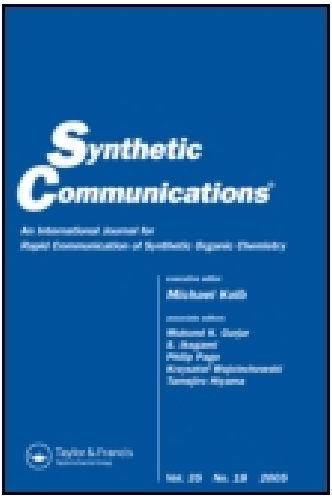

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N-Methylmorpholine N-Oxide: A Rare Nonmetallic Catalyst for the Most Efficient Silylcyanation of Aldehydes

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N-Methylmorpholine *N*-Oxide: A Rare Nonmetallic Catalyst for the Most Efficient Silylcyanation of Aldehydes

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ABSTRACT

An efficient method of addition of trimethylsilyl cyanide (TMSCN) to aldehydes by employing *N*-methylmorpholine *N*-oxide (NMO) alone as the catalyst has been described. Most of aromatic, aliphatic, cyclic, and heterocyclic aldehydes have been converted into their corresponding trimethylsilyl ethers in excellent yield within 10-min period. The mechanism of silylcyanation reaction has been also described.

Key Words: NMO; Aldehydes; TMSCN; Silylcyanation.

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INTRODUCTION

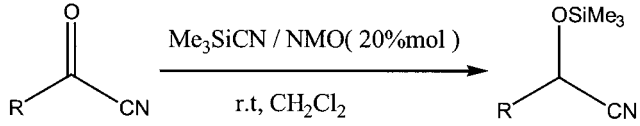
Cyanohydrins[1] occupy very important role in organic synthesis due to its synthetic versatility that can easily be converted into various polyfunctionalized building blocks, including α-hydroxy compounds and β-amino alcohols. Diorganotin dichloride[2] catalyzes the addition of trimethylsilyl cyanide (TMSCN) to various ketones and aldehydes. A very similar addition to the carbonyl compounds[3] was also found to be catalyzed by copper(II) triflate. Silylcyanation of aromatic ketones[4] is strongly promoted in organic solutions of lithium perchlorate and lithium tetrafluoroborate. Layered zirconium hydrogen phosphate exchanged with potassium ion[5] was found to be an efficient catalyst for silylcyanation of carbonyl compounds. Indium tribromide ($InBr_3$) is a very effective catalyst for the addition of TMSCN to functionalized ketones. Silylcyanations of ketones[7] were also initiated by *N*-oxides/$Ti(i\text{Pro})_4$ as the catalysts. Chiral salen–titanium complex[8] proved to be an effective catalyst for the enantioselective silylcyanation of aldehydes. A new bifunctional asymmetric catalyst[9] was devised for the silylcyanation of various aldehydes. It[9] is assumed that aluminum would work as a Lewis acid to activate the carbonyl group and the oxygen atom of the phosphine oxide would work as a Lewis base to activate the silylated nucleophiles. The asymmetric addition of TMSCN to aldehydes[10] can be catalyzed by chiral (salen)–titanium complexes. Chiral (salen) VO catalyst[11] is found to be more enantioselective than the previous titanium-based systems[10] for the silylcyanation.

N-Oxide was used in asymmetric synthesis such as allylation of aldehydes[12] and addition of $ZnEt_3$ to aldehydes.[13] However, there is no report about the utilization of *N*-oxide alone as the catalyst for silylcyanation of aldehyde. We wish to report herein the first example about silylcyanation reaction of aldehydes by using a cheap, easy handling, and easily available chemical *N*-methylmorpholine *N*-oxide (NMO) alone as catalyst to efficiently offer racemic trimethylsilyl ethers.

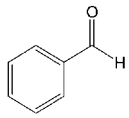
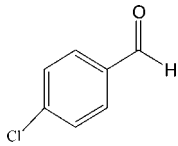
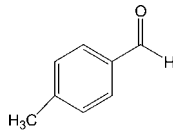
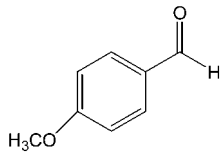
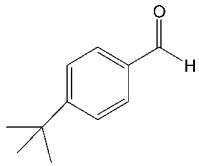
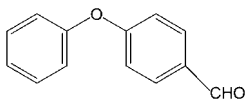
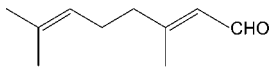
RESULTS AND DISCUSSION

Representative and successful examples for the synthesis of various trimethylsilyl ethers from aromatic, aliphatic, and cyclic aldehydes are collected in Table 1. Unsubstituted and substituted aromatic aldehydes (entries 1–6) undergo very smooth silylcyanation with over 95% yield. The substituents on the phenyl group have no significant effect on reaction time (entries 2–6). Aliphatic allylic aldehydes (entries 7 and 8) were silylcyanated in excellent yields for a little longer reaction time of 15–20 min. Especially, it should be

Table 1. Addition of TMSCN to aldehydes catalyzed by NMO.

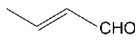
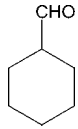
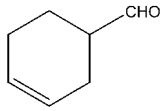
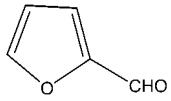


NMO (*N*-Methylmorpholine *N*-Oxide)

Entry	Substrate	Time (min)	Yield (%)[a]
1		10 30 18 18	97 90[2] 81[3] 98[5]
2		10 18	95 75[3]
3		10	93
4		10 12	97 96[5]
5		10	95
6		10	98
7		20	97

(*continued*)

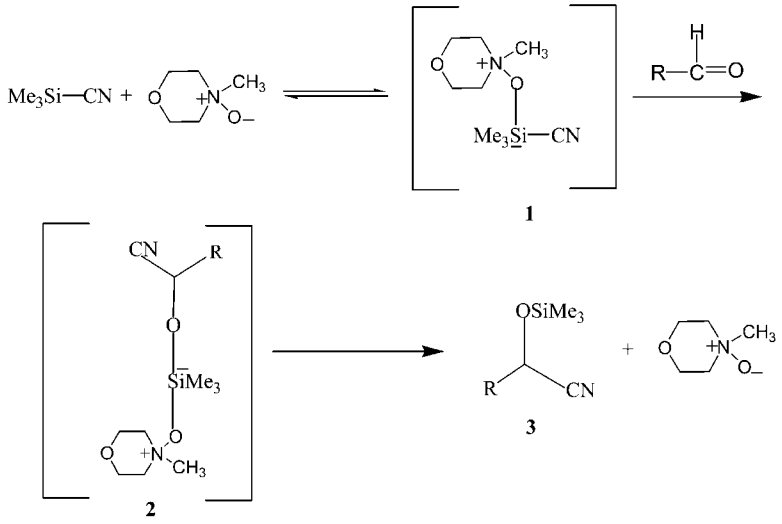
Table 1. Continued.

Entry	Substrate	Time (min)	Yield (%)[a]
8		15	95
9	$(CH_3)_3$-C-CHO	10 330	93 71[2]
10		5	95
11		10	90
12		5 18	90 75[3]

[a]Isolated yield. The addition reactions to various ketones have been pressed in *Synthesis* 2003.

noted that the sterically hindered pivalaldehyde (entry 9) which branched at the α-position to the carbonyl group was transformed into the corresponding silylether in 93% yield for 10 min. The cyclic aliphatic aldehydes (entries 10 and 11) were converted into the corresponding cyanohydrin silylethers with excellent yield. Furfural, a heterocyclic aldehyde (entry 12), gives corresponding silylether in good yield (90%). This result indicates that NMO can selectively activate the carbonyl function of furfural, keeping the furan ring intact. To test the catalytic activity of NMO, a model reaction was carried out with benzaldehyde without NMO and was found that there is no reaction taking place within the typical reaction time. NMO is superior in activity to TMSCN when compared with recently reported achiral catalytic system combination of *N*,*N*-dimethyl-*N*-oxide/Ti(O*i*Pr)$_4$ used for the silylcyanation of carbonyl compounds.[7] The present system indicates greater yield with quite short reaction time. It is also worthwhile to note that the addition reaction of TMSCN to aldehydes was done without any metal catalyst.

The possible mechanism for the reaction is as follows. The formation of hypervalent silicate **1** is formed from the *N*-oxide and TMSCN **1** reacts with the aldehyde to generate complex **2** which on fragmentation provides the corresponding silylether **3** and *N*-oxide (Sch. 1).



Scheme 1.

CONCLUSION

An efficient catalytic system for silylcyanation of various kinds of aldehydes with greater yield has been developed. The mild experimental conditions, extremely short reaction time, inexpensive catalyst, and the wide range of substrate applicability represent the notable features of this procedure. Although variety of catalysts are known for this reaction, NMO has greater potential for extension into asymmetric version of the reaction which is also at progress in our laboratory.

EXPERIMENTAL SECTION

Typical Procedure for Silylcyanation of Benzaldehyde

To a stirred solution of benzaldehyde (1 mmol) and NMO (20 mol%) in dry CH_2Cl_2 (1 mL) was added TMSCN (1.5 equiv.) dropwise. The resulting solution was stirred continuously and progress of the reaction was followed by TLC. The reaction mixture was purified by silica gel flash chromatography by using EtOAc/hexanes (1 : 9) mixture as eluent. The desired 2-phenyl-2-(trimethylsilyloxy)acetonitrile was obtained as colorless oil (yield: 97%).

2-Phenyl-2-(trimethylsilyloxy)acetonitrile (entry 1). ^{1}H NMR ($CDCl_3$, 200 MHz): $\delta = 0.25$ (s, 9H), 5.52 (s, 1H), 7.41–7.47 (m, 5H). ^{13}C NMR ($CDCl_3$, 50 MHz): $\delta = -0.33$, 63.59, 119.12, 126.29, 128.87, 129.27, 136.18.

2-(4-Cholorophenyl)-2-(trimethylsilyloxy)acetonitrile (entry 2). ^{1}H NMR ($CDCl_3$, 200 MHz): $\delta = 0.25$ (s, 9H), 5.48 (s, 1H), 7.37–7.38 (m, 5H). ^{13}C NMR ($CDCl_3$, 50 MHz): $\delta = -0.33$, 62.93, 118.76, 127.64, 129.12, 134.80, 135.28.

2-(4-Methylphenyl)-2-(trimethylsilyloxy)acetonitrile (entry 3). ^{1}H NMR ($CDCl_3$, 200 MHz): $\delta = 0.21$ (s, 9H), 2.36 (s, 3H), 5.45 (s, 1H), 7.22 (d, 2H, $J = 7.8$ Hz), 7.37 (d, 2H, $J = 7.8$ Hz). ^{13}C NMR ($CDCl_3$, 50 MHz): $\delta = -0.25$, 55.78, 63.87, 114.66, 119.47, 127.88, 128.77, 160.23.

2-(4-Methoxyphenyl)-2-(trimethylsilyloxy)acetonitrile (entry 4). ^{1}H NMR ($CDCl_3$, 200 MHz): $\delta = 0.24$ (s, 9H), 3.84 (s, 3H), 5.45 (s, 1H), 6.96 (d, 2H, $J = 8.8$ Hz), 7.38 (d, 2H, $J = 8.8$ Hz). ^{13}C NMR ($CDCl_3$, 50 MHz): $\delta = -0.23$, 55.34, 63.34, 114.25, 119.32, 127.93, 128.46, 160.33.

2-(4-*tert*-Butylphenyl)-2-(trimethylsilyloxy)acetonitrile (entry 5). ^{1}H NMR ($CDCl_3$, 200 MHz): $\delta = 0.25$ (s, 9H), 1.34 (s, 9H), 5.49 (s, 1H), 7.43–7.44 (m, 5H). ^{13}C NMR ($CDCl_3$, 50 MHz): $\delta = -0.39$, 31.10, 34.52, 63.32, 119.18, 125.73, 126.04, 133.19, 152.37.

2-(4-Phenoxyphenyl)-2-(trimethylsilyloxy)acetonitrile (entry 6). ^{1}H NMR ($CDCl_3$, 200 MHz): $\delta = 0.22$ (s, 9H), 5.46 (s, 1H), 6.99–7.13 (m, 5H), 7.31–7.44 (m, 4H). ^{13}C NMR ($CDCl_3$, 50 MHz): $\delta = -0.26$, 63.18, 117.50, 118.75, 119.48, 120.42, 124.04, 124.94, 128.02, 128.41, 129.92, 130.73, 131.98, 156.38, 158.84.

4-Phenyl-2-trimethylsilyloxybutyronitrile (entry 7). ^{1}H NMR ($CDCl_3$, 200 MHz): $\delta = 0.22$ (s, 9H), 1.62 (s, 3H), 1.70–1.80 (m, 6H), 2.10–2.12 (m, 4H), 5.09–5.13 (m, 2H), 5.31–5.33 (m, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): $\delta = -0.12$, 16.76, 17.65, 23.18, 25.83, 39.13, 58.42, 119.50, 120.59, 123.14, 133.04, 142.82.

4,8-Dimethyl-2-trimethylsilyloxynona-3,7-dienenitrile (entry 8). ^{1}H NMR ($CDCl_3$, 200 MHz): $\delta = 0.20$ (s, 9H), 1.79 (dd, 3H, 2.4 Hz, 2.4 Hz), 4.90 (d, 1H, 8.4 Hz), 5.51–5.62 (m, 1H), 5.93–6.04 (m, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): $\delta = -0.39$, 17.16, 61.91, 118.55, 126.06, 130.98. HRMS (EI): m/z calcd for $C_8H_{15}NOSi$ (M^+): 169.0922; found: 169.0917.

3,3-Dimethyl-2-trimethylsilyloxybutyronitrile (entry 9). ^{1}H NMR ($CDCl_3$, 200 MHz): $\delta = 0.22$ (s, 9H), 1.03 (s, 9H), 4.00 (s, 1H).

Cyclohexyl trimethylsilyloxyacetonitrile (entry 10). ^{1}H NMR ($CDCl_3$, 200 MHz): $\delta = 0.20$ (s, 9H), 1.19–1.28 (m, 5H), 1.61–1.85 (m, 6H), 4.17 (d, 1H, 6.2 Hz). ^{13}C NMR ($CDCl_3$, 50 MHz): $\delta = -0.59$, 25.40, 25.92, 27.99, 42.82, 66.37, 119.28. HRMS (EI): m/z calcd for $C_{11}H_{21}NOSi$ (M^+): 211.1392; found: 211.1387.

Cyclohex-3-enyl trimethylsilyloxyacetonitrile (entry 11). ^{1}H NMR ($CDCl_3$, 200 MHz): $\delta = 0.23$ (s, 9H), 1.60–2.12 (m, 7H), 4.27 (m, 1H), 5.70 (s, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz): $\delta = -0.67$, 23.72, 24.26, 26.48, 65.59, 119.07, 124.72, 126.75. HRMS (EI): m/z calcd for $C_{11}H_{19}NOSi$ (M^+): 209.1235; found: 209.1239.

Furan-2-yl-trimethylsilanyloxy-acetonitrile (entry 12). ^{1}H NMR ($CDCl_3$, 200 MHz): $\delta = 0.22$ (s, 9H), 5.55 (s, 1H), 6.41–6.43 (m, 1H), 6.55–6.57 (m, 1H), 7.28–7.48 (m, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): $\delta = -0.43$, 57.41, 109.70, 110.78, 117.11, 143.84, 148.20. HRMS (EI): m/z calcd for $C_9H_{13}NO_2Si$ (M^+): 195.0715; found: 195.0712.

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