

Note

# Efficient one-pot synthesis of cyanoferrocene from ferrocenecarboxaldehyde using $\text{NH}_2\text{OH} \cdot \text{HCl}/\text{KI}/\text{ZnO}/\text{CH}_3\text{CN}$ system

Arif Kivrak, Metin Zora \*

*Department of Chemistry, Faculty of Arts and Sciences, Middle East Technical University, 06531 Ankara, Turkey*

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## Abstract

A new and efficient one-pot synthesis of cyanoferrocene from ferrocenecarboxaldehyde is described by employing the  $\text{NH}_2\text{OH} \cdot \text{HCl}/\text{KI}/\text{ZnO}/\text{CH}_3\text{CN}$  system.

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## 1. Introduction

Recently, nitrile chemistry has experienced a major change by involvement of molecules with  $\text{C}\equiv\text{N}$  bonds in organic synthesis since nitriles serve as useful synthetic intermediates for pharmaceuticals, agricultural chemicals, dyes and material chemistry [1–8]. In particular, nitriles can be transformed to a variety of heterocyclic compounds including imidazoles [2], oxazoles [3], 2-oxazolines [4], thiazoles [5], triazoles [6] and tetrazoles [7], which possess a broad spectrum of biological activity. In addition, they can be converted to amines, ketones, carboxylic acids, esters and amides [8]. It should be noted that for the synthesis of nitriles, numerous methods are available [9,10], and new variants continue to appear. The most widely used general method is based on the dehydration of the corresponding aldoximes [10]. It is also well known that the cyano group itself is present in biologically important molecules including HIV protease inhibitors and 5-lipoxygenase inhibitors [11].

In this regard, cyanoferrocene [12,13] has occupied an important position since it can be converted to a structurally diverse set of ferrocenyl compounds that are attractive

synthetic targets due to their chemical and biological properties [14]. Ferrocenyl group is often incorporated into a bioactive compound to obtain unexpected or enhanced biological activities [15]. In addition, ferrocenyl group is ideal for use in drug design due to its low toxicity, stability and lipophilicity [16]. Therefore, the development of a general synthetic entry to cyanoferrocene would be great interest. Although numerous methods are known for preparation of nitriles [9,10], SciFinder search has revealed only few reports for the synthesis of cyanoferrocene [17–19]. Pauson research group tried several procedures to synthesize cyanoferrocene but the highest yield (78%) was obtained by the dehydration of the corresponding oximes with dicyclohexylcarbodiimide [17]. Zhang and co-workers prepared cyanoferrocene in 60% yield by refluxing ferrocenecarboxaldehyde with *N*-methylpyrrolidone,  $\text{Et}_3\text{N}$  and  $\text{NH}_2\text{OH} \cdot \text{HCl}$  [18]. Nekrasov and Yur'eva synthesized cyanoferrocene in 86% yield by cyanation of ferricenium salts with hydrocyanic acid through an electrochemical process [19]. Although, since its discovery, ferrocene and its derivatives are among the most thoroughly studied compounds, we were surprised that there has been limited study of ferrocenyl nitriles. In continuation of our interest in ferrocene chemistry [20,21], we now wish to describe a new and efficient one-pot method for synthesis of cyanoferrocene from ferrocenecarboxaldehyde [22].

\* Corresponding author. Tel.: +90 312 2103213; fax: +90 312 2103200.  
E-mail address: [zora@metu.edu.tr](mailto:zora@metu.edu.tr) (M. Zora).

## 2. Results and discussion

Firstly, as will be discussed later, we tried several protocols available for aromatic nitriles but all afforded cyanoferrocene in relatively low yields. Sometimes, as compared to the corresponding aromatic molecules, ferrocenyl compounds can behave somewhat differently. That's why; we undertook a detailed study to optimize reaction conditions for higher yield of cyanoferrocene. The results from a systematic study are summarized in Table 1.

Initially, ferrocenecarboxaldehyde was refluxed with a slight excess of hydroxylamine hydrochloride in acetonitrile for 2 h (entry 1). From this reaction, mostly corresponding oxime isomers were isolated and cyanoferrocene was obtained in very low yield. When the same reaction was performed in the presence of varying amounts of sodium iodide as used previously in similar reactions [10u,10aa], cyanoferrocene formed in 49–60% yields (entries 2–4). It is noteworthy that the use of excess NaI did not improve the yield (entry 3). The reactions carried out with KCl, KBr and KI gave relatively lower yields of cyanoferrocene (15–32%, entries 5–7).

In the light of recent studies [10w,23], we thought that surface properties of ZnO might accelerate the dehydration of in situ formed ferrocenecarboxaldehyde oximes to cyanoferrocene. When the reactions were carried out in the presence of ZnO and metal halide, they afforded cyanoferrocene in higher yields (entries 8–11), as compared to

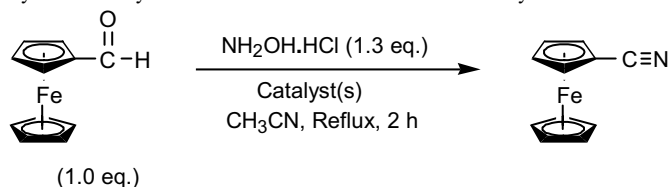
those performed without ZnO (entries 4–7). The highest yield (85%) was obtained with a 1/1 KI/ZnO combination (entry 11). To the best of our knowledge, KI/ZnO system was used for the first time for synthesis of a nitrile compound [24]. We repeated this reaction for varying reaction times as well and found that the reaction was almost complete in 2.0–2.5 h. Longer reaction times did not improve the yield. It should be noted that CH<sub>3</sub>CN appeared to be the most effective and appropriate solvent to convert ferrocenecarboxaldehyde to cyanoferrocene since it is polar enough and easily removed at the end of reaction. The reactions performed under refluxing conditions in CH<sub>3</sub>OH and THF yielded mostly ferrocenecarboxaldehyde oximes. When carried out in refluxing DMF or benzonitrile, the reaction mostly produced decomposition products.

It should be noted that other combinations of KI/ZnO gave slightly lower yields (entries 12 and 13) or seriously lowered the yield (entry 14). The reaction with I<sub>2</sub>/ZnO also yielded cyanoferrocene in low yield (40%, entry 15). Interestingly, the use of ZnO without metal halide was not so effective that moderate yields of cyanoferrocene were observed (entries 16 and 17).

As shown in Table 2, we also tried several other methods including NH<sub>2</sub>OSO<sub>3</sub>H/KI/ZnO, NH<sub>2</sub>OCH<sub>3</sub>·HCl/KI/ZnO, I<sub>2</sub>/NH<sub>3</sub> [10j], cyanuric chloride/DMF [10i], and CH<sub>3</sub>COCl/ZnO [10w] (entries 18–22), but all produced cyanoferrocene in lower yields (20–50%).

We reasoned that reaction conditions present in entry 11 provided the highest yield of cyanoferrocene. We repeated this reaction many times, even with varying amount of ferrocenecarboxaldehyde (100 mg, 500 mg, 1 g, 2 g and 3 g), and in each case we obtained similar and reproducible results. We also observed that oil bath temperature during the reflux should not exceed 100 °C since over this temperature some decomposition occurred and slightly lowered the yield of cyanoferrocene.

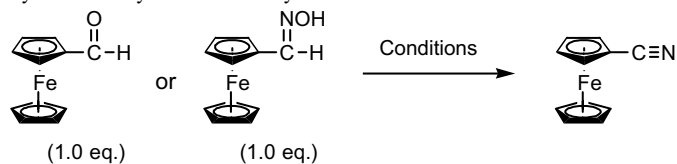
Table 1  
Synthesis of cyanoferrocene from ferrocenecarboxaldehyde



Entry	Catalyst(s)	Equivalent(s)	Isolated yield (%)
1	–	–	5
2	NaI	0.5	56
3	NaI	1.0	60
4	NaI	1.5	49
5	KCl	1.0	15
6	KBr	1.0	18
7	KI	1.0	32
8	NaI/ZnO	1.0/1.0	79
9	KCl/ZnO	1.0/1.0	50
10	KBr/ZnO	1.0/1.0	55
<b>11<sup>a</sup></b>	<b>KI/ZnO</b>	<b>1.0/1.0</b>	<b>85</b>
12	KI/ZnO	1.5/1.0	81
13	KI/ZnO	1.0/1.5	82
14	KI/ZnO	1.5/1.5	40
15	I <sub>2</sub> /ZnO	1.0/1.0	40
16	ZnO	1.0	53
17	ZnO	1.5	63

<sup>a</sup> When the reaction was carried out for 0.5 and 1 h, instead of 2 h, cyanoferrocene was obtained in 18% and 64% yields, respectively.

Table 2  
Synthesis of cyanoferrocene by other methods



Entry	Starting compound	Conditions (equivalents)	Isolated yield (%)
18	Aldehyde	NH <sub>2</sub> OSO <sub>3</sub> H (1.3), KI/ZnO (1.0/1.0), CH <sub>3</sub> CN, reflux, 2 h	27
19	Aldehyde	NH <sub>2</sub> OCH <sub>3</sub> ·HCl (1.3), KI/ZnO (1.0/1.0), CH <sub>3</sub> CN, reflux, 2 h	29
20	Aldehyde	I <sub>2</sub> (1.1), NH <sub>3</sub> , THF, rt	37
21 <sup>a</sup>	Oxime	Cyanuric chloride (1.3), DMF, rt	50
22 <sup>a</sup>	Oxime	CH <sub>3</sub> COCl/ZnO (3.0/3.0), 80 °C	20

<sup>a</sup> In this reaction, a mixture of oxime isomers was used.

### 3. Conclusion

In summary, we disclosed a new and efficient one-pot reaction for synthesis of cyanoferrrocene from ferrocenecarboxaldehyde through dehydration of in situ formed the corresponding oximes using the  $\text{NH}_2\text{OH} \cdot \text{HCl}/\text{KI}/\text{ZnO}/\text{CH}_3\text{CN}$  system, which offers a useful method for the preparation of cyanoferrrocene due to its simplicity and high yield. We anticipate that this new method will be of value in the continued development of the synthetic applications of cyanoferrrocene in organic and organometallic chemistry.

### 4. Experimental

*Procedure for synthesis of cyanoferrrocene.* To a homogeneous mixture of ferrocenecarboxaldehyde (107.0 mg, 0.5 mmol),  $\text{NH}_2\text{OH} \cdot \text{HCl}$  (45.2 mg, 0.65 mmol), KI (83.0 mg, 0.5 mmol) and ZnO (40.7 mg, 0.5 mmol) in a round-bottom flask at room temperature under argon was added acetonitrile (5.5 ml). The resulting mixture was then refluxed for 2 h with efficient stirring and heating (note that oil bath temperature during the reflux should not exceed 100 °C). Subsequently, aqueous  $\text{Na}_2\text{S}_2\text{O}_3$  (5%, 1 mL) was added to the cooled mixture and the stirring was continued for additional 15 min. After the mixture was filtrated to remove solid particles, it was diluted with water (10 mL) and extracted with ethyl acetate ( $2 \times 25$  mL). Collected organic layers were dried on  $\text{MgSO}_4$  and concentrated in a rotary evaporator. The crude cyanoferrrocene was purified by flash chromatography on silica gel using 19:1 hexane/ethyl acetate followed by 9:1 and 4:1 hexane/ethyl acetate, respectively, as the eluent. The orange fraction with  $R_f = 0.7$  (2:1 hexane/ethyl acetate) was collected to give cyanoferrrocene (89.7 mg, 85% yield; mp 106.4–106.7 °C, lit. 17 mp 107–108 °C).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ; 400 MHz):  $\delta$  4.59 (pseudo t, 2H,  $J = 1.75$  Hz), 4.32 (pseudo t, 2H,  $J = 1.75$  Hz), 4.27 (s, 5H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ; 100 MHz):  $\delta$  120.1 (CN), 71.7 ( $\text{C}_5\text{H}_4$ ), 70.6 ( $\text{C}_5\text{H}_4$ ), 70.5 ( $\text{C}_5\text{H}_5$ ), 51.8 (*ipso*- $\text{C}_5\text{H}_4$ ); IR ( $\text{CH}_2\text{Cl}_2$ ): 2225.8 (CN)  $\text{cm}^{-1}$ .

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