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A Convenient One-Pot Cyanosilylation of Aldehydes and Ketones Using Potassium or Sodium Cyanide Impregnated on Amberlite XAD Resin and Trimethylsilyl Chloride

Kazuaki SUKATA
Nihon Tokushu Kagaku Kogyo Co., Ltd., 1 Takijiri-aza-hashimoto, Izumi-cho, Iwaki, Fukushima 970-04

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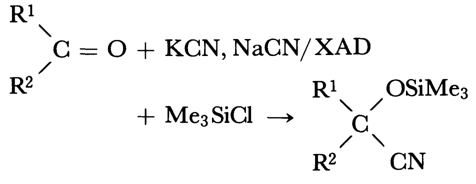
Synopsis. In the cyanosilylation of benzaldehyde, the combination of potassium or sodium cyanide impregnated on Amberlitė XAD resin and trimethylsilyl chloride has been found to be a good one-pot cyanosilylation agent. Although acetonitrile is the best solvent, substantial yields of the product is obtained even in a nonpolar solvent or without any solvent. In the reaction with other aldehydes or ketones, this method gives the corresponding silylated cyanohydrins in extremely high yields.

Cyanosilylation of aldehydes and ketones using trimethylsilyl cyanide (Me_3SiCN) gives the corresponding α-trimethylsilyloxy nitriles which are versatile and important as acyl anion equivalents[1] and intermediates.[2] Although this reaction gives good yields of the products,[3] independently prepared Me_3SiCN, which is toxic and moisture sensitive, has been used. Furthermore, in general, the synthesis of Me_3SiCN is tedious and the isolated yields are not very good.[2,4] To overcome this disadvantage, a one-pot cyanosilylation using trimethylsilyl chloride (Me_3SiCl) and KCN with or without catalysts has been reported.[5] This method, however, requires very long reaction times and high reaction temperatures in acetonitrile or *N,N*-dimethylformamide, even in the presence of 18-crown-6 or ZnI_2 as a catalyst.

On the other hand, in a previous paper,[6] it has been shown that the reaction of alkylsilyl chloride with KCN or NaCN impregnated on Amberlite XAD resins (KCN/XAD, NaCN/XAD) produces good yields of alkylsilyl cyanide. This paper describes a mild and convenient method for the one-pot cyanosilylation of aldehydes and ketones using KCN/XAD or NaCN/XAD and Me_3SiCl.



$$\begin{matrix} R^1 \\ & \diagdown \\ & & C=O + KCN, NaCN/XAD \\ & \diagup \\ R^2 \end{matrix} \quad + Me_3SiCl \longrightarrow \begin{matrix} R^1 & & OSiMe_3 \\ & C & \\ R^2 & & CN \end{matrix}$$

Results and Discussion

In a preliminary experiment, the one-pot cyanosilylation was performed with benzaldehyde, Me_3SiCl, and KCN/XAD-4 in various solvents. Table 1 shows the results. In acetonitrile, the reaction was very fast and the complete conversion of the aldehyde occured at 60 °C in 4 h. Interestingly, in nonpolar solvents or without any solvent, 50—63% of the product was obtained at 60 °C in 8 h and the reaction was substantially faster than those in more polar solvents such as 1,2-dimethoxyethane (DME) and tetrahydrofuran (THF). The order of reaction rates was acetonitrile ≫ hexane ≥ benzene ≈ none > dichloromethane > DME ≈ THF. This order is in contrast to that in the reaction of Me_3SiCl with KCN/XAD-4, that is, acetonitrile ≫ DME ≈ THF ≈ none > benzene ≈ hexane.[6]

Table 1. Cyanosilylation of Benzaldehyde with KCN/XAD-4 and Me_3SiCl in Various Solvents[a)]

Solvent	Time/h	Temp/°C	Yield/%[b)]
Acetonitrile	4	60	≈98
	4	60	≈98[c)]
DME	8	60	27
THF	8	60	21
CH_2Cl_2	8	40	20
	24	40	30
Benzene	8	60	55
	8	40	36
	24	40	43
Hexane	8	60	63
None	8	60	50

a) Unless otherwise noted, reactions were carried out with benzaldehyde (5 mmol), KCN (15 mmol)/XAD-4 (3.75 g), Me_3SiCl (7.5 mmol), and a solvent (20 ml). b) Determined by GLC. c) Sodium cyanide (15 mmol) was used.

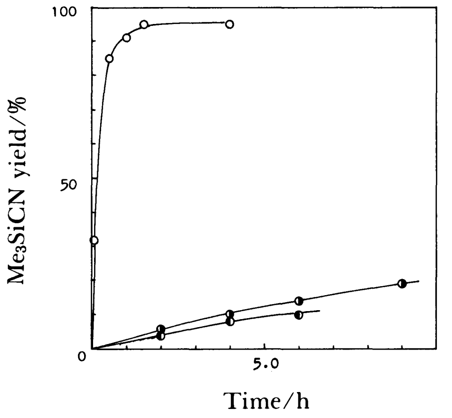
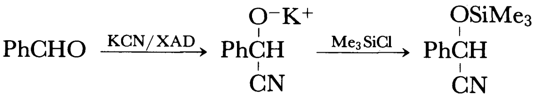


Fig. 1. Plots of Me_3SiCN yield vs time. Reactions were carried out with KCN (15 mmol)/XAD-4 (3.75 g), Me_3SiCl (7.5 mmol), and a solvent (20 ml) at 60 °C. ○: In acetonitrile; ◑: in DME; ◐: in benzene.

Figure 1 shows the relationship between the yield of Me_3SiCN and reaction time in the reaction of Me_3SiCl with KCN/XAD-4. The yields of Me_3SiCN in acetonitrile and other solvents were ca. 85% (0.5 h) and 1—2% (0.5 h), respectively. This finding indicates that the cyanosilylation of benzaldehyde in acetonitrile is performed predominantly by the process of Eq. 1, whereas those in the other solvents are performed mainly by the process of Eq. 2.

$$\mathrm{Me_3SiCl} \xrightarrow{\mathrm{KCN/XAD}} \mathrm{Me_3SiCN} \xrightarrow{\mathrm{PhCHO}} \mathrm{Ph}\overset{\mathrm{OSiMe_3}}{\underset{\mathrm{CN}}{\mathrm{CH}}} \quad (1)$$



$$\mathrm{PhCHO} \xrightarrow{\mathrm{KCN/XAD}} \mathrm{Ph}\overset{\mathrm{O^-K^+}}{\underset{\mathrm{CN}}{\mathrm{CH}}} \xrightarrow{\mathrm{Me_3SiCl}} \mathrm{Ph}\overset{\mathrm{OSiMe_3}}{\underset{\mathrm{CN}}{\mathrm{CH}}} \quad (2)$$

This also indicates that the cyanosilylation in acetonitrile occurs in the bulk organic phase, while those in the other solvents occur on the surface of the XAD resin. In the reaction using other solvents with the exception of acetonitrile, mass transfer seems to be important similar to the reaction of acyl chloride with KCN/XAD.[7]

Figure 2 shows the relationship between the conversion of benzaldehyde and the molar ratio Me_3SiCl/KCN. The reactions were carried out in acetonitrile. In both cases of the molar ratio KCN/benzaldehyde=3 and Me_3SiCl/benzaldehyde=1.5, the conversion of benzaldehyde rapidly slowed down over the molar ratio Me_3SiCl/KCN=0.5. Although at present I have no explanation for this fact, it is clear that the molar ratio Me_3SiCl/KCN=0.5 is the optimum value.

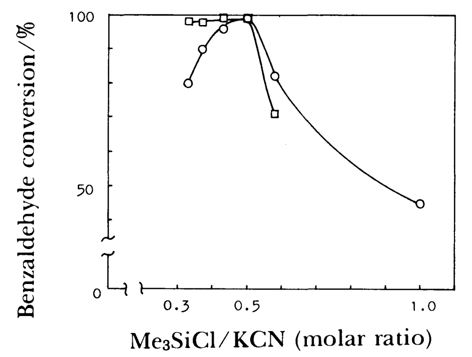
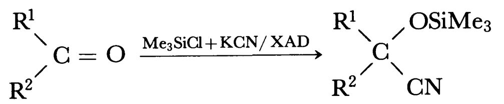


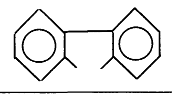
Fig. 2. Plots of benzaldehyde conversion vs. Me_3SiCl/KCN molar ratio. Reactions were carried out in acetonitrile. □: Me_3SiCl/benzaldehyde=1.5, ○: KCN/benzaldehyde=3.0.

The method using Me_3SiCl and KCN/XAD was applied to the cyanosilylation of other aldehydes and ketones. Table 2 shows the results. In both cases of aliphatic and aromatic carbonyl compounds, the reaction was smooth and gave the corresponding silylated cyanohydrins in extremely high yields in the absence of any catalyst such as crown ether or Lewis acids. The impregnated KCN, which has strong nucleophilicity,[8] catalyzed the reaction. In the reaction of enolizable carbonyl compounds, it is predicted that silyl enol ethers are formed as by-products.[5] The present method, however, gave substantially no silyl enol ethers. In the case of crotonaldehyde, only 1,2-adduct was obtained as expected.[3] The reaction of fluorenone required higher reaction temperature than those of the other carbonyl compounds probably because of its

Table 2. Cyanosilylation of Aldehydes and Ketones Using KCN/XAD and Me_3SiCl[a)]



$$\mathrm{R^1R^2C{=}O} \xrightarrow{\mathrm{Me_3SiCl+KCN/XAD}} \mathrm{R^1R^2C(OSiMe_3)CN}$$

R^1	R^2	Resin[c)]	Time h	Yield[b)] %	Bp(θ_b/°C)/mmHg (Mp(θ_m/°C)) Found	Lit
CH_3CH_2	H	A	4	81 (97)	87—9/29	168—70/760[3c)]
		B	4	82 (97)		
$CH_3CH{=}CH$	H	A	4	85 (97)	80—1/12	80.5/12[3b)]
		B	4	80 (95)		
C_6H_5	H	A	4	93 (98)	89—90/2	64/0.5[3b)]
		B	8	95 (98)		
4-$CH_3C_6H_4$	H	A	6	96 (99)	84—5/0.35	87/0.45[5)]
		B	8	(92)		
4-$CH_3OC_6H_4$	H	A	6	95 (97)	103—4/0.35	95/0.13[5)]
		B	8	(92)		
2-ClC_6H_4	H	A	6	91 (96)	85—6/0.4	92—3/0.45[5)]
		B	8	(84)		
CH_3CH_2	CH_3	A	6	83 (98)	86—8/30	165—6/760[3c)]
-$(CH_2)_5$-		A	6	92 (99)	96—7/14	92.5/12[3b)]
-$(CH_2)_4$-		A	6	93 (99)	85—6/13.5	197—8/760[3c)]
C_6H_5	CH_3	A	8	97 (≈100)	84—5/3	237—8/760[3c)]
		B	8	90 (94)		
C_6H_5	C_6H_5	A	6	97 (99)	105—6/0.3	104/0.5[3b)]
		B	8	(92)		
		A	25	93 (98)	(94.5—95.5)	(95—6)[3b)]
		A	8[d)]	90 (96)		

a) Unless otherwise noted, reactions were carried out with carbonyl compound (10 mmol), KCN (30 mmol)/XAD (7.5 g), Me_3SiCl (15 mmol) in acetonitrile (40 ml) at 60 °C. b) Isolated yields. Values in parentheses are the yields determined by GLC. c) A: XAD-4, B: XAD-2. d) The reaction was carried out at 80 °C.

steric hindrance. In general, XAD-4 more rapidly produced products than XAD-2, which was probably due to the difference in the surface area.

In conclusion, the combination of Me_3SiCl and KCN or NaCN/XAD was found to be a good reagent for the cyanosilylation of aldehydes and ketones. This reagent can be used for other cyanosilylations in substitution for Me_3SiCN.

Experimental

Materials. Actonitrile, benzene, and hexane were dried with molecular sieves 4A. Tetrahydrofuran was passed through an alumina column, distilled, and dried with molecular sieves 4A. 1,2-Dimethoxyethane was refluxed with Na and distilled. Dichloromethane was washed with aqueous Na_2CO_3, distilled, and dried with molecular sieves 3A. Trimethylsilyl chloride (Toray Silicone Co.) was used as obtained. Carbonyl compounds (Wako Pure Chemicals Ind. Co.) were used without further purification. Amberlite XAD resins (Organo Co.) were washed with methanol, methanol-benzene, and methanol, and then dried under vacuum. KCN/XAD and NaCN/XAD were prepared by the method previously reported:[8] To a solution of KCN or NaCN (15 mmol) in 4 ml of aqueous methanol (50 vol%) was added XAD resin (3.75 g) and then the solvent was removed under reduced pressure (≈15 mmHg, 1 mmHg=133.322Pa) at 60 °C with vigorous shaking. The half-dried KCN or NaCN/XAD was further dried under vacuum (0.1 mmHg) for 4 h at 90 °C.

Typical Procedure for the Cyanosilylation with KCN or NaCN/XAD and Me_3SiCl. In all reactions, Me_3SiCl and carbonyl compounds were added directly to the flask in which the KCN or NaCN/XAD had been made and dried. All the products were known compounds and satisfactory IR spectra for these compounds, which had no CN absorption band, were obtained.[3c]

Cyanosilylation of Benzaldehyde Using Me_3SiCl and KCN/XAD-4 in Various Solvents. After a mixture of KCN (0.98 g, 15 mmol)/XAD-4 (3.75 g), Me_3SiCl (0.81 g, 7.5 mmol), and a solvent (20 ml) was stirred for several minutes, benzaldehyde (0.53 g, 5.0 mmol) was added to the mixture. The resulting mixture was stirred at 60 °C for the indicated time. The yield of the product was determined by GLC (Silicone OV-17, 3 m×3 mm, 160 °C) using tetradecane as an internal standard.

Crotonaldehyde Cyanohydrin Trimethylsilyl Ether: A mixture of KCN (1.95 g, 30 mmol)/XAD-4 (7.5 g), Me_3SiCl (1.62 g, 15 mmol), and acetonitrile (40 ml) was stirred for several minutes at room temperature, followed by the addition of crotonaldehyde (0.70 g, 10 mmol). The mixture was stirred at 60 °C for 4 h. GLC (Silicone OV-17, 3 m×3 mm, 140 °C) showed almost complete conversion of the aldehyde. The solid material was filtered and washed well with benzene (100 ml). After removal of the solvent, the residue was distilled under reduced pressure, giving 1.44 g (85%) of the product, bp 80—81 °C/12 mmHg (lit,[3b] 80.5 °C/12 mmHg). IR (neat): 1670 (C=C), 1253, 1100, 1056, 960, 870, 844, 752 cm^{-1} no CN.

4-Methoxybenzaldehyde Cyanohydrin Trimethylsilyl Ether: A mixture of KCN (1.95 g, 30 mmol)/XAD-4 (7.5 g), Me_3SiCl (1.62 g, 15 mmol), and acetonitrile (40 ml) was stirred for several minutes at room temperature followed by the addition of 4-methoxybenzaldehyde (1.36 g, 10 mmol). The mixture was stirred at 60 °C for 6 h. After the same treatment as crotonaldehyde, the solvent was removed and the residue was distilled under reduced pressure, giving 2.23 g (95%) of the product, bp 103—104 °C/0.35 mmHg (lit,[5] 95 °C/0.13 mmHg). IR (neat): 1250, 1088, 872, 844, 760 cm^{-1} no CN.

Cyclohexanone Cyanohydrin Trimethylsilyl Ether: The reaction of cyclohexanone (0.98 g, 10 mmol) similar to that of 4-methoxybenzaldehyde was performed. The same treatment as 4-methoxybenzaldehyde gave 1.81 g (92%) of the product, bp 96—97 °C/14 mmHg (lit,[3b] 92.5 °C/12 mmHg). IR (neat): 1250, 1122, 878, 844, 754 cm^{-1} no CN and no C=C.

Acetophenone Cyanohydrin Trimethylsilyl Ether: The reaction of acetophenone (1.20 g, 10 mmol) similar to that of 4-methoxybenzaldehyde was performed. The same treatment as 4-methoxybenzaldehyde gave 2.12 g (97%) of the product, bp 84—85 °C/3mmHg (lit,[3c] 237—238 °C/760 mmHg). IR (neat): 1252, 1116, 845, 758 cm^{-1} no CN and no C=C.

Fluorenone Cyanohydrin Trimethylsilyl Ether: The reaction of fluorenone (1.80 g, 10 mmol) similar to that of 4-methoxybenzaldehyde was performed at 80 °C for 8 h. The solid material was filtered and washed well with benzene (100 ml). Removal of the solvent gave 2.80 g of the crude product as the residual solid, mp 88—94 °C, recrystallization of which gave 2.51 g (90%) of the pure product, mp 94.5—95.5 °C (lit,[3b] 95—96 °C). IR (Nujol): 1250, 1114, 1096, 868, 844, 764, 752, 726 cm^{-1} no CN.

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