Conjugate Hydrocyanation of Aromatic Enones Using Potassium Hexacyanoferrate(II) as an Eco-Friendly Cyanide Source

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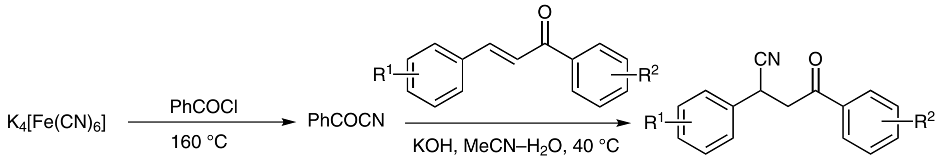
Abstract: A selective conjugate hydrocyanation of aromatic enones by a one-pot, two-step procedure using potassium hexacyanoferrate(II) as an original eco-friendly cyanide source, potassium hydroxide as a base, and benzoyl chloride as a promoter was described. This protocol has the advantages of a nontoxic cyanide source, high yield, and simple workup procedure.

Key words: conjugate hydrocyanation, 1,4-addition, aromatic enone, green chemistry, nucleophilic addition, potassium hexacyanoferrate(II)

The conjugate hydrocyanation of α,β-unsaturated ketones, especially aromatic enones, is an important C–C bond-forming reaction in synthetic organic chemistry which can produce significant β-cyano ketones. β-Cyano ketones are valuable synthons in synthetic organic chemistry.[1] Therefore, many different methods for the synthesis of β-cyano carbonyl compounds have been reported in the past years, which mainly take advantage of HCN,[2] KCN,[3] and Et_2AlCN[4] as original cyanide sources. However, these cyanide sources are strong toxic chemicals. Recently, it has been reported that β-cyano carbonyl compounds can be synthesized from α,β-unsaturated carbonyls using trimethylsilyl cyanide as a cyanide source.[5] In addition, β-cyanocarbonyl compounds have also been reported to be obtained by using acetone cyanohydrin as a cyanide source.[6] However, trimethylsilyl cyanide is very sensitive to moisture and can easily release toxic hydrogen cyanide. Acetone cyanohydrin is unstable and also easily releases toxic hydrogen cyanide under heating conditions. Furthermore, the preparations for both of them also require strong toxic hydrogen cyanide as original material. Therefore, there is a need to explore environmentally benign cyanating agents for cyanation reactions.

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 anti-agglutinating 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. Recently, $K_4[Fe(CN)_6]$ has been used as a cyanide source for some substitution reactions to synthesize benzonitriles,[7] aroyl cyanides,[8] benzyl cyanides,[9] and cinnamonitriles.[10] Our current research focused on the cyanation of unsaturated compounds including C=O or C=N by nucleophilic addition reactions using $K_4[Fe(CN)_6]$ as an eco-friendly cyanide source.[11] In this study, we report an efficient method for the conjugate hydrocyanation of unsaturated compounds bearing both C=O and C=C bonds, aromatic enones, using $K_4[Fe(CN)_6]$ as an original eco-friendly cyanide source.

First chalcone was selected as a substrate for the conjugate hydrocyanation of aromatic enones by a one-pot, two-step procedure using $K_4[Fe(CN)_6]$ as an original eco-friendly cyanide source (Scheme 1, R^1, R^2 = H). The reaction was attempted under different conditions such as using Lewis acids, Lewis bases, and organometallic compounds as catalysts at different temperatures in various solvents. However, no product could be obtained for this reaction because $K_4[Fe(CN)_6]$ is too stable to release cyanide ions under the studied conditions. In the later study it was found that some acyl chlorides could efficiently promote the process of conjugate hydrocyanation of $K_4[Fe(CN)_6]$ to chalcone to give 1,4-adduct, β-cyano ketone. The thermodynamically less stable 1,2-addition product and other side reactions were not observed (Table 1). Among the studied acyl chlorides, acetyl chloride had no promoting effect on the reaction. It may be caused by their volatility and instability (Table 1, entry 1). Furoyl chloride could promote the reaction to gain the corresponding product in moderate yield (Table 1, entry 4). Aroyl chlorides could effectively promote the reaction to



Scheme 1 Conjugate hydrocyanation of aromatic enones using $K_4[Fe(CN)_6]$ as a cyanide source

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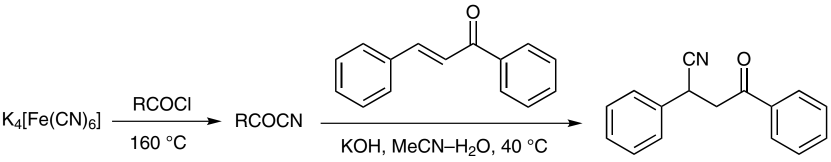
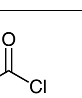
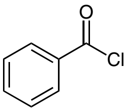
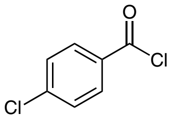
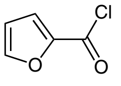
give 1,4-adduct in high yield (Table 1, entries 2 and 3). Especially benzoyl chloride could afford the best yield (Table 1, entry 2). The intermediates, acyl cyanides, could be isolated and identified from the reaction system.[12] In addition, it was also found that only 0.2 equivalents of $K_4[Fe(CN)_6]$ were needed for 1 mol of chalcone, which indicated that six CN^- of $K_4[Fe(CN)_6]$ could be fully utilized in this reaction. It is noteworthy to mention that $K_4[Fe(CN)_6]\cdot 3H_2O$ could not be used as cyanide source because it may cause hydration of promoters, acyl chlorides, to form carboxylic acids in the first step of the one-pot, two-step reaction.

In addition, it was found that bases also played a critical role in the studied reaction. Some bases were examined for the reaction of chalcone with $K_4[Fe(CN)_6]$ using benzoyl chloride as a promoter. Potassium carbonate had no effect on the reaction. *N*,*N*-Dimethylaminopyridine (DMAP), 1,4-diazabicyclo-[2.2.2]octane (DABCO), and triethylamine (Et_3N) could give the product in low yield (Table 2, entries 2–4). However, the reaction could proceed smoothly in the presence of potassium hydroxide to give β-cyano ketone in high yield (Table 2, entry 5).

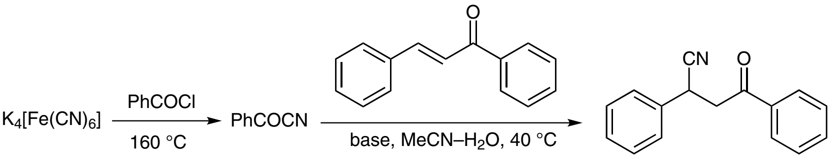
Table 1 The Effect of Different Promoters on the Yield of Conjugate Hydrocyanation of Chalcone Using $K_4[Fe(CN)_6]$ as a Cyanide Source[a]



Entry	Promoter	Reaction time (h)	Yield (%)[b]
1		24	0
2		19	87
3		19	72
4		19	48

[a] Reaction conditions: $K_4[Fe(CN)_6]$ (0.4 mmol), promoter (2 mmol), chalcone (1.5 mmol) in MeCN (5 mL) and KOH (2.4 mmol) in H_2O (3 mL).
[b] Isolated yield.

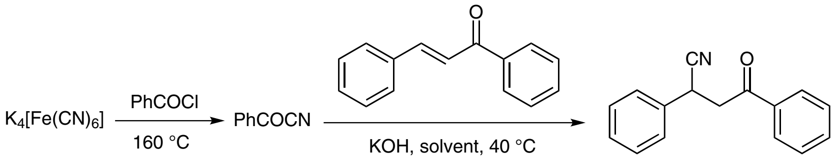
Table 2 The Effect of Bases on the Yield of Conjugate Hydrocyanation of Chalcone Using $K_4[Fe(CN)_6]$ as a Cyanide Source[a]



Entry	Base	Reaction time (h)	Yield (%)[b]
1	K_2CO_3	24	0
2	DMAP	19	17
3	DABCO	19	15
4	Et_3N	19	35
5	KOH	19	87

[a] Reaction conditions: $K_4[Fe(CN)_6]$ (0.4 mmol), benzoyl chloride (2 mmol), chalcone (1.5 mmol) in MeCN (5 mL) and base (2.4 mmol) in H_2O (3 mL).
[b] Isolated yield.

Table 3 The Effect of Solvents on the Yield of Conjugate Hydrocyanation of Chalcone Using $K_4[Fe(CN)_6]$ as a Cyanide Source[a]



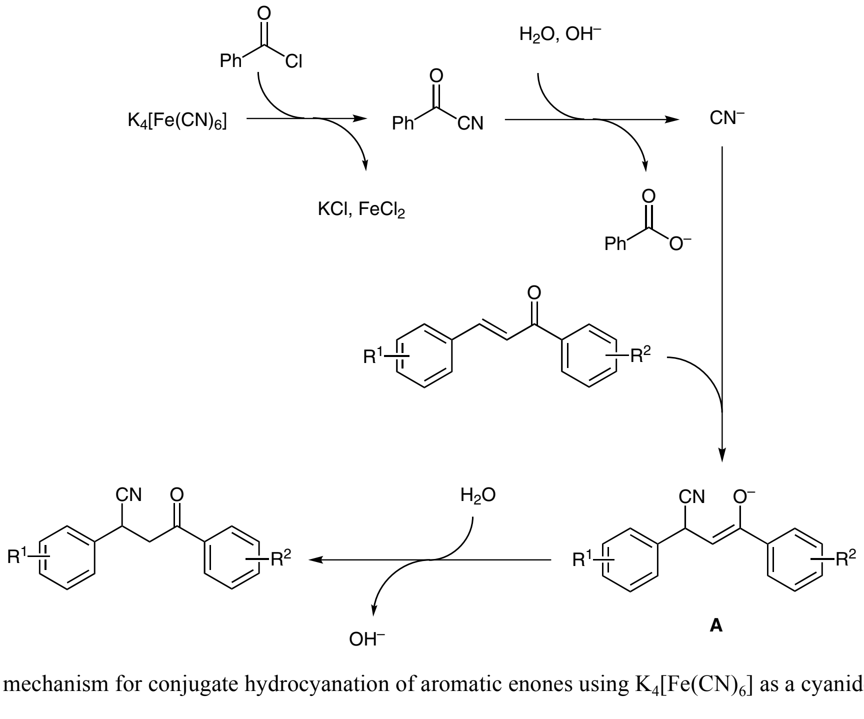
Entry	Solvent	Reaction time (h)	Yield (%)[b]
1	PhMe	24	0
2	Et_2O	24	0
3	THF	19	27
4	DMF	19	23
5	MeOH	19	65
6	EtOH	19	74
7	MeCN	19	87

[a] Reaction conditions: $K_4[Fe(CN)_6]$ (0.4 mmol), benzoyl chloride (2 mmol), chalcone (1.5 mmol) in solvent (5 mL) and KOH (2.4 mmol) in H_2O (3 mL).
[b] Isolated yield.

The solvents also have significant effects on the reaction (Table 3). It was found that some nonpolar solvents, such as diethyl ether and toluene, were not available for the reaction (Table 3, entries 1 and 2). However, the reaction in polar solvents such as THF, DMF, MeOH, EtOH, and MeCN could give the desired product in moderate to high yield (Table 3, entries 3–7). Among them, MeCN was the best solvent for the reaction.

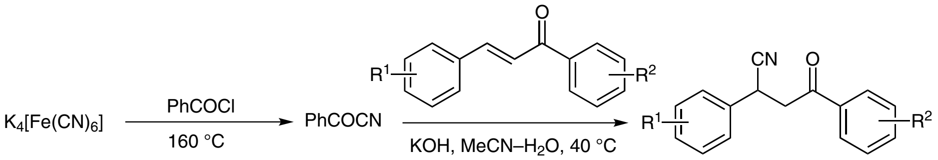
Depending on the promising findings above, various conjugate hydrocyanations of $K_4[Fe(CN)_6]$ to aromatic enones were examined using benzoyl chloride as a promoter and potassium hydroxide as a base (Scheme 1 and Table 4).[13] The different aromatic enones bearing electron-donating groups, such as methyl and methoxy, and electron-withdrawing groups, such as chloro, bromo, and nitro, could conduct 1,4-addition reactions smoothly to give β-cyano ketones in high yield. The substituents on aromatic enones have no obvious effect on the yield of products.

A plausible mechanism for conjugate hydrocyanation of $K_4[Fe(CN)_6]$ to aromatic enones is shown in Scheme 2. $K_4[Fe(CN)_6]$ first reacts with benzoyl chloride to form



Scheme 2 The proposed mechanism for conjugate hydrocyanation of aromatic enones using $K_4[Fe(CN)_6]$ as a cyanide source

Table 4 Conjugate Hydrocyanation of Aromatic Enones Using $K_4[Fe(CN)_6]$ as a Cyanide Source[a]



Entry	R^1	R^2	Reaction time (h)	Yield (%)[b]
1	H	H	19	87
2	H	4-Me	24	78
3	H	4-OMe	20	78
4	H	4-Cl	18	85
5	H	4-O_2N	20	74
6	4-Me	H	18	82
7	4-Me	4-Me	20	85
8	4-Me	4-Cl	18	88
9	4-OMe	H	22	75
10	4-OMe	4-Me	18	82
11	4-Cl	H	20	88
12	4-Cl	4-Me	17	92
13	4-Cl	4-Cl	15	89
14	2,4-Cl_2	H	22	71
15	3-Br	H	20	86
16	4-O_2N	H	21	76

[a] Reaction conditions: $K_4[Fe(CN)_6]$ (0.4 mmol), benzoyl chloride (2 mmol), aromatic enones (1.5 mmol) in MeCN (5 mL) and KOH (2.4 mmol) in H_2O (3 mL).

[b] Isolated yield.

benzoyl cyanide. Then benzoyl cyanide is attacked by water in the presence of hydroxyl ions to produce a cyanide ion in situ, which subsequently reacts with aromatic enones by 1,4-additions to form intermediates **A**. Intermediates **A** combine with the hydrogen ion from water to produce the final products, β-cyano ketones.

In summary, an efficient method for conjugate hydrocyanation of aromatic enones by a one-pot, two-step procedure using $K_4[Fe(CN)_6]$ as an original eco-friendly cyanide source, benzoyl chloride as a promoter, and potassium hydroxide as a base by selective 1,4-addition reactions has been developed. The protocol has advantages of using nontoxic, nonvolatile, and inexpensive cyanide source, high yield, and simple workup procedure. Further investigations employing other kinds of enones are under way and will be reported in due course.

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(12) The analytical data for the isolated representative acyl cyanides are given below.

Benzoyl Cyanide

White solid. IR (KBr): 2224 (CN), 1679 (C=O) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.15–8.13 (m, 2 H), 7.82–7.78 (m, 1 H), 7.63–7.59 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.8, 136.8, 133.2, 130.4, 129.5, 112.6.

(13) **General Procedure**

The mixture of $K_4[Fe(CN)_6]$ (0.4 mmol) and benzoyl chloride (2 mmol) was heated at 160 °C for 3 h, then the reaction system was cooled to 40 °C, and aromatic enone (1.5 mmol) in MeCN (5 mL) and KOH (2.4 mmol) in H_2O (3 mL) were added. The mixture was further stirred at 40 °C for the appropriate time indicated in Table 4. After completion of the reaction, monitored by TLC, the resulting mixture was filtered to remove the solids, and the filtrate was concentrated and isolated by column chromatography using PE–EtOAc (10:1) as eluent to give the pure product. The analytical data for representative products are shown below.

4-Oxo-2,4-diphenylbutanenitrile (Table 4, Entry 1)

White solid; mp 120–122 °C. IR (KBr): 1681 (C=O), 2238 (CN) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.51 (dd, 1 H, J = 5.6, 18.0 Hz, CHCH_aHCO), 3.74 (dd, 1 H, J = 7.6, 18.0 Hz, CHCH_bHCO), 4.58 (dd, J = 6.0, 6.4 Hz, 1 H, ArC$H$$CH_2$), 7.26–7.43 (m, 7 H, ArH), 7.58–7.62 (m, 1 H, ArH), 7.92–7.94 (m, 2 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 31.9, 44.5, 120.6, 127.5, 128.1, 128.4, 128.8, 129.3, 133.9, 135.2, 135.6 194.6 ppm. Anal. Calcd for $C_{16}H_{13}NO$ (235.28): C, 81.68; H, 5.57; N, 5.95. Found: C, 81.59; H, 5.56; N, 5.97.

4-(4-Methoxyphenyl)-4-oxo-2-phenylbutanenitrile (Table 4, Entry 3)

Oil. IR (KBr): 1676 (C=O), 2243 (CN) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.37 (dd, J = 6.0, 17.6 Hz, 1 H, CHCH_aHCO), 3.60 (dd, J = 8.4, 17.6 Hz, 1 H, CHCH_bHCO), 3.79 (s, 3 H, CH_3), 4.49 (dd, J = 6.0, 8.0 Hz, 1 H, ArC$H$$CH_2$), 6.85 (d, J = 6.8 Hz, 2 H, ArH), 7.23–7.37 (m, 5 H, ArH), 7.83 (d, J = 6.8 Hz, 2 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 31.9, 44.1, 55.5, 113.9, 120.8, 127.4, 128.3, 128.7, 129.2, 130.4, 135.4, 164.0, 193.0 ppm. Anal. Calcd for $C_{17}H_{15}NO_2$ (265.31): C, 76.96; H, 5.70; N, 5.28. Found: C, 76.80; H, 5.71; N, 5.30.