4-Ferrocenylpyridine- and 4-Ferrocenyl-3-ferrocenylmethyl-3,4-dihydropyridine-3,5-dicarbonitriles: Multi-Component Synthesis, Structures and Electrochemistry

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Abstract: The reactions of 2-cyano-3-ferrocenylacrylonitrile (1) with malononitrile (2) in a MeOH/H2O or 2-PrOH/H2O medium in the presence of Na2CO3 afforded 6-alkoxy-2-amino-4-ferrocenylpyridine-3,5-dicarbonitriles 3a,b (multi-component condensation) and 6-alkoxy-2-amino-4-ferrocenyl-3-ferrocenylmethyl-3,4-dihydropyridine-3,5-dicarbonitriles 4a,b (multi-component cyclodimerization). Analogous reactions of 1 with 2 in an MeOH/H2O medium in the presence of NaOH, piperidine, or morpholine gave compounds 3a, 4a and 2-amino-4-ferrocenyl-6-hydroxy-, 6-piperidino- and 6-morpholinopyridine-3,5-dicarbonitriles 3c–e, respectively. The structures of the compounds 3b, 4a and 4b were established by the spectroscopic data and X-ray diffraction analysis. The electrochemical behaviour of compounds 3b, 3d and 4b was investigated by means of cyclic voltammetry.

Keywords: ferrocene; 2-cyano-3-ferrocenylacrylonitrile; malononitrile; X-ray diffraction; amino(ferrocenyl)pyridine-3,5-dicarbonitriles; cyclic voltammetry
1. Introduction

Pyridine derivatives have been studied for over a century as an important class of heterocyclic compounds and they still continue to attract considerable attention due to the wide range of medicinal properties they possess, such as vasodilators, anticoagulants, hypolipidemic, tuberculostatic, antihistamine, antihypertensive, cardiovascular and gastrointestinal activities [1,2]. Pyridine systems are also found in important vitamins (PP, B6), alkaloids and herbicides [1].

The incorporation of one or two iron-containing ferrocene substituents into a pyridine molecule will enlarge the spectrum of valuable characteristics. In addition, ferrocene compounds are known to exhibit chemotherapeutic properties [3]. Ferrocenyl-substituted pyridines have been extensively studied as ligands, in the synthesis of non-linear optical materials, etc. [4–6]. However, their biological activities have not hitherto been studied. Various methods to prepare ferroceno-containing pyridines have been reported [7–10]. Syntheses of ferrocenylpyridines are mainly carried out via Negishi cross-coupling reactions of FcZnCl with bromopyridines [7], the condensations of 1,3-diketones with ferrocenecarboxaldehyde in the presence of AcONH4 [8]; the interactions of ferrocenyl-1,2-enones with 3-aminocrotononitrile [9], ethyl 3-aminocrotonate [9] or acetonitrile in the presence of Me3COK [10]. The interest in heterocyclic compounds bearing ferrocenyl substituents in the molecules can be traced back to the discovery of ferrocene [11–14]. This is determined by a peculiar chemical behavior of such compounds due to mutual influence of the metallocene and heterocyclic moieties. In particular, biological activities of many nitrogen heterocycles, such as quinuclidines, pyrazolines, pyrazoles, pyrimidines, tetrahydropyridazines, bearing ferrocenyl substituents, have been reported [8,15–20]. It may be expected that ferrocenylpyridines and cyano(ferrocenyl)pyridines will also prove valuable, because they possess diverse biological activity, find use as potential bio-receptor ligands [13–15], new drugs [16–20], and significant intermediates for the synthesis of important materials [21–23]. For these reasons, development of new compounds containing cyano and ferrocenyl groups in the pyridines is strongly desired.

Herein we report results from our investigations into reactions of the condensation of 2-cyano-3-ferrocenylacrylonitrile (1) with malononitrile (2) and of the tandem-transformations of 1 in alcohols/aqueous medium in the presence of bases and nucleophiles. The electrochemical behavior of the 6-alkoxy-2-amino-4-ferrocenylpyridine-3,5-dicarbonitriles and 6-alkoxy-2-amino-4-ferrocenyl-3-ferrocenylmethyl-3,4-dihydropyridine-3,5-dicarbonitriles was studied.

2. Results and Discussion

2.1. Synthesis of 6-Alkoxy-2-amino-4-ferrocenylpyridine-3,5-dicarbonitriles and 6-alkoxy-2-amino-4-ferrocenyl-3-ferrocenylmethyl-3,4-dihydropyridine-3,5-dicarbonitriles

We found that two competitive processes occur upon reaction of 2-cyano-3-ferrocenylacrylonitrile (1) with malononitrile (2) in MeOH/H2O or 2-PrOH/H2O medium in the presence of Na2CO3, viz, formation of 6-alkoxy-2-amino-4-ferrocenylpyridine-3,5-dicarbonitriles 3a,b (multi-component condensation) and of cyclodimeric products 4a,b (multi-component cyclodimerization). In addition, other minor reaction products of the starting compounds were also isolated, however their structures
could not be established from their $^1$H and $^{13}$C-NMR spectroscopy and mass spectrometry data (Scheme 1).

**Scheme 1.** Reaction of 2-cyano-3-ferrocenylacrylonitrile (1) with malononitrile (2) in the presence of Na$_2$CO$_3$.

\[
\begin{align*}
\text{CC} & \text{CN} \\
\text{Fc} & \text{H} \\
\text{CN} & \\
\end{align*}
\]

\[
\begin{align*}
\text{CN} & \text{CN} \\
\text{CH}_2 & \text{CN} \\
\text{1} & \text{2} \\
\end{align*}
\]

\[
\begin{align*}
\text{ROH, H}_2\text{O} & \text{Na}_2\text{CO}_3 \\
\end{align*}
\]

\[
\begin{align*}
\text{NC} & \text{CN} \\
\text{Fc} & \text{NH}_2 \\
\text{RO} & \\
\text{3a,b} & \\
\end{align*}
\]

\[
\begin{align*}
\text{NC} & \text{CN} \\
\text{Fc} & \text{NH}_2 \\
\text{RO} & \\
\text{4a,b} & \\
\end{align*}
\]

\[
\begin{align*}
\text{Other} & \text{products} \\
\end{align*}
\]

\[
\begin{align*}
\text{R=} & \text{Me (a); R=} \text{2-Pr (b)} \\
\text{Fc=} & \text{C}_5\text{H}_5\text{FeC}_5\text{H}_4 \\
\end{align*}
\]

The compounds 3a,b and 4a,b were isolated by column chromatography on alumina and their structures were characterized by IR and NMR spectroscopy, mass spectrometry, and elemental analysis (see Experimental section). According to the $^1$H- and $^{13}$C-NMR data, the cyclodimerization of 1 occurs with high diastereoselectivity, and compounds 4a and 4b were isolated as a single diastereomeric form. One cannot rule out the formation of minor diastereomeric products; however they could not be isolated and characterized.

The molecular structures of compounds 3b, 4a, and 4b were determined by X-ray diffraction analysis of their single crystals. The general views of molecules 3b, 4a, and 4b are shown in Figures 1–3, respectively, while the principal geometric parameters are listed in Table 1.

**Figure 1.** Crystal structure of 3b.
X-Ray diffraction analysis confirmed the aromatic ferrocenylpyridine structure for compound 3b, and diferoacenyl(dihydro)pyridine structures for compounds 4a and 4b. Central fragment of the molecule 3b is a flat six-membered ring with one nitrogen atom. The N(1)-C(14) bond length in the compound 3b is somewhat shorter [\(d = 1.318(2) \text{ Å}\)] compared to the standard length (cf. \(d = 1.338 \text{ Å}\) [24]). The bond lengths of the C–Fe and C–C bonds in the ferrocenyl substituents as well as the geometric parameters of the ferrocene sandwiches are close to standard values [25].
Table 1. Selected bond lengths and bond angles for compounds 3b, 4a and 4b.

| Selected bond lengths (Å) | Selected bond angles (°) |
|---------------------------|--------------------------|
| 3b                        |                          |
| N(1)-C(13)                | 1.346(2)                 | C(15)-C(11)-C(12) | 116.21(15) |
| N(1)-C(14)                | 1.318(2)                 | N(1)-C(13)-C(12) | 122.50(16) |
| N(4)-C(13)                | 1.337(2)                 | N(1)-C(14)-O(1)  | 120.55(15) |
| N(3)-C(16)                | 1.1150(2)                | N(1)-C(14)-C(15) | 124.42(16) |
| C(12)-C(13)               | 1.422(2)                 | C(11)-C(15)-C(14) | 119.28(16) |
| C(11)-C(12)               | 1.406(2)                 | C(13)-N(1)-C(14) | 117.46(15) |
| O(1)-C(14)                | 1.338(2)                 | N(4)-C(13)-N(1)  | 116.87(16) |
| C(11)-C(15)               | 1.404(2)                 | C(14)-O(1)-C(18) | 119.91(14) |
| C(15)-C(14)               | 1.417(2)                 | C(17)-C(12)-C(13) | 116.37(15) |
| O(1)-C(18)                | 1.466(2)                 | C(12)-C(11)-C(6) | 120.99(15) |
| 4a                        |                          |
| N(1)-C(23)                | 1.319(3)                 | N(1)-C(23)-C(22) | 120.62(18) |
| C(24)-N(1)                | 1.381(3)                 | N(1)-C(24)-C(25) | 124.48(19) |
| C(22)-C(23)               | 1.530(3)                 | N(1)-C(24)-O(1)  | 116.55(18) |
| C(21)-C(22)               | 1.568(3)                 | C(23)-C(22)-C(21) | 106.96(16) |
| C(21)-C(25)               | 1.512(3)                 | C(22)-C(21)-C(25) | 106.41(16) |
| C(25)-C(24)               | 1.352(3)                 | C(21)-C(25)-C(24) | 118.82(18) |
| C(22)-C(27)               | 1.566(3)                 | N(1)-C(23)-N(2)  | 120.29(19) |
| C(23)-N(2)                | 1.312(3)                 | N(2)-C(23)-C(22) | 118.99(18) |
| C(24)-O(1)                | 1.345(2)                 | C(27)-C(22)-C(26) | 107.67(17) |
| 4b                        |                          |
| N(1)-C(25)                | 1.378(4)                 | C(24)-C(23)-C(22) | 105.9(3) |
| N(1)-C(26)                | 1.291(4)                 | N(4)-C(28)-C(24) | 177.4(4) |
| N(2)-C(26)                | 1.334(5)                 | N(2)-C(26)-C(22) | 118.3(3) |
| N(3)-C(27)                | 1.137(5)                 | N(3)-C(27)-C(22) | 178.0(4) |
| N(4)-C(28)                | 1.147(4)                 | C(26)-C(22)-C(23) | 103.3(3) |
| C(22)-C(21)               | 1.595(5)                 | C(24)-C(25)-N(1) | 124.1(3) |
| C(22)-C(26)               | 1.532(5)                 | N(2)-C(26)-N(1)  | 119.3(3) |
| C(23)-C(22)               | 1.569(4)                 | C(21)-C(22)-C(23) | 111.6(3) |
| C(24)-C(25)               | 1.359(5)                 | C(26)-N(1)-C(25) | 117.0(3) |
| C(23)-H(23)               | 0.9800                   | C(22)-C(26)-N(1) | 122.4(3) |
| C(25)-O(1)                | 1.345(4)                 | O(1)-C(25)-N(1)  | 116.8(3) |
| C(29)-O(1)                | 1.443(5)                 | C(27)-C(22)-C(23) | 109.9(3) |
| C(24)-C(23)               | 1.510(5)                 | C(26)-C(22)-C(23) | 106.3(3) |

Key elements of the molecules 4a and 4b are the central six-membered ring with one nitrogen atom in the half-chair conformation. The N(1)-C(23) (for 4a) and N(1)-C(26) (for 4b) bond lengths are equal to $d = 1.319(3)$ Å, and $d = 1.291(4)$ Å, respectively. The ferrocenyl and ferrocenylmethyl substituents at C-4 and C-5 of 4a and 4b are trans oriented relative to the 6-membered cycle.

We found further that 2-cyano-3-ferrocenylacrylonitrile (1) reacted analogously with malononitrile (2) in MeOH/H$_2$O medium in the presence of NaOH, piperidine or morpholine to give compounds 3a-c–e and 4a (Schemes 2 and 3). Cyclodimeric products 4c,d,e with hydroxy-, piperidino- or morpholino-substituents
were not detected (Schemes 2 and 3). As in the case of reaction of 1 with 2 in the presence Na₂CO₃, the polymerization products of the starting compounds were also present in minor quantities.

**Scheme 2.** Reaction of 2-cyano-3-ferrocenylacrylonitrile (1) with malononitrile (2) in the presence of NaOH.

![Scheme 2](image)

**Scheme 3.** Reaction of 2-cyano-3-ferrocenyl-acrylonitrile (1) with malononitrile (2) in the presence of piperidine or morpholine.

![Scheme 3](image)

Both reaction mixtures were separated by column chromatography on alumina, and the structures of the isolated products were characterized by IR, ¹H and ¹³C-NMR spectroscopy, mass spectrometry, and elemental analysis. These physicochemical characterizations of compounds 3c–e corroborate completely their structures.

The formation of 2-amino-4-ferrocenylpyridine-3,5-dicarbonitriles 3a–e in the presence of bases and nucleophiles proceeds, in our opinion, via multi-component condensation reaction [26] (Scheme 4). Possibly the intermediate 5 is generated in one step and then transformed into pyridines 3a–e.

**Scheme 4.** Possible mechanism for the formation of compounds 3a–e.
A tentative mechanism for the formation of the diferrocenyl(dihydro)pyridine-3,5-dicarbonitriles 4a,b is represented in Scheme 5.

**Scheme 5.** Possible mechanism for the formation of compounds 4a,b.

To verify the mechanism described in Scheme 5 above, the cyclodimerization of 2-cyano-3-ferrocenylacrylonitrile (1) was carried out under identical conditions in 2-propanol in the presence of water and Na2CO3. The product of the cyclodimerization, 2-amino-4-ferrocenyl-3-ferrocenylmethyl-6-isopropoxy-3,4-dihydropyridine-3,5-dicarbonitrile (4b), was obtained with ~27% yield. Thus, cyclodimerization of compound 1 represents a novel type of the three-component anomalous reaction of [4+2]-cycloadition, absolutely different from the Diels-Alder reaction.

### 2.2. Electrochemistry

Figure 4 shows a typical voltammogram of compound 3b recorded from open circuit potential to positive direction using a platinum electrode. It was observed one oxidation signal Ia with anodic peak potential value $E_{pa}(Ia) = 0.247$ V/Fc-Fc$^+$ and, one reduction signal Ic, with cathodic peak potential value $E_{pc}(Ic) = 0.184$ V/Fc-Fc$^+$. The $\Delta E_p = 0.063$ was independent of scan rate (from 0.1 to 1 V·s$^{-1}$). The cathodic peak current and the anodic peak current were proportional to $v^{1/2}$, indicating that I is a diffusion-controlled process [27]. The evidence presented above suggests that process I can be attributed to the reversible electron transfer for the ferrocene moiety Fc-Fc$^+$. The formal potential electrode value was $E_0' = 0.215$ V/Fc-Fc$^+$, estimated as $E_0' = 1/2(E_{pa} + E_{pc})$. The electrochemical behaviour of compound 3d is very similar to that observed for 3b. There are slight changes in peak potential values: $E_{pa}(Ia) = 0.241$ V/Fc-Fc$^+$, $E_{pc}(Ic) = 0.174$ V/Fc-Fc$^+$, $\Delta E_p = 0.067$ V and $E_0' = 0.207$ V/Fc-Fc$^+$.

Figure 5 shows a cyclic voltammogram of compound 4b. When the scan was started from open circuit potential to positive direction two oxidation signals (Ia) and (IIa) were observed. The anodic peak potentials values for these signals are $E_{pa}(Ia) = 0.198$ V/Fc-Fc$^+$ and $E_{pa}(IIa) = 1.149$ V/Fc-Fc$^+$. When the cycle was complete only one reduction signal Ic (related to the oxidation process Ia) was observed. The estimated cathodic peak potential value was $E_{pc}(Ic) = 0.099$ V/Fc-Fc$^+$. Despite the use of different scan rates (0.1 V·s$^{-1}$–1.0 V·s$^{-1}$) in the voltammetric experiments, the product of the
electrochemical reduction in the process IIa was not detected. This result points out the absence of electronic communication between the two proximal ferrocenyl centres, which is contrary to the observations reported recently [28], where the communication between ferrocenyl fragments was detected in 3,5-diferrocenylpyridine. The electrochemical process I is attributed to the ferrocene moiety at the para position to the nitrogen atom of the heterocycle, Fc_{para}^-/Fc_{para}^+. The estimated formal potential electrode value was E_0' = 0.1485 V/Fc-Fc^+.

**Figure 4.** Cyclic voltammogram of compound 3b in the presence of 0.1 M TBABF₄ in MeCN. Scan rate 0.1 V·s⁻¹. The working electrode used was platinum.

**Figure 5.** Cyclic voltammogram of compound 4b in the presence of 0.1 M TBABF₄ in MeCN. The scan rate 0.10 V·s⁻¹. The working electrode used was platinum.

The second oxidation process (IIa) is related to the ferrocene moiety at the meta position to the nitrogen atom of the heterocycle (Fc_{meta}/Fc_{meta}^+) with high positive electronic density due to its proximity to the CN group. The absence of the reduction signal in the process II could be attributed to
a low stabilization of the electro-generated dication (Fe$_{\text{para}}^+$-Fe$_{\text{meta}}^+$) by the solvent [29,30]. This fact was confirmed when the experiment was performed in a coordinative solvent such as DMSO, where electrochemical response becomes more irreversible.

3. Experimental

3.1. General

All the solvents were dried according to the standard procedures and were freshly distilled before use [31]. Column chromatography was carried out on alumina (Brockmann activity III). The $^1$H and $^{13}$C-NMR spectra were recorded on a Unity Inova Varian spectrometer (300 and 75 MHz, Palo Alto, CA, USA) for solutions in CDCl$_3$, with Me$_4$Si as the internal standard. The IR spectra were measured on a Spectrophotometer FT-IR (Spectrum RXI Perkin Elmer instruments, Waltham, MA, USA) using KBr pellets. The mass spectra were obtained on a Varian MAT CH-6 instrument (EI MS, 70 eV). Elementar Analysensysteme LECO CHNS-900 (St. Joseph, MI, USA) was used for elemental analysis.

The electrochemical behavior of compounds 3b, 3d and 4b was explored with a Biologic SP-50 (Grenoble, France) potentiostat/galvanostat. The current interrupt method was used for $iR$ compensation during all the experiments. The sample concentration employed was ca. 1 mM in acetonitrile in the presence of 0.1 M tetra-$N$-butylammonium tetrafluoroborate (TBABF$_4$). A platinum disk and a platinum wire were used as working electrode and counter-electrode, respectively. A silver wire was used as a pseudo reference electrode. All solutions were bubbled with nitrogen 5 minutes prior each measurement. Cyclic voltammetry experiments were initiated from open circuit potential ($E_{\text{ocp}}$) to positive direction, using scan rates from 0.1 to 1.0 V·s$^{-1}$. All potentials were reported versus the couple Fc/Fc$^+$ according to IUPAC convention [32]. The following reagents were purchased from Aldrich (Toluca, Mexico): ferrocenecarboxaldehyde, 99%; malononitrile, 99%; methyl alcohol, 99.9%; 2-propanol, 99.9%; morpholine, 99+%; piperidine, 99%. 2-Cyano-3-ferrocenylacrylonitrile (1) was prepared by condensation of ferrocenecarbaldehyde with malononitrile in benzene in the presence of piperidinium acetate [33]. The physical and $^1$H-NMR spectroscopic characteristics of compound 1 were in accordance with the literature data [34].

Reactions of 2-cyano-3-ferrocenylacrylonitrile (1) with malononitrile (2) in the presence of Na$_2$CO$_3$. A mixture of compound 1 (1.13 g, 5.0 mmol), malononitrile 2 (0.4 g, 6.0 mmol), methanol or 2-propanol (100 mL), H$_2$O (10 mL) and Na$_2$CO$_3$ (0.5 g, 5.0 mmol) was stirred and refluxed for 8 h. The solvents were removed in vacuo and the residue was dissolved in dichloromethane (50 mL). The solution was mixed with Al$_2$O$_3$ (activity III, 20 g) and the solvent was evaporated in air. This sorbent was applied onto a column with Al$_2$O$_3$ (the height of alumina is ca. 20 cm) and the reaction products were eluted from the column first with petroleum ether, then with a 2:1 hexane–dichloromethane to give compounds 3a,b, 4a,b and polymeric compounds.

2-Amino-4-ferrocenyl-6-methoxypyridine-3,5-dicarbonitrile (3a). Red crystals, yield 0.93 g (52%), m.p. 162–163 °C; IR (KBr): 425, 497, 509, 575, 812, 843, 911, 1004, 1044, 1107, 1185, 1223, 1259, 1295, 1321, 1340, 1386, 1424, 1468, 1482, 1541, 1557, 1613, 2212, 2216, 2231, 2982, 3101, 3226, 3372, 3462 cm$^{-1}$; $^1$H-NMR: 4.00 (s, 3H, CH$_3$), 4.28 (s, 5H, C$_2$H$_5$), 4.59 (m, 2H, C$_2$H$_4$), 5.21 (m, 2H,
C₃H₄), 5.57 (bs, 2H, NH₂); ¹³C-NMR: 55.43 (CH₃), 71.00 (C₃H₃), 70.49, 71.17 (C₃H₄), 84.91 (CipsoFc), 116.27, 117.60 (2CN), 160.17, 160.43, 160.52, 164.88, 167.50 (5C); MS: m/z 358 [M⁺]. Anal. Calcd. for C₁₉H₁₈FeN₄O: C 60.36, H 3.94, Fe 15.60, N 15.63. Found: C 60.45, H 4.04, Fe 15.46, N 15.49.

2-Amino-4-ferrocenyl-6-isopropoxypyridine-3,5-dicarbonitrile (3b). Red crystals, yield 0.9 g (48%), m.p. 176–177 °C; IR (KBr): 425, 502, 541, 584, 813, 845, 912, 1003, 1044, 1106, 1185, 1253, 1296, 1322, 1334, 1365, 1383, 1425, 1477, 1483, 1542, 1556, 1612, 2200, 2217, 2325, 2979, 3103, 3224, 3369, 3459 cm⁻¹; ¹H-NMR: 1.39 (d, 6H, 2CH₃, J = 6.3 Hz), 4.28 (s, 5H, C₃H₅), 4.57 (m, 2H, C₃H₄), 5.20 (m, 2H, C₃H₅), 5.32 (m, 1H, CH, J = 6.3 Hz), 5.53 (bs, 2H, NH₂); ¹³C-NMR: 21.95 (2CH₃), 71.16 (CH), 71.01 (C₃H₃), 70.51, 71.07 (C₃H₄), 82.05 (CipsoFc), 116.32, 117.77 (2CN), 160.14, 160.21, 161.56, 165.38, 166.86 (5C); MS: m/z 386 [M⁺]. Anal. Calcd. for C₂₀H₁₈FeN₄O: C 62.60, H 4.70, Fe 14.46, N 14.50. Found: C 62.31, H 4.63, Fe 14.58, N 14.67.

2-Amino-4-ferrocenyl-3-ferrocenylmethyl-6-methoxy-3,4-dihydropyridine-3,5-dicarbonitrile (4a). Yellow crystals, yield 0.25 g (18%), m.p. dec. ca. 272 °C; IR (KBr): 484, 559, 691, 799, 811, 1002, 1029, 1041, 1103, 1190, 1235, 1282, 1321, 1371, 1387, 1452, 1472, 1534, 1550, 1597, 1641, 1663, 2217, 2225, 3090, 3321, 3429 cm⁻¹; ¹H-NMR: 2.91 (d, 1H, CH₂, J = 14.1 Hz), 3.10 (d, 1H, CH₂, J = 14.1 Hz), 3.47 (s, 1H, CH), 3.91 (s, 3H, CH₃), 4.18 (s, 5H, C₃H₅), 4.27 (s, 5H, C₃H₅), 3.87 (m, 1H, C₃H₄), 4.08 (m, 1H, C₃H₄), 4.12 (m, 1H, C₃H₄), 4.17 (m, 1H, C₃H₄), 4.22 (m, 2H, C₃H₄), 4.23 (m, 1H, C₃H₄), 4.41 (m, 1H, C₃H₄), 5.59 (bs, 2H, NH₂); ¹³C-NMR: 42.19 (CH₂), 55.13 (CH₃), 63.61 (CH), 69.23, 69.79 (C₃H₅), 67.84, 68.36, 68.75, 68.99, 69.12, 69.56, 69.97, 70.44 (2C₃H₅), 80.21, 82.45 (CipsoFc), 119.21, 120.50 (2CN), 64.45, 160.62, 164.86, 167.72 (4C); MS: m/z 558 [M⁺]. Anal. Calcd. for C₂₀H₂₀FeN₄O: C 62.40, H 4.70, Fe 20.01, N 10.03. Found: C 62.29, H 4.61, Fe 19.89, N 10.12.

2-Amino-4-ferrocenyl-3-ferrocenylmethyl-6-isopropoxy-3,4-dihydropyridine-3,5-dicarbonitrile (4b). Yellow crystals, yield 0.29 g (19%), m.p. dec. ca. 302 °C; IR (KBr): 483, 553, 682, 721, 783, 821, 915, 1001, 1026, 1042, 1106, 1142, 1181, 1249, 1294, 1316, 1355, 1371, 1383, 1423, 1475, 1544, 1585, 1629, 2191, 2300, 2930, 2978, 3095, 3241, 3335, 3466 cm⁻¹; ¹H-NMR: 1.39 (d, 6H, 2CH₃, J = 6.0 Hz), 2.90 (d, 1H, CH₂, J = 13.8 Hz), 3.09 (d, 1H, CH₂, J = 13.8 Hz), 3.81 (s, 1H, CH), 4.13 (s, 5H, C₃H₅), 4.28 (s, 5H, C₃H₅), 4.08 (m, 1H, C₃H₄), 4.16 (m, 2H, C₃H₄), 4.23 (m, 2H, C₃H₄), 4.28 (m, 2H, C₃H₄), 4.42 (m, 1H, C₃H₄), 5.07 (m, 1H, CH, J = 6.0 Hz), 5.54 (bs, 2H, NH₂); ¹³C-NMR: 21.94 (2CH₃), 36.96 (CH₂), 41.40, 66.26 (2CH₃), 69.04, 69.56 (2CH₃), 68.20, 68.54, 68.90, 68.94, 69.09, 69.84, 70.38, 71.52 (2C₃H₅), 79.25, 83.68 (CipsoFc), 119.16, 120.49 (2CN), 51.28, 160.43, 165.37, 166.82 (4C); MS: m/z 586 [M⁺]. Anal. Calcd. for C₂₁H₂₀FeN₄O: C 63.51, H 5.16, Fe 19.05, N 9.55. Found C 63.67, H 5.03, Fe 19.13, N 9.41.

Reaction of 2-cyano-3-ferrocenylacrylonitrile (1) with malononitrile (2) in the presence of NaOH. The reaction of compound 1 (1.13 g, 5.0 mmol) with malononitrile 2 (0.4 g, 6.0 mmol) and 0.4 g NaOH in methanol (100 mL) and H₂O (10 mL) was carried out under conditions described above; subsequent chromatography afforded 3a (15%), 3c and 4a (12%).

2-Amino-4-ferrocenyl-6-hydroxy pyridine-3,5-dicarbonitrile (3c). Red crystals, yield 0.98 g (57%), m.p. 146–147 °C; IR (KBr): 423, 495, 508, 580, 814, 839, 910, 1004, 1042, 1103, 1181, 1242, 1290,
Reactions of 2-cyano-3-ferrocenylacrylonitrile (1) with malononitrile (2) in the presence of amines. A solution of compounds 1 (5.0 mmol) and 2 (6.0 mmol), piperidine or morpholine (2.0 mL) in methanol (100 mL) was stirred for 6 h at 60 °C. The reaction mixture was evaporated in vacuo, and the residue was subjected to TLC on SiO₂ (hexane–dichloromethane, 2:1) to give compounds 3a (~20%, Rf = 0.78), 4a (~9%, Rf = 0.67) and 3d, e (58–61%, Rf = 0.35–0.54).

2-Amino-4-ferrocenyl-6-piperidinopyridine-3,5-dicarbonitrile (3d). Red crystals, yield 1.25 g (61%), m.p. 182–183 °C; IR (KBr): 416, 481, 503, 585, 814, 912, 1001, 1019, 1100, 1177, 1251, 1289, 1311, 1343, 1392, 1425, 1464, 1472, 1546, 1553, 1612, 2217, 2226, 2334, 2973, 3101, 3239, 3388, 3469 cm⁻¹; ¹H-NMR: 1.70 (m, 2H, CH₂), 1.83 (m, 4H, 2 CH₂), 3.18 (m, 4H, 2CH₂), 4.32 (s, 5H, C₅H₅), 4.56 (m, 2H, C₅H₄), 5.05 (m, 2H, C₅H₄), 5.34 (bs, 2H, NH₂); ¹³C-NMR: 24.55 (CH₂), 26.05 (2CH₂), 49.83 (2CH₂), 70.86 (C₅H₅), 70.66, 70.90 (C₅H₄), 83.00 (CipsoFc), 118.52, 119.29 (2CN), 160.51 (2C), 155.51, 160.74, 163.32 (3C); MS: m/z 411 [M⁺]. Anal. Calcd. for C₂₂H₂₁FeN₅: C 64.25, H 5.15, Fe 13.58, N 17.02. Found: C 64.33, H 5.07, Fe 13.61, N 16.89.

2-Amino-4-ferrocenyl-6-morpholinopyridine-3,5-dicarbonitrile (3e). Red crystals, yield 1.20 g (58%), m.p. 190–192 °C; IR (KBr): 432, 491, 512, 591, 815, 861, 908, 1002, 1041, 1101, 1120, 1215, 1251, 1299, 1312, 1340, 1396, 1442, 1470, 1510, 1567, 1621, 1692, 2212, 2227, 2989, 3138, 3278, 3363, 3476 cm⁻¹; ¹H-NMR: 3.26 (m, 4H, 2CH₂), 3.80 (m, 4H, 2CH₂), 4.37 (s, 5H, C₅H₅), 4.68 (m, 2H, C₅H₄), 5.01 (m, 2H, C₅H₄), 5.65 (bs, 2H, NH₂); ¹³C-NMR: 50.98 (2CH₂), 70.99 (C₅H₅), 67.17, 70.66 (C₅H₄), 80.35 (CipsoFc), 116.03, 118.31 (2CN), 157.68 (2C), 155.25, 161.21, 168.65 (3C); MS: m/z 413 [M⁺]. Anal. Calcd. for C₂₁H₁₉FeN₅O: C 61.04, H 5.15, Fe 13.58, N 16.89. Found: C 60.94, H 4.48, Fe 13.44, N 17.08.

Chemical transformations of 2-cyano-3-ferrocenylacrylonitrile (1) in the presence of 2-PrOH, H₂O and Na₂CO₃. A mixture of compound 1 (1.13 g, 5.0 mmol), 2-propanol (60 mL), H₂O (10 mL) and Na₂CO₃ (1.0 g, 10mmol) was stirred for 12 h at 80 °C. The reaction mixture was worked up as described above, subsequent chromatography on Al₂O₃ gave compounds 3b (25%) and 4b (27%), respectively, and polimeric compounds.

3.2. Crystal Structures of 3b, 4a and 4b

Single crystals of 3b and 4b were obtained by crystallization from chloroform, while crystals of 4a were obtained by crystallization from methanol. The unit cell parameters and the X-ray diffraction intensities were recorded on a Gemini (detector Atlas CCD, Cryojet N₂, Loveland, CO, USA) diffractometer. The structures of compounds 3b, 4a and 4b were solved by the direct method (SHELXS-97 [35]) and refined using full-matrix least-squares on F².
Crystal data for C$_{20}$H$_{18}$FeN$_4$O (3b): M = 386.23 g·mol$^{-1}$, orthorhombic P bca, a = 12.4557(8), b = 14.9714(6), c = 18.4217(7) Å, α = 90, β = 90, γ = 90°, V = 3435.3(3) Å$^3$, T = 130(2) K, Z = 8, ρ = 1.494 Mg·m$^{-3}$, wavelength 1.71073 Å, F(000) = 1,600, absorption coefficient 0.895 mm$^{-1}$, index ranges −15 ≤ h ≤ 15, −18 ≤ k ≤ 17, −23 ≤ l ≤ 23, scan range 3.54 ≤ θ ≤ 26.73°, 3633 independent reflections, R$_{int}$ = 0.0326, 26385 total reflections, 243 refinable parameters, final R indices [I > 2σ(I)] R$_1$ = 0.0301, wR$_2$ = 0.0705, R indices (all data) R$_1$ = 0.0398, wR$_2$ = 0.0775, goodness-of-fit on F$^2$ 1.074, largest difference peak and hole 0.555/−0.310 eÅ$^{-3}$.

Crystal data for C$_{29}$H$_{26}$Fe$_2$N$_4$O·CH$_3$OH (4a): M = 590.28 g·mol$^{-1}$, monoclinic P2$_1$/n, a = 13.1816(4), b = 10.0587(2), c = 20.4566(6) Å, α = 90, β = 107.323(3), γ = 90°, V = 2589.31(12) Å$^3$, T = 130(2) K, Z = 4, ρ = 1.514 Mg·m$^{-3}$, wavelength 1.71073 Å, F(000) = 1,224, absorption coefficient 1.157 mm$^{-1}$, index ranges −13 ≤ h ≤ 16, −12 ≤ k ≤ 12, −25 ≤ l ≤ 25, scan range 3.62 ≤ θ ≤ 26.05°, 5113 independent reflections, R$_{int}$ = 0.0387, 18671 total reflections, 354 refinable parameters, final R indices [I > 2σ(I)] R$_1$ = 0.0323, wR$_2$ = 0.0720, R indices (all data) R$_1$ = 0.0441, wR$_2$ = 0.0781, goodness-of-fit on F$^2$ 1.034, largest difference peak and hole 0.419/−0.337 eÅ$^{-3}$.

Crystal data for C$_{31}$H$_{30}$Fe$_2$N$_4$O (4b): M = 586.29 g·mol$^{-1}$, triclinic P-1, a = 10.5168(8), b = 11.7533(9), c = 12.4547(10) Å, α = 90.551(6), β = 111.455(7), γ = 107.402(7)°, V = 1354.90(18) Å$^3$, T = 293(2) K, Z = 2, ρ = 1.437 Mg·m$^{-3}$, wavelength 1.71073 Å, F(000) = 608, absorption coefficient 1.102 mm$^{-1}$, index ranges −12 ≤ h ≤ 11, −14 ≤ k ≤ 14, −11 ≤ l ≤ 15, scan range 3.55 ≤ θ ≤ 26.06°, 5346 independent reflections, R$_{int}$ = 0.0500, 9894 total reflections, 344 refinable parameters, final R indices [I > 2σ(I)] R$_1$ = 0.0558, wR$_2$ = 0.1336, R indices (all data) R$_1$ = 0.0785, wR$_2$ = 0.1551, goodness-of-fit on F$^2$ 1.050, largest difference peak and hole 0.877/−0.748 eÅ$^{-3}$.

CCDC-878738 (for 3b), CCDC–878739 (for 4a) and CCDC–878741 (for 4b) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/const/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge DB2 1EZ, UK; Fax: (internat.) +44-1223-336-033; E-Mail: deposit@ccdc.cam.ac.uk].

4. Conclusions

The reaction of 2-cyano-3-ferrocenylacrylonitrile (1) with malononitrile (2) in a MeOH/H$_2$O or 2-PrOH/H$_2$O medium in the presence of Na$_2$CO$_3$, NaOH, piperidine or morpholine affords products of multi-component condensation: 6-alkoxy-2-amino-, 2-amino-6-hydroxy-, 2,6-diamino-4-ferrocenylpyridine-3,5-dicarbonitriles 3a–e, respectively, as well as products of multi-component cyclodimerization: 6-alkoxy-2-amino-4-ferrocenyl-3-ferrocenylmethyl-3,4-dihydropyridine-3,5-dicarbonitriles 4a,b. This method can be widely used in the synthesis of various pyridine derivatives with ferrocenyl substituents. The reactions described in this study should be of interest to synthetic, theoretical and practical organic chemists seeking ways to prepare functionalized ferrocenylpyridines. The electrochemical behavior of compounds 3b, 3d and 4b was investigated by means of cyclic voltammetry. For 3b and 3d two electrochemical processes (Ia,Ic), attributed to the oxidation and reduction of the ferrocene moieties were found. On the other hand, for compound 4b a double electron transfer for both ferrocene groups (Ia,IIa) and the electrochemical monogeneration of the dication species (Ic) were detected.
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Conflict of Interest

The authors declare no conflict of interest.

References

1. Eicher, T.; Hauptmann, S. The Chemistry of Heterocycles, Structures, Reactions, Synthesis and Applications; Wiley-VCH GmbH & Co. KGaA: Weinheim, Germany, 2006; pp. 269–316.
2. Abdel-Latif, N.A.; Sabry, N.M.; Mohamed, A.M.; Abdulla, M.M. Synthesis, analgesic, and antiparkinsonian profiles of some pyridine, pyrazoline, and thiopyrimidine derivatives. Monatsh. Chem. 2007, 138, 715–724.
3. Kopf-Maier, P.; Kopf, H. Non-platinum-group metal antitumor agents: History, current status, and perspectives. Chem. Rev. 1987, 87, 1137–1152.
4. Miller, T.M.; Ahmed, K.J.; Wrighton, M.S. Complexes of rhenium carbonyl containing ferrocenyl-derived ligands: Tunable electron density at rhenium by control of the redox state of the ferrocenyl ligand. Inorg. Chem. 1989, 28, 2347–2355.
5. Rajput, J.; Hutton, A.T.; Moss, J.R.; Su, H.; Imrie, C. Ferrocenyl-nitrogen donor ligands. Synthesis and characterization of Rhodium(I) complexes of ferrocenylpyridine and related ligands. J. Organomet. Chem. 2006, 691, 4573–4588.
6. Beletskaya, I.P.; Tsvetkov, A.V.; Latyshev, G.V.; Tafeenko, V.A.; Lukashev, N.V. Bis(ferrocenyl)mercury as a source of ferrocenyl moiety in Pd-catalyzed reactions of carbon-carbon bond formation. J. Organomet. Chem. 2001, 637–639, 653–663.
7. Mamane, V. Metal-catalyzed cross-coupling reactions for ferrocene functionalization: Recent applications in synthesis, material science and asymmetric catalysis. Mini-Rev. Org. Chem. 2008, 5, 303–312.
8. Schvekhgeimer, M.-G.A. Hetaryferrocenes. Russ. Chem. Rev. 1996, 65, 66–69.
9. Shibata, K.; Katsuyama, I.; Izoe, H.; Matsui, M.; Muramatsu, H. Synthesis of 4,6-disubstituted 2-methylpyridines and their 3-carboxamides. J. Heterocycl. Chem. 1993, 30, 277–281.
10. Shibata, K.; Katsuyama, I.; Matsui, M.; Muramatsu, H. Synthesis of ferrocenyl-substituted 3-cyano-2-methylpyridines. Bull. Chem. Soc. Jpn. 1990, 63, 3710–3712.
11. Zhou, W.-J.; Ji, S.-J.; Shen, Z.-L. An efficient synthesis of ferrocenyl substituted 3-cyanopyridine derivatives under ultrasound irradiation. J. Organomet. Chem. 2006, 691, 1356–1360.
12. Zhuang, Q.; Jia, R.; Tu, S.; Zhang, J.; Jiang, B.; Zhang, Y.; Yao, C. Green chemistry approach to the synthesis of 2-amino-4-aryl-6-ferrocenylpyridine derivatives by a one-pot reaction in aqueous medium. J. Heterocycl. Chem. 2007, 44, 895–900.
13. Zhu, H.; Lin, H.; Guo, H.; Yu, L. Microwave absorbing property of Fe-filled nanotubes synthesized by a practical route. Mat. Sci. Eng. B 2007, 138, 101–104.
14. Biot, C.; Chavain, N.; Dubar, F.; Pradines, B.; Trivelli, X.; Brocard, J.; Forfar, I.; Dive, D. Structure-activity relationships of 4-N-substituted ferroquine analogues: Time to re-evaluate the mechanism of action of ferroquine. *J. Organomet. Chem.* **2009**, *694*, 845–854.

15. Yao, T.; Rechnitz, G.A. Amperometric enzyme-immunosensor based on ferrocene-mediated amplification. *Biosensors* **1987**, *3*, 307–312.

16. Epton, R.; Marr, G.; Regers, G.K. The ferrocene analogues of salicylic acid and aspirin. *J. Organomet. Chem.* **1976**, *110*, C42–C44.

17. Biot, C.; Delhaes, L.; N’Diaye, C.M.; Maciejewski, L.A.; Camus, D.; Dive, D. Synthesis and antimalarial activity *in vitro* of potential metabolites of ferrochloroquine and related compounds. *Bioorg. Med. Chem.* **1999**, *7*, 2843–2847.

18. Hartinger, C.G.; Dyson, P.J. Bioorganometallic chemistry—From teaching paradigms to medicinal applications. *Chem. Soc. Rev.* **2009**, *38*, 391–401.

19. Gasser, G.; Ott, I.; Metzler-Nolte, N. Organometallic anticancer compounds. *J. Med. Chem.* **2011**, *54*, 3–25.

20. Chavain, N.; Vezin, V.; Dive, D.; Touati, N.; Paul, J.-F.; Buisine, E.; Biot, C. Investigation of the redox behavior of ferroquine, a new antimalarial. *Mol. Pharm.* **2008**, *5*, 510–516.

21. Kaifer, A.E.; de Mendoza, J. *Comprehensive Supramolecular Chemistry*; Elsevier: Oxford, UK, 1996; Volume 1, pp. 701–725.

22. Kowalski, K.; Winter, R.F. The synthesis and electrochemistry of 2,5-dimethylazaferrocenes with heteroaryl bridges. *J. Organomet. Chem.* **2012**, *700*, 58–68.

23. Kowalski, K.; Koeceva-Chyla, A.; Pieniazek, K.; Bernasinska, J.; Skiba, J.; Rybarczyk-Pirek, A.J.; Józwiak, Z. The synthesis, structure, electrochemistry and *in vitro* anticancer activity studies of ferrocenyl-thymine conjugates. *J. Organomet. Chem.* **2009**, *694*, 1041–1048.

24. Allen, F.H.; Kennard, O.; Watson, D.G.; Brammer, L.; Guy Orpen, A.; Taylor, R. Tables of bond lengths determined by X-ray and neutron diffraction. Part 1. Bond lengths in organic compounds. *J. Chem. Soc. Perkin Trans. II* **1987**, S1–S19.

25. Postnov, V.N.; Klimova, E.I.; Pushin, A.N.; Meleshonkova, N.N. The interaction of the 1,3-bis(p-methoxyphenyl)allylic cation with ferrocenyl-1,3-butadienes. *Metalloorg. Chem.* **1992**, *5*, 564–569.

26. Tietze, L.F.; Brasche, G.; Gerike, K.M. *Domino Reactions in Organic Synthesis*; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, 2006.

27. Bard, A.J.; Faulkner, L.R. *Electrochemical Methods, Fundamentals and Applications*, 2nd ed.; John Wiley and Sons: New York, NY, USA, 2001; Chapter 5.

28. Wright, J.R.; Shaffer, K.J.; McAdam, C.J.; Crowley, J.D. 3,5-Diferrocenylpyridine: Synthesis, characterisation, palladium(II) dichloride complex and electrochemistry. *Polyhedron* **2012**, *36*, 73–78.

29. Bard, A.J.; Faulkner, L.R. *Electrochemical Methods, Fundamentals and Applications*; John Wiley and Sons: New York, NY, USA, 1980.

30. Zanello, P. *Inorganic Electrochemistry, Theory, Practice and Application*; The Royal Society of Chemistry: Cambridge, UK, 2003.

31. Robin, M.B.; Day, P. Mixed valence chemistry. A survey and classification. *Adv. Inorg. Chem. Radiochem.* **1967**, *10*, 247–422.
32. Gritzner, G.; Küta, J. Recommendations on reporting electrode potentials in nonaqueous solvents. *Pure Appl. Chem.* **1984**, *4*, 461–466.

33. Postnov, V.N.; Polivin, Y.N.; Sazonova, V.A. Fragmentation of β-dicarbonyl-compounds with ferrocenyI group. *Dokl. Akad. Nauk SSSR* **1983**, *271*, 1402–1404.

34. Toma, S.; Putala, M.; Salisava, M. Ultrasound-accelerated synthesis of ferrocene-containing pyrimidine derivatives. *Collect. Czech. Chem. Commun.* **1987**, *52*, 395–398.

35. Sheldrick, G.M. *SHELXS-97, Program for the Refinement of Crystal Structures*; University of Göttingen: Göttingen, Germany, 1994.

*Sample Availability*: Samples of the compounds 3a,b,d and 4a,b are available from the authors.

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