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Synthesis of 5-Aryl-1-benzothiazolyl-3-ferrocenyl-2-pyrazoline by Condensation of Ferrocenyl Chalcones with 2-Hydrazinyl-benzothiazole

MANMAN LIU, QIAN LIU and JIAN ZHANG*

College of Chemistry and Materials, South-Central University for Nationalities, Wuhan 430074, P.R. China

*Corresponding author: E-mail: jianzhangye@gmail.com

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Condensation reactions of chalcone containing ferrocene unit with 2-hydrazinyl-benzothiazole afforded five novel 5-aryl-1-benzothiazolyl-3-ferrocenyl-2-pyrazolines in alkaline solution. The efficiency of using NaOH as catalyst is higher than acetic acid or piperidine. The structures of these compounds **5a-e** were confirmed by IR, ^{1}H NMR and HRMS.

Keywords: Pyrazoline, Dihydropyridine, Ferrocene, Catalysis.

INTRODUCTION

Derivatives of ferrocene are widely used in application of biology and medical areas[1-6] due to ferrocene's special characteristic of structure and nature. Ferrocene with excellent aromaticity 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 can also interact with intracellular enzyme. The derivatives of dihydropyridine 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.

In the past decade, pyrazolines were emerged as a new class of heterocyclic compounds[7-11], which have important pharmacological activities including antimicrobial[12-15], antiamoebic[16,17], antinociceptive[18], anticancer[19], *etc*. Recently, the pyrazolines were also found to have fluorescent properties[10]. Because of these mentioned bioactivities and other activities, scientists are increasingly focusing on this field. In particular, many researches focus on synthesis of 2-pyrazoline[10,11]. In this paper we report the synthesis of novel 5-aryl-1-benzothiazolyl-3-ferrocenylyl-2-pyrazolines bearing ferrocenyl and heteroaryl moieties by the reaction of ferrocenyl chalcones with 1-(benzo-[d]thiazol-2-yl)hydrazine.

EXPERIMENTAL

All chemicals were of reagent grade, purchased from commercial sources and used without further purification. Aromatic aldehydes, ethyl acetoacetate phosphorus oxychloride and hydrazine were purchased from the Alladin Chemical Company and were used without further purification. All the solvents were dried using standard methods before use. IR spectra were recorded on a Nexus-470 IR spectrometer, ^{1}H NMR were recorded on a Bruker 400 for $CDCl_3$ solutions. X4-digital melting point reader was used to determine the melting points. HRMS spectra were obtained on a MAT95XP spectrograph (Thermo).

General prrocedure for the preparation of ferrocenyl chalcones (3): The preparation of ferrocenyl chalcones were executed according to literature[20-22].

General procedure for the preparation of 5-aryl-1-benzothiazolyl-3-ferrocenyl-2-pyrazolines (5a-e): To a flask containing ferrocenyl chalcones (1 mmol) and 2-hydrazinyl-benzothiazole (1.2 mmol) dissolved in 30 mL of alcohol, a certain amount of sodium hydroxide solution was added. The mixture was refluxed for about 8 h, monitored by TLC. Once the reaction completed, the reaction solution was poured into 100 mL of ice cold water. 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 dichloromethane and petroleum ether (v/v, 10:1) to give compound **5**.

1-Benzothiazolyl-3-ferrocenyl-5-(4-methoxyphenyl)-2-pyrazoline (5a): Brown solid, Yield (54.7 %). m.p. 209-210 °C; IR (KBr pellet, ν_{max}, cm^{-1}): 3090 (Ar-H), 2919 (C-H), 1600 (C=N), 1540 (C=C), 558, 483 (Cp-Fe-Cp); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, *J* = 7.0 Hz, 1H, Ar-H), 7.53 (d, *J* = 7.7 Hz, 1H, Ar-H), 7.30-7.22 (m, 3H, Ar-H), 7.09 (m, 1H, Ar-H), 6.89

(d, *J* = 8.7 Hz, 2H, Ar-H), 5.73 (dd, *J* = 11.5, 4.4 Hz, 1H, pyrazoline- H), 4.77 (s, 1H, Cp), 4.60 (s, 1H, Cp), 4.44 (d, *J* = 7.2 Hz, 2H, Cp), 4.15 (s, 5H, Cp), 3.83 (dd, *J* =16.8, 11.6 Hz, 1H, pyrazoline- H), 3.78 (s, 3H, -OCH_3), 3.14 (dd, *J* =17.1, 4.5 Hz, 1H, pyrazoline-H); HR-ESIMS calcd for $[M + H]^+$ $C_{27}H_{24}FeN_3OS^+$: 494.0935, found: 494.0929.

1-Benzothiazolyl-5-(4-chlorophenyl)-3-ferrocenyl-2-pyrazoline (5b): Brown solid, Yield (68.4 %), m.p. 242-243 °C; IR (KBr pellet, ν_{max}, cm^{-1}): 3077(Ar-H), 2913 (C-H), 1599 (C=N), 1539 (C=C), 555, 476 (Cp-Fe-Cp); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 7.8 Hz, 1H, Ar-H), 7.54 (d, *J* = 8.0 Hz, 1H, Ar-H), 7.38-7.29 (m, 5H, Ar-H), 7.10 (m, 1H, Ar-H), 5.79 (dd, *J* = 11.5, 4.4 Hz, 1H, pyrazoline-H), 4.78 (s, 1H, Cp), 4.60 (s, 1H, Cp), 4.44 (d, *J* = 7.2 Hz, 2H, Cp), 4.14 (s, 5H, Cp), 3.86 (dd, *J* = 17.0, 11.6 Hz, 1H, pyrazoline-H),3.16 (dd, *J* = 17.1, 4.4 Hz, 1H, pyrazoline-H); HR-ESIMS calcd for [M + H]$^+$ $C_{26}H_{21}ClFeN_3S^+$: 498.0422, found: 494.0416.

1-Benzothiazolyl-3-ferrocenyl-5-phenyl-2- pyrazoline (5c): Reddish brown solid, Yield (80.6 %), m.p. 214-215 °C; IR (KBr pellet, ν_{max}, cm^{-1}): 3081(Ar-H), 2920 (C-H), 1597 (C=N), 1539 (C=C), 525, 473 (Cp-Fe-Cp); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 7.8 Hz, 1H, Ar -H), 7.54 (d, *J* = 8.0 Hz, 1H, Ar-H), 7.38 (d, *J* = 4.2 Hz, 4H, Ar-H), 7.29 (m, 2H, Ar-H), 7.10 (m, 1H, Ar-H), 5.79 (dd, *J* = 11.5, 4.4 Hz, 1H, pyrazoline-H), 4.78 (s, 1H, Cp), 4.60 (s, 1H, Cp), 4.44 (d, *J* = 7.2 Hz, 2H, Cp), 4.14 (s, 5H, Cp), 3.86 (dd, *J* = 17.0, 11.6 Hz, 1H, pyrazoline-H), 3.16 (dd, *J* = 17.1, 4.4 Hz, 1H, pyrazoline-H); HRESIMS calcd for [M+H]$^+$ $C_{26}H_{22}ClFeN_3S^+$: 464.0844, found: 464.0836.

1-Benzothiazolyl-3-ferrocenyl-5-furyl-2-pyrazoline (5d): Brown solid, Yield (55.4 %), m.p. 205-206 °C. IR (KBr pellet, ν_{max}, cm^{-1}): 3069 (Ar-H), 2937 (C-H), 1599 (C=N), 1536 (C=C), 527, 471(Cp-Fe-Cp).; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (m, 2H), 7.39 (s, 1H), 7.31 (m, 1H), 7.12 (m, 1H), 6.52 (s, 1H), 6.36 (s, 1H), 5.83 (dd, *J* = 10.5, 3.4Hz, 1H, pyrazoline-H), 4.84 (s, 1H, Cp), 4.58 (s, 1H, Cp), 4.45 (d, *J* = 10.4 Hz, 2H, Cp), 4.24 (s, 5H, Cp), 3.67 (dd, *J* = 16.7, 12.0 Hz, 1H, pyrazoline-H), 3.49 (dd, *J* = 17.1, 11.2 Hz, 1H, pyrazoline-H); HR-ESIMS calcd for [M + H]$^+$ $C_{26}H_{20}FeN_3OS^+$: 454.0628, found: 454.0636.

1-Benzothiazolyl-3-ferrocenylyl-5-thienyl-2-pyrazoline (5e): Brown solid, Yield (61.6 %), m.p. 224-225 °C; IR (KBr pellet, ν_{max}, cm^{-1}): 3082 (Ar-H), 2931 (C-H), 1598 (C=N), 1539 (C=C), 551, 487 (Cp-Fe-Cp); ^{1}H NMR (400 MHz, $CDCl_3$) δ7.66 (d, *J* = 7.0Hz, 1H), 7.60 (d, *J* = 7.6 Hz, 1H), 7.31(m, 1H), 7.23 (d, *J* = 7.7 Hz, 1H), 7.18 (s, 1H), 7.14 (m, 1H), 6.98 (s, 1H), 6.05 (dd, *J* =10.8, 3.6 Hz, 1H, pyrazoline-H), 4.81 (s, 1H, Cp), 4.60 (s, 1H, Cp), 4.45 (d, *J* = 8.4 Hz, 2H, Cp), 4.19 (s, 5H, Cp), 3.83 (dd, *J* = 17.2, 11.4 Hz, 1H, pyrazoline-H), 3.36 (dd, *J* = 16.9, 4.4Hz, 1H, pyrazoline-H); HR-ESIMS calcd for [M + H]$^+$ $C_{24}H_{20}FeN_3S_2^+$: 470.0437, found: 470.0427.

RESULTS AND DISCUSSION

Synthesis of 5-aryl-1-benzothiazolyl-3-ferrocenylyl-2-pyrazolines (5): As mentioned before, both ferrocene and 2-pyrazoline compounds have important biological activity, making them useful substances in drug research. In view of affording new heterocyclic compounds possessing both a ferrocene and a pyrazoline group, we considered the easiest approach was that reacting ferrocenyl chalcones with 2-hydrazinyl-benzothiazole to get the target product. Compounds **3** were reacted with 2-hydrazinyl-benzothiazole in glacial acetic acid to afford compounds **5** in low yields (60 %), while the reaction was in alkaline solution with good yield of 83 % (Fig. 1). The structures of these compounds **5a-e** were confirmed by IR, ^{1}H NMR and HRMS. Both HRMS and the chemical shifts of protons accord with 5-aryl-1-benzothiazolyl-3-ferrocenyl-2-pyrazolines. On the other hand, ^{1}H NMR spectra of **5a-e** also indicate that the three protons (C4-C5) of the 2-pyrazoline conform to an ABX spin system.

To establish a methodology of efficient and environmentally friendly for synthesis of compounds **5**, we used the method as described. The reaction mixture was refluxed in solvent at room temperature. Unfortunately, the yield in all cases was very low even if the reaction was carried out for 18 h. In order to improve the reaction efficiency, screening of different catalyst, solvent and reaction temperature. Results present that with the increase of temperature, the yield of continuous improvement. The results are summarized in Table-1. It is evident that the best result was obtained by the application

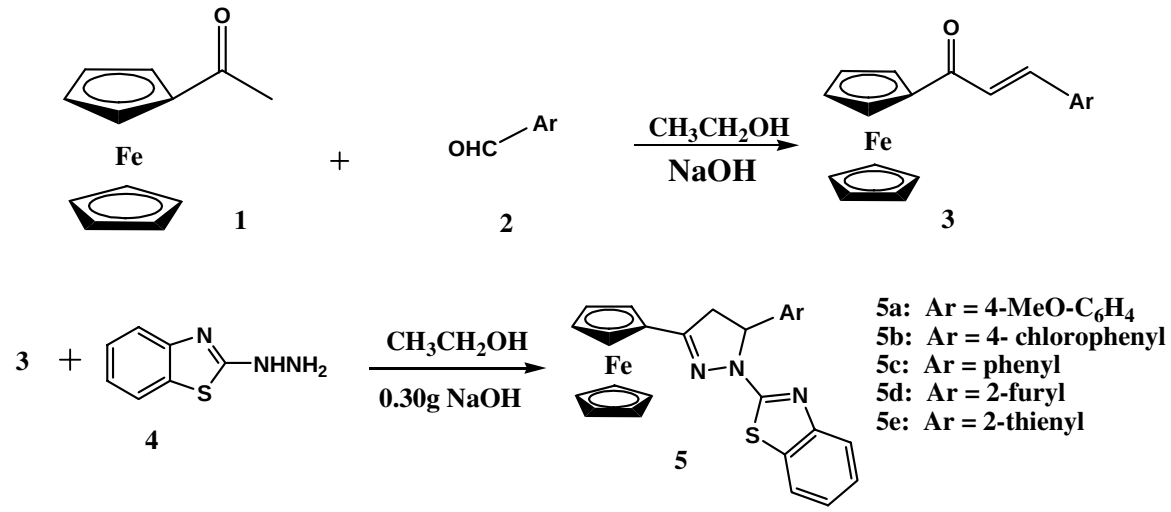

Fig. 1. Synthesis of 5-aryl-1-benzothiazol-2-yl-3-ferrocenyl-2-pyrazolines (**5a-e**)

TABLE-1
CONDENSATION OF FERROCENYL CHALCONES AND 2-HYDRAZINYL-BENZOTHIAZOLE UNDER DIFFERENT TEMPERATURE, REACTION TIME AND CATALYST SYSTEMS

Entry	Catalyst	Temp. (°C)	Time (h)	Yield (%)
1	Piperidine	70	8	60
2	NaOH	78	8	83
3	NaOH	85	8	85
4	NaOH	90	8	78
5	Acetic acid	78	6	71
6	Piperidine	78	8	80
7	Acetic cid	78	10	82
8	NaOH	78	12	85
9	Piperidine	78	15	76
10	Acetic acid	78	8	60
11	Piperidine	78	8	65
12	NaOH	78	8	83

using 8 mol % of NaOH in ethanol at 78 °C for 8 h (Table-1, entry 8). Higher temperature substantially reduces the amount of yield due to the formation of by-products.

In order to optimize the reaction conditions, we applied subsequence to the reaction between ferrocenyl chalcones and 2-hydrazinyl-benzothiazole in solvent at reflux temperature to obtain the required derivatives with higher yields at 80 ºC in ethanol in most cases. The efficiency of using acetic acid or piperidine as catalyst is still lower than NaOH (Table-1, entry 10, entry 11 and entry 12). In a typical procedure, 1 mmol of ferrocenyl chalcones and 1.2 mmol of 2-hydrazinyl-benzothiazole and 8 mol % of NaOH were mixed in alcohol was stirred for 8 h at 80 °C, it produced the corresponding 5-aryl-1-benzothiazolyl-3-ferrocenyl-2-pyrazolines (**5a-e**) with good yields.

Conclusion

Five novels 5-aryl-1-benzothiazolyl-3-ferrocenyl-2-pyrazoline derivatives has been synthesized and confirmed by IR, ^{1}H NMR and HRMS. The desired derivatives were obtained with higher yields at 80 ºC in ethanol. The efficiency of using NaOH as catalyst is higher than acetic acid or piperidine.

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