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Synthesis of ferrocenyl pyrazoles by the reaction of (2-formyl-1-chlorovinyl)ferrocene with hydrazines

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Abstract

Synthesis of ferrocenyl-substituted pyrazoles via the reaction between (2-formyl-1-chlorovinyl)ferrocene and hydrazine derivatives is described. Depending upon the substitution pattern of hydrazine, the reaction affords 1-alkyl/aryl-5-ferrocenylpyrazoles and/or 1-alkyl/aryl-3-ferrocenylpyrazoles. The reaction appears to be general for a variety of hydrazine derivatives.

Keywords: Ferrocene; Ferrocenyl; Pyrazole; Hydrazine; Hydrazinium salt; Hydrazide; Propenal; Density functional theory; B3LYP

1. Introduction

Pyrazoles have occupied a unique position in the design and synthesis of novel biologically active agents that exert remarkable anticancer activities [1]. In fact, 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 broad range of biological activities they possess, including analgesic, antimicrobial, antiviral, anti-inflammatory, hypoglycemix, anti-hypertensive and antitumor properties [1,2]. Recent studies have shown that the integration of a ferrocenyl group into such structures may enhance their biological activities or generate new medicinal properties [3,4]. Due to its unique structure, different membrane-permeation properties and anomalous metabolism, ferrocene is often incorporated into a compound in order to obtain unexpected or enhanced biological activities [3,4]. Thus, in recent years, considerable 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 thoroughly studied compounds [7], we were surprised that there has been very limited study of the ferrocenyl-substituted pyrazoles [8]. In this regard, as shown by Terent'ev and co-workers [9], the reaction between (2-formyl-1-chlorovinyl)ferrocene (**1**) and hydrazines (**2**) represents a rapid entry into ferrocenyl pyrazoles (**3**) (Scheme 1), but this reaction was not studied in much detail and the low yields of ferrocenyl pyrazoles **3** were obtained. As part of a program to synthesize new ferrocenyl-substituted heterocyclic compounds as potential pharmaceuticals, we have reinvestigated this reaction and improved the yields [10]. We herein report the results of this study.

2. Results and discussion

2.1. Synthesis of starting materials

(2-Formyl-1-chlorovinyl)ferrocene (3-chloro-3-ferrocenylpropenal) (**1**) was synthesized from acetylferrocene according to the well-known literature procedure [11], in which treatment of acetylferrocene with phosphorous oxychloride in DMF led to formation of (2-formyl-1-chlorovinyl)ferrocene (**1**). Acetylferrocene is readily available in large quantities from ferrocene according to a standard

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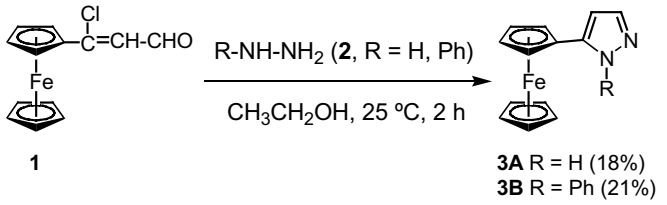


Scheme 1.

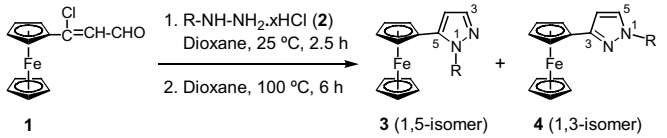
protocol [12]. Hydrazine derivatives **2** used in this study were all commercially available.

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

The reaction was initially examined under a variety of conditions, and the best results were obtained as follows: 3-chloro-3-ferrocenylpropenal (**1**) was first reacted with the excess amounts (3 equivalents) of hydrazine derivative (**2**) at 25 °C in dioxane under argon for 2.5 h. The resulting mixture was then refluxed at 100 °C for 6 h, and the products were isolated by flash chromatography. The results are summarized in Table 1. If available, hydrazinium salts, instead of hydrazines, were used in these reactions since they gave relatively higher yields of pyrazoles.

As can be seen from Table 1, 1-alkyl/aryl-5-ferrocenylpyrazoles (**3**) and/or 1-alkyl/aryl-3-ferrocenylpyrazoles (**4**) were resulted from these reactions, which are commonly called 1,5- and 1,3-isomers, respectively. It should be noted that 1,5- and 1,3-isomers of pyrazoles can be differentiated on the basis of their ^{13}C NMR spectra, as concluded from the spectral data of similar pyrazole derivatives [13]. In general, C5 peak in 1,5-isomer is relatively upfield and appears around 140 ppm while corresponding C3 peak in 1,3-isomer is relatively downfield and resonates around 150 ppm (see Table 1 for atom numbering). Moreover, in 1,5-isomer, the absolute value of chemical shift difference between C5 and C3 carbons is mostly smaller than that between respective C3 and C5 carbons in 1,3-isomer, i.e. $|\Delta\delta(C5–C3)_{1,5\text{-isomer}}| < |\Delta\delta(C3–C5)_{1,3\text{-isomer}}|$.

Table 1
Reaction of (2-formyl-1-chlorovinyl)ferrocene (**1**) with hydrazines **2**



Entry[a]	R	*x*	Products (isolated yield, %)
A	H	2	**3A** (51)
B	Ph	1	**3B** (67) + **4B** (4)
C	CH_2-CH_2-OH	2	**3C** (3) + **4C** (34)
D	CH_2-Ph	2	**3D** (55)
E	*p*-C_6H_4-CO_2H	1	**3E** (47)
F	*o*-C_5H_4N	0	**3F** (60)
G	CO-*p*-C_6H_4-OH	0	**4G** (43) + **3A** (50)

[a] Entry letters define R group for compounds **2**, **3** and **4**, and *x* for compound **2**.

The reaction between ferrocenylpropenal **1** and hydrazine dihydrochloride (**2A**) led to formation of a pyrazole derivative, which was tentatively assigned as 5-ferrocenylpyrazole (**3A**) (entry A). It should be noted that owing to annular tautomerism, pyrazoles can exist in two tautomeric forms such as **3A** and **4A**. In fact, proton transfer in pyrazoles is a formally 1,5-hydrogen shift and the barriers for such processes in both solution and solid state are in the range of 10–14 kcal/mol [14]. As anticipated, tautomers **3A** and **4A** can be in equilibrium or interconvert in part. Unfortunately, we were unsuccessful to obtain a well-resolved ^{13}C NMR spectrum from this compound at 25 °C and even −15 °C to identify the corresponding tautomer(s). In fact, pyrazole **3A** is a known compound [9], but there is a lack of specific spectroscopic data (such as ^{13}C NMR data) in the literature to differentiate it from its tautomer **4A**. Our efforts to spectroscopically distinguish between pyrazoles **3A** and **4A** are going on.

We also calculated the relative energies of pyrazoles **3A** and **4A** at the density functional theory (DFT) level (B3LYP/6-31G*) [15,16] by using the GAUSSIAN-98 program package [17], and found that **4A** is more stable than **3A** by 0.3 kcal/mol. Note that, in gas phase (DFT calculations), **4A** is the more stable while, in solution and solid state, it might correspond to a metastable structure, which requires further study. As shown by Elguero and co-workers [13d], pyrazoles can exist in different tautomeric forms depending upon their physical phase or state. For instance, in gas phase and solution, 3-phenylpyrazole is more stable than its tautomer, 5-phenylpyrazole. However, in solid state, crystals of 3-phenylpyrazole evolved to be 5-phenylpyrazole [13d].

The reaction of ferrocenylpropenal **1** with phenylhydrazine dihydrochloride (**2B**) afforded 5-ferrocenyl-1-phenylpyrazole (**3B**) along with a very small amount of 3-ferrocenyl-1-phenylpyrazole (**4B**) (entry B). Interestingly, the reaction between ferrocenylpropenal **1** and (2-hydroxyethyl)hydrazinium dichloride (**2C**) [18] produced 2-(3-ferrocenylpyrazol-1-yl)ethanol (**4C**) as the major product, accompanied by the very small amount of 2-(5-ferrocenylpyrazol-1-yl)ethanol (**3C**) (entry C). On the other hand, the reaction of ferrocenylpropenal **1** with benzylhydrazine dihydrochloride (**2D**) led to a single pyrazole derivative, 1-benzyl-5-ferrocenylpyrazole (**3D**) (entry D). It should be noted that tautomeric assignments of pyrazoles **3B–D** and **4B–C** were based on both chemical shifts and absolute values of chemical shift differences of corresponding C3 and C5 carbons, as mentioned before. Note that the structures of ferrocenyl pyrazoles **3B**, **3D** and **4C** were unambiguously identified by X-ray analysis as well, but the results of this study will be reported separately as a part of another study.

The reaction of ferrocenylpropenal **1** with 4-hydrazinobenzoic acid (**2E**) yielded 4-(5-ferrocenylpyrazol-1-yl)benzoic acid (**3E**) (entry E). Similarly, the reaction between

ferrocenylpropenal **1** and 2-pyridiniohydrazinium dichloride (**2F**) [19] led to 2-(5-ferrocenylpyrazol-1-yl)pyridine (**3F**) (entry F). On the other hand, the reaction of ferrocenylpropenal **1** with 4-hydroxybenzhydrazide (**2G**) afforded two products, namely (3-ferrocenylpyrazol-1-yl)(4-hydroxyphenyl)methanone (**4G**) and 5-ferrocenylpyrazole (**3A**) (entry G).

For the formation of pyrazoles **3** (1,5-isomer) and **4** (1,3-isomer), three mechanistic pathways are available as depicted in Scheme 2. The reaction proceeds via tandem conjugate addition–elimination of hydrazine **2** with ferrocenylpropenal **1** followed by cyclization and/or condensation of the resulting β-hydrazinoenones **5** and **6** (pathways A and B), or via condensation of hydrazine **2** with ferrocenylpropenal **1** followed by cyclization through tandem conjugate addition–elimination of the resulting α,β-unsaturated hydrazone **7** (pathway C). It should be noted that pathway A leads to 1,3-pyrazole isomer **4** while pathways B and C go to 1,5-pyrazole isomer **3**. Apparently, depending upon the substitution pattern of hydrazine derivative **2**, one pathway or more than one pathway can be operative during the course of the reaction.

Interestingly, the reaction of ferrocenylpropenal **1** with 4-hydroxybenzhydrazide (**2G**) produced 5-ferrocenylpyrazole (**3A**) in addition to pyrazole **4G** (entry G). For the formation of pyrazole **3A**, we have proposed two mechanistic pathways as illustrated in Scheme 3. According to pathway A, formation of pyrazole **3A** may not actually represent a different reactivity pattern since it is a secondary product of the reaction and results from the initially formed pyrazole **4G** by hydrolysis. Nucleophilic addition of benzhydrazide **2G** to carbonyl function of pyrazole **4G** provides a hydrazide derivative, **8**, which is not normally stable and eliminates benzoic acid hydrazide **9** to give pyrazole **4A**. As mentioned before, pyrazole **4A** can be in equilibrium with and/or interconvert to its tautomer **3A**. Alternatively, as outlined in pathway B, benzhydrazide **2G** may react with itself via nucleophilic addition, yielding hydrazide derivative **10**. Elimination of benzoic acid hydrazide **9** from **10** then affords in situ hydrazine, the reaction of which with ferrocenylpropenal **1** yields pyrazole **3A** as well (Scheme 3). At present, it is not clear which mechanism is operating but there are precedents for both pathways [20,21].

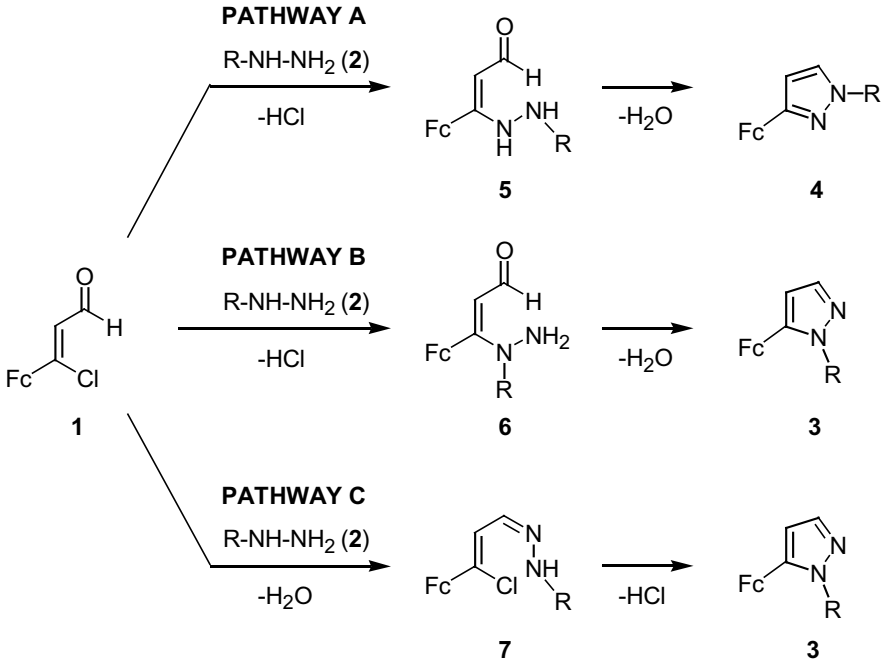
3. Conclusion

In summary, we have reinvestigated in detail the reaction between (2-formyl-1-chlorovinyl)ferrocene (**1**) and hydrazines **2** and improved the yields of pyrazoles **3** and/or **4**. In most cases, 1,5-pyrazole isomers **3** has 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**. Due to the ready availability of ferrocenylpropenal **1** and hydrazines **2**, this method represents a versatile synthesis of ferrocenyl-substituted pyrazoles **3** and/or **4**.

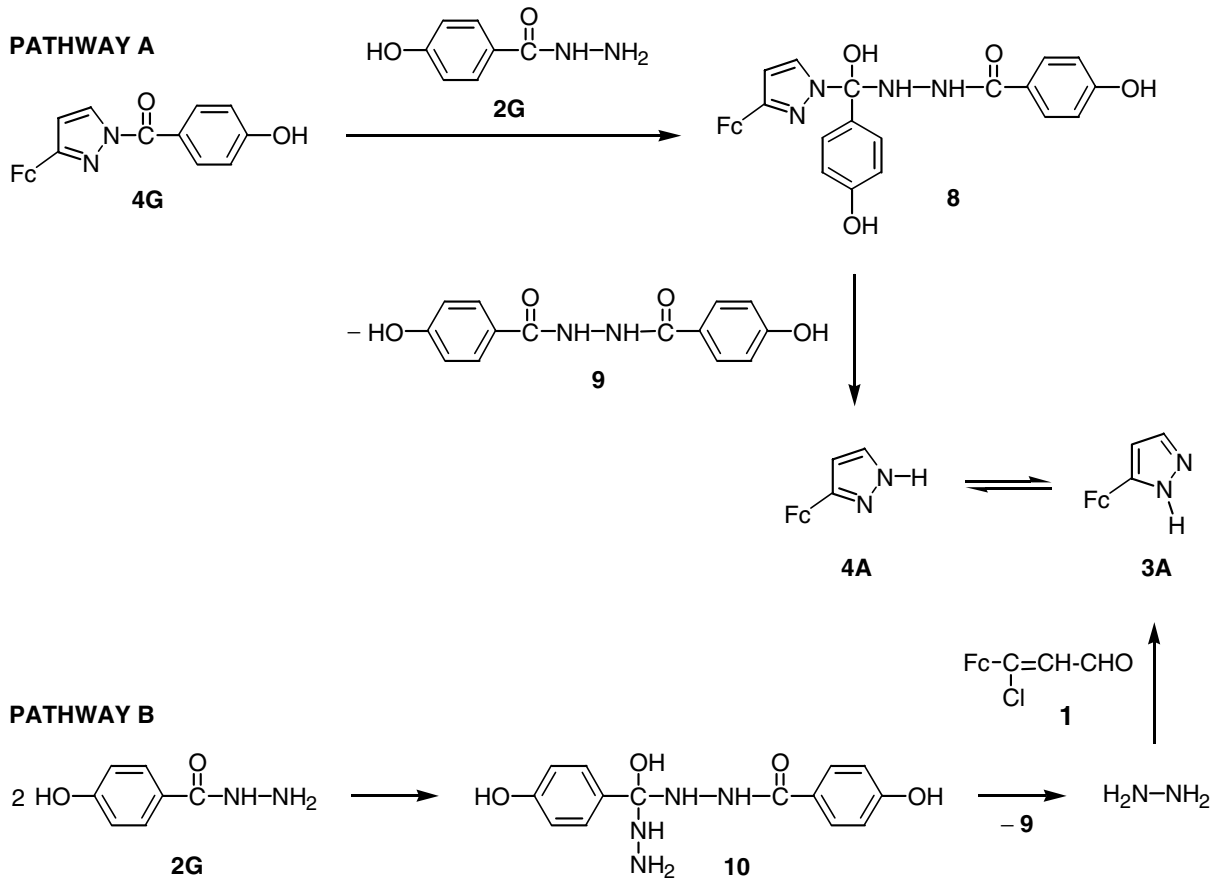
4. Experimental

4.1. General consideration

Nuclear magnetic resonance (^{1}H and ^{13}C) spectra were recorded on a Bruker Spectrospin Avance DPX400 Ultra-



Scheme 2.



Scheme 3.

shield (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 Perkin–Elmer 1600 Series FT-IR spectrometer or on a Bruker Vertex 70 Spectrometer using attenuated total reflection (ATR). Band positions are reported in reciprocal centimeters (cm^{-1}). Mass spectra (MS) were obtained on a Finnigan MAT 95 spectrometer, using electron impact (EI) at 70 eV; m/z values are reported. High resolution mass spectra (HRMS) were obtained on a Finnigan MAT 95 spectrometer by preselected-ion peak matching at $R \approx 10{,}000$ to be within ± 3 ppm of the exact masses. Flash chromatography was performed using thick-walled glass columns and 'flash grade' silica (Merck 230–400 mesh). Routine thin layer chromatography (TLC) was effected by using precoated 0.25 mm silica gel plates purchased from Merck. The relative proportion of solvents in mixed chromatography solvents refers to the volume:volume ratio. (2-Formyl-1-chlorovinyl)ferrocene (**1**) [14] and acetylferrocene [15] were synthesized according to the well-known literature procedures. All other commercially available reagents and reactants were obtained in reagent grade and used without purification. All reaction solvents were distilled for purity. Diethyl ether, THF and dioxane were distilled from sodium/benzophenone ketyl. 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 the solution of (2-formyl-1-chlorovinyl)ferrocene (**1**) (100 mg, 0.364 mmol) in dioxane (25 mL) under argon was added hydrazine derivative or salt (**2**) (1.092 mmol). The resulting mixture was stirred for 2.5 h at room temperature and then heated at reflux for 6 h. 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

4.3.1. 5-Ferrocenyl-1H-pyrazole (**3A**)

^{1}H NMR ($CDCl_3$): δ 7.52 (s, 1H), 6.33 (s, 1H), 4.58 (s, 2H), 4.28 (s, 2H), 4.04 (s, 5H), NH peak was not observed due to H/D exchange and/or tautomerism; IR (neat): 3115, 3026, 2875, 2840, 2816, 1598, 1565, 1463, 1415, 1289, 1102, 1053, 999, 937, 810, 764 cm^{-1}; MS (EI): 252 (M^+), 250, 224, 187, 166, 158, 133, 121, 103, 77; HRMS (EI): calcd. for $C_{13}H_{12}FeN_2$: 252.0350. Found: 252.0352.

4.3.2. 5-Ferrocenyl-1-phenyl-1H-pyrazole (**3B**)

^{1}H NMR ($CDCl_3$): δ 7.62 (s, 1H), 7.40 (m, 5H), 6.50 (s, 1H), 4.17 (s, 2H), 4.14 (s, 2H), 4.05 (s, 5H); ^{13}C NMR ($CDCl_3$): δ 141.5 (C), 140.4 (C), 140.0 (CH), 128.8 (CH), 128.0 (CH), 126.1 (CH), 106.8 (CH), 75.1 (C), 69.9 (CH), 68.8 (CH), 68.6 (CH); IR (CH_2Cl_2): 3089, 3036, 1665, 1597, 1557, 1498, 1402, 1259, 1145, 971, 923, 870 cm^{-1}; MS (EI): 328 (M^+), 326, 263, 235, 207, 170, 153, 121, 77, 56; HRMS (EI): calcd. for $C_{19}H_{16}FeN_2$: 328.0663. Found: 328.0661.

4.3.3. 3-Ferrocenyl-1-phenyl-1H-pyrazole (**4B**)

^{1}H NMR ($CDCl_3$): δ 7.84 (d, 1H, $J = 2.4$ Hz), 7.71 (d, 2H, $J = 7.8$ Hz), 7.44 (t, 2H, $J = 7.8$ Hz), 7.25 (t, 1H, $J = 7.8$ Hz), 6.48 (d, 1H, $J = 2.4$ Hz), 4.76 (s, 2H), 4.29 (s, 2H), 4.07 (s, 5H); ^{13}C NMR ($CDCl_3$): δ 152.5 (C), 140.3 (C), 129.4 (CH), 127.4 (CH), 126.0 (CH), 119.0 (CH), 105.6 (CH), 78.4 (C), 69.6 (CH), 68.7 (CH), 66.9 (CH); IR (CH_2Cl_2): 3090, 3030, 2959, 2865, 1681, 1649, 1598, 1557, 1506, 1458, 1257, 1129, 1043, 868, 820 cm^{-1}; MS (EI): 328 (M^+), 326, 263, 246, 206, 178, 149, 121, 91, 77, 56; HRMS (EI): calcd. for $C_{19}H_{16}FeN_2$: 328.0663. Found: 328.0665.

4.3.4. 2-(5-Ferrocenylpyrazol-1-yl)ethanol (**3C**)

^{1}H NMR ($CDCl_3$): δ 7.46 (d, 1H, $J = 1.8$ Hz), 6.30 (d, 1H, $J = 1.8$ Hz), 4.49 (s, 2H), 4.36 (s, 2H), 4.33 (t, 2H, $J = 4.5$ Hz), 4.18 (s, 5H), 4.02 (t, 2H, $J = 4.5$ Hz), 3.09 (br s, 1H); ^{13}C NMR ($CDCl_3$): δ 141.4 (C), 138.7 (CH), 106.0 (CH), 74.9 (C), 69.6 (CH), 68.9 (CH), 68.8 (CH), 61.8 (CH_2), 51.0 (CH_2); IR (neat): 3331, 2965, 2937, 1562, 1460, 1331, 1070, 1043, 824, 800 cm^{-1}; MS (EI): 296 (M^+), 294, 265, 252, 231, 200, 187, 146, 121, 103; HRMS (EI): calcd. for $C_{15}H_{16}FeN_2O$: 296.0612. Found: 296.0610.

4.3.5. 2-(3-Ferrocenylpyrazol-1-yl)ethanol (**4C**)

^{1}H NMR ($CDCl_3$): δ 7.31 (s, 1H), 6.22 (s, 1H), 4.76 (s, 2H), 4.35 (s, 2H), 4.21 (t, 2H, $J = 4.3$ Hz), 4.12 (s, 5H), 3.97 (t, 2H, $J = 4.3$ Hz), 3.52 (br s, 1H); ^{13}C NMR ($CDCl_3$): δ 151.3 (C), 130.8 (CH), 103.0 (CH), 78.3 (C), 69.4 (CH), 68.3 (CH), 66.6 (CH), 62.1 (CH_2), 53.5 (CH_2); IR (neat): 3229, 3142, 2950, 2869, 1556, 1502, 1408, 1349, 1230, 1067, 824, 764 cm^{-1}; MS (EI): 296 (M^+), 294, 278, 264, 231, 213, 199, 173, 148, 121, 103, 81; HRMS (EI): calcd. for $C_{15}H_{16}FeN_2O$: 296.0612. Found: 296.0614.

4.3.6. 1-Benzyl-5-ferrocenyl-1H-pyrazole (**3D**)

^{1}H NMR ($CDCl_3$): δ 7.44 (s, 1H), 7.23 (t, 2H, $J = 7.28$ Hz), 7.15 (t, 1H, $J = 7.28$ Hz), 6.96 (d, 2H, $J = 7.28$ Hz), 6.35 (s, 1H), 5.42 (s, 2H), 4.29 (s, 2H), 4.17 (s, 2H), 4.00 (s, 5H); ^{13}C NMR ($CDCl_3$): δ 141.7 (C), 139.1 (C), 137.7 (CH), 128.6 (CH), 127.3 (CH), 126.2 (CH), 106.0 (CH), 74.9 (C), 70.5 (CH), 68.8 (CH), 68.4 (CH), 53.3 (CH_2); IR (neat): 3142, 3109, 2950, 2896, 1556, 1502, 1409, 1321, 1231, 1071, 873, 825, 765 cm^{-1}; MS (EI): 342 (M^+), 277, 252, 223, 185, 157, 121, 91, 65, 56; HRMS (EI): calcd. for $C_{20}H_{18}FeN_2$: 342.0819. Found: 342.0817.

4.3.7. 4-(5-Ferrocenylpyrazol-1-yl)benzoic acid (**3E**)

^{1}H NMR ($CDCl_3$): δ 8.00 (d, 2H, $J = 7.5$ Hz), 7.86 (d, 1H, $J = 8.5$ Hz), 7.05 (d, 2H, $J = 7.5$ Hz), 6.68 (d, 1H, $J = 8.5$ Hz), 4.63 (t, 2H, $J = 1.7$ Hz), 4.37 (t, 2H, $J = 1.7$ Hz), 4.19 (s, 5H), carboxylic acid peak was not observed due to H/D exchange; ^{13}C NMR ($CDCl_3$): δ 170.5 (C), 139.1 (CH), 137.8 (C), 137.0 (C), 132.3 (CH), 120.3 (C), 117.8 (CH), 111.9 (CH), 83.0 (C), 70.2 (CH), 70.1 (CH), 67.4 (CH); IR (CH_2Cl_2): 3057, 2928, 2851, 2671, 2542, 1727, 1694, 1603, 1451, 1417, 1316, 1286, 1262, 1171, 1127, 1070, 746, 733, 719 cm^{-1}; MS (EI): 372 (M^+), 370, 329, 307, 251, 234, 205, 178, 137, 120, 65, 56; HRMS (EI): calcd. for $C_{20}H_{16}FeN_2O_2$: 372.0561. Found: 372.0559.

4.3.8. 2-(5-Ferrocenylpyrazol-1-yl)pyridine (**3F**)

^{1}H NMR ($CDCl_3$): δ 8.11 (ddd, 1H, $J = 8.6$, 7.5, 1.8 Hz), 7.87 (d, 1H, $J = 9.0$ Hz), 7.58 (ddd, 1H, $J = 8.6$, 7.5, 1.8 Hz), 7.22 (d, 1H, $J = 8.5$ Hz), 6.77 (ddd, 1H, $J = 8.6$, 7.5, 1.8 Hz), 6.65 (d, 1H, $J = 9.0$ Hz), 4.58 (t, 2H, $J = 1.9$ Hz), 4.35 (t, 2H, $J = 1.9$ Hz), 4.18 (s, 5H); ^{13}C NMR ($CDCl_3$): δ 155.9 (C), 146.9 (CH), 139.1 (CH), 138.5 (CH), 136.7 (C), 118.1 (CH), 115.8 (CH), 107.6 (CH), 83.4 (C), 70.1 (CH), 70.0 (CH), 67.3 (CH); IR (neat): 3178, 3142, 3048, 2951, 1561, 1535, 1435, 1301, 1141, 1088, 867, 805, 769 cm^{-1}; MS (EI): 329 (M^+), 302, 300, 271, 264, 237, 210, 184, 156, 149, 120, 89, 67; HRMS (EI): calcd. for $C_{18}H_{15}FeN_3$: 329.0615. Found: 329.0613.

4.3.9. (3-Ferrocenylpyrazol-1-yl)(4-hydroxyphenyl)-methanone (**4G**)

^{1}H NMR ($CDCl_3$): δ 8.33 (s, 1H), 8.21 (d, 2H, $J = 7.95$ Hz), 6.89 (d, 2H, $J = 7.95$ Hz), 6.51 (s, 1H), 5.87 (s, OH), 4.81 (s, 2H), 4.40 (s, 2H), 4.14 (s, 5H); ^{13}C NMR ($CDCl_3$): δ 165.1 (C), 160.3 (C), 156.6 (C), 134.5 (CH), 131.5 (CH), 123.6 (C), 115.3 (CH), 107.9 (CH), 78.2 (C), 71.2 (CH), 71.1 (CH), 68.6 (CH); IR (neat): 3353, 3149, 1699, 1606, 1558, 1417, 1384, 1357, 1311, 1271, 1231, 1190, 1057, 895, 821, 756 cm^{-1}; MS (EI): 372 (M^+), 370, 307, 252, 224, 187, 158, 141, 121, 93, 84; HRMS (EI): calcd. for $C_{20}H_{16}FeN_2O_2$: 372.0561. Found: 372.0563.

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