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Mild and efficient silylcyanation of ketones catalyzed by cesium fluoride

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Abstract

An efficient method of addition of trimethylsilylcyanide to ketones by employing cesium fluoride as catalyst has been described. A variety of aromatic, aliphatic, cyclic and heterocyclic ketones have been converted into their corresponding trimethylsilyl ethers in excellent yield.

Keywords: Silylcyanation; CsF; TMSCN; Ketone; Silylethers; Cyanohydrins

1. Introduction

It is well established that the addition of trimethylsilylcyanide (TMSCN) to carbonyl compounds affords silylated cyanohydrins. Both the hydroxy and the nitrile part of the cyanohydrin functionality can undergo transformation to a range 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]. Existing methods for the preparation of cyanohydrins include both enzymatic and chemical processes [4]. Several chiral titanium metal complexes [5] have been widely used for the addition of TMSCN to various types of ketones. Shibasaki [6] disclosed enantioselective catalytic addition of TMSCN to carbonyl compounds by using carbohydrate based ligands and Ti(O*i*Pr)$_4$. Chiral titanium reagents derived from optically active sulfoximine/Ti(O*i*Pr)$_4$ [7] and chiral sulfoxide/Ti(O*i*Pr)$_4$ [8] promote the asymmetric addition of TMSCN to carbonyl compounds affording the cyanohydrin. Enantioselective addition of TMSCN to ketones is achieved by a catalytic double activation method using chiral Lewis acid and achiral *N*-oxide have been reported [9]. Several metal based catalysts have been used both in stoichiometric and catalytic amount for the silylcyanation of carbonyl compounds to offer racemic cyanohydrins. Yb(CN)$_3$ [10], Yb(OTf)$_3$ [11], Cu(OTf)$_2$ [12], ZnI$_2$ [13], LiClO$_4$ [14], R$_2$SnCl$_2$ [15], Zr(KPO$_4$)$_2$ [16] and InBr$_3$ [17] proved to be the efficient catalyst for the purpose. There have been reports of the use of lanthanide salts of alkoxides, dialkylamides, chlorides, cyanides or triflates [18] in the catalysis of silylcyanation and hydrocyanation of aldehydes and ketones. The in situ generated catalyst containing achiral Lewis acid and *N*,*N*-dimethyl-*N*-oxide [19] have been used for the generation of racemic cyanohydrins. CsF has been used as catalyst for several organic transformations [20]. Recently it has been widely used for trifluoromethylation of esters, aldehydes and ketones with (trifluoromethyl)trimethylsilane [21]. The silylcyanation methods mentioned above required longer reaction time (refer to Table 1). We wish to herein report the first example about the silylcyanation reaction of ketones by using a cheap, easy handling and readily available chemical, CsF as catalyst to offer racemic trimethylsilyl ethers in excellent yields in relatively shorter reaction time.

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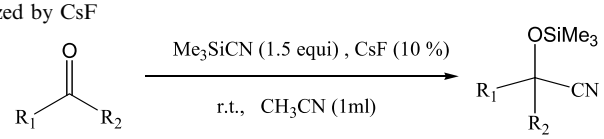
Table 1
Addition of TMSCN to ketones catalyzed by CsF



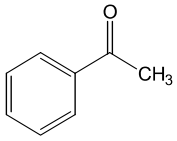
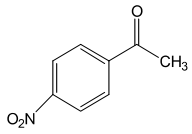
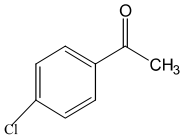
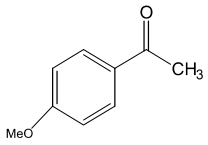
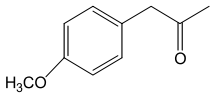
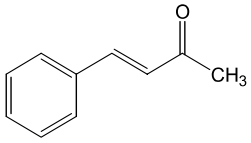
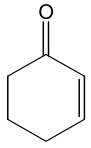
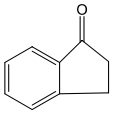
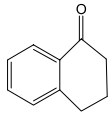
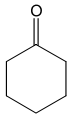
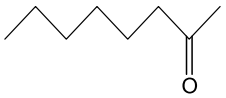
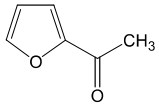
Entry	Substrate	Time (h)	Yield (%)[a]
1		1 62 [19c] 20 [12] 45 [15] 8 [14]	95 82 [19c] 85 [12] 93 [15] 98 [14]
2		1 80 [19c] 21 [14]	95 86 [19c] 71 [14]
3		1 8 [14]	97 93 [14]
4		1	95
5		0.8	97
6		1 96 [19c] 5 [19a]	97 80 [19c] 91 [19a]
7		1 8 [16]	95 92 [16]
8		1	96
9		1 50 [12]	95 80 [12]
10		1	91

Table 1(*continued*)

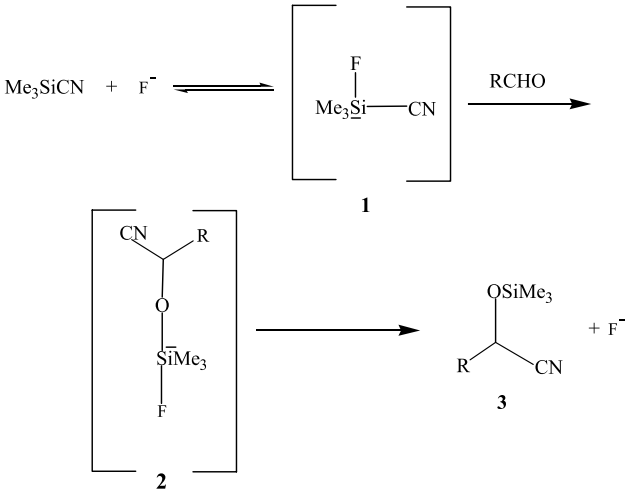
Entry	Substrate	Time (h)	Yield (%)[a]
11		1.3	91
12		1.3 25 [19a]	90 94 [19a]

[a] Isolated yield.

2. Results and discussion

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 silylcyanation with over 90% yield. The introduction of methylene group (entry 5) increases the reaction rate and thereby 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 and 9). Both the cyclic and open chain aliphatic ketones (entries10 and 11) were converted into the corresponding cyanohydrin silylethers with excellent yield. 2-acetyl furan, a heterocyclic ketone (entry 12) gives corresponding silylether in good yield. This result indicates that CsF can selectively activate the carbonyl function of the ketone, keeping the furan ring intact.

CsF is superior in activity to TMSCN when compared with previously reported metal based achiral catalytic system [10–16]. Present results are compared with previously reported methods where metal salts were used as catalysts (entries 1, 2, 3, 6, 7, 9 and 12). Comparison of reaction conditions (time and yield) indicates that our system affords greater yield with shorter reaction time. CsF (being an inexpensive catalyst) can be employed in the silylcyanation of ketones which makes the method more practical. The possible mechanism for the reaction is as follows. The formation of hypervalent silicate **1** is formed from the addition of F^- ion to TMSCN. **1** reacts with the aldehyde to generate complex **2** which on fragmentation provides the corresponding silylether **3** and F^- (Scheme 1).



Scheme 1.

3. Conclusion

An efficient catalytic system for silylcyanation 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.

4. Experimental

4.1. Silylcyanation of acetophenone

To stirred solution of acetophenone (1 mmol) and CsF (10 mol%) in dry CH_3CN (1 ml) was added TMSCN (1.5 equiv.) dropwise. The resulting solution was stirred continuously and progress of the reaction was followed by TLC. After 1 h the reaction mixture was purified by silica gel flash chromatography by using EtOAc/hexanes (1:9) mixture as an eluent. 2-Trimethylsilyloxy-2-phenylpropanenitrile was obtained as colourless oil (Yield: 95%). The other substrates (entries 2–12) were also silylcyanated by using the same procedure. The silylethers thus obtained gave excellent ^1H and ^{13}C NMR, HRMS, IR and elemental analysis data which are consistent with the structure.

4.1.1. 2-Trimethylsilyloxy-2-phenylpropanenitrile (entry 1)

^{1}H NMR ($CDCl_3$, 200 MHz): $\delta = 0.17$ (s, 9H), 1.86 (s, 3H), 7.36–7.53 (m, 5H).

^{13}C NMR($CDCl_3$, 100 MHz): $\delta = 0.89$, 33.40, 71.45, 121.43, 124.45, 128.49, 141.86.

HRMS (EI): m/z calcd. for $C_{12}H_{17}NOSi$ (M^+): 219.1079. Found: 219.1086.

IR (neat): ν(C≡N) 2362 cm^{-1}.

4.1.2. 2-Trimethylsilyloxy-2-(4′-nitrophenyl)phenylpropanenitrile (entry 2)

^{1}H NMR ($CDCl_3$, 200 MHz): $\delta = 0.25$ (s, 9H), 1.88 (s, 3H), 7.77 (d, 2H, $J = 9.2$ Hz), 8.30 (d, 2H, $J = 9.2$ Hz).

^{13}C NMR($CDCl_3$, 100 MHz): $\delta = 1.07$, 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%.

IR (neat): ν(C≡N) 2360 cm^{-1}.

4.1.3. 2-Trimethylsilyloxy-2-(4′-cholorophenyl)phenylpropanenitrile (entry 3)

^{1}H NMR ($CDCl_3$, 200 MHz): $\delta = 0.21$ (s, 9H), 1.85 (s, 3H), 7.41–7.48 (m, 4H).

^{13}C NMR($CDCl_3$, 100 MHz): $\delta = 1.00$, 33.45, 71.01, 121.18, 126.04, 128.79, 134.55, 140.68.

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

IR (neat): ν(C≡N) 2366 cm^{-1}.

4.1.4. 2-Trimethylsilyloxy-2-(4′-methoxyphenyl)phenylpropanenitrile (entry 4)

^{1}H NMR ($CDCl_3$, 200 MHz): $\delta = 0.17$ (s, 9H), 1.86 (s, 3H), 3.84 (s, 3H), 6.95 (d, 2H, $J = 8.8$ Hz), 7.50 (d, 2H, $J = 8.8$ Hz).

^{13}C NMR($CDCl_3$, 100 MHz): $\delta = 0.98$, 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.

IR (neat): ν(C≡N) 2362 cm^{-1}.

4.1.5. 2-Trimethylsilyloxy-3-(4′-methoxyphenyl)-2-methylphenylpropanenitrile (entry 5)

^{1}H NMR ($CDCl_3$, 200 MHz): $\delta = 0.15$ (s, 9H), 1.51 (s, 3H), 2.92(d, 2H, $J = 3.4$ Hz), 3.80 (s, 3H), 6.88 (d, 2H, $J = 8.8$ Hz), 7.22 (d, 2H, $J = 8.4$ Hz).

^{13}C NMR($CDCl_3$, 100 MHz): $\delta = 1.06$, 28.64, 48.21, 55.21, 69.98, 113.57, 121.76, 126.76, 131.66, 158.98.

IR (neat): ν(C≡N) 2368 cm^{-1}.

4.1.6. 2-Trimethylsilyloxy-2-methyl-4-phenyl-3-butenenitrile (entry 6)

^{1}H NMR ($CDCl_3$, 200 MHz): $\delta = 0.27$ (s, 9H), 1.77 (s, 3H), 6.20 (d, 1H, $J = 15.83$ Hz), 6.95 (d, 1H, $J = 15.8$ Hz), 7.34–7.44 (m, 5H).

^{13}C NMR($CDCl_3$, 100 MHz): $\delta = 1.30$, 30.79, 69.89, 120.60, 126.82, 128.53, 128.70, 129.47, 130.89, 135.06.

IR (neat): ν(C≡N) 2360 cm^{-1}.

4.1.7. 1-Trimethylsilyloxy-2-cyclohexenecarbonitrile (entry 7)

^{1}H NMR ($CDCl_3$, 200 MHz): $\delta = 0.25$ (s, 9H), 1.81–1.84 (m, 2H), 2.08–2.13 (m, 4H), 5.77 (m, 1H), 5.94–5.99 (m, 1H).

^{13}C NMR($CDCl_3$, 100 MHz): $\delta = 1.40$, 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.

IR (neat): ν(C≡N) 2355 cm^{-1}.

4.1.8. 1-Trimethylsilyloxy-1-indancarbonitrile (entry 8)

^{1}H NMR ($CDCl_3$, 200 MHz): $\delta = 0.12$ (s, 9H), 2.29–2.42 (m, 1H), 2.57–2.70(m, 1H), 2.82–3.08 (m, 2 H), 7.24–7.55 (m, 4H).

^{13}C NMR($CDCl_3$, 100 MHz): $\delta = 1.12$, 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.

IR (neat): ν(C≡N) 2360 cm^{-1}.

4.1.9. 1-Trimethylsilyloxy-1,2,3,4-tetrahydronaphthalene-1- carbonitrile (entry 9)

^{1}H NMR ($CDCl_3$, 200 MHz): $\delta = 0.24$ (s, 9H), 1.85–2.41 (m, 4H), 2.83 (t, 2H, 7.00 Hz), 7.07–7.28 (m, 3H), 7.60–7.67 (m, 1H).

^{13}C NMR($CDCl_3$, 100 MHz): $\delta = 1.33$, 18.69, 28.32, 37.73, 69.87, 122.11, 126.63, 128.02, 129.06, 129.26, 135.68, 136.11.

IR (neat): ν(C≡N) 2356 cm^{-1}.

4.1.10. 1-Trimethylsilyloxy-1-cyclohexanecarbonitrile (entry 10)

^{1}H NMR ($CDCl_3$, 200 MHz): $\delta = 0.23$ (s, 9H), 1.51–1.68 (m, 8H), 2.02–2.08 (m, 2H).

^{13}C NMR($CHCl_3$, 100 MHz): $\delta = 1.37$, 22.59, 24.48, 39.31, 70.59, 121.91.

IR (neat): ν(C≡N) 2352 cm^{-1}.

4.1.11. 2-Trimethylsilyloxy-2-methyloctanenitrile (entry 11)

^{1}H NMR ($CDCl_3$, 200 MHz): $\delta = 0.22$ (s, 9H), 0.91 (t, 3H, 6.60 Hz), 1.31–1.74 (m, 8H), 1.57 (s, 3H), 1.68–1.74 (m, 2H).

^{13}C NMR($CDCl_3$, 100 MHz): $\delta = 1.15$, 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.

IR (neat): ν(C≡N) 2350 cm^{-1}.

4.1.12. 2-Trimethylsilyloxy-2-furan-2-yl-propanenitrile (entry 12)

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

^{13}C NMR($CDCl_3$, 100 MHz): $\delta = 0.49$, 28.37, 65.89, 108.14, 110.68, 120.23, 143.09, 151.63.

HRMS (EI): m/z calcd. for $C_{10}H_{15}NO_2Si(M^+)$: 209.0872. Found: 209.0888.

IR (neat): ν(C≡N) 2355 cm^{-1}.

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