20. *General procedure for the reduction of amides: N,N-diethyl-toluamide* **1a**: To a nitrogen purged screw-caped vial containing **1a** (1.0 mL, 5.2 mmol, 1.0 equiv) in 2.8 mL of methylcyclohexane were added TMDS (920 μL, 5.2 mmol, 1.0 equiv) and Ti(O*i*Pr)$_4$ (1.5 mL, 5.2 mmol, 1.0 equiv) at rt. The mixture was stirred at rt until analysis by TLC showed the complete consumption of the starting material (ca. 15 h). The mixture was then diluted with methylcyclohexane (20 mL) and acidified using 1 M HCl (11.0 mL, 2.1 equiv.). The organic layer was washed with 1 M HCl (3 × 10 mL), then dried (MgSO$_4$) and concentrated in vacuo. Flash column chromatography on silica gel (cyclohexane/ethyl acetate; 8:2) afforded the aldehyde **2a** with 70% yield.
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