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Copper perchlorate hexahydrate: a highly efficient catalyst for the cyanosilylation of aldehydes

Anjoy Majhi, Sung Soo Kim* and Ho Sub Kim

$Cu(ClO_4)_2\cdot 6H_2O$ has been found to be an efficient catalyst for cyanosilylation reaction of aldehydes in THF at room temperature with low catalytic loading (1.0 mol%) in short reaction time (mostly within 10 min). Copyright © 2008 John Wiley & Sons, Ltd.

Keywords: catalysis; cyanohydrins; $Cu(ClO_4)_2 \cdot 6H_2O$; aldehydes

Introduction

Cyanosilylation reactions of carbonyl compounds are one of the most powerful procedures for the synthesis of polyfunctionalized molecules. In fact, the cyano moiety has considerable synthetic potential as a building block in organic synthesis.[1–4] Trimethylsilylcyanide (TMSCN) has been used as the source of cyanide ions. Generally, in the absence of a catalyst, no reaction occurs between TMSCN and carbonyl compounds. Several reagents, including Lewis acids, Lewis bases, metal alkoxides, bifunctional catalysts, iodine and inorganic salts, have been found to effectively transfer the cyano group from TMSCN to carbonyl compounds.[5–16] Several additives both in stoichiometric and catalytic amounts have been used as promoting agents for such reactions.[17–24] There has been one report on the cyanosilylation reaction of aromatic ketone using diethyl ether solutions of lithium perchlorate.[25] A 3 M solution of $LiClO_4$ catalyst was required for the reaction and the reaction was conducted over a longer time (2–24 h).

Furthermore, transition metal perchlorates have not been fully exploited for the cyanosilylation reaction of aldehydes. As for metallic perchlorates as catalysts or reagents, there is a common understanding that there is an explosion hazard with heating. In spite of such notoriety,[26,27] these compounds are not explosive in solution, and are frequently used in synthetic chemistry. For instance, not only $Cu(ClO_4)_2$, but also $Fe(ClO_4)_3$, $Zn(ClO_4)_2$ and $Mg(ClO_4)_2$, have been shown to serve as Lewis acid catalysts in various organic transformations such as acylation of alcohols,[28,29] decarboxylative esterifiction of carboxylic acids[30,31] and condensation of β-ketoesters with amines.[32]

We have tested various metal perchlorates such as Na, Mg, Mn, Fe, Cu, Zn and Li for cyanosilylation reaction of aldehydes. $Cu(ClO_4)_2 \cdot 6H_2O$ was found to be the most efficient catalyst compared with the other metal perchlorates (Table 1).

Experimental

Materials and instruments

All the chemicals and solvents were purchased from commercial suppliers. Flash chromatography silica gel (230–400 mesh) was used for column chromatography and thin-layer chromatography was performed on Merck-precoated silica gel 60-F_{254} plates.

General procedure for the synthesis of cyanohydrin trimethylsilylether

To a solution of aldehyde (1 mmol) in THF (1 ml) was added TMSCN (1 mmol). After stirring for 2 min, $Cu(ClO_4)_2\cdot 6H_2O$ (3.7 mg, 1 mol%) was added and the reaction mixture was stirred vigorously at room temperature (r.t.) (Table 2). The reaction mixture was concentrated under vacuum, diluted with water and extracted with diethyl ether (3 × 5 ml). The extract was concentrated and the viscous mass was subjected to silica gel flash column chromatography (Silica gel, 2% EtOAc in hexane) to obtain pure cyanohydrin trimethylsilyl ether compound.

Control experiment for the possibility of cyanation by HCN generated from hydrolysis of TMSCN

Three control experiments were designed to determine the cyanation of the aldehydes by HCN that could be formed through hydrolysis of TMSCN. Water that might be present in small amounts in THF did not induce hydrolysis of TMSCN to generate HCN (Figure 1). Benzaldehyde was reacted with TMSCN and H_2O. The cyanation of benzaldehyde did not take place, indicating that TMSCN is not hydrolyzed by H_2O (Figure 2). The cyanosilylation was carried out without success in the presence of 2,6-di-*tert*-butylpyridine (Figure 3). This may indicate that H_2O contained in $Cu(ClO_4)_2 \cdot 6H_2O$ induces hydrolysis of TMSCN to give off HCN. HCN thus produced could be trapped by 2,6-di-tert-butylpyridine, so as not to cause silylcyanation. It is, however, puzzling why only H_2O contained in $Cu(ClO_4)_2 \cdot 6H_2O$ could induce hydrolysis.

The spectral (^1H and ^{13}C NMR and HRMS) data of some representative products are given below.

2-(4-methoxyphenyl)-2-(trimethylsilyloxy)acetonitrile (entry 2)

^1H NMR ($CDCl_3$, 200 MHz): δ (ppm) $=$ 0.38 (s, 9H, OTMS), 3.83 (s, 3H, OCH_3), 5.44 (s, 1H, H-1), 6.96 (d, $J = 8.4$ Hz, 2H,

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Table 1. Cyanosilylation of anisaldehyde using different metal perchlorates in the presence of different solvents

Entry	Catalyst	Amount of catalyst (mol%)	Solvent	Time	Conversion (%)	Yield (%)
1	$LiClO_4$	1.0	THF	2–3 min	50–60	–[a]
				1 h	80	77
2	$NaClO_4 \cdot H_2O$	1.0	THF	2–3 min	35	–
				1 h	50	
3	$Mg(ClO_4)_2$	1.0	THF	10 min	30–40	–
				1h	50	–
4	$Mn(ClO_4)_2 \cdot 6H_2O$	1.0	THF	10 min	65	–
5	$Fe(ClO_4)_3 \cdot 6H_2O$	(a) 0.05	THF	30 min	60	–
			THF	2–3 min	75	–
		(b) 1.0		10 min	75–80	–
				30 min	85	81
		(c) 2.0	THF	30 min	70–80	–
6	$Cu(ClO_4)_2 \cdot 6H_2O$	(a) 0.05	THF	10 min	75–80	–
		(b) 1.0	THF	2–3 min	98	95
		(c) 1.0	CH_2Cl_2	10 min	70–75	–
		(d) 1.0	MeCN	30 min	70–75	–
		(e) 1.0	MeOH	30 min	70–75	–
		(f) 1.0	Et_2O	10 min	80–85	–
		(g) 1.0	toluene	10 min	–	
		(h) 1.0	water	10 min	–	
		(i) 2.0	THF	2–3 min	80–85	–
		(j) 5.0	THF	2–3 min	75–80	–
		(k) 1.0	Solvent free	10 min	–	–
7	$CuCl_2$	1.0	THF	1 h	–	–

[a] The products were not isolated.

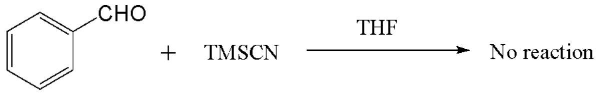


Figure 1. Benzaldehyde (1 mmol), TMSCN (1 mmol) and THF (1ml).

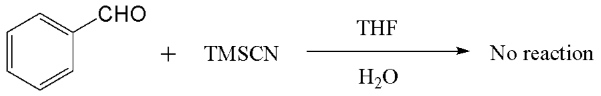


Figure 2. Benzaldehyde (1 mmol), TMSCN (1 mmol), THF (1 ml) and H_2O (0.01 mmol).

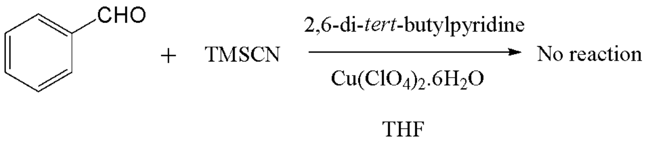


Figure 3. Benzaldehyde (1 mmol), TMSCN (1 mmol), 2,6-di-*tert*-butylpyridine (0.05 mmol), $Cu(ClO_4)_2 \cdot 6H_2O$ (0.01 mmol) and THF (1 ml).

H-4, 6), 7.42 (d, $J = 8.4$ Hz, 2H, H-3, 7). ^{13}C NMR ($CDCl_3$, 400 MHz): δ (ppm) $= -0.26$ (OTMS), 55.34 (OCH_3), 63.34 (C-1), 114.25 (C-4, 6), 119.32 (CN), 127.93 (C-2), 128.46 (C-3, 7), 160.33 (C-5). HRMS(M^+) calcd for $C_{12}H_{17}NO_2Si$ 235.1029; found 235.1032 (Scheme 1).

2-(4-tert-butylphenyl)-2-(trimethylsilyloxy)acetonitrile (entry 4)

^1H NMR ($CDCl_3$, 200 MHz): δ (ppm) $= 0.23$ (s, 9H, OTMS), 1.32 (s, 9H, C-$(CH_3)_3$), 5.38 (s, 1H, H-1), 7.09–7.21 (m, 5H, Ar-H). ^{13}C NMR ($CDCl_3$, 400 MHz): δ (ppm) $= -0.39$ (OTMS), 31.12 [C-$(CH_3)_3$], 34.52 (C-8), 63.33 (C-1), 119.28 (CN), 125.73 (C-4, 6), 126.04 (C-3, 7), 133.19 (C-2), 152.47 (C-5). HRMS(M^+) calcd for $C_{15}H_{23}NOSi$ 261.1549; found 261.1552 (Scheme 2).

2-(4-chlorophenyl)-2-(trimethylsilyloxy)acetonitrile (entry 9)

^1H NMR ($CDCl_3$, 200 MHz): δ (ppm) $= 0.286$ (s, 9H, OTMS), 5.62 (s, 1H, H-1), 7.38 (d, $J = 8.0$ Hz, 2H, H-3, 7), 7.42 (d, $J = 8.0$ Hz, 2H, H-4, 6). ^{13}C NMR ($CDCl_3$, 400 MHz): δ (ppm) $= -0.28$ (OTMS), 65.02 (C-1), 118.35 (CN), 128.25 (C-4, 6), 130.54 (C-3, 7), 131.8 (C-2), 133.12 (C-5). HRMS(M^+) calcd for $C_{11}H_{14}ClNOSi$ 239.0533; found 239.0539 (Scheme 3).

4-phenyl-2-(trimethylsilyloxy)but-3-enenitrile (entry 13)

^1H NMR ($CDCl_3$, 200 MHz): δ (ppm) $= 0.286$ (s, 9H, OTMS), 4.91 (m, 1H, H-1), 6.25 (m, 1H, H-2), 6.65 (d, $J = 8.0$ Hz, 1H, H-3), 7.22–7.41 (m, 5H, Ar-H). ^{13}C NMR ($CDCl_3$, 400 MHz): δ (ppm) $= -0.28$ (OTMS), 64.42 (C-1), 118.42 (CN), 127.91 (C-7), 128.51 (C-3), 128.55 (C-5,9), 128.84 (C-2, 6, 8), 136.45 (C-4). HRMS(M^+) calcd for $C_{13}H_{17}NOSi$ 231.1079; found 231.1082 (Scheme 4).

4-phenyl-2-(trimethylsilyloxy)butanenitrile (entry 14)

^1H NMR ($CDCl_3$, 200 MHz): δ (ppm) $= 0.286$ (s, 9H, OTMS), 2.14 (t, $J = 7.4$ Hz, 2H, H-2), 2.53 (t, $J = 7.6$ Hz, 2H, H-3), 4.21

Table 2. Cyanosilylation of aldehydes using $Cu(ClO_4)_2.6H_2O$ in presence THF at r.t.[a]

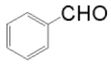
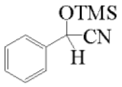
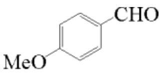
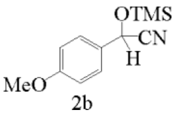
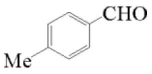
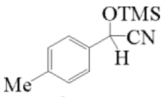
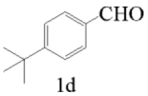
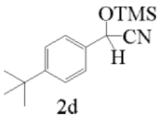
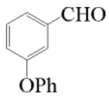
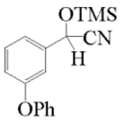
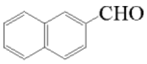
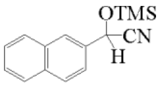
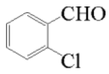
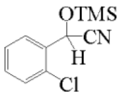
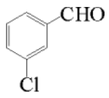
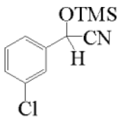
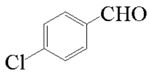
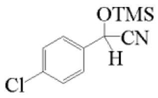
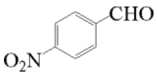
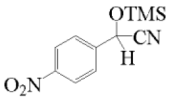
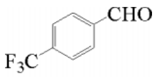
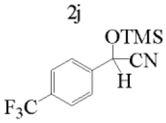
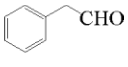
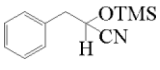
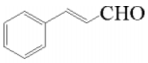
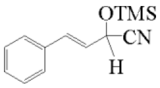
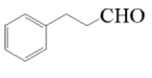
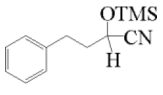
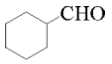
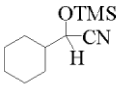
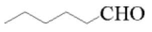
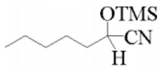
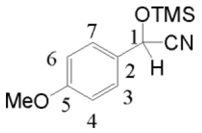
Entry	Aldehyde	Product	Time	Isolated yield (%)
1	 1a	 2a	3 min 3 h	92 95[8,41]
2	 1b	 2b	3 min 40 min	95 65[45]
3	 1c	 2c	5 min 2 h 12 h	89 80[42] 80[44]
4	 1d	 2d	3 min 2 h	91 85[45]
5	 1e	 2e	3 min 15 min	94 83[45]
6	 1f	 2f	8 min	92
7	 1g	 2g	15 min 30 min	58 70[45]
8	 1h	 2h	15 min 10 min	76 65[45]
9	 1i	 2i	15 min 24 h 3 h 3 h 10 min	88 70[8,42] 75[41] 81[43] 58[45]
10	 1j	 2j	1 h	–
11	 1k	 2k	1 h	–
12	 1l	 2l	6 min	83
13	 1m	 2m	8 min 3.5 h	94 78[45]

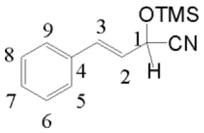
Table 2. (*Continued*)

Entry	Aldehyde	Product	Time	Isolated yield (%)
14	 1n	 2n	5 min	91
15	 1o	 2o	7 min	93
16	 1p	 2p	13 min	80

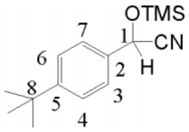
[a] The structures of the products were settled from spectral (^{1}H and ^{13}C NMR and HRMS) data and compared with the literature.[9,10,33–40]



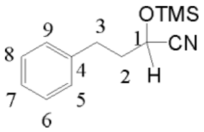
Scheme 1. 2-(4-methoxyphenyl)-2-(trimethylsilyloxy) acetonitrile.



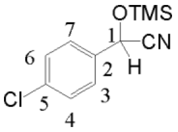
Scheme 4. 4-phenyl-2-(trimethylsilyloxy)but-3-enenitril.



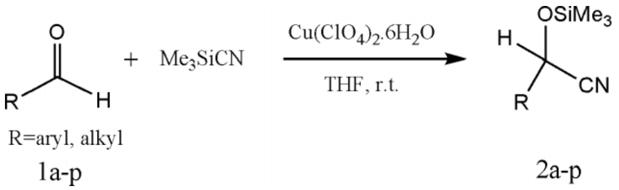
Scheme 2. 2-(4-tert-butylphenyl)-2-(trimethylsilyloxy) acetonitrile.



Scheme 5. 4-phenyl-2-(trimethylsilyloxy)butanenitrile.



Scheme 3. 2-(4-chlorophenyl)-2-(trimethylsilyloxy) acetonitrile.



Scheme 6. Cyanosilylation of aldehydes.

(s, 1H, H-1), 7.29–7.41 (m, 5H, Ar-H). ^{13}C NMR ($CDCl_3$, 400 MHz): δ (ppm) $= -0.28$ (OTMS), 28.31 (C-3), 36.13 (C-2), 60.02 (C-1), 119.35 (CN), 126.15 (C-7), 128.14 (C-5, 9), 128.82 (C-6, 8), 142.02 (C-4). HRMS(M^+) calcd for $C_{13}H_{19}NOSi$ 233.1234; found 233.1231 (Scheme 5).

Results and Discussion

As a part of our on-going interest in the development of useful synthetic methodologies[33–40] we have discovered that $Cu(ClO_4)_2 \cdot 6H_2O$ can efficiently catalyze the addition of TMSCN to aldehydes in THF at r.t. (Scheme 6).

$Cu(ClO_4)_2 \cdot 6H_2O$ is an interesting catalyst for its unique reactivities under mild reaction conditions at r.t.[29] Only catalytic quantities of $Cu(ClO_4)_2 \cdot 6H_2O$ are required for the preparation of cyanohydrin trimethylsilylether compound.

In our preliminary experiments, we used anisaldehyde as the model substrate with the reaction of TMSCN where various metal perchlorates with different solvents were employed (Table 1). It is noteworthy that this cyanosilylation reaction with $Fe(ClO_4)_3 \cdot 6H_2O$ in the presence of THF showed comparative activity with $Cu(ClO_4)_2 \cdot 6H_2O$. However with 1 mol% $Fe(ClO_4)_3 \cdot 6H_2O$ only 81% yield was obtained even after 30 min. Reaction with $LiClO_4$ gave 77% yield after 1 h in THF, whereas $Cu(ClO_4)_2 \cdot 6H_2O$ in THF gave 95% yield within 2–3 min (Table 1, entry 6b). Na, Mg and Mn perchlorates are found to be less active than Li, Fe and Cu. From the summary of the results we emphasize that transition metal perchlorates (Mn, Fe, Cu) are much more active than s- and p-block metal perchlorates (Li, Na, Mg) for the cyanosilylation reaction of aldehydes. Considering the reaction time and yield, $Cu(ClO_4)_2 \cdot 6H_2O$ (1 mol%) was found to be the best catalyst in THF to afford the desired cyanohydrin trimethylsilylether in high yields. Accordingly the result was optimal when a mixture of anisaldehyde (1 mmol), trimethylsilyl cyanide (1 mmol) and $Cu(ClO_4)_2 \cdot 6H_2O$ (1 mol%) was used.

A variety of aromatic and aliphatic aldehydes were treated with TMSCN in the presence of 1 mol% $Cu(ClO_4)_2 \cdot 6H_2O$ (Table 2). Unsubstituted benzaldehyde and electron-donating substituted benzaldehydes gave rise to excellent yield within short reaction time (3 min; entries 1–4). The weakly electron-attracting *m*-phenoxy group still gave a high yield (entry 5). Naphthaldehyde reacted with TMSCN to also give an excellent yield (entry 6). The aldehydes containing weakly electron-withdrawing groups such as *m*- and *p*-chlorobenzaldehyde furnished the desired cyanohydrins in good yield (76 and 88% respectively, entries 8 and 9), whereas a 58% yield for *o*-chlorobenzaldehyde was obtained due to the electronic effects plus steric hindrance (entry 7). However a strongly electron-withdrawing group in the aromatic ring such as *p*-nitrobenzaldehyde and trifluoro-*p*-tolualdehyde gave no products even after 1 h (entries 10 and 11). The long chain and cyclic aliphatic aldehydes (entry 12–16) were converted into the corresponding cyanohydrin silylethers in good to excellent yield. Some comparative results are also collected in Table 2. In contrast to our reaction time of 3–15 min, 3–12 h were required in the presence of 4.5 mol% silica-based scandium(III) interphase catalyst.[41] With N-heterocyclic carbenes as a catalyst (1 mol%), 91% yield was obtained in 10 min.[42] A time of 3.0 h was necessary for completion of the reaction in the presence of 5 mol% $Cu(OTf)_2$ as a catalyst.[43] A 10 mol% solution of diamino functionalized mesoporous material was required for the completion of the reaction in 2–12 h.[44] With 1 mol% $NbCl_5$ 10 min to 3.5 h are necessary for the reaction.[45] From these results it is evident that 1 mol% $Cu(ClO_4)_2 \cdot 6H_2O$ is very efficient catalyst in terms of time and yield for the synthesis of cyanohydrin silylethers from aldehydes and trimethylsilyl cyanide.

Conclusion

We have demonstrated the methodology using the readily available transition metal perchlorate $Cu(ClO_4)_2 \cdot 6H_2O$ that promotes the cyanosilylation of aldehydes in excellent yield at r.t. in short reaction time. Aromatic aldehyde reveals a distinct electronic effect. Electron-donating substituents accelerate the reaction while electron-withdrawing ones retard the reaction. The mild experimental conditions, the low loading of catalyst and the general applicability represent the notable features of the procedure.

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