Journal of Molecular Structure 930 (2009) 83–87

Contents lists available at ScienceDirect

Journal of Molecular Structure

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

Synthesis and single-crystal characterization of novel 2-ferrocenyl-4*H*-pyrazolo[5,1-c][1,4]oxazin-4-one derivatives

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ARTICLE INFO

Article history:
Received 2 March 2009
Received in revised form 24 April 2009
Accepted 27 April 2009
Available online 6 May 2009

Keywords:
Ferrocene
Pyrazole-fused oxazinone
Synthesis
X-ray structure

ABSTRACT

A series of novel 2-ferrocenyl-6-substituted-4*H*-pyrazolo[5,1-c][1,4]oxazin-4-one derivatives were synthesized by the intra-esterification reaction of ethyl 1-(2-aryl-2-oxoethyl)-3-ferrocenyl-1*H*-pyrazole-5-carboxylate in the presence of magnesium bromide and diisopropylethylamine in one-pot procedure. The structures of compounds were characterized by ^{1}H NMR, ^{13}C NMR, IR, HRMS and X-ray diffraction analysis.

1. Introduction

Ferrocene and its derivatives have been attracted much more attention in wide fields such as organometallic chemistry, materials science, catalysis and biological activities since the discovery of ferrocene in 1951. Incorporation of a ferrocene fragment into a molecule of an organic compound often obtained unexpected biological activity, which is rationalized as being due to their different membrane permeation properties and anomalous metabolism. Many ferrocenyl compounds display interesting cytotoxic, antitumor, antimalarial, antifungal and DNA-cleaving activity [1–10]. Furthermore, the stability and non-toxicity of the ferrocenyl moiety is of particular interest rendering such drugs compatible with other treatment [11]. Therefore, the integration of one or more ferrocene units into a heterocyclic ring molecule has been recognized as an attractive way to endow a novel molecule functionally [12–18].

On the other hand, it is well known that pyrazole derivatives are associated with various pharmaceutical activities such as cannabinoid hCB1 and hCB2 receptor, anti-inflammatory, inhibitors of p38 Kinase, CB1 receptor antagonists, antimicrobial activity [19–23]. The incorporation of heterocyclic rings into prospective pharmaceutical candidates is a major strategy to obtain activity and safety advantages. As a consequence, much attention has been paid to the design and synthesis of fused-pyrazole derivatives [24–27]. As part of an ongoing program aimed at developing new anticancer agents, we synthesized a series of novel fused-pyrazole derivatives including 6-(aroxymethyl)-2-aryl-6,7-dihydropyrazolo[5,1-*c*][1,4]-oxazin-4-one derivatives [28], 5-alkyl-2-ferrocenyl-6,7-dihydropyrazolo[1,5-*a*]pyrazin-4(5*H*)-one [29,30] and 5-alkyl-2-aryl-6,7- dihydropyrazolo[1,5-*a*]pyrazin-4(5*H*)-one [31]. Oxazinones constitute an important class of heterocycles, which has attracted much synthetic interest due to their wide range of biological activities [32–35]. However, a search of the literature revealed very few reports concerning pyrazole fused oxazinone [36]. Therefore, the synthesis of pyrazole-fused oxazinone derivatives directly linked to a ferrocene unit is of considerable interest.

Herein, we would like to report the synthesis and structural characterization of novel ferrocenyl pyrazole-fused oxazinone derivatives.

2. Results and discussion

2.1. Chemistry

The synthesis of 2-ferrocenyl-6-substituted-4*H*-pyrazolo[5,1-c][1,4]oxazin-4-one **4** has been accomplished as outlined in Scheme 1. The key intermediate in the present study is the ethyl 1-(2-aryl-2-oxoethyl)-3-ferrocenyl-1*H*-pyrazole-5-carboxylate **3** that can be synthesized from α-bromo-arylethanone **2** and ethyl 3-ferrocenyl-1*H*-pyrazole-5-carboxylate **1**, which can be obtained from acetylferrocene and diethyl oxalate, with hydrazine hydrate in the presence of acetic acid at room temperature as

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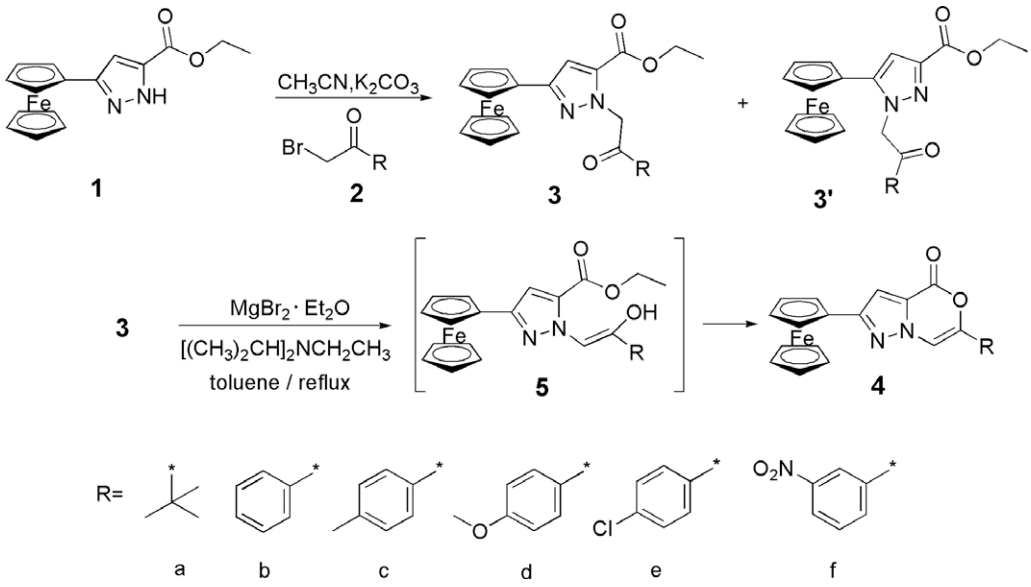
doi:10.1016/j.molstruc.2009.04.042



Scheme 1.

previous report [29]. The structure was determined by IR, ^{1}H NMR, ^{13}C NMR, HRMS and X-ray diffraction analysis. In the IR spectrum, the carbonyl group absorptions were observed in the region of 1743–1748 cm^{-1}. The physical property and HRMS spectrum data of compounds **4** are shown in Table 1. The data of ^{1}H NMR and ^{13}C NMR of the compounds **4** are given in Table 2.

*2.1.1. Synthesis of ethyl 1-(2-aryl-2-oxoethyl)-3-ferrocenyl-1H-pyrazole-5-carboxylate **3***

It is known that nitrogen atom at *N*-1 position of a pyrazole moiety possesses nucleophilic ability to react with alkyl halide under a suitable condition [29]. Thus, according to our previous paper, the *N*-alkylation reaction between ethyl 3-ferrocenyl-1*H*-pyrazole-5-carboxylate **1** and α-bromo-arylethanone **2** was achieved in the presence of potassium carbonate as the base in acetonitrile. After flash chromatography on silica gel, the ethyl 1-(2-aryl-2-oxoethyl)-3-ferrocenyl-1*H*-pyrazole-5-carboxylate **3** and the isomer, 1-(2-aryl-2-oxoethyl)-5-ferrocenyl-1*H*-pyrazole-3-carboxylate **3′** were obtained (Scheme 1). Two isomers can be distinguished by comparing the chemical shift, especially the signals of methylene bonded to nitrogen of pyrazole moiety and protons of ferrocene moiety in ^{1}H NMR spectra as described in our previous paper [29]. For example, the signals of two protons in methylene bonded to nitrogen in **3d** appear at 5.95 ppm while corresponding protons in **3′d** appear at 5.71 ppm. Two protons in substituted Cp of Fc moiety peaks in **3d** are relatively downfield and appear around 4.70 ppm while corresponding protons in **3′d** are relatively upfield and resonate around 4.38 ppm. In the case of **3b** and **3′b**, the signals of two protons in methylene are 6.03 and 5.76, respectively. Furthermore, two protons in substituted Cp of Fc moiety peaks in **3b** and **3′b** are 4.72 and 4.34 ppm.

*2.1.2. Synthesis of 2-ferrocenyl-6-substituted-4H-pyrazolo[5,1-c][1,4]oxazin-4-one **4***

Ethyl 1-(2-aryl-2-oxoethyl)-3-ferrocenyl-1*H*-pyrazole-5-carboxylate **3** undergo intramolecular esterification reaction via soft enolate formation on treatment with $MgBr_2Et_2O$ and *i*-Pr_2NEt to afford 2-ferrocenyl-6-substituted-4*H*-pyrazolo[5,1-c][1,4]oxazin-4-one **4**. It is reported that in soft enolization, a weak base and a Lewis acid act in concert to effect deprotonation reversibly. Here, the Lewis acid, $MgBr_2Et_2O$, interacts with the carbonyl oxygen to polarize it beyond its normal state, resulting in a substantial increase in the acidity of the α-proton, to the extent that it can be removed appreciably by the weak base. Since enolization in this case is reversible, it is conducted in a direct fashion in the presence of the electrophilic species, further simplifying the procedure [37].

2.2. Single-crystal structure

The spatial structure of compound **4b** was determined by using X-ray diffraction analysis. Crystals suitable for X-ray diffraction were obtained by slow evaporation of a solution of the solid in ethyl acetate/dichloromethane at room temperature for 4 days. The molecular view of **4b** is shown in Fig. 1. A summary of crystallographic data collection parameters and refinement parameters for **4b** are compiled in Table 3, meanwhile important bond lengths and angles are depicted in Table 4.

The asymmetric unit of **4b** contains two crystallographically independent molecules A (containing O1) and B (containing O3). Fig. 1 shows **4b** contained a ferrocenyl bound to pyrazole ring which fused with plane oxazinone connected benzene ring. The corresponding bond lengths and angles of pyrazole rings in A and B agree well with each other, but that of oxazinone rings in A

Table 1
Formula, melting points, HRMS and IR spectrum data of compounds **4**.

4	Formula	M.p. °C	Required HRMS $[M+H]^+$	Found HRMS $[M+H]^+$	IR (KBr) ν(cm^{-1}) C=O,
4a	$C_{20}H_{20}FeN_2O_2$	161–163	377.0947	377.0944	1747.9
4b	$C_{22}H_{16}FeN_2O_2$	240–241	397.0634	397.0627	1747.5
4c	$C_{23}H_{18}FeN_2O_2$	277–279	411.0790	411.0782	1742.9
4d	$C_{23}H_{18}FeN_2O_3$	218–220	427.0740	427.0747	1743.8
4e	$C_{22}H_{15}ClFeN_2O_2$	220–222	431.0244	431.0233	1746.5
4f	$C_{22}H_{15}FeN_3O_4$	246–248	442.0485	442.0471	1745.3

Table 2
The data of ^{1}H NMR and ^{13}C NMR for compounds **4**.

4	^{1}H NMR (400 MHz, δ, $CDCl_3$) and ^{13}C NMR (100 MHz, δ, $CDCl_3$)
4a	^{1}H NMR: 7.28 (s, 1H, NCH═C), 7.04 (s, 1H, PyzH), 4.82 (s, 2H, C_5H_4), 4.43 (s, 2H, C_5H_4), 4.15 (s, 5H, C_5H_5), 1.32 (s, 9H, CH_3); ^{13}C NMR: 154.4, 153.8, 153.0, 127.1, 105.4, 104.8, 70.2, 69.8, 67.3, 34.4, 27.6.
4b	^{1}H NMR: 7.90 (s, 1H, NCH═C), 7.76-7.40 (m, 5H, PhH), 7.16 (s, 1H, PyzH), 4.82 (s, 2H, C_5H_4), 4.42 (s, 2H, C_5H_4), 4.13 (s, 5H, C_5H_5); ^{13}C NMR: 154.6, 153.7, 142.3, 129.9, 129.8, 129.1, 127.5, 124.4, 106.8, 105.6, 70.2, 69.9, 67.3.
4c	^{1}H NMR: 7.85 (s, 1H, NCH═C), 7.63 (d, *J* = 7.8 Hz, 2H, PhH), 7.28 (d, *J* = 7.8 Hz, 2H, PhH), 7.15 (s, 1H, PyzH), 4.80 (s, 2H, C_5H_4), 4.39 (s, 2H, C_5H_4), 4.10 (s, 5H, C_5H_5), 2.41 (s, 3H, CH_3); ^{13}C NMR: 154.4, 153.8, 143.0, 140.2, 129.8, 127.4, 127.0, 124.4, 106.2, 105.4, 69.8, 69.5, 67.1, 21.4.
4d	^{1}H NMR: 7.76 (s, 1H, NCH═C), 7.66 (d, *J* = 8.7 Hz, 2H, PhH), 7.10 (s, 1H, PyzH), 6.99 (d, *J* = 8.7 Hz, 2H, PhH), 4.88 (s, 2H, C_5H_4), 4.48 (s, 2H, C_5H_4), 4.18 (s, 5H, C_5H_5), 3.87 (s, 3H, OCH_3); ^{13}C NMR: 161.0, 154.3, 153.8, 143.1, 127.1, 126.0, 122.2, 114.6, 114.3, 105.4, 71.2, 70.9, 68.0, 55.5.
4e	^{1}H NMR: 7.88 (s, 1H, NCH═C), 7.68 (d, *J* = 8.6 Hz, 2H, PhH), 7.46 (d, *J* = 8.6 Hz, 2H, PhH), 7.17 (s, 1H, PyzH), 4.79 (s, 2H, C_5H_4), 4.40 (s, 2H, C_5H_4), 4.10 (s, 5H, C_5H_5); ^{13}C NMR: 154.9, 153.4, 141.8, 135.9, 129.4, 128.3, 127.4, 125.6, 106.9, 105.8, 69.8, 69.6, 67.1.
4f	^{1}H NMR: 8.62-7.65 (m, 5H, PhH and NCH═C), 7.20 (s, 1H, PyzH), 4.81 (s, 2H, C_5H_4), 4.42 (s, 2H, C_5H_4), 4.11 (s, 5H, C_5H_5); ^{13}C NMR: 155.5, 152.8, 148.9, 140.2, 131.7, 130.3, 129.7, 127.6, 124.2, 119.2, 108.3, 106.3, 69.9, 69.8, 67.2.

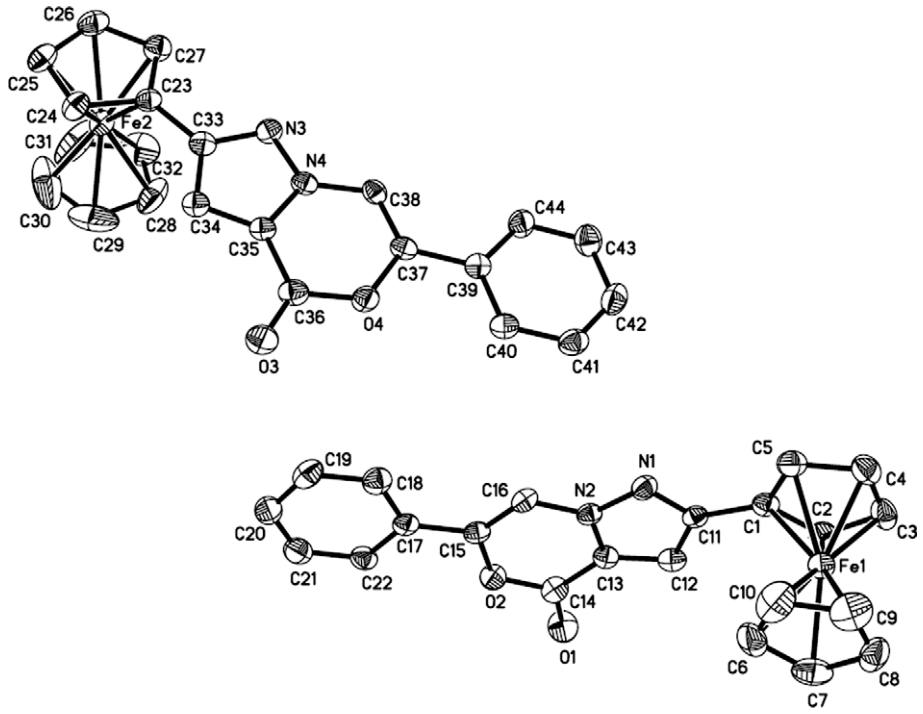


Fig. 1. The molecular structure of **4b**, showing displacement ellipsoids drawn at the 50% probability level for non-H atoms.

and B have obvious differences (Table 1). In the ferrocenyl moiety, the cyclopentadienyl (Cp) rings are perfectly planar but deviate slightly from being parallel being 3.7(4)° in A and 2.4(4)° in B, twisted from the eclipsed conformation by 1.11–2.70° in A and 15.11–18.37° in B, respectively. The distances Cg1–Fe1, Cg2–Fe1 in A and Cg3–Fe2, Cg4–Fe2 in B are 1.638(3) Å, 1.652(3) Å, 1.642(3) Å and 1.655(4) Å, respectively. The angles Cg1–Fe–Cg2 and Cg3–Fe2–Cg4 are 177.87(16)° and 178.59(17)°. The dihedral angles between the substituted Cp ring and the pyrazole ring are 8.3(3)° in A and 8.4(3)° in B which are less than that of ferrocenyl substituted pyrazole pyrazinone we have reported (16.08°). The distances C1–C11 and C23–C33 [1.457(8) and 1.454(8) Å] are slightly shorter than that of ferrocenyl substituted pyrazole pyrazinone (1.464(3) Å) [29]. In the crystal structure, the pyrazole, oxazinone and benzene rings are almost planar.

The dihedral angles of oxazinone with the pyrazole plane are 2.6(3)° in A and 3.0(3)° in B. However, the dihedral angles of benzene rings with the pyrazole plane are 1.5(3)° in A and B.

The crystal packing is mainly stabilized by van der Waals interactions. However, there is a significant intermolecular contact with hydrogen bond symmetry code of '1–X, 2–Y, 1–Z' between a Cp ring hydrogen (C26–H26) and Cg2, which may be attributed to a C—H···π interaction, and contact distance being C26–H26 0.98 Å, H26···Cg1 2.88 Å, C26···Cg1 3.714(7) Å and C26–H26 ··· Cg1 144°.

3. Summary

In summary, we have elaborated the facile synthesis of a series of novel 2-ferrocenyl-6-substituted-4*H*-pyrazolo[5,1-c][1,4]oxazin-4-one derivatives from ethyl 1-(2-aryl-2-oxoethyl)-3-ferrocenyl-1*H*-pyrazole-5-carboxylate via intramolecular esterification in one-pot procedure in the presence of magnesium bromide ethyl etherate and *N,N*-diisopropylethylamine. This strategy could open new entries for the preparation of pyrazole fused oxazinone derivatives owing to the ready availability of the starting materials. These novel compounds were characterized by ^{1}H NMR, IR, HRMS and single-crystal of compound **4b** as representative has been determined by X-ray diffraction analysis.

Table 3
Summary of crystallographic data and structure refinement details for **4b**.

	4b
Empirical formula	$C_{22}H_{16}Fe_1N_2O_2$
Formula weight	396.22
Temperature	293(2) K
Wavelength	0.71069 Å
Crystal system	Triclinic
Space group	P-1
Unit cell dimensions	a = 7.634(4) Å, α = 80.33(1)° b = 11.188(6) Å, β = 88.62(1)° c = 20.62(1) Å, γ = 89.48(1)°
Volume	1736.0(17) A^3
Z	4
Calculated density	1.516 Mg/m^3
Absorption coefficient	0.89 mm^{-1}
F(000)	816
Crystal size	0.12 × 0.10 × 0.06 mm
θ range for data collection	2.5–23.6°
Limiting indices	$-8 \le h \le 9$, $-11 \le k \le 13$, $-23 \le l \le 24$
Reflections collected/unique	8889/6078 [R(int) = 0.036]
Completeness to θ = 25.05°	99.0%
Absorption correction	Multi-scan
Max. and min. transmission	0.901 and 0.949
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	6078/0/487
Goodness-of-fit on F^2	1.03
Final R indices [$I > 2\sigma(I)$]	R_1 = 0.0637, wR_2 = 0.1454
R indices (all data)	R_1 = 0.1134, wR_2 = 0.1691
Largest diff. peak and hole	0.753 and −0.669 e.$Å^{-3}$

Table 4
Selected bond lengths (Å) and angles (°) for **4b**.

Cg1–Fe1	1.638(3)	Cg2–Fe1	1.652(3)
Cg3–Fe2	1.642(3)	Cg4–Fe2	1.655(4)
Cg1–Fe–Cg2	177.87(16)	Cg3–Fe2–Cg4	178.59(17)
O1–C14	1.219(7)	O3–C36	1.193(7)
O2–C14	1.361(7)	O4–C36	1.380(7)
O2–C15	1.387(7)	O4–C37	1.385(7)
N1–N2	1.349(6)	N1–C11	1.347(7)
N2–C13	1.353(7)	C11–C12	1.408(8)
N2–C16	1.371(7)	N4–C38	1.390(7)
C15–C17	1.468(9)	C37–C39	1.484(9)
C17–C18	1.398(8)	C39–C44	1.386(8)
C17–C22	1.395(8)	C39–C40	1.383(8)
C18–C19	1.378(9)	C44–C43	1.387(9)
C19–C20	1.381(8)	C43–C42	1.375(8)
C20–C21	1.364(9)	C42–C41	1.364(8)
C1–Fe1–C2	41.4(2)	C23–Fe2–C24	41.0(2)
C3–Fe1–C6	158.7(3)	C25–Fe2–C28	168.9(3)
N2–N1–C11	104.1(4)	C14–O2–C15	122.0(4)
O1–C14–O2	117.7(5)	O3–C36–O4	118.6(5)
N4–C35–C36–O4	1.1(7)	C37–O4–C36–O3	−179.2(5)

Where Cg1/Cg3 and Cg2/Cg4 are the centroids of substituted and unsubstituted cyclopentadienyl rings, respectively.

4. Experimental

4.1. General consideration

All solvents were pre-dried and distilled prior to use. All reactions were carried out under nitrogen and monitored by TLC on silica gel 60 F_{254} plates (Merck KGaA). ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance 400 spectrometer, using $CDCl_3$ as solvents and tetramethylsilane (TMS) as internal standard. Melting points were determined on an XD-4 digital micro melting point apparatus. IR spectra were recorded with an IR spectrophotometer Avtar 370 FT-IR (Termo Nicolet). HRMS spectra were recorded on a LTQ Orbitrap Hybrid mass spectrograph. X-ray diffraction data were recorded on a Bruker Smart CCD diffractometer.

4.2. The following procedure is representative of the synthesis of (**3a**-**3f**)

4.2.1. Ethyl 1-(3,3-dimethyl-2-oxobutyl)-3-ferrocenyl-1H-pyrazole-5-carboxylate (**3a**)

To a stirred solution of ethyl 3-ferrocenyl-1*H*-pyrazole-5-carboxylate (1.62 g, 5.0 mmol) and 1-bromo-3,3-dimethylbutan-2-one (1.34 g, 7.5 mmol) in dry acetonitrile (30 mL) was added potassium carbonate (2.07 g, 15 mmol) and potassium iodide (166 mg, 1.0 mmol) under N_2. After refluxed for 4 h, the reaction mixture was cooled to room temperature, filtered and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel with the eluent system of ethyl acetate/petroleum ether (v/v = 1:4). The product **3a** was obtained as yellow crystal in 62% yield (1.31 g). M.p. 124–126 °C. ^1H NMR (400 MHz, $CDCl_3$): 6.88 (s, 1H, PyzH), 5.55 (s, 2H, NCH_2), 4.67 (s, 2H, C_5H_4), 4.30 (q, J = 7.2 Hz, 2H, CH_2CH_3), 4.27 (s, 2H, C_5H_4), 4.08 (s, 5H, C_5H_5), 1.38 (t, J = 7.2 Hz, 3H, CH_2CH_3), 1.29 (s, 9H, CCH_3).

4.2.2. Ethyl 1-(2-phenyl)-2-oxoethyl)-3-ferrocenyl-1H-pyrazole-5-carboxylate (**3b**)

Starting from the corresponding 2-bromo-1-phenylethanone: Flash column chromatography over silica gel using ethyl acetate/petroleum ether (v/v = 1:4) give the product (**3b**) in 40% yield. M.p. 144–146 °C. ^1H NMR (400 MHz, $CDCl_3$): 8.02 (d, J = 7.7 Hz, 2H, PhH), 7.65 (t, J = 7.5 Hz, 1H, PhH), 7.54 (t, J = 7.5 Hz, 2H, PhH), 6.97 (s, 1H, PyzH), 6.03 (s, 2H, NCH_2), 4.72 (s, 2H, C_5H_4), 4.32–4.29 (m, 4H, CH_2CH_3 and C_5H_4), 4.12 (s, 5H, C_5H_5), 1.36 (t, J = 7.1 Hz, 3H, CH_2CH_3). The compound **3′b** was obtained as a yellow crystal in 58% yield. M.p. 142–144 °C; ^1H NMR (400 MHz, $CDCl_3$): 7.96 (d, J = 7.5 Hz, 2H, PhH), 7.65 (t, J = 7.2 Hz, 1H, PhH), 7.53 (t, J = 7.4 Hz, 2H, PhH), 6.97 (s, 1H, PyzH), 5.76 (s, 2H, NCH_2), 4.43 (q, J = 7.0 Hz, 2H, CH_2CH_3), 4.34 (s, 2H, C_5H_4), 4.28 (s, 2H, C_5H_4), 4.19 (s, 5H, C_5H_5), 1.42 (t, J = 7.0 Hz, 3H, CH_2CH_3).

4.2.3. Ethyl 1-(2-oxo-2-p-tolylethyl)-3-ferrocenyl-1H-pyrazole-5-carboxylate (**3c**)

Starting from the corresponding 2-bromo-1-*p*-tolylethanone: Flash column chromatography over silica gel using ethyl acetate/petroleum ether (v/v = 1:4) give the product (**3c**) in 32% yield. M.p. 122–124 °C. ^1H NMR (400 MHz, $CDCl_3$): 7.89 (d, J = 8.1 Hz, 2H, PhH), 7.30 (d, J = 8.1 Hz, 2H, PhH), 6.94 (s, 1H, PyzH), 5.98 (s, 2H, NCH_2), 4.70 (s, 2H, C_5H_4), 4.30 (s, 2H, C_5H_4), 4.28 (q, J = 7.2 Hz, 2H, CH_2CH_3), 4.10 (s, 5H, C_5H_5), 2.44 (s, 3H, CH_3), 1.33 (t, J = 7.2 Hz, 3H, CH_2CH_3).

4.2.4. Ethyl 1-(2-(4-methoxyphenyl)-2-oxoethyl)-3-phenyl-1H-pyrazole-5-carboxylate (**3d**)

Starting from the corresponding 2-bromo-1-(4-methoxyphenyl)ethanone: Flash column chromatography over silica gel using ethyl acetate/petroleum ether (v/v = 1:4) give the product (**3d**) in 43% yield. M.p. 131–133 °C. ^1H NMR (400 MHz, $CDCl_3$): 7.96 (d, J = 8.8 Hz, 2H, PhH), 6.98 (d, J = 8.8 Hz, 2H, PhH), 6.94 (s, 1H, PyzH), 5.95 (s, 2H, NCH_2), 4.70 (s, 2H, C_5H_4), 4.30–4.25 (m, 4H, CH_2CH_3 and C_5H_4), 4.10 (s, 5H, C_5H_5), 3.89 (s, 3H, OCH_3), 1.33 (t, J = 7.1 Hz, 3H, CH_2CH_3). The compound **3′d** was obtained as a yellow crystal in 51% yield. M.p. 135–137 °C; ^1H NMR (400 MHz, $CDCl_3$): 7.94 (d, J = 7.6 Hz, 2H, PhH), 6.98 (d, J = 7.6 Hz, 2H, PhH), 6.92 (s, 1H, PyzH), 5.71 (s, 2H, NCH_2), 4.42 (q, J = 6.8 Hz, 2H, CH_2CH_3), 4.38 (s, 2H, C_5H_4), 4.30 (s, 2H, C_5H_4), 4.21 (s, 5H, C_5H_5), 3.90 (s, 3H, OCH_3), 1.41 (t, J = 6.7 Hz, 3H, CH_2CH_3).

4.2.5. Ethyl 1-(2-(4-chlorophenyl)-2-oxoethyl)-3-phenyl-1H-pyrazole-5-carboxylate (**3e**)

Starting from the corresponding 2-bromo-1-(4-chlorophenyl)ethanone: Flash column chromatography over silica gel

using ethyl acetate/petroleum ether (v/v = 1:4) give the product (**3e**) in 61% yield. M.p. 148–149 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 7.93 (d, J = 8.5 Hz, 2H, PhH), 7.49 (d, J = 8.5 Hz, 2H, PhH), 6.95 (s, 1H, PyzH), 5.96 (s, 2H, NCH_2), 4.69 (s, 2H, C_5H_4), 4.31–4.25 (m, 4H, CH_2CH_3 and C_5H_4), 4.09 (s, 5H, C_5H_5), 1.34 (t, J = 7.1 Hz, 3H, CH_2CH_3). The compound **3′e** was obtained as a yellow crystal in 32% yield. M.p. 168–170 °C; ^{1}H NMR (400 MHz, $CDCl_3$): 7.88 (d, J = 8.5 Hz, 2H, PhH), 7.50 (d, J = 8.5 Hz, 2H, PhH), 6.96 (s, 1H, PyzH), 5.70 (s, 2H, NCH_2), 4.43 (q, J = 7.1 Hz, 2H, CH_2CH_3), 4.31 (s, 2H, C_5H_4), 4.28 (s, 2H, C_5H_4), 4.18 (s, 5H, C_5H_5), 1.42 (t, J = 7.1 Hz, 3H, CH_2CH_3).

*4.2.6. Ethyl 1-(2-(3-nitrophenyl)-2-oxoethyl)-3-phenyl-1H-pyrazole-5-carboxylate (**3f**)*

Starting from the corresponding 2-bromo-1-(3-nitrophenyl)ethanone, but the reaction mixture cannot be heated and was stirred at room temperature for 24 h: Flash column chromatography over silica gel using ethyl acetate/petroleum ether (v/v = 1:4) give the product (**3f**) in 18% yield. M.p. 146–148 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 8.81 (s, 1H, PhH), 8.48 (d, J = 8.1 Hz, 1H, PhH), 8.29 (d, J = 7.6 Hz, 1H, PhH), 7.73 (t, J = 7.9 Hz, 1H, PhH), 6.87 (s, 1H, PyzH), 6.00 (s, 2H, NCH_2), 4.85 (s, 2H, C_5H_4), 4.46 (s, 2H, C_5H_4), 4.28 (q, J = 7.1 Hz, 2H, CH_2CH_3), 4.23 (s, 2H, C_5H_4), 1.35 (t, J = 7.1 Hz, 3H, CH_2CH_3).

*4.3. The following procedure is representative of the synthesis of (**4a**–**4f**)*

To a stirred solution of **3** (1 mmol) and *N,N*-diisopropylethylamine (5 mmol) in toluene (10 ml) was added $MgBr_2Et_2O$ (5 mmol) under N_2. After refluxed for 4 h, the reaction mixture was cooled to room temperature and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel with the eluent system of dichloromethane/petroleum ether (v/v = 1:1) to afford desired derivatives **4** in moderate yields. The mass analysis data, IR spectrum data and ^{1}H NMR spectra of **4** were listed in Tables 1 and 2, respectively.

*4.3.1. 6-tert-Butyl-2-ferrocenyl-4H-pyrazolo[5,1-c][1,4]oxazin-4-one (**4a**)*

Yellow solid, 44% yield.

*4.3.2. 2-Ferrocenyl-6-phenyl-4H-pyrazolo[5,1-c][1,4]oxazin-4-one (**4b**)*

Yellow solid, 37% yield.

*4.3.3. 2-Ferrocenyl-6-p-tolyl-4H-pyrazolo[5,1-c][1,4]oxazin-4-one (**4c**)*

Yellow solid, 14% yield.

*4.3.4. 2-Ferrocenyl-6-(4-methoxyphenyl)-4H-pyrazolo[5,1-c][1,4]oxazin-4-one (**4d**)*

Yellow solid, 14% yield.

*4.3.5. 6-(4-Chlorophenyl)-2-ferrocenyl-4H-pyrazolo[5,1-c][1,4]oxazin-4-one (**4e**)*

Yellow solid, 37% yield.

*4.3.6. 2-Ferrocenyl-6-(3-nitrophenyl)-4H-pyrazolo[5,1-c][1,4]oxazin-4-one (**4f**)*

Yellow solid, 11% yield.

Acknowledgment

This study was supported by the Natural Science Foundation of Shandong Province (Z2008B10).

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