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Synthesis of ferrocenyl pyrazoles by the reaction of 3-ferrocenylpropynal with hydrazinium salts

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Abstract

Synthesis of ferrocenyl-substituted pyrazoles via the reaction between 3-ferrocenylpropynal and hydrazinium salts is described. Depending upon the substitution pattern of hydrazine derivative, the reaction affords 1-alkyl/aryl-5-ferrocenylpyrazoles and/or 1-alkyl/aryl-3-ferrocenylpyrazoles. Structures of 5-ferrocenyl-1-phenyl-1*H*-pyrazole, 1-benzyl-5-ferrocenyl-1*H*-pyrazole and 2-(3-ferrocenylpyrazol-1-yl)ethanol were identified by X-ray crystallography.

Keywords: Ferrocene; Pyrazole; Hydrazine; Propynal; Cyclization; Condensation

1. Introduction

The rapid spread of cancer has sparked an intense chemical search for new structure leads which may be of use in designing novel antitumor drugs. In this regard, pyrazoles have been the focus of a large number of investigations in the design and synthesis of novel biologically active agents that show remarkable anticancer activities [1]. Pyrazoles have been studied for over a century as an important class of heterocyclic compounds and still continue to attract considerable attention due to the wide range of medicinal activities they possess, such as analgesic, antimicrobial, antiviral, anti-inflammatory, hypoglycemic, antihypertensive and antitumor properties [1,2]. Recent studies have shown that substitution of an aromatic nucleus of such structures with a ferrocene unit can lead to products with enhanced or unexpected biological activity which is absent or less manifest in the parent molecule [3,4]. Owing to its unique structure, different membrane-permeation behavior and anomalous metabolism, ferrocene is often integrated into a compound in order to obtain unexpected or enhanced biological activities [3,4]. Thus, in recent years, substantial effort has been devoted to the synthesis of new ferrocene derivatives since the properly functionalized derivatives could be potential antitumor substances [5,6]. Although pyrazoles are among the most intensely studied compounds [7–9], ferrocenyl-substituted derivatives are relatively less explored [10,11]. In this regard, the reactions of acetylenic ketones (alkynones) with hydrazines have been frequently used to synthesize pyrazole derivatives [8,9]. However, analogous reactions between acetylenic aldehydes (alkynals) and hydrazines are almost unknown since, to the best of our knowledge, there is only one example of such reaction [9]. It has been reported that the microwave-assisted reaction of 3-phenylpropynal with phenylhydrazine provided 1,3- and 1,5-diphenylpyrazoles in 58% and 28% yields, respectively [9]. As a part of our general

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involvement in ferrocene containing potential pharmaceuticals, we have investigated the reaction of 3-ferrocenylpropynal (**1**) with hydrazinium salts (**2**) since it provides an easy access to ferrocenyl pyrazoles **3** and/or **4** (Table 1) [12]. We herein report the results of this study.

2. Results and discussion

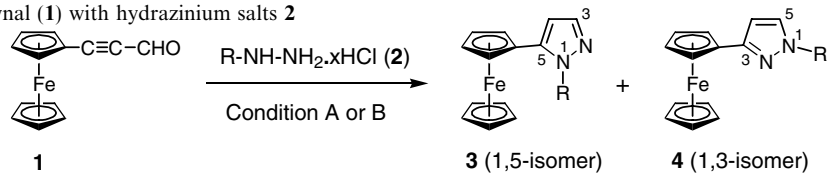
2.1. Synthesis of starting materials

3-Ferrocenylpropynal (**1**) was synthesized from ethynylferrocene by a Vilsmeier-Haack-type formylation [13]. Ethynylferrocene was prepared from acetylferrocene according to a well-known literature procedure [14]. Acetylferrocene is easily obtainable in large quantities from ferrocene according to a standard protocol [15]. Hydrazinium salts (**2**) were all commercially available, except (2-hydroxyethyl)hydrazinium dichloride (**2C**) which was prepared according to a standard procedure [16].

2.2. Synthesis of ferrocenyl pyrazoles *3* and *4*

The reactions were carried out in refluxing dioxane (Condition A) or methanol (Condition B) with a mole

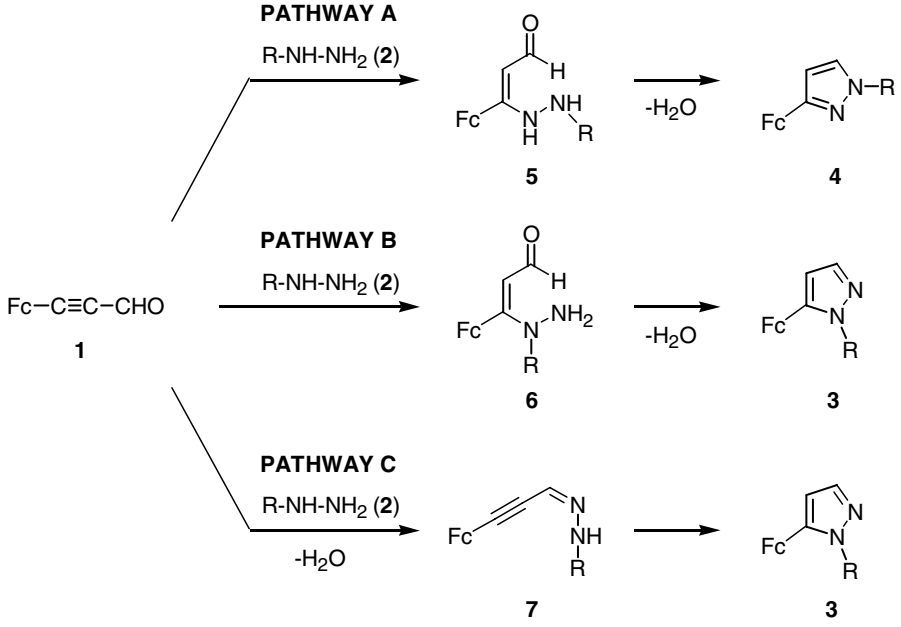
Table 1
Reaction of 3-ferrocenylpropynal (**1**) with hydrazinium salts **2**



1 **3** (1,5-isomer) **4** (1,3-isomer)

Entry[a]	R	*x*	Products (isolated yield, %)	
			Condition A[b]	Condition B[c]
A	H	2	**3A** (47)	**3A** (70)
B	Ph	1	**3B** (45) + **4B** (14)	**3B** (70) + **4B** (20)
C	CH_2–CH_2–OH	2	**3C** (6) + **4C** (19)	**3C** (31) + **4C** (25)
D	CH_2–Ph	2	**3D** (63)	**3D** (46) + **4D** (30)

[a] Entry letters define R group for compounds **2**, **3** and **4**, and *x* for compound **2**.
[b] Condition A: dioxane, 100 °C, 8 h.
[c] Condition B: CH_3OH, 65 °C, 5 h.



Scheme 1.

ratio of ferrocenylpropynal (**1**) to hydrazinium salt (**2**) of about 1:1.5, and the products were isolated by flash chromatography. The results are summarized in Table 1. Hydrazinium salts, instead of hydrazines, were employed in these reactions since they gave relatively higher yields of pyrazoles. According to our recent study, (2-formyl-1-chlorovinyl)ferrocene reacted with hydrazine derivatives to give pyrazoles, and we found the reactions in refluxing dioxane to give better results [11]. It is for the reason that the reactions between 3-ferrocenylpropynal (**1**) and hydrazinium salts (**2**) were initially carried out in refluxing dioxane (Condition A). However, in this condition,

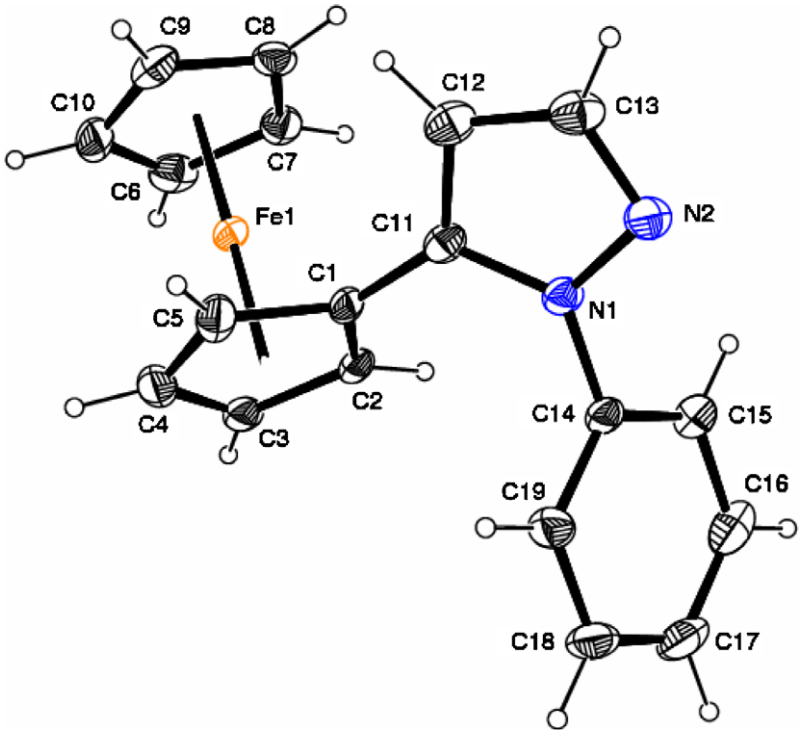


Fig. 1. ORTEP diagram of 5-ferrocenyl-1-phenyl-1*H*-pyrazole (**3B**). Ellipsoids are drawn at 20% probability.

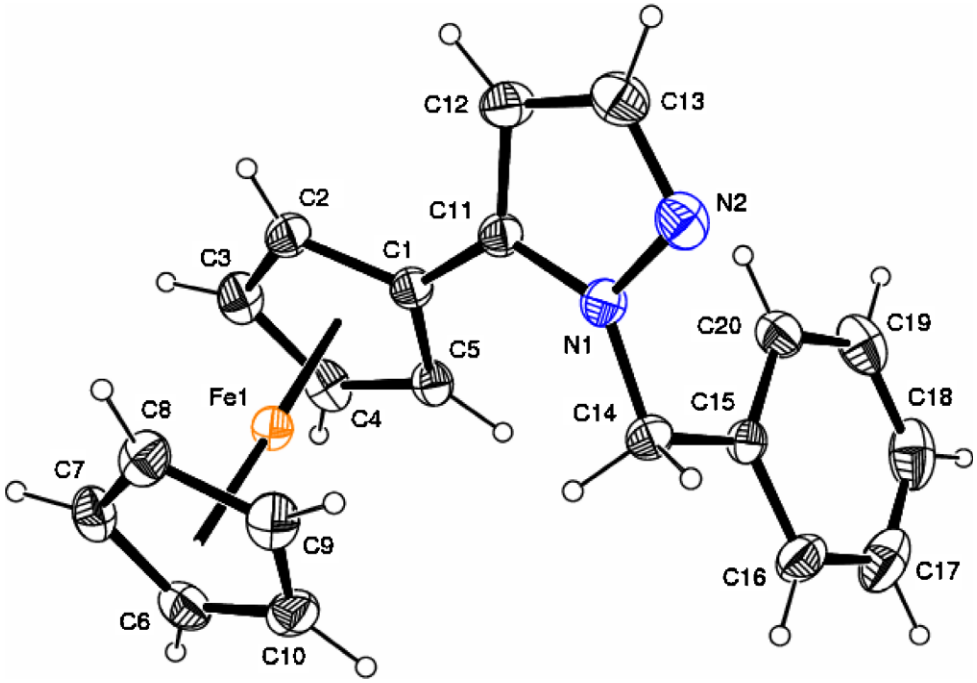


Fig. 2. ORTEP diagram of 1-benzyl-5-ferrocenyl-1*H*-pyrazole (**3D**). Ellipsoids are drawn at 20% probability.

pyrazole derivatives were obtained in relatively low yields. The same reactions were then performed in different solvents and refluxing methanol (Condition B) was found to shorten the reaction time with higher yields (Table 1).

As seen from Table 1, the reactions between 3-ferrocenylpropynal (**1**) and hydrazinium salts (**2**) yielded two kinds of pyrazoles, namely 1-alkyl/aryl-5-ferrocenylpyrazoles (**3**) and 1-alkyl/aryl-3-ferrocenylpyrazoles (**4**), which we will refer to as 1,5- and 1,3-isomers, respectively. 1,5- and 1,3-isomers of these types of pyrazoles can easily be identified on the basis of their ^{13}C NMR spectra [11]. In general, the C5 peak in 1,5-isomer is relatively upfield and resonates near 140 ppm while the corresponding C3 peak in 1,3-isomer is comparatively downfield and appears around 150 ppm (see Table 1 for atom numbering). Furthermore, in 1,5-isomer, the absolute value of chemical shift difference between C5 and C3 carbons is

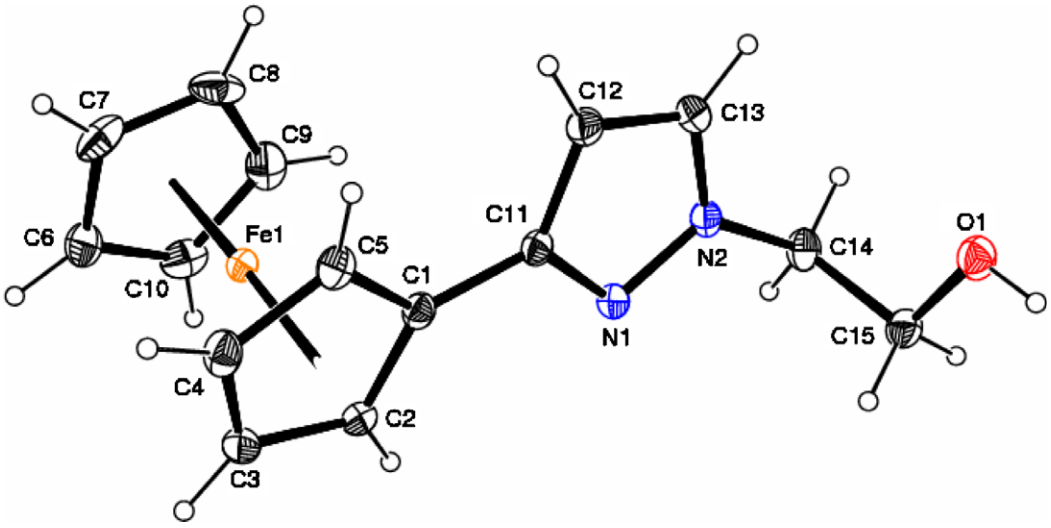


Fig. 3. ORTEP diagram of 2-(3-ferrocenylpyrazol-1-yl)ethanol (**4C**). Ellipsoids are drawn at 20% probability.

Table 2
Crystallographic data and structure refinement parameters for **3B**, **3D** and **4C**

	3B	**3D**	**4C**
Empirical formula	$C_{19}H_{16}FeN_2$	$C_{20}H_{18}FeN_2$	$C_{15}H_{16}FeN_2O$
Formula weight	328.19	342.21	296.15
Crystal size (mm)	$0.470 \times 0.380 \times 0.260$	$0.640 \times 0.570 \times 0.440$	$0.780 \times 0.423 \times 0.210$
Temperature (K)	293(2)	293(2)	296(2)
Crystal system	Orthorhombic	Triclinic	Monoclinic
Space group	$Pca2_1$	$P\bar{1}$	$P2_1/c$
a (Å)	21.999(2)	9.2923(5)	9.3038(17)
b (Å)	5.9827(6)	10.7911(6)	14.0340(3)
c (Å)	11.4051(9)	16.9299(9)	10.6563(16)
α (°)	90.000(0)	75.493(4)	90.000(0)
β (°)	90.000(0)	89.605(4)	110.482(13)
γ (°)	90.000(0)	75.870(4)	90.000(0)
V (Å^3)	1501.1(2)	1591.12(15)	1303.4(4)
Z	4	4	4
D_x (g cm^{-3})	1.452	1.429	1.509
μ (Mo Kα) (mm^{-1})	1.001	0.948	1.149
Radiation/wavelength (Å)	Mo Kα/0.71073	Mo Kα/0.71073	Mo Kα/0.71073
θ_{max} (°)	27.06	27.90	26.00
Index range (hkl)	−22/27, −7/7, −14/14	−12/12, −14/14, −22/22	−11/11, −17/17, −13/13
Reflections measured	7738	30561	15701
Independent reflections (R_{int})	3217	7544	2563
Reflections with $I > 2\sigma(I)$	2645	6232	2270
Number of parameters	199	415	172
Number of restraints	1	0	0
$R[F^2 > 2\sigma(F^2)]$	0.0399	0.028	0.0251
$wR(F^2)$	0.1236	0.0759	0.0660
Goodness-of-fit (F^2)	1.201	1.050	1.046
Maximum, minimum $\Delta\rho$ (e/Å^3)	0.882, −0.750	0.198, −0.351	0.217, −0.268

generally smaller than that between respective C3 and C5 carbons in 1,3-isomer [11], i.e. $|\Delta\delta(C5–C3)_{1,5\text{-isomer}}| < |\Delta\delta(C3–C5)_{1,3\text{-isomer}}|$.

The reaction between ferrocenylpropynal (**1**) and hydrazine dihydrochloride (**2A**) under both conditions led to formation of a pyrazole derivative, which was tentatively identified as 5-ferrocenylpyrazole (**3A**) (entry A). It is noteworthy to mention that owing to annular tautomerism, pyrazoles can exist in two tautomeric forms such as **3A** and **4A** [17]. Proton transfer in pyrazoles is a formal [1,5]-hydrogen shift and the barriers for such processes in both solid state and solution are about 10–14 kcal/mol [17c]. As we noted previously [11], we were unable to get a well-resolved ^{13}C NMR spectrum from this compound at both 25 and −15 °C to determine its tautomeric identity. In fact, pyrazole **3A** is a known compound [10c] but specific spectroscopic data (such as ^{13}C NMR data) to distinguish it from its tautomer **4A** has not been reported. Our efforts to differentiate these tautomers spectroscopically from each other are continuing.

The reaction of ferrocenylpropynal (**1**) with phenylhydrazine dihydrochloride (**2B**) afforded 5-ferrocenyl-1-phenylpyrazole (**3B**) and 3-ferrocenyl-1-phenylpyrazole (**4B**) (entry B). In both conditions, pyrazole **3B** was isolated as the major product. The reaction between ferrocenylpropynal **1** and (2-hydroxyethyl)hydrazinium dichloride (**2C**) [16] led to formation of 2-(5-ferrocenylpyrazol-1-yl)ethanol (**3C**) and 2-(3-ferrocenylpyrazol-1-yl)ethanol (**4C**) (entry C). Interestingly, in Condition A, pyrazole **4C** was obtained as the major product of the reaction while in Condition B, pyrazole **3C** was the major one. On the other hand, the reaction of ferrocenylpropynal (**1**) with benzylhydrazine dihydrochloride (**2D**) produced 1-benzyl-5-ferrocenylpyrazole (**3D**) and/or 1-benzyl-3-ferrocenylpyrazole (**4D**) depending upon the condition employed (entry D). In Condition B, pyrazole **3D** was isolated as the major product of the reaction. Note that the tautomeric assignments of these pyrazole isomers were based on both the chemical shifts and chemical shift differences of corresponding C3 and C5 carbons, as mentioned earlier [11]. The structures of ferrocenyl pyrazoles **3B**, **3D** and **4C** were also elucidated by X-ray analysis.

For the formation of pyrazoles **3** (1,5-isomer) and **4** (1,3-isomer), three mechanistic pathways are possible as illustrated in Scheme 1. In pathways A and B, the reaction occurs via a conjugate addition of hydrazine **2** to ferrocenylpropynal **1**, followed by cyclization and/or cyclocondensation of the resulting β-hydrazinoenones **5** and **6**. However, in pathway C, the reaction happens via condensation of hydrazine **2** with ferrocenylpropynal **1**, followed by cyclization through conjugate addition of the resulting α,β-unsaturated hydrazone **7**. It is noteworthy that pathway A leads to 1,3-pyrazole isomer **4** while pathways B and C go to 1,5-pyrazole isomer **3**. It seems that depending upon the substitution pattern of hydrazine derivative **2**, one pathway or more than one pathway can be functioning during the course of the reaction.

*2.3. Crystal structures of 5-ferrocenyl-1-phenyl-1H-pyrazole (**3B**), 1-benzyl-5-ferrocenyl-1H-pyrazole (**3D**) and 2-(3-ferrocenylpyrazol-1-yl)ethanol (**4C**)*

The structures of pyrazoles **3B**, **3D** and **4C** were determined by X-ray crystal analysis as well. ORTEP diagrams of **3B**, **3D** and **4C** are shown in Figs. 1–3, respectively. Note that although two molecules are present in the asymmetric unit of **3D**, only one molecule is shown in Fig. 2 for clarity. Details of cell data, X-ray data collection, structure solution and refinement are summarized in Table 2. Selected bond distances and angles are given in Table 3. A complete list of atomic coordinates, bond distances and angles, anisotropic thermal parameters, hydrogen atom coordinates for these structures have been deposited and are available upon request (see Section Appendix A).

The most striking feature for these structures is the deviation of the substituted cyclopentadienyl (Cp) and

Table 3
Selected bond distances (Å), bond angles (°) and torsion angles (°) for **3B**, **3D** and **4C**[a]

	3B	**3D**	**4C**
C1–Fe1	2.064(4)	2.0460(14)	2.0449(16)
C1–C2	1.413(6)	1.425(2)	1.427(2)
C1–C5	1.448(6)	1.425(2)	1.428(2)
C1–C11	1.444(6)	1.464(2)	1.462(2)
C2–C3	1.427(6)	1.415(2)	1.418(3)
C3–C4	1.405(7)	1.408(3)	1.416(3)
C4–C5	1.402(7)	1.421(2)	1.418(3)
C6–Fe1	2.028(4)	2.0484(17)	2.0393(19)
C11–N1	1.358(4)	1.3552(19)	1.337(2)
C11–C12	1.385(5)	1.375(2)	1.404(2)
C12–C13	1.385(6)	1.384(3)	1.364(3)
C13–N2	1.321(6)	1.313(2)	1.336(2)
C14–N1	1.422(4)	1.4414(19)	NA
C15–O1	NA	NA	1.410(2)
N1–N2	1.365(4)	1.3637(18)	1.3585(19)
C2–C1–C11	128.8(4)	122.48(14)	128.43(15)
C11–C1–Fe1	129.3(3)	130.41(10)	125.43(11)
C11–N1–N2	112.5(3)	112.26(13)	104.84(13)
C12–C11–C1	132.1(3)	128.49(14)	127.37(16)
C13–N2–N1	104.1(3)	104.21(14)	111.87(14)
C13–C12–C11	105.7(3)	105.76(15)	105.22(15)
C14–C15–O1	NA	NA	109.05(15)
C15–C14–N1	119.3(3)	113.90(12)	NA
N1–C11–C1	122.6(3)	126.00(13)	122.07(15)
C1–C11–N1–C14	−1.5(6)	3.7(2)	NA
C2–C1–C11–N1	−43.8(6)	156.31(15)	−12.9(3)
C5–C1–C11–C12	−46.9(7)	148.51(17)	−10.7(3)
C5–C1–C11–N1	133.1(4)	−29.5(2)	168.70(15)
C15–C14–N1–C11	117.3(4)	89.17(18)	NA
C15–C14–N2–C13	NA	NA	94.4(2)
C15–C14–N1–C11	117.3(4)	89.17(18)	NA
C15–C14–N1–N2	−64.7(5)	−84.20 (17)	NA
C15–C14–N2–N1	NA	NA	−81.4(2)
C2–C1–C11–N1	−43.8(6)	156.31(15)	−12.9(3)
C5–C1–C11–N1	133.1(4)	−29.5(2)	168.70(15)
N1–C14–C15–C16	179.9(4)	175.42(14)	NA
N2–C14–C15–O1	NA	NA	−69.0(2)

[a] NA, not applicable.

pyrazolyl (Py) rings from coplanarity depending upon steric effects, resulting interruption of the conjugation between these aromatic moieties. This deviation is 45.36(2)° in **3B**, 26.85(11)° and 33.52(6)° in **3D**, and 11.87(12)° in **4C**. The deviation angle increases in the order of **4C** < **3D** < **3B** depending upon the steric hindrance between Fc group and the substituent (2-hydroxyethyl, benzyl or phenyl) on N1 or N2 atom of pyrazolyl residue. The maximum steric interaction is observed between the Fc and Ph groups of **3B** (Fig. 1), and as a result, Ph ring in this compound is tilted from the pyrazolyl ring plane by an angle of 64.95(2)° as well, severely interrupting the conjugation. This is further supported by the dihedral angle of 57.6(2)° between the Ph and substituted Cp ring planes. It is noteworthy that the conjugation between aromatic moieties of **4C** is largely maintained as compared to those of **3B** and **3D**. Noticeably, pyrazolyl and phenyl rings in the molecules of **3D** are nearly perpendicular with an angle of 87.67(6)° and 83.90(6)° although these rings are separated by a methylene unit (Fig. 2). Another important structural characteristic is that, in **4C**, pyrazolyl and hydroxyl groups on C14 and C15 atoms, respectively, adopt a gauche conformation in the solid state, as indicated by the N2–C14–C15–O1 angle of −69.0(2)°, although C14 and C15 atoms exist in a staggered conformation (Fig. 3).

Bond distances in the pyrazolyl units of these structures are quite similar. N–N bond distances change from 1.359(19) to 1.365(17) Å, N–C bond lengths from 1.313(2) to 1.358(4) Å and C–C bond distances from 1.364(3) to 1.404(2) Å (Table 3), which are indicative of electron delocalization.

Fc group in**3B** and **3D** is almost in the eclipsed conformation since the average C–Cg_s–Cg_{as}–C torsion angle varies between −2.57(3)° and 3.58(3)°, where Cg_s and Cg_{as} are the substituted and unsubstituted Cp ring centroids, respectively. However, in **4C**, Fc group exists in a noticeably distorted eclipsed conformation as indicated by the average C–Cg_s–Cg_{as}–C torsion angle of 19.74(6)°. On the other hand, in all structures, the centroids of Cp rings are equidistant from Fe atom since the Fe–Cg_s and Fe–Cg_{as} distances are in the range of 1.641(9)–1.654(15) Å, and the Cg_s–Fe–Cg_{as} angles are between 177.65(7)° and 178.85(7)°. The C–C bond distances in Cp rings alter from 1.379(8) to 1.448(6) Å, while Fe–C bond lengths vary between 2.024(2) and 2.064(4) Å, all of which are as expected [6i,10m,10n,10o,10p].

In terms of crystal packing, each compound shows different molecular arrangement, which are stabilized by C–H…N or O–H…N intermolecular hydrogen bonds, and/or C–H…π interactions. The molecules of **3B** are stabilized by both C–H…N intermolecular hydrogen bonds and C–H…π interactions. In fact, there is a single type of intermolecular hydrogen bond, [C8–H8…N2:H…N = 2.694(4) Å, C…N = 3.407(5) Å, C–H…O = 137.03(3)°], which links the molecules and generate the C(9) chains along the [0 0 1] direction [18] (Fig. 4). In addition, C(9) chains are connected through C15–H15…$Cg1^{i}$ [Cg1 is the centroid of the C1–C6 ring; H15…Cg1 = 3.034 Å, C15…Cg1 = 3.884(5) Å, C15–H15…Cg1 = 152.77°, (i) $x, y+1, z$], C17–H17…$Cg2^{ii}$ [Cg2 is the centroid of the C6–C10 ring; H17…Cg2 = 3.083 Å, C17…Cg2 = 3.662(5) Å, C17–H17…Cg2 = 122.04° (ii) $x, y, z+1$] and C13–H13…$Cg3^{iii}$ [Cg1 is the centroid of the C14–C19 ring; H13…Cg3 = 2.867 Å, C13…Cg3 = 3.666(5) Å, C13–H13…Cg3 = 144.66°, (i) $1-x, 2-y, z+1/2$] interactions.

On the other hand, the molecules of **3D** are stabilized only by C–H…π interactions. Interestingly, C39–H39…π interactions [C39–H39…$Cg1^{i}$; Cg1 is the centroid of the

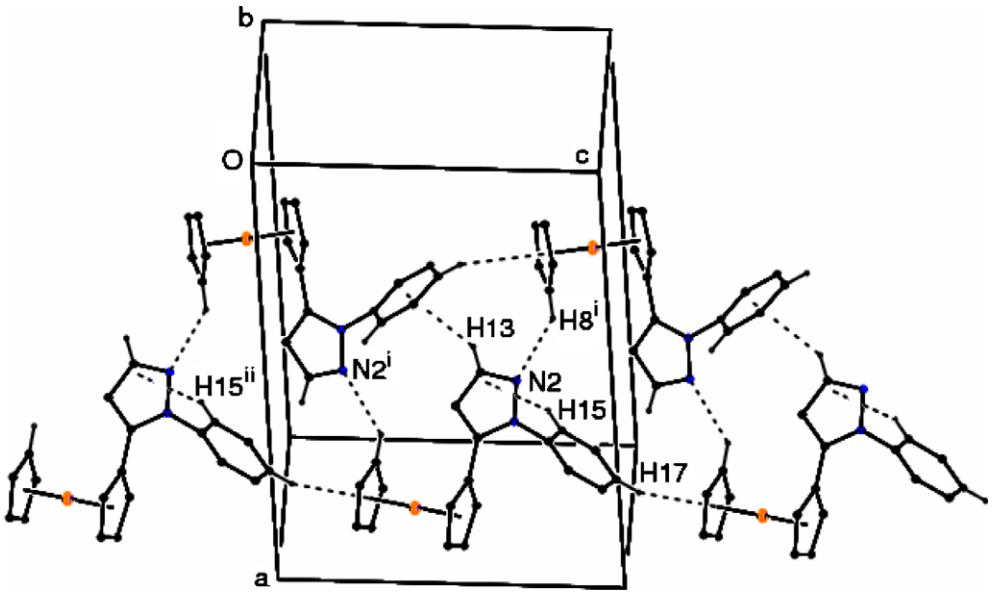


Fig. 4. Part of the crystal structure of **3B**, showing C–H…N intermolecular hydrogen bonds and C–H…π interactions as dashed lines. H atoms not involved in hydrogen bonds have been omitted for clarity [Symmetry code: (i) $x, 1-y, 1-z$, (ii) $x, 1+y, 1+z$].

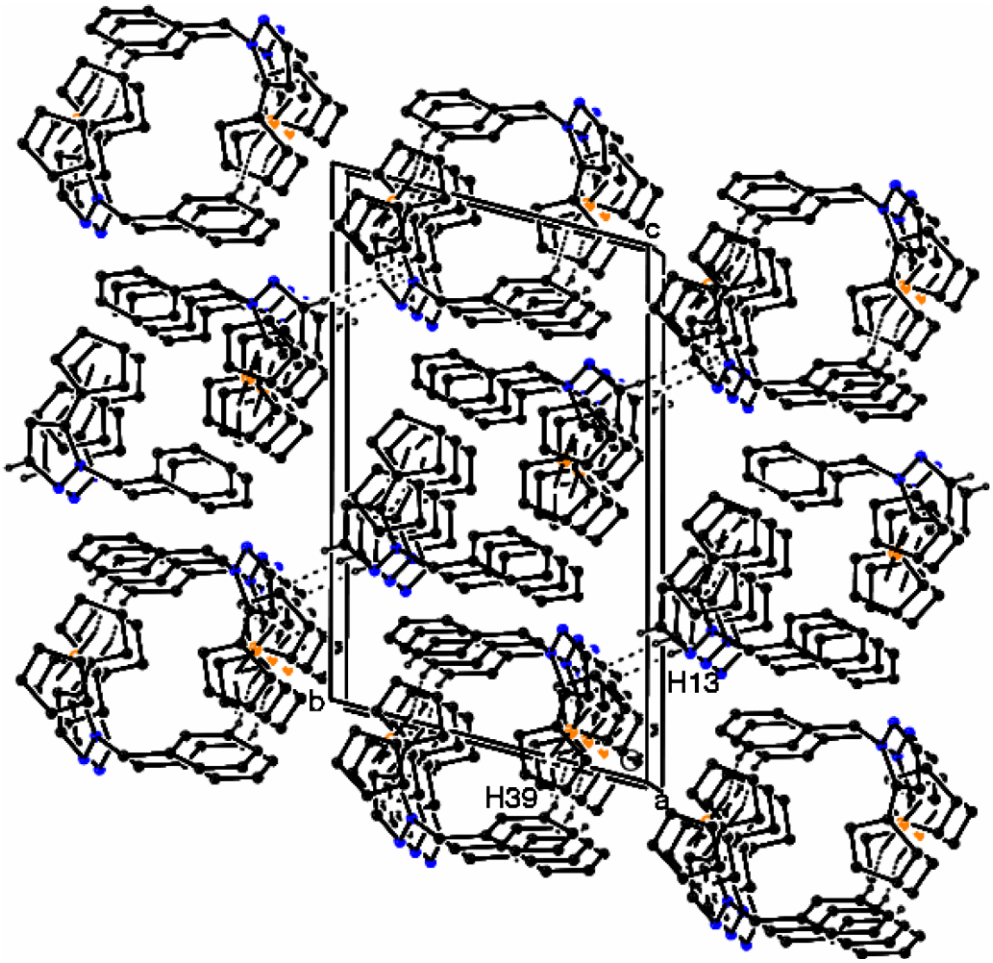


Fig. 5. A packing diagram of the crystal structure of **3D**, showing centrosymmetric $R_2^2(16)$ dimers and C–H. . .π interactions as dashed lines. H atoms not involved in hydrogen bonds have been omitted for clarity.

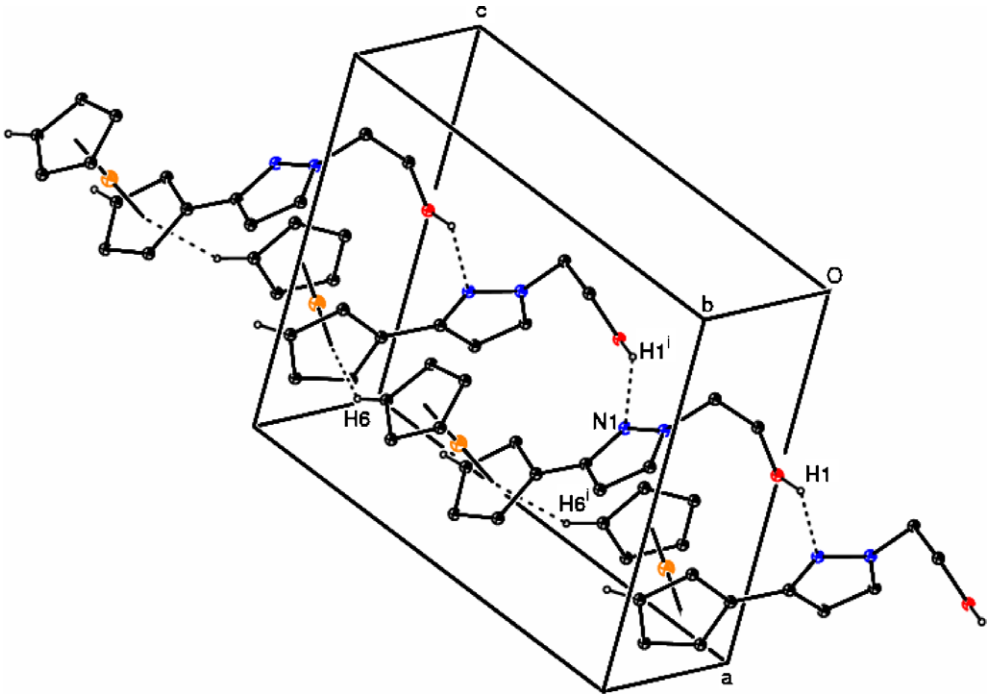


Fig. 6. Part of the crystal structure of **4C**, showing both O–H. . .N intermolecular hydrogen bonds and C–H. . .π interactions as dashed lines. H atoms not involved in hydrogen bonds have been omitted for clarity [Symmetry code: (i) x, $3/2 - y$, $z - 1/2$].

C21–C25 ring; H39...Cg1 = 2.853 Å, C39...Cg1 = 3.767(2) Å, C39–H39...Cg1 = 167.53°, (i) $x+1$, $y-1/2$, z] generate centrosymmetric $R_2^2(16)$ dimers [18] (Fig. 5), which are linked to each other through C13–H13...π interactions [C13–H13...Cg2^{ii}; Cg2 is the centroid of the N3/N4–C33 ring; H13...Cg2 = 2.676 Å, C13...Cg2 = 3.561(2) Å, C13–H13...Cg2 = 159.39°, (ii) $1/2-x$, $2-y$, $z-1/2$]. Fascinatingly, as seen in Fig. 5, tunnels are formed inside these dimer heaps, a rare occurrence, which was not observed in the crystal structures of **3B** and **4C**.

The molecules of **4C** are stabilized by both O–H...N intermolecular hydrogen bonds and C–H...π interactions. Actually, there is a single type of intermolecular hydrogen bond, [O1–H1...N2: H...N1 = 2.16(2) Å, C...N = 2.881(2) Å, C–H...O = 177.00(3)°], which connects the molecules and yields the C(6) chains [18] (Fig. 6). It should be noted that C(6) chains are linked to each other through C6–H6...Cg1^{i} interactions [Cg1 is the centroid of the C1–C6 ring; H6...Cg1 = 3.094 Å, C6...Cg1 = 3.853(2) Å, C6–H6...Cg1 = 140.00°, (i) x, $1/2-y$, $3/2-z$].

3. Conclusion

The reaction between 3-ferrocenylpropynal (**1**) and hydrazines **2** is investigated in this work, yielding pyrazoles **3** (1,5-isomer) and/or **4** (1,3-isomer). In most cases, 1,5-pyrazole isomers **3** have resulted from these reactions as the single or the major products. The regioselectivity of the reactions is mainly governed by the nature of the substituents in hydrazines **2**. Owing to the ready availability of 3-ferrocenylpropynal (**1**) and hydrazines **2**, this method represents a versatile synthesis of ferrocenyl-substituted pyrazoles **3** and/or **4**.

The structures of compounds **3B**, **3D** and **4C** were identified by X-ray crystal analysis. Depending upon steric effects, ferrocenyl and pyrazolyl groups in these structures depart from coplanarity, and, as a result, conjugation between these aromatic moieties is interrupted to some extent. The maximum steric interaction is observed between Fc and Ph groups of **3B**, considerably tilting both from the pyrazolyl ring plane, severely interrupting conjugation.

We have demonstrated that, when treated with hydrazinium salts, acetylenic aldehydes, i.e. alkynals, afford pyrazoles, as in the case of acetylenic ketones or alkynones.

4. Experimental

4.1. General consideration

Nuclear magnetic resonance (^{1}H and ^{13}C) spectra were recorded on a Bruker Spectrospin Avance DPX400 Ultrashield (400 MHz) spectrometer. Chemical shifts are reported in parts per million (δ) downfield from an internal tetramethylsilane reference. Coupling constants (J values) are reported in hertz (Hz), and spin multiplicities are indicated by the following symbols: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). DEPT ^{13}C NMR information is given in parenthesis as C, CH, CH_2 and CH_3. Infrared spectra were recorded on a Varian 5000 FT-IR spectrometer. Band positions are reported in reciprocal centimeters (cm^{-1}). Mass spectra (MS) were obtained on an Agilent 1100 Series LC MSD spectrometer, using electrospray ionization (ESI) (Fragmentor 100 eV, positive polarity). Elemental analyses were carried out on a LECO CHNS-932 instrument. Flash chromatography was performed using thick-walled glass columns and 'flash grade' silica (Merck 230–400 mesh). The relative proportion of solvents in mixed chromatography solvents refers to the volume:volume ratio. 3-Ferrocenylpropynal (**1**) [13–15] and (2-hydroxyethyl)hydrazinium dichloride (**2C**) [16] were synthesized according to the known literature procedures. All other commercially available reagents and reactants were obtained in reagent grade and used without purification. All reaction solvents were distilled and/or dried for purity according to standard literature procedures. The inert atmosphere was created by slight positive pressure (ca. 0.1 psi) of argon.

4.2. General procedure for the synthesis of ferrocenyl pyrazoles *3* and *4* (*Table 1*)

To a solution of 3-ferrocenylpropynal (**1**) (100 mg, 0.420 mmol) in 10 mL of dioxane (Condition A) or methanol (Condition B) under argon was added hydrazine derivative (**2**) (1.260 mmol). The resulting mixture was then heated at reflux for 8 h (Condition A) or 5 h (Condition B). After the reaction was complete, the mixture was cooled to 25 °C, and the solvent was removed on a rotary evaporator. The residue was dissolved in water (20 mL) and extracted with chloroform (3 × 30 mL). The combined chloroform layers were dried over magnesium sulfate and removed in a rotary evaporator. Final purification was achieved through flash chromatography on silica gel (eluent: hexane/EtOAc from 19:1 to 1:1). The products given in Table 1 were isolated with the indicated yields.

4.3. Spectral data for products

We have recently reported the synthesis of ferrocenyl pyrazoles **3A–D** and **4B–C** by using a similar method [11]. Please refer to this study for the spectral data of these compounds.

4.3.1. 1-Benzyl-3-ferrocenyl-1H-pyrazole (*4D*)

^{1}H NMR ($CDCl_3$): δ 7.40–7.31 (m, 3H), 7.28 (s, 1H), 7.23 (d, 2H, J = 7.2 Hz), 6.32 (s, 1H), 5.34 (s, 2H), 4.77 (s, 2H), 4.34 (s, 2H), 4.14 (s, 5H); ^{13}C NMR ($CDCl_3$): δ 150.8 (C), 137.0 (C), 130.1 (CH), 128.7 (CH), 127.9 (CH), 127.5 (CH), 103.7 (CH), 79.0 (C), 69.6 (CH), 68.5 (CH), 66.7 (CH), 55.8 (CH_2); IR (KBr): 3108, 3079, 3030, 2941, 1556, 1497, 1435, 1404, 1303, 1230, 1102, 1060, 1000, 874, 833, 813, 761, 716 cm^{-1}; MS (ESI, m/z): 343.1 $[M+H]^+$, 252.0; Anal. Calc. for $C_{20}H_{18}FeN_2$ with

0.263 mol $CHCl_3$ incorporation: C, 65.14; H, 4.93; N, 7.50. Found: C, 65.14; H, 5.62; N, 7.50% [19].

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Appendix A. Supplementary material

CCDC 653294, 653295 and 653296 contain the supplementary crystallographic data for **3B**, **3D** and **4C**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jorganchem.2007.10.035.

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