

Selective Monohydrocyanation of Diimine using Potassium Hexacyanoferrate(II)-Benzoyl Chloride Reagent System as a Cyanide Source

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Abstract. The selective monohydrocyanation of diimines using potassium hexacyanoferrate(II)-benzoyl chloride reagent system as a cyanide source under catalyst-free condition is described. The advantages of this protocol are the non-toxic, non-volatile and inexpensive cyanide source, high yield, and simple work-up procedure.

Keywords. Aminonitrile; monohydrocyanation; diamine; potassium hexacyanoferrate(II)

1. Introduction

Nucleophilic addition of cyanide to imine is an important way to access α -aminonitriles.¹ α -Aminonitriles are very useful building blocks in the construction of a variety of organic intermediates, such as natural and unnatural α -amino acids,² different nitrogen-containing heterocycles like imidazoles,³ thiadiazoles.⁴ Over the past decade, lots of synthetic protocols for the preparation of α -aminonitriles have been reported. The direct introduction of cyano groups into molecules which contain unsaturated carbon-nitrogen bonds appears to be one of the most straightforward methods. However, some of these approaches use strongly toxic chemicals, such as HCN,⁵ NaCN⁶ and KCN,⁷ as cyanating agents, which render nucleophilic additions unsafe and environmentally unfriendly. Recently, some safer cyanating agents, such as Zn(CN)₂,⁸ TMSCN⁹ and acetone cyanohydrin,¹⁰ were also reported. However, the exploration for green cyanide sources still has very important meaning to the environment.

Potassium hexacyanoferrate(II), K₄[Fe(CN)₆], is a byproduct of the coal chemical industry and commercially available on a ton scale. It is also used in the food industry for metal precipitation. In addition, it has been described as an anti-agglutinating auxiliary for table salt (NaCl). Recently, K₄[Fe(CN)₆] has been used as a cyanide source for some substitution reactions to

synthesize benzonitriles,^{11–14} aryl cyanides,¹⁵ sulfonyl cyanides,¹⁶ benzyl cyanides,¹⁷ and cinnamonitriles.¹⁸ Our current research interests focused on the cyanation of unsaturated compounds including C=O, C=N and/or C=C bonds by nucleophilic addition reactions using K₄[Fe(CN)₆] as a cyanide source.^{19–24} Especially, our research group recently has reported some examples for the hydrocyanation of enones,^{25–28} imines,^{29–31} unsaturated esters³² and unsaturated nitriles³³ by using K₄[Fe(CN)₆] as a cyanide source. As an extension, in this work, we report an efficient method for the selective monohydrocyanation of substrates bearing two C=N bonds, diimines, using K₄[Fe(CN)₆]-benzoyl chloride reagent system as a cyanide source under catalyst-free condition.

2. Experimental

2.1 General information

IR spectra were recorded using KBr pellets on an Alpha Centauri FTIR spectrophotometer. ¹H NMR and ¹³C NMR spectra were recorded on a Mercury-400BB instrument using CDCl₃ as solvent and Me₄Si as internal standard. Elemental analyses were performed on a Vario El Elemental Analysis instrument. Melting points were observed in an electrothermal melting point apparatus. Potassium hexacyanoferrate(II) was dried at 80°C under vacuum for 24 h and finely powdered prior to use. Diimines were prepared according to literature procedure.³⁴

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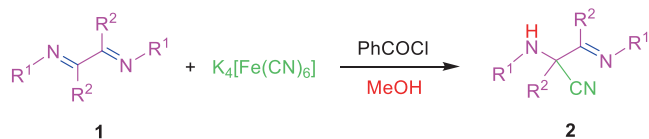
2.2 The general procedure for the monohydrocyanation of diimines

The mixture of $K_4[Fe(CN)_6]$ (0.2 mmol) and benzoyl chloride (1.2 mmol) was heated at 160°C for 3 h, then the reaction system was cooled to room temperature and diimine (1 mmol) in 20 mL of MeOH was added. The mixture was stirred at room temperature for appropriate times indicated in Table 2. After completion of the reaction monitored by TLC, the resulting mixture was filtered, and the filtrate was concentrated under reduced pressure, and the residue was isolated by column chromatography using petroleum ether and ethyl acetate as an eluent to obtain pure product.

3. Results and Discussion

Previous work in our group showed that $K_4[Fe(CN)_6]$ can abstract cyanide ions when using an efficient promoter without transition metal catalysts. It was found that benzoyl chloride could efficiently promote $K_4[Fe(CN)_6]$ to release cyanide ions and yield an intermediate, benzoyl cyanide, which could be identified and isolated from the reaction system.³⁵ In this paper, we focus on the hydrocyanation of diimines with $K_4[Fe(CN)_6]$ by a one-pot two-step procedure using benzoyl chloride as a promoter.

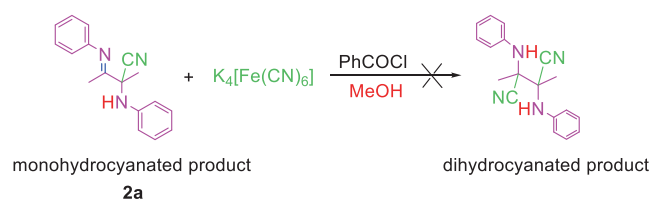
Initially, *N,N'*-diphenylbutane-2,3-diimine (**1a**) (Scheme 1, $R^1 = Ph$, $R^2 = Me$) was selected as a substrate to examine the feasibility of hydrocyanation with $K_4[Fe(CN)_6]$. It was found that **1a** could be hydrocyanated smoothly under catalyst-free condition to afford 2-methyl-2-(phenylamino)-3-(phenylimino)butanenitrile (**2a**) as sole product in 91% yield only using benzoyl chloride as a promoter. This reaction was even conducted using bases, acids or transition metal complexes as catalysts. However, no improved yield was observed. In this reaction, it was found that for 1 mol of **1a**, only 0.2 equiv. of $K_4[Fe(CN)_6]$ was required, which indicated that all six CN^- groups in $K_4[Fe(CN)_6]$ could be readily utilized in this reaction. However, the dihydrocyanated product was not observed under the studied conditions. This result indicates the high monohydrocyanating selectivity of **1a** to **2a**.



Scheme 1. Selective monohydrocyanation of diimines with $K_4[Fe(CN)_6]$.

In order to further confirm the possibility of dihydrocyanation, the isolated product **2a** was further reacted with $K_4[Fe(CN)_6]$ -benzoyl chloride reagent system under similar condition, including the use of an excess amount of $K_4[Fe(CN)_6]$, prolonged reaction time and elevated reaction temperature (Scheme 2). However, no dihydrocyanated product was obtained. This result further demonstrated the monohydrocyanation selectivity of **1a**. The possible reason is that steric hindrance of monohydrocyanated product **2a** efficiently blocked further hydrocyanation of the second $C=N$ bond of **2a** with $K_4[Fe(CN)_6]$.

The solvent also played an important role in this reaction. It was found that the model reaction in toluene could not take place (Table 1, entry 1). The reaction in THF, 1,4-dioxane, CH_2Cl_2 , MeCN, DMSO and DMF could give the desired product in moderate yield (Table 1, entries 2–7). In contrast, the reaction in MeOH and EtOH afforded the desired product in high yield (Table 1, entries 8–9). Among them, MeOH was the best solvent for the reaction (Table 1, entry 8).



Scheme 2. Further hydrocyanation of monohydrocyanated product **2a**.

Table 1. The effect of solvents on the yield of the monohydrocyanation of **1a** with $K_4[Fe(CN)_6]$ ^a.

Entry	Solvent	Time (h)	Yield (%) ^b
1	toluene	24	0
2	THF	24	26
3	1,4-dioxane	24	38
4	CH_2Cl_2	24	43
5	MeCN	24	48
6	DMSO	24	53
7	DMF	24	59
8	MeOH	10	91
9	EtOH	10	79

^a Reaction condition: **1a** (1 mmol), potassium hexacyanoferrate(II) (0.2 mmol), benzoyl chloride (1.2 mmol) in 20 mL of solvent.

^b Isolated yields.

Table 2. Monohydrocyanation of diimines with $K_4[Fe(CN)_6]$ -benzoyl chloride reagent system ^a.

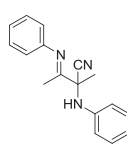
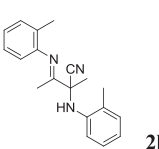
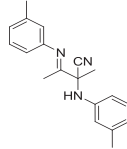
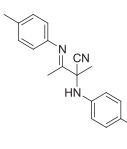
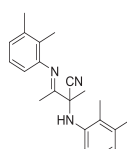
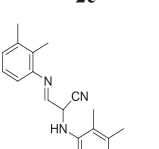
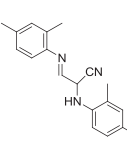
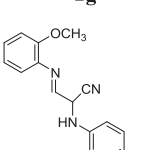
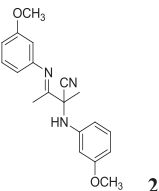
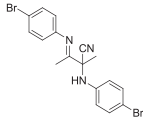
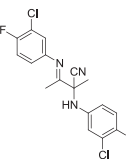
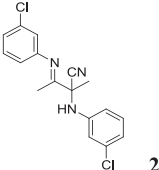

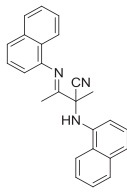
Entry	R ¹	R ²	Product	Time (h)	Yield (%) ^b
$ \begin{array}{c} \text{R}^1\text{-N} \\ \diagdown \\ \text{C}=\text{C} \\ \diagup \\ \text{R}^2\text{-N} \\ \text{R}^2 \end{array} + K_4[Fe(CN)_6] \xrightarrow[\text{MeOH}]{\text{PhCOCl}} \begin{array}{c} \text{R}^1\text{-N} \\ \\ \text{C} \\ \\ \text{R}^2 \\ \\ \text{CN} \\ \diagup \\ \text{C} \\ \diagdown \\ \text{R}^2\text{-N} \\ \text{R}^1 \end{array} $					
1	C ₆ H ₅	CH ₃	 2a	10	91
2	2-CH ₃ C ₆ H ₄	CH ₃	 2b	12	87
3	3-CH ₃ C ₆ H ₄	CH ₃	 2c	12	89
4	4-CH ₃ C ₆ H ₄	CH ₃	 2d	10	98
5	2,3-(CH ₃) ₂ C ₆ H ₃	CH ₃	 2e	12	83
6	2,3-(CH ₃) ₂ C ₆ H ₃	H	 2f	12	89
7	2,4-(CH ₃) ₂ C ₆ H ₃	H	 2g	12	87
8	2-CH ₃ OC ₆ H ₄	H	 2h	12	86

Table 2. Continued.

Entry	R ¹	R ²	Product	Time (h)	Yield (%) ^b
9	3-CH ₃ OC ₆ H ₄	CH ₃	 2i	10	87
10	4-BrC ₆ H ₄	CH ₃	 2j	10	91
11	3-Cl-4-FC ₆ H ₃	CH ₃	 2k	12	83
12	3-ClC ₆ H ₄	CH ₃	 2l	24	85
13		CH ₃	 2m	24	81

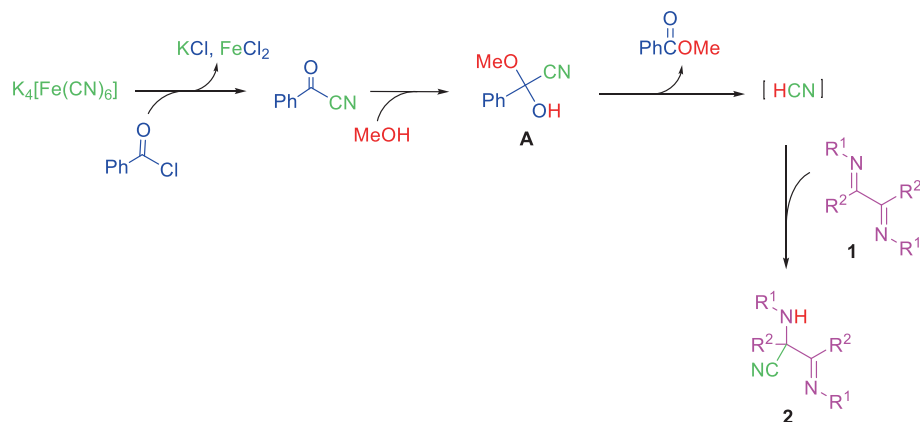
^a Reaction conditions: diimine (1 mmol), K₄[Fe(CN)₆] (0.2 mmol), benzoyl chloride (1.2 mmol), MeOH (20 mL).

^b Isolated yield.

Based on the above findings, a series of diimines **1** were used as substrates to conduct the monohydrocyanation in MeOH with K₄[Fe(CN)₆]-benzoyl chloride reagent system as a cyanide source under catalyst-free conditions (Scheme 1 and Table 2). Diimines **1** with electron-donating groups on the aromatic rings of R¹ afforded the products in slightly higher yield than diimines **1** with electron-withdrawing groups. In addition, diimines **1** bearing *ortho*-substituted aromatic rings could give slightly lower yields than the *meta*- and *para*-substituted analogues because of the large steric hindrance. The monohydrocyanation of unsymmetrical diimines was also investigated under similar conditions. However, complex mixtures were observed for each

substrate. This indicated that R¹ and R² groups had no selective effect on the monohydrocyanation.

A plausible mechanism for the monohydrocyanation of diimines using K₄[Fe(CN)₆]-benzoyl chloride reagent system as a cyanide source is shown in Scheme 3. First, K₄[Fe(CN)₆] reacts with benzoyl chloride to form benzoyl cyanide as an intermediate, which was confirmed by its isolation and identification. Then, benzoyl cyanide is attacked by methanol to yield nucleophilic addition intermediate **A**. Intermediate **A** undergoes the loss of methyl benzoate to produce hydrogen cyanide *in situ*. Nucleophilic additions of hydrogen cyanide to diimines **1** yield α -aminonitriles **2** as final products.



Scheme 3. The proposed mechanism for the monohydrocyanation of diimines with $K_4[Fe(CN)_6]$ -benzoyl chloride reagent system.

4. Conclusions

In summary, an efficient method has been developed for the selective monohydrocyanation of diimines to synthesize α -aminonitriles bearing C=N bonds by one-pot two-step procedure using $K_4[Fe(CN)_6]$ and benzoyl chloride reagent system as a cyanide source under transition metal catalyst-free condition. Non-toxic, non-volatile and inexpensive cyanide source, high yield and simple work-up procedures are the advantages of this protocol.

Supplementary Information (SI)

Full set of characterization data (IR, 1H and ^{13}C NMR spectra) and Figures S1–S39 are available at www.ias.ac.in/chemsci.

Acknowledgements

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