

An efficient synthesis of ferrocenyl substituted 3-cyanopyridine derivatives under ultrasound irradiation

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Abstract

An efficient synthesis of 2-alkoxy-4-aryl-6-ferrocenyl-3-cyanopyridines via the condensation of ferrocenyl substituted chalcones with malononitrile in a freshly prepared sodium alkoxide solution under ultrasound irradiation was investigated. Especially noteworthy, the reaction of 1-ferrocenyl-3-(pyridin-2-yl)prop-2-ene-1-one with malononitrile afforded 2-alkoxy-4-pyridyl-6-ferrocenylpyridine, with the loss of CN group on the 3-position of pyridine ring was first observed.

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1. Introduction

Metallocenes are known to exhibit a wide range of biological activity [1]. Among them, ferrocene has attracted special attention since it is neutral, chemically stable, non-toxic and able to cross cell membranes [2]. In fact, it is now well established that the incorporation of ferrocene units in organic molecules introduces significant and new properties in these materials [3]. In addition, it has been demonstrated that molecules containing cyanopyridine moiety may be able to work as ligands towards transition-metal ions [4], new drugs [5], and significant intermediates for the synthesis of important vitamins [6] such as nicotinic acids [7] and nicotinamides [8]. To the best of our knowledge, although the synthesis of 3-cyanopyridine compounds via the condensation of chalcone with malononitrile has been studied previously [5,9], such kind of reaction with ferrocenyl (Fc) substituent has not been investigated till now. In continuation of our efforts for

the synthesis of ferrocene-containing compounds with special properties and usefulness [10], herein we wish to report the synthesis of ferrocenyl substituted 3-cyanopyridine compounds via the condensation of ferrocenyl substituted chalcone with malononitrile in a freshly prepared sodium alkoxide solution.

A survey of the literature shows that various organic reactions could be accelerated by ultrasonic irradiation with a higher yield, shorter reaction time and milder conditions [11,12]. Therefore, an ultrasound-assisted method was applied to the reaction of chalcone **1(a–j)** and malononitrile **2** in our research (Schemes 1–3).

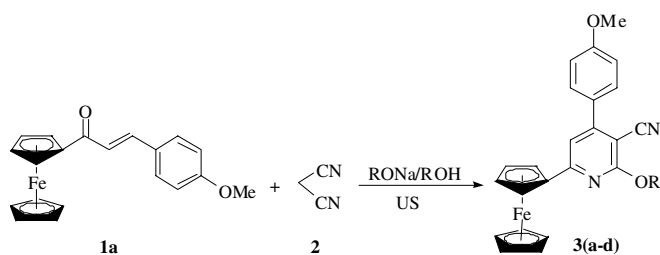
2. Results and discussion

Initial studies were focused on the reaction of ferrocenyl substituted chalcone **1a** with malononitrile **2** in various freshly prepared sodium alkoxide solutions under ultrasound irradiation (Scheme 1).

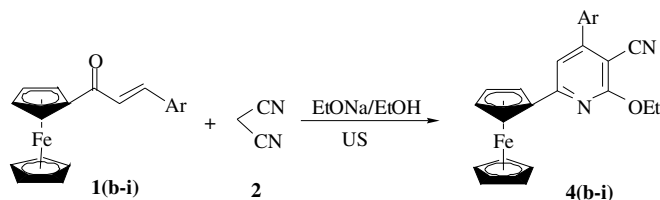
First, the reaction of **1a** with **2** proceeded smoothly to afford the corresponding product **3**, 2-alkoxy-4-(4-methoxyphenyl)-6-ferrocenyl-3-cyanopyridine, in moderate yields in the presence of different sodium alkoxide solutions

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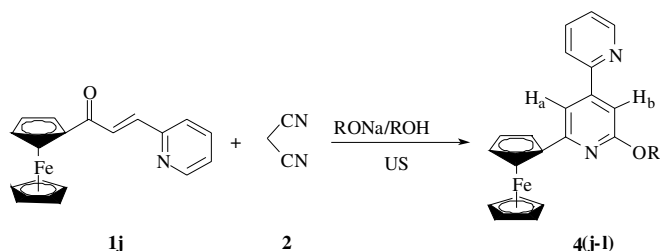
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Scheme 1.



Scheme 2.



Scheme 3.

under ultrasonication (entries 1–4, Table 1). Although the yields were almost the same in different alcoholic solvents, considering the reaction time and the demand for an innocuous and low-cost solvent, ethanol proved to be the best one among them.

Second, we investigated the effect of reaction time on the yield. The reaction was carried out for a longer duration, the yield was no significant increasing (entry 5, Table 1). And also it was found that the reaction without ultrasonic irradiation for a longer duration, with no compromise in yield.

With the above observations, the following studies were chosen to be conducted in EtOH system under ultrasonic

Table 1
The reaction of chalcone **1a** with malononitrile **2** in different alcoholic solvents^a

Entry	Solvent	Time (h)	Product	Yield (%) ^b
1	MeOH	18	3a	67
2	<i>n</i> -PrOH	10	3c	66
3	<i>n</i> -BuOH	5	3d	67
4	EtOH	4	3b	68
5	EtOH	8	3b	70

^a Reactions were carried out under ultrasound irradiation unless otherwise stated.

^b Isolated yields.

irradiation (Scheme 2). And the results were listed in Table 2.

As shown in Table 2, both the phenyl ring substituted chalcones (entries 1–4, Table 2), and the heterocyclic ring containing chalcones (entries 5–8, Table 2) reacted efficiently with malononitrile to afford the target products. In all cases, the reaction proceeded smoothly to give ferrocenyl substituted 3-cyanopyridine derivatives in moderate to good yields. All the products were satisfactorily characterized by their ¹H NMR, IR and HRMS.

Unexpectedly when 1-ferrocenyl-3-(pyridine-2-yl)prop-2-ene-1-one (**1j**) was subjected to the same reaction conditions, the formation of 2-alkoxy-4-pyridyl-6-ferrocenylpyridine (**4(j-l)**, Scheme 3) was observed, instead of the corresponding 3-cyanopyridine product. The structure of **4k** has been determined by its IR, HRMS and ¹H NMR. An additional singlet at 7.57 ppm (H_b) has been observed in the ¹H NMR spectrum other than the commonly-observed singlet at about 7.00 ppm (H_a). Together with the disappearance of the strong absorption at about 2220 cm^{-1} that attributed to CN stretching in the IR spectrum, and the mass information, we can confirm the structure of **4k** evidently.

Propelled by these encouraging results, we optimized the reaction by running in various alcohols as solvents. As showing the results obtained in entries 1–3 (Table 3), the reactions proceeded smoothly under ultrasound irradiation to generate the corresponding de-cyano-ferrocenyl substituted pyridines with good yields. And the highest yield was obtained in ethanol (entry 2, Table 3). In addition, the effect of ultrasonication is clearly manifested in the de-cyanation reaction, with a significant yield reduction of **4k** (entry 4, Table 3).

However, when ethyl cyanoacetate was applied to this reaction instead of malononitrile, several by-products were obtained other than the usual cyano-ferrocenyl substituted pyridine and the de-cyano-ferrocenyl substituted pyridine.

3. Conclusion

In conclusion, we have described a mild, efficient and ultrasound-assisted method for the synthesis of a new series of ferrocenyl substituted pyridine derivatives which might be able to work as important intermediates, ligands for transition-metal ions and potential new drugs. With regard to the different results obtained for substrate **1j**, the further research is now in progress to explain the phenomena.

4. Experimental

Melting points were determined on a XT-5A digital melting points apparatus and uncorrected. IR Spectra were obtained on a Nicolet FT-IR500 spectrophotometer using KBr pellets. Elemental analyses were performed on a Carlo-Erba 1110 Elemental analysis instrument. ¹H NMR was recorded on Varian Inova 400 MHz NMR spectrometer in CDCl_3 . High resolution mass spectra were

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