An Efficient Synthesis of Dinitrile Derivatives by the Reaction of **Oxime Esters or Acid Anhydrides with Cyanotrimethylsilane** Catalyzed by La(OⁱPr)₃

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The reaction of oxime esters with cyanotrimethylsilane (Me₃SiCN) under the influence of a catalytic amount of lanthanide compounds produced α -trimethylsilyloxydinitrile derivatives in excellent yields accompanied with the formation of trimethylsilyl oxime ethers. Among the lanthanoid catalysts examined, $La(O'Pr)_3$ was found to be the best catalyst. The reaction seems to proceed through the formation of acyl cyanides as intermediates, followed by the addition of Me₃SiCN to them. Additionally, the reaction of acetic anhydride with Me₃SiCN catalyzed by La(O⁴Pr)₃ gave 1-trimethylsilyloxyethane dinitrile. Thus, various α -trimethylsilyloxydinitriles were synthesized in good yields by allowing oxime esters or acid anhydrides to react with Me₃SiCN in the presence of a catalytic amount of La(OⁱPr)₃.

Introduction of a cyano group to carbonyl compounds through a catalytic or noncatalytic process has been often used as a synthetic tool. Among many cyanating reagents, cyanotrimethylsilane (Me₃SiCN) is recognized as a useful reagent.¹⁻⁶ It has been reported that the reaction of carbonyl compounds such as ketones and aldehydes with Me₃SiCN catalyzed by Yb(CN)₃ affords α -trimethvlsilvloxycyanides.⁴ In addition, acid chlorides react with Me₃SiCN without any catalyst to give carbonitrile derivatives.⁵ However, there are few papers on the synthesis of dinitrile derivatives which are precursors of α -hydroxy carboxylic acids or malnonitiriles. Classically, the dinitrile compounds were prepared by the reaction of acyl chlorides with Me₃SiCN in the presence of pyridine at 120 °C.6 Recently, Shioiri et al. showed that dicyanophosphates can be prepared by the reaction of carboxylic acids with diethyl phosphorocyanidate in the presence of triethylamine.7

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In a previous paper, we have reported the efficient acetylcyanation of aldehydes in the presence of acetonecyanohydrin and isopropenyl acetate under the influence of a lanthanide compound such as $Cp*Sm(thf)_2$ as a catalyst.⁸ Now, we find that the reaction of oxime esters or acid anhydrides with Me₃SiCN catalyzed by La(O⁴Pr)₃ affords the corresponding α -trimethylsilyloxydinitriles in high yields (eq 1). To our best knowledge, this is the first catalytic method for the synthesis of α -trimethylsilyloxydinitrile derivatives.



Cyclohexanoneoxime acetate (1) was chosen as a model substrate and allowed to react with Me₃SiCN (2) under the influence of a catalytic amount of various lanthanide compounds (Table 1). The reaction of 1 with 2 (2.5 equiv with respect to 1) catalyzed by $Cp*Sm(thf)_2$ in toluene at room temperature gave 1-trimethylsilyloxyethane dinitrile (3) in 88% yield at 92% conversion (run 1). In this reaction, trimethylsilyl oxime ether (4) was formed in 92% yield along with 3 (eq 1). Previously, we showed that the reaction of 1 with acetonecyanohydrin catalyzed by Cp*Sm(thf)₂ produced 1-cyano-N-cyclohexylhydroxyamine O-acetate (eq 2).8 Thus, different types of cyano compounds were prepared by the reaction of 1 with Me₃-

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 Table 1. Reaction of 1 with 2 under the Influence of Various Catalysts^a

run	catalyst	convn (%)	yield (%)
1 ^b	Cp*2Sm(thf)2	92	88
2	SmI_2	>99	61
3	SmI_3	96	48
4	SmCl ₃	79	64
5	Sm(O ⁱ Pr) ₃	>99	56 ^c
6	La(O ⁱ Pr) ₃	>99	86
7	Al(O ^{<i>i</i>} Pr) ₃	no reaction	
8	$Zr(O^{i}Pr)_{3}$	no reaction	

 a **1** (1 mmol) was allowed to react with **2** (2.5 mmol) in the presence of catalyst (0.1 mmol) in THF (1 mL) at room temperature for 15 h. b Toluene (1 mL) was used as a solvent. c Acetyl cyanide was obtained in 35% yield.

 Table 2. Reaction of Various Oximeesters with 2

 Catalyzed by La(OⁱPr)₃^a



 a Oximeester (1 mmol) was allowed to react with 2 (2.5 mmol) in the presence of La(O^fPr)₃ (0.1 mmol) in THF (1 mmol) at room temperature for 15 h.

SiCN or acetonecyanohydrin as the cyanating agent under the influence of $Cp*Sm(thf)_2$.



Other samarium compounds such as SmI₂, SmI₃, and SmCl₃ afforded **3** in low yields (runs 2–4). It was found that La(O'Pr)₃ produced **3** in high yield (86%), while the Sm(O'Pr)₃-catalyzed reaction showed lower selectivity to form **3** in 56% yield (runs 5 and 6). Al(O'Pr) ₃ and Zr(O'Pr)₄ were inert in this reaction (runs 7 and 8). It is interesting that the present reaction is catalyzed only by lanthanide compounds.

Table 2 shows the reaction of various types of oxime esters with **2** in the presence of La(O'Pr)₃ catalyst. All oxime esters used were successfully converted into the corresponding α -trimethylsilyloxy dinitrile compounds in good yields. The reaction of the sterically hindered acetoneoxime pivaloate with 2.5 equiv of **2** catalyzed by La(O'Pr)₃ for 15 h produced 2,2-dimethyl-1-trimethylsilyloxypropane dinitrile in 97% yield (run 3). Similarly, cyclohexanoneoxime benzoate (**5**) under these reaction conditions gave the corresponding dinitirile, 1-phenyl-1trimethylsilyloxymethane dinitrile (**6**) (90%) (run 4).

The dinitrile **6** could be converted into α -hydroxycarboxylic acid. After the reaction of **5** and **2** catalyzed by

Scheme 1. A Possible Reaction Path



 $La(O^{J}Pr)_{3}$, the excess amount of *concentrated* HCl was added to the reaction mixture, followed by stirring at refluxing temperature to form 2-hydroxyphenyl acetic acid in 50% yield (eq 3).

5 + 2
$$\xrightarrow{cat.} La(O^{i}Pr)_{3} \xrightarrow{conc.} HCl$$

THF, r.t., 15 h rf, 12 h Ph COOH (3)
50%

....

Treatment of **5** with 1 equiv of **2** in the presence of $La(O'Pr)_3$ for 0.5 h produced benzoyl cyanide (7) as a major product (30%) along with dinitrile compound **6** (4%) at 48% conversion (eq 4). This fact shows that α -trimethylsilyloxy dinitriles are formed via stepwise reactions: the substitution of the oxime moiety by a cyanide group, giving a mono cyanated compound like **7**, and the addition of **2** to the resulting **7** to form dinitrile compound like **6**.

5 + 2
$$\frac{\operatorname{Cat. La}(O'\operatorname{Pr})_{3}}{\operatorname{THF, r.t., 0.5 h}}$$
Conv. 48 % (4)
$$\operatorname{O}_{Ph} \operatorname{CN}^{+} \operatorname{Ph} \operatorname{CN}^{+} \operatorname{CN}$$
7 30% 6 4%

A possible reaction path is shown in Scheme 1. The reaction may be initiated by the reaction of $La(OiPr)_3$ with Me₃SiCN to form $La(CN)_3$ whose formation is confirmed by the observation of a strong absorption band at 1986 cm⁻¹. Utimoto et al. reported that Yb(CN) ₃ was obtained by the reaction of Yb(O'Pr)₃ with 3 equiv of Me₃-SiCN.⁴ Thus, it is reasonable to assume that La(CN)₃ (**A**), generated in situ from La(O'Pr)₃ and Me₃SiCN, was reacted with **1**, followed by **2** to form a lanthanide alkoxide **D** together with **4**. The alkoxide **D** is attacked by another **2** to give **3**, and the **A** is regenerated.

In the present cyanation reaction, the formation of trimethylsilyl oxime ether **4** from oxime acetate **1** seems to be favorable to promote the reaction.

Recently, we have shown that the reaction of alcohol with 1 by $La(O^{i}Pr)_{3}$ under neutral conditions produces the corresponding acetate and oxime in almost quantita-

 Table 3. Reaction of Acyl Compounds with 2 Catalyzed

 by La(O'Pr)3^a



^{*a*} Acyl compound (1 mmol) was allowed to react with **2** (2.5 mmol) in the presence of $La(O^{i}Pr)_{3}$ (0.1 mmol) in THF (1 mmol) at room temperature for 15 h. ^{*b*} Reaction temperature was 50 °C.

Table 4. Reaction of Several Acid Anhydrides with 2
Catalyzed by $La(O^{j}Pr)_{3}^{a}$

Run	Acid Anhydride	Product	Yield (%)	
	0 0	отмз		
	ROR			
1	R = C	$R = CH_3$		
2	$R = {}^{n}C_{4}H_{9}$		74	
3	$\mathbf{R} = {}^{i}\mathbf{C}_{3}\mathbf{H}_{7}$		78	
4	R = ^t C₄H ₉		92	
5	R = Ph		75	
^{<i>a</i>} Acid anhydride (1 mmol) was allowed to react with 2				

(2.5 mmol) in the presence of $La(O^iPr)_3$ (0.1 mmol) in THF (1 mmol) at 50 °C for 15 h.

tive yield.⁹ Although it is known that acyl chloride and acid anhydride can be used as acylating reagents, **1** could be used as an efficient acylating reagent, which reaction can be carried out under neutral conditions. Thus, we next examined the reaction of several acetyl compounds with Me₃ SiCN in the presence of a catalytic amount of La(O⁷Pr)₃ (Table 3).

The reaction of isopropenyl acetate (8) with 2 catalyzed by La(O'Pr)₃ gave 3 in 12% yield (run 2). Similarly, acyl chloride (9) resulted in 3 in 13% yield under these reaction conditions (run 3).¹⁰ The low yield of the product 3 from 8 and 2 may be due to the difficulty of the formation of isopropenyl silyl ether. Similarly, the difficulty of the formation of 3 from 9 and 2 is attributed to the difficulty of the generation of Me₃SiCl. However, it was found that the reaction of acetic anhydride (10) with 2.5 equiv of **2** under the influence of $La(O^{2}Pr)_{3}$ in THF produced 3 in 60% yield along with trimethylsilyl acetate (run 4). When this reaction was carried out at 50 °C, the yield of 3 was improved to 74% (run 5). Hence, various acid anhydrides were allowed to react with Me₃SiCN in the presence of La(OⁱPr)₃ at 50 °C (Table 4). The reaction took place smoothly to give the corresponding dinitrile compounds in good yields (runs 1 and 5).

In conclusion, a new route to α -trimethylsiloxy dinitrile derivatives has been developed by the reaction of oxime

esters with Me₃SiCN in the presence of a catalytic amount of La(O'Pr)₃. In addition, the reaction of acid anhydrides with Me₃SiCN catalyzed by La(O'Pr)₃ at 50 °C produced the corresponding dinitrile compounds in satisfactory yields.

Experimental Section

General Procedure. ¹H and ¹³C NMR spectra were measured at 270 and 67.5 MHz, respectively, in CDCl₃ with TMS as the internal standard. IR spectra were measured as films on NaCl plates. GLC analysis was performed with a flame ionization detector using a 1 mm \times 30 m capillary column (OV-1). Oxime esters were synthesized by the reaction of the corresponding oximes with acid chlorides or acid anhydrides in THF at room temperature and were purified by distillation or recrystallization. Other starting materials were commercially available and used after distillation or recrystallization. Cp*Sm(thf)₂,¹¹ SmI₂,¹² and SmI₃¹³ were prepared according to the literature procedures. Sm(O/Pr)₃ and La(O/Pr)₃ were purchased from High Purify Chemical Laboratory Co. Ltd.

General Produre for the Reaction of Oximeester with 2 Catalyzed by La(O'Pr)₃. To a Schlenk tube containing a THF solution (1.0 mL) of La(O'Pr)₃ (0.1 mmol) were added Me₃-SiCN (2.5 mmol) and oxime ester (1.0 mmol). The reaction mixture was stirred at room temperature for 15 h under Ar. After the reaction, wet diisopropyl ether was added to the solution, and the catalyst precipitated was removed by simple filtration. The products were purified by the use of HPLC and identified by the NMR and IR measurements and were obtained as oil. Benzoyl cyanide (7) was commercially available and identified through comparison of the isolated product with an authentic sample.

1-Trimethylsilyloxyethane dinitrile (3):^{6b} ¹H NMR (CDCl₃/TMS) δ 1.94 (s, 3H), 0.29 (s, 9H); ¹³C NMR (CDCl₃/TMS) δ 115.6, 59.1, 30.4, 0.3; IR (neat) 2964, 1261, 1167, 993, 853 cm⁻¹.

Trimethylsilyloxime ester (4):¹⁴ ¹H NMR (CDCl₃/TMS) δ 2.31 (m, 2H), 2.24–2.20 (m, 2H), 1.52–1.32 (m, 6H), 0.19 (s, 9H); ¹³C NMR (CDCl₃/TMS) δ 164.4, 32.3, 27.1, 26.0, 25.8, 25.0, -0.7; IR (neat) 2971, 1746, 1463, 1377, 1250 cm⁻¹.

1-Trimethylsilyloxypentane dinitrile: ¹H NMR (CDCl₃/ TMS) δ 2.16–2.08 (m, 2H), 1.66–1.52 (m, 2H), 1.50–1.37 (m, 2H), 0.97 (t, J = 7.2 Hz, 3H), 0.36 (s, 9H); ¹³C NMR (CDCl₃/ TMS) δ 115.3, 63.3, 42.2, 25.5, 21.7, 13.6; IR (neat) 2963, 1258, 1139, 852, 760 cm⁻¹.

2-Methyl-1-trimethylsilyloxypropane dinitrile:¹⁵ ¹H NMR (CDCl₃/TMS) δ 2.03 (heptet, J = 6.6 Hz, 1H), 0.96 (d, J = 6.6 Hz, 6H), 0.13 (s, 9H); ¹³C NMR (CDCl₃/TMS) δ 114.7, 68.4, 39.9, 16.3, 0.2.

2,2-Dimethyl-1-trimethylsilyloxypropane dinitrile:^{6b} ¹H NMR (CDCl₃/TMS) δ 0.95 (s, 9H), 0.13 (s, 9H); ¹³C NMR (CDCl₃/TMS) δ 120.5, 114.8, 71.9, 41.5, 23.7; IR (neat) 2972, 2243, 1258, 1134, 851 cm⁻¹.

1-Phenyl-1-trimethylsilyloxymethane dinitrile (6):⁶ ¹H NMR (CDCl₃/TMS) δ 7.71–7.50 (m, 5H), 2.36–2.23 (m, 4H), 0.36 (s, 9H); ¹³C NMR (CDCl₃/TMS) δ 134.5, 131.0, 129.4, 125.5, 115.0, 65.1, 0.5; IR (neat) 2963, 2243, 1682, 1453, 1258, 1198, 1103 cm⁻¹.

Procedure for the Synthesis of 2-Hydroxyphenylacetic Acid from 5. To a Schlenk tube containing a THF solution (1.0 mL) of $La(O'Pr)_3$ (0.1 mmol) were added Me₃SiCN (2.5 mmol) and 5 (1.0 mmol). The reaction mixture was stirred at room temperature for 15 h under Ar. Then, 3.0 mL of *concentrated* HCl was added, and the mixture was stirred at

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refluxing temperature for 12 h. After the reaction, the mixture was extracted with Et₂O (10 mL \times 3), and dried over anhydrous MgSO₄. After removal of the solvent in vacuo, the product was purified by recrystallization from ethanol, and identified through comparison of the isolated product with an authentic sample which was purchased from Aldrich (mp 147–149 °C). The isolated yield is shown.

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Supporting Information Available: Copies of ¹³C and ¹H NMR and IR spectra for the compounds **3**, **4**, 1-trimethyl-silyloxypentane dinitrile, 2-methyl-1-trimethylsilyloxypropane dinitrile, **2**,2-dimethyl-1-trimethylsilyloxypropane dinitrile, **6**, and 2-phenyl-2-hydroxyactetic acid. This information available free of charge via the Internet at http://pubs.acs.org.

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