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# One-pot synthesis of 2-ferrocenyl-substituted pyridines

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## ABSTRACT

A facile, one-pot method for the synthesis of 2-ferrocenylpyridines is described. When reacted with propargylamine,  $\alpha$ , $\beta$ -alkynic ketones produced *N*-propargylic  $\beta$ -enaminones in situ, which, in the presence of copper(I) chloride, underwent electrophilic cyclization to afford 2-ferrocenylpyridine derivatives in good to high yields. This cyclization was found to be general for a variety of  $\alpha$ , $\beta$ -alkynic ketones and tolerated the presence of aryl groups with electron-withdrawing and electron-donating substituents. The enrichment of the pyridine core with a ferrocenyl moiety, in addition to benzoyl groups, may offer potential for the synthesis of molecules of pharmacological interest.

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Pyridines form one of the most important classes of heterocyclic compounds and their prevalence in natural products and pharmaceuticals as well as their potent bioactivities have created significant interest in academia and the pharmaceutical industry.<sup>1</sup> Indeed, pyridines have been studied for over a century as a result of their range of applications in many branches of chemistry, such as catalysis, drug design, molecular recognition, and material science.<sup>2</sup> Notably, many pyridine derivatives exhibit remarkable medicinal properties, including hypnotic and sedative,<sup>3</sup> HIV antiviral,<sup>4</sup> bone calcium regulator,<sup>5</sup> cholesterol and triglyceride regulator,<sup>6</sup> antidiabetic,<sup>7</sup> antihistaminic,<sup>8</sup> antiulcerant,<sup>9</sup> antineoplastic, and anticancer activities.<sup>10</sup> Pyridines also form integral parts of structurally diverse natural products, such as diploclidine and nakinadine A.11 Most pyridine-based alkaloid natural products are derivatives of nicotinic acid, also known as vitamin B3 and niacin.<sup>12</sup> Moreover, pyridines are utilized in the preparation of conjugated polymers and functional materials which are employed in light-emitting devices (LEDs).<sup>13</sup> Although many methods for the synthesis of the pyridine ring have been reported, they are generally constructed by two approaches that rely on the condensation of carbonyl compounds with amines, and the cycloaddition of azadienes and nitriles with alkenes and alkynes, respectively.<sup>14</sup> In fact, a wide range of methods have been developed for the preparation of pyridines, and new ones continue to emerge due to their use as crucial building blocks for the synthesis of many drugs and natural products.15

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Recently, ferrocene, the first sandwich-type metallocene discovered, has gained considerable importance in medicinal chemistry since it is neutral, chemically stable, non-toxic, and able to cross cell membranes. Indeed, it is well established that the integration of a ferrocene unit into potentially bioactive organic compounds can introduce significant, new and/or novel properties in these molecules.<sup>16</sup> Many ferrocene derivatives have been reported to exhibit antimalarial<sup>17</sup> and antitumor<sup>18</sup> activities. For instance, ferrocifen, a ferrocenyl analog of tamoxifen, displays antiproliferative activity on both hormone-dependent and hormone-independent breast cancer cells with good efficacies, while tamoxifen only shows antiestrogenic activity on hormone-dependent breast cancer cells.<sup>18</sup> The dual effect of ferrocifen has initiated the synthesis and biological investigation of further ferrocifen-like complexes. Accordingly, functionally substituted ferrocene derivatives may have great potential for biological studies; therefore, it is crucial to develop new methodologies for their formation.

In particular, ferrocenylpyridines (or pyridylferrocenes) have attracted considerable interest due to their applications in catalysis,<sup>19,20</sup> self-assembly devices,<sup>21</sup> electrochemical sensing,<sup>22</sup> molecular electronics and machines,<sup>23</sup> non-linear optics,<sup>24</sup> and as antitumor agents.<sup>25</sup> In particular, ferrocenylpyridines have emerged as important ligands for the synthesis of heterobimetallic complexes via the metal-binding ability of the pyridine nitrogen atom. In this way, many metal complexes of ferrocenylpyridines have been prepared in order to facilitate electronic communication between metal centers.<sup>26</sup> In fact, changing the oxidation state of the pendant ferrocenyl unit could allow the tuning of electron density, and hence reactivity, at the second metal center without changing

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its immediate coordination sphere. *N*-Heterocyclic carbene adducts of cyclopalladated ferrocenylpyridines have been reported as catalysts in Heck and Suzuki coupling reactions.<sup>19</sup> Ferrocenylpyridines and/or their heterobimetallic complexes have also been evaluated for their anticancer activities against human tumor cell lines.<sup>25</sup> Notably, some have exhibited even higher activity than cisplatin,<sup>25b</sup> a widely used chemotherapeutic and reference agent. In brief, ferrocenylpyridines are valuable compounds that have wide usage and application range. Therefore, the development of new methods for ferrocenylpyridines continues to attract the interest of researchers from synthetic, material, and biological points of view.

Recently, *N*-propargylic  $\beta$ -enaminones have been reported as intermediates for the synthesis of a range of privileged heterocycles,<sup>27</sup> including pyrroles, pyridines, and dihydropyridines.<sup>28</sup> In this respect, we have recently prepared *N*-propargylic  $\beta$ -enaminones **3** from  $\alpha$ , $\beta$ -alkynic ketones **1** and explored their cyclizations (Scheme 1).<sup>29</sup> Upon treatment with molecular iodine in the presence of sodium bicarbonate, *N*-propargylic  $\beta$ -enaminones **3** underwent electrophilic cyclization to afford iodopyridines **4** in good to high yields. Iodo-substituted pyridines **4** were further functionalized with aryl and alkynyl moieties via the Suzuki–Miyaura and Sonogashira coupling reactions, respectively (Scheme 1).<sup>30</sup>

According to the strategy presented in Scheme 1, it was anticipated that ferrocenyl-substituted  $\alpha$ , $\beta$ -alkynic ketones, such as **1** ( $\mathbb{R}^1 = \mathrm{Fc}$ ), would provide ferrocenylpyridine derivatives, such as **4**, through the intermediacy of *N*-propargylic  $\beta$ -enaminones **2** and **3**. Interestingly, in initial studies, we observed that the reaction of propargylamine with ferrocenyl-substituted  $\alpha$ , $\beta$ -alkynic ketones, particularly in the presence of a metal Lewis acid, afforded 2-ferrocenylpyridines in a one-pot manner, along with, or without, the expected conjugate addition products. Our growing interest<sup>31</sup> in the synthesis of novel ferrocenyl, carbocyclic, and heterocyclic molecules as potential pharmaceuticals and scaffolds therefore encouraged us to explore this new reaction, and herein, we report the preliminary results of this study.

Initially, we prepared the requisite ferrocenyl-substituted  $\alpha,\beta$ -alkynic ketones **7** (i.e. 3-ferrocenylprop-2-yn-1-ones) via the coupling of ethynylferrocene with acyl chlorides (ESI). Next, we examined the model reaction of 3-ferrocenyl-1-phenylprop-2-yn-1-one (**7a**) with propargylamine under different conditions in order to find the optimal reaction conditions (Table 1). Initially, we performed the reaction in methanol and DMF at 65 °C and 110 °C, respectively, under an argon atmosphere (Entries 1 and 2). Interestingly, the reaction in methanol produced the conjugate addition product  $\beta$ -enaminone **8a** while in DMF 2-ferrocenylpyridine **9a** was formed, but both in low yields. In fact, as shown later in the proposed mechanism, ferrocenylpyridine **9a** is a secondary product of the reaction and results from initially

formed  $\beta$ -enaminone **8a** via a 6-endo-dig cyclization. In order to improve the yield of 9a using DMF, the reaction was carried out in the presence of various catalysts. First, the reaction was conducted in the presence of 0.2 equiv of AuCl and AuCl<sub>3</sub> in DMF and/or THF (Entries 3-5), which afforded a mixture of N-propargylic  $\beta$ -enaminone **8a** and 2-ferrocenylpyridine **9a**, with the former as the major product. Subsequently, the reaction was tested in the presence of 0.2 equiv of InCl<sub>3</sub> and AlCl<sub>3</sub> (Entries 6 and 7). These reactions also produced a mixture of β-enaminone 8a and 2-ferrocenylpyridine **9a**, but with the latter as the major product. The reactions conducted in the presence of 0.2 equiv of CuI, CuBr, and CuCl (Entries 8-10) all yielded 2-ferrocenylpyridine 9a as the sole product, where the highest yield (49%) was obtained with CuCl. Next, the reaction with CuCl was carried out in methanol, THF, and acetonitrile (Entries 11-13), however, in these solvents, 9a was isolated in lower vields (16-35%). When the reaction was performed with 1.0 equiv of CuCl. 2-ferrocenvlpyridine 9a was formed in 60% yield (Entry 14). The reaction was also carried out with 2.0 equiv of CuCl (Entry 15), however, this reaction provided 9a in the same yield (60%), indicating that higher equivalents of CuCl did not improve the yield. The reaction was conducted under air and in the presence of *p*-benzoquinone, since, during the reaction, oxidation may be required for aromatization. When the reaction with 1.0 equiv of CuCl was conducted open to air, 2-ferrocenylpyridine 9a was produced in 77% yield (Entry 16). The reaction in the presence of 1.1 and 3.0 molar equivalents of *p*-benzoquinone produced **9a** in 72% and 61% yields, respectively (Entries 17 and 18). Notably, excess p-benzoquinone was found to interfere with the reaction to some extent and slightly decreased the yield of 9a. In summary, the optimal conditions were 1.0 equiv of CuCl in DMF at 110 °C and open to air (Entry 16).

A range of substituted  $\alpha$ , $\beta$ -alkynic ketones **7** were employed to synthesize a variety of 2-ferrocenylpyridine derivatives **9** (Table 2). In general, the reactions proceeded smoothly and afforded the corresponding ferrocenylpyridines **9** in good to high yields (69–90%). The reactions demonstrated good tolerance for both electron-donating and electron-withdrawing groups. Notably,  $\alpha$ , $\beta$ -alkynic ketones with electron-withdrawing substituents provided the corresponding ferrocenylpyridines **9** in relatively higher yields (71–90%) (Entries 4–6) than did those with electron-donating substituents (69–70%) (Entries 2–3).

A possible mechanism for the formation of 2-ferrocenylpyridines **9** is outlined in Scheme 2. First, conjugate addition of propargylamine to  $\alpha$ , $\beta$ -alkynic ketones **7** gives *N*-propargylic  $\beta$ -enaminones **8**. Although not isolated,  $\beta$ -enaminones **8** presumably form as the (*Z*)-isomers on the basis of NOESY experiments of our and the Cacchi research groups using similar compounds.<sup>28,29</sup> Moreover, as a result of their geometry, the presence of an intramolecular hydrogen bond between the amine hydrogen



**Scheme 1.** Synthesis of iodopyridines from  $\alpha,\beta$ -alkynic ketones and their further functionalization via coupling reactions.

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## E. Karadeniz, M. Zora/Tetrahedron Letters xxx (2016) xxx-xxx

#### Table 1

Optimization studies for the formation of 2-ferrocenylpyridine **9a**<sup>a</sup>



Entry	Catalyst or additive (equiv)	Atmosphere (atm) or oxidant (equiv)	Solvent	Temp. (°C)	Product yield <sup>b</sup> (%)
1	_	Ar (1 atm)	MeOH	65	<b>8a</b> (40)
2	_	Ar (1 atm)	DMF	110	<b>9a</b> (25)
3	AuCl (0.2)	Ar (1 atm)	DMF	110	<b>8a</b> (28) + <b>9a</b> (7)
4	AuCl <sub>3</sub> (0.2)	Ar (1 atm)	DMF	110	<b>8a</b> (34) + <b>9a</b> (16)
5	AuCl <sub>3</sub> (0.2)	Ar (1 atm)	THF	66	<b>8a</b> (30) + <b>9a</b> (18)
6	InCl <sub>3</sub> (0.2)	Ar (1 atm)	DMF	110	<b>8a</b> (7) + <b>9a</b> (16)
7	AlCl <sub>3</sub> (0.2)	Ar (1 atm)	DMF	110	<b>8a</b> (14) + <b>9a</b> (20)
8	CuI (0.2)	Ar (1 atm)	DMF	110	<b>9a</b> (40)
9	CuBr (0.2)	Ar (1 atm)	DMF	110	<b>9a</b> (43)
10	CuCl (0.2)	Ar (1 atm)	DMF	110	<b>9a</b> (49)
11	CuCl (0.2)	Ar (1 atm)	MeOH	65	<b>8a</b> (50) + <b>9a</b> (16)
12	CuCl (0.2)	Ar (1 atm)	THF	66	<b>9a</b> (30)
13	CuCl (0.2)	Ar (1 atm)	ACN	81	<b>9a</b> (35)
14	CuCl (1.0)	Ar (1 atm)	DMF	110	<b>9a</b> (60)
15	CuCl (2.0)	Ar (1 atm)	DMF	110	<b>9a</b> (60)
16	CuCl (1.0)	Air (1 atm)	DMF	110	<b>9a</b> (77)
17	CuCl (1.0)	<i>p</i> -Benzoquinone (1.1)	DMF	110	<b>9a</b> (72)
18	CuCl (1.0)	<i>p</i> -Benzoquinone (3.0)	DMF	110	<b>9a</b> (61)

<sup>a</sup> Reactions were carried out using  $\alpha$ ,β-alkynic ketone **7a** (0.25 mmol), propargylamine (0.30 mmol), solvent (3 mL) under the indicated conditions. For work-up and purification, see "General Procedure for the synthesis of 2-ferrocenyl-substituted pyridines **9**" (ESI). <sup>b</sup> Isolated yield.

#### Table 2

One-pot synthesis of 2-ferrocenylpyridines **9**<sup>a</sup>



Entry	α,β-Alkynic ketone <b>7</b>	2-Ferrocenylpyridine <b>9</b>	Time (h)	Yield <sup>b</sup> (%)
1	Fe Fe	$r_{Fe}$	2.0	77
2	Fe Fe 7b	H <sub>3</sub> C Fe 9b	2.0	69
3	Fe Fe 7c	H <sub>3</sub> CO Fe 9c	2.0	70

(continued on next page)

#### E. Karadeniz, M. Zora/Tetrahedron Letters xxx (2016) xxx-xxx

#### Table 2 (continued)



<sup>a</sup> Reagents and conditions: α,β-alkynic ketone **7** (0.25 mmol), propargylamine (0.30 mmol), CuCl (0.25 mmol), DMF (3 mL), 110 °C. For the full procedure, including workup and purification, see "General Procedure for the synthesis of 2-ferrocenyl-substituted pyridines **9**" (ESI).





Scheme 2. Proposed mechanism for the formation of 2-ferrocenylpyridines 9.

and carbonyl oxygen (N–H···O) governs their tautomeric equilibria and stability.<sup>32</sup> Subsequently, coordination of the alkyne moiety to copper produces complex **10**, which initiates electrophilic cyclization to afford intermediate **11**. Hydrogen atom transfer into copper and concomitant regeneration of CuCl, possibly via reductive elimination, gives 2,5-dihydropyridines **12**. Finally, aerobic oxidation yields the corresponding pyridines **9**.<sup>33</sup> It is also possible that 2,5-dihydropyridines **12** are first converted into 1,2-dihydropyridines **13** via a hydrogen shift; then aerobic oxidation affords pyridines **9** (Scheme 2).

The synthesized pyridine derivatives show characteristic peaks in their <sup>1</sup>H and <sup>13</sup>C NMR spectra which relate to the regiochemistry of pyridine ring formation. In the <sup>1</sup>H NMR spectra, owing to conjugation and electron density, H atoms at C4, C5, and C6 of the pyridine ring resonate at approximately 7.49–7.65, 7.17–7.28, and 8.67–8.78 ppm, respectively. Each resonance typically appears as a doublet of doublet where there is no overlap with other aromatic hydrogens (see Table 2 for atom numbering). In the <sup>13</sup>C NMR spectra, the peaks of C4, C5, and C6 were observed at approximately 135.4–136.9, 119.6–120.2, and 150.0–150.8 ppm, respectively. On the other hand, the C2 atom, connected to the ferrocenyl group, resonated nearly at 156.2–158.3 ppm while the C3 atom, attached to benzoyl group, appeared around 132.1–134.5 ppm. In brief, the combined NMR data clearly support the indicated regiochemistry of pyridine ring formation.

In conclusion, we have developed a one-pot method for the synthesis of 2-ferrocenyl-substituted pyridines from  $\alpha$ , $\beta$ -alkynic ketones **7** and propargylamine, via in situ formation of *N*-propargylic  $\beta$ -enaminones **8**, followed by subsequent cyclization upon treatment with CuCl. Notably, this cyclization has proven to be a powerful and versatile tool for the generation of 2-ferrocenyl-substituted pyridines. It is anticipated that the efficiency and operational simplicity of the method could make it potentially attractive for the library construction of ferrocenylpyrazoles, particularly in the area of pharmaceuticals.

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## Supplementary data

Supplementary data (experimental procedures, characterization data and copies of <sup>1</sup>H and <sup>13</sup>C NMR spectra for all  $\alpha$ , $\beta$ -alkynic ketones and 2-ferrocenylpyridines) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet. 2016.09.080.

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