One-Pot Three-Component Solvent-Free Cyanoaroylation of Aldehydes Using Potassium Hexacyanoferrate(II) as an Environmentally Benign Cyanide Source

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Abstract: An efficient method for one-pot three-component solvent-free cyanoaroylation of aldehydes using potassium hexacyanoferrate(II) as an environmentally benign cyanide source and triethylamine as a catalyst has been described. This method has advantages of not using strongly toxic cyanating agents and volatile organic solvents. In addition, the product was obtained in high yield using a simple workup procedure.

Key words: aldehydes, cyanohydrins, green chemistry, multicomponent reaction, nucleophilic addition

Acylated cyanohydrins are important synthetic targets due to their use as insecticides[1] and as precursors to many useful classes of organic compounds.[2] Acylated cyanohydrins are generally synthesized by cyanoacylation of carbonyl compounds using HCN,[3] NaCN,[4] TMSCN,[5] $(R_2N)_2BCN$,[6] cyanoformate,[7] acetone cyanohydrin,[8] and acyl cyanide[9] as cyanide sources. However, these cyanating agents are strongly toxic and hazardous which render the nucleophilic additions of carbonyl compounds unsafe and environmentally unfriendly. Therefore, there is a need to explore environmentally friendly cyanating agents for the addition reactions of carbonyl compounds.

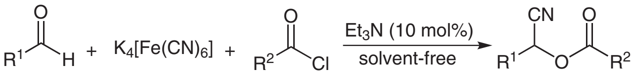
Potassium hexacyanoferrate(II), $K_4[Fe(CN)_6]$, is nontoxic and is even used in the food industry for metal precipitation. In addition, it has been described as an antiagglutinating auxiliary for table salt (NaCl). $K_4[Fe(CN)_6]$ is a byproduct of coal chemical industry, and commercially available on a ton scale and is even cheaper than KCN. Very recently, $K_4[Fe(CN)_6]$ has been shown to be an efficient cyanide source for the cyanation of halogenated arenes and aroyl chlorides to prepare benzonitriles[10] and aroyl cyanides.[11] However, these reported reactions for the use of $K_4[Fe(CN)_6]$ as a cyanating agent were all substitution reactions. No examples have been reported for addition reactions, especially for the cyanation addition of carbonyl compounds.

In this paper, we would like to report an efficient method for one-pot three-component cyanoaroylation of aldehydes using $K_4[Fe(CN)_6]$ as an environmentally friendly cyanide source and as a nucleophilic addition reagent under solvent-free conditions.

In order to explore the application of $K_4[Fe(CN)_6]$ as an environmentally friendly cyanating agent for the nucleophilic addition reactions, the three-component reaction of benzoyl chloride, $K_4[Fe(CN)_6]$ and benzaldehyde was investigated. Various reaction conditions, including the catalysts, solvents, reaction temperature and the reactant mole ratios, were studied. Firstly, many catalytic systems were tried out for the model reaction (Table 1). It was found that some metal salts (Table 1, entries 3–11), Lewis acids (Table 1, entries 12 and 13) and phase-transfer catalysts (Table 1, entries 14–16) had no obvious activities for the reaction. However, triethylamine was found to be an efficient catalyst for the reaction (Table 1, entries 17–19). The reaction was also tested using DMF, NMP, DMSO, THF, CH_2Cl_2, $CHCl_3$, or toluene as solvent, and it was found that DMF and NMP could be used as solvent for the reaction in the presence of triethylamine as a catalyst. However, the best yield was obtained under solvent-free conditions (Table 1, entry 19).

The temperature effect also is an important factor for the reaction. A suitable temperature should be favored to the decomposition of $K_4[Fe(CN)_6]$ and release of cyano groups from the iron complex because it is quite stable. Many tests showed that benzoyl chloride first reacted with $K_4[Fe(CN)_6]$ at 160 °C, then the mixture further reacted with benzaldehyde, catalyzed by triethylamine at room temperature. These were the optimal conditions.

The effect of reactant ratios on the yield of cyanoaroylation of benzaldehyde was also examined. It was found that when the mole ratio of benzoyl chloride, potassium hexacyanoferrate(II) and benzaldehyde was 5:1:5, the addition product could be obtained in high yield. This indicated that all cyano groups in $K_4[Fe(CN)_6]$ could be readily utilized in this reaction.



Scheme 1 Cyanoaroylation of aldehydes using $K_4[Fe(CN)_6]$ as cyanide source

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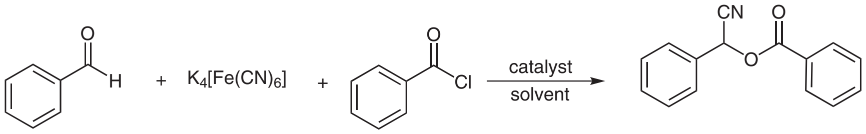
Table 1 The Effect of Catalysts and Solvents on the Yield of Cyanobenzoylation of Benzaldehyde[a]



Entry	Catalyst	Solvent	Yield (%)[b]
1	none	none	0
2	none	DMF	0
3	CuCl	DMF	0
4	CuI	DMF	10
5	$ZnCl_2$	DMF	26
6	ZnI_2	DMF	32
7	$NiCl_2$	DMF	34
8	NiI_2	DMF	20
9	AgCl	DMF	35
10	AgI	DMF	40
11	$Pd(OAc)_2$	DMF	55
12	$BiCl_3$	DMF	53
13	$AlCl_3$	NMP	47
14	18-crown-6	DMF	38
15	PEG-400	NMP	52
16	Et_4NI	DMF	33
17	Et_3N	DMF	78
18	Et_3N	NMP	75
19	Et_3N	none	89

[a] Reaction conditions: benzoyl chloride (15 mmol), potassium hexacyanoferrate(II) (3 mmol) and benzaldehyde (15 mmol).

[b] Isolated yield.

To explore the generality and scope of this reaction, representative aldehydes and acyl chlorides as substrates were examined (Scheme 1, Table 2).[12] Not only aromatic aldehydes (Table 2, entries 1–14) but also aliphatic aldehydes (Table 2, entries 19–23) were smoothly reacted under the reaction conditions to give the corresponding products. Methoxy, methyl and chloro groups on aromatic rings of various aromatic aldehydes were tolerated under this condition. Aromatic heterocyclic aldehyde, furfuraldehyde, was also active for the cyanoaroylation (Table 2, entries 15–18). Various aroyl chlorides, such as chloro-, bromo- and methyl-substituted benzoyl chlorides, were good substrates for the reactions to give the corresponding products in high yield. In addition, furoyl chloride was also converted into the corresponding products without difficulty.

A plausible mechanism, similar to that proposed by Deng[13] and Shi,[9b] is shown in Scheme 2. We suppose that aroyl chloride first reacts with $K_4[Fe(CN)_6]$ to afford aroyl cyanide, which could be isolated and identified,[14] then aroyl cyanide is activated by a nucleophilic attack by Et_3N to form the corresponding intermediate **A**, which reacts with aldehyde to give the cyanoalkoxide intermediate **B**. Then, intramolecular nucleophilic attack of the cyanoalkoxide on the carbonyl group in intermediate **B** produces the final *O*-aroyl cyanohydrin ester **C** and regenerates the Et_3N catalyst.

In conclusion, an efficient method for the one-pot three-component cyanoaroylation of aldehydes using potassium hexacyanoferrate(II) as an environmentally friendly cyanide source and triethylamine as catalyst under solvent-free conditions has been developed. The major advantages of this method are no use of strongly toxic cyanating agents, no use of volatile organic solvents, high yield, and simple workup procedure.

Table 2 Cyanoaroylation of Aldehydes Using $K_4[Fe(CN)_6]$ as Cyanide Source[a]

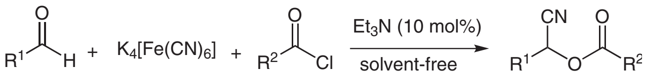
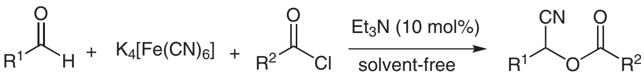
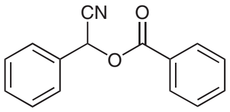
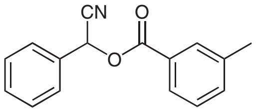
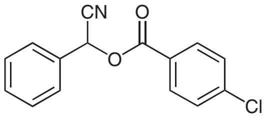
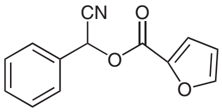
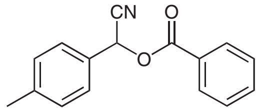
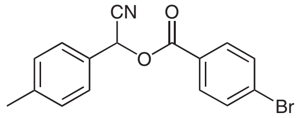
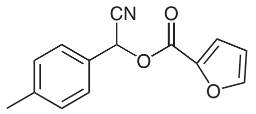
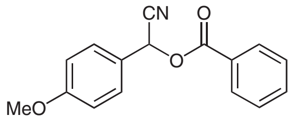
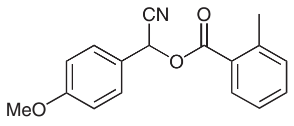
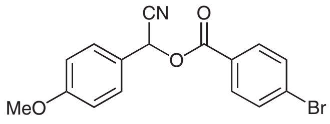
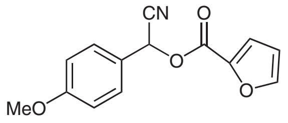
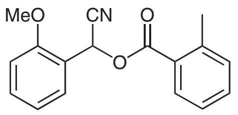
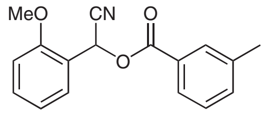
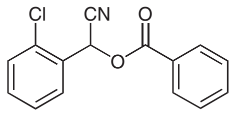
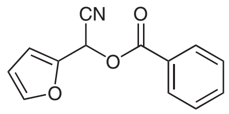
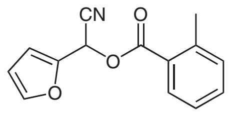
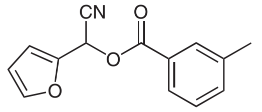
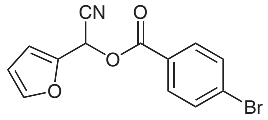
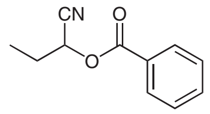
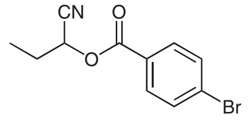
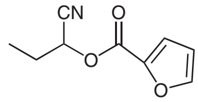
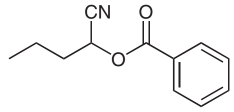
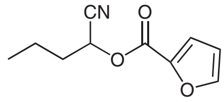


Table 2 Cyanoaroylation of Aldehydes Using $K_4[Fe(CN)_6]$ as Cyanide Source[a] (continued)



Entry	Product[15]	Time (h)	Yield (%)[b]
1		4	89
2		5	82
3		5	80
4		6	79
5		4	86
6		5	81
7		6	78
8		4	83
9		5	77
10		5	73
11		6	80
12		5	70
13		5	74
14		5	72
15		4	87
16		5	75
17		5	78
18		5	73
19		4	69
20		5	66
21		6	71
22		5	68
23		5	61

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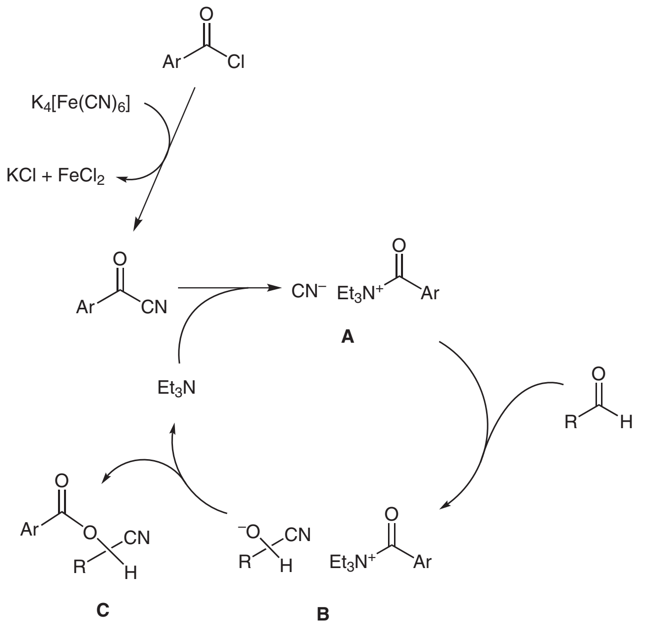
[a] All products were characterized by comparison of their melting points or boiling points, IR, and ^{1}H NMR spectra with those of authentic samples.

[b] Yields refer to isolated products.



Scheme 2 Proposed mechanism of Et_3N-catalyzed cyanoaroylation of aldehydes using $K_4[Fe(CN)_6]$ as cyanide source

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(12) **General Procedure**: To a 50-mL round-bottomed flask equipped with an air condenser, acyl chloride (15 mmol) and potassium hexacyanoferrate(II) (3 mmol) were added. Then the mixture was heated at 160 °C for the time indicated in Table 2. After the resulting mixture was cooled to r.t., aldehyde (15 mmol) and Et_3N (1.5 mmol) were added. The mixture was further stirred for 5–8 min at r.t. The progress of the reaction was monitored by TLC. After completion of the reaction, CH_2Cl_2 (20 mL) was added, and the solid was removed by filtration. The filtrate was then washed with icy H_2O (3×30 mL), and dried with anhyd $MgSO_4$. After removal of the solvent under reduced pressure, the residue was subjected to silica gel flash column chromatography (PE–EtOAc, 20:1) to obtain pure product. The analytical data for the representative products are given below.
Cyano(4-methoxyphenyl)methyl Benzoate (Table 2, entry 8): white solid. IR (KBr): 3057, 2250, 1731, 1610, 1514, 1250, 1060, 702 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 8.05$ (d, $J = 6.8$ Hz, 2 H), 7.56–7.62 (m, 5 H), 7.25 (d, $J = 6.8$ Hz, 2 H), 6.65 (s, 1 H), 3.83 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 164.6$, 161.1, 133.9, 130.1, 129.6, 128.6, 128.2, 123.9, 116.4, 114.6, 63.1, 55.4. Anal. Calcd for

$C_{16}H_{13}NO_3$: C, 71.90; H, 4.90; N, 5.24. Found: C, 71.96; H, 4.88; N, 5.21.

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(14) The analytical data for the isolated representative aroyl cyanide are given below. **Benzoyl Cyanide**: white solid. IR (KBr): 3073, 2224, 1679, 1594, 1448, 1255, 974, 697 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 8.13–8.15$ (m, 2 H), 7.78–7.82 (m, 1 H), 7.59–7.63 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 167.8$, 136.8, 133.2, 130.4, 129.5, 112.6.

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