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Reduction of nitriles into aldehydes using a TMDS/V(O)(O*i*Pr)$_3$ reducing system

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ABSTRACT

A simple and convenient method for the chemoselective reduction of nitriles into aldehydes using a 1,1,3,3-tetramethyldisiloxane (TMDS)/triisopropoxyvanadium(V) oxide reducing system is described. Aromatic as well as aliphatic nitriles are reduced into the corresponding aldehydes in moderate to good yields.

Introduction

The reduction of nitriles to aldehydes is a challenge in synthetic organic chemistry. Indeed, the chemoselective reduction of the unreactive cyano group presents a difficulty. More precisely, the imine intermediate that produces the aldehyde is usually much more reactive than the nitrile and thus conducts to the over-reduced amine. Since the Stephen Reduction,[1] conventional methods for this transformation use strong hydride donors such as Li(OEt)$_3$-AlH,[2] DIBAL-H,[3] and their derivatives.[4–6] Borohydride reagents have also been reported for this reduction but less than aluminum hydrides.[7] However, the previous methods suffer from serious drawbacks such as the use of potentially hazardous water-soluble solvents, exothermic workup, handling under anhydrous conditions, and production of stoichiometric amounts of salts as by-products. Other reducing systems have also been reported including the reductions by photo-irradiation[8] or with the association of PtO$_2$/aqueous formic acid,[9] Ni-Raney/hydrazine hydrate,[10] Ni-Raney/sodium hypophosphite,[11] nickel-based bimetallic systems in acidic medium,[12] and Ru- and Pt-loaded zeolites.[13]

Over the past decade, hydrosilanes have attracted more attention since they can be used for the introduction of silyl groups in organic molecules and also for the reduction of unsaturated functions. Easy to handle and readily available, they have found applications for the reduction of a large number of functional groups.[14] Nevertheless, probably because of the robustness of the cyano group, only few examples concerning the mono-silylation of the carbon-nitrogen triple bond have been published. In 1966, Calas et al. first reported the zinc catalyzed addition of trialkylhydrosilane on nitriles to yield *N*-silylimines, protected forms of aldehydes.[15] In 1970, A. J. Chalk published the 1,4-addition of HSiClMe$_2$ on methacrylonitrile in the presence of dicobalt octacarbonyl.[16] The reaction afforded the corresponding *N*,*N*-disilylenamine in 20% yield after 6 days. Corriu studied the combination of bis-silanes and Fe(CO)$_5$ for the stoichiometric hydrosilylation of aliphatic nitriles into *N*,*N*-disilylenamines under UV-irradiation.[17] Bis-silanes were also associated with Ni,[18a] Pt,[18b] and Rh[18c] catalysts to reduce nitriles with α-H into cyclic *N*-silylenamines and aromatic nitriles into cyclic *N*-silylimines. Ru,[19a,b] W,[19c,d] and Mo[19d,e] complexes bearing a Si–H moiety have been designed for the stoichiometric hydrosilylation of nitriles but few examples have been published and yields are low to moderate. Recently, Nikonov and co-workers reported the reduction of nitriles into imines with hydrosilanes in the presence of Mo and Ru catalysts.[20] Whereas the Mo-complex catalyzed slowly the hydrosilylation of benzonitrile in the presence of PhSiH$_3$,[20a] the [Cp(*i*Pr$_3$P)Ru(NCCH$_3$)$_2$][B(C$_6$F$_5$)$_4$]/Me$_2$PhSiH system reduced at

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room temperature aliphatic and aromatic nitriles into *N*-silylimines in good to excellent yields.[20b] Nevertheless, these methodologies use expensive hydrosilanes known to be hazardous and dangerous by generating toxic, pyrophoric SiH_4 gas.[21]

For several years now, our group has been studying the behavior of 1,1,3,3-tetramethyldisiloxane (TMDS) as a safer source of hydrides for the reduction of phosphine oxides,[22a–c] amides,[22d,e] nitro,[22f,g] acetals,[22h–j] ketones,[22k] and carboxylic acids,[22l] in the presence of an appropriate transition metal. Associated with a relatively inexpensive titanium(IV) isopropoxide, TMDS is able to reduce nitriles into amines.[23] Recently, we have shown that the combination of TMDS and V(O)(O*i*Pr)$_3$ is efficient for the reduction of esters into alcohols.[24] To the best of our knowledge, it was the first time that a vanadium complex was associated with an hydrosiloxane for the reduction of an organic function. Moreover, TMDS was never reported for the reduction of nitriles into aldehydes. Herein, we extend the scope of the TMDS/V(O)(O*i*Pr)$_3$ reducing system to the chemoselective reduction of aromatic and aliphatic nitriles into aldehydes.

Results and discussion

In our previous work, we have shown that a reducing system composed of 1.0 mol % of V(O)(O*i*Pr)$_3$ and 4.0 Si–H of TMDS in toluene at 100 °C was efficient to reduce a large number of esters into alcohols.[24] However, under these reaction conditions, reduction of *p*-cyanomethylbenzoate failed because of the presence of the nitrogen atom. The cyano group might coordinate the metal and thus block the reduction. Consequently, we concentrated our efforts in order to determine the feasibility of reducing a cyano group by a TMDS/V(O)(O*i*Pr)$_3$ reducing system and investigated the reduction of 4-chlorobenzonitrile **1a** as a model substrate. Depending on the reaction conditions and after an acid-base treatment of the crude mixture, two products were detected in the organic layer by GC–MS analysis: 4-chlorobenzaldehyde **2a** which comes from the hydrolysis of an *N*-silylimine intermediate and imine **3a** (Table 1). It is important to note that imine **3a** is not a direct product of the reduction but it results from the condensation of 4-chlorobenzylamine (which comes from the hydrolysis of an *N,N*-disilylamine intermediate) with aldehyde **2a** after a basic treatment. Consequently, imine **3a** implies the formation of 4-chlorobenzylamine as a minor product of the reduction of **1a**.

First reactions were conducted in toluene at 60 °C for 20 h with 1.0 equiv of V(O)(O*i*Pr)$_3$ and it appeared that the amount of TMDS is essential to reach complete conversion of **1a**. Indeed, increasing the quantity of hydrides from 6.0 to 8.0 and 20.0 Si–H/CN increased the conversion of the starting material from 35% to 55% and 100%, respectively (Table 1, entries 1, 2, and 5). With intermediate quantities 12.0 and 16.0 Si–H/CN, **1a** was not fully consumed (Table 1, entries 3 and 4). In all the experiments, aldehyde **2a** is the major product but the chemoselectivity of the reduction is decreased by the presence of imine **3a** which indicates the formation of 4-chlorobenzylamine as the co-product. The best result was obtained with 20.0 Si–H/CN of TMDS where aldehyde **2a** was formed in 75% GC yield (Table 1, entry 5). Using the same amount of TMDS, the conversion drastically dropped when decreasing the loading of vanadium catalyst even in the presence of phosphorus ligands (Table 1, entries 6–8).

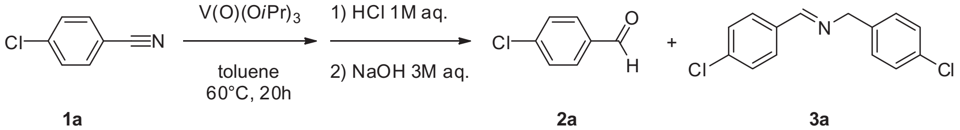
The efficiency of other vanadium complexes with different oxidation states such as V(O)Cl$_3$ (1.0 equiv), V(acac)$_3$ (1.0 equiv), VF$_4$ (1.0 equiv), V(O)(acac)$_2$ (1.0 equiv), and *N,N′*-bis(salicylidene)-*o*-phenylenediamine vanadium(IV) oxide complex (0.02 equiv) was also investigated for the reduction of **1a** in association with 20.0 Si–H/CN of TMDS. Nevertheless, they proved to be inefficient since **1a** was totally recovered after 20 h reaction and even after longer reaction time.

Consequently, a reducing system composed of 20.0 Si–H/CN of TMDS, 1.0 equiv of V(O)(O*i*Pr)$_3$ in toluene at 60 °C for 20 h gave satisfactory results for the chemoselective reduction of nitriles into aldehydes. Under these reaction conditions, we extended the reduction to other aromatic as well as aliphatic nitriles (Table 2).[25]

Aromatic nitriles **1b** and **1c** bearing a methoxy and a methyl group at the *para*-position were reduced into the corresponding aldehydes **2b** and **2c** in 67% and 63% GC yields, respectively (Table 2, entries 2 and 3). In the case of **1c**, after 24 h reduction, the crude mixture was hydrolyzed with an aqueous solution of *ortho*phosphoric acid to liberate aldehyde **2c** in the organic layer. Without further purification, **2c** reacted with *tert*-butylcarbazate to give the corresponding hydrazone in 62% isolated yield (Scheme 1).

The *p*-tolyl group at the *ortho*-position of nitrile **1d** did not affect the reduction and aldehyde **2d** was obtained in 70% GC yield (Table 2, entry 4). Reduction of 1-cyanonaphthalene **1e** gave 1-naphthaldehyde **2e** in 60% GC yield (Table 2, entry 5). After acidic treatment using aqueous H_3PO_4 followed by flash column chromatography, **2d** and **2e** were isolated in 60% and 45% yields, respectively. The long chain aliphatic nitrile **1f** was reduced in the corresponding fatty aldehyde **2f** in 84% GC yield (Table 2, entry 6). 1-Cyclohexenylacetonitrile **1g** bearing a non-conjugated C═C was not reduced into the expected aldehyde. The volatile and more stable conjugated 2-cyclohexylidene-acetaldehyde **2g**, resulting from the rearrangement of the double bond, was

Table 1
Reduction of 4-chlorobenzonitrile **1a** under various TMDS-V(O)(O*i*Pr)$_3$ reaction conditions



Entry	TMDS (moles Si–H/mole CN)	Moles V(O)(O*i*Pr)$_3$/mole CN	Ligand[b]	Conv.[a] (%)	Ratio **2a**:**3a**[a]
1	6.0	1.0	–	35	32: 3
2	8.0	1.0	–	55	52: 3
3	12.0	1.0	–	86	60:26
4	16.0	1.0	–	87	64:23
5	20.0	1.0	–	100	67:33
6	20.0	0.5	–	28	26:2
7	20.0	0.2	(Ph)$_3$P═O	24	16:8
8	20.0	0.2	(Ph)$_3$P	17	17:0

[a] Determined by GC–MS analysis of the organic layer after a first acidic treatment (aq 1 m HCl) followed by basification (aq 3 m NaOH until pH >11).
[b] 0.6 equiv/CN.