Versatile and Fluoride-Free Cyanation of Alkyl Halides and Sulfonates with Trimethylsilyl Cyanide

Osamu Yabe, Hideya Mizufune, Tomomi Ikemoto*

Chemical Development Laboratories, CMC Center, Pharmaceutical Production Division, Takeda Pharmaceutical Company Limited, 2-17-85, Jusohonmachi, Yodogawa-ku, Osaka, 532-8686, Japan
Fax +81(6)63006251; E-mail: Ikemoto_Tomomi@takeda.co.jp
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Abstract: Cyanation of biphenyl-4-ylmethyl methanesulfonate with trimethylsilyl cyanide using fluoride-free inorganic salts, such as Cs_2CO_3, K_2CO_3, and $LiOH·H_2O$, as additives in MeCN quantitatively gave biphenyl-4-ylacetonitrile. This methodology was applied to various alkyl halides to give the corresponding nitrile compounds in good to excellent yields. Of note, 4-(hydroxymethyl)benzyliodide O-protected by the silyl group was converted into phenylacetonitrile derivative in 99% yield without desilylation.

Key words: cyanation, trimethylsilyl cyanide, fluoride-free inorganic salt

Cyanation is an important means of constructing C–C bonds in organic synthesis. The resulting products can be further transformed to a wide range of important synthetic intermediates including amines,[1] carboxylic acids,[2] and heterocycles.[3] Trimethylsilyl cyanide (TMSCN) is a useful reagent as a stabilized hydrogen cyanide, and is often used in combination with an additive (Lewis acid,[4–10] metal oxide,[11] and fluoride compound[11–13]). For ring-opening reaction of epoxides[11a,14,15] and the hydrocyanation of carbonyl compounds,[16–18] many reactions have been explored because various additives have afforded regiospecific, chemoselective, and asymmetric reactions. In contrast, the substitution reaction of alkyl halides with TMSCN, using Lewis acid ($TiCl_4$,[9] $SnCl_4$,[10] and $AgClO_4$[19]) and CsF[13] as an additive, has received relatively less attention because treatment of alkyl halides with TMSCN using Lewis acid was limited to the synthesis of secondary and tertiary compounds as substrates.[9,10] Although the reaction of primary halides with Lewis acid gave isocyanides or a mixture of polymeric products,[9] Deshong's group reported an efficient TMSCN-promoted cyanation of primary alkyl halides by employing tetra-*n*-butylammonium fluoride (TBAF) as an additive in 1999.[12] However, substrates protected by the silyl group cannot be used because the fluoride anion affords desilylation.[20] In addition, fluoride anion generally causes the difficulty to waste and the limitation of vessel's material considering the preparation for large scale. Therefore, it is important to explore versatile and practical alternatives to cyanide. Here, we describe a method for preparing nitrile compounds from alkyl halides and sulfonates with TMSCN using fluoride-free inorganic salts.

Preliminarily, fluoride compounds as an additive (1.2 equiv) were re-examined in the cyanation of biphenyl-4-ylmethyl methanesulfonate (**1a**) as a model substrate with TMSCN (1.2 equiv). Compound **1a** was treated with TBAF in MeCN at room temperature for 6 hours to give **2** in 96% yield according to methods described in the literature.[12] Although the reported example was the secondary methanesulofonate,[13] the treatment of **1a** with CsF in MeCN for 24 hours at room temperature gave **2** in 99% yield. Comparatively, KF provided **2** after 6 days in 73% yield. Differences in reactivity with the species of fluoride and metals in the inorganic fluoride salt were found from these results, which led us to investigate inorganic and organic salts other than fluoride salts.

The cyanation of **1a** with TMSCN (1.2 equiv) using Cs_2CO_3 or K_2CO_3 as an additive (1.2 equiv) in MeCN at room temperature was carried out, as shown in Table 1. Surprisingly, the two fluoride-free reactions proceeded. Thus, although Cs_2CO_3 system required 24 hours to complete the reaction (entry 1, 99% yield), the reaction with K_2CO_3 provided a similar result to TBAF, giving **2** after 8 hours in 98% yield (entry 2).[21] $KHCO_3$ converted **1a** into **2** in 90% yield, however, the reaction took 7 days (entry 3). Other heterogeneous bases, such as $LiOH·H_2O$, NaOH, K_3PO_4, and KOAc, also afforded more than 90% yield after 24 hours (entries 4–7). In the case of organic salts, NaOMe gave **2** in 85% yield, whereas NaSMe gave a mixture of **2** and methyl thioether (entries 8 and 9). Of note, neither KOAc nor NaOMe afforded the corresponding acetate or ether (entries 7 and 8). Changing the solvent from MeCN to EtOAc, acetone, THF, and DMSO resulted in a slower reaction and less selectivity compared to that in MeCN (entries 10–13). In the case of MeOH, the corresponding methyl ether was obtained in 54% yield (entry 14).

The reaction of alkyl bromide **1b** and alkyl chloride **1c** as substrates with TMSCN and K_2CO_3 in MeCN also gave **2** in 99 and 90% yield, respectively (entries 15 and 18). In the case of **1b**, the rate of cyanation was higher with $LiOH·H_2O$ than with K_2CO_3 (entries 15 vs. 16). Interestingly, the reaction of **1b** with NaOH at 50 °C for 13 hours in MeCN proceeded smoothly, giving **2** in 94% yield without hydroxylation (entry 17). From these results, it is thought that the bases could coordinate to TMSCN, simi-

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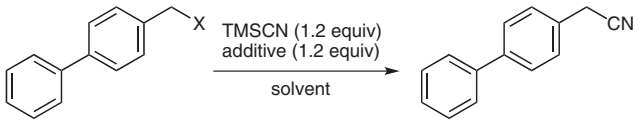
Table 1 Cyanation of **1** to **2** with TMSCN under Various Conditions



1a; X = OMs
1b; X = Br
1c; X = Cl

2

Entry	Substrate	Solvent	Additive	Conditions	Yield (%)[a]
1	**1a**	MeCN	Cs_2CO_3	r.t., 24 h	99 (93)
2	**1a**	MeCN	K_2CO_3	r.t., 8 h	98 (88)
3	**1a**	MeCN	$KHCO_3$	r.t., 7 d	90
4	**1a**	MeCN	$LiOH·H_2O$	r.t., 24 h	99 (91)
5	**1a**	MeCN	NaOH[b]	r.t., 24 h	99 (92)
6	**1a**	MeCN	K_3PO_4	r.t., 24 h	93
7	**1a**	MeCN	KOAc	r.t., 24 h	95
8	**1a**	MeCN	NaOMe	r.t., 24 h	85
9	**1a**	MeCN	NaSMe	r.t., 30 h	31[c]
10	**1a**	EtOAc	K_2CO_3	r.t., 48 h	94
11	**1a**	Me_2CO	K_2CO_3	r.t., 48 h	84
12	**1a**	THF	K_2CO_3	r.t., 48 h	93
13	**1a**	DMSO	K_2CO_3	r.t., 8 h	84
14	**1a**	MeOH	K_2CO_3	r.t., 8 h	30[d]
15	**1b**	MeCN	K_2CO_3	50 °C, 8 h	99
16	**1b**	MeCN	$LiOH·H_2O$	r.t., 6 h	100
17	**1b**	MeCN	NaOH[b]	50 °C, 13 h	94
18	**1c**	MeCN	K_2CO_3	80 °C, 12 h	90
19	**1c**	MeCN	$LiOH·H_2O$	r.t., 17 d	91
20	**1c**	MeCN	NaOH[b]	r.t., 7 d	55

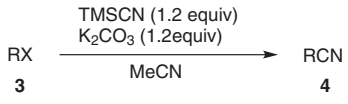
[a] The yields were determined by HPLC analysis, and values in parentheses show the isolated yields after chromatography.
[b] TOSO pale (TOSO Corp. Ltd.) was used as NaOH.
[c] 4-[(Methylsulfanyl)methyl]biphenyl was given in 53% yield with **2**.
[d] 4-(Methoxymethyl)biphenyl was given in 54% yield with **2**.

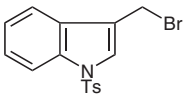
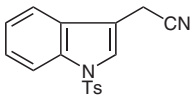
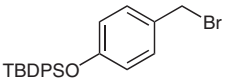
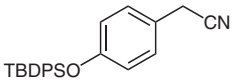
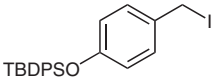
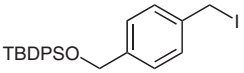
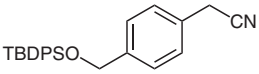
lar to the reported reaction mechanism, resulting in the acceleration of cyanation rather than the nucleophillic displacement with an additive, for example acetoxylation, etherification, and hydroxylation.[11,12,16]

To verify the generality of our methodology, a variety of substrates were examined.[22–25] As shown in Table 2, each substrate reacted with TMSCN and K_2CO_3 in MeCN to give the corresponding nitrile in good to excellent yield.[26] The benzylic bromides with the electron-withdrawing group, **3b** and **3d**, showed higher reactivity than the bromide with the electron-donating group **3a** (entries 1, 2, and 4). The reaction of the phenylethyl bromide (**3e**), which is prone to β-elimination to give styrene, also afforded **4e** in 97% yield (entry 5). The secondary bromide **3f** provided **4f** in 80% yield with a byproduct, which could not be isolated (entry 6). The cyanation of **3g**, N-protected by a *p*-toluenesulfonyl group, gave **4g** in 84% yield without desulfonylation (entry 7). Compound **3i** with a phenol protected by a *tert*-butyldiphenylsilyl (TBDPS) group was reacted at room temperature for 24 hours to give **4h** in 92% yield, whereas **3h** gave **4h** in 81% yield with a desilylated compound (entries 8 vs. 9). On the other hand, **3j** with an alcohol protected by a TBDPS group was converted into **4i** in 99% yield (entry 10).

In conclusion, we have demonstrated that the reaction of alkyl halides and sulfonates with TMSCN using fluoride-

Table 2 Cyanation of Various Alkyl Halides with TMSCN



Entry		Substrate	Temp (°C)	Time (h)		Product	Yield (%)[a]
1	**3a**	4-$MeC_6H_4CH_2Br$	80	18	**4a**	4-$MeC_6H_4CH_2CN$	98 (86)
2	**3b**	3-$MeO_2CC_6H_4CH_2Br$	60	15	**4b**	3-$MeO_2CC_6H_4CH_2CN$	(98)
3	**3c**	2-(bromomethyl)naphthalene	60	8	**4c**	2-naphthylacetonitrile	94 (78)
4	**3d**	4-$ClC_6H_4CH_2Br$	60	10	**4d**	4-$ClC_6H_4CH_2CN$	97 (78)
5	**3e**	$PhCH_2CH_2Br$	80	28	**4e**	$PhCH_2CH_2CN$	97 (78)
6	**3f**	PhCHBrMe	80	48	**4f**	PhCH(CN)Me	80[b] (79)
7	**3g**		60	9	**4g**		84 (75)
8	**3h**		25	72	**4h**		81 (72)
9	**3i**		25	24	**4h**		92
10	**3j**		80	3	**4i**		99 (95)

[a] The yields were determined by HPLC analysis, and values in parentheses show the isolated yields after chromatography.
[b] Determined by GC analysis.

free inorganic salts in MeCN provided the corresponding nitrile compounds in good to excellent yield. The noteworthy feature of this methodology is that alkyl halides with protective groups, such as *N*-sulfonyl and *O*-silyl groups, smoothly underwent cyanation without deprotection. Further advantage over the reported method is that the reaction can be carried out using readily available, inexpensive, and environmentally friendly reagents. This new methodology is expected to be useful not only for the synthesis of complicated natural products but also for large-scale preparation.

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(26) **General Procedure**
To a mixture of alkyl halide or methanesulfonate (5.40 mmol) and K_2CO_3 (6.49 mmol) in MeCN (10 mL) was added TMSCN (6.49 mmol). The reaction mixture was stirred at the required temperature until the reaction was completed. At the end of the reaction, 1 N NaOH (25 mL) was added to the reaction mixture, which was extracted with toluene (30 mL). The organic layer was washed with 1 N NaOH (25 mL) and then brine (25 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to give pure nitrile compounds.

Biphenyl-4-ylacetonitrile (2)[27]
White solid; mp 94–96 °C. IR (ATR): ν = 3033, 2360, 2249, 1485, 1406, 1005, 907, 812, 750, 684, 461 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, TMS): δ = 3.78 (2 H, s), 7.33–7.47 (5 H, m), 7.56–7.61 (4 H, m). MS: *m/z* = 193 [M^+]. Anal. Calcd for $C_{14}H_{11}N$: C, 87.01; H, 5.74; N, 7.25. Found: C, 86.80; H, 5.70; N, 7.05.

{1-[(4-Methylphenyl)sulfonyl]-1*H*-indole-3-yl}acetonitrile (4g)
White solid; mp 161–163 °C. IR (KBr): ν = 3117, 2929, 2258, 1595, 1450, 1364, 1175, 1135, 1095, 979, 814, 670, 532 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, TMS): δ = 2.34 (3 H, s), 3.74 (2 H, s), 7.23 (2 H, d, *J* = 8.2 Hz), 7.25–7.31 (1 H, m), 7.35–7.40 (1 H, m), 7.49 (1 H, d, *J* = 7.8 Hz), 7.60 (1 H, s), 7.77 (2 H, d, *J* = 8.4 Hz), 8.01 (1 H, d, *J* = 8.3 Hz). MS: *m/z* = 310 [M^+]. Anal. Calcd for $C_{17}H_{14}N_2O_2S$: C, 65.79; H, 4.55; N, 9.03; S, 10.33. Found: C, 65.69; H, 4.58; N, 8.94; S, 10.37.

(4-{[*tert*-Butyl(diphenyl)silyl]oxy}phenyl)acetonitrile (4h)
Colorless oil. IR (neat): ν = 3071, 2930, 2891, 2857, 2250, 1736, 1609, 1509, 1427, 1256, 1113, 914, 821, 699, 611 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, TMS): δ = 1.10 (9 H, s), 3.57 (2 H, s), 6.74 (2 H, d, *J* = 8.6 Hz), 7.02 (2 H, d, *J* = 8.7 Hz), 7.34–7.43 (6 H, m), 7.68–7.71 (4 H, m). MS: *m/z* = 371 [M^+]. Anal. Calcd for $C_{24}H_{25}NOSi$: C, 77.58; H, 6.78; N, 3.77. Found: C, 77.70; H, 6.94; N, 3.72.

[4-({[*tert*-Butyl(diphenyl)silyl]oxy}methyl)phenyl]acetonitrile (4i)
White solid; mp 88–90 °C. IR (ATR): ν = 2930, 2857, 2245, 1588, 1514, 1427, 1112, 1083, 817, 704, 504, 490, 468 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, TMS): δ = 1.10 (9 H, s), 3.73 (2 H, s), 4.76 (2 H, s), 7.11–7.46 (10 H, m), 7.67–7.70 (4 H, m). MS: *m/z* = 386 [M + H^+]. Anal. Calcd for $C_{25}H_{27}NOSi$: C, 77.88; H, 7.06; N, 3.63. Found: C, 77.74; H, 7.04; N, 3.70.

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