



## A mild and efficient method for the reduction of nitriles

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### ABSTRACT

A simple and useful method for the reduction of nitriles into the corresponding amines using a tetramethyldisiloxane/titanium(IV) isopropoxide reducing system is described. The synthetic approach is straightforward and provides primary amines as hydrochloride salt in almost quantitative yield. Other advantages of this method, such as easy-to-handle hydride source, inert by-products, that is, TiO<sub>2</sub> and oligomeric siloxanes, make it very attractive to prepare primary amines.

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The reduction of nitriles to yield amines is a fundamental process in synthetic organic chemistry. Conventional methods for accomplishing this transformation use catalytic hydrogenation or strong hydride donors such as aluminum hydrides or boranes.<sup>1</sup> However, these latter methods suffer from serious drawbacks such as the use of potentially hazardous water-soluble solvents, exothermic workup, maintenance of anhydrous conditions, and formation of stoichiometric amount of salts as by-products. Nitriles can also be reduced using non-pyrophoric sodium borohydride. However, NaBH<sub>4</sub> requires activation with Brønsted acid,<sup>2a</sup> or transition metal salt such as Ni(II).<sup>2b–d</sup> Recently, it has been shown that diisopropylaminoborane in the presence of catalytic amount of lithium borohydride can effectively reduce various nitriles.<sup>3</sup> Nevertheless, the development of new and improved ways to reduce aromatic and aliphatic nitriles continues to be a challenging goal.<sup>4</sup>

Hydrosiloxane derivatives have emerged as attractive potent reducing reagents since they are stable to air and moisture.<sup>5</sup> However, and because of their lack of reactivity, these compounds are not sufficiently potent hydride sources themselves and require activation.<sup>5,6</sup> Transition metals have been used which mediate reduction via the corresponding metal hydride species.<sup>6</sup> Fluoride ion has also been used, but in this case, the reduction occurs via the formation of hypervalent hydridosilicate species.<sup>5</sup> Among the

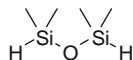
transition metals, titanium-mediated reductions<sup>7</sup> are attractive because of the low cost of Ti(Oi-Pr)<sub>4</sub> as well as the inertness of the by-products, that is, TiO<sub>2</sub>. Recently, we became interested in the use of 1,1,3,3-tetramethyldisiloxane (TMDS), the lowest molecular weight commercially available hydrosiloxane derivative (Fig. 1). We have shown that, using a catalytic amount of Ti(Oi-Pr)<sub>4</sub> in an aliphatic solvent, phosphine oxides are readily converted into the corresponding phosphines in high yield.<sup>8</sup>

We began our investigation with the reduction of 4-bromophenylacetone nitrile **1a** using 1,1,3,3-tetramethyldisiloxane (TMDS) (Fig. 1) activated by a non-toxic titanium(IV) isopropoxide (Ti(OiPr)<sub>4</sub>), and the results are summarized in Table 1.

The reduction of **1a** did not occur in the presence of 10 mol % of Ti(OiPr)<sub>4</sub> and 200 or 500 mol % of TMDS (Table 1, entries 1 and 2). Remarkably, when using 100 mol % of Ti(OiPr)<sub>4</sub>, the conversion was quantitative after 24 h at 60 °C (Table 1, entry 3). The amine **1b** could be isolated in 96% yield as the hydrochloride salt after hydrolysis of the crude with 1 N HCl and filtration.

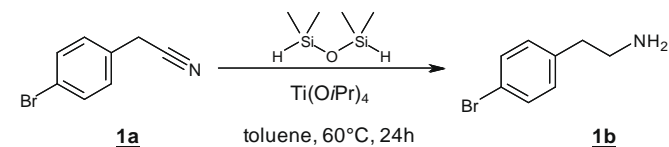
With 60 mol % of Ti(OiPr)<sub>4</sub> and 500 mol % of TMDS, the reaction gave diminished conversion (entry 4). Under those conditions, an increase of the reaction time (48 h) did not improve the conversion. Titanium- and zirconium-based catalyst have already been used for the reduction of a wide range of organic functional groups.<sup>7–9</sup> However, it should be noted that under previously published conditions, the nitrile functionality remains unchanged using hydrosiloxane derivatives and various transition metals.<sup>7b,9</sup>

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**Figure 1.** Structure of 1,1,3,3-tetramethyldisiloxane.

**Table 1**  
Effect of TMDS and  $\text{Ti}(\text{OiPr})_4$  on the reduction of 4-bromophenylacetonitrile **1a** to 4-bromophenylethylamine **1b**



Entry	TMDS (mol %)	$\text{Ti}(\text{OiPr})_4$ (mol %)	Conv. <sup>a</sup> (%)	Isolated yield <sup>b,c</sup> (%)
1	200	10	<5	—
2	500	10	<5	—
3	500	100	100	96
4	500	60	95	Nd
5	200	100	100	Nd
6	100	100	100	90

<sup>a</sup> Determined by  $^1\text{H}$  NMR of the crude reaction mixture.

<sup>b</sup> Isolated as hydrochloride salt after hydrolysis with 1 M HCl.

<sup>c</sup> Purity >99%.

Based on experimental results, we can show that TMDS activated with  $\text{Ti}(\text{OiPr})_4$  could be used as an efficient system for the reduction of nitriles. Thus, we examined the generality of this reaction with various nitriles under the optimized conditions (Table 1, entry 6), and the results are summarized in Table 2.<sup>10,11</sup>

As shown in Table 2, the reduction of aromatic nitriles (Table 2, entry 1) as well as halogen- substituted aromatic nitriles (Table 2, entries 2 and 3) showed good results. As expected from the literature data the nitro group was not reduced under our conditions.<sup>7c</sup> Unfortunately, in this case, the conversion was not complete and the yields were slightly lower than those with other substrates. This is probably due to oxophilic character of titanium that decreases its reactivity by coordination with the nitro group. Aliphatic nitriles also produced the corresponding amines in good yield (Table 2, entry 5). Furthermore, no reduction of the unsaturation and no isomerization could be detected when nitrile **7a** was reduced (Table 2, entry 6).

In summary we have developed a mild, safe, and efficient reduction procedure for the direct conversion of a variety of nitriles to the corresponding amines. The present method uses TMDS and  $\text{Ti}(\text{OiPr})_4$  in stoichiometric quantity. The acidic workup allows us to isolate the amine by crystallization of the hydrochloride salt. So TMDS activated with  $\text{Ti}(\text{OiPr})_4$  provides a simple and useful method that can substitute the use of aluminum and boron hydrides.

**Table 2**  
TMDS reduction of nitriles to amines<sup>a</sup>

Entry	Nitrile	Amines	Isolated yield <sup>b</sup> (%)
1		<b>12a,b</b>	95 <sup>c</sup>
2		<b>12a,c</b>	95
3		<b>12d</b>	98
4		<b>12a</b>	86
5		<b>12a</b>	95
6		<b>12e,f</b>	93
	<i>E/Z</i> = 30/70	<i>E/Z</i> = 30/70	

<sup>a</sup> Conditions: nitriles (5.1 mmol),  $\text{Ti}(\text{OiPr})_4$  (5.1 mmol), TMDS (5.1 mmol), toluene, 60 °C, 24 h.

<sup>b</sup> Isolated as hydrochloride salt with >99% purity.

<sup>c</sup> Use of methylcyclohexane as solvent.

## Acknowledgment

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- Typical procedure for the reduction of nitrile*: To a nitrogen-purged screw-capped vial containing 5.1 mmol of nitrile in 6.0 mL of toluene was added TMDS (902  $\mu$ L, 5.1 mmol, 1.0 equiv) and Ti(OiPr)<sub>4</sub> (1.5 mL, 5.1 mmol, 1.0 equiv) at rt. The mixture was then heated at 60 °C for 24 h (the colorless solution turned into black-brown and the conversion of the substrate can be followed up by <sup>1</sup>H NMR) and cooled to room temperature. The clear solution was acidified using 1 M HCl (7.7 mL, 1.5 equiv) and the crude mixture was concentrated under reduced pressure. The resulting solid was filtered and washed with pentane. Then it was dissolved in methanol and filtered on Celite® or Millipore filter (0.1  $\mu$ m vpp). The filtrate was finally concentrated under reduced pressure and the amine hydrochloride isolated as amorphous powder with 86–98% yield.
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