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One-pot three-component synthesis of α-aminonitriles using potassium hexacyanoferrate(II) as an eco-friendly cyanide source

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A B S T R A C T

An efficient and environmentally friendly method has been developed for the synthesis of α-aminonitriles via one-pot three-component condensation of carbonyl compounds, amines, and potassium hexacyanoferrate(II) in the presence of benzoyl chloride as a promoter. This protocol has the features of use of eco-friendly cyanide source, high yield, and simple work-up procedure.

α-Aminonitriles are significantly important intermediates for the synthesis of a wide variety of amino acids, amides, diamines, and nitrogen-containing heterocycles.[1] Among the methods reported for the synthesis of α-aminonitriles, Strecker reaction, nucleophilic addition of cyanide ion to imines, is of great importance to modern organic chemistry as it offers one of the most direct and viable methods for the synthesis of α-aminonitriles.[2] In general, α-aminonitriles are synthesized by the reactions of aldehydes/ketones with amines in the presence of a cyanide source such as HCN,[3] KCN,[4] TMSCN,[5] $(EtO)_2P(O)CN$,[6] Et_2AlCN,[7] Bu_3SnCN,[8] MeCOCN,[9] acetone cyanohydrin,[10] and ethyl cyanoformate,[11] which are often hazardous, toxic, and involve harsh reaction conditions. Recently, modified methods using one-pot procedure via three-component condensation of aldehyde/ketone, amine, and trimethylsilyl cyanide catalyzed by $Cu(OTf)_2$,[12] $BiCl_3$,[13] $NiCl_2$,[14] InI_3,[15] $RuCl_3$,[16] $Sc(OTf)_3$,[17] $La(NO_3)_3{\cdot}6H_2O$ or $GdCl_3{\cdot}6H_2O$,[18] I_2,[19] $H_4SiW_{12}O_{40}/Al_2O_3$,[20] and metal complexes[21] in conventional organic solvents have been described. However, trimethylsilyl cyanide is sensitive to moisture and can easily liberate toxic hydrogen cyanide. Meanwhile many of these reported methods involve the use of expensive reagents, toxic organic solvents, tedious work-up procedure, and longer reaction times. The development of environmentally friendly organic reactions (green chemistry) is a very active field of research, emerging as a response to the increasing regulatory pressure directed to the elimination/reduction of chemical waste.[22] Implementation of methods that avoid the use of toxic reagents and/or metal-based catalysts is a fundamental strategy in this field. Therefore, it is still desirable to search for an environmentally friendly cyanating agent and develop an efficient and practical method for the Strecker reaction under mild conditions.

Potassium hexacyanoferrate(II), $K_4[Fe(CN)_6]$, is non-toxic and is even used in the food industry for metal precipitation. In addition, it has been described as an anti-agglutinating auxiliary for table salt (NaCl). $K_4[Fe(CN)_6]$ is a by-product of coal chemical industry and commercially available on a ton scale, and is even cheaper than KCN. Very recently, $K_4[Fe(CN)_6]$ has been used as a cyanide source in the synthesis of benzonitriles[23] and aroyl cyanides.[24] However, it is noteworthy to mention that all the reported reactions using $K_4[Fe(CN)_6]$ as a cyanide source belong to substitution reactions. There are no examples reported for nucleophilic addition reactions. In this study, we report an efficient method for the synthesis of α-aminonitriles using $K_4[Fe(CN)_6]$ as an efficient nucleophilic addition reagent and as an environmentally friendly cyanide source.

In order to explore the use of $K_4[Fe(CN)_6]$ as an environmentally friendly addition reagent in cyanation reactions, the initial research was focused on the synthesis of α-aminonitrile by one-pot three-component reaction of benzaldehyde, aniline, and $K_4[Fe(CN)_6]$. The three-component reaction was attempted at different catalytic systems such as Lewis acids, Lewis bases, and some metal complexes under different temperature in various solvents. Unfortunately, no products were observed in the studied conditions. However, in the later research, it was found that some acyl chlorides could efficiently

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promote the three-component reaction of benzaldehyde, aniline, and $K_4[Fe(CN)_6]$ (Table 1). Among the selected acyl chlorides, acetyl chloride and oxalyl chloride were not valid for the reaction because of their volatility and instability (Table 1, entries 1 and 2), phenylsulfonyl chloride and furoyl chloride could promote the reaction to give the corresponding α-aminonitrile in moderate yield (Table 1, entries 5 and 6), meanwhile aroyl chlorides could promote the reaction to afford the desired α-aminonitrile in high yield (Table 1, entries 3 and 4), especially benzoyl chloride could afford the best result (Table 1, entry 3). In addition, it was also found that for 1 mol of benzaldehyde and aniline, only 0.2 equiv of $K_4[Fe(CN)_6]$ was required, which indicated that six CN^- in $K_4[Fe(CN)_6]$ could be readily utilized in this reaction.

The further research showed that solvents also played a crucial role in the one-pot three-component reaction of benzaldehyde, aniline, and $K_4[Fe(CN)_6]$ using benzoyl chloride as a promoter (Table 2). It was found that no α-aminonitrile was observed in some nonpolar solvents such as diethyl ether and toluene (Table 2, entries 1 and 2). However, the reaction in polar solvents such as THF, CH_3CN, CH_2Cl_2, DMF, MeOH, and EtOH could give the desired product in moderate to high yield (Table 2, entries 3–8). Especially the reaction in EtOH afforded α-aminonitrile in highest yield within shortest time.

Based on these promising findings, a series of one-pot three-component reactions of aldehydes or ketones, amines, and $K_4[Fe(CN)_6]$ were investigated in EtOH using benzoyl chloride as a promoter (Scheme 1).[25] Aromatic aldehydes bearing electron-donating or electron-withdrawing groups could participate in the reactions to afford the desired α-aminonitriles in high yield. The substituents on the aryl rings have no obvious effect on the yield of reactions. Aliphatic aldehydes were also effective for the reactions to produce the corresponding product in slightly lower yield. Heteroaromatic aldehyde such as furaldehyde had the similar manner to that of aromatic aldehydes for the reactions. Ketones, such as acetophenone, cyclopentanone, and cyclohexanone, are also suitable for the three-component reactions although the reaction rate is slightly slower than aldehydes. Meanwhile most aromatic amines were effective to the one-pot three-component reactions except for the amines bearing strong electron-withdrawing groups on the aryl ring, such as nitro, which could not give α-aminonitriles because the nucleophilic property of amines was weakened by nitro. The promoter, benzoyl chloride, was transformed into benzoic acid in the reactions, which could be easily recovered from the reaction system and further reused after regeneration.

Table 2
One-pot synthesis of α-aminonitrile under different solvents[a]

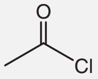
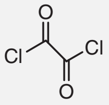
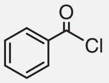
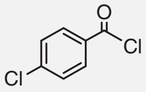
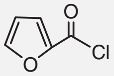
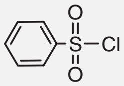
Entry	Solvent	Reaction time (h)	Yield[b] (%)
1	Et_2O	24	0
2	PhMe	24	0
3	THF	22	55
4	MeCN	19	60
5	CH_2Cl_2	24	84
6	DMF	18	71
7	MeOH	10	80
8	EtOH	8	88

[a] Reaction conditions: benzaldehyde (2 mmol), aniline (2 mmol), benzoyl chloride (2 mmol), and $K_4[Fe(CN)_6]$ (0.4 mmol) in 5 mL of solvent.
[b] Isolated yield.

A plausible mechanism for the synthesis of α-aminonitriles using $K_4[Fe(CN)_6]$ as a cyanide source, according to Hunig's review,[26] is shown in Scheme 2. Firstly $K_4[Fe(CN)_6]$ reacts with benzoyl chloride to form benzoyl cyanide. Then benzoyl cyanide is attacked by water to produce hydrogen cyanide in situ. Finally, nucleophilic addition of cyanide ion to the imines, which is formed from condensation of aldehydes and amines, yields α-aminonitriles.

In summary, an efficient and environmentally friendly method for the synthesis of α-aminonitriles through one-pot three-component condensation of aldehydes/ketones, amines, and $K_4[Fe(CN)_6]$ using benzoyl chloride as a promoter in ethanol was developed. The significant features of this method are the use of non-toxic, inexpensive $K_4[Fe(CN)_6]$ as the cyanide source to replace the traditional strong toxic and volatile cyanating agents, the simplicity of

Table 1
One-pot synthesis of α-aminonitrile using different promoters[a]

Entry	Promoter	Reaction time (h)	Reaction temperature (°C)	Yield[b] (%)
1		8	50	0
2		8	63	0
3		8	160	88
4		8	160	76
5		8	160	62
6		8	160	66

[a] Reaction condition: benzaldehyde (2 mmol), aniline (2 mmol), promoter (2 mmol), and $K_4[Fe(CN)_6]$ (0.4 mmol).
[b] Isolated yield.

Table 3
One-pot three-component synthesis of α-aminonitriles using $K_4[Fe(CN)_6]$ as cyanide source[a]

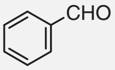
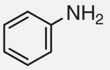
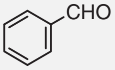
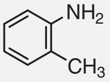
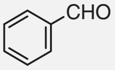
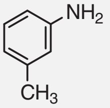
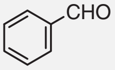
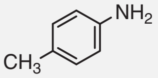
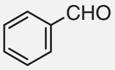
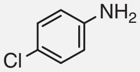
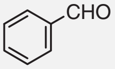
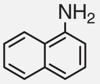
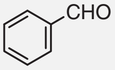
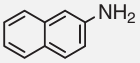
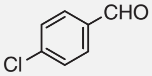
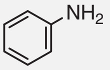
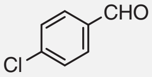
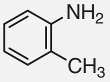
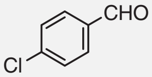
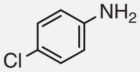
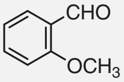
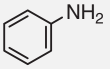
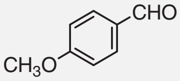
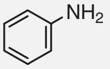
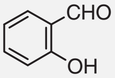
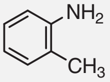
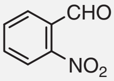
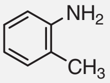
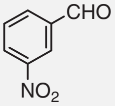
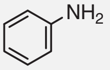
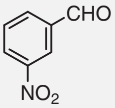
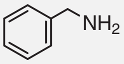
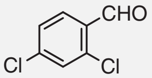
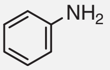
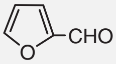
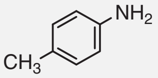
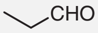
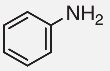
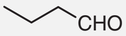
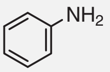
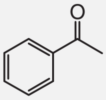
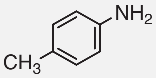
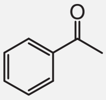
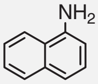
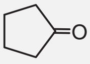
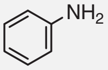
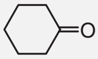
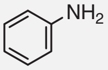
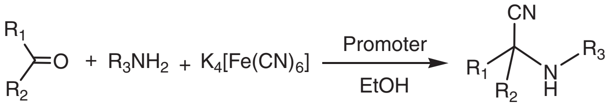
Entry	Aldehyde or ketone	Amine	Reaction time (h)	Yield[b] (%)	Mp (°C)
1			8	88	76–78
2			7	89	86–87
3			7	85	94–96
4			8	90	81–83
5			8	82	91–92
6			5	83	112–113
7			5	84	135–136
8			8	87	120–121
9			6	87	110–112
10			9	80	144–145
11			8	84	61–62
12			8	81	95–97
13			5	84	153–154
14			4	79	157–160
15			4	83	85–87
16			6	80	Oil
17			6	89	112–114
18			7	78	67–68
19			9	70	Oil
20			9	72	Oil

Table 3 (*continued*)

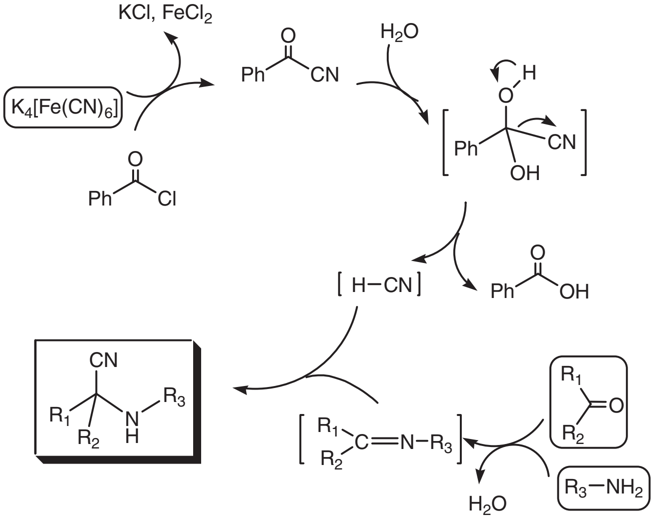
Entry	Aldehyde or ketone	Amine	Reaction time (h)	Yield[b] (%)	Mp (°C)
21			10	74	152–154
22			10	70	138–140
23			12	73	67–68
24			11	76	70–71

[a] Reaction condition: aldehyde or ketone (2 mmol), amine (2 mmol), benzoyl chloride (2 mmol), and $K_4[Fe(CN)_6]$ (0.4 mmol) in 5 mL of ethanol.

[b] Isolated yield.



Scheme 1. Synthesis of α-aminonitriles using $K_4[Fe(CN)_6]$ as cyanide source.



Scheme 2. Proposed mechanism for Strecker reactions using $K_4[Fe(CN)_6]$ as cyanide source.

reaction and work-up procedure, the high yield, and the avoiding use of acids or metal catalysts.

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25. *The general procedure for the synthesis of α-aminonitriles*: The mixture of $K_4[Fe(CN)_6]$ (0.4 mmol) and benzoyl chloride (2 mmol) was heated at 160 °C for 2 h, then the reaction system was cooled to room temperature; carbonyl compound (2 mmol) and aniline (2 mmol) in 5 mL of ethanol were added. The resulting mixture was stirred at room temperature to 80 °C for appropriate time indicated in Table 3. After completion of the reaction, monitored by TLC, the resulting mixture was filtered to remove the solids and the liquor was

concentrated and isolated by column chromatography to give pure product. The analytical data of representative compounds are given below. *2-Anilino-2-phenylacetonitrile* (Table 3, entry 1): Yellow solid, mp 76–78 °C; IR (KBr): 3337, 3030, 2942, 2236, 1599, 1514, 1446, 1282, 924, 752 cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 4.04 (br s, 1H), 5.42 (s, 1H), 6.76–6.79 (m, 2H), 6.88–6.92 (m, 1H), 7.25–7.30 (m, 2H), 7.41–7.48 (m, 3H), 7.58–7.61 (m, 2H); ^{13}C NMR (CDCl$_3$, 100 MHz): δ 50.2, 114.1, 118.1, 120.3, 127.2, 129.3, 129.5, 129.6, 133.9, 144.6. Anal. Calcd for $C_{14}H_{12}N_2$: C, 80.74; H, 5.81; N, 13.45. Found: C, 80.67; H, 5.80; N, 13.41. *2-(4-Toluidino)-2-phenylacetonitrile* (Table 3, entry 4): Yellow solid, mp 81–83 °C; IR (KBr): 3329, 3026, 2922, 2241, 1615, 1520, 1449, 1282, 926, 750 cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 2.28 (s, 3H), 3.90 (s, 1H), 5.40 (s, 1H), 6.69–6.72 (m, 2H), 7.07–7.09 (m, 2H), 7.43–7.48 (m, 3H), 7.59–7.61 (m, 2H); ^{13}C NMR (CDCl$_3$, 100 MHz): δ 20.5, 50.7, 114.5, 118.3, 127.2, 129.3, 129.5, 129.8, 130.0, 134.1, 142.4. Anal. Calcd for $C_{15}H_{14}N_2$: C, 81.05; H, 6.35; N, 12.60. Found: C, 81.11; H, 6.37; N, 12.55. *2-Anilino-2-(4-methoxyphenyl)acetonitrile* (Table 3, entry 12): White solid, mp: 95–97 °C; IR (KBr): 3329, 3011, 2932, 2210, 1602, 1507, 1436, 1241, 1023, 757 cm^{-1}. ^{1}H NMR (CDCl$_3$, 400 MHz): δ 3.84 (s, 3H), 4.00 (br s, 1H), 5.36 (s, 1H), 6.76–6.78 (m, 2H), 6.96–6.98 (m, 2H), 7.25–7.30 (m, 3H), 7.50–7.52 (m, 2H); ^{13}C NMR (CDCl$_3$, 100 MHz): δ 49.6, 55.4, 114.0, 114.6, 118.4, 120.2, 125.9, 128.6, 129.5, 144.7, 160.4. Anal. Calcd for $C_{15}H_{14}N_2O$: C, 75.61; H, 5.92; N, 11.76. Found: C, 75.67; H, 5.90; N, 11.79. *2-Anilino-2-(2,4-dichlorophenyl)acetonitrile* (Table 3, entry 17): White solid, mp 112–114 °C; IR (KBr): 3323, 3018, 2949, 2241, 1598, 1514, 1383, 1288, 937, 748 cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 4.00 (br s, 1H), 5.68 (s, 1H), 6.76–6.78 (m, 2H), 6.91–6.95 (m, 1H), 7.28–7.30 (m, 2H), 7.37–7.40 (m, 1H), 7.51–7.52 (d, 1H, J = 2.4 Hz), 7.68–7.70 (d, 1H, J = 8.0 Hz); ^{13}C NMR (CDCl$_3$, 100 MHz): δ 47.6, 114.3, 117.3, 120.7, 128.1, 129.6, 129.9, 130.3, 130.4, 134.3, 136.5, 144.2. Anal. Calcd for $C_{14}H_{10}Cl_2N_2$: C, 60.67; H, 3.64; N, 10.11. Found: C, 60.63; H, 3.65; N, 10.07. *2-(4-Toluidino)-2-phenylpropanenitrile* (Table 3, entry 21): White solid, mp 152–153 °C; IR (KBr): 3386, 3024, 2988, 2226, 1618, 1519, 1302, 1258, 807, 696 cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 1.94 (s, 3H), 2.19 (s, 3H), 4.16 (s, 1H), 6.45–6.47 (d, 2H, J = 8.4 Hz), 6.92–6.94 (d, 2H, J = 8.4 Hz), 7.33–7.42 (m, 3H), 7.62–7.64 (m, 2H). ^{13}C NMR (CDCl$_3$, 100 MHz): δ 20.4, 33.3, 57.4, 116.1, 120.8, 124.9, 128.5, 129.2, 129.4, 129.5, 140.0, 141.0. Anal. Calcd for $C_{16}H_{16}N_2$: C, 81.32; H, 6.82; N, 11.85. Found: C, 81.25; H, 6.83; N, 11.82. *1-(Anilino)cyclopentanecarbonitrile* (Table 3, entry 23): White solid, mp 67–68 °C; IR (KBr): 3365, 2982, 2942, 2235, 1602, 1520, 1310, 1258, 747, 691 cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 1.89–1.92 (m, 4H), 2.12–2.17 (m, 2H), 2.36–2.41 (m, 2H), 3.84 (s, 1H), 6.81–6.89 (m, 3H), 7.23–7.27 (m, 2H). ^{13}C NMR (CDCl$_3$, 100 MHz): δ 23.8, 40.2, 57.4, 115.6, 119.8, 122.2, 129.3, 144.0. Anal. Calcd for $C_{12}H_{14}N_2$: C, 77.38; H, 7.58; N, 15.04. Found: C, 77.45; H, 7.56; N, 15.01.

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