Mild and Efficient Silylcyanation of Ketones Catalyzed by *N*-Methylmorpholine *N*-Oxide

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Abstract: An efficient method for achiral addition of TMSCN to ketones by employing *N*-methylmorpholine *N*-oxide (NMO) alone as the catalyst is described. A variety of aromatic, aliphatic, cyclic and heterocyclic ketones are converted into their corresponding trimethylsilyl ethers in excellent yields (>90%).

Key words: silylcyanation, NMO, TMSCN, ketone, cyanohydrins

The addition reaction of trimethylsilyl cyanide (TMSCN) to carbonyl compounds is an area of active study due to the synthetic versatility of cyanohydrins, which can easily be converted into a wide variety of important synthetic intermediates including α -hydroxy acids, α -amino acids and β-amino alcohols.² They are also components of commercially important compounds such as the pyrethroid insecticides, cypermetrin and fluvaliate.³ A number of catalytic methods have been reported for the synthesis of cyanohydrins including the use of enzymes, peptides, Lewis acids and Lewis bases.⁴ Belokon⁵ has reported chiral Ti-catalyzed addition of TMSCN to various types of ketones, in which tetradentate Schiff's bases were employed as chiral ligands. Shibasaki⁶ disclosed enantioselective catalytic addition of TMSCN to carbonyl compounds by using carbohydrate based ligands and Ti(*i*-PrO)₄. Chiral titanium reagents derived from optically active sulfoximine/Ti(i- $PrO)_4^7$ and chiral sulfoxide/Ti(*i*-PrO)₄⁸ promote the asymmetric addition of TMSCN to carbonyl compounds affording cyanohydrins. Enantioselective addition of TMSCN to ketones by a catalytic double activation method using chiral Lewis acid and achiral N-oxide has been reported.9 Recently, chiral vanadium¹⁰ complexes has been used for cyanohydrin synthesis . There have been reports on the use of lanthanide salts of alkoxides, dialkylamides, chlorides, cyanides or triflates¹¹ in the catalysis of silylcyanation and hydrocyanation of aldehydes and ketones. Indium tribromide-catalyzed¹² addition of TMSCN to a-hetero substituted ketones also affords silvlated cyano compounds. Diorganotin dichlorides^{13a} and Cu(II) triflate^{13b} can be used as effective catalysts for the cyanation reaction of carbonyl compounds. The layered zirconium hydrogen phosphate¹⁴ exchanged with potassium ion was found to be an efficient catalyst for silylcyanation of carbonyl compounds. The in situ generated catalyst containing achiral Lewis acid and N,N-dimethylaniline N- oxide¹⁵ have been used for the generation of racemic cyanohydrins by the addition reaction of TMSCN to ketones. The other *N*-oxides¹⁶ such as N-(2'-pyridylmethyl)-2-diphenylhydroxymethylpyrrolidine N-oxide, N-benzyl-N,N-dihydroxyethylamine N-oxide were used along with $Ti(i-PrO)_4$ for silvlcyanation reaction of ketones, recently. The silvlcyanation methods mentioned above^{9,16} required longer reaction time (51-98 h) and were carried out in the presence of both Lewis acid and Lewis base. Although chiral N-oxides were used in asymmetric synthesis such as allylation of aldehydes,¹⁷ addition of Et₃Zn to aldehydes¹⁸ and enantioselective reduction of ketones,¹⁹ there is no report about the application of N-oxide alone as catalyst for the silylcyanation reaction. We wish to report herein the first example about the silvlcyanation reaction of ketones by using a cheap, easy to handle and readily available chemical, NMO, alone as catalyst to offer racemic trimethylsilyl ethers in excellent yields in relatively shorter reaction time.

Representative and successful examples for the synthesis of various trimethylsilyl ethers from aromatic, aliphatic and cyclic ketones are collected in Table 1. Unsubstituted and substituted acetophenones (entries 1-4) undergo very smooth silvlcvanation with over 90% yield. The substituents on the phenyl group have little effect on reaction time and yield (entries 2-4). The introduction of methylene group (entry 5) increases the reaction rate and reduces the reaction time due to release of steric strain. Both aromatic (entry 6) and aliphatic (entry 7) α , β -unsaturated ketones undergo silylcyanation in excellent yields. It should be noted that 1-indanone and α -tetralone were also proved as good substrates for silylcyanation reaction (entries 8, 9). Both the cyclic and open chain aliphatic ketones (entries10, 11) were converted into the corresponding cyanohydrin silyl ethers with excellent yield. 2-Acetylfuran, a heterocyclic ketone (entry 12) gives corresponding silyl ether in good yield (91%). This result indicates that NMO can selectively activate the carbonyl function of the ketone, keeping the furan ring intact. To the test the catalytic activity of NMO, a model reaction was carried out with acetophenone without NMO. No reaction took place within the typical reaction time.

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Table 1 Addition of TMSCN to Ketones Catalyzed by NMO

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^a Isolated yield.

(continued)

NMO is superior in activity to TMSCN when compared with recently reported achiral catalytic system, 15,16 combination of N-oxide/Ti(i-PrO)₄ used for the silvlcyanation of carbonyl compounds. Further the present system gave greater yield with shorter reaction time (entries 1, 3 and 6). It is worthwhile to note that the addition reaction of TMSCN to ketone is done without any metal catalyst. So this N-oxide alone (being an inexpensive catalyst) can be employed in the silvlcyanation of ketones, which makes the method more practical. The mechanistic details of the process are uncertain at present. But it is believed that the *N*-oxide might activate both the ketone and TMSCN for the formation of trimethysilyl ethers.

In summary, an efficient catalytic system for silvlcyanation of various kinds of ketones with better yield has been developed. The mild experimental conditions of shorter reaction time, inexpensive catalyst and the wide range of substrate applicability represent the notable features of this procedure. Although varieties of catalysts are known for this reaction, NMO has greater potential for extension into asymmetric version of the reaction, which is also under progress in our laboratory.

Silylcyanation of Acetophenone; 2-Trimethylsilyloxy-2-phenylpropanenitrile (Entry 1); **Typical Procedure**

To stirred solution of acetophenone (120 mg, 1 mmol) and NMO (30 mol%) in anhyd CH₂Cl₂ (1 mL) was added TMSCN (1.5 equiv) dropwise. The resulting solution was stirred continuously and the progress of the reaction was followed by TLC. After 8 h, the reaction mixture was purified by silica gel flash chromatography by using EtOAc-hexanes (1:9) mixture as eluent. 2-Trimethylsilyloxy-2phenylpropanenitrile was obtained as a colorless oil; yield: 215 mg (98%). The other substrates (entries 2-12) were also silylcyanated by using the same procedure. The products gave excellent ¹H and ¹³C NMR, HRMS, elemental analyses and IR data consistent with the structure.

IR (neat): 2362 cm⁻¹ (C≡N).

¹H NMR (CDCl₃, 200 MHz): δ = 0.17 (s, 9 H), 1.86 (s, 3 H), 7.36–7.53 (m, 5 H).

¹³C NMR (CDCl₃, 100 MHz): δ = 0.89, 33.40, 71.45, 121.43, 124.45, 128.49, 141.86.

HRMS (EI): m/z calcd for C₁₂H₁₇NOSi (M⁺): 219.1079; found: 219.1086.

2-(4'-Cholorophenyl)-2-trimethylsilyloxyphenylpropanenitrile (Entry 2)

IR (neat): 2366 cm⁻¹ (C \equiv N).

¹H NMR (CDCl₃, 200 MHz): δ = 0.21 (s, 9 H), 1.85 (s, 3 H), 7.40–7.48 (m, 4 H).

¹³C NMR (CDCl₃, 100 MHz): δ = 1.00, 33.45, 71.01, 121.18, 126.04, 128.79, 134.55, 140.68.

Anal. Calcd for $C_{12}H_{16}CINOSi: C, 56.79; H, 6.35; N, 5.52$. Found: C, 56.86; H, 6.69; N, 5.51.

2-Trimethylsilyloxy-2-(4'-nitrophenyl)phenylpropanenitrile (Entry 3)

IR (neat): 2360 cm⁻¹(C \equiv N).

¹H NMR (CDCl₃, 200 MHz): $\delta = 0.25$ (s, 9 H), 1.88 (s, 3 H), 7.77 (d, 2 H, J = 9.2 Hz), 8.30 (d, 2 H, J = 9.2 Hz).

¹³C NMR (CDCl₃, 100 MHz): δ = 1.07, 29.31, 76.43, 120.98, 124.02, 127.26, 129.89, 142.54.

Anal. Calcd for $C_{12}H_{16}N_2O_3Si:$ C, 54.52; H, 6.10; N, 10.60. Found: C, 54.44; H, 6.47; N, 10.50.

2-(4'-Methoxyphenyl)-2-trimethylsilyloxyphenylpropanenitrile (Entry 4)

IR (neat): 2362 cm⁻¹ (C \equiv N).

¹H NMR (CDCl₃, 200 MHz): δ = 0.17 (s, 9 H), 1.86 (s, 3 H), 3.84 (s, 3 H), 6.95 (d, 2 H, *J* = 8.8 Hz), 7.50 (d, 2 H, *J* = 8.8 Hz).

¹³C NMR (CDCl₃, 100 MHz): δ = 0.98, 33.31, 55.21, 71.18, 113.80, 121.70, 125.96, 133.95, 159.72.

HRMS (EI): m/z calcd for $C_{13}H_{19}NO_2Si$ (M⁺): 249.1185; found: 249.1183.

3-(4'-Methoxyphenyl)-2-methyl-2-trimethylsilyloxyphenylpropanenitrile (Entry 5)

IR (neat): 2368 cm⁻¹ (C \equiv N).

¹H NMR (CDCl₃, 200 MHz): $\delta = 0.15$ (s, 9 H), 1.51 (s, 3 H), 2.92 (d, 2 H, J = 3.4 Hz), 3.80 (s, 3 H), 6.88 (d, 2 H, J = 8.8 Hz), 7.22 (d, 2 H, J = 8.4 Hz).

¹³C NMR (CDCl₃, 100 MHz): δ = 1.06, 28.64, 48.21, 55.21, 69.98, 113.57, 121.76, 126.76, 131.66, 158.98.

2-Methyl-2-trimethylsilyloxy-4-phenylbut-3-enenitrile (Entry 6)

IR (neat): 2360 cm⁻¹(C \equiv N).

¹H NMR (CDCl₃, 200 MHz): $\delta = 0.24$ (s, 9 H), 1.74 (s, 3 H), 6.16 (d, 1 H, J = 15.83 Hz), 6.92 (d, 1 H, J = 15.8 Hz), 7.31–7.41 (m, 5 H).

¹³C NMR (CDCl₃, 100 MHz): δ = 1.30, 30.79, 69.89, 120.60, 126.82, 128.53, 128.70, 129.47, 130.89, 135.06.

1-Trimethylsilyloxycyclohex-2-enecarbonitrile (Entry 7)

IR (neat): 2355 cm⁻¹ (C \equiv N).

¹H NMR (CDCl₃, 200 MHz): δ = 0.24 (s, 9 H), 1.77–1.87 (m, 2 H), 1.94–2.11 (m, 4 H), 5.77 (m,1 H), 5.94–5.99 (m, 1 H).

¹³C NMR (CDCl₃, 100 MHz): δ = 1.40, 18.26, 24.20, 36.86, 66.71, 121.75, 127.53, 132.49.

HRMS (EI): m/z calcd for $C_{10}H_{17}NOSi$ (M⁺): 195.1079; found: 195.1073.

1-Trimethylsilyloxy-1-indancarbonitrile (Entry 8) IR (neat): 2360 cm⁻¹ (C=N).

¹H NMR (CDCl₃, 200 MHz): δ = 0.12 (s, 9 H), 2.29–2.42 (m, 1 H), 2.57–2.70 (m, 1 H), 2.82–3.08 (m, 2 H), 7.24–7.55 (m, 4 H).

¹³C NMR (CDCl₃, 100 MHz): δ = 1.12, 29.37, 42.79, 76.46, 121.04, 124.08, 125.44, 127.71, 129.94, 142.08, 142.58

HRMS (EI): m/z calcd for $C_{13}H_{17}NOSi$ (M⁺): 231.1079; found: 231.1079.

1-Trimethylsilyloxy-1,2,3,4-tetrahydronaphthalene-1-carbonitrile (Entry 9)

IR (neat): 2356 cm⁻¹ (C \equiv N).

 1H NMR (CDCl₃, 200 MHz): δ = 0.24 (s, 9 H), 1.85–2.41 (m, 4 H), 2.83 (t, 2 H, 7.00 Hz), 7.07–7.28 (m, 3 H), 7.60–7.67 (m, 1 H).

 ^{13}C NMR (CDCl₃, 100 MHz): δ = 1.33, 18.69, 28.32, 37.73, 69.87, 122.11, 126.63, 128.02, 129.06, 129.26, 135.68, 136.11.

1-Trimethylsilyloxy-1-cyclohexanecarbonitrile (Entry 10) IR (neat): 2352 cm^{-1} (CN).

¹H NMR (CDCl₃, 200 MHz): δ = 0.23 (s, 9 H), 1.51–1.68 (m, 8 H), 2.02–2.08 (m, 2 H).

¹³C NMR (CHCl₃, 100 MHz): δ = 1.37, 22.59, 24.48, 39.31, 70.59, 121.91.

2-Methyl-2-trimethylsilyloxyoctanenitrile (Entry 11)

IR (neat): 2350 cm⁻¹ (C \equiv N).

¹H NMR (CDCl₃, 200 MHz): $\delta = 0.22$ (s, 9 H), 0.91 (t, 3 H, J = 6.60 Hz), 1.31–1.54 (m, 8 H), 1.57 (s, 3 H), 1.68–1.74 (m, 2 H).

 ^{13}C NMR (CDCl₃, 100 MHz): δ = 1.15, 13.88, 22.38, 24.09, 28.76, 28.84, 31.47, 43.25, 69.56, 121.91.

HRMS (EI): m/z calcd for $C_{12}H_{25}NOSi$ (M⁺): 227.1705; found: 227.1710.

2-Trimethylsilyloxy-2-furan-2-ylpropanenitrile (Entry 12) IR (neat): 2355 cm⁻¹ (CN).

 ^1H NMR (CDCl_3, 200 MHz): δ = 0.09 (s, 9 H), 1.93 (s, 3 H), 6.37–6.40 (m, 1 H), 6.49–6.51 (m, 1 H), 7.42–7.44 (m, 1 H).

 ^{13}C NMR (CDCl₃, 100 MHz): δ = 0.49, 28.37, 65.89, 108.14, 110.68, 120.23, 143.09, 151.63.

HRMS (EI): m/z calcd for $C_{10}H_{15}NO_2Si$ (M⁺): 209.0812; found: 227.0888.

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