Acetylcyanation of Aldehydes with Acetone Cyanohydrin and Isopropenyl Acetate by Cp*2Sm(thf)2

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There are a number of potentially useful methods for hydrocyanation using various cyanating reagents such as hydrogen cyanide,[1] alkali or alkaline-earth metal cyanides,[2] organoaluminum cyanides,[3] organosilicone cyanides,[4] and acetone cyanohydrin[5] which can generate cyanide ion in the presence of a base. Among them, the hydrocyanation using acetone cyanohydrin is known as the Nazarov method.[5] However, the reactivity of acetone cyanohydrin is generally low because of the difficulty of raising the cyanide concentration in the reaction medium. If the reactivity of this reagent can be improved by using an appropriate catalyst, acetone cyanohydrin is thought to be a practical cyanating reagent compared to hydrogen cyanide which is volatile and very toxic. Recently, trans-hydrocyanation from acetone cyanohydrin to aldehydes and ketones is reported to be catalyzed by Ln(O^{i}Pr)3 (Ln = La, Sm, and Yb).[6]

In contrast, there are very few investigations on the acylcyanation of carbonyl compounds,[7-9] although acylated cyanohydrins are one of the important synthetic targets for their application as pesticides and their utility as precursors to many useful classes of organic compounds.[3] McIntosh reported the synthesis of cyanohydrin ethers and cyanohydrin acetates by the phase-transfer catalyzed reaction of aldehydes with potassium cyanide in the presence of allylic bromide and acetic anhydride, respectively.[8] Aldehydes were converted into acylated cyanohydrins upon treatment with acyl cyanides under the influence of tributyltin cyanide as a catalyst.[9] An alternative approach using acyl cyanides in the presence of DABCO has been shown by Ismail et al.[10]

In a previous paper, we showed that Cp*2Sm(thf)2 is an effective catalyst for the acylation of alcohols and amines with an oxime acetate in combination with isopropenyl acetate as an acylating agent.[11a] By using this method, a variety of tertiary alcohols and terpene alcohols which are sensitive to acids and bases are successfully acetylated under mild conditions, since the reaction is capable of being carried out under neutral conditions. To extend the present Cp*2Sm(thf)2-catalyzed acylation, we now examine the Cp*2Sm(thf)2-catalyzed acylcyanation of aldehydes using acetone cyanohydrin and isopropenyl acetate under neutral and mild conditions.

In this paper, we describe a new versatile method for the acetylcyanation using acetone cyanohydrin and isopropenyl acetate and for the hydrocyanation of carbonyl compounds with acetone cyanohydrin catalyzed by Cp*2-Sm(thf)2 under ambient conditions (eq 1).
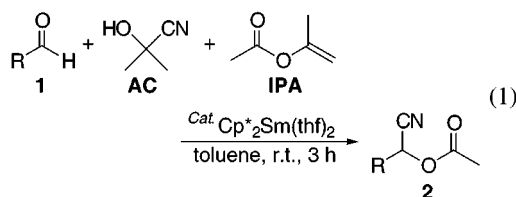
A 1:1:1 mixture of butanal (**1a**), acetone cyanohydrin (AC), and isopropenyl acetate (IPA) was allowed to react under the influence of Cp*2Sm(thf)2 in toluene at room temperature for 3 h, giving 2-acetoxybutanenitrile (**2a**) in 61% yield (Table 1). When 2 equiv of IPA with respect to **1a** and AC was employed under the same reaction conditions, **2a** was obtained in 82% yield. However, a reaction using 2 equiv of AC resulted in a decrease in the yield of **2a** (59%). The reaction of **1a** with AC in the absence of IPA by Cp*2Sm(thf)2 afforded the corresponding cyanohydrin, 2-hydroxybutanenitrile, in moderate yield (63%) (run 3). This shows that the equilibrium is capable of lying to the right by using IPA, in contrast to the simple transhydrocyanation between aldehyde and AC.

To determine the catalytic activity of various lanthanoid complexes, **1a** was reacted with AC and IPA (2 equiv) under these conditions. Among the lanthanoid complexes examined, Cp*2Sm(thf)2 and Sm(O^{i}Pr)3 were found to be good catalysts for the synthesis of cyanohydrin ester **2a**. The Yb complex, Cp*2Yb(thf)2, was less active than the corresponding samarium complex. Although SmI2 showed slight catalytic activity for the present reaction, SmI3 and Sm(OTf)3 which serve as Lewis acids were inactive in this transformation.

On the basis of these results, the acetylcyanation of a variety of aldehydes by Cp*2Sm(thf)2 was examined under the influence of AC (1 equiv) and IPA (2 equiv) at room temperature for 15 h (Table 2).

The reaction was capable of being extended to the acetylcyanation of a variety of aldehydes in satisfactory yields except for benzaldehyde (**1g**). In particular, sterically hindered aldehydes such as 2-methylpropanal (**1c**) and 2,2-dimethylpropanal (**1e**) were smoothly subjected to the acetylcyanation to give the corresponding acetylated cyanohydrins, **2c** and **2e**, respectively in good yields (runs 2 and 4). Cyclohexanecarboxaldehyde (**1f**) afforded 2-acetoxy-2-cyclohexylacetonitrile (**2f**) in high yield (90%), but benzaldehyde (**1g**) reacted with difficulty to form

(1) Lapworth, A. *J. Chem. Soc.* **1903**, *83*, 995.

(2) (a) Kurtz, P. *Ann. Chem.* **1951**, *23*, 572. (b) Allen, C. F. H.; Johnson, H. B. *Organic Syntheses*; Wiley: New York, 1963; Collect Vol. IV, p 804.

(3) Nagata, W.; Yoshioka, M. *Organic Reactions*; Dauben, W. G., Ed.; John Wiley & Sons: New York, 1977; Vol. 25, p 255 and references cited therein.

(4) Groutas, W. C.; Felker, D. *Synthesis* **1980**, 861 and references therein.

(5) Nazarov, I. N.; Zav'yalov, J. *Gen. Chem., USSR (Engl. Transl.)* **1954**, *24*, 475.

(6) Ohno, H.; Mori, A.; Inoue, S. *Chem. Lett.* **1993**, 375.

(7) Elliot, M. *The Future for Insecticide; Needs and Prospect*s, Vol. 6; Metcalf, M. L., Mckelvey. J. J., Eds.; John Wiley & Sons: New York, 1976; pp 163–190.

(8) McIntosh, J. M. *Can. J. Chem.* **1977**, *55*, 4200.

(9) Scholl, M.; Lim, C.-K.; Fu, G. C. *J. Org. Chem.* **1995**, *60*, 6229.

(10) Hoffmann, H. M. R.; Ismail, Z. M.; Hollweg, R.; Zein, A. R. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 1807.

(11) (a) Tashiro, D.; Kawasaki. Y.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* **1997**, *62*, 8141. (b) Shiraishi, H.; Kawasaki, Y.; Sakaguchi, S.; Nishiyama, Y.; Ishii, Y. *Tetrahedron Lett.* **1996**, *37*, 7291.

Table 1. Acetylcyanation of Butanal (1a) with Acetone Cyanohydrin (AC) and Isopropenyl Acetate (IPA) to 2-Acetoxybutanenitrile (2a) under Selected Conditions[a]

| run	catalyst	solvent	yield (%)
1[b]	Cp*$_2$Sm(thf)$_2$	toluene	61
2	Cp*$_2$Sm(thf)$_2$	toluene	82
3[c]	Cp*$_2$Sm(thf)$_2$	toluene	63
4	Cp*$_2$Yb(thf)$_2$	toluene	41
5	Sm(O^{i}Pr)$_3$	THF	62
6	SmI$_2$	THF	17
7	SmI$_3$	THF	no reaction
8	Sm(OTf)$_3$	THF	no reaction

[a] **1a** (1 mmol) was allowed to react with AC (1 mmol) and IPA (2 mmol) in the presence of catalyst (0.1 mmol) in solvent (1 mL) at room temperature for 3 h. [b] IPA (1 mmol) was used. [c] In the absence of IPA. Yield of 1-hydroxybutanonitrile.

Table 2. Acetylcyanation of Various Aldehydes with Acetone Cyanohydrin (AC) and Isopropenyl Acetate (IPA) Catalyzed by Cp*$_2$Sm(thf)$_2$[a]

Run	Substrate	Product	Yield (%)
1	**1b**	**2b**	87
2	**1c**	**2c**	86
3	**1d**	**2d**	82
4	**1e**	**2e**	77
5	**1f**	**2f**	90
6	**1g**	**2g**	49
7	**1h**	Complex mixture	
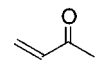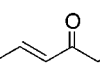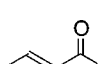
[a] Substrate (1 mmol) was allowed to react with AC (1 mmol) and IPA (2 mmol) in the presence of Cp*$_2$Sm(thf)$_2$ (0.1 mmol) in toluene (1 mL) at room temperature for 15 h.

acetoxycyanohydrin, **2g**, in 49% yield. α,β-Unsaturated aldehydes such as acrolein (**1h**) resulted in a complex mixture under these conditions, but *trans*-2-hexenal (**1i**) reacted with 2 equiv of AC to give 2-hydroxy-4-cyano-heptanenitrile (**2i**) in which HCN added to both carbon–carbon and carbon–oxygen double bonds of **1i** (eq 2).

$$\text{(2)}$$

2i 61 %
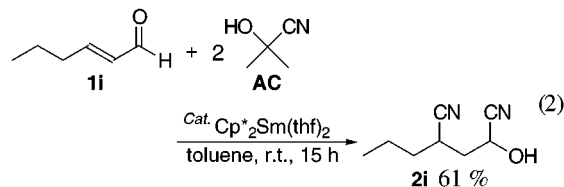
Since the Michael addition of hydrogen cyanide to **1i** was efficiently promoted by Cp*$_2$Sm(thf)$_2$, several α,β-unsaturated carbonyl compounds were reacted with AC in the presence of Cp*$_2$Sm(thf)$_2$ at room temperature for 15 h (Table 3). Early procedures for the addition of hydrogen cyanide to α,β-unsaturated ketones employed a reaction with sodium or potassium cyanide in aqueous

Table 3. Cyanohydration of Various α,β-Unsaturated Compounds with Acetone Cyanohydrin (AC) Catalyzed by Cp*$_2$Sm(thf)$_2$[a]

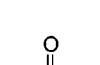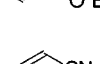|	Substrate		Product		Yield
1		**3**		**4**	90 (80)
2[c]		**5**		**6**	67 (11)
3		**7**		**8**	39 (40)
4		**9**		**10**	41 (27)
5		**11**		**12**	89 (46)

[a] Substrate (1 mmol) was allowed to react with AC (2 mmol) and in toluene (1 mL) by Cp*$_2$Sm(thf)$_2$ at room temperature for 15 h. [b] Parentheses show the yield by Sm(O^{i}Pr)$_3$ (0.1 mmol). [c] 3 h.

or aqueous ethanolic solution.[12] Nagata et al. have developed the efficient hydrocyanation system using hydrogen cyanide and triethylaluminum in an inert solvent such as ether, THF, or benzene for this purpose.[3]

The reaction of methyl vinyl ketone (**3**) with AC afforded a Michael adduct, 4-cyanobutan-2-one (**4**), in 90% yield. The same reaction by Sm(O^{i}Pr)$_3$ gave **4** in somewhat lower yield than that by Cp*$_2$Sm(thf)$_2$. Similarly, 4-hexen-3-one (**5**) gave 5-cyanohexan-3-one (**6**) in 67% yield under the influence of Cp*$_2$Sm(thf)$_2$ at room temperature for 3 h. The reaction of *trans*-chalcone (**7**) with AC afforded the corresponding adduct, **8**, in moderate yield. Butyl acrylate (**9**) gave butyl 3-cyanopropionate (**10**) in 41% yield. Since the Michael addition of hydrogen cyanide to α,β-unsaturated carbonyl compounds was achieved in satisfactory yields by Cp*$_2$Sm(thf)$_2$ and Sm-(O^{i}Pr)$_3$, acrylonitrile (**11**) is expected to react with AC in the same way as α,β-unsaturated carbonyl compounds. As expected, hydrogen cyanide added to **11** in the presence of Cp*$_2$Sm(thf)$_2$ to give malononitrile (**12**) in good yield (89%). Sm(O^{i}Pr)$_3$ also catalyzed the reaction, but it was less active than Cp*$_2$Sm(thf)$_2$, giving **12** in a somewhat lower yield (46%).

In a previous paper, we reported that imines which are synthetic equivalents of carbonyl compounds are activated by SmI$_2$ to form aldol-type condensation products.[11b] Hence the reaction of *N*-butylidenebutylamine (**13**) with AC was examined in the presence of some samarium complexes, but the reaction did not proceed even in the presence of SmI$_2$, Cp*$_2$Sm(thf)$_2$, and Sm(O^{i}Pr)$_3$.

$$\text{(3)}$$

Catalyst : SmI$_2$, Cp*$_2$Sm(thf)$_2$ and Sm(O^{i}Pr)$_3$
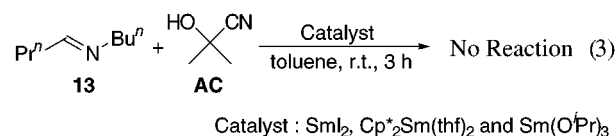
It is interesting to note that cyclohexanone oxime acetate (**14**) reacts with AC in the presence of Cp*$_2$Sm-(thf)$_2$ to give adduct **15**, in which hydrogen cyanide added to the carbon–nitrogen double bond of **14** in 50% yield

(12) House, H. O. *Modern Synthetic Reactions*, 2nd ed.; Benjamin, Inc.: New York, 1972; pp 623–628.

along with cyclohexanoneoxime (**16**) (eq 4). However, Sm-(O*i*Pr)$_3$ promoted the hydrolysis of oxime acetate **14** to oxime **16** rather than the addition of hydrogen cyanide. Compound **15** is an attractive precursor of an α-amino acid. The present lanthanide-catalyzed hydrocyanation of oxime ester provides an alternative route for the synthesis of α-acetylaminonitrile, although the optimum reaction conditions must be further investigated.
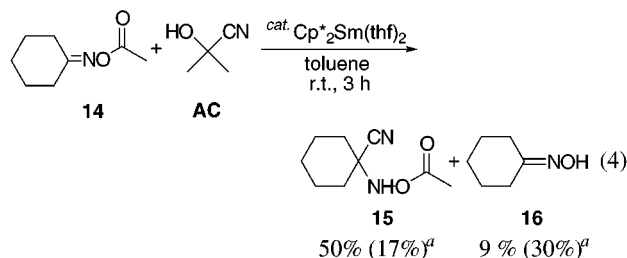
^{a} Parenthesis shows the yield by Sm(O*i*Pr)$_3$ in THF.

In conclusion, we found a direct acetylcyanation method of aldehydes with AC in the presence of IPA catalyzed by Cp*$_2$Sm(thf)$_2$ under mild conditions. α,β-Unsaturated carbonyl compounds produced Michael addition products under neutral conditions.

Experimental Section

General Procedure. ^{1}H and ^{13}C NMR spectra were measured at 270 and 67.5 MHz, respectively, in CDCl$_3$ with TMS as the internal standard. IR spectra were measured as thin films on NaCl plates or KBr pressed disks. GLC analysis was performed with a flame ionization detector using a 1 mm × 30 m capillary column (OV-1). Mass spectra were determined at an ionizing voltage of 70 eV. Isopropenyl acetate and acetone cyanohydrin were purchased from a commercial origin and distilled prior to use. Cp*$_2$Sm(thf)$_2$,^{13} Cp*$_2$Yb(thf)$_2$,^{13} Sm(O*i*Pr)$_3$,^{14}

(13) (a) Evans, W. J.; Bloom, I.; Hunter, W. E.; Atwood, J. L. *J. Am. Chem. Soc.* **1981**, *103*, 6507. (b) Evans, W. J.; Grate, J. W.; Choi, H. W.; Bloom, I.; Hunter, W. E.; Atwood, J. L. *J. Am. Chem. Soc.* **1985**, *107*, 941. (c) Evans, W. J.; Bloom, I.; Hunter, W. E.; Atwood, J. L. *Organometallics* **1985**, *4*, 112.
(14) Mazdiyasin, K. S.; Lynch, C. T.; Smith, J. S. *Inorg. Chem.* **1966**, *5*, 342.
(15) (a) Thom, K. F. U.S. Patent 3615169, 1971; *Chem Abstr.* **1972**, *76*, 5436a. (b) Forsberg, J. H.; Spaziano, V. T.; Balasubramanian, T. M.; Lin, G. K.; Kinsley, S. A.; Duckworth, C. A.; Poteruca, J. J.; Brown, P. S.; Miller, J. L. *J. Org. Chem.* **1987**, *52*, 1017. (c) Collins, S.; Hong, Y. *Tetrahedron Lett.* **1987**, *28*, 4391. (d) Almasio, M. C.; Arnaud-Neu, F.; Schming-weill, M. J. *Helv. Chim. Acta* **1983**, *66*, 1296. (e) Kobayashi, S.; Hachiya, I. *J. Org. Chem.* **1994**, *59*, 3590.
(16) Girard, P.; Namy, J. L.; Kagan, H. B. *J. Am. Chem. Soc.* **1980**, *102*, 2693.

Sm(OTf)$_3$,^{15} SmI$_2$,^{16} and SmI$_3$^{17} were prepared according to literature procedures.

General Procedure for the Cp*$_2$Sm(thf)$_2$-Catalyzed Acetylcyanation of Aldehydes with Acetone Cyanohydrin and Isopropenyl Acetate. To a Schlenk tube containing a toluene solution (1 mL) of Cp*$_2$Sm(thf)$_2$ (0.1 mmol) were added aldehydes (1 mmol), acetone cyanohydrin (1 mmol), and isopropenyl acetate (2 mmol). The reaction mixture was stirred at room temperature for 15 h under argon. After the reaction, wet diisopropyl ether was added to the solution, and the catalyst was removed by filtration. Removal of the solvent under reduced pressure afforded a yellow liquid, which was purified by column chromatography on silica gel with *n*-hexane/ethyl acetate (10/1 v/v) as eluent to give the corresponding acetates.

2-Acetoxybutyronitrile (2b):^{18} ^{1}H NMR (CDCl$_3$) δ 1.11 (t, *J* = 7.4 Hz, 3H), 1.89−2.05 (m, 2H), 2.14 (s, 3H), 5.28 (t, *J* = 6.6 Hz, 1H); ^{13}C NMR (CDCl$_3$) δ 8.9, 20.3, 25.8, 62.2, 116.7, 169.2.

2-Acetoxyisovaleronitrile (2c): ^{1}H NMR (CDCl$_3$) δ 1.08 (d, *J* = 6.8 Hz, 3H), 1.12 (d, *J* = 6.8 Hz, 3H), 2.10−2.25 (m, 1H), 2.16 (s, 3H), 5.18 (d, *J* = 5.1 Hz, 1H); ^{13}C NMR (CDCl$_3$) δ 17.3, 17.7, 20.3, 31.0, 66.3, 116.0, 169.2.

2-Aetoxy-4-methylvaleronitrile (2d): ^{1}H NMR (CDCl$_3$) δ 0.98 (d, *J* = 6.5 Hz, 3H), 0.99 (d, *J* = 6.5 Hz, 3H), 1.76−1.90 (m, 3H), 2.13 (s, 3H), 5.36 (t, *J* = 7.3 Hz, 1H); ^{13}C NMR (CDCl$_3$) δ 20.3, 22.0, 22.1, 24.4, 40.7, 59.8, 117.0, 169.1.

2-Aetoxy-3,3-dimethylbutyronitrile (2e): ^{1}H NMR (CDCl$_3$) δ 1.15 (s, 9H), 2.22 (s, 3H), 5.12 (s, 1H); ^{13}C NMR (CDCl$_3$) δ 20.1, 25.0, 34.5, 69.2, 115.9, 169.1.

2-Aetoxy-2-cyclohexylacetonitrile (2f): ^{1}H NMR (CDCl$_3$) δ 1.12−1.32 (m, 5H), 1.67−1.93 (m, 6H), 2.14 (s, 3H), 5.18 (d, *J* = 7.3 Hz, 1H); ^{13}C NMR (CDCl$_3$) δ 20.3, 25.2, 25.3, 25.7, 27.8, 28.0, 40.0, 65.5, 116.1, 169.2.

2-Aetoxy-2-phenylacetonitrile (2g): ^{1}H NMR (CDCl$_3$) δ 2.16 (s, 3H), 6.41 (s, 1H), 7.44−7.53 (m, 5H); ^{13}C NMR (CDCl$_3$) δ 20.4, 62.8, 116.1, 127.8, 129.2, 130.3, 131.7, 168.9.

2-Hydroxy-4-cyanoheptanenitrile (2i): ^{1}H NMR (CDCl$_3$) δ 0.99 (t, *J* = 6.8 Hz, 3H), 1.36−1.78 (m, 4H), 2.05−2.14 (m, 2H), 2.88−3.02 (m, 1H), 3.15−3.22 (m, 1H), 4.65−4,80 (m, 1H); ^{13}C NMR (CDCl$_3$) δ 13.3, 20.1, 27.1, 33.7, 36.9, 58.0, 119.2, 120.7.

1-Cyano-*N*-cyclohexylhydroxyamine *O*-acetate (15): ^{1}H NMR (CDCl$_3$) δ 1.18−2.08 (m, 10H), 2.11 (d, *J* = 2.7 Hz, 3H), 7.58 (s, 1H); ^{13}C NMR (CDCl$_3$) δ 18.7, 21.7, 27.1, 24.6, 32.9, 59.4, 119.9, 169.9.

Supporting Information Available: ^{1}H NMR, ^{13}C NMR, IR, and MS spectral for compounds **2b−g**, **2i**, **4**, **6**, **8**, **10**, and **15** and IR and MS spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

JO990030O

(17) Yu, Y.; Lim, R.; Zhang, Y. *Tetrahedron Lett.* **1993**, *34*, 4547.
(18) Castells, J.; Jaime, C.; Lopez-Calahorra, F.; Santaio, N.; Velasco, D. *J. Org. Chem.* **1988**, *53*, 5363.

Additions and Corrections

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Bruno Linclau, Ashvani K. Sing, and Dennis P. Curran*. Organic-Fluorous Phase Switches: A Fluorous Amine Scavenger for Purification in Solution Phase Parallel Synthesis.

Page 2835. Ashvani K. Sing's surname should be spelled Singh.

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