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Nucleophilic Addition of α-(Dimethylsilyl)nitriles to Aldehydes and Ketones

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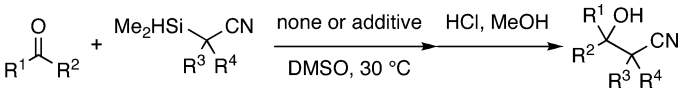
ABSTRACT



α-Alkylated (dimethylsilyl)acetonitriles ($Me_2HSiCR^3R^4CN$) react spontaneously with aldehydes in DMSO to give β-hydroxynitriles in good to high yields. The addition to ketones is effectively promoted by using $MgCl_2$ or $CaCl_2$. (Dimethylsilyl)acetonitrile (Me_2HSiCH_2CN) shows lower reactivity than the α-alkylated analogues. However, the parent reagent adds efficiently to aldehydes and ketones under catalysis by AcOLi or $MgCl_2$.

β-Hydroxynitriles are versatile synthetic intermediates because the cyano group is convertible to various functionalities. Carbonyl addition of α-metallonitriles has frequently been used for the synthesis of β-hydroxynitriles.[1−4] The conventional methods include successive deprotonation−carbonyl addition of nitriles using strong bases and the Reformatsky reaction of α-halonitriles.[1] These methods are not necessarily efficient due to the reversibility of the carbonyl addition as well as condensation leading to α,β-unsaturated nitriles. Therefore, recent attention has been focused on Lewis base-promoted addition of α-(trimethylsilyl)nitriles (α-TMS-nitriles), stable equivalents of α-cyano carbanions. Several methods for this silicon-mediated carbonyl addition have been reported.[4c,5−8] However, these studies mostly deal with the reaction of TMS-acetonitrile (Me_3SiCH_2CN). There are only a few examples for carbonyl addition of sterically congested α-TMS-nitriles.[6] Additionally some silicon-based methods have limited scope of available carbonyls. There is still much room for development of a new silicon-based method for efficient synthesis of various β-hydroxynitriles.

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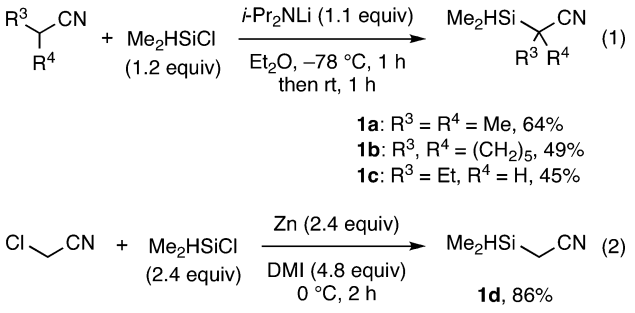
In our study on synthesis and synthetic use of dimethylsilyl (DMS)-protected carbon nucleophiles,[9] we have disclosed that ethyl DMS-acetate ($Me_2HSiCH_2CO_2Et$) and other α-DMS-esters add smoothly to various aldehydes and ketones in the presence of metal chlorides such as LiCl, $CaCl_2$, and $MgCl_2$.[10] In contrast, ethyl TMS-acetate is insensitive to carbonyls under the same conditions. Thus, the DMS-protected carbon nucleophiles show much higher reactivity than the TMS analogues. With this finding, our interest was next focused on synthetic use of α-DMS-nitriles. We herein report nucleophilic addition of α-DMS-nitriles to carbonyl compounds.

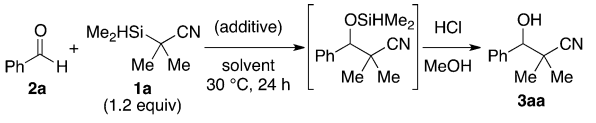
α-DMS-nitriles **1a**–**c** were prepared by treatment of a diethyl ether solution of the corresponding nitrile and chlorodimethylsilane (DMS-Cl) with LDA (eq 1 in Scheme 1). The reaction of in situ generated α-lithionitriles with DMS-Cl provided better results than a stepwise method via deprotonation and subsequent silylation. We failed to obtain pure DMS-acetonitrile (**1d**) from acetonitrile by the LDA-mediated method shown in eq 1. After many attempts, we succeeded in an efficient preparation of pure **1d** by the reaction among chloroacetonitrile, DMS-Cl, and zinc powder (eq 2).[11]

Scheme 1. Synthesis of α-DMS-nitriles



We initially examined solvent effect on the reaction of **1a** with benzaldehyde (**2a**). The carbonyl addition of **1a** proceeded spontaneously at 30 °C in DMSO and DMF (Scheme 2). Particularly the reaction in DMSO gave β-hydroxynitrile **3aa** in high yield following treatment with acidic MeOH. Other solvents (THF, CH_2Cl_2, PhMe, hexane) did not promote the carbonyl addition. In the presence of $CaCl_2$ or LiCl (1 equiv), the reaction in DMSO was complete in 1 h.

Scheme 2. Solvent Effect on Reaction of α-DMS-nitrile **1a**

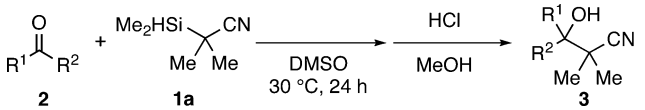


solvent (yield / %): DMSO (89, 94[a]), DMF (74), THF (0), CH_2Cl_2 (0), PhMe (0), hexane (0), DMSO (84)[b], DMSO (85)[c]

[a] With 1.5 equiv of **1a**. [b] With $CaCl_2$ (1 equiv) for 1 h. [c] With LiCl (1 equiv) for 1 h.

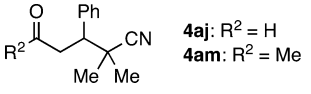
The results of the reaction of **1a** with various carbonyl compounds are summarized in Table 1. Aromatic aldehydes **2b**–**e** were efficiently converted into β-hydroxynitriles (entries 1–4). The addition of **1a** to *p*-nitrobenzaldehyde (**2f**) resulted in a low yield of **3af**, and competitive reduction leading to *p*-nitrobenzyl alcohol was observed (entry 5). An excess amount of **1a** was required for complete conversion of 4-hydroxybenzaldehyde (**2g**) into **3ag** (entry 6). This is probably due to desilylation of **1a** by the acidic hydroxy group. Enolizable aldehydes **2h** and **2i** also underwent spontaneous addition of **1a** (entries 7 and 8). The reaction of cinnamaldehyde (**2j**) mainly gave 1,2-adduct **3aj** along with 1,4-adduct **4aj** (entry 9). Although ketones are generally less reactive toward nucleophilic addition than aldehydes, **1a** showed enough reactivity for the addition to acetophenone (**2k**) and cyclohexanone (**2l**) (entries 10 and 11). Use of $MgCl_2$ effectively promoted the reaction of **2l**. α,β-Unsaturated ketone **2m** as well as **2j** underwent both 1,2- and 1,4-addition in favor of 1,2-addition (entry 12).

Table 1. Reaction of **1a** with Aldehydes and Ketones[a]



	carbonyl compound				
entry	R^1	R^2		product	isolated yield (%)
1	4-$MeOC_6H_4$	H	**2b**	**3ab**	90
2	4-MeC_6H_4	H	**2c**	**3ac**	86
3	4-BrC_6H_4	H	**2d**	**3ad**	86
4	4-ClC_6H_4	H	**2e**	**3ae**	90
5	4-$O_2NC_6H_4$	H	**2f**	**3af**	24[b]
6	4-HOC_6H_4	H	**2g**	**3ag**	22, 92[c]
7	$Ph(CH_2)_2$	H	**2h**	**3ah**	71
8	*c*-C_6H_{11}	H	**2i**	**3ai**	99
9	(*E*)-PhCH=CH	H	**2j**	**3aj**	59,[d,e]
10	Ph	Me	**2k**	**3ak**	90
11	$(CH_2)_5$		**2l**	**3al**	72, 99[f]
12	(*E*)-PhCH=CH	Me	**2m**	**3am**	62[d]

[a] Unless otherwise noted, all reactions were carried out with **2** (0.50 mmol) and **1** (0.60 mmol) in DMSO (1.0 mL) at 30 °C for 24 h. [b] *p*-Nitrobenzyl alcohol was also obtained in 53% NMR yield. [c] With 1.2 mmol of **1a**. [d] 1,4-Adducts **4aj** (entry 9) and **4am** (entry 12) were obtained in 9% and 27% yields, respectively. [e] The reaction time was 48 h. [f] With 0.50 mmol of $MgCl_2$.



We next examined the reaction of α-DMS-nitrile **1b** with aldehydes and ketones (Table 2). The addition of **1b** to aldehydes **2a** and **2i** proceeded slowly without additive (entries 1 and 2). However, prolonged reaction time brought about high yields of the desired adducts. In the presence of $CaCl_2$, the addition to **2a** was completed in 24 h.

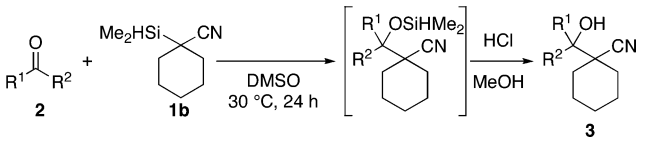
(10) Miura, K.; Nakagawa, T.; Hosomi, A. *Synlett* **2005**, 1917.

(11) A similar Zn-mediated method is valuable for the synthesis of TMS-acetonitrile. For the original method, see: Matsuda, I.; Murata, S.; Ishii, Y. *J. Chem. Soc., Perkin Trans. 1* **1979**, 26.

The uncatalyzed reaction of ketones was rather slow, and use of metal chlorides ($CaCl_2$ or $MgCl_2$) was essential to efficient addition of **1b** (entries 3 and 4).

α-DMS-nitrile **1c**, derived from butanenitrile, added smoothly to aromatic aldehydes (entries 1−5 in Table 3). The desired adducts were obtained as diastereomeric mixtures with low stereoselectivity. The reaction of **1c** with aliphatic aldehydes proceeded slowly and needed prolonged reaction time (entries 6 and 7). The uncatalyzed reaction with ketones **2k** and **2l** was very sluggish (entries 8 and 9). Adding $MgCl_2$ effectively accelerated the addition of **1c** to aliphatic aldehydes and ketones.

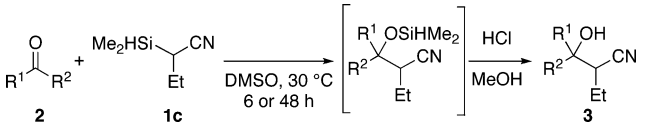
Table 2. Reaction of **1b** with Aldehydes and Ketones[a]



	carbonyl compound				
entry	R^1	R^2		product	isolated yield (%)
1	Ph	H	**2a**	**3ba**	45, 87,[b] 89[c]
2	*c*-C_6H_{11}	H	**2i**	**3bi**	71, 80[b]
3	Ph	Me	**2k**	**3bk**	35, 87[c]
4	$(CH_2)_5$		**2l**	**3bl**	23, 74[d]

[a] See footnote [a] in Table 1. [b] The reaction time was 48 h. [c] With 0.50 mmol of $CaCl_2$. [d] With 0.50 mmol of $MgCl_2$.

Table 3. Reaction of **1c** with Aldehydes and Ketones[a]

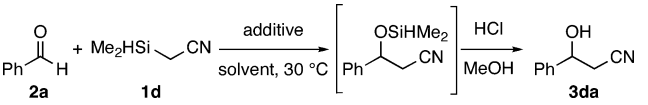


	carbonyl compound					
entry	R^1	R^2		product	isolated yield (%)	*syn*:*anti*[b]
1	Ph	H	**2a**	**3ca**	98	56:44
2	4-MeO-C_6H_4	H	**2b**	**3cb**	95	59:41
3	4-Me-C_6H_4	H	**2c**	**3cc**	96	58:42
4	4−Br-C_6H_4	H	**2d**	**3cd**	85	57:43
5	4−Cl-C_6H_4	H	**2e**	**3ce**	92	55:45
6	$Ph(CH_2)_2$	H	**2h**	**3ch**	80, 73[c]	55:45[d,e]
7	*c*-C_6H_{11}	H	**2i**	**3ci**	56, 87[c]	60:40[d]
8	Ph	Me	**2k**	**3ck**	94[c]	62:38[e]
9	$(CH_2)_5$		**2l**	**3cl**	79[c]	

[a] See footnote [a] in Table 1. The reaction time was 6 h (entries 1−5) or 48 h (entries 6−7). [b] Determined by ^{1}H NMR analysis of the isolated product. [c] With 0.50 mmol of $MgCl_2$ for 24 h. [d] The same diastereomeric ratio was observed in the absence and presence of $MgCl_2$. [e] The relative configuration of the major isomer was not determined.

As described above, TMS-acetonitrile (Me_3SiCH_2CN, **1d′**) is well-known to serve as a cyanomethyl anion equivalent. We were therefore interested in the reactivity and synthetic utility of DMS-acetonitrile (**1d**). In addition, we aimed to disclose the effect of the α-alkyl groups on the reactivity of α-DMS-nitriles **1a**−**c**. Initially, the reaction of **1d** with **2a** was carried out in DMSO (Table 4). The desired carbonyl addition proceeded spontaneously but more slowly than the reactions of **1a**−**c** (entries 1 and 2). $MgCl_2$ was effective in promoting the addition of **1d** (entry 3). Catalysis by LiOAc, as introduced by Mukaiyama and co-workers,[6] brought about a rapid addition leading to *β*-hydroxynitrile **3da** (entry 4). The reaction using 2.5 mol % of LiOAc was completed in 1 h at 0 °C to give **3da** in 93% yield.

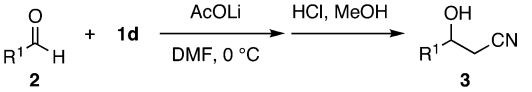
Table 4. Reaction of **1d** with Benzaldehyde[a]



entry	additive (/equiv)	solvent	time (h)	NMR yield[b] (%)
1	none	DMSO	24	40
2	none	DMSO	48	56
3	$MgCl_2$ (1)	DMSO	24	74
4	AcOLi (0.025)	DMF	1	93[c]

[a] Unless otherwise noted, all reactions were carried out with **2a** (0.50 mmol) and **1d** (0.65 mmol) in solvent (1 mL) at 30 °C. [b] Determined by ^{1}H NMR analysis of the crude product. [c] At 0 °C.

Table 5. Reaction of **1d** with Aldehydes[a]

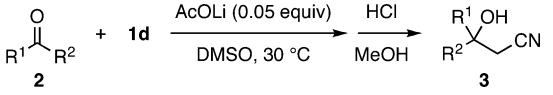


entry	R^1		AcOLi (equiv)	time (h)	product	isolated yield (%)
1	4-$MeOC_6H_4$	**2b**	0.025	3	**3db**	90
2	4-ClC_6H_4	**2e**	0.025	3	**3de**	95
3	$Ph(CH_2)_2$	**2h**	0.05	24	**3dh**	65
4	$Ph(CH_2)_2$	**2h**	0.05	24	**3dh**	67[b]
5	*c*-C_6H_{11}	**2i**	0.05	24	**3di**	71
6	*c*-C_6H_{11}	**2i**	0.05	6	**3di**	87[b]
7	(*E*)-PhCH=CH	**2j**	0.05	24	**3dj**	84

[a] Unless otherwise noted, all reactions were carried out with **2** (0.50 mmol), **1d** (0.65 mmol), and AcOLi (0.013 or 0.025 mmol) in DMF (1 mL) at 0 °C. [b] In DMSO at 30 °C.

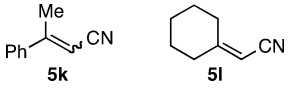
The scope of the LiOAc-catalyzed addition of **1d** was examined with several aldehydes (Table 5). Similar to the TMS-analogue **1d′**, **1d** added smoothly to aromatic aldehydes (entries 1 and 2). The reaction of linear and α-branched aliphatic aldehydes, **2h** and **2i**, also gave the corresponding *β*-hydroxynitriles in good isolated yields (entries 3−6). In contrast to the case of **1a**, 1,2-addition of **1d** to **2j** proceeded efficiently without 1,4-addition (entry 7). These results are comparable with those of the addition of **1d′**.[6]

Table 6. Reaction of **1d** with Ketones[a]



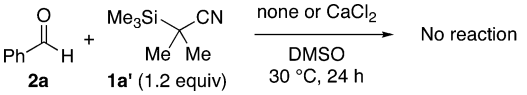
	ketone					
entry	R^1	R^2		time (h)	product	isolated yield (%)
1	Ph	Me	**2k**	24	**3dk**	60[b]
2	Ph	Me	**2k**	24	**3dk**	69[b,c]
3	$(CH_2)_5$		**2l**	24	**3dl**	40[d]
4	$(CH_2)_5$		**2l**	48	**3dl**	72[c,d]
5	(*E*)-PhCH=CH	Me	**2m**	6	**3dm**	75
6	4-$O_2NC_6H_4$	Me	**2n**	6	**3dn**	92

[a] Unless otherwise noted, all reactions were carried out with **2** (0.50 mmol), **1d** (0.65−0.75 mmol), and AcOLi (0.025 mmol) in DMSO (1 mL) at 30 °C. [b] α,β-Unsaturated nitrile **5k** was obtained in 15% (*E*:*Z* = 1:1, entry 1) and 17% (*E*:*Z* = 3:2, entry 2) NMR yields. [c] $MgCl_2$ (0.50 mmol) was used instead of AcOLi. [d] α,β-Unsaturated nitrile **5l** was obtained in 32% (entry 3) and 13% (entry 4) NMR yields.



Ketones were also subjected to the reaction with **1d** (Table 6). When **2k** was employed, **3dk** and dehydrated product **5k** were formed in 75% combined yield (entry 1). This result indicates that, unlike the case of **1d′**, the carbonyl addition of **1d** is faster than α-deprotonation of **2k** under catalysis by AcOLi.[12] Although the reaction was carried out under neutral conditions using $MgCl_2$ instead of AcOLi, our efforts to suppress the formation of **5k** was not successful (entry 2). Similarly, the addition to **2l** was accompanied by the subsequent elimination to **5l** (entry 3). However, the side reaction was inhibited effectively by using $MgCl_2$ as promoter (entry 4). Conjugated ketones **2m** and **2n** underwent efficient cyanomethylation with **1d** (entries 5 and 6).

Scheme 3. Reactivity of α-TMS-nitrile **1a′**



To gain a mechanistic insight, we attempted the reaction of α-TMS-nitrile **1a′** with **2a** (Scheme 3). In sharp contrast with **1a**, **1a′** did not add to **2a** in DMSO even in the presence of $CaCl_2$. Judging from this result, nucleophilic activation of the DMS-based reagents **1** by DMSO or counteranions of metal salts would promote the present reaction.[10,13] The low reactivity of **1a′** can be rationalized by the steric hindrance around silicon, which inhibits the nucleophilic activation. Our efforts to detect a reactive species generated from **1a** by NMR analysis were not successful. As described above, the addition of α-DMS-nitriles **1** is applicable to enolizable ketones. The less basic behavior of **1** indicates that a highly coordinated silicate is more likely than a naked α-cyano carbanion as the reactive species.[14]

In conclusion, we have developed new reagents that serve as α-cyano carbanion equivalents for carbonyl addition. α-DMS-nitriles **1** added to various aldehydes and ketones spontaneously or in the presence of metal salts. In particular, α-alkylated DMS-acetonitriles **1a**−**c** showed high reactivity, which enabled an efficient synthesis of sterically congested β-hydroxynitriles. The present method is complementary to the known method using TMS-acetonitrile, which is valuable for the synthesis of less congested β-hydroxynitriles. It is also interesting that DMS-acetonitrile **1d** is much less reactive than sterically congested α-DMS-nitriles **1a**−**c** although the reason is not clear at present.

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Supporting Information Available. Experimental details and characterization data (^{1}H NMR, ^{13}C NMR, IR, MS). This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

(12) Mukaiyama and co-workers reported that the AcOLi-catalyzed reaction of **2k** with **1d′** resulted in a low yield of **3dk** due to competitive deprotonation affording the TMS enolate of **2k**. See ref 6.

(13) For DMSO-promoted carbonyl addition of TMS-protected carbon nucleophiles, see: (a) Iwanami, K.; Oriyama, T. *Synlett* **2006**, 112. (b) Génisson, Y.; Gorrichon, L. *Tetrahedron Lett.* **2000**, *41*, 4881. In these cases, MS 4A as well as DMSO were used for effcient addition.

(14) Naked enolates generated from ester silyl enolates and α-silyl esters deprotonate enolizable ketones efficiently. Kuwajima, I.; Nakamura, E. *Acc. Chem. Res.* **1985**, *18*, 181.