Synthesis of Substituted 1, 4-dihydro-4-ferrocenylpyridines and 3-ferrocenyl-2-pyrazolines Catalyzed by Ionic Liquid [Bmim] OH

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(Received on 26th July 2012, accepted in revised form 19th July 2013)

Summary: 5-aryl-3-ferrocenyl-1-phenyl-2-pyrazolines have been synthesized by the reaction of α, β-unsaturated ketones with phenylhydrazine in ionic liquid [Bmim]OH. While 4-ferrocenyl-1,4-dihydropyridine-2,6-dimethyl-3,5-dicarboxylic acid alkyl ester have been synthesized by the Hantzsch reaction in ionic liquid [Bmim]OH. Structures of all new compounds have been elucidated by microanalyses, ^{1}H and ^{13}C NMR spectroscopies.

Key Words: Pyrazoline, Dihydropyridine, Ferrocene, Hantzsch reaction, Catalysis.

Introduction

Recently due to ferrocene's special characteristic of structure and nature, derivatives of ferrocene are widely used in application of biology and medical areas [1-6], Ferrocene with excellent aromatic easily to be replaced and modified and keep most particular stable in most media. The derivatives are lipophilic and can easily permeate the cell membrane so react with the enzyme in the cell. The derivatives with less toxicity, Oxidation and reduction and also can interact with intracellular enzyme. The derivatives of dihydropridine and pyrazoline possessing bioactivities attached a group of Ferrocene can be expected to enhance the bioactivity of the derivatives of the interest and screened out of more active compounds.

Pyrazolines are important and useful five-membered heterocyclic compounds and various procedures have been worked out for their synthesis [7-11]. Several pyrazoline derivatives were found to possess important bioactivities, such as antibacterial [12, 13], antiviral [14], antifungal [15], immunosuppressive [16], central nervous system [17], molluscicidal [18, 19], *etc*. activities. Recently, 3-(2-pyridyl)-2-pyrazoline derivatives have been used as novel fluorescent probes [20]. All these mentioned bioactivities and other utilities stimulated the research in this field. 2-Pyrazolines proved to be the most useful pyrazoline type compounds and various methods have been developed for their synthesis [10, 11]. A generally used simple and convenient procedure is based on the reaction of α, β-unsaturated aldehydes and ketones with hydrazines or phenylhydrazines. By this method, herein we describe the synthesis of new 5-aryl-3-ferrocenyl-1-phenyl-2-pyrazolines bearing ferrocenyl and polycyclic aryl and/or heteroaryl moieties by the reaction of α, β-unsaturated ketones with phenylhydrazines.

1, 4-dihydropyridine derivatives are a class of important heterocyclic compounds, and was used as high-performance calcium antagonists since 1960's. Because of their potential biological activity [21-23] and use in treatment such as anti-hypertensive[24], anti-inflammatory[25] and antiangina[26] drugs , it has been paid more and more attention in recent years.

We are also currently interested in synthesizing 1,4-dihydropyridine derivatives analogues bearing ferrocene moiety such as 4-ferrocenyl-1,4-dihydropyridine-2,6-dimethyl-3,5-di carboxylic acid alkyl ester as shown Fig. 1, the synthesis of compounds has been carried out by reaction of ferrocenecarboxaldehyde, β-ketoester and ammonium acetate. All these compounds showed analytical and spectroscopic data in good agreement with their structure.

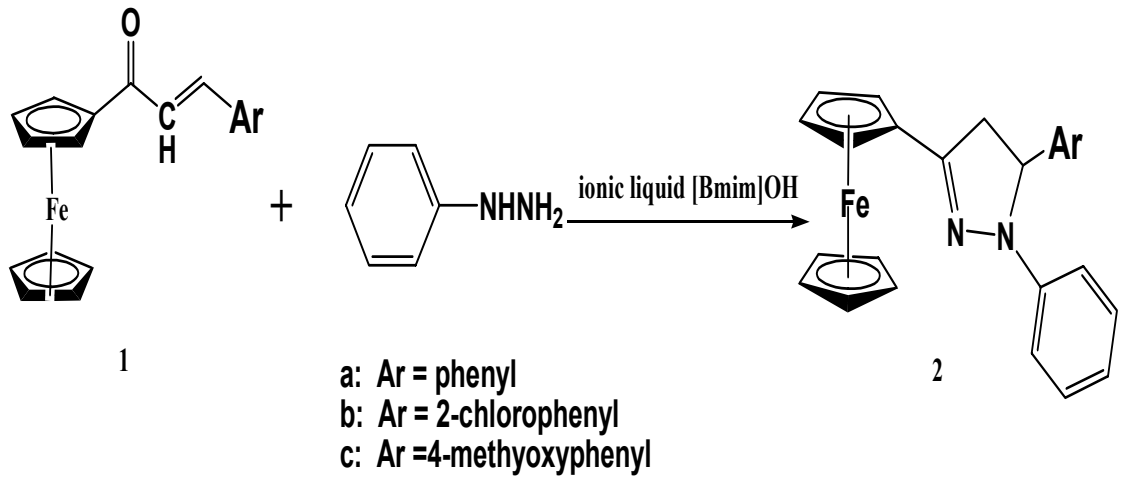

Fig. 1: Synthesis of 5-aryl-3-ferrocenyl-1-phenyl-2-pyrazoline derivatives.

Results and Discussion

Synthesis of 5-aryl-3-ferrocenyl-1-phenyl-2-pyrazoline derivatives

As described in the introduction, both the ferrocene and the 2-pyrazolines possess important bioactivities which render them useful substances in drug research. On this basis, it appeared expedient to synthesize new heterocyclic compounds bearing both a ferrocene moiety and a 2-pyrazoline unit. Reaction of ferrocenyl chalcones, as easily available, α , β-unsaturated ketones, with phenylhydrazines seemed to be a convenient route to fulfil this aim. 3-Aryl-1-ferrocenylpropen-1-ones **1a-c** were allowed to react with phenylhydrazine in glacial acetic acid to afford 5-aryl-3-ferrocenyl-1-phenyl-2-pyrazolines **2a-c** in low yields (40-48%), while the reaction was in ionic liquid [Bmim] OH with good yield of 67-87%. (Fig 1).

Structures of all new 5-aryl-3-ferrocenyl-1-phenyl-2-pyrazolines **2a-c** have been elucidated by elemental analyses, IR, ^{1}H nmr spectroscopic measurements. In the ^{1}H nmr spectra of substances **11-35**, the three protons attached to the C-4 and C-5 carbon atoms of the 2-pyrazoline unit gave an ABX spin system. Both the chemical shifts and the coupling constant values (*cf.* Experimental) unequivocally prove the 3-ferrocenyl -2-pyrazoline structure.

Synthesis of 4-ferrocenyl-3,5- substituted 1,4-dihydropyridines

In the efforts to develop an efficient and environmentally benign methodology for the synthesis of DHPs, either we initiated our studies by subjecting catalytic amount of ionic liquid [Bmim]OH to mixture of ferrocenecarboxaldehyde, ethyl acetoacetate and ammonium acetate in solvent at room temperature. Unfortunately, the resulted yield all was very poor even after 24 h of stirring. To effect the reaction, various solvent systems were screened at different temperatures. We were pleased to see that the synthesis of DHP was efficiently in ionic liquid [Bmim]OH in solvent at elevated temperature leading to high yield of product (Fig. 2). The reaction condition was then optimized by conducting the reaction in different temperatures and employing different catalyst loadings. The results are summarized in Table-1. It is evident that the best result was obtained by the application in ionic liquid [Bmim]OH at 80 °C (Table-1, entry 8). Higher amount of the ionic liquid substantially reduce the amount of yield as side products formed.

The optimized reaction conditions were subsequently applied to the reaction between ferrocenecarboxaldehyde and β-ketoesters in presence of ammonium acetate in solvent at reflux temperature. In most cases, the desired symmetrical DHP derivatives were obtained with higher yields at 80 ºC in ionic liquid [Bmim]OH than in ethanol. The efficiency of the mixed solvent consisted of the ionic liquid and ethanol is still lower than full ionic liquid (Table-1, entry 8 and 10; entry 7 and 12). In a typical procedure, 2 mmol of ferrocenecarboxaldehyde, 4 mmol of β-ketoester and 8 mmol of ammonium acetate were mixed in presence of 10 ml % of ionic liquid [Bmim]OH was stirred for 1.5-3 h at 80 °C, after work-up, it produced the corresponding 4-ferrocenyl-3,5-substituted 1,4-dihydropyridines (**3a-d**) with good yields.

Experimental

All of the reagents are AR grade. Melting points were determined on an X4-degital melting points reader and uncorrected. ^{1}HNMR spectra were run at a Bruker 400 for $CDCl_3$ solutions and shifts are given in parts per million downfield from TMS as an internal standard. Elemental analyses were performed in a Flash 1112 Elemental analyzer. The IR spectra were taken on a NEXUS 470 FT-IR spectrometer (KBr disks). Mass spectra were recorded on ESQUIRE 3000 Mass Spectrometer.

Table-1: Condensation of ferrocenecarboxaldehyde, ethyl acetoacetate and ammonium acetate under different ionic liquid [Bmim] OH loadings, temperature and solvent systems

Entry	ionic liquid load (ml)	Solvents	Temperature (°C)	Time (h)	Yield (%)
1	10	neat	rt	30	40
2	10	EtOH	rt	30	43
3	3	EtOH	60	3	67
4	3	neat	60	3	66
5	3	neat	80	2	76
6	6	neat	80	1.5	78
7	15	neat	80	3	89
8	10	neat	80	3	90
9	6	EtOH	80	3	77
10	10	EtOH	80	3	86
11	15	EtOH	60	1.5	86
12	15	EtOH	80	3	88

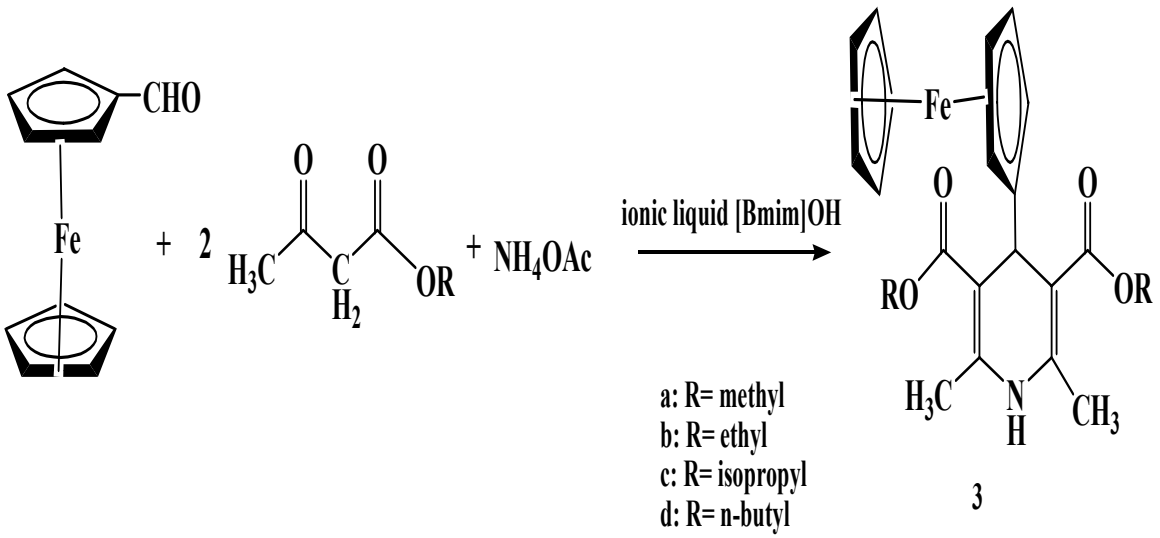

Fig. 2: Synthesis of 4-ferrocenyl-1,4-dihydropyridine-2,6-dimethyl-3,5-dicarboxylic acid alkyl ester derivatives.

Preparation of the ionic liquid [Bmim]OH

Synthesis of the ionic liquid [Bmim]OH was according to literature.

General procedure for the preparation of 5-aryl-3-ferrocenyl-1-phenyl-2-pyrazoline derivatives (**2a-c**).

A mixture of ferrocenyl chalcones (**1a-c**, 0.03 moles), phenylhydrazine (0.05 moles), the ionic liquid [Bmim]OH (10 ml) was refluxed for about 6 hours, monitored by TLC. Once the reaction completed, was cooled in ice bath for 15 min. The precipitate was separated by filtration, washed with water. The crude products were purified by passing through column of silica gel eluted with mixture of petroleum ether and ethyl acetate (v/v, 8:1) to give compound **2** as shown in Fig. 1.

*General procedure for the Preparation of 4-ferrocenyl-1, 4-dihydropyridine (**3a-d**)*

A solution of ferrocenecarboxaldehyde (2 mmol), alkyl acetoacetate or (4 mmol), ammonium acetate (8 mmol) and in ionic liquid [Bmim]OH (10 ml) was stirred at 80°C or at reflux temperature for 1.5–3 h. The reaction was monitored by TLC. After the reaction mixture was cooled to room temperature, and was poured into ice-water (50 ml). The precipitated solid was filtered, washed with ice-water, dried and subjected to flash column chromatography on silica using ethyl ether/petrol (2 : 1) as eluent to obtain the target compound **3a** which was recrystallized from EtOH. Compounds **3b-d** was prepared with the same procedure as **3a**.

3-ferrocenyl-1,5-diphenyl-2-pyrazoline **(2a):** yellow plates. In 87% Yield, mp 237-239°C. Anal. Calcd for $C_{25}H_{22}FeN_2$: C, 73.90; H, 5.46; N, 6.89 found: found: C, 73.81; H, 5.76; N, 7.02. ^{1}HNMR (400Hz, $CDCl_3$) δ: 3.00 (dd, 1H, C4-H, J=5.0 Hz, C4-H_{trans}), 3.76(dd, 1H,

C4-H, J=11.0 Hz, C4-H_{cis}), 4.15(s, 5H, C_5H_5), 4.38-4.47(m, 4H, C_5H_4), 5.29(dd, 1H, J=5.0, 11.0 Hz, C5-H), 6.71-7.36(m, 10H, ArH). IR (KBr) ν: 3089, 3025, 2934, 1662, 1589, 1537, 1455, 1336, 1107, 998, 880, 821, 745, 652, 571, 492cm^{-1}.

5-(2-chlorophenyl)-3-ferrocenyl-1-phenyl-2-pyrazoline (**2b**): yellow plates. In 71% Yield, mp 211-214°C. Anal. Calcd for Calcd for $C_{25}H_{21}ClFeN_2$: C, 68.13; H, 4.80; N, 6.36 found: C, 68.21; H, 4.85; N, 6.26. ^{1}HNMR (400Hz, $CDCl_3$) δ: 3.02(dd, 1H, J=5.0 Hz, C4-H_{trans}), 3.83(dd, 1H, J=11 Hz, C4-H_{cis}), 4.17(s, 5H, C_5H_5), 4.47-4.54(m, 4H, C_5H_4), 5.31(dd, 1H, J=5.0, 11.0 Hz, C5-H), 6.68-7.34(m, 9H, ArH). IR (KBr) ν: 3091, 3014, 2900, 1659, 1540, 1491, 1447, 1121, 1009, 938, 892, 817, 740, 661, 497cm^{-1}.

3-ferrocenyl-5-(4-methoxyphenyl)--1-pheny l-2-pyrazoline (**2c**): yellow plates. In 80 % Yield, mp 199-202°C. Anal. Calcd for Calcd for $C_{26}H_{24}FeN_2O$: C, 71.56; H, 5.50; N, 6.42 found: C, 71.54; H, 5.68; N, 6.37. ^{1}HNMR (400Hz, $CDCl_3$) δ: 3.11 (dd, 1H, J=5.0 Hz, C4-H_{trans}), 3.77(s, 3H, OCH_3), 3.92(dd, 1H, J=11.0 Hz, C4-H_{cis}), 4.15(s, 5H, C_5H_5), 4.43-4.64(m, 4H, C_5H_4), 5.31(s, 1H, J=5.0, 11.0 Hz, C5-H), 6.68-7.34(m, 9H, ArH). IR (KBr) ν: 3099, 3030, 2926, 1668, 1591, 1445, 1400, 1100, 1007, 940, 856, 818, 720, 642, 486cm^{-1}.

Dimethyl 4-ferrocenyl-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate(**3a**): yellow plates. In 87 % Yield, mp 223-225 °C, (225 °C, lit[28]). Anal. Calcd. for $C_{21}H_{23}FeNO_4$: C: 61.63, H: 5.66, N: 3.42, Found. C: 61.68, H: 5.50, N: 3.38; ^{1}HNMR (400Hz, $CDCl_3$) δ: 5.64(s, 1H, NH); 4.83(s, 1H, CH), 4.37(s, 5H, C_5H_5), 4.35-4.29(m, 4H, C_5H_4), 3.96(s, 6H, 2×OCH_3), 2.27(s, 6H, 2×CH_3), IR (KBr ν_{max} cm^{-1}): 3347(N-H), 1706(C = O), 1665 (C = C), 1266, 1103(C-O).

Diethyl 4-ferrocenyl-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate (**3b**): yellow plates. In 88 % Yield, mp 217-219 °C (218-220 °C, lit [29]). Anal. Calcd. for $C_{23}H_{27}FeNO_4$: C: 63.17, H: 6.22, N: 3.20, Found. C: 63.26, H: 6.30, N: 3.15; ^{1}HNMR (400Hz, $CDCl_3$) δ: 5.66(s, 1H, NH), 4.77(s, 1H, CH), 4.35(s, 5H, C_5H_5), 4.27 ~ 4.31(m, 4H, C_5H_4), 3.96-4.01(q, J=6.8 Hz, 4H, 2×CH_2), 2.27(s, 6H , 2×CH_3), 1.33-1.37(t, J=6.8 Hz, 6H, 2×CH_3). IR (KBr ν_{max} cm^{-1}): 3340(N-H), 1691(C = O), 1650(C = C), 1212, 1118(C-O).

Diisopropyl 4-ferrocenyl-1,4-dihydro-2,6-dimethyl-pyridine-3,5-dicarboxylate (**3c**): yellow plates. In 76 % Yield, mp148-150 °C (149 °C, lit[28]). Anal. Calcd. for $C_{25}H_{29}FeNO_4$: C: 64.52, H: 6.71, N: 3.01, Found. C: 64.56, H: 6.79, N: 2.98; ^{1}HNMR (400Hz, $CDCl_3$) : ^{1}HNMR (400Hz, $CDCl_3$) δ: 5.71 (s, 1H, NH), 4.98 (s, 1H, CH) ,4.78-4.83 (m, 2H, 2×CH), 4.06 (s, 5H, C_5H_5) ,3. 94-3.98 (m, 4 H, C_5H_4), 2.35 (s, 6H, 2×CH_3), 1.33 (d, J=7.2 Hz, 12H, 4×CH_3). IR (KBr ν_{max} cm^{-1}):3373 (N-H), 1721 (C = O), 1639 (C = C), 1227, 1116 (C-O).

Dibutyl 4-ferrocenyl-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate (**3d**): yellow plates. In 71 % Yield, mp157-159 °C (158 °C, lit[28]). Anal. Calcd. for $C_{27}H_{35}FeNO_4$: C: 65.72, H: 7.15, N: 2.84, Found. C: 65.66, H: 7.13, N: 2.78; ^{1}HNMR (400Hz, $CDCl_3$) : 5. 69 (s, 1H, NH), 4.95(s, 1H, CH), 4.16-4.24 (t, J=7.8 Hz, 4H, 2×CH_2), 4.07 (s, 5H, C_5H_5), 3.95-3.98 (m, 4H, C_5H_4), 2.33 (s, 6H, 2×CH_3), 1.68-1.75 (m, 4H, 2×CH_2), 1.44-1.51 (m, 4H, 2×CH_2), 0. 96-0. 99 (t, J = 6. 4Hz, 6H, 2×CH_3). IR (KBr ν_{max} cm^{-1}): 3339(N-H), 1699(C=O), 1661 (C = C), 1219, 1119 (C-O).

Conclusion

In conclusion, we have synthesized some new 5-aryl-3-ferrocenyl-1-phenyl-2-pyrazolines in ionic liquid [Bmim]OH in good yield and developed a simple and efficient synthetic protocol for the synthesis of 4-ferrocenyl-1,4-dihydropyridines in

ionic liquid [Bmim]OH at 80 ºC in excellent yields. In addition to the synthesis were achieved successfully in one-pot four-component fashion starting from ferrocenecarboxaldehyde, two β-ketoesters and ammonium acetate following the same protocols. Mild reaction condition, cost efficiency, simplicity in operation, lower catalyst loading, and reduction of reaction steps constitute significant features of this protocol.

Acknowledgement

The authors express their thanks to the Nature Science Foundation of Hubei Province of China (No. 2012FFB07410) for financial support during this investigation.

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