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Metal and solvent-free cyanosilylation of carbonyl compounds with tris(pentafluorophenyl)borane

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A highly effective method of the cynaosilylation of aldehydes and ketones with TMSCN in the presence of catalytic amount of $B(C_6F_5)_3$ [tris(pentafluorophenyl)borane] has been developed. Cyano transfer from TMSCN to carbonyl group proceeds at room temperature under solvent-free conditions. Various alehydes and ketones have been converted into the corresponding trimethylsilylether within short reaction times with excellent yield under mild conditions. Copyright © 2008 John Wiley & Sons, Ltd.

Keywords: aldehydes; ketones; cyanosilylation; $B(C_6F_5)_3$; solvent-free; metal-free

Introduction

Cyanosilylation of carbonyl compounds is an efficient procedure for synthesis of the cyanohydrins, which can be readily converted into useful functionalized compounds such as α-hydroxy acid, α-hydroxy alehyde, α-amino alcohol and 1,2-diol.[1,2] These compounds are important in organic synthesis and pharmaceutical chemistry. The cyanosilylation of carbonyl compounds with trimethylsilylcyanide (TMSCN) is the most commonly used method. Transfer of the cyano group from TMSCN to a carbonyl compound is catalyzed by metal halides, organocatalyst, Lewis acid, Lewis bases, bifunctional catalyst, solubilizd anionic species, heterogeneous catalyst, ionic liquid and inorganic salts.[3–9] The combination of chiral Lewis acid–Lewis catalytic systems has been also reported for asymmetric cyanosilylation.[10]

Recently solvent-free organocatalyzed methods have attracted much attention.[11] Because of the growing concern about the influence of organic solvents on the environment as well as on the human body, organic reactions without organic solvents have become important in synthetic organic chemistry. Although a number of solvents such as fluorous media, supercritical carbon dioxide, ionic liquids and water have recently been studied, the reaction without a solvent is still the best option. Hence the development of solvent-free organic reactions is gaining prominence.[12,13]

$B(C_6F_5)_3$, **1**, (Figure 1) is a convenient commercially available Lewis acid.[14,15] It is a non-conventional, air-stable, water-tolerant and thermally stable Lewis acid, **1**, shows comparable acid strength compared with BF_3 but induces no problems associated with a reactive B–F bond. The commercial application of **1** consists of the cocatalyst in metallocene-mediated olefin polymerization.[16,17] Compound **1** functions in a typical carbonyl-activating capacity in aldol and Diels–Alder type reactions.[14,15] Recently, this substance has found many applications, such as hydrosilation of alcohols,[18] carbonyl groups[19] and imines,[20] Ferrier azaglycosylation with sulfonamides and carbamate,[21] reduction of carbonyl groups to methylene,[22] aziridines ring opening[23] and hydrogenation of imines.[24]

Experimental

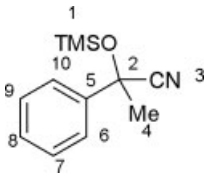
In all the cases the ^{1}H NMR (400MHz) spectra were recorded using a Varian Gemini 400 instrument. Chemical shifts are reported in ppm in $CDCl_3$ with tetramethylsilane as an internal standard. ^{13}C NMR data were collected on a Varian Gemini 200 instrument (50 MHz). Compounds were identified by HRMS (EI) with Jeol DMX 303 and GCMS (EI 70 eV). Data were collected through a 1200L Single Quadrupole GC/MS system with 3800GC/Varian.

General procedure for the $B(C_6F_5)_3$-catalyzed cyanosilylation of aldehydes and ketones

$B(C_6F_5)_3$ (0.5 mol%) was added to the mixture of ketone (aldehyde; 1.0 mmol) and TMSCN (1.2 mmol). The reaction mixture was stirred at room temperature for the appropriate time (see Table 2). The reaction was monitored by TLC. After completion the reaction mixture was concentrated and loaded onto a silica gel column (eluting with 90 : 10 hexanes–ethyl acetate) to give the product.

The spectral (^{1}H, ^{13}C NMR, and HRMS) data of some representative products are given below. The NMR data of all products were compared with the literature values.[26,27,32,33,36,39]

Table 2, entry 1



^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.19 (s, 9H, $Si(CH_3)_3$), 1.90 (s, 3H, Me), 7.33–7.48 (m, 5H, aromatic) ^{13}C NMR ($CDCl_3$, 100 MHz) δ 1.0 (C-1),

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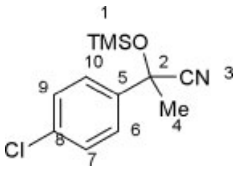
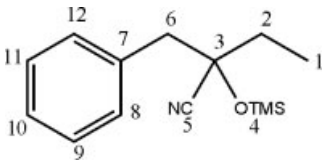
33.5 (C-4), 71.6 (C-2), 121.6 (C-3), 124.6 (C-10,6), 128.6 (C-9,7,8) abd 141.9(C-5). HRMS *m/z* calcd for $C_{12}H_{17}NOSi$ $[M + H]^+$ 219.1079, found 219.1082.

Table 2, entry 2



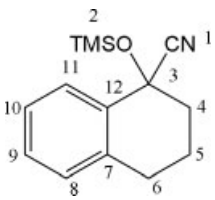
^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.24 (s, 9H, $Si(CH_3)_3$), 1.89 (s, 3H, 4-Me), 7.32 (m, 2H, aromatic), 7.44 (m, 2H, aromatic). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 1.0 (C-1), 33.5 (C-4), 71.0 (C-2), 121.2 (C-3), 126.0 (C-10,6), 128.8 (C-9,7), 134.5 (C-8), 140.7 (C-5). HRMS *m/z* calcd for $C_{12}H_{16}ClNOSi$ $[M + H]^+$ 253.0690, found 253.0687.

Table 2, entry 8

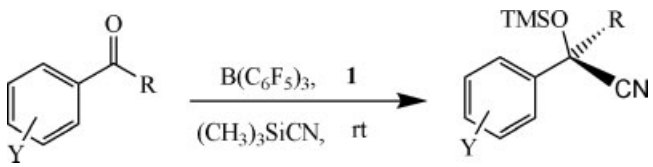


^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.15 (s, 9H, -$Si(CH_3)_3$), 1.08 (t, J = 16 Hz, 3H, 1-CH_3), 1.77 (q, J = 20 Hz, 2H, 2-CH_2) 2.98 (d, 2H, J = 4 Hz, 6-CH_2), 7.25–7.38 (m, 5H, aromatic) ^{13}C NMR ($CDCl_3$, 100 MHz) δ 0.9 (C-4), 8.6 (C-1), 34.4 (C-2), 46.8 (C-6), 73.9 (C-3), 120.8 (C-5), 127.3 (C-10), 128.2 (C- 11,9), 130.8 (C-12,8), 134.6 (C-7). HRMS *m/z* calcd for $C_{14}H_{21}NOSi$ $[M + H]^+$ 247.1392 found 247.1398.

Table 2, entry 11



^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.23 [s, 9H, $Si(CH_3)_3$], 1.97–20.02 (m, 2H, cyclic-H), 2.19–2.22 (m, 1H, cyclic-H), 2.31–2.34 (m, 1H, cyclic-H), 2.81–2.85 (m, 2H, cyclic-H), 7.09–7.11 (m, 1H, phenyl), 7.25–7.27 (m, 2H, phenyl), 7.64–7.66 (m, 1H, phenyl). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 1.3 (C-2), 18.7 (C-5), 28.5 (C-6), 37.7 (C-4), 69.9 (C-3), 122.1 (C-1), 126.6 (C-10), 128.0 (C-9), 129.1 (C-11), 129.3 (C-8), 135.6 (C-7), 136.1(C-12). HRMS *m/z* calcd for $C_{14}H_{19}NOSi$ $[M + H]^+$ 245.1236, found 245.1243.



Scheme 1. Cynosilylation of ketone with TMSCN in presences of $B(C_6F_5)_3$.

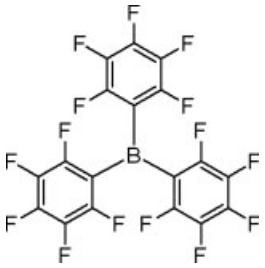
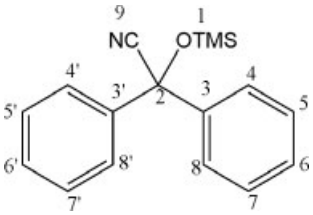


Figure 1. Tris(pentafluorophenyl)borane.

Table 2, entry 12



^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.23 [s, 9H, $Si(CH_3)_3$], 7.24–7.35 (m, 6H, aromatic), 7.41–7.48 (m, 4H, aromatic). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 0.9 (C-1), 73.6 (C-2), 120.7 (C-9), 125.9 (C-4,8,4′,8′,), 128.5 (C-5,7,5′,7′), 128.6 (C-6,6′), 141.9 (C-3,3′). HRMS *m/z* calcd for $C_{17}H_{19}NOSi$ $[M + H]^+$ 281.1236 found 281.1231.

Results and Discussions

Numerous outstanding catalytic systems have been presented for cyanosilyaltion of aldehydes. However ketones present challenges as substrate due to both steric and electronic effects. Hence cyanosilylation of ketones is normally produced less yield and longer reaction time than that of aldehydes. Our group have developed several chiral[25–28] and achiral[29–34] catalytic methods for the cyanosilylation of carbonyl compounds. We report herein **1** as simple but effective catalyst for the cyanosilylation of both aldehydes and ketones with TMSCN at room temperature under solvent-free conditions. In preliminary experiments, for the screening of optimum reaction conditions (solvent, catalyst loading and reaction time) acetophenone was reacted with TMSCN in presence of different amount of catalyst **1** in various solvents at room temperature (Scheme 1, Table 1).

Table 1. Cyanosilylation of acetophenone under various reaction conditions[a]

Entry	Catalyst loading (mol%)	Solvent	Time (min)	Yield[b]
1	4.0	CH_2Cl_2	–	–
2	4.0	$CHCl_3$	8 h	Trace
3	4.0	THF	12 h	67
4	4.0	CH_3CN	1 h	85
5	1.0	CH_3CN	1 h	50
6	4.0	No solvent	8 min	97
7	1.0	No solvent	8 min	95
8	0.5	No solvent	8 min	95

[a] 1.0 mmol of acetophenone, 1.2 mmol of TMSCN. [b] Isolated yield.

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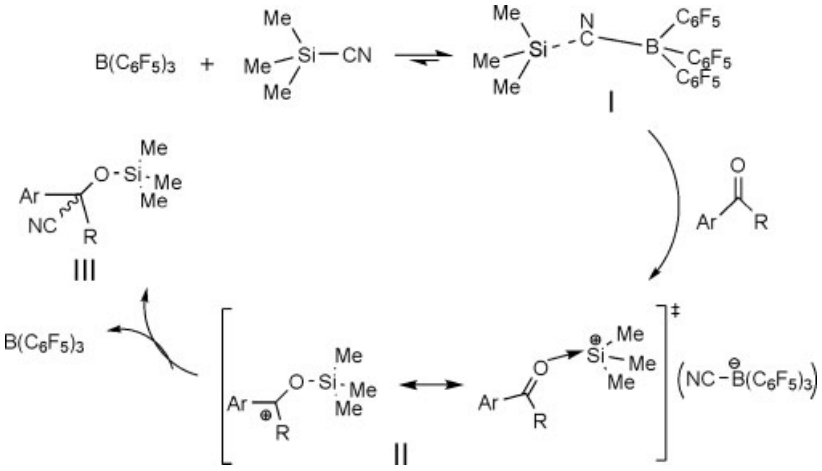

Figure 2. Proposed reaction pathway.

Finally, we performed a reaction without solvent. Accordingly 0.5 mol% of catalyst without any solvent at room temperature is chosen as the best and optimum reaction condition for cyanosilylation of acetophenone (entry 8).

Acetophenone and benzaldehyde show quite similar reactivity in terms of reaction time and yield (Table 2, entries 1 and 14). This is very remarkable phenomenon because ketones have usually shown less reactivity than aldehydes due to steric and electronic influence. *p*- and *m*-Chlorine substituted acetophenones give product with excellent yields (entries 2 and 3). However, *o*-chloroacetphenone had a longer reaction time with relatively lower yield compared with *p*- and *m*-chloroacetophenone. This indicates that the electronic effect of chlorine atom may play an important role on cyanosilylation reaction. The steric hinderance caused by the *ortho* position of the chlorine atom may be of minor importance judging from the reactivity of diisopropyl phenyl ketone in entry 10 (entry 4). The electron-withdrawing power is dramatically exemplified by the reaction of *p*-nitroacetophenone (yield 68%, reaction time 1 h, entry 5). In contrast, electron-donating *p*-methoxyacetophenone and *p*-methylacetophenone yield the corresponding silylcyanoether with excellent yields (entries 6 and 7). This indicates that the electron-donating ability is favorable for the reactions. Cyanosilylation of acyclic aliphatic and cyclic ketones was found to proceed efficiently under similar reaction conditions (entries 8, 9 and 11). It is interesting that cyanosilylation of sterically hindered ketone was readily achieved under the mild reaction conditions (entry 10). The same catalytic method was also equally applicable to other ketones that produce the corresponding products with good yield in short reaction time (entries 12 and 13). The slightly lower yield (97 and 89%) and longer reaction time (4 and 25 min) observed with benzophenone may be due to the steric hindrance exerted by the benzene ring (compare entries 12 and 13).

It is interesting to note that **1** exerts similar catalytic activity toward the aldehydes and ketones (entries 1 and 14). *p*-Methoxybenzaldehyde and *p*-methylbenzaldehyde produce corresponding cyanosilylether with high yields (entries 15 and 16). Cyanobenzaldehyde with the electron-withdrawing group has comparable but slightly reduced results (entry 17) in contrast to the previous cases (entries 15 and 16). Aldehyde, having α,β-unsaturation on the adjacent carbon atom, needs a longer reaction time with relatively lower yield (87%) (entry 18). Similarly, heterocyclic furfuraldehyde is also able to produce the corresponding product but requires a longer reaction time (35 min) and gave lower yield (78%) relative to the aromatic aldehydes of entries 14–17 (entry 19). In both cases (entries 18 and 19) the carbonyl carbon loses positive charge through the conjugation, which may be responsible for the reduced reactivity. Unfortunately long-chain aliphatic aldehyde and the compound containing the ester group did not undergo cyanosilylation under the present reaction condition even after 12 h reaction time (entries 20 and 21).

Phosphonium salt (5 mol%) needs 24 and 48 h for the cyanosilylation of acetonaphthone and benzophenone, respectively, in chloroform,[35] while the present catalyst requires only 4 and 25 min, respectively with less catalyst loading (0.5 mol%) without solvent (entries 12 and 13). Tetramethylguaganide[36] (2 mol%) requires 10 h reaction time for the conversion of α-tetralone and *p*-methylacetophenone to corresponding cyanosilylethers (compare 8 min for entry 7 and 11 min for entry 11). Cyanosilylation of ketone catalyzed by 30 mol% of methyl morphine oxide[37] and 5 mol% of phenolic *N*-oxide has a 15 h reaction time.[38]

Compound **1**-catalyzed cyanosilylation reaction may follow the catalytic pathway as shown in Fig. 2. Abstraction of cyanide anion from the silane by **1** in the presence of the carbonyl substrate can lead to the formation of silyloxonium–cyanoborate ion pair (II), which may collapse to the product. The proposed reaction pathway is consistent with the analagous mechanism for hydrosilation of carbonyl[19] and imines.[20] The catalysis of **1** for the formation of the silyloxonium/cyanoborate ion pair (II) could be the rate-determining step during the reaction path. Benzaldehyde (entry 14), acetophenone (entry 1) and isobutyrophenone (entry 10) manifest very similar reactivities in spite of the steric hindrance, which is consistent with the rate controlling formation of II (Fig. 2).

Conclusion

A metal and solvent-free method for cyanosilylation of carbonyl compounds by $B(C_6F_5)_3$, **1**, has been developed. Alehydes and ketones undergo facile cyanosilylation with TMSCN in presence of 0.5 mol% of **1** without solvent at room temperature. Compound **1** exhibits quite high catalytic activity for cyanosilylation reaction, as evidenced by the shorter reaction time at lower catalyst amount. Other reported catalysts need longer reaction times for ketones relative to aldehydes, but the present catalytic systems have similar reactivities towards the aldehydes and ketones.

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Table 2. $B(C_6F_5)_3$-catalyzed cyanosilylation of carbonyl compounds without solvent[a]

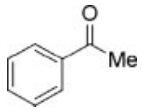
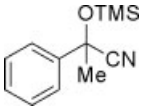
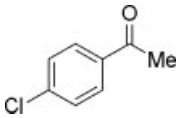
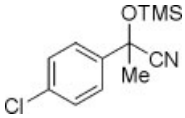
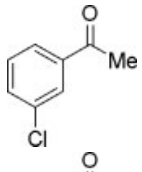
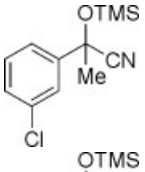
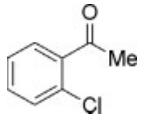
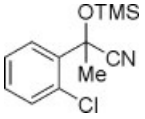
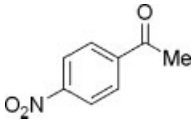
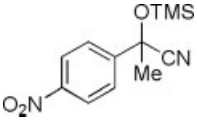
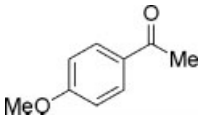
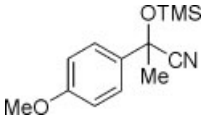
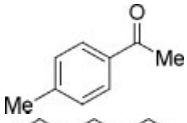
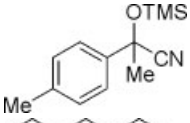
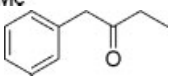
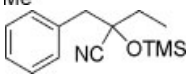
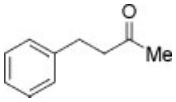
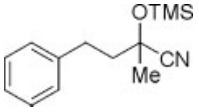
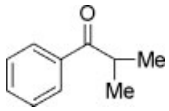
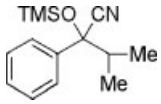
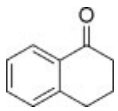
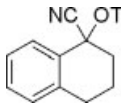
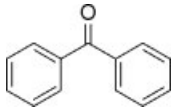
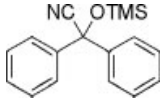
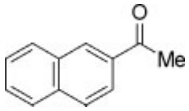
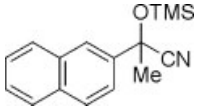
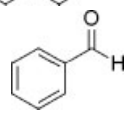
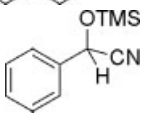
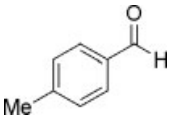
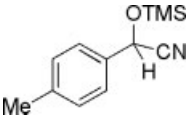
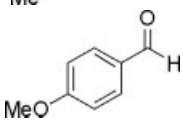
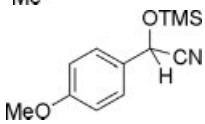
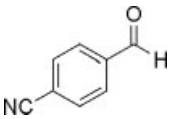
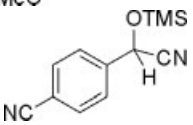
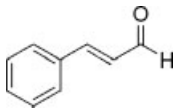
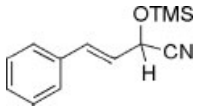
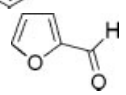
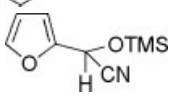
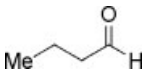
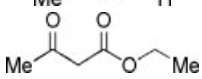
Entry	Substrate	Time (min)	Product	Yield[b]
1		8		97
2		15		98
3		15		91
4		35		81
5		1 h		68
6		7		96
7		8		94
8		10		98
9		12		95[c]
10		10		96

Table 2. (*Continued*)

Entry	Substrate	Time (min)	Product	Yield[b]
11		10		94
12		25		89
13		4		97
14		5		94
15		10		94
16		8		92
17		15		91
18		35		87
19		50		78
20		12 h	–	–
21		12 h	–	–

[a] Reagent and conditions: carbonyl compound (1.00 mmol), TMSCN (1.2 mmol), 0.5 mol % of $B(C_6F_5)$. [b] Isolated yield. [c] 2.0 mol% of catalyst was used.

Supporting information

Supporting information can be found in the online version of this article.

Acknowledgments

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