One-Pot Three-Component Synthesis of α-Amino Nitriles Catalyzed by 2,4,6-Trichloro-1,3,5-triazine (Cyanuric Acid)[1])

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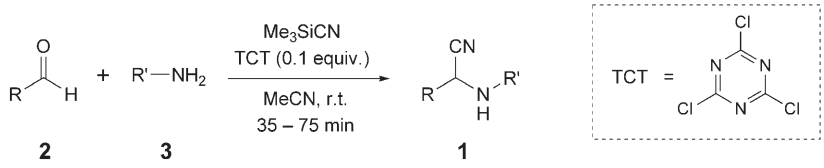
A simple and efficient method has been developed for the synthesis of α-amino nitriles from aldehydes, amines and trimethylsilyl cyanide (Me_3SiCN) in the presence of a catalytic amount of cyanuric acid at room temperature.

Introduction. – α-Amino nitriles are important intermediates in the preparation of amino acids [1] and various nitrogen heterocycles [2] such as imidazoles and thiadiazoles. They are generally prepared by nucleophilic addition of the cyanide anion (CN^-) to imines (*Strecker*-type reaction). Several modifications of the *Strecker* reaction have been reported with a variety of cyanating agents such as HCN [3], KCN [4], Et_2AlCN [5], $(EtO)_2P(O)CN$ [6], Bu_3SnCN [7], or Me_3SiCN [8]. Trimethylsilyl cyanide (Me_3SiCN) is an especially safe and effective source of CN^- for nucleophilic addition reactions of imines. However, many of the methods applying this cyanating agent involve the use of expensive catalysts, and require extended reaction times and harsh reaction conditions.

In continuation of our work [9] on the development of useful synthetic methodologies, we report herein a facile synthesis of α-amino nitriles **1** by treatment of an aldehyde **2** and an amine **3** with Me_3SiCN at room temperature in the presence of a catalytic amount of 2,4,6-trichloro-1,3,5-triazine (TCT; *Scheme 1*). TCT, which is better known as 'cyanuric chloride', has been used in various organic transformations due to its excellent catalytic activity [10], and because it is a safe and inexpensive reagent.

Scheme 1



2 **3** **1**

Results and Discussion. – We have tested TCT for the first time in the preparation of α-amino nitriles from various aldehydes and amines. The results of our studies are summarized in the *Table* for 20 different pairs of substrates. Initially, we studied the

[1]) Part 138 in the series 'Studies on Novel Synthetic Methodologies'; IICT Communication No. 070516.

Table. *Cyanuric Acid Catalyzed Synthesis of α-Amino Nitriles.* For details, see *Scheme 1* and *Exper. Part*. The structures of the products were settled by ^{1}H-NMR and MS, and confirmed by elemental analyses.

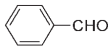
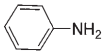
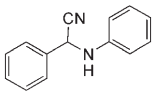
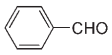
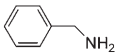
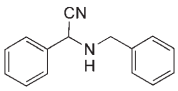
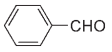
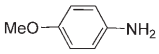
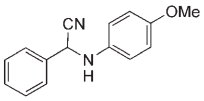
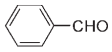
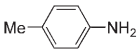
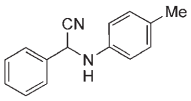
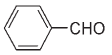
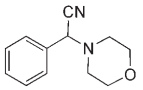
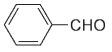
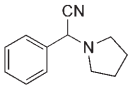
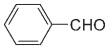
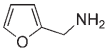
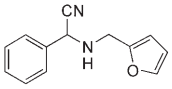
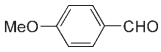
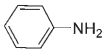
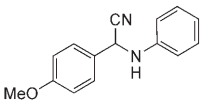
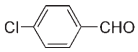
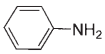
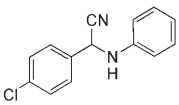
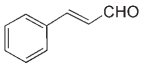
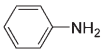
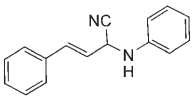
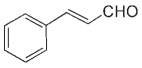
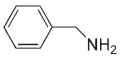
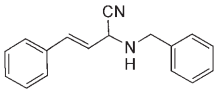
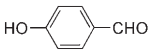
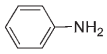
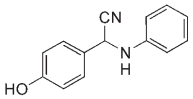
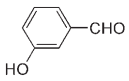
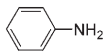
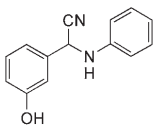
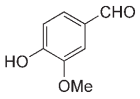
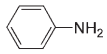
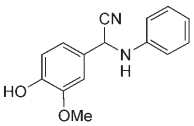
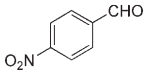
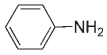
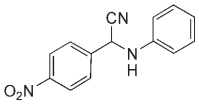
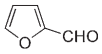
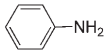
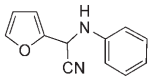
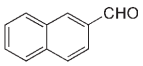
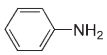
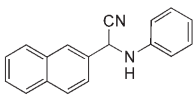
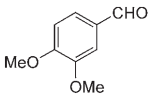
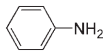
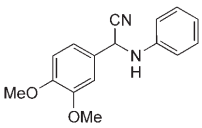
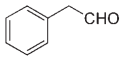
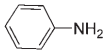
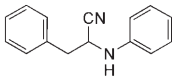
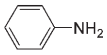
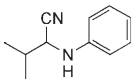
Series	Aldehyde (**2**)	Amine (**3**)	Product (**1**)	Time [min]	Isolated yield [%]
a				35	96
b				45	88
c				50	89
d				45	92
e				75	87
f				75	85
g				60	89
h				35	93
i				40	92
j				60	85
k				70	80

Table (cont.)

Series	Aldehyde (**2**)	Amine (**3**)	Product (**1**)	Time [min]	Isolated yield [%]
l				40	93
m				45	91
n				45	92
o				50	90
p				65	87
q				45	94
r				60	89
s				65	87
t				70	86

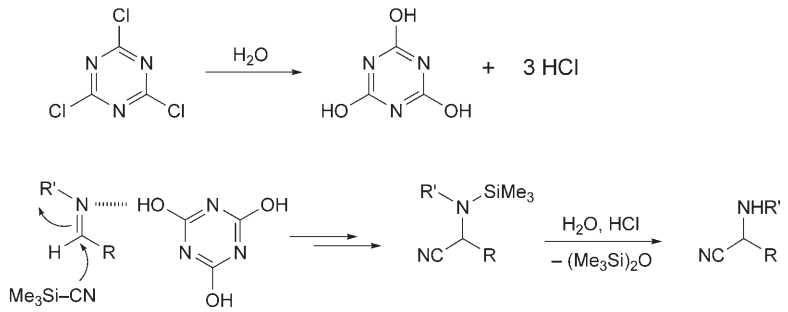
Strecker-type reaction of benzaldehyde (**2a**) and aniline (**3a**) (*Table*) in the presence of Me_3SiCN and a catalytic amount of TCT at room temperature, which afforded the corresponding α-amino nitrile **1a** in high yield (96%). Among various solvent systems, including $CHCl_3$, CH_2Cl_2, MeCN, THF, EtOH, and Et_2O, the conversion proceeded best in MeCN.

A variety of other aldehydes, including aromatic, aliphatic, as well as α,β-unsaturated ones, were treated with different primary or secondary amines in the

presence of TCT in MeCN. In all cases, high yields (80–94%) of the desired products **1** were obtained, typically within 1 h or less (*Table*). Aromatic aldehydes with both electron-donating and -withdrawing groups underwent the condensation very smoothly. Aliphatic and unsaturated aldehydes also afforded the corresponding products (**1j**,**k**,**s**,**t**) in good yields. However, ketones did not yield any product under these reaction conditions. For α,β-unsaturated aldehydes (**2j**,**k**), the reaction was highly regioselective, the conjugated C=C bond basically being unaffected.

TCT is known to react with 'incipient' moisture to form HCl along with 2,4,6-trihydroxy-1,3,5-trazine, which can activate [9a] the imine system through H-bonding and facilitate cyanation (*Scheme 2*). The above conversion, thus, completely failed under perfectly anhydrous conditions. Also, with dilute HCl, instead of TCT, only the corresponding imines (rather than the α-amino nitriles) were isolated. Further, in the absence of TCT as catalyst, only very low yields (7–12%) of the α-amino nitriles were obtained (data not shown).

Scheme 2



In conclusion, we have developed a simple, mild, efficient, and fast protocol for the TCT-catalyzed synthesis of α-amino nitriles in high yields through one-pot three-component coupling of aldehydes, amines, and Me_3SiCN.

We wish to thank *CSIR* and *UGC* (New Delhi, India) for financial assistance.

Experimental Part

General. ^{1}H-NMR Chemical shifts δ and coupling constants J are provided in ppm (rel. to Me_4Si) and in Hz, resp. Mass-spectrometric data are given as m/z values. MeCN as solvent was purchased from *Aldrich* (purity 99%) and used as received. Trimethylsilyl cyanide (Me_3SiCN) and 2,4,6-trichloro-1,3,5-triazine (cyanuric acid) were obtained from *Aldrich* (purity 99%) and used without further purification.

General Procedure for the Synthesis of α-Amino Nitriles. To a mixture of an aldehyde **2** (1 mmol), an amine **3** (1 mmol), and Me_3SiCN (1.2 mmol) in MeCN (5 ml), TCT (10 mol-%) was added. The mixture was stirred at r.t., and the reaction was monitored by TLC. After completion of the reaction, the solvent was evaporated, and H_2O (5 ml) was added. The mixture was extracted with AcOEt (3×5 ml), and the org. layer was concentrated. The residue was purified by column chromatography (SiO_2; AcOEt/hexane 5:95) to afford the corresponding pure α-amino nitrile **1** (see *Table*). The anal. data of some representatives are given below.

(3-Hydroxyphenyl)(phenylamino)acetonitrile (**1m**). ^{1}H-NMR (200 MHz, $CDCl_3$): 7.35–7.16 (*m*, 3 H); 7.02 (br. *s*, 2 H); 6.92–6.81 (*m*, 2 H); 6.80 (*dd*, J = 8.0, 2.0, 2 H); 6.30 (br. *s*, 1 H); 5.31 (*d*, J = 8.0,

1 H); 4.03 (*d*, *J* = 8.0, 1 H). FAB-MS: 225 ([*M* + 1]$^+$). Anal. calc. for $C_{14}H_{12}N_2O$: C 75.00, H 5.35, N 12.50; found: C 75.06, H5.37, N 12.56.

(4-Hydroxy-3-methoxyphenyl)(phenylamino)acetonitrile (**1n**). ^{1}H-NMR (200 MHz, $CDCl_3$): 7.22 (*t*, *J* = 8.0, 2 H); 7.09 (*d*, *J* = 2.0, 1 H); 7.07 (*dd*, *J* = 8.0, 2.0, 1 H); 6.88 – 6.82 (*m*, 2 H); 6.71 (*dd*, *J* = 8.0, 2.0, 2 H); 5.64 (br. *s*, 1 H); 5.25 (*d*, *J* = 8.0, 1 H); 3.98 (*d*, *J* = 8.0, 1 H); 3.92 (*s*, 3 H). FAB-MS: 254 ([*M* + 1]$^+$). Anal. calc. for $C_{15}H_{14}N_2O_2$: C 70.86, H 5.51, N 11.02; found: C 70.90, H 5.55, N 11.13.

Naphthalen-2-yl(phenylamino)acetonitrile (**1q**). ^{1}H-NMR (200 MHz, $CDCl_3$): 8.12 (*d*, *J* = 2.0, 1 H); 7.96 – 7.82 (*m*, 3 H); 7.66 – 7.50 (*m*, 3 H), 7.34 – 7.21 (*m*, 2 H); 6.92 – 6.3 (*m*, 3 H); 5.53 (*d*, *J* = 8.0, 1 H); 4.02 (*d*, *J* = 8.0, 1 H). FAB-MS: 259 ([*M* + 1]$^+$). Anal. calc. for $C_{18}H_{14}N_2$: C 83.72, H 5.42, N 10.85; found: C 83.78, H 5.48, N 11.00.

(3,4-Dimethoxyphenyl)(phenylamino)acetonitrile (**1r**). ^{1}H-NMR (200 MHz, $CDCl_3$): 7.39 – 7.22 (*m*, 2 H); 7.14 (*dd*, *J* = 8.0, 2.0, 1 H); 7.03 (*dd*, *J* = 2.0, 1 H); 6.91 6.83 (*m*, 2 H); 6.72 (*dd*, *J* = 8.0, 2.0, 2 H); 5.31 (*d*, *J* = 8.0, 1 H); 3.96 (*d*, *J* = 8.0, 1 H); 3.90 (*s*, 6 H). FAB-MS: 258 ([*M* + 1]$^+$). Anal. calc. for $C_{16}H_{16}N_2O_2$: C 74.41, H 6.20, N 10.85; found: C 74.50, H 6.31, N 11.02.

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