Monohydrocyanation of Symmetrical Azines Using Potassium Hexacyanoferrate(II) as an Environmentally Friendly Cyanide Source

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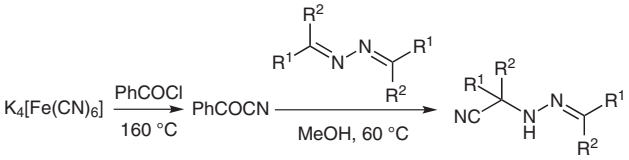
Abstract: The monohydrocyanation of symmetrical azines to synthesize α-hydrazinonitriles using potassium hexacyanoferrate(II) as cyanide source and benzoyl chloride as a promoter under catalyst-free conditions is described. The advantages of this protocol are the environmentally friendly cyanide source, high yield, and simple work-up procedure.

Key words: green chemistry, hydrocyanation, nucleophilic addition, synthetic methods, azines

α-Hydrazinonitriles are important organic intermediates that can be easily transformed into α-hydrazino acids,[1] and further into α-hydrazino peptides, α-amino acids, and even nitrogen-containing heterocycles.[2] Although α-hydrazinonitriles have been synthesized by substitution of cyanohydrin with phenylhydrazine in ethanol[3] and reduction of *N*-(cyanomethyl)-*N*-phenylnitrous amide with zinc in acetic acid,[4] a more general route is the hydrocyanation of substances containing the C=N–N fragment, such as *N*,*N*-dialkylhydrazones[5] and *N*-acylhydrazones.[6] However, these hydrocyanation reactions usually use HCN[7] or KCN[8] as cyanide sources. Clearly, these compounds are highly toxic, unfriendly and unsafe for the environment. Recently, the use of TMSCN as a cyanide source for hydrocyanation reactions has been investigated because of the lower toxicity of this reagent compared to the alternatives.[6] However, TMSCN is sensitive to moisture and can easily liberate highly toxic hydrogen cyanide. Therefore, there remains a need to develop an environmentally friendly cyanide source for the synthesis of α-hydrazinonitriles.

Potassium hexacyanoferrate(II), $K_4[Fe(CN)_6]$, is mainly used as a carburizing agent in the iron and steel industry, however, it is also used in the food industry for metal precipitation and as an anticoagulant for table salt (NaCl). $K_4[Fe(CN)_6]$ is a byproduct of the coal chemical industry and is commercially available on a ton scale. Furthermore, it is even cheaper than KCN. Recently, $K_4[Fe(CN)_6]$ has been used as a cyanide source in substitution reactions to synthesize benzonitriles,[9] aroyl cyanides,[10] benzyl cyanides,[11] cinnamonitriles,[12] dihaloacrylonitriles,[13] and cyano-substituted heterocycles.[14] Our recent research interests focused on the cyanation of unsaturated compounds by nucleophilic addition reactions using $K_4[Fe(CN)_6]$ as an environmentally friendly cyanide source, which included the cyanation of aldehydes and ketones to cyanohydrins,[15] the cyanation of aldimines, ketimines, and sulfonylimines to α-aminonitriles,[16] and the cyanation of α,β-unsaturated ketones and esters to the corresponding β-cyano compounds.[17] As an extension of such research, in this work, we report the selective monohydrocyanation of substrates including the C=N–N=C fragment, azines, to synthesize α-hydrazinonitriles by using $K_4[Fe(CN)_6]$ as an environmentally friendly cyanide source under catalyst-free conditions.

Initially, the hydrocyanation of azines was attempted by using benzalazine **1a** (R^1 = Ph, R^2 = H; Scheme 1)[18] as substrate and $K_4[Fe(CN)_6]$ as an environmentally friendly cyanide source. The reaction was conducted under different conditions including the use of Lewis acids, Lewis bases, and organometallic compounds as catalysts or catalyst-free conditions at different temperature in various solvents. Unfortunately, no products were observed for this reaction because of the stability of $K_4[Fe(CN)_6]$. However, in subsequent research, it was found that benzoyl chloride could react with $K_4[Fe(CN)_6]$ to liberate CN^- and form benzoyl cyanide as an intermediate, which subsequently reacted with **1a** to give monohydrocyanation product, α-hydrazinonitrile, in high yield. 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 dihydrocyanation product was not observed under the studied conditions including the use of an excess amount of $K_4[Fe(CN)_6]$, prolonged reaction time, and elevated reaction temperature.



Scheme 1 The monohydrocyanation of symmetrical azines using $K_4[Fe(CN)_6]$ as an environmentally friendly cyanide source

It was also confirmed that the solvent played a key role in the reaction (Table 1). It was found that no α-hydrazinonitriles were obtained in solvents such as *N*,*N*-dimethylformamide, dimethyl sulfoxide, or toluene (Table 1,

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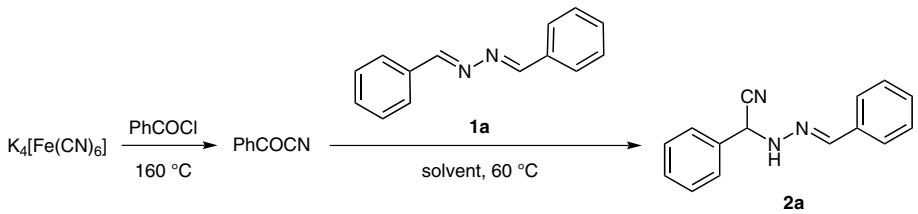
Table 1 Effect of Solvent on the Yield of Monohydrocyanation of **1a** with $K_4[Fe(CN)_6]$ as Cyanide Source[a]



Entry	Solvent	Time (h)	Yield (%)[b]
1	DMF	16	0
2	DMSO	16	0
3	toluene	16	0
4	MeOH	6	85
5	EtOH	16	73
6	THF	18	50
7	MeCN	16	60

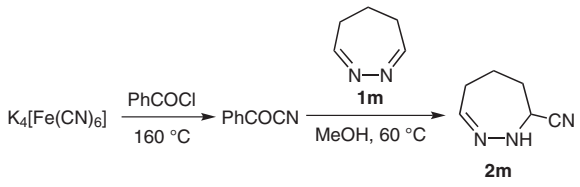
[a] Reaction conditions: **1a** (1 mmol), $K_4[Fe(CN)_6]$ (0.2 mmol), benzoyl chloride (1.2 mmol), solvent (20 mL).
[b] Isolated yield.

entries 1–3). However, the reaction in methanol, ethanol, acetonitrile or tetrahydrofuran afforded the desired product in moderate to high yield (Table 1, entries 4–7), with the best result being obtained in methanol (Table 1, entry 4).

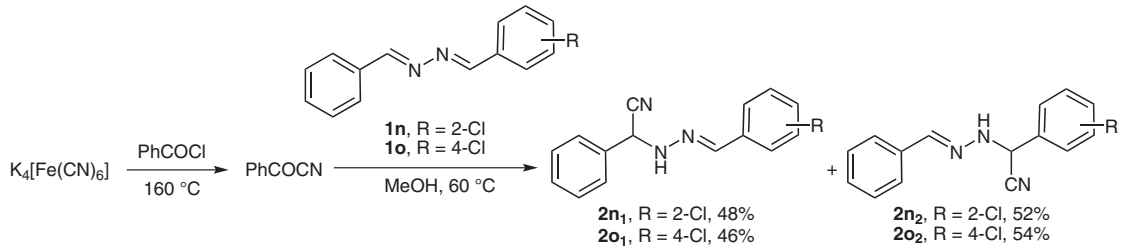
Based on the above findings, a series of symmetrical azines were employed in the monohydrocyanation using $K_4[Fe(CN)_6]$ in MeOH as an environmentally friendly cyanide source and benzoyl chloride as a promoter under catalyst-free conditions (Table 2).[19] It was found that symmetrical azines with electron-donating groups on the aromatic rings of R^1 gave the products in high yield (Table 2, entries 2–5). Whereas, symmetrical azines with electron-withdrawing groups on the aromatic rings of R^1 gave slightly lower yield and required longer reaction time (Table 2, entries 6–10). The substituents in the *ortho*- and *para*-position of the aromatic rings had no clear effect on the product yield. For symmetrical azines with R^2 = Me, the reactions slowed down significantly because of the steric hindrance imparted by the methyl group, and the yield was also lower than their analogues with R^2 = H (Table 2, entries 11 and 12).

A symmetrical azine with an aliphatic ring, 5,6-dihydro-4*H*-1,2-diazepine (**1m**), reacted more rapidly and afforded the monohydrocyanation product in 93% yield (Scheme 2).

The monohydrocyanation of unsymmetrical azines (Scheme 3), such as azine **1n** (R = 2-Cl) and **1o** (R = 4-Cl), was also investigated under similar conditions. However, mixtures of two kinds of monohydrocyanation products were obtained in almost 1:1 ratio for each substrate in 79% (for $\mathbf{2n_1}$ and $\mathbf{2n_2}$) and 83% (for $\mathbf{2o_1}$ and $\mathbf{2o_2}$) overall yield. This indicated that R groups on the aromatic rings had no clear effect on the monohydrocyanation.

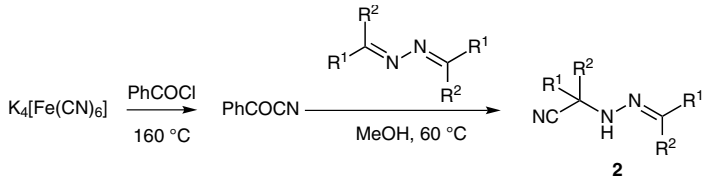


Scheme 2 The monohydrocyanation of 5,6-dihydro-4*H*-1,2-diazepine using $K_4[Fe(CN)_6]$ as an environmentally friendly cyanide source



Scheme 3 The monohydrocyanation of unsymmetrical azines using $K_4[Fe(CN)_6]$ as an environmentally friendly cyanide source

Table 2 Monohydrocyanation of Symmetrical Azines with $K_4[Fe(CN)_6]$ as Cyanide Source[a]



2

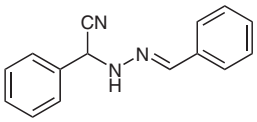
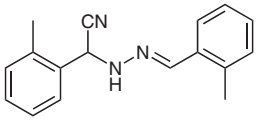
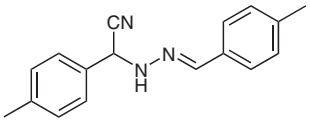
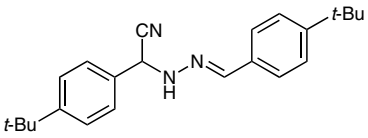
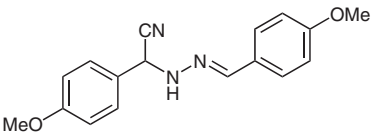
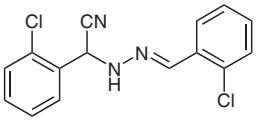
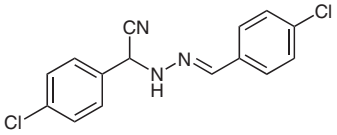
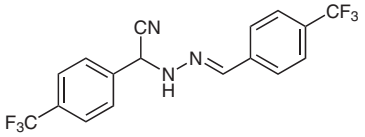
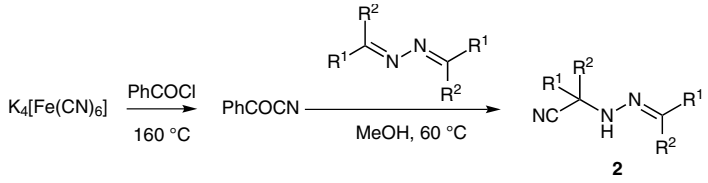
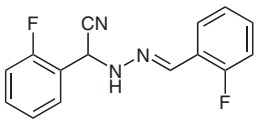
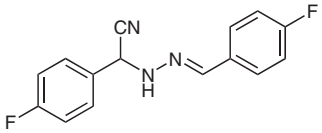
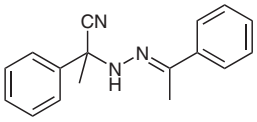
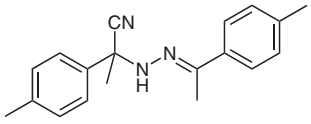
Entry	R^1	R^2	Product	Time (h)	Yield (%)[b]	Mp (°C)
1	Ph	H	 **2a**	6	85	100–102
2	2-MeC_6H_4	H	 **2b**	4	86	108–110
3	4-MeC_6H_4	H	 **2c**	6	87	104–106
4	4-*t*-BuC_6H_4	H	 **2d**	8	80	98–100
5	4-$MeOC_6H_4$	H	 **2e**	10	85	93–95
6	2-ClC_6H_4	H	 **2f**	16	76	112–114
7	4-ClC_6H_4	H	 **2g**	18	77	103–105
8	4-$F_3CC_6H_4$	H	 **2h**	16	73	77–79

Table 2 Monohydrocyanation of Symmetrical Azines with $K_4[Fe(CN)_6]$ as Cyanide Source[a] (continued)

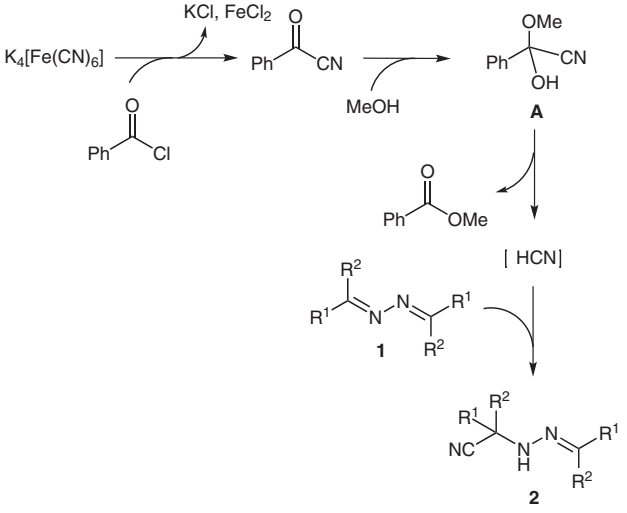


Entry	R^1	R^2	Product	Time (h)	Yield (%)[b]	Mp (°C)
9	2-FC_6H_4	H	 **2i**	19	66	42–44
10	4-FC_6H_4	H	 **2j**	20	70	139–141
11	Ph	Me	 **2k**	24	60	110–112
12	Ph	Me	 **2l**	24	63	140–142

[a] Reaction conditions: azine (1 mmol), $K_4[Fe(CN)_6]$ (0.2 mmol), benzoyl chloride (1.2 mmol), MeOH (20 mL).
[b] Isolated yield.

A plausible mechanism for the monohydrocyanation of azines using $K_4[Fe(CN)_6]$ as a cyanide source is shown in Scheme 4. First, $K_4[Fe(CN)_6]$ reacts with benzoyl chloride to form benzoyl cyanide as an intermediate, which was confirmed by its isolation and identification.[15a] 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 addition of hydrogen cyanide to azines **1** then yields α-hydrazinonitriles **2** as final products.

In summary, an environmentally friendly method has been developed for the monohydrocyanation of symmetrical azines to synthesize α-hydrazinonitriles using $K_4[Fe(CN)]_6$ as a cyanide source and benzoyl chloride as a promoter. The advantages for this protocol are the use of nontoxic, inexpensive cyanide source, simple work-up procedures, and catalyst-free conditions.



Scheme 4 Proposed mechanism for monohydrocyanation of azines using $K_4[Fe(CN)_6]$ as a cyanide source

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(19) **Monohydrocyanation of Azines; General Procedure**: A mixture of $K_4[Fe(CN)_6]$ (0.2 mmol) and benzoyl chloride (1.2 mmol) was heated at 160 °C for 3 h. After the reaction system was cooled to room temperature, azine (1 mmol) in methanol (20 mL) was added. The resulting mixture was further stirred at 60 °C for the appropriate time indicated in Table 2. After completion of the reaction, monitored by TLC, the resulting mixture was filtered to remove the solids, the liquor was concentrated, and the residue was subjected to alkaline Al_2O_3 column chromatography (PE–EtOAc, 30:1) to give the pure product. The analytical data for representative products are given.
(*E*)-2-(2-Benzylidenehydrazinyl)-2-phenylacetonitrile (2a): White solid; mp 100–102 °C. IR (KBr): 3241 (NH), 2226 (CN) cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.77 (s, 1 H, CH), 7.60–7.63 (m, 4 H, ArH), 7.44–7.46 (m, 3 H, ArH), 7.36–7.38 (m, 3 H, ArH), 5.53 (s, 1 H, CH). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 143.4, 134.2, 132.6, 129.5, 129.4, 129.1, 128.6, 127.7, 126.7, 118.5, 55.8 ppm.
(*Z*)-3,4,5,6-Tetrahydro-2*H*-1,2-diazepine-3-carbonitrile (2m): White solid; mp 240–242 °C. IR (KBr): 3176 (NH), 2226 (CN) cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 4.04–4.06 (m, 1 H, CH), 3.58–3.60 (m, 1 H, CH), 2.97 (s, 1 H, NH), 1.69–1.99 (m, 6 H, CH_2). ^{13}C NMR ($CDCl_3$, 100 MHz,): δ = 115.9, 75.2, 53.8, 28.6, 28.0, 19.4.

