Available online at www.sciencedirect.com
SCIENCE DIRECT®
Journal of Organometallic Chemistry 690 (2005) 1226–1232
Journal of Organometallic Chemistry
www.elsevier.com/locate/jorganchem

Synthesis, structures and biological activity research of novel ferrocenyl-containing 1*H*-1,2,4-triazole derivatives

Zhong Jin, Aihong Huo, Tao Liu, Yan Hu, Jianbing Liu, Jianxin Fang *

Institute and State Key Laboratory of Elemento-Organic Chemistry, Nankai University, Weijin Road 94, Tianjin 300071, PR China

Received 21 September 2004; accepted 16 November 2004

Abstract

Novel ferrocene-containing propenones have been synthesized from acetylferrocene via a Mannich-type intermediate. Sequential condensation cyclization of these propenones with phenylhydrazine afforded highly substituted 4,5-dihydropyrazole derivatives, which structures have been characterized by spectra data and single crystal X-ray diffraction analysis. In addition, these new ferrocene-containing derivatives have been evaluated for in vitro fungicidal activities against five selected fungi.

Keywords: Ferrocene; 1*H*-1,2,4-triazole; 4,5-Dihydropyrazole; Fungicidal activity

1. Introduction

Although ferrocene, as an organometallic compound, was discovered in the early 1950s [1], their biological activities have received more attention since two decades ago. Due to its unique structure, different membrane-permeation properties and anomalous metabolism, ferrocene was often incorporated into a molecule of an organic compound by chemists in order to obtained unexpected biological activity [2–4]. A successful example is a ferrocene–chloroquine analogue, i.e., ferrochloroquine (FQ: 7-chloro-4[2-(*N*′,*N*′-dimethylaminomethyl)-*N*-ferrocenyl–methylamino]quinoline), in which one ferrocene unit was integrated into chloroquine (CQ) [5–7]. In vitro, FQ proved to be about 22 times more schizontocide than CQ against chloroquino-resistant strains of *P. falciparum* and showed more high activity in vivo on mice infected with *P. berghei* N and *P. yoelii* NS. Furthermore, the stability and non-toxicity of the ferrocenyl moiety is of particular interest rendering such drugs compatible with other treatment. Accordingly, using ferrocenyl-containing derivatives as medicals and other chemotherapeutants has long been recognized as an attractive way.

Compounds containing the 1*H*-1,2,4-triazole ring system are well known to highly active as fungicides [8], especially on the *Basidiomycete* and *Ascomycete* groups of fungi. These compounds are known to inhibit the biosynthesis of ergosterol in fungi. It has also been found that, in addition to their fungicidal activity, they possess a very high level of plant-growth regulatory activity on a wide variety of crops [9]. Following our interest in search of novel 1*H*-1,2,4-triazole compounds with potent biological activities, we have sought to synthesis such triazole compounds involving ferrocenyl units.

In the present work, we herein report the synthesis and structures of a series of novel ferrocenyl-substituted 1,2,4-triazole derivatives, which have been characterized by spectra data and crystal X-ray diffraction analysis. These compounds containing ferrocene unit were also evaluated for their biological activity including in vitro fungicidal activities.

* Corresponding author. Tel.: +86 0 22 2350 5330.
E-mail address: jinzhong2000@263.net (J. Fang).

0022-328X/$ - see front matter © 2004 Elsevier B.V. All rights reserved.
doi:10.1016/j.jorganchem.2004.11.028

2. Result and discussion

2.1. Syntheses of 2-((1H-1,2,4-triazol-1-yl)methyl)-1-ferrocenyl-3-aryl-2-en-1-one derivatives 5

Firstly, acetylferrocene **1** was prepared from ferrocene and acetyl chloride in 93% yield as described by Bozak [10]. Subsequently, it has proven to be unsuccessful that attempt to directly synthesis α,β-unsaturated ferrocenyl ketone **2** from **1** and paraformadehyde under aldol reaction conditions (Scheme 1).

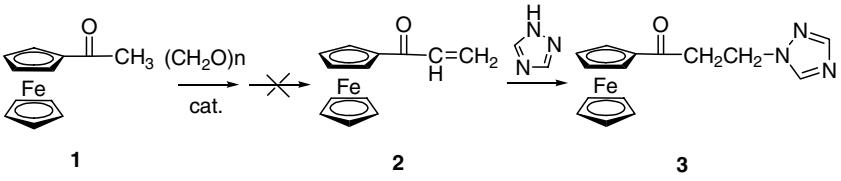
Consequently, an alternative procedure for synthesis of **3** has been carried out via Mannich-type intermediate starting from acetylferrocene **1** as outline in Scheme 2. Thus, acetylferrocene was first condensed with paraformaldehyde in the presence of dimethylamine hydrochloride under nitrogen atmosphere. After refluxed in ethanol for 6 h, 3-(*N*,*N*-dimethylamino)-1-ferrocenyl propan-1-one **4** was obtained. It was unnecessary to separate this intermediate. With excess 1*H*-1,2,4-triazole, the intermediate **4** resulted was converted to relative 1,2,4-triazole derivative **3**, after workup, in 20.5% overall yield.

Sequentially, aldo condensation reactions between 3-(1*H*-1,2,4-triazol-1-yl)-1-ferrocenyl–propan-1-one **3** and substituted aromatic aldehydes were carried out under nitrogen atmosphere. Initial condensation of compound **3** and aromatic aldehydes utilizing sodium hydroxide or sodium alkoxide as a base, however, caused an unexpected product with the triazole group lost. Hence, aldo reactions between **3** and aromatic aldehydes were achieved in the presence of catalytic piperidine and glacial acetic acid. After separated by silica gel column chromatography, the *E*-2-((1*H*-1,2,4-triazol-1-yl)-methyl)-1-ferrocenyl-3-aryl-prop-2-en-1-ones **5** were obtained as unique product in poor to moderate yields. Because the condensation step which produces α,β-unsaturated ferrocenyl ketones involved steric resistance, the bulkiness of ferrocene group was speculated to be in charge of poor yield of condensation reactions. It has also been confirmed from the single crystal structure of compound **5m**, in which the bulky ferrocenyl group and substituted aromatic cycle was in the *E*-side of C=C double bond (Fig. 1) [11].

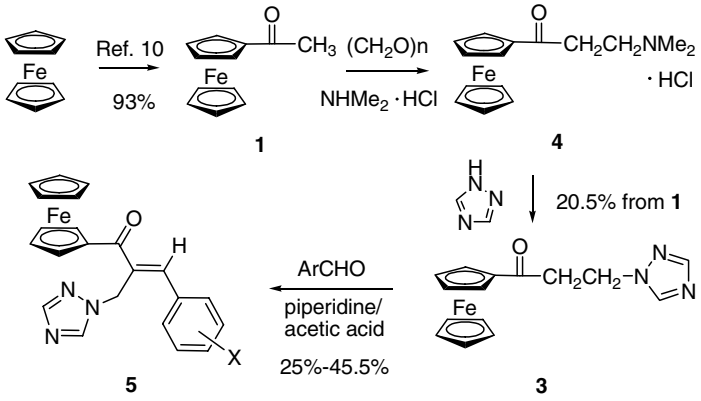
2.2. Syntheses of 1-((4,5-dihydro-5-aryl-3-ferrocenyl-1-phenyl-1H-pyrazol-4-yl)methyl)-1H-1,2,4-triazole 6

In previous paper [4] we have described the synthesis and anti-bacterial activities of ferrocenyl-containing azaheterocycle derivatives and glacial acetic acid proven to be an effective catalyst for the cyclization composition of those highly substituted dihydropyrazole derivatives. In addition, because of the bulkiness of ferrocenyl group, cyclization of analogous α,β-unsaturated ferrocenyl ketones with phenylhydrazine proceeded via 1,4-addition procedure of *N*-1 in the phenylhydrzine to the propenones **5**.

Accordingly, *E*-2-((1*H*-1,2,4-triazol-1-yl)methyl)-1-ferrocenyl-3-aryl-prop-2-en-1-ones **5** were condensed with phenylhydrazine in refluxing ethanol with glacial



Scheme 1.



Scheme 2.

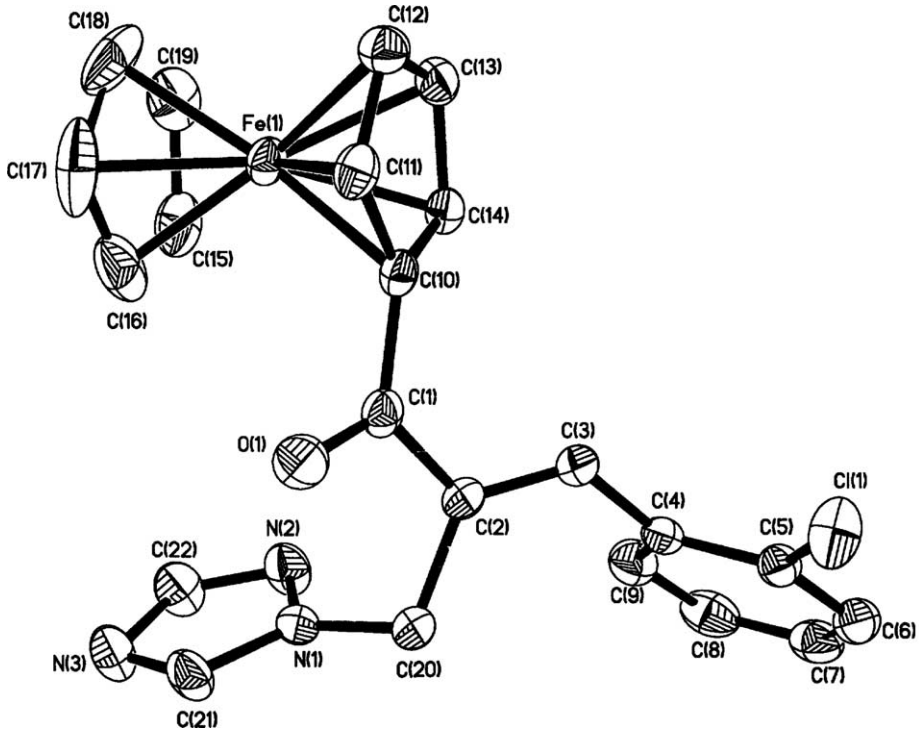


Fig. 1. Molecular structure and crystallographic numbering scheme for compound **5m**. Selected bond lengths (Å): C(1)–O(1) 1.223(3); C(1)–C(2) 1.498(3); C(1)–C(10) 1.469(3); C(2)–C(3) 1.330(3); C(2)–C(20) 1.506(3); C(3)–C(4) 1.482(3); C(5)–C(1) 1.731(3); C(20)–N(1) 1.453(3). Selected bond angles (°): C(21)–N(1)–N(2) 109.3(2); C(21)–N(1)–C(20) 128.7(2); N(2)–N(1)–N(20) 121.97(18); O(1)–C(1)–C(10) 121.7(2); O(1)–C(1)–C(2) 119.0(2); C(10)–C(1)–C(2) 119.25(19); C(3)–C(2)–C(1) 120.0(2); C(3)–C(2)–C(20) 123.0(2); C(1)–C(2)–C(20) 115.88(19); C(2)–C(3)–C(4) 127.5(2); C(9)–C(4)–C(5) 117.5(2); C(9)–C(4)–C(3) 121.3(2); C(5)–C(4)–C(3) 121.0(2); C(6)–C(5)–C(4) 122.1(2); C(6)–C(5)–C(11) 118.3(2); C(4)–C(5)–C(11) 119.56(18).

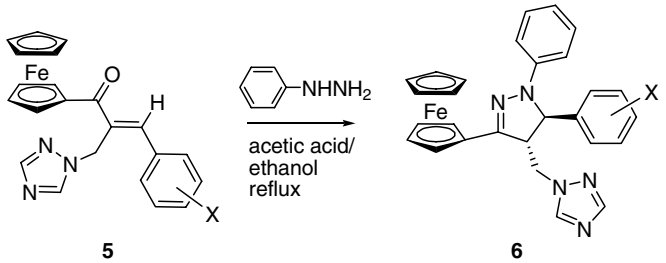
acetic acid as catalyst. And 1-((4,5-dihydro-5-aryl-3-ferrocenyl-1-phenyl-1*H*-pyrazol-4-yl)methyl)-1*H*-1,2,4-triazole **6** were produced as major product along with a small amount of unidentified by-products (Scheme 3).

Single crystal X-ray diffraction analysis of compound **6b** revealed that substituted aryl group and 1*H*-1,2,4-triazol-1-yl methyl group are always in the relative *trans*-position of dihydropyrazole ring plane in the target molecule (Fig. 2) [11]. It has been postulated that the steric resistance in the highly substituted dihydropyrazole ring accounted for the *trans*-figuration.

2.3. Biological activities

The assessments of in vitro fungicidal activity for these ferrocenyl-containing compounds **5** and **6** were proceeding against five selected fungi including *P. zeae*, *A. solani*, *C. fulvum*, *P. piricola* and *C. ara*. Their relative inhibitory ratios (%) against these fungi were determined and the results of such studies were reported in Table 1.

The screening data revealed that compounds **6** showed relatively higher fungicidal activity than that of compounds **5**. To the best of our knowledge, a linkage between the triazole ring and substituted aryl group via no more than two single or double bond(s) is essential for their fungicidal activity. In our previously works [12], it has been proved that an extended carbon backbone linking the triazole ring and aryl group in an almost linear fashion possesses higher activity than a distorted backbone. In addition, we have synthesized a series of ferrocenyl-containing triazole derivatives with a triazolyl group instead of a triazolylmethyl group in



5 6

Scheme 3.

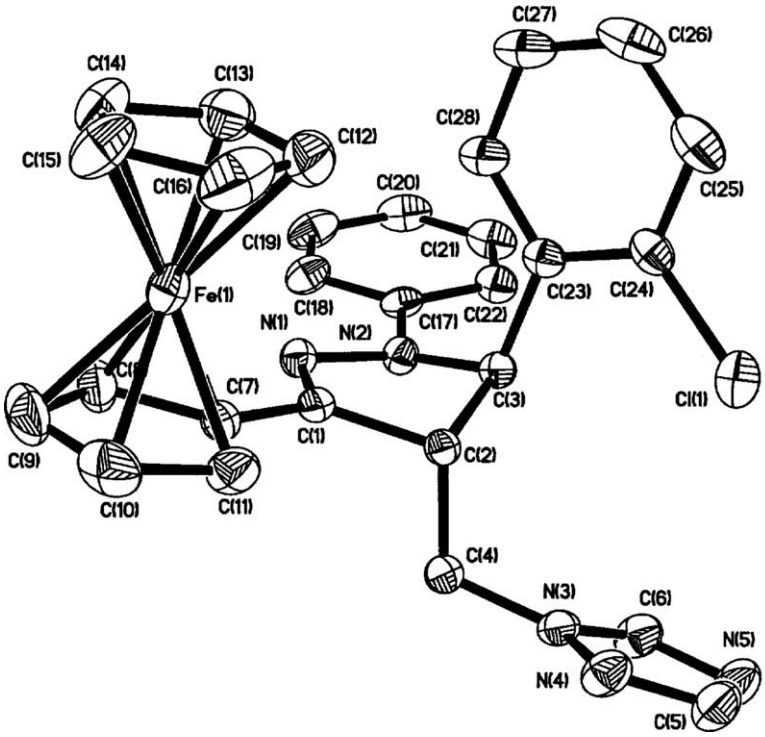


Fig. 2. Molecular structure and crystallographic numbering scheme for compound **6b**. Selected bond lengths (Å): C(1)–C(24) 1.742(3); N(1)–C(1) 1.291(3); N(1)–N(2) 1.398(2); N(2)–C(17) 1.404(3); N(2)–C(3) 1.470(3); N(3)–C(4) 1.451(3); C(1)–C(7) 1.449(3); C(1)–C(2) 1.523(3); C(2)–C(4) 1.537(3); C(2)–Cl(3) 1.546(3); C(3)–C(23) 1.525(3). Selected bond angles (°): C(1)–N(1)–N(2) 107.55(18); N(1)–N(2)–C(17) 107.88(18); N(1)–N(2)–C(3) 110.71(16); C(17)–N(2)–C(3) 126.10(17); C(6)–N(3)–C(4) 129.9(2); N(4)–N(3)–C(4) 121.09(18); N(1)–C(1)–C(7) 122.5(2); N(1)–C(1)–C(2) 112.50(18); C(7)–C(1)–C(2) 124.9(2); C(1)–C(2)–C(4) 108.18(17); C(25)–C(24)–Cl(1) 117.9(2); C(23)–C(24)–Cl(1) 120.44(18); C(24)–C(23)–C(3) 121.1(2); C(28)–C(23)–C(3) 121.8(2).

Table 1
Fungicidal activity of compounds **5** and **6**

Entry	Substituent X	Relative inhibitory ratio (%)				
		P. zeae	*A. solani*	*C. fulvum*	*P. piricola*	*C. ara*
5a	H	14.6	17.9	0	0	0
5b	4-OMe	12.2	10.3	0	20.0	0
5c	3-OMe-4-OH	0	10.3	0	0	0
5d	2,4-Me_2	17.1	17.9	20.8	35.0	20.0
5e	2-OMe	17.1	20.5	16.7	15.0	0
5f	4-Me	0	17.9	16.7	15.0	0
5g	2,4-OMe_2	0	17.9	0	0	0
5h	3,4-OMe_2	31.7	25.6	20.8	35.0	0
5i	3,4-Me_2	22.0	17.9	0	25.0	20.0
5j	3,4-OCH_2O–	22.0	20.5	0	40.0	0
5l	2-F-4-Br	19.5	10.3	0	15.0	0
5m	2-Cl	14.6	17.9	0	20.0	0
5n	2,4-Cl_2	34.2	10.3	0	0	0
5o	2-F	17.1	10.3	0	12.5	0
6a	4-OMe	31.7	30.8	20.8	27.5	32.0
6b	2-Cl	22.0	30.8	16.7	25.0	0
6c	3,4-OCH_2O–	22.0	23.1	20.8	35.0	0
6d	4-Me	19.5	23.1	16.7	15.0	0

6. Because of the bulkiness of ferrocene, the triazole ring and the aryl group are not connected in such a way, but via a bent linkage, and the compounds do not display predominant fungicidal activity [4]. In contrary to them, compounds **6** herein synthesized showed obviously increasing fungicidal activities. It has been presumed that, due to the presence of an additive methylene group, the linkage between the triazole ring and substi-

tuted aryl group became more flexible and might adopt the extended fashion.

However, compared with known commercial agents, the fungicidal activities of these compounds were not encouraging although some compounds manifested certain fungicidal activity. Further structural modification and optimization of these triazole derivatives are in need. Other biological activities such as anti-proliferation, anti-inflammation, were tested at the moment and the results will be reported in the future.

3. Summary

To summarize, we have synthesized a series of highly substituted ferrocenyl-containing 1*H*-1,2,4-triazole derivatives and their structures have been verified by elemental analysis, ^{1}H NMR and single crystal X-ray diffraction analysis. These novel 1*H*-1,2,4-triazole derivatives containing ferrocene unit have also been screened for their fungicidal activities against five selected fungi.

4. Experimental

All reactions were carried out under nitrogen and monitored by TLC. All solvents were pre-dried and distilled prior to use. All melting points were determined on a Yanaco-241 apparatus and thermometer was uncorrected. The ^{1}HNMR spectra were measured on a Brucker AC-300 Spectrometer in $CDCl_3$ or d_6-DMSO solution with TMS as internal standard. Elemental analyses were determined on a Yanaco CHN Corder elemental analyzer. X-ray diffraction data were recorded at 293 K on a Bruker Smart 1000 diffractometer (graphite-monochromatized Mo Kα radiation $\lambda = 0.71073$ Å). Acetylferrocene **1** was synthesized in 93% yield as described by Bozak [10].

*4.1. Synthesis of 3-(1H-1,2,4-triazol-1-yl)-1-ferrocenyl–propan-1-one (**3**)*

To a vigorous stirred suspension of acetylferrocene **1** (20 g, 0.09 mol) and paraformaldehyde (3.0 g, 0.1 mol) in 20 mL ethanol was added dimethylamine hydrochloride (9.0 g, 0.11 mol) in one portion. The reaction mixture was then warmed and solid dissolved. The mixture was refluxed with stirring for 6 h and then cooled to room temperature.

To stirred above-mentioned mixture was added a solution of 1 *H*-1,2,4-triazole (10.35 g, 0.15 mol) in 20 mL water droppwise. Resulting solution was then refluxed for another 8 h and cooled to room temperature. The mixture was extracted by chloroform (20 mL × 2) and combined organic phase was dried over anhydrous $MgSO_4$. The solvent was evaporated off in vacuum and the residue was purified by chromatography on silica gel with the solvent system of ethyl acetate/petroleum ether (60–90 °C) (v/v: 1:1). The product **3** was obtained as yellow needle crystal in 20.5% yield (6.9 g). An analysis sample was obtained after recrystallization form chloroform–petroleum ether. M.p. 112–114 °C. ^{1}HNMR δ (300 M Hz, $CDCl_3$): 8.15 (s, 1H), 8.06 (s,

Table 2
Physical properties and elemental analysis data for compounds **5** and **6**

Entry	X	M.p. (°C)	Yield (%)	Elemental analysis data (Calc. %)		
				C	H	N
5a	H	142–143	25.0	66.57 (66.52)	4.87 (4.82)	10.71 (10.58)
5b	4-OMe	139–141	40.5	64.44 (64.65)	5.05 (4.95)	10.03 (9.83)
5c	3-OMe-4-OH	176–177	35.2	62.23 (62.32)	4.73 (4.77)	9.46 (9.48)
5d	2,4-Me_2	151–152	42.3	67.66 (67.78)	6.35 (5.45)	10.07 (9.88)
5e	2-OMe	206–208	41.6	64.69 (64.65)	4.78 (4.95)	9.90 (9.83)
5f	4-Me	159–161	38.9	67.14 (67.17)	5.16 (5.15)	10.07 (10.22)
5g	2,4-OMe_2	170–172	40.6	63.15 (63.04)	4.93 (5.07)	9.13 (9.19)
5h	3,4-OMe_2	139–141	40.3	63.12 (63.04)	4.98 (5.07)	9.30 (9.19)
5i	3,4-Me_2	141–143	41.2	67.90 (67.78)	5.38 (5.45)	10.03 (9.88)
5j	3,4-OCH_2O–	77–79	32.1	62.47 (62.60)	4.12 (4.34)	9.51 (9.52)
5k	2,6-Cl_2	168–170	45.5	56.74 (56.69)	3.74 (3.68)	8.97 (9.01)
5l	2-F-4-Br	154–156	36.6	53.32 (53.48)	3.29 (3.47)	8.58 (8.50)
5m	2-Cl	171–172	35.7	61.32 (61.21)	4.13 (4.20)	9.79 (9.73)
5n	2,4-Cl_2	153–155	37.4	56.80 (56.69)	3.68 (3.68)	8.93 (9.01)
5o	2-F	136–138	36.5	63.73 (63.63)	4.50 (4.37)	9.93 (10.12)
6a	4-OMe	183–184	61.5	67.39 (67.32)	5.35 (5.26)	13.44 (13.54)
6b	2-Cl	192–194	45.6	64.35 (64.45)	4.62 (4.64)	13.50 (13.42)
6c	3,4-OCH_2O–	212–214	57.3	65.40 (65.55)	4.88 (4.74)	13.29 (13.18)
6d	4-Me	185–187	50.4	68.56 (68.72)	5.47 (5.56)	14.29 (14.31)
6e	2-OMe	124–125	40.2	67.40 (67.32)	5.22 (5.26)	13.60 (13.53)

Table 3
^{1}HNMR spectra data for compounds **5** and **6**

Entry	X	^{1} HNMR spectra data (δ)
5a	H	8.61(s, 1H, TrH), 8.09(s, 1H, TrH), 7.83–7.45(m, 6H, PhH and C=CH), 5.29(s, 2H, TrCH_2), 4.85(s, 2H, C_5H_4), 4.62(s, 2H, C_5H_4), 3.97(s, 5H, C_5H_5)
5b	4-OMe	8.60(s, 1H, TrH), 8.10(s, 1H, TrH), 7.80–7.05(m, 5H, PhH and C=CH), 5.31(s, 2H, TrCH_2), 4.83(s, 2H, C_5H_4), 4.61(s, 2H, C_5H_4), 3.98(s, 5H, C_5H_5), 3.81(s, 3H, OCH_3)
5c	3-OMe-4-OH	9.59(s, 1H, OH), 8.58(s, 1H, TrH), 8.09(s, 1H, TrH), 7.77–6.87(m, 4H, PhH and C=CH), 6.08(s, 2H, TrCH_2), 4.82(s, 2H, C_5H_4), 4.60(s, 2H, C_5H_4), 3.98(s, 5H, C_5H_5), 3.78(s, 3H, OCH_3)
5d	2,4-Me_2	8.51(s, 1H, TrH), 8.04(s, 1H, TrH), 7.77–7.11(m, 4H, PhH and C=CH), 5.15(s, 2H, TrCH_2), 4.83(s, 2H, C_5H_4), 4.63(s, 2H, C_5H_4), 4.01(s, 5H, C_5H_5), 2.32(s, 3H, CH_3), 2.30(s, 3H, CH_3)
5e	2-OMe	8.53(s, 1H, TrH), 8.08(s, 1H, TrH), 7.92–7.09(m, 5H, PhH and C=CH), 5.22(s, 2H, TrCH_2), 4.80(s, 2H, C_5H_4), 4.63(s, 2H, C_5H_4), 4.09(s, 5H, C_5H_5), 3.86(s, 3H, OCH_3)
5f	4-Me	8.60(s, 1H, TrH), 8.09(s, 1H, TrH), 7.80 (s, 1H, C=CH), 7.68–7.66(d, 2H, PhH), 7.33–7.31(d, 2H, PhH), 5.29(s, 2H, TrCH_2), 4.84(s, 2H, C_5H_4), 4.63(s, 2H, C_5H_4), 3.98(s, 5H, C_5H_5), 2.36(s, 3H, CH_3)
5g	2,4-OMe_2	8.59(s, 1H, TrH), 7.89(s, 1H, TrH), 8.00–6.70(m, 4H, PhH and C=CH), 5.24 (s, 2H, TrCH_2), 4.77(s, 2H, C_5H_4), 4.61(s, 2H, C_5H_4), 4.09(s, 5H, C_5H_5), 3.83(s, 3H, OCH_3), 3.81(s, 3H, OCH_3)
5h	3,4-OMe_2	8.62(s, 1H, TrH), 8.11(s, 1H, TrH), 7.80–7.07(m, 4H, PhH and C=CH), 5.35(s, 2H, TrCH_2), 4.84(s, 2H, C_5H_4), 4.62(s, 2H, C_5H_4), 3.98(s, 5H, C_5H_5), 3.78(s, 3H, OCH_3), 3.76(s, 3H, OCH_3)
5i	3,4-Me_2	8.57(s, 1H, TrH), 8.07(s, 1H, TrH), 7.78–7.28(m, 4H, PhH and C=CH), 5.29(s, 2H, TrCH_2), 4.83(s, 2H, C_5H_4), 4.62(s, 2H, C_5H_4), 3.99(s, 5H, C_5H_5), 2.27(s, 6H, $2CH_3$)
5j	3,4-OCH_2O–C_5H_5)	8.59(s, 1H, TrH), 8.10(s, 1H, TrH), 7.75–7.07(m, 4H, PhH and C=CH), 6.10(s, 2H, OCH_2O), 5.29(s,2H, TrCH_2), 4.82(s, 2H, C_5H_4), 4.62(s, 2H, C_5H_4), 3.97(s, 5H,
5k	2,6-Cl_2	8.36(s, 1H, TrH), 7.94(s, 1H, TrH), 7.62–7.47(m, 4H, PhH and C=CH), 5.76(s, 2H, TrCH_2), 4.94(s, 2H, C_5H_4), 4.69(s, 2H, C_5H_4), 4.10(s, 5H, C_5H_5)
5l	2-F-4-Br	8.56(s, 1H, TrH), 8.03(s, 1H, TrH), 7.94–7.58(m, 4H, PhH and C=CH), 5.21(s, 2H, TrCH_2), 4.84(s, 2H, C_5H_4), 4.66(s, 2H, C_5H_4), 4.06(s, 5H, C_5H_5)
5m	2-Cl	8.48(s, 1H, TrH), 8.00(s, 1H, TrH), 7.91–7.45(m, 5H, PhH and C=CH), 5.16(s, 2H, TrCH_2), 4.85(s, 2H, C_5H_4), 4.65(s, 2H, C_5H_4), 4.14(s, 5H, C_5H_5)
5n	2,4-Cl_2	8.54(s, 1H, TrH), 8.01(s, 1H, TrH), 7.98–7.59(m, 4H, PhH and C=CH), 5.17(s, 2H, TrCH_2), 4.88(s, 2H, C_5H_4), 4.67(s, 2H, C_5H_4), 4.07(s, 5H, C_5H_5)
5o	2-F	8.31(s, 1H, TrH), 7.89(s, 1H, TrH), 7.55–7.33(m, 5H, PhH and C=CH), 5.42(s, 2H, TrCH_2), 4.84(s, 2H, C_5H_4), 4.65(s, 2H, C_5H_4), 4.06(s, 5H, C_5H_5)
6a	4-OMe	8.78(s, 1H, TrH), 8.11(s, 1H, TrH), 7.16–6.78(m, 9H, PhH), 5.27(s, 1H, N–C*H*), 4.46–4.43(m, 3H, Tr–CH_2-C*H*), 4.83(s, 2H, C_5H_4), 4.65(s, 2H, C_5H_4), 4.07(s, 5H, C_5H_5), 3.80(s, 3H, OCH_3)
6b	2-Cl	8.71(s, 1H, TrH), 8.00(s, 1H, TrH), 7.43–6.71(m, 9H, PhH), 5.64(s, 1H, N–C*H*), 4.84–4.65(m, 3H, Tr–CH_2-C*H*), 4.64–4.43(m, 4H, C_5H_4), 3.95(s, 5H, C_5H_5)
6c	3,4-OCH_2O–C_5H_4), 4.09(s, 5H, C_5H_5)	8.74(s, 1H, TrH), 8.10(s, 1H, TrH), 7.18–6.32(m, 8H, PhH), 5.94(s, 2H, OCH_2O), 5.26(s, 1H, N–C*H*), 4.84–4.63(m, 3H, Tr–CH_2-C*H*), 4.64(s, 2H, C_5H_4), 4.43(s, 2H,
6d	4-Me	8.78(s, 1H, TrH), 8.12(s, 1H, TrH), 7.14–6.72(m, 9H, PhH), 5.29(s, 1H, N–C*H*), 4.84–4.47(m, 3H, Tr–CH_2-C*H*), 4.65(s, 2H, C_5H_4), 4.43(s, 2H, C_5H_4), 4.07(s, 5H, C_5H_5), 2.20(s, 3H, CH_3)
6e	2-OMe	8.78(s, 1H, TrH), 8.11(s,1H, TrH), 7.16–6.72(m, 9H, PhH), 5.29(s, 1H, N–C*H*), 4.56–4.53(m, 3H, Tr–CH_2-C*H*), 4.73(s, 2H, C_5H_4), 4.55(s, 2H, C_5H_4), 4.10(s, 5H, C_5H_5), 3.70(s, 3H, OCH_3)

1H), 4.67 (m, 2H), 4.55 (m, 2H), 4.15 (s, 5H), 3.88 (t, 2H), 2.38 (t, 2H). MS: *m/z* = 309 [M^+], Anal. Calc. for $C_{15}H_{15}FeN_3O$ (309.14) C 58.28; H 4.89; N 13.59. Found. C 58.02; H 4.91; N 13.65%.

*4.2. General procedure for syntheses of 2-((1H-1,2,4-triazol-1-yl)methyl)-1-ferrocenyl-3-aryl-2-en-1-one derivatives (**5**)*

To a stirred solution of 3-(1H-1,2,4-triazol-1-yl)-1-ferrocenyl–propan-1-one **3** (3.09 g, 0.01 mol) and substituted aromatic aldehyde (0.015 mol) in dry toluene (60 mL) was added catalytic piperidine (0.1 mL) and glacial acetic acid (0.1 mL), respectively. After refluxed for 8–12 h, the reaction mixture was then cooled to room temperature. Water (40 mL) and another 40 mL toluene was added. The organic layer was separated and washed by water and brine. The resulting solution was dried over anhydrous $MgSO_4$ and evaporated to dryness in vacuum. The residue was purified by chromatography on silica gel with the solvent system of ethyl acetate/petroleum ether (60–90 °C) to afford desired 2-((1 *H*-1,2,4-triazol-1-yl)methyl)-1-ferrocenyl-3-aryl-2-en-1-one derivatives **5** in various yields. The physical properties, elemental analysis data and ^{1}H NMR spectra of compounds **5** thus synthesized were reported in the Tables 2 and 3, respectively.

*4.3. General procedure for syntheses of 1-((4,5-dihydro-5-aryl-3-ferrocenyl-1-phenyl-1H-pyrazol-4-yl)methyl)-1H-1,2,4-triazole (**6**)*

To a Schlenk reaction flask were added 2-((1*H*-1,2,4-triazol-1-yl)methyl)-1-ferrocenyl-3-aryl-2-en-1-one derivatives **5** (2 mmol), phenylhydrazine (5 mmol), ethanol (10 mL), and glacial acetic acid (0.5 mol%). The reaction mixture was heated to refluxing. After stirred at the temperature for 48 h, the mixture was cooled to room temperature and the solvent was removed in vacuum. Chromatography on a silica gel column afforded the target 4,5-dihydropyrazole derivatives **6** in moderate yields. The physical properties, elemental analysis data and ^{1}H NMR spectra of compounds **6** thus synthesized were reported in the Tables 2 and 3, respectively.

Acknowledgements

We gratefully acknowledge the National Natural Science Foundation of China (NNSFC) (No. 29872022, 20172030) and the Research Fund for the Doctoral Program of Higher Education (RFDP) (No. 9805520) for financial support.

References

[1] P.L. Pauson, T.J. Kealy, Nature 168 (1951) 1039.
[2] C. Biot, L. Delhaes, L.A. Maciejewaski, M. Mortuaire, D. Camus, D. Divd, J.S. Brocard, Eur. J. Med. Chem. 35 (2000) 707.
[3] H. Sun, Q. Wang, R. Huang, H. Li, Y. Li, J. Organomet. Chem. 655 (2002) 182.
[4] J. Fang, Z. Jin, Z. Li, W. Liu, J. Organomet. Chem. 674 (2003) 1.
[5] C. Biot, G. Glorian, L.A. Maciejewski, J.S. Brocard, J. Med. Chem. 40 (1997) 3715.
[6] O. Domarle, G. Blampain, H. Agnanet, T. Nzadiyabi, J. Lebibi, J. Brocard, L. Maciejewski, C. Biot, A.J. Georges, P. Millet, Antimicrob. Agents Chemother. 42 (1998) 540.
[7] C. Biot, L. Delhaes, C.M. N'Diaye, L.A. Maciejewski, D. Camus, D. Dive, J.S. Brocard, Bioorg. Med. Chem. 7 (1999) 2843.
[8] H. Buchenauer, Proc. Br. Crop. Protect. Conf. 2 (1977) 699.
[9] H. Buchenauer, J. Plant. Dis. Protect. (Z. Pflanzenkr. Pflanzenschutz) 10 (1979) 341.
[10] R.E. Bozak, J. Chem. Edu. 43 (1966) 73.
[11] Crystallographic data for the structures **5m** and **6b** have been deposited with the Cambridge Crystallographic Data Centre, CCDC Nos. 250557 and 250558. Copies of this information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK. (fax: +44 (1223) 336033; e-mail: deposit@ccdc.cam.ac.uk; www: http://www.ccdc.cam.ac.uk).
[12] J. Fang, Z. Jin, Z. Li, W. Liu, Appl. Organomet. Chem. 17 (2003) 145.