Cyanosilylation of Aldehydes and Ketones. A Convenient Route to Cyanohydrin Derivatives

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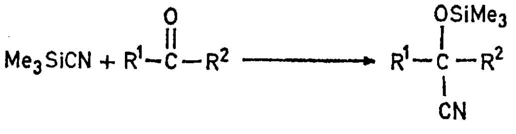
Summary A wide variety of aldehydes and ketones reacts with trimethylsilyl cyanide under both thermal and catalytic conditions to give α-silyloxy nitriles which may be useful intermediates and protective groups in organic synthesis.

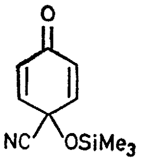
We have observed that trimethylsilyl cyanide (Me$_3$SiCN)[1] in an apparently uncatalysed process adds readily to aldehydes affording the cyanosilylated adducts (**1**; R^1 = alkyl, R^2 = H) in good yields. The only contaminant in the addition process is the silyl enol ether which does not appear to be derived from (**1**). The reaction may be simply carried out by combining equimolar amounts of aldehyde and Me$_3$SiCN and heating for several hours in the absence of added solvent. Ketones, on the other hand, react slowly with Me$_3$SiCN, *e.g.* cyclohexanone requires heating at 115° for 24 h for complete reaction.

We have discovered that minute amounts of zinc iodide dramatically enhance the rate of Me$_3$SiCN carbonyl addition while simultaneously suppressing the formation of silyl enol ether. Using this method of catalysis, a wide variety of aldehydes and ketones may be cyanosilylated rapidly and in excellent yields at room temperature (Table).[2]† With both $\alpha\beta$-unsaturated ketones and aldehydes only 1,2-addition is observed. In no instance, have we ever detected any 1,4-adducts employing a variety of conditions and catalysts.‡ The silyloxy nitrile adducts (**2**) and (**3**) resulting from the addition of either 1 or 2 equiv. of Me$_3$SiCN to *p*-benzoquinone,§ illustrate the kinetic preference for 1,2-addition.

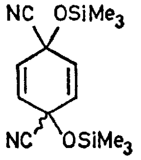


$$\mathrm{Me_3SiCN} + \mathrm{R^1{-}\overset{\displaystyle O}{\overset{\|}{C}}{-}R^2} \longrightarrow \mathrm{R^1{-}\underset{\displaystyle CN}{\underset{|}{\overset{\displaystyle OSiMe_3}{\overset{|}{C}}}}{-}R^2}$$

(1)



(2)



(3)

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† Recently Parham and Roosevelt[2] reported a more involved synthesis of the cyclohexanone and indan-1-one adduct in yields of 35 and 42%, respectively. Our direct route gives the adducts in yields of 94 and 87%.

‡ Aluminium chloride, tetra-n-butylammonium cyanide, and alkali-metal cyanide–crown ether complexes are effective catalysts for cyanosilylation of aldehydes and ketones.

§ The bisadducts (**4**) were prepared using 2 equiv. Me$_3$SiCN–1 equiv. *p*-benzoquinone in the presence of KCN,18-crown-6 catalyst.

TABLE[a]

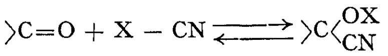
R^1	R^2	Uncatalysed[b] yield (%)	ZnI_2 catalysed[c] yield (%)
Paraformaldehyde		—	67
Pr^i	H	53	96
n-Pentyl	H	60	94
Ph	H	87	—
$CH_2{=}CH$	H	67	—
MeCH=CH	H	78	98
PhCH=CH	H	99	—
Furyl	H	88	99
MeCH=CMe	Me	—	92
Cyclohexanone		89	94
Indan-1-one ..		25	87
Ph	Ph	—	98
Et	Et	—	85
p-Benzoquinone ..		95[d]	0

[a] Consistent spectral data and combustion analyses were obtained on all compounds reported. All adducts, other than that from *p*-benzoquinone (m.p. 67°), are liquids isolated by distillation at reduced pressure. [b] Equimolar amounts of carbonyl and Me_3SiCN are heated in the absence of solvent. [c] 1 equiv. (50 mmol) of carbonyl compound was added to 1 equiv. (50 mmol) of Me_3SiCN and 1 mg ZnI_2. Hindered ketones may require gentle heating. [d] Mono-adduct obtained when one equiv. of Me_3SiCN is used. ZnI_2 does not catalyse this reaction.

As a consequence of the apparent rapid equilibration of silyl cyanide and isocyanide isomers [equation (1)],[4] the chemistry of Me_3SiCN may in part parallel that of other isocyanides.[5] In fact, the existence of both silicon tautomers suggests many uses for Me_3SiCN. One application of the cyanosilylation reaction is as a means of protecting carbonyl functions. The silyloxy nitriles can be formed in high yield; they are stable in aprotic media; and the carbonyl derivative may be readily regenerated in dilute aqueous acid or base. In wet methanol, adduct (**2**) has a half-life of 30 min at room temperature. We have verified that the silyloxy nitrile adducts can be reduced with lithium aluminium hydride in good yield to β-amino-alcohols.[2]

$$Me_3Si - C{\equiv}N \rightleftharpoons Me_3Si - \overset{+}{N}{\equiv}C{:}^- \qquad (1)$$

By replacing a proton for silicon in the cyanohydrin equilibrium in equation (2) the reaction can be made more exothermic by *ca.* 20 kcal mol^{-1} ($\Delta H_{Si} - \Delta H_H$). It is therefore not surprising that direct cyanosilylation affords cyanohydrin derivatives not accessible from the parent cyanohydrins.¶



$$\rangle C{=}O + X - CN \rightleftharpoons \rangle C\langle^{OX}_{CN} \qquad (2)$$

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¶ Neither benzophenone nor indan-1-one form isolable cyanohydrins, *cf.* D. T. Mowry, *Chem. Rev.*, 1948, **42**, 189.

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[2] W. E. Parham and C. S. Roosevelt, *Tetrahedron Letters*, 1971, 923.

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[4] D. Seyferth and N. Kahlen, *J. Amer. Chem. Soc.*, 1960, **82**, 1080.