ACETYLATION AND FORMYLATION OF 3-FERROCENYLPYRROLES

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Acetylations of 3-ferrocenyl-1-methylpyrrole as well as 3-cyano-4-ferrocenylpyrrole and 3-cyano-4-ferrocenyl-1-methylpyrrole were performed. The course of the acylation is highly dependent on the acylation agent, that is acetyl chloride/aluminum chloride (method *A*), trifluoroacetic anhydride–acetic acid mixture (method *B*) or acetic anhydride/$Sc(OTf)_3$ (method *C*). Method *A* gives the acetylation on ferrocene moiety, method *B* affords the trifluoroacetylation on pyrrole moiety and method *C* affords pyrrole moiety acetylation. Vielsmeier–Haack formylation gives the products of substitution on pyrrole moiety.

Key words: Metallocenes; Ferrocenes; Pyrroles; Electrophilic aromatic substitution; Acylation; Formylation.

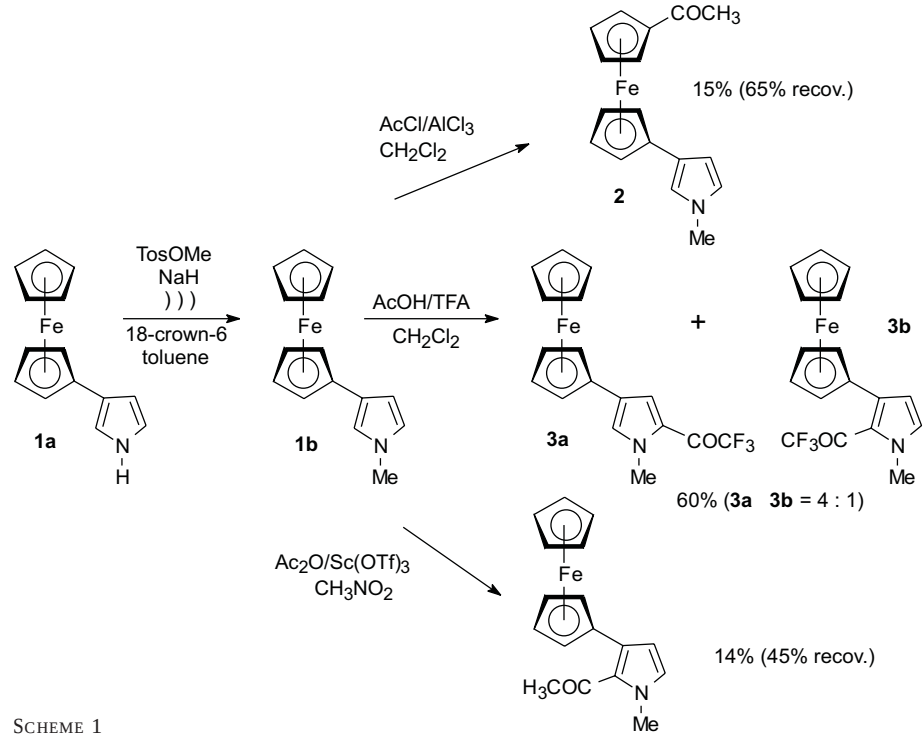
In our previous papers we studied the acetylation of substances having both ferrocenyl and 1-methylpyrrol-2-yl moieties in the molecule. Such acetylation was performed on chalcones having the structure Fc–CH=CH–CO–Ar or Fc–CO–CH=CH–Ar (Ar = 1-methylpyrrol-2-yl) and it was found[1] that acetylation took place both on the double bond and the pyrrole moiety. Recently we have studied the acetylation of 2-ferrocenyl-1-methylpyrrole[2] and found that reaction took place on the ferrocene moiety, but yield of the acetylation product was rather low.

The main goal of this work was to study the Friedel–Crafts acetylation as well as Vielsmeier–Haack formylation of 3-ferrocenylpyrrole and 3-cyano-4-ferrocenylpyrrole and to investigate whether the course of the reaction differs from that in acetylation of 2-ferrocenylpyrrole.

3-Ferrocenylpyrrole (**1a**) prepared according to ref.[3] proved to be unstable under the conditions of Friedel–Crafts acetylation and was therefore converted to its *N*-methyl derivative *via* the sonochemical methylation of its sodium salt with methyl tosylate. Methylation was highly improved when 1 mole % of 18-crown-6 was added to the reaction mixture. Acetylation of

3-ferrocenyl-1-methylpyrrole (**1b**) with acetyl chloride mediated by aluminum chloride afforded 3-(1′-acetylferrocen-1-yl)-1-methylpyrrole (**2**) in low yield. These results can be explained by pre-formation of the complex of the aluminum chloride with the pyrrole moiety which is then inaccessible to the attack of an electrophile. Similar deactivation of the pyrrole ring by $SnCl_4$ was described[4,5]. The next experiment was an acylation of **1b** with the mixed anhydride of acetic and trifluoroacetic acids[3], prepared from trifluoroacetic anhydride and acetic acid. In this case no blocking of the pyrrole moiety was possible.

Good yields of the mixture of products **3a** and **3b** (Scheme 1) were isolated. The structure of the products was determined by ^1H and ^{19}F NMR

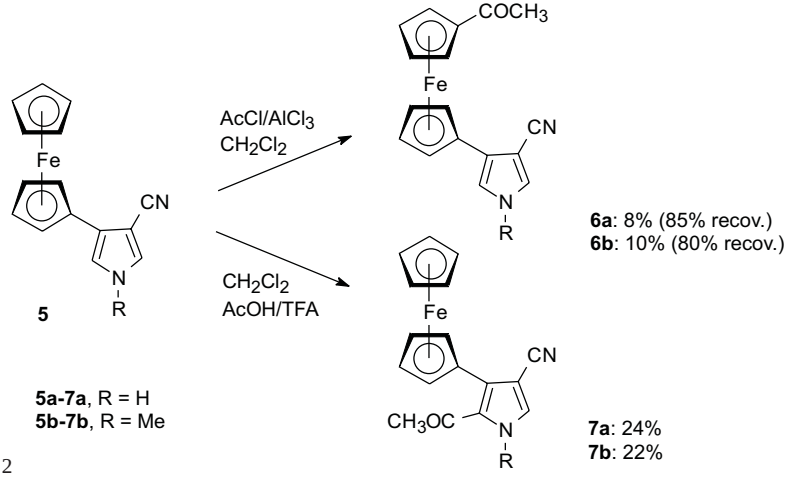


SCHEME 1

spectra. In the ^1H NMR spectrum of the **3a** a pseudoquintet splitting of the resonance at 7.19 ppm (H-4) was found. The additional splitting was the result of coupling to the CF_3 group. As from this multiplet, it was not possible

to determine coupling constant ^5J(HF) correctly, the ^{19}F NMR spectra were measured. A doublet with ^5J(HF) = 2.4 Hz at δ 4.24 relative to CF_3COOD was observed for **3a**, while for isomeric **3b**, a singlet at δ 4.22. It is of interest to note that the reaction took place on the pyrrole moiety only and only the products of trifluoroacetylation were detected. This is an indirect proof that **1b** is rather reactive compound and the acylation proceeded *via* an early transition state. The product of pyrrole acetylation (**4**) was isolated when acetylation was performed with acetic anhydride using $Sc(OTf)_3$ as the catalyst[6]. This proves that no complexation of the pyrrole ring took place.

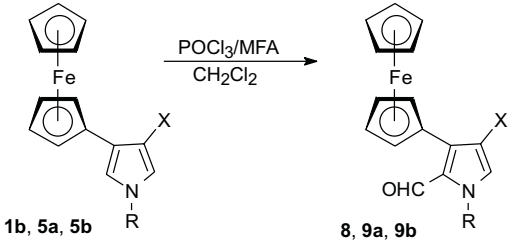
3-Cyano-4-ferrocenylpyrrole (**5a**) is stable enough to withstand the Friedel–Crafts acetylation. Just a very low yield of the ferrocene moiety acetylation product **6a** was isolated (Scheme 2) which can be explained similarly as described above. Very similar results were achieved when the



SCHEME 2

reaction was performed on its *N*-methyl derivative **5b**. Our next attempt was the acylation of **5a** and **5b** with the mixed acetic acid–trifluoroacetic acid anhydride. As can be seen from Scheme 2, the yields of the acetylation products **7a** and **7b** were rather low again. This can be rationalized by the deactivation effect of the cyano group. Interestingly, only the product of acetylation, but no product of trifluoroacetylation was detected. This suggests that acylations of **5a** and **5b** with the mixed anhydride must go *via* a late transition state.

Our next aim was to find out whether the Vielsmeier–Haack formylations of the ferrocenylpyrroles will follow the same course as their acylations. Reactions were performed at room temperature in dichloromethane and even in such case some polymerization was observed and low or moderate yields of the products **8**, **9a** and **9b** were isolated. It is interesting that only the formylation of the pyrrole moiety was observed (Scheme 3). The substitution in position 2 of the pyrrole can be explained by the stabilization of the cationic intermediate by the adjacent ferrocenyl group. Nuclear Overhauser difference spectroscopy was used for the correct determination of the position of the formyl group on the pyrrole ring. Irradiation of the methyl protons of **8** gives positive NOE for H-5 and CHO protons, while irradiation of the H-5 gives positive NOE for H-4 and N-CH_3 protons. This NOE experiment proved also the correct assignment of the chemical shifts for protons H-4 and H-5.



	R	X	product	(yield)
1b	Me	H	**8**	(67%)
5a	H	CN	**9a**	(27%)
5b	Me	CN	**9b**	(23%)

SCHEME 3

The structure of some synthesized compounds (**1b**, **5b**, **7a**, **7b**, **8**, **9a** and **9b**) was confirmed by ^{13}C NMR spectra. HMQC spectra of some compounds (**5b**, **7a and 8**) inverse detected ^{1}H-^{13}C chemical shifts correlation spectra uniquely confirmed assigment of the ^{13}C chemical shifts. The starting 3-ferrocenylpyrrole derivatives have the chemical shifts of the C_β at lower field than the C_α. In the case of derivatives substituted in the position 2 of pyrrole ring, the order of the chemical shifts for the C_α and C_β is changed.

EXPERIMENTAL

All NMR experiments were carried out on a Varian GEMINI 2000 spectrometer operating at 300 MHz frequency for ^{1}H NMR spectra, 282 MHz for ^{19}F NMR spectra and 75 MHz for ^{13}C NMR spectra at 301 K. ^{1}H and ^{13}C NMR spectra (δ, ppm; J in Hz) were obtained for $CDCl_3$ solutions using tetramethylsilane as internal standard. ^{1}H NMR spectra were measured under the following conditions: spectral width 4 500 Hz, over 32 k data points, 1 s de-

lay. NOE difference spectra were measured with the 4 s delay. ^{13}C NMR spectra were acquired with broad band decoupling. HMQC method using a BIRD pulse sequence was used for ^{1}H-^{13}C correlation spectra. ^{19}F NMR spectra were measured under the following conditions: spectral width 800 Hz, 16 k data points, 4 s delay, without lock. Chemical shifts (δ, ppm) were standardized relative to CF_3COOD in $CDCl_3$. Melting points were measured on a Kofler hot plate apparatus and are uncorrected. Solvents were purified and dried according to the published methods. 3-Ferrocenylpyrrole and 3-cyano-4-ferrocenylpyrrole were prepared according to the known methods[3,7].

General Procedure for *N*-Methylation of 3-Ferrocenylpyrroles

The corresponding 3-ferrocenylpyrrole (10 mmol) was dissolved in toluene (80 ml). Sodium hydride (1 200 mg, 50 mmol) was then added and the reaction mixture was sonicated in an ultrasonic cleaning bath (Tesson 1, TESLA Vrable, 35 kHz) for 5 min. Methyl tosylate (4 650 mg, 25 mmol) and 18-crown-6 (26 mg, 0.1 mmol) were then added and the mixture was sonicated for 1 h under Ar. Water was added and the organic material was extracted into diethyl ether. The etherical solution was dried over sodium sulfate, filtered and the solvent was evaporated. The residue was chromatographed on a silica gel (200 g) column using 2-methylpentane–ethyl acetate (8 : 1) mixture as the eluent.

3-Ferrocenyl-1-methylpyrrole (**1b**), 92% yield, yellow crystals, m.p. 83–85 °C. For $C_{15}H_{15}FeN$ (265.1) calculated: 67.95% C, 5.70% H, 5.28% N; found: 67.84% C, 5.67% H, 5.18% N. ^{1}H NMR: 3.63 s, 3 H (CH_3); 4.04 s, 5 H (Cp); 4.14 t, 2 H (H_β); 4.39 t, 2 H (H_α); 6.22 dd, J(2,4) = 1.9, J(4,5) = 2.5, 1 H (H-4); 6.52 dd, J(2,5) = 2.2, 1 H (H-2); 6.62 dd, 1 H (H-5). ^{13}C NMR: 36.42 (NCH_3), 66.16 (C_α), 67.50 (C_β), 69.51 (Cp), 82.71 (C_i), 107.54 (C-4), 118.39 (C-5), 121.75 (C-3), 122.12 (C-2).

3-Cyano-4-ferrocenyl-1-methylpyrrole (**5b**), 96% yield, yellow crystals, m.p. 162–164 °C. For $C_{16}H_{14}FeN_2$ (290.1) calculated: 66.23% C, 4.86% H, 9.66% N; found: 66.16% C, 4.86% H, 9.54% N. ^{1}H NMR: 3.65 s, 3 H (CH_3); 4.14 s, 5 H (Cp); 4.25 t, 2 H (H_β); 4.64 t, 2 H (H_α); 6.58 d, J(2,5) = 2.3, 1 H (H-2); 7.03 d, 1 H (H-5). ^{13}C NMR: 37.06 (NCH_3), 66.31 (C_α), 68.42 (C_β), 69.85 (Cp), 78.21 (C_i), 91.44 (CN), 117.37 (C-4), 119.26 (C-5), 125.72 (C-3), 129.75 (C-2).

Without 18-crown-6 reaction yields were lower, products were isolated in 45 and 68% yields, respectively, after 5 h sonication.

Friedel–Crafts Acylation of 3-Ferrocenylpyrroles with Acetyl Chloride/Aluminum Chloride (Method *A*)

A 3-ferrocenylpyrrole (1.2 mmol) was dissolved in dry dichloromethane (5 ml) and the mixture was cooled down to 0 °C. Acetyl chloride (110 mg, 1.4 mmol) was added to the vigorously stirred mixture followed by portionwise addition of aluminum chloride (187 mg, 1.4 mmol) during 30 min. The reaction mixture was stirred at 0 °C for another 15 min and then 4 h at room temperature under N_2. The reaction mixture was then poured onto crushed ice, and the organic material was extracted into dichloromethane. Dichloromethane solution was washed with 10% water solution of potassium hydrogencarbonate, water and dried over sodium sulfate. The solution was filtered, the solvent evaporated and the residue chromatographed on a silica gel (50 g) column using 2-methylpentane–ethyl acetate (4 : 1) mixture as the eluent.

Acetylation of 3-ferrocenyl-1-methylpyrrole (**1b**) afforded 65% of the starting material and 15% of *3-(1′-acetylferrocen-1-yl)-1-methylpyrrole* (**2**), orange crystals, m.p. 79–81 °C. For

$C_{17}H_{17}FeNO$ (307.2) calculated: 66.47% C, 5.58% H, 4.56% N; found: 66.34% C, 5.53% H, 4.49% N. ^{1}H NMR: 2.15 s, 3 H ($COCH_3$); 3.64 s, 3 H (CH_3); 4.19 s, 2 H (H_β); 4.38 s, 2 H ($H_{\beta'}$); 4.42 s, 2 H (H_α); 4.62 s, 2 H ($H_{\alpha'}$); 6.20 dd, *J*(2,4) = 1.9, *J*(4,5) = 2.5, 1 H (H-4); 6.54 dd, *J*(2,5) = 2.5, 1 H (H-2); 6.65 dd, 1 H (H-5). If the reaction was carried out with 2.2 equivalents of $AlCl_3$, the product was obtained in 22% yield.

Acetylation of 3-cyano-4-ferrocenylpyrrole (**5a**) afforded 85% of the starting material and 8% of *3-(1′-acetylferrocen-1-yl)-4-cyanopyrrole* (**6a**), red crystals, m.p. 110–112 °C. For $C_{17}H_{14}FeN_2O$ (318.2) calculated: 64.15% C, 4.43% H, 8.81% N; found: 64.13% C, 4.39% H, 8.77% N. ^{1}H NMR: 2.21 s, 3 H ($COCH_3$); 4.30 t, 2 H (H_β); 4.53 t, 2 H ($H_{\beta'}$); 4.73 m, 4 H ($H_{\alpha+\alpha'}$); 6.82 dd, *J*(1,2) = 2.4, *J*(2,5) = 2.2, 1 H (H-2); 7.30 dd, *J*(1,5) = 3.0, 1 H (H-5); 9.52 bs, 1 H (NH).

Acetylation of 3-cyano-4-ferrocenyl-1-methylpyrrole (**5b**) afforded 80% of the starting material and 10% of *3-(1′-acetylferrocen-1-yl)-4-cyano-1-methylpyrrole* (**6b**), red crystals, m.p. 122–123 °C. For $C_{18}H_{16}FeN_2O$ (333.2) calculated: 64.89% C, 5.14% H, 8.41% N; found: 64.78% C, 5.11% H, 8.32% N. ^{1}H NMR: 2.21 s, 3 H ($COCH_3$); 3.67 s, 3 H (CH_3); 4.28 t, 2 H (H_β); 4.48 t, 2 H ($H_{\beta'}$); 4.69 m, 4 H ($H_{\alpha+\alpha'}$); 6.61 d, *J*(2,5) = 2.2, 1 H (H-2); 7.07 d, 1 H (H-5).

Acylation of 3-Ferrocenylpyrroles with Trifluoroacetic Acid Anhydride/Acetic Acid Mixture (Method *B*)

A 3-ferrocenylpyrrole (1 mmol) was dissolved in the mixture of acetic acid (1 ml) and dry dichloromethane (2 ml). Trifluoroacetic acid anhydride (252 mg, 1.2 mmol) was added and the reaction mixture was stirred at room temperature under N_2 for 4 h. Water (50 ml) was then added, and the aqueous solution was alkalized by addition of 25% water solution of potassium hydrogencarbonate. The organic material was extracted into dichloromethane and the organic solution was washed with water. The residue left after evaporation of the solvent was chromatographed on a silica gel (50 g) column using 2-methylpentane–ethyl acetate (9 : 1) mixture as the eluent.

Acylation of 3-ferrocenyl-1-methylpyrrole (**1b**) afforded 60% of the mixture of *3-ferrocenyl-1-methyl-5-(trifluoroacetyl)pyrrole* (**3a**) and *3-ferrocenyl-1-methyl-2-(trifluoroacetyl)-pyrrole* (**3b**) in the ratio 4 : 1 according to the ^{1}H NMR spectrum. Crystallization from mixture 2-methylpentane–diethyl ether afforded red crystals of **3a**, m.p. 145–147 °C and orange crystals of **3b**, m.p. 127–129 °C. These were mechanically separated and pure products were isolated. For $C_{17}H_{14}F_3FeNO$ (361.1) calculated: 56.54% C, 3.91% H, 3.88% N; found: for **3a**: 56.48% C, 3.89% H, 3.72% N; for **3b**: 56.45% C, 3.87% H, 3.76% N. ^{1}H NMR of **3a**: 3.99 s, 3 H (CH_3); 4.06 s, 5 H (Cp); 4.24 t, 2 H (H_β); 4.45 t, 2H (H_α); 7.08 d, *J*(2,4) = 2.4, 1 H (H-2); 7.19 m, 1 H (H-4). ^{1}H NMR of **3b**: 3.81 s, 3 H (CH_3); 4.12 s, 5 H (Cp); 4.25 t, 2 H (H_β); 4.45 t, 2 H (H_α); 6.51 d, *J*(4,5) = 2.5, 1 H (H-4); 6.91 d, 1 H (H-5). ^{19}F NMR of **3a**: 4.24 d, ^5J(HF) = 2.4, CF_3. ^{19}F NMR of **3b**: 4.22 s, CF_3.

Acetylation of **5a** afforded 24% of *2-acetyl-4-cyano-3-ferrocenylpyrrole* (**7a**), orange crystals, m.p. 85–87 °C. For $C_{17}H_{14}FeN_2O$ (318.2) calculated: 64.18% C, 4.44% H, 8.80% N; found: 64.13% C, 4.39% H, 8.77% N. ^{1}H NMR: 2.32 s, 3 H ($COCH_3$); 4.29 s, 5 H (Cp); 4.42 t, 2 H (H_β); 4.68 t, 2 H (H_α); 7.45 d, *J*(1,5) = 3.2, 1 H (H-5); 9.65 bs, 1 H (NH). ^{13}C NMR: 28.48 (CH_3), 69.00 (C_β), 70.40 (C_α), 70.56 (Cp), 77.46 (C_i), 95.97 (CN), 116.25 (C-4), 130.13 (C-5), 130.68 (C-3), 131.47 (C-2), 189.75 (CO).

Acetylation of **5b** afforded 22% of *2-acetyl-4-cyano-3-ferrocenyl-1-methylpyrrole* (**7b**), orange crystals, m.p. 173–175 °C. For $C_{18}H_{16}FeN_2O$ (332.2) calculated: 65.08% C, 4.86% H, 8.43% N;

found: 65.04% C, 4.83% H, 8.36% N. ^{1}H NMR: 2.20 s, 3 H ($COCH_3$); 3.76 s, 3 H (CH_3); 4.24 s, 5 H (Cp); 4.37 t, 2 H (H_β); 4.56 t, 2 H (H_α); 7.19 s, 1 H (H-5). ^{13}C NMR: 30.87 (CH_3), 38.15 (NCH_3), 68.86 (C_β), 69.76 (C_α), 70.44 (Cp), 77.45 (C_i), 93.62 (CN), 116.31 (C-4), 130.90 (C-3), 131.78 (C-2), 133.99 (C-5), 193.12 (CO).

Acetylation of 3-Ferrocenyl-1-methylpyrrole with Acetic Anhydride/$Sc(OTf)_3$ (Method *C*)

3-Ferrocenyl-1-methylpyrrole (**1b**) (133 mg, 0.5 mmol) was dissolved in dry nitromethane (2 ml) and acetic anhydride (61 mg, 0.6 mmol) was added to the vigorously stirred mixture followed by addition of $Sc(OTf)_3$ (25 mg, 0.05 mmol). Reaction mixture was heated to 50–55 °C in a water bath under N_2 and stirred at this temperature for 1 h. Water (50 ml) was added and the organic material was extracted into dichloromethane (50 ml), and the organic layer was dried over sodium sulfate. The solution was filtered, the solvent was evaporated, and the residue was chromatographed on a silica gel (50 g) column using 2-methylpentane–ethyl acetate (9 : 1) mixture as the eluent. Besides the 45% of starting material, *2-acetyl-3-ferrocenyl-1-methylpyrrole* (**4**) was obtained in 14% yield as orange oil. For $C_{17}H_{17}FeNO$ (307.2) calculated: 66.47% C, 5.58% H, 4.56% N; found: 66.36% C, 5.48% H, 4.41% N. ^{1}H NMR: 2.06 s, 3 H ($COCH_3$); 3.84 s, 3 H (CH_3); 4.19 s, 5 H (Cp); 4.26 t, 2 H (H_β); 4.35 t, 2 H (H_α); 6.41 d, *J*(4,5) =2.5, 1 H (H-4); 6.72 d, 1 H (H-5).

Vielsmeier–Haack Formylation of 3-Ferrocenylpyrroles

A 3-ferrocenylpyrrole (2 mmol) was dissolved in dry dichloromethane (8 ml) and the solution was added to the vigorously stirred mixture of $POCl_3$ (312 mg, 2 mmol) and *N*-methylformanilide (MFA; 270 mg, 2 mmol) at 0 °C. The reaction mixture was stirred at this temperature for 1 h and at room temperature under N_2 for 20 h. Then a 20% aqueous sodium acetate (50 ml) was added and resulting mixture was stirred for 4 h. Organic material was extracted into dichloromethane, the organic solution was washed with water and dried over sodium sulfate. Solution was filtered, the solvent was evaporated and the residue was chromatographed on a silica gel (100 g) column using 2-methylpentane–ethyl acetate (9 : 1) mixture as the eluent.

Formylation of **1b** afforded *3-ferrocenyl-2-formyl-1-methylpyrrole* (**8**) in 67% yield, orange crystals, m.p. 153 °C (dec.). For $C_{16}H_{15}FeNO$ (292.8) calculated: 65.64% C, 5.16% H, 4.78% N; found: 65.60% C, 5.14% H, 4.71% N. ^{1}H NMR: 3.94 s, 3 H (CH_3); 4.11 s, 5 H (Cp); 4.31 t, 2 H (H_β); 4.48 t, 2 H (H_α); 6.29 d, *J*(4,5) = 2.5, 1 H (H-4); 6.77 d, 1 H (H-5); 10.00 s, 1 H (CHO). ^{13}C NMR: 37.67 (NCH_3), 69.00 (C_β), 69.45 (C_α), 69.97 (Cp), 79.02 (C_i), 110.10 (C-4), 128.12 (C-3), 131.28 (C-5), 137.20 (C-2), 180.03 (CHO).

Formylation of **5a** afforded *4-cyano-3-ferrocenyl-2-formylpyrrole* (**9a**) in 27% yield, orange crystals, m.p. 198 °C (dec.). For $C_{16}H_{12}FeN_2O$ (304.1) calculated: 63.19% C, 3.98% H, 9.21% N; found: 63.16% C, 3.92% H, 9.17% N. ^{1}H NMR: 4.25 s, 5 H (Cp); 4.49 t, 2 H (H_β); 4.80 t, 2 H (H_α); 7.52 d, *J*(1,5) = 2.1, 1 H (H-5); 9.88 s, 1 H (CHO); 10.10 bs, 1 H (NH). ^{13}C NMR: 69.10 (C_β), 70.28 (C_α), 70.52 (Cp), 77.43 (C_i), 95.97 (CN), 115.73 (C-4), 129.58 (C-3), 131.99 (C-5), 137.25 (C-2), 179.62 (CHO).

Formylation of **5b** afforded *4-cyano-3-ferrocenyl-2-formyl-1-methylpyrrole* (**9b**) in 23% yield, orange crystals, m.p. 163–165 °C. For $C_{17}H_{14}FeN_2O$ (318.2) calculated: 64.18% C, 4.44% H, 8.80% N; found: 64.16% C, 4.40% H, 8.73% N. ^{1}H NMR: 3.96 s, 3 H (CH_3); 4.24 s, 5 H (Cp); 4.44 t, 2 H (H_β); 4.71 t, 2 H (H_α); 7.25 s, 1 H (H-5); 9.99 s, 1 H (CHO). ^{13}C NMR: 38.59

(NCH_3), 69.53 (C_β), 69.86 (C_α), 70.50 (Cp), 77.47 (C_i), 93.65 (CN), 115.83 (C-4), 128.48 (C-3), 136.20 (C-5), 139.62 (C-2), 180.61 (CHO).

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