Lewis Base-catalyzed Cyanomethylation of Carbonyl Compounds with (Trimethylsilyl)acetonitrile

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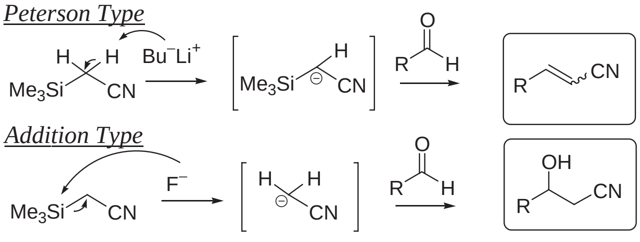
Catalytic cyanomethylation of various carbonyl compounds with (trimethylsilyl)acetonitrile ($TMSCH_2CN$) in the presence of Lewis bases such as cesium or lithium acetate proceeded smoothly to afford the corresponding cyanomethylated adducts in good yields.

β-Hydroxy nitriles are known as useful building blocks since they may readily be converted to β-hydroxycarboxylic acids or γ-amino alcohols.[1] In general, β-hydroxy nitriles are prepared by the condensation of carbonyl compounds with alkali acetonitriles that are formed by α-deprotonation of nitriles.[2] However, the yields of this condensation are not always satisfactory because this reaction is a reversible one, and the produced β-hydroxy nitrile is dehydrated easily to afford the α,β-unsaturated nitrile. Therefore, several methods have been devised and tried to improve yields in preparing β-hydroxy nitriles.[3,4] Among them, the method that uses $TMSCH_2CN$ is considered quite synthetically efficient because the reverse reaction is prevented in the starting carbonyl compounds and nitrile by trapping the formed alkoxide with $TMSCH_2CN$.[4] Palomo et al. reported a TASF[5]-catalyzed cyanomethylation in the presence of $TMSCH_2CN$ to give the adduct in moderate yields.[4c] More recently, Shibasaki et al. reported on a copper fluoride-catalyzed cyanomethylation of carbonyl compounds in the presence of $(EtO)_3SiF$.[4d]

Trimethylsilylacetonitrile is a popular reagent for Peterson olefination as an excellent precursor of α-cyano carbanions.[6] Behaviors of $TMSCH_2CN$ in synthetic reactions are also interesting mechanistic problems (Scheme 1).

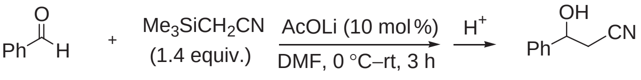
It was reported in the previous communications that the oxygen containing-anions generated from carboxylic acids were shown to be effective Lewis base catalysts for the activation of carbon-silicon bond of Me_3SiCN or Me_3SiCF_3.[7] In order to extend the synthetic utility of a Lewis base catalyst, a cyanomethylation reaction between $TMSCH_2CN$ and carbonyl compounds was considered.

In the first place, cyanomethylation of benzaldehyde with $TMSCH_2CN$ was tried in the presence of 10 mol % of AcOLi in DMF at room temperature and the desired product was obtained in 98% yield (Table 1).[8] The above reaction proceeded smoothly even when the amount of AcOLi decreased to 1 mol % (Entry 2). The acetates having such counter cations as sodium, potassium, cesium, or ammonium ion also worked effectively in the above reaction to afford the desired products in high yields (Entries 3–6). In the absence of the catalyst, on the other hand, the cyanomethylated adduct was not detected.



Scheme 1.

Table 1. Screening of catalyst on cyanomethylation

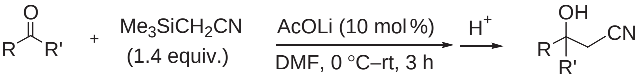


Entry	Cat. (10 mol %)	Yield[a]/%	Entry	Cat. (10 mol %)	Yield[a]/%
1	AcOLi	98 (96)[b]	5	AcOCs	94
2	AcOLi (1 mol %)	91	6	AcO-*n*NBu$_4$	96
3	AcONa	97	7	AcOLi (THF)[c]	N.D.
4	AcOK	94	8	none	N.D.

[a]Yield was determined by ^1H NMR analysis (270 MHz) using $Cl_2HCCHCl_2$ as an internal standard. [b]Isolated yield. [c]THF was used as a solvent.

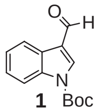
The reactions with various carbonyl compounds under the optimized conditions are summarized in Table 2. Aromatic aldehydes having electron-donating or -withdrawing groups reacted smoothly to afford the cyanomethylated adducts in excellent yields. Acid- or base-sensitive aldehydes also afforded the desired products in high yields (Entries 4, 5, and 13). Further, an

Table 2. Cyanomethylation of various carbonyl compounds



Entry	RC(O)R′	Yield/%	Entry	RC(O)R′	Yield/%
1	4-MeOC$_6$H$_4$CHO	94	10	(*E*)-PhCH=CHCHO	99
2	C$_6$H$_5$CHO	98	11	C$_6$H$_{11}$CHO	80
3	4-ClC$_6$H$_4$CHO	95	12	PhCH$_2$CH$_2$CHO	61
4	4-MeCO$_2$C$_6$H$_4$CHO	97	13	**1**	81
5	4-NCC$_6$H$_4$CHO	91	14	**2**	85
6	4-NO$_2$C$_6$H$_4$CHO	94	15	**3**	42
7	2-NaphthylCHO	95	16	**4**	77
8	2-FurylCHO	99	17	**5**	92
9	2-QuinolylCHO	97	18	**6**	85

[a]Yield was determined by ^1H NMR analysis (270 MHz) using 1,1,2,2-tetrachloroethane as an internal standard.



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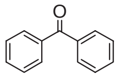

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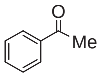

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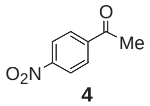

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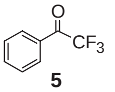

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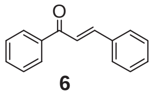

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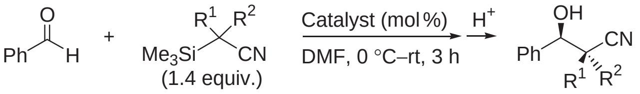
Table 3. Cyanomethylation with various (trimethylsilyl)-acetonitrile derivatives

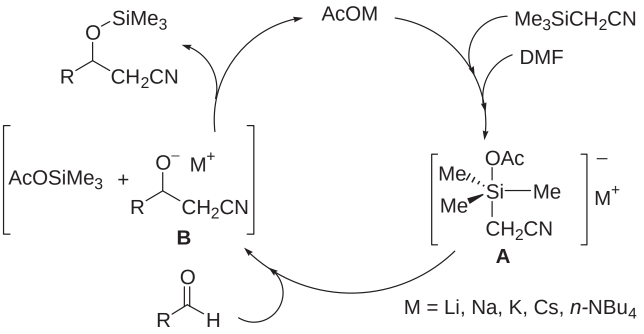


Entry	Reagent		Catalyst (mol %)	Yield[a]/%	*syn*:*anti*
1	$R^1 = Me, R^2 = Me$	**7**	AcOLi (10)	14	—
2	$R^1 = Me, R^2 = Me$	**7**	AcOCs (10)	98[b]	—
3	$R^1 = Me, R^2 = H$	**8**	AcOCs (10)	98	57:43
4	$R^1 = Et, R^2 = H$	**9**	AcOCs (10)	97	58:42

[a] Yield was determined by ^{1}H NMR analysis (270 MHz) using 1,1,2,2-tetrachloroethane as an internal standard. [b] The reaction time was 6 h.

α,β-unsaturated carbonyl compound gave the corresponding 1,2-adduct as a sole product (Entries 10 and 18). However, enolizable ketones that were less reactive afforded the desired products in moderate yields because the competitive abstraction of α-proton took place to give the corresponding silyl enol ether (Entry 15).

Next, the Lewis base-catalyzed cyanomethylation reaction was tried by using several trimethylsilylacetonitriles (Table 3). When trimethylsilylacetonitrile derivative **7** was used as a substrate, the corresponding β-hydroxy nitrile was obtained in low yields only because of the steric hindrance. Then, various Lewis bases were screened and reaction conditions were optimized so as to improve the yields. Consequently, it was noted that the corresponding cyanomethylated adduct was obtained in high yield when the reaction was carried out in the presence of a catalytic amount of AcOCs (Entry 2). Similarly, trimethylsilylacetonitrile derivatives **8** or **9** smoothly reacted with carbonyl compounds to afford the desired product in good yields, although the diastereoselectivity must to be optimized (Entries 3 and 4).



Scheme 2.

Although the mechanism of this reaction is not clear yet, an assumed catalytic cycle is illustrated in Scheme 2.[9,10] In the first place, a Lewis base catalyst coordinates to a silicon atom of $TMSCH_2CN$ to form a hypervalent silicate **A** or a corresponding hexacoordinate silicate with an additional coordination of the solvent. The nucleophilicity of the silicate **A** is then grow sufficient to react with carbonyl compounds to form alkoxide **B** and TMSOAc. Subsequent silylation of **B** by thus formed TMSOAc afforded *O*-silyl ether along with the regeneration of the catalyst to establish a catalytic cycle.

Thus, it is noted that a catalytic cyanomethylation of various carbonyl compounds with $TMSCH_2CN$ by using Lewis base catalysts such as lithium acetate proceeded smoothly via the activation of carbon–silicon bond of $TMSCH_2CN$. This method is applied to the synthesis of various β-hydroxy nitriles under mild conditions. Further investigation on this reaction is now in progress.

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References and Notes

1 Y. Fukuda and Y. Okamoto, *Tetrahedron*, **58**, 2513 (2002).

2 a) E. W. Kaiser and C. R. Hauser, *J. Am. Chem. Soc.*, **89**, 4566 (1967). b) E. W. Kaiser and C. R. Hauser, *J. Org. Chem.*, **33**, 3402 (1968).

3 a) J. J. P. Zhou, B. Zhong, and R. B. Silverman, *J. Org. Chem.*, **60**, 2261 (1995). b) P. Kisanga, D. McLeod, B. D'Sa, and J. Verkade, *J. Org. Chem.*, **64**, 3090 (1999). c) N. Kumagai, S. Matsunaga, and M. Shibasaki, *J. Am. Chem. Soc.*, **126**, 13632 (2004).

4 a) B. A. Gostevskii, O. A. Kruglaya, A. I. Albanov, and N. S. Vyazankin, *J. Organomet. Chem.*, **187**, 157 (1980). b) R. Latouche, F. Texier-Boullet, and J. Hamelin, *Tetrahedron Lett.*, **32**, 1179 (1991). c) C. Palomo, J. M. Aizpurua, M. C. López, and B. Lecea, *J. Chem. Soc., Perkin Trans. 1*, **1989**, 1692. d) Y. Suto, N. Kumagai, S. Matsunaga, M. Kanai, and M. Shibasaki, *Org. Lett.*, **5**, 3147 (2003). e) Y. Kawanami, H. Yuasa, F. Toriyama, S. Yoshida, and T. Baba, *Catal. Commun.*, **4**, 455 (2003).

5 TASF: Tris(dimethylamino)sulfur(trimethylsilyl)difluoride.

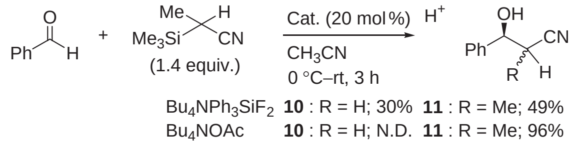
6 a) L. Birkofer, A. Ritter, and H. Wiedden, *Chem. Ber.*, **95**, 971 (1962). b) I. Matsuda, S. Murata, and Y. Ishii, *J. Chem. Soc., Perkin Trans. 1*, **1979**, 26. c) Y. Yamakado, M. Ishiguro, N. Ikeda, and H. Yamamoto, *J. Am. Chem. Soc.*, **103**, 5568 (1981).

7 a) T. Mukaiyama, Y. Kawano, and H. Fujisawa, *Chem. Lett.*, **34**, 88 (2005). b) Y. Kawano, H. Fujisawa, and T. Mukaiyama, *Chem. Lett.*, **34**, 422 (2005). c) E. Takahashi, H. Fujisawa, T. Yanai, and T. Mukaiyama, *Chem. Lett.*, **34**, 318 (2005).

8 Typical experimental procedure is as follows (Table 1, Entry 1): to a stirred solution of AcOLi (2.6 mg, 0.04 mmol) in DMF (0.7 mL) were added successively a solution of benzaldehyde (42.4 mg, 0.4 mmol) in DMF (0.3 mL) and $TMSCH_2CN$ (76.5 µL, 0.56 mmol) at 0 °C. And the reaction mixture slowly warmed to room temperature. The mixture was stirred for 3 h at the same temperature and quenched with 1 M HCl (1.0 mL) and MeOH (1.0 mL). The mixture was extracted with AcOEt and organic layer was washed with brine and dried over anhydrous Na_2SO_4, and evaporated. The crude product was purified by passing through short SiO_2 column to afford the desired product (56.6 mg, 96%) as colorless oil.

9 It is reported that the reaction with $TMSCH_2CN$ in acetonitrile forms a pentacoordinate silicon species: D. J. Adams, J. H. Clark, L. B. Hansen, V. C. Sanders, and S. J. Tavener, *J. Fluorine Chem.*, **92**, 123 (1998).

10 Cyanomethylation reaction was studied by using trimethylsilyl acetonitrile derivatives **8** in CH_3CN. When $Bu_4NPh_3SiF_2$ was used as a catalyst, the β-hydroxy nitrile **10** was obtained in 30% yield along with the desired β-hydroxy nitrile **11**. However, the β-hydroxy nitrile **10** was not detected when Bu_4NOAc was used. It is considered that these reactions proceeded via two different mechanisms.



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