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Organocatalytic activation of TMSCN by basic ammonium salts for efficient cyanation of aldehydes and imines

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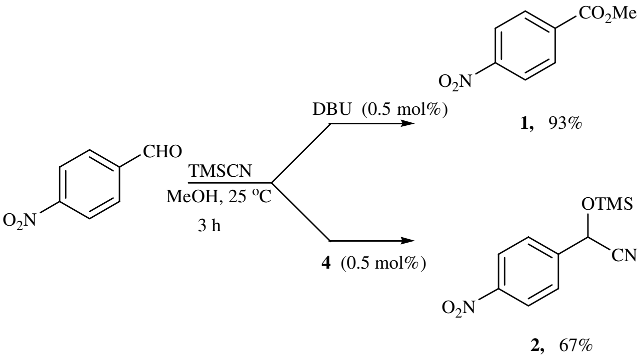
Abstract—Basic ammonium salts act as highly effective catalysts for the cyanosilylation of aldehydes and in Strecker-type aminonitrile synthesis using TMSCN as cyanide source at 25 °C under extremely mild conditions, affording very good to excellent yields of silylated cyanohydrins and α-aminonitriles.

Hydrocyanation and cyanosilylation of aldehydes are important C–C bond-forming reactions[1] in organic synthesis, as they provide versatile intermediates such as cyanohydrins and cyanohydrin silyl ethers, respectively. In particular, cyanohydrin silyl ethers **2** are industrially valuable and important intermediates for the synthesis of α-hydroxy acids and esters, acyloins, vicinal diols, β-amino alcohols and other biologically active compounds.[2] They are generally prepared by the addition of trimethylsilyl cyanide (TMSCN), a safe and easily handled reagent compared to HCN or KCN,[3] to carbonyl compounds in the presence of Lewis acids,[4] Lewis bases,[5] metal alkoxides,[6] bifunctional catalysts[7] and inorganic salts.[8] However, many of these methods suffer from several disadvantages such as prolonged reaction times, use of heavy metal catalysts and poor yields of the corresponding cyanotrimethylsilyl ethers. Our particular interest in this transformation stems from the fact that metal-free organocatalysis for the cyanation of aldehydes and imines with TMSCN should lead to efficient syntheses of cyanotrimethyl silyl ethers without any metal contamination. In this regard, we screened several Lewis bases such as DBU (1,8-diazabicyclo[5.4.0]undec-7-ene), DABCO (1,4-diazabicyclo[2.2.2]octane), or (−)-sparteine, in catalytic amounts, for the cyanation of 4-nitro- and 4-cyanobenzaldehydes and unexpectedly observed the formation of new products, that is, their respective methyl esters **1** instead of the cyanohydrins, when the reaction was carried out in methanol (Scheme 1). This observation led us to modify the Lewis basicity in DBU by quaternizing one of the nitrogen atoms with benzyl bromide. Thus, quaternary basic ammonium salt **4** was prepared and, when employed for this transformation, gave exclusively cyanohydrin silyl ether **2**. Similarly, ammonium salts **3** and **5** were prepared from the corresponding diamines by quaternizing with benzyl bromide and methyl iodide, respectively, in toluene as solvent. Organocatalysts **3** (mp: 259 °C), **4** (mp: 169 °C) and **5** (mp: 201 °C) were characterized by ^{1}H, ^{13}C NMR and IR spectroscopy and by single crystal XRD and elemental analysis. Figure 2 shows the ORTEP diagram of catalyst **4** where quaternization with benzyl bromide occurred at the imine nitrogen atom.[9]



Scheme 1. Base catalyzed reaction of 4-nitrobenzaldehyde with TMSCN.

Keywords: Aldehydes; Aminonitriles; Cyanosilylation; Cyanohydrin; Multicomponent reactions; TMSCN.

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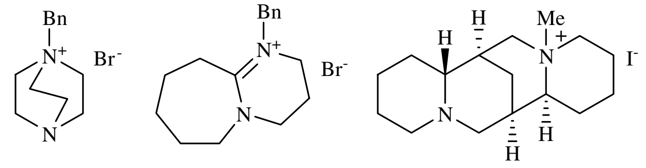
In this Letter, we report a new high-yielding procedure for the synthesis of trimethylsilyl cyanides **2** and α-aminonitriles **6** catalyzed by monoquaternized bases **3**, **4** and **5** (Fig. 1) under ambient conditions. A systematic study on the hydrocyanation of 4-nitrobenzaldehyde as a test substrate in various solvents was carried out using catalytic amount of either diamines or their ammonium salts **3**, **4** and **5** and the results are summarized in Table 1. Ammonium salt **4** was found to be the best catalyst for the hydrocyanation of 4-nitrobenzaldehyde with TMSCN as cyanide source. Encouraged by this result, a wide range of aldehydes were subjected to cyanosilylation using a catalytic quantity of **4** (0.5 mol %) under optimized reaction conditions (1 equiv of TMSCN, 25 °C, CH_2Cl_2). Table 2 shows the scope of the reaction wherein moderate to high yields of **2** were obtained in all the cases studied. For aromatic substrates with electron-donating substituents, the reaction time was longer giving moderate yields of **2**. Notably, the cyanosilylation of (*E*)-cinnamaldehyde afforded the corresponding 1,2-addition product exclusively (entry i). However, the reaction failed in the case of ketones, probably due to steric reasons.

The Strecker reaction between an aldehyde, an amine and hydrogen cyanide is widely regarded as the first multi-component reaction.[10] α-Aminonitriles **6** are the precursors for several amino acids and also for popular bifunctional synthons that have found numerous synthetic applications.[11] We have extended the present catalytic system to Strecker-type α-aminonitrile synthesis, the results of which are presented in Table 3. After initial experimentation, again catalyst **4**[14] was found to be the most effective for the three-component reaction. Many aldehydes possessing both electron-donating as well as electron-withdrawing groups underwent this condensation to afford the corresponding α-aminonitriles **6** in good yields. However, both the cyanosilylation and Strecker reaction failed to give optical induction when chiral catalyst **5** was employed, only racemic products **2** and **6** were produced.



3 **4** **5**

Figure 1. Quaternized organocatalysts for TMSCN addition to aldehydes and imines.

Scheme 2 shows a possible mechanistic pathway in which activation of the silyl group in TMSCN by catalyst **4** leads to the formation of ion-pair **7**. Reaction of

Table 1. Organocatalytic reaction of 4-nitrobenzaldehyde with TMSCN: screening of bases[a]

Entry	Base	Solvent	Product (% yield)[b]	
			1	**2**
1	DBU	MeOH	93, 87[c]	—
2	DABCO	MeOH	92, 78[c]	—
3	Et_3N	MeOH	81	—
4	**3**	MeOH	—	57
5	**4**	CH_2Cl_2	—	92
6	**4**	MeOH	—	64
7	**5**	MeOH	—	61

[a] Reagents and conditions: 4-nitrobenzaldehyde (5.0 mmol), TMSCN (6.0 mmol), base (0.5 mol %), solvent, 25 °C, 3 h.

[b] Isolated yield after column chromatographic purification.

[c] Yield corresponds to 4-cyanomethylbenzoate when 4-cyanobenzaldehyde was used.

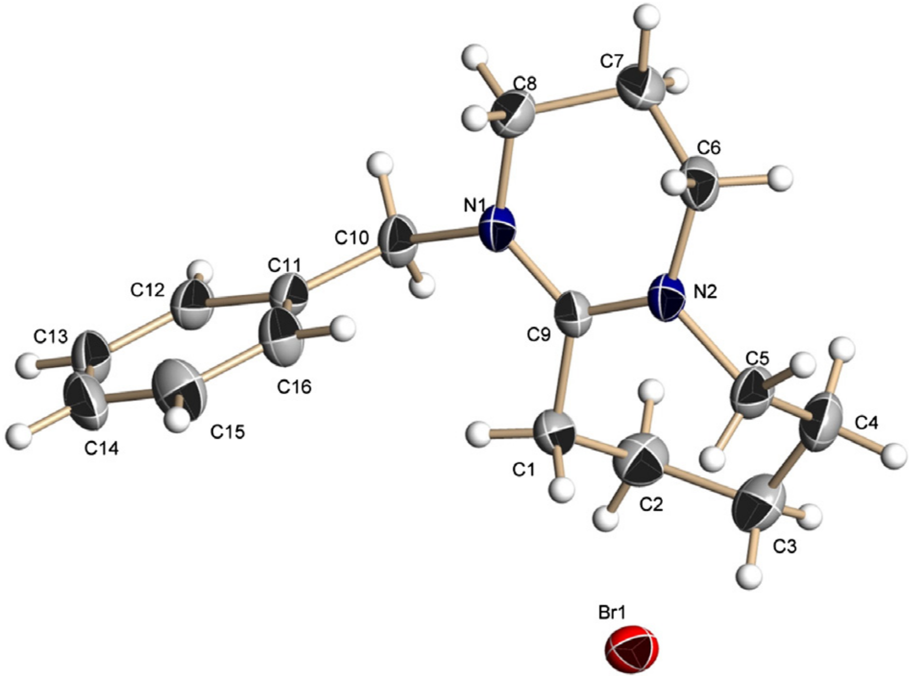
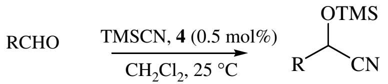


Figure 2. ORTEP diagram of catalyst **4**.

Table 2. Cyanosilylation of various aldehydes using organocatalyst **4**[a]



2a-l

Entry	R	*T* (h)	Yield[b] (%)
a	C_6H_5	24	51
b	$4\text{-}MeOC_6H_4$	24	52
c	$4\text{-}MeC_6H_4$	24	62
d	$4\text{-}HOC_6H_4$	24	57
e	$4\text{-}FC_6H_4$	10	73
f	$4\text{-}NCC_6H_4$	3	72, 53[c], 58[d]
g	$4\text{-}O_2NC_6H_4$	3	92
h	$Ph(CH_2)_2$	10	80
i	Ph–CH=CH	10	60
j	$BnO(CH_2)_4$	10	83
k	$BnO(CH_2)_5$	10	81
l	$(CH_3)_2CH$	10	90

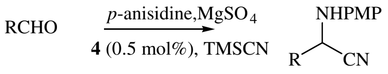
[a] Reagents and conditions: aldehyde (5.0 mmol), TMSCN (6.0 mmol), organocatalyst **4** (0.5 mol %), CH_2Cl_2, 25 °C.

[b] Isolated yield after column chromatographic purification.

[c] % Yield when catalyst **3** was used.

[d] % Yield when catalyst **5** was used.

Table 3. Strecker-type α-aminonitrile synthesis using **4** as catalyst and TMSCN as cyanide source[a]



6

Entry	R	Yield (%)[b]
1	C_6H_5	77
2	$4\text{-}MeOC_6H_4$	79
3	$3,4\text{-}(MeO)_2C_6H_3$	67
4	$Ph(CH_2)_2$	81
5	$4\text{-}O_2NC_6H_4$	81
6	$4\text{-}ClC_6H_4$	69
7	$3\text{-}O_2NC_6H_4$	72
8	3,4-Methylenedioxyphenyl	68
9	$CH_3{-}(CH_2)_3$	73
10	$CH_3{-}(CH_2)_3$	83[c]
11	$CH_3{-}(CH_2)_3$	90[d]

[a] Reagents and conditions: aldehyde (5.0 mmol), TMSCN (6.0 mmol), *p*-anisidine (5.0 mmol), **4** (0.5 mol %), anhyd $MgSO_4$, CH_2Cl_2 (25 mL), 25 °C, 12 h.

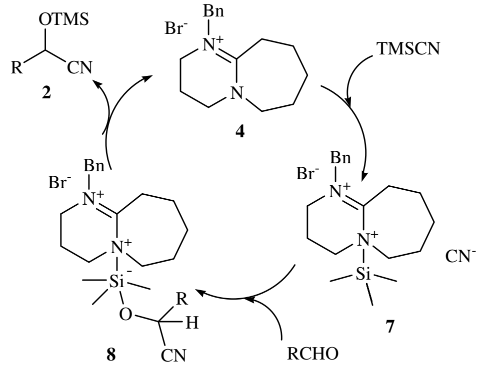
[b] Isolated yield after column chromatographic purification.

[c] Yield when morpholine was used as the amine source.

[d] Yield when *n*-butylamine was used as the amine source.

7 with aldehydes gives intermediate **8**, which subsequently dissociates into silylated cyanohydrin **2** with the regeneration of catalyst **4**.

In conclusion, we have shown, for the first time, the use of ammonium salts as new Lewis base catalysts for cyanosilylation of aldehydes and the three-component Strecker- type α-aminonitrile synthesis under ambient conditions.[12,13] Both the methods are effective and utilize the readily available cyanide source TMSCN. These catalysts have also shown advantages in terms of chemical stability and high solubility in organic solvents.



Scheme 2. Possible pathway for the cyanosilylation of aldehydes.

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9. The crystallographic data have been deposited with the Cambridge Crystallographic Data Centre as deposition No. CCDC 651284. Copies of the data can be obtained,

free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk].

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12. *General experimental procedure for cyanosilylation*: To a solution of catalyst **3**, **4** or **5** (0.5 mol %) in dichloromethane (25 mL) under an argon atmosphere at 25 °C was added aldehyde (5.0 mmol) followed by TMSCN (6.0 mmol). The resulting mixture was stirred at 25 °C and the reaction was monitored by TLC. After completion, the reaction mixture was concentrated in vacuum. The crude product was purified by column chromatography on silica gel using 5% ethyl acetate in petroleum ether as eluent to afford the pure product.
13. All the compounds listed were characterized by ^{1}H, ^{13}C NMR, FT-IR and elemental analysis.
14. Spectral data for catalyst **4**: Colourless solid; mp: 169 °C (crystallized from CH_2Cl_2); IR ($CHCl_3$, cm^{-1}): 3417, 2936, 2176, 1621, 1525, 1453, 1327, 1200, 924, 733; ^{1}H NMR(200 MHz, $CDCl_3$): δ 1.68–1.71 (m, 6H), 2.18–2.29 (m, 2H), 2.94–3.0 (m, 2H), 3.71–3.84 (m, 6H), 4.91 (s, 2H), 7.23–7.43 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 19.95, 22.24, 25.71, 28.06, 29.09, 47.52, 49.32, 55.45, 56.72, 126.11, 127.90, 128.91, 134.11, 167.04. Anal. Calcd for $C_{16}H_{23}BrN_2$: C, 59.45; H, 7.17; N, 8.67; Br, 24.72. Found: C, 59.41; H, 7.19; N, 8.69; Br, 24.70.