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A Facile Synthesis of Cyanohydrin Trimethylsilyl Ethers by the Addition Reaction of Trimethylsilyl Cyanide with Aldehydes under Basic Condition

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In the presence of a catalytic amount of Lewis base such as amine, phosphine, arsine or antimony, trimethylsilyl cyanide (TMS-CN) smoothly reacts with aldehydes to afford the corresponding cyanohydrin trimethylsilyl ethers in excellent yields.

Cyanohydrin trimethylsilyl ethers are versatile intermediates in organic synthesis,[1] and one of the most convenient preparative methods of these compounds is addition reaction of trimethylsilyl cyanide (TMS-CN) with aldehydes under the influence of Lewis acids such as zinc iodide (ZnI_2), aluminum chloride ($AlCl_3$), or under almost neutral condition using anionic catalysis.[2] Herein we wish to report an alternative method; the addition reaction of TMS-CN with aldehydes catalyzed by Lewis base such as an amine, a phosphine, an arsine or an antimony. The reaction is smoothly carried out in the presence of a catalytic amount of base to afford the corresponding cyanohydrin trimethylsilyl ether in an excellent yield under basic condition.

Recently, some unique characters of hypervalent silicates have been reported,[3] for examples, Sakurai et al. reported that pentacoordinate allylsilicates reacted with aromatic aldehydes to afford the corresponding homoallyl alcohols in high yields.[3a] It is also pointed out there that hypervalent allylsilicates are more reactive than tetracoordinate silicon analogues due to the electron donation from hypervalent silicons to the allyl π systems (σ-π conjugation). Based on these results, a new possibility was considered that an amine may coordinate to TMS-CN to form the intermediate pentacoordinate silicate which bears a potential for reacting with aldehydes to give the corresponding cyanohydrin trimethylsilyl ethers. Then, the model reaction of 3-phenylpropionaldehyde with TMS-CN was tried in the presence of a catalytic amount of triethylamine (10 mol%). The reaction proceeded smoothly even at -78 °C to give the corresponding cyanohydrin trimethylsilyl ether in an excellent yield, while no reaction occurred in the absence of triethylamine. Effect of amines in this reaction was summarized in Table 1.

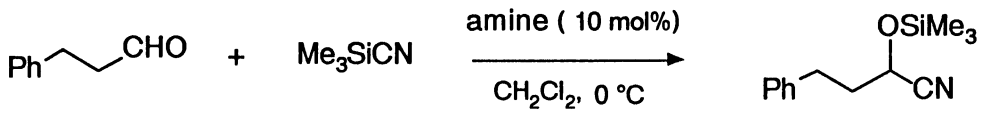
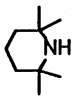


Table 1. Effect of Amines

Entry	Amine	Yield/%	Entry	Amine	Yield/%
1	Et_3N	94	6		91
2	$^{i}Pr_2NEt$	99	7	pyrrolidine	0
3		94	8	pyridine	63
4	TMEDA [a)]	86	9	aniline	0
5	$^{i}Pr_2NH$	93	10	$PhCH_2NH_2$	7

a) N, N, N', N' - Tetramethylethylenediamine.

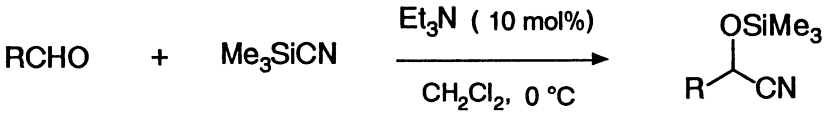
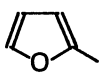


Table 2. Synthesis of Cyanohydrin Trimethylsilyl Ethers

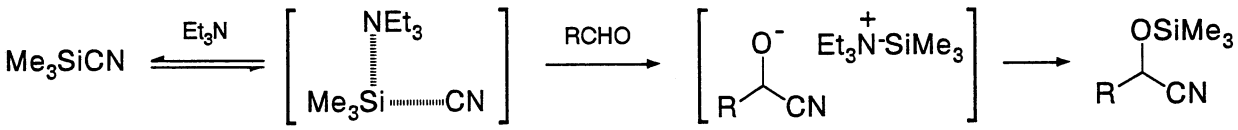
Entry	R	Yield/%	Entry	R	Yield/%
1	$Ph(CH_2)_2$	94	6	^{t}Bu	90
2	$^{n}C_8H_{17}$	91	7	Ph	96
3	$^{n}C_{11}H_{23}$	94	8	p-Cl Ph	96
4	c-C_6H_{11}	quant.	9		95
5	PhCH=CH	98			

Tertiary and hindered secondary amines promoted this reaction effectively and the cyanohydrin trimethylsilyl ether was obtained in excellent yield. On the other hand, the desired cyanohydrin trimethylsilyl ether was obtained in 0-7% yield when common secondary and primary amines such as pyrrolidine, benzylamine and aniline were employed as catalysts.

Various cyanohydrin trimethylsilyl ethers are synthesized by the present recipe (Table 2). Cyclohexanone and p-quinone also react with TMS-CN under the same reaction conditions to give the corresponding cyanohydrin trimethylsilyl ethers in good yields (74% in each case).[4)]

A typical experimental procedure is described for the reaction of TMS-CN with 3-phenylpropionaldehyde; to a dichloromethane solution[5)] (2 ml) of TMS-CN (0.5 mmol) and 3-phenylpropionaldehyde (0.5 mmol) was added a catalytic amount (5-10 mol%) of triethylamine at 0 °C. The mixture was stirred for 2 h at the same temperature and the solvent was removed under reduced pressure. The residue was pure enough for usual use (94% yield, determined by ^{1}H NMR).

At present, hypervalent silicate **1**, formed from triethylamine and TMS-CN, is assumed to be an active cyanation intermediate. This silicate **1** readily reacts with an aldehyde to produce **2** since nucleophilicity of cyano group of **1** is enhanced by the electron donation from the pentavalent silicon, followed by immediate silylation to give the corresponding cyanohydrin trimethylsilyl ether along with triethylamine.



1 **2**

Further, as shown in Table 3, tributylphosphine (^{n}Bu$_3$P), triphenylarsine (Ph$_3$As) and triphenylantimony (Ph$_3$Sb) instead of tertiary amine are also effective in this reaction.

It should be noted that the present method makes it possible to prepare cyanohydrin trimethylsilyl ether by a quite simple procedure under non-acidic condition. The application of this methodology to the enantioselective addition reaction of TMS-CN with aldehydes is now in progress.

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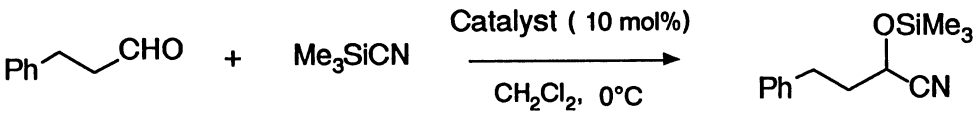

Table 3. Effect of Catalysts Other than Amines

Catalyst	Yield/%
$^{n}Bu_3P$	96
Ph_3P	27
Ph_3As	91
Ph_3Sb	88

References

1) W. P. Weber, "Silicon Reagents for Organic Synthesis," Springer-Verlag, Berlin (1983); E. W. Colvin, "Silicon in Organic Synthesis," Butterworths, London (1981), and references cited therein.

2) D. A. Evans and L. K. Truesdale, *Tetrahedron Lett.*, **1973**, 4929; D. A. Evans, L. K. Truesdale, and G. L. Carroll, *J. Chem. Soc., Chem. Commun.*, **1973**, 55.

3) a) M. Kira, K. Sato, and H. Sakurai, *J. Am. Chem. Soc.*, **110**, 4599 (1988); b) G. Cerveau, C. Chuit, R. J. P. Corriu, and C. Reye, *J. Organomet. Chem.*, **328**, C17 (1987); c) A. Hosomi, S. Kohra, and Y. Tominaga, *J. Chem. Soc., Chem. Commun.*, **1987**, 1517; d) G. Majetich, A. Casares, P. Chapman, and M. Behnke, *J. Org. Chem.*, **51**, 1745 (1986).

4) It was reported that p-quinone reacted with TMS-CN in the presence of a catalytic amount of triphenylphophine in acetonitrile at 0 °C to produce the corresponding cyanohydrin trimethylsilyl ether in an essentially quantative yield. D. A. Evans and R. Y. Wong, *J. Org. Chem.*, **42**, 350 (1977). In the present case, as shown in Table 3, triphenylphosphine was not so efficient catalyst in the reaction of TMS-CN with 3-phenylpropionaldehyde.

5) Other solvents such as diethyl ether, THF, benzene, toluene, acetonitrile, pentane and methanol are also available.

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