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$Cu(OTf)_2$ or Et_3N-catalyzed three-component condensation of aldehydes, amines and cyanides: a high yielding synthesis of α-aminonitriles

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Abstract—Copper(II) triflate or Et_3N have been found to catalyze, under ambient conditions, the addition of a cyanide anion, such as trimethylsilyl cyanide or acetone cyanohydrin, onto in situ generated imines, furnishing α-aminonitriles in excellent yields.

The Strecker reaction between an aldehyde, an amine and an hydrogen cyanide is widely regarded as the first multicomponent reaction.[1] Its reliability, the ready availability of the starting materials, and the versatility of the resulting products make it a very important process for the large-scale production of amino acids, herbicides and chelating agents. Aminonitriles are precursors for several amino acids and also for popular bifunctional synthons that have found numerous synthetic applications.[2] Generally, α-aminonitriles are prepared by the reaction of aldehydes with amines in the presence of cyanide sources such as HCN,[2] KCN,[3] TMSCN,[4] $(EtO)_2P(O)CN$,[5] Et_2AlCN[6] and Bu_3SnCN,[7] often involving harsh reaction conditions.[8] The handling of gaseous HCN and liquid Bu_3SnCN, Et_2AlCN and $(EtO)_2P(O)CN$ is cumbersome due to their hazardous nature, while special equipment and care are needed for transfer of these materials on large scale. In order to overcome some of these problems, a new safe and inexpensive catalytic procedure for the synthesis of α-aminonitriles is highly desirable. In this paper, we report a three-component reaction comprising hydrocyanation of imines generated in situ from aldehydes and amines, with acetone cyanohydrin or trimethylsilyl cyanide (TMSCN) as the cyanide source and Et_3N or $Cu(OTf)_2$, respectively, as catalysts for Strecker-type α-aminonitrile synthesis.

In continuation of our work on Cu(II)-mediated reactions,[9] we decided to explore the effectiveness of $Cu(OTf)_2$ as a Lewis acid catalyst for the Strecker α-aminonitrile synthesis. When a mixture of benzaldehyde (**1a**) and *p*-anisidine, in the presence of anhydrous $MgSO_4$, was treated with TMSCN using $Cu(OTf)_2$ (1 mol %) in acetonitrile at 25 °C, the corresponding α-aminonitrile (**2a**) was obtained in 95% yield (Table 1, entry 3). We then turned our attention to systematically study the effectiveness of cyanide sources such as TMSCN and acetone cyanohydrin, under the influence of various Lewis acid catalysts and organic bases on the hydrocyanation of in situ generated imines and the results are summarized in Table 1.

Among various Lewis acid catalysts screened such as $LaCl_3$, $La(OTf)_3$, $Cu(OTf)_2$, CuCN and $Ti(OiPr)_4$, only $Cu(OTf)_2$ in combination with TMSCN was found to be effective and gave **2a** in 95% yield.

Recently, the use of organic catalysts has provided attractive alternatives to the more traditional metal-catalyzed variants and in many cases has obviated the need for prior activation of the requisite nucleophile in a separate step.[10] Thus, when acetone cyanohydrin, one of the most stable and cheap cyanide sources,[11] was employed in combination with a catalytic amount of Et_3N (5 mol %) in CH_3CN, we obtained α-aminonitrile **2a** in 93% yield (Table 1). Control experiments indicated that no reaction took place in the absence of either $Cu(OTf)_2$ or Et_3N. Among several organic bases screened, Et_3N, 1,4-diazabicyclo[2.2.2]octane (DABCO)

Keywords: Aldehydes; Aminonitriles; Strecker reaction; Multicomponent reactions; Organocatalyst.

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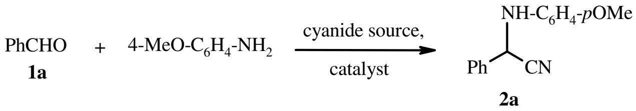
Table 1. Lewis acid[a] or organic base[b]-catalyzed three-component synthesis of α-aminonitriles **2a**



Entry	Catalyst (mol %)	Cyanide source	Solvent	Yield of **2a**[c] (%)
1	None	TMSCN	CH_3CN	0
2	$Cu(OTf)_2$ (0.5)	TMSCN	CH_3CN	87
3	$Cu(OTf)_2$ (1)	TMSCN	CH_3CN	95
4	$Cu(OTf)_2$ (1)	TMSCN	CH_2Cl_2	91
5	$Cu(OTf)_2$ (1)	TMSCN	THF	84
6	CuCN (10)	TMSCN	CH_3CN	23
7	$LaCl_3$ (10)	TMSCN	CH_3CN	18
8	$La(OTf)_3$ (10)	TMSCN	CH_3CN	48
9	$Ti(OiPr)_4$ (10)	TMSCN	CH_2Cl_2	12
10	I_2 (10)	TMSCN	CH_3CN	72
11	None	Acetone cyanohydrin	CH_3CN	5
12	Et_3N (5)	Acetone cyanohydrin	CH_3CN	93
13	Pyridine (10)	Acetone cyanohydrin	CH_3CN	7
14	Pyridine (100)	Acetone cyanohydrin	CH_3CN	89
15	DABCO[d] (5)	Acetone cyanohydrin	CH_3CN	88
16	DBU[e] (5)	Acetone cyanohydrin	CH_3CN	92
17	Quinine (5)	Acetone cyanohydrin	CH_3CN	79[f]
18	L-Proline (20)	Acetone cyanohydrin	DMSO	12[f]
19	Brucine (5)	Acetone cyanohydrin	CH_3CN	67[f]
20	Nicotine (5)	Acetone cyanohydrin	CH_3CN	56[f]

[a] Lewis acid-catalyzed reaction conditions:[12] benzaldehyde **1a** (2 mmol), *p*-anisidine (2 mmol), anhyd $MgSO_4$, TMSCN (2 mmol), CH_3CN, 25 °C, 6 h.

[b] Organic base-catalyzed reaction conditions:[12] benzaldehyde **1a** (2 mmol), *p*-anisidine (2 mmol), acetone cyanohydrin (2 mmol), CH_3CN, 25 °C, 6 h.

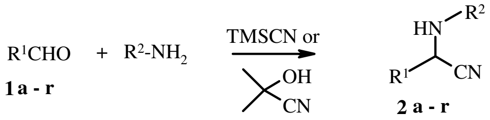
[c] Isolated yield after column chromatographic purification.

[d] 1,4-Diazabicyclo[2.2.2]octane.

[e] 1,5-Diazabicyclo[4.3.0]undec-7-ene.

[f] No chiral induction was observed.

Table 2. $Cu(OTf)_2$[a] or Et_3N[b]-catalyzed synthesis of α-aminonitriles **2**



Entry	R^1	R^2	Yield of **2**[c] (%)	
			$Cu(OTf)_2$	Et_3N
a	C_6H_5	4-MeO–C_6H_4	95	93
b	C_6H_5	C_6H_5–CH_2	98	99
c	C_6H_5	$C_6H_5(CH_3)CH$	65	87
d	C_6H_5	C_6H_5	89	74
e	4-Cl–C_6H_4	4-MeO–C_6H_4	90	85
f	4-MeO–C_6H_4	4-MeO–C_6H_4	99	95
g	4-NC–C_6H_4	4-MeO–C_6H_4	88	90
h	4-HO–C_6H_4	4-MeO–C_6H_4	85	88
i	2-HO–C_6H_4	4-MeO–C_6H_4	82	85
j	4-O_2N–C_6H_4	4-MeO–C_6H_4	78	73
k	3-O_2N–C_6H_4	4-MeO–C_6H_4	81	72
l	3,4-$(MeO)_2$–C_6H_3	4-MeO–C_6H_4	92	95
m[13]	3,4-(O–CH_2–O)$_2$–C_6H_3	4-MeO–C_6H_4	90	93
n[13]	2,4-(*tert*-Bu)$_2$-6-(MeO)-C_6H_2	4-MeO–C_6H_4	56	69
o	2-Methoxy-1-naphthyl	4-MeO–C_6H_4	83	91
p	*trans*-Cinnamyl	4-MeO–C_6H_4	59	87
q	2-Furyl	4-MeO–C_6H_4	74	78
r	*n*-C_9H_{19}	4-MeO–C_6H_4	65	72

[a] $Cu(OTf)_2$ catalyzed reaction conditions:[12] aldehydes **1a**–**r** (2 mmol), amine (2 mmol), anhyd $MgSO_4$, TMSCN (2 mmol), CH_3CN, 25 °C, 6 h.

[b] Et_3N-catalyzed reaction conditions:[12] aldehydes **1a**–**r** (2 mmol), *p*-anisidine (2 mmol), acetone cyanohydrin (2 mmol), CH_3CN, 25 °C, 6 h.

[c] Isolated yield after column chromatographic purification.

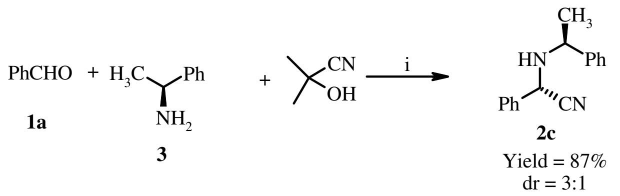
and 1,5-diazabicyclo[4.3.0]undec-7-ene (DBU) were found to be equally effective in catalyzing the reaction.

It was of interest to subject various substituted aldehydes **1a**–**r** to the three-component Strecker-type reaction using a catalytic amount of either $Cu(OTf)_2$–TMSCN or Et_3N–acetone cyanohydrin and the results are shown in Table 2.

As can be seen, the reaction conditions are mild [$Cu(OTf)_2$) (1 mol %) or Et_3N (5 mol %), CH_3CN, 25 °C]. Aldehydes possessing both electron-donating as well as electron-withdrawing groups underwent condensation to afford the corresponding α-aminonitriles **2a**–**r**. Even sterically hindered aldehyde **1n** underwent the reaction producing the corresponding α-aminonitriles **2n** in 56–69% yield. Aliphatic, heterocyclic and unsaturated aldehydes also underwent the Strecker-type reaction giving the corresponding α-aminonitriles in moderate yields. However, the reaction failed in the case of acetophenone under both sets of reaction conditions.

In our attempt to obtain optically pure α-aminonitriles, we employed various chiral bases but reactions failed to deliver optical induction (Table 1). However, when (S)-(−)-α-methylbenzylamine (**3**) and benzaldehyde were subjected to hydrocyanation in the presence of a catalytic amount of Et_3N, we obtained a 3:1 diastereomeric mixture[8b] of α-aminonitrile **2c** in 87% yield (Scheme 1).

The mechanism of the $Cu(OTf)_2$ catalyzed reaction is believed to involve the formation of imine **4** so that addition of CN^- is facilitated to afford the α-aminonitrile.[9] In the case of the Et_3N-catalyzed reaction, the probable mechanistic pathway is shown in Figure 1, wherein the adduct Et_3N–HCN (**A**), formed by the reaction of acetone cyanohydrin with Et_3N, transfers CN^- to imine **4** generated in situ, to afford α-aminonitrile **2** along with regeneration of Et_3N.



Scheme 1. Reagents and conditions: (i) cat. Et_3N (5 mol %), CH_3CN, 25 °C, 5 h, 87%.

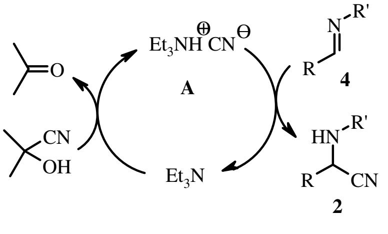


Figure 1. Proposed catalytic cycle for the Et_3N-catalyzed hydrocyanation of imines.

In conclusion, we have shown, for the first time, the use of either $Cu(OTf)_2$/TMSCN or Et_3N/acetone cyanohydrin as new catalytic systems for the three-component Strecker-type α-aminonitrile synthesis under ambient conditions. Both catalytic systems are effective and utilize cheap available cyanide sources giving corresponding α-aminonitriles in excellent yields.

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12. *General experimental procedure for Cu(OTf)$_2$ catalyzed α-aminonitrile synthesis*: A mixture of aldehyde (2 mmol), amine (2 mmol) and anhydrous $MgSO_4$ (0.5 g) in acetonitrile (10 mL) was stirred at 25 °C for 30 min and then trimethylsilyl cyanide (2 mmol) followed by $Cu(OTf)_2$ (0.02 mmol) were added. The resulting reaction mixture was stirred at 25 °C and was monitored by TLC. After completion of the reaction, it was extracted with ethyl acetate (20 mL) and washed with water and brine. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to give the crude product, which was purified by column chromatography on silica gel using 15% ethyl acetate in petroleum ether as eluent to afford the pure product **2a**–**r**.

    General experimental procedure for Et$_3$N-catalyzed α-aminonitrile synthesis: A mixture of aldehyde (2 mmol), amine (2 mmol), acetone cyanohydrin (2 mmol) followed by Et_3N (0.1 mmol) in acetonitrile (10 mL) was stirred at 25 °C and was monitored by TLC. After completion of the reaction, it was extracted with ethyl acetate (20 mL) and washed with water and brine. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to give the crude product, which was purified by column chromatography on silica gel using 15% ethyl acetate in petroleum ether as eluent to afford the pure product.

13. All the compounds listed in Table 2 were thoroughly characterized by ^1H NMR and FT-IR spectroscopy. Spectral data for selected new compounds:

    2-(4-Methoxyphenylamino)-2-(benzo[d][1,3]dioxol-5-yl)acetonitrile (**2m**): Yield: 93%; brown coloured solid; mp: 112–114 °C (crystallized from EtOAc); IR (neat, cm^{-1}): 692, 769, 1009, 1090, 1251, 1393, 1470, 1488, 1604, 1655, 1800, 1888, 1952, 2232, 2840, 2935, 2973, 3228, 3334; ^1H NMR (200 MHz, $CDCl_3$): δ 3.76 (s, 3H), 3.82 (s, 1H), 5.20 (s, 1H), 6.00 (s, 2H), 6.66–6.84 (m, 5H), 7.01–7.09 (m, 2H); ^{13}C NMR (50 MHz, acetone-d_6): δ 50.60, 55.42, 101.92, 107.98, 108.57, 114.93, 116.25, 119.20, 121.18, 129.16, 139.71, 148.56, 153.86. Analysis: $C_{16}H_{14}N_2O_3$ calcd C, 68.07; H, 5.00; N, 9.92; found C, 68.00; H, 5.00; N, 10.00.

    2-(4-Methoxyphenylamino)-2-(2,4-di-tert-butyl-6-methoxyphenyl)acetonitrile (**2n**): Yield: 69%; dark brown coloured solid; mp: 85–88 °C (crystallized from EtOAc); IR (neat, cm^{-1}): 560, 665, 783, 1014, 1108, 1252, 1390, 1470, 1490, 1600, 1660, 1800, 1883, 1955, 2230, 2856, 2932, 2976, 3233, 3339; ^1H NMR (200 MHz, $CDCl_3$): δ 1.36 (s, 9H), 1.41 (s, 9H), 3.78 (s, 3H), 3.81 (s, 3H), 5.56 (s, 1H), 6.76 (dd, $J = 9.40$ Hz each, 4H), 7.41 (d, $J = 2.35$ Hz, 1H), 7.48 (d, $J = 2.35$ Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 31.16, 31.49, 45.90, 55.46, 63.18, 115.04, 115.78, 119.27, 123.65, 126.00, 128.20, 138.61, 142.94, 147.24, 153.97, 154.74. Analysis: $C_{24}H_{32}N_2O_2$ calcd C, 75.75; H, 8.48; N, 7.36; found C, 75.83; H, 8.50; N, 7.27.