Tetrahedron Letters xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

One-pot synthesis of 2-ferrocenyl-substituted pyridines

Eda Karadeniz, Metin Zora *

Department of Chemistry, Middle East Technical University, 06800 Ankara, Turkey

ARTICLE INFO

Article history:
Received 19 August 2016
Revised 20 September 2016
Accepted 23 September 2016
Available online xxxx

Keywords:
Pyridine
Ferrocene
Propargylamine
α,β-Alkynic ketone
N-Propargylic β-enaminone
Electrophilic cyclization

ABSTRACT

A facile, one-pot method for the synthesis of 2-ferrocenylpyridines is described. When reacted with propargylamine, α,β-alkynic ketones produced *N*-propargylic β-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 α,β-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.

© 2016 Elsevier Ltd. All rights reserved.

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.[1] 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.[2] Notably, many pyridine derivatives exhibit remarkable medicinal properties, including hypnotic and sedative,[3] HIV antiviral,[4] bone calcium regulator,[5] cholesterol and triglyceride regulator,[6] antidiabetic,[7] antihistaminic,[8] antiulcerant,[9] antineoplastic, and anticancer activities.[10] 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.[12] Moreover, pyridines are utilized in the preparation of conjugated polymers and functional materials which are employed in light-emitting devices (LEDs).[13] 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.[14] 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]

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.[16] Many ferrocene derivatives have been reported to exhibit antimalarial[17] and antitumor[18] 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.[18] 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,[19,20] self-assembly devices,[21] electrochemical sensing,[22] molecular electronics and machines,[23] non-linear optics,[24] and as antitumor agents.[25] 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.[26] 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

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

http://dx.doi.org/10.1016/j.tetlet.2016.09.080
0040-4039/© 2016 Elsevier Ltd. All rights reserved.

its immediate coordination sphere. *N*-Heterocyclic carbene adducts of cyclopalladated ferrocenylpyridines have been reported as catalysts in Heck and Suzuki coupling reactions.[19] Ferrocenylpyridines and/or their heterobimetallic complexes have also been evaluated for their anticancer activities against human tumor cell lines.[25] Notably, some have exhibited even higher activity than cisplatin,[25b] 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.

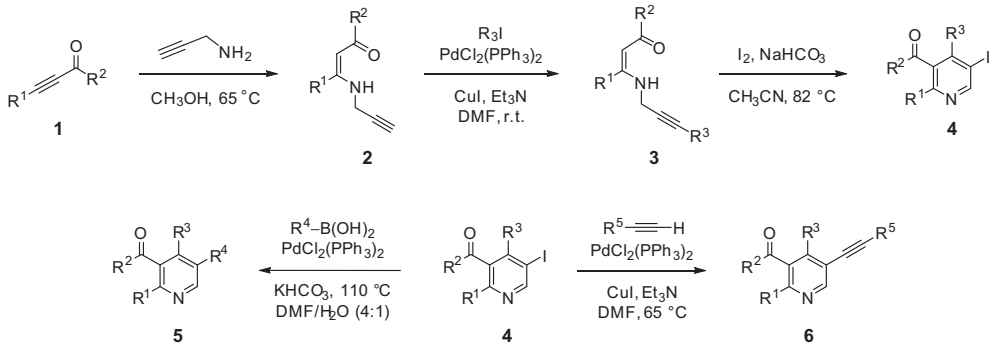
Recently, *N*-propargylic β-enaminones have been reported as intermediates for the synthesis of a range of privileged heterocycles,[27] including pyrroles, pyridines, and dihydropyridines.[28] In this respect, we have recently prepared *N*-propargylic β-enaminones **3** from α,β-alkynic ketones **1** and explored their cyclizations (Scheme 1).[29] Upon treatment with molecular iodine in the presence of sodium bicarbonate, *N*-propargylic β-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).[30]

According to the strategy presented in Scheme 1, it was anticipated that ferrocenyl-substituted α,β-alkynic ketones, such as **1** (R^1 = Fc), would provide ferrocenylpyridine derivatives, such as **4**, through the intermediacy of *N*-propargylic β-enaminones **2** and **3**. Interestingly, in initial studies, we observed that the reaction of propargylamine with ferrocenyl-substituted α,β-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[31] 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 α,β-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 β-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 β-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 $AuCl_3$ in DMF and/or THF (Entries 3–5), which afforded a mixture of *N*-propargylic β-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 $InCl_3$ and $AlCl_3$ (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 yields (16–35%). When the reaction was performed with 1.0 equiv of CuCl, 2-ferrocenylpyridine **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 α,β-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, α,β-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 α,β-alkynic ketones **7** gives *N*-propargylic β-enaminones **8**. Although not isolated, β-enaminones **8** presumably form as the (*Z*)-isomers on the basis of NOESY experiments of our and the Cacchi research groups using similar compounds.[28,29] Moreover, as a result of their geometry, the presence of an intramolecular hydrogen bond between the amine hydrogen



Scheme 1. Synthesis of iodopyridines from α,β-alkynic ketones and their further functionalization via coupling reactions.

Download English Version:

https://daneshyari.com/en/article/5260628

Download Persian Version:

https://daneshyari.com/article/5260628

Daneshyari.com