Synthesis of *N*-Substituted 3-Aryl-4-cyanopyrrole Derivatives

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3-Aryl-4-cyanopyrroles, where aryl is phenyl, 2,3-(difluoromethylenedioxy)phenyl, and ferrocenyl were prepared *via* TosMIC addition to the corresponding ethyl 3-aryl-2-cyanoacrylates. Their transformation to *N*-substituted pyrrole derivatives, the substituents being methoxycarbonyl, formamidomethyl, aminomethyl, and in one case isocyanomethyl, was also accomplished. Attempts at the preparation of *N*-formyl derivatives failed.

The pyrrole skeleton is frequently found in different natural products and other biologically active compounds. Many biologically active pyrrole derivatives as 3-chloro-4-(2-nitro-3-chlorophenyl)pyrrole (pyrrolenitrine) and 3-(2,3-dichlorophenyl)-4-nitropyrrole (neoisopyrrolenitrine) were prepared *via* TosMIC (*p*-tolylsulfonylmethylisocyanide) addition to the corresponding methyl 3-aryl-2-chloro-(2-nitro)acrylates [1]. The same method was applied in the synthesis of other 3-aryl-4-nitropyrroles as well as 3-aryl-4-ethoxycarbonylpyrroles and 3-aryl-4-benzoylpyrroles, when appropriate α,β-unsaturated carbonyl compounds were used as the starting material for their synthesis [2]. 3-Cyano-4-phenylpyrrole is known for many years [3, 4], but its *N*-substituted derivatives were not described. Preparation of fungicidal 3-aryl-4-cyanopyrroles was described [5, 6] and patented [7, 8]. Interesting helical polypyrroles were also prepared *via* TosMIC addition to approriate 3,4-disubstituted pyrroles [9]. Base-catalyzed TosMIC addition to the appropriate substituted alkenes was used also for preparation of 3-ferrocenyl-4-R-pyrroles, where R is one of the following groups: acetyl, cyano, benzoyl, and methoxycarbonyl [10].

To our surprise there are just few *N*-substituted pyrrole derivatives, with the exception of *N*-alkyl derivatives, described. Reaction of potassium salt of pyrroles with ethyl chloroformate afforded *N*-(ethoxycarbonyl)pyrroles [11, 12] and *N*-(methoxycarbonyl)pyrroles were formed when methyl chloroformate was used as reagent [13]. *N*-Formylpyrrole, as well as *N*-formyl-2,5-dimethylpyrrole were prepared by *Alessandri* [14, 15] *via* the reaction of the magnesium salt of the corresponding pyrroles with ethyl formate. *N*-(Hydroxymethyl)pyrrole and *N*-(dimethylaminomethyl)pyrrole were described, too [16, 17]. An interesting pyrrole derivative – *N*-hydroxy-3-cyano-4-[2,3-(difluoromethylenedioxy)-phenyl]pyrrole, a metabolite of CIBA fungicide CGA-173506 3-cyano-4-[2,3-(difluoromethylenedioxy)phenyl]pyrrole – was described very recently [18].

The main aim of this work was to prepare several 3-aryl-4-cyanopyrroles, and to examine the possibility to prepare their *N*-substituted derivatives.

Synthesis of 3-aryl-4-cyanopyrroles was performed by a base-catalyzed TosMIC addition to the corresponding ethyl 3-aryl-2-cyanoacrylates (Scheme 1).

The best results were obtained when a methanolic solution of sodium methoxide was used as a base and the reaction was performed in boiling toluene. The isolation of the products caused no problems and pure *Ia—Ic* were isolated in 50—80 % yields. For ferrocenyl derivative (*Ic*) m.p. = 111 °C according to [10], but we measured m.p. = 138—140 °C. The great difference may be due to polymorphism of this compound.

The formation of potassium salt of the pyrroles was a first reaction step at the synthesis of their *N*-substituted derivatives. The desirable salt was formed by heating of the appropriate 3-aryl-4-cyanopyrrole with metallic potassium in boiling toluene and was immediately used in reaction either with methyl chloroformate or *N*-(*p*-tolylsulfonylmethyl)formamide (Scheme 1). Yields of 13 to 32 % of both *N*-methoxycarbonyl (*IIa—IIc*) as well as *N*-formamidomethyl derivatives (*IIIa—IIIc*) were obtained, which points to some unidentified side reaction that was taking place.

The easy exchange of tosyl group in *N*-tosylmethylformamide for *N*-(3-cyano-4-aryl)pyrrole group is quite surprising as just the exchange of tosyl group for RS group was described [19].

The routine hydrolysis of *IIIa—IIIc* resulted in the formation of the chlorides of *N*-ammoniomethyl derivatives *IVa—IVc*, and the desired *N*-aminomethyl

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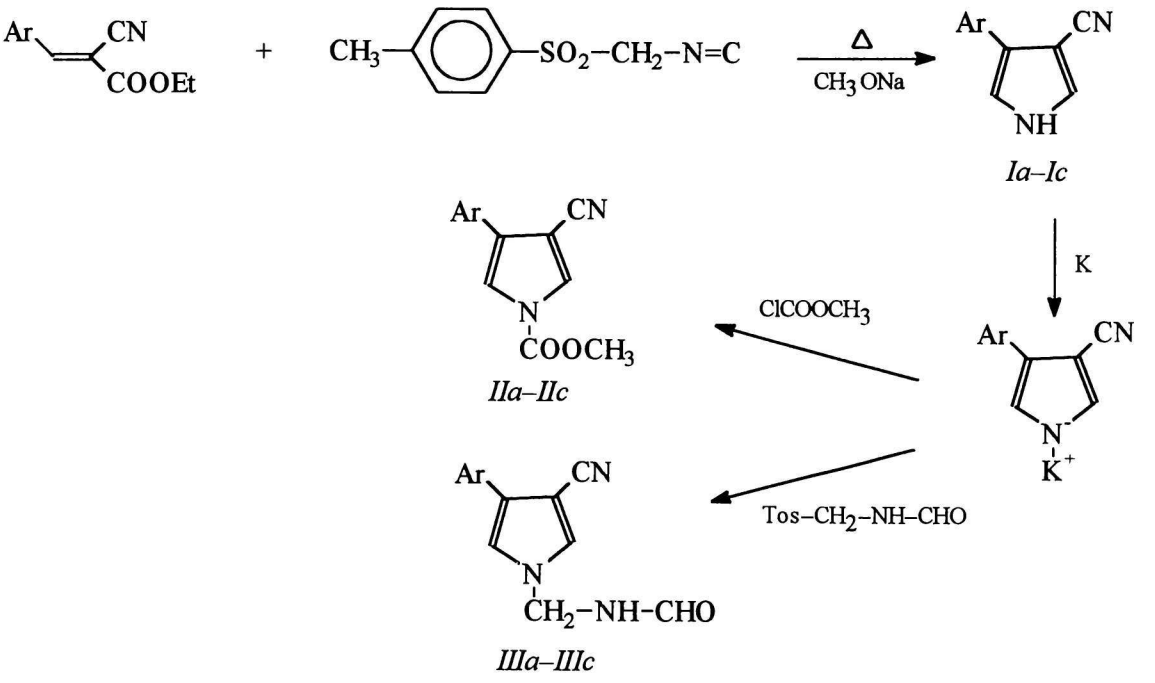
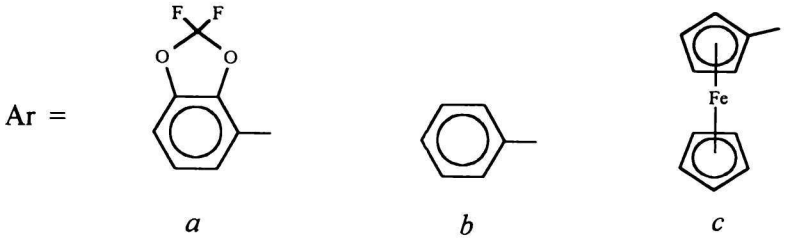
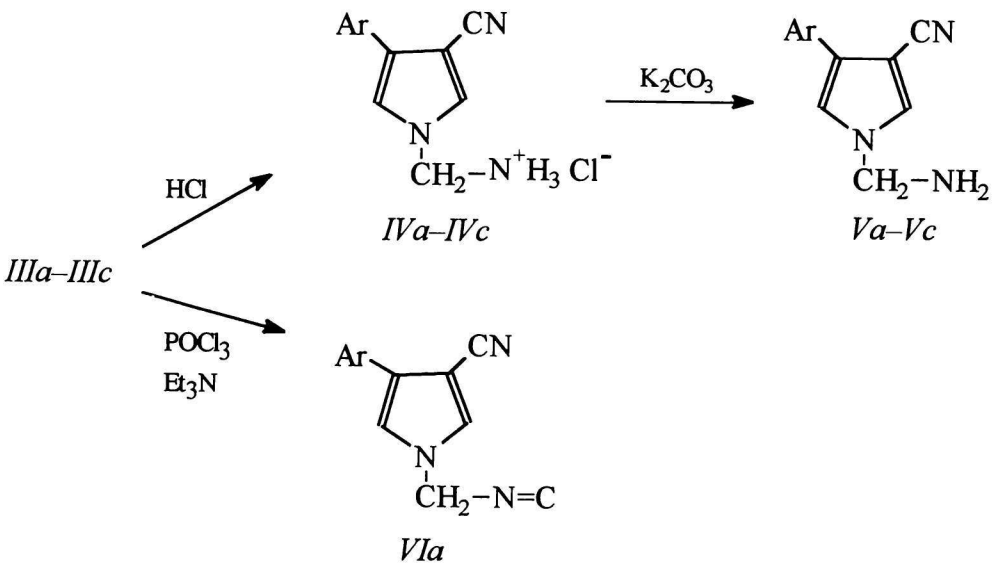




Scheme 1



Scheme 2

derivatives *Va*—*Vc* were isolated after the alkalization of the aqueous solution of *IVa*—*IVc* with potassium carbonate (Scheme 2).

The transformation of formamidomethyl group to isocyanomethyl was performed only in the case of the most stable *IIIa* (Scheme 2). Dehydration of *IIIa* leading to *IVa* opens a way to the rare *N*-methylisocyanides [20]. The attempts at the reactions of *VIa* in similar conditions as they are described for TosMIC failed, but only *Ia* was isolated when *VIa* came in contact with a base.

Similar negative results were achieved in our attempts to prepare the *N*-formyl derivatives of pyrroles *Ia*—*Ic via* the reaction of their potassium and magnesium salts with ethyl formate.

EXPERIMENTAL

^{1}H NMR spectra of the samples were recorded on a Tesla BS 487 (80 MHz) instrument with TMS as internal standard. Melting points were measured on a Kofler hot plate apparatus. Solvents were purified according to the published methods. Ethyl 3-aryl-2-cyanoacrylates were prepared analogously, as was described [10]. The compound *Ia* was prepared analogously as described [21].

3-Aryl-4-cyanopyrroles *I*

Appropriate ethyl 3-aryl-2-cyanoacrylate (1 mmol) and TosMIC (1 mmol) were dissolved in toluene (5 cm^3). The methanolic solution of sodium methoxide prepared from sodium (1.2 mmol) and methanol (1 cm^3) was dropwise added to the reaction mixture and the mixture was heated to the boiling point of toluene for 1—3 h. The reaction mixture was then poured into ice water and the product was extracted into diethyl ether. The solution was washed with water and dried (Na_2SO_4). The solvent was evaporated and the residue was purified on a SiO_2-column, using the 2-methylpentane—ethyl acetate (φ_r = 4:1) mixture as the eluent. The product was eluted as the second fraction.

4-Cyano-3-[2,3-(difluoromethylenedioxy)phenyl]-pyrrole (*Ia*), 82 % yield, white crystals, m.p. = 194—196 °C. For $C_{12}H_6F_2N_2O_2$ (M_r = 248.19) w_i(calc.): 58.07 % C, 2.44 % H, 11.29 % N; w_i(found): 57.93 % C, 2.39 % H, 11.22 % N. ^{1}H NMR spectrum (CD_3SOCD_3), δ: 7.17—7.76 (m, 5H, H_{arom}), 12.11 (bs, 1H, NH).

4-Cyano-3-phenylpyrrole (*Ib*), 52 % yield, white crystals, m.p. = 124—126 °C (Ref. [4] gives m.p. = 123—126 °C). For $C_{11}H_8N_2$ (M_r = 168.20) w_i(calc.): 78.55 % C, 4.79 % H, 16.66 % N; w_i(found): 78.00 % C, 4.71 % H, 16.52 % N. ^{1}H NMR spectrum ($CDCl_3$), δ: 6.96—7.71 (m, 7H, H_{arom}), 8.81 (bs, 1H, NH).

4-Cyano-3-ferrocenylpyrrole (*Ic*), 60 % yield, yellow crystals, m.p. = 138—140 °C (Ref. [10] gives m.p. = 111 °C). For $C_{15}H_{12}FeN_2$ (M_r = 276.12) w_i(calc.): 65.25 % C, 4.38 % H, 10.15 % N; w_i(found): 65.28 % C, 4.25 % H, 9.94 % N. ^{1}H NMR spectrum ($CDCl_3$), δ: 4.13 (s, 5H, Cp), 4.26 (t, 2H, H_β), 4.65 (t, 2H, H_α), 6.76 (d, 1H, H-2), 7.25 (d, 1H, H-5), 9.08 (bs, 1H, NH). IR spectrum (nujol), $\tilde{\nu}$/cm^{-1}: 496, 598, 639, 820, 1102, 1520, 2225, 3262.

N-(Methoxycarbonyl)-3-aryl-4-cyanopyrroles *II*

Potassium (4 mmol) was added to the solution of the appropriate pyrrole *Ia*—*Ic* (3 mmol) in toluene (80 cm^3), and the reaction mixture was heated till the evolution of hydrogen was ceased (1—3 h). Mixture was then cooled to 0—5 °C, and methyl chloroformate (4.5 mmol) was added to the stirred reaction mixture. The temperature of the reaction mixture rose to 40—50 °C and the mixture was stirred for 30 min. Water was added and the organic material was extracted into diethyl ether. The organic solution was washed with water and dried (Na_2SO_4). The residue left after the evaporation of the solvent was purified on a SiO_2-column, the 2-methylpentane—ethyl acetate (φ_r = 3 1) mixture being as the eluent.

N-(Methoxycarbonyl)-4-cyano-3-[2,3-(difluoromethylenedioxy)phenyl]pyrrole (*IIa*), 22 % yield, white crystals, m.p. = 142—144 °C. For $C_{14}H_8F_2N_2O_4$ (M_r = 306.23) w_i(calc.): 54.91 % C, 2.63 % H, 9.15 % N; w_i(found): 54.70 % C, 2.61 % H, 9.00 % N. ^{1}H NMR spectrum ($CDCl_3$), δ: 4.10 (s, 3H, OCH_3), 6.99—7.92 (m, 5H, H_{arom}).

N-(Methoxycarbonyl)-4-cyano-3-phenylpyrrole (*IIb*), 13 % yield, white crystals, m.p. = 110—113 °C. For $C_{13}H_{10}N_2O_2$ (M_r = 226.23) w_i(calc.): 69.02% C, 4.46 % H, 12.38% N; w_i(found): 68.99 % C, 4.39 % H, 12.19 % N. ^{1}H NMR spectrum ($CDCl_3$), δ: 4.05 (s, 3H, OCH_3), 7.35—7.85 (m, 7H, H_{arom}).

N-(Methoxycarbonyl)-4-cyano-3-ferrocenylpyrrole (*IIc*), 32 % yield, yellow crystals, m.p. = 158—160 °C. For $C_{17}H_{14}FeN_2O_2$ (M_r = 334.16) w_i(calc.): 61.11 % C, 4.22 % H, 8.38 % N; w_i(found): 60.89 % C, 4.19 % H, 8.28 % N. ^{1}H NMR spectrum ($CDCl_3$), δ: 4.03 (s, 3H, OCH_3), 4.15 (s, 5H, Cp), 4.31 (t, 2H, H_β), 4.68 (t, 2H, H_α), 7.23 (d, 1H, H-2), 7.75 (d, 1H, H-5).

N-(Formamidomethyl)-3-aryl-4-cyanopyrroles *III*

Potassium (4 mmol) was added to the solution of the appropriate pyrrole *Ia*—*Ic* (3 mmol) in toluene (80 cm^3), and the reaction mixture was heated till the evolution of hydrogen was ceased (1—3 h). The reaction mixture was then cooled to 30—40 °C and *N*-tosylmethylformamide (3 mmol) was then added portionwise during 30 min. The formed thick suspension was stirred at room temperature overnight. Water was added and the organic material was extracted into

ethyl acetate. Solution was dried (Na_2SO_4), solvent evaporated and the residue left to crystallize in the freezer. The crystals were washed with a small amount of cold chloroform.

N-(Formamidomethyl)-4-cyano-3-[2,3-(difluoromethylenedioxy)phenyl]pyrrole (*IIIa*), 31 % yield, white crystals, m.p. = 153—155 °C. For $C_{14}H_9F_2N_3O_3$ (M_r = 305.24) w_i(calc.): 55.09 % C, 2.97 % H, 13.77 % N; w_i(found): 54.94 % C, 2.68 % H, 13.53 % N. ^{1}H NMR spectrum ($CDCl_3$), δ: 5.40 (d, 2H, CH_2), 6.65 (bs, 1H, NH), 7.01—7.72 (m, 5H, H_{arom}), 8.33 (s, 1H, CHO).

N-(Formamidomethyl)-4-cyano-3-phenylpyrrole (*IIIb*), 16 % yield, white crystals, m.p. = 105—107 °C. For $C_{13}H_{11}N_3O$ (M_r= 225.25) w_i(calc.): 69.32 % C, 4.92 % H, 18.65 % N; w_i(found): 69.09 % C, 5.01 % H, 17.79 % N. ^{1}H NMR spectrum ($CDCl_3$), δ: 5.34 (d, 2H, CH_2), 6.59 (bs, 1H, NH), 6.99—7.56 (m, 7H, H_{arom}), 8.29 (s, 1H, CHO).

N-(Formamidomethyl)-4-cyano-3-ferrocenylpyrrole (*IIIc*), 30% yield, yellow crystals, m.p. = 98—101 °C. For $C_{17}H_{15}FeN_3O$ (M_r = 333.17) w_i(calc.): 61.29 % C, 4.54 % H, 12.61 % N; w_i(found): 61.31 % C, 4.55 % H, 12.49 % N. ^{1}H NMR spectrum ($CDCl_3$), δ: 4.12 (s, 5H, Cp), 4.27 (t, 2H, H_β), 4.61 (t, 2H, H_α), 5.23 (d, 2H, CH_2), 6.77 (d, 1H, H-2), 7.09 (bs, 1H, NH), 7.24 (d, 1H, H-5), 8.23 (s, 1H, CHO).

Chlorides of *N*-(Ammoniomethyl)-3-aryl-4-cyanopyrroles *IV*

The appropriate *III* (2 mmol) was dissolved in the mixture of methanol (24 cm^3) and hydrochloric acid (2 cm^3) and the mixture was stirred overnight at room temperature. The solid material was filtered off, washed with cold methanol and dried.

N-(Ammoniomethyl)-4-cyano-3-[2,3-(difluoromethylenedioxy)phenyl]pyrrole chloride (*IVa*), 80 % yield, white solid, m.p. > 250 °C. For $C_{13}H_{10}ClF_2N_3O_2$ (M_r = 313.69) w_i(calc.): 12.11 % F, 11.30 % Cl; w_i(found): 11.73 % F, 11.78 % Cl. ^{1}H NMR spectrum (CD_3SOCD_3), δ: 5.35 (s, 2H, CH_2), 7.31—7.64 (m, 3H, H_{arom}), 7.72 (d, 1H, H-2), 8.10 (d, 1H, H-5), 9.30 (bs, 3H, N^+H_3).

N-(Ammoniomethyl)-4-cyano-3-phenylpyrrole chloride (*IVb*), 50 % yield, white crystals, m.p. > 250 °C. For $C_{12}H_{12}ClN_3$ (M_r = 233.70) w_i(calc.): 61.67 % C, 5.18 % H, 17.98 % N; w_i(found): 61.78 % C, 5.32 % H, 18.01 % N. ^{1}H NMR spectrum (CD_3SOCD_3), δ: 5.24 (s, 2H, CH_2), 7.38—7.93 (m, 7H, H_{arom}), 9.17 (bs, 3H, N^+H_3).

N-(Ammoniomethyl)-4-cyano-3-ferrocenylpyrrole chloride (*IVc*), 78 % yield, yellow solid, m.p. > 250 °C. For $C_{16}H_{16}ClFeN_3$ (M_r = 341.62) w_i(calc.): 56.25 % C, 4.72 % H, 12.30 % N; w_i(found): 56.04 % C, 4.62 % H, 12.08 % N. ^{1}H NMR spectrum (CD_3SOCD_3), δ: 4.13 (s, 5H, Cp), 4.26 (t, 2H, H_β), 4.60 (t, 2H, H_α), 5.23 (s, 2H, CH_2), 6.78 (d, 1H, H-2), 7.26 (d, 1H, H-5), 9.11 (bs, 3H, N^+H_3).

N-(Aminomethyl)-3-aryl-4-cyanopyrroles *V*

The appropriate *IV* (1 mmol) and potassium carbonate (2 mmol) were dissolved in water (20 cm^3). Diethyl ether (20 cm^3) was added to the aqueous solution of reactants and the reaction mixture was stirred for 30 min. The organic solution was separated, dried (Na_2SO_4) and filtered. The product was isolated after evaporation of the solvent.

N-(Aminomethyl)-4-cyano-3-[2,3-(difluoromethylenedioxy)phenyl]pyrrole (*Va*), 74 % yield, white solid, m.p. = 129—132 °C. For $C_{13}H_9F_2N_3O_2$ (M_r = 277.23) w_i(calc.): 56.32 % C, 3.27 % H, 15.16 % N; w_i(found): 56.21 % C, 3.16 % H, 14.87 % N. ^{1}H NMR spectrum ($CDCl_3$), δ: 2.10 (bs, 2H, NH_2), 4.88 (s, 2H, CH_2), 6.90—7.77 (m, 5H, H_{arom}).

N-(Aminomethyl)-4-cyano-3-phenylpyrrole (*Vb*), 40 % yield, white crystals, m.p. = 86—89 °C. For $C_{12}H_{11}N_3$ (M_r= 197.24) w_i(calc.): 73.07 % C, 5.62 % H, 21.30 % N; w_i(found): 74.52 % C, 5.60 % H, 20.93 % N. ^{1}H NMR spectrum ($CDCl_3$), δ: 2.00 (bs, 2H, NH_2), 4.77 (s, 2H, CH_2), 6.93—7.68 (m, 7H, H_{arom}).

N-(Aminomethyl)-4-cyano-3-ferrocenylpyrrole (*Vc*), 76 % yield, yellow crystals, m.p. = 130—133 °C. For $C_{16}H_{15}FeN_3$ (M_r = 305.16) w_i(calc.): 62.98 % C, 4.95 % H, 13.77 % N; w_i(found): 62.67 % C, 4.85 % H, 13.54 % N. ^{1}H NMR spectrum ($CDCl_3$), δ: 1.93 (bs, 2H, NH_2), 4.14 (s, 5H, Cp), 4.25 (t, 2H, H_β), 4.64 (t, 2H, H_α), 4.76 (s, 2H, CH_2), 6.73 (d, 1H, H-2), 7.24 (d, 1H, H-5).

N-(Isocyanomethyl)-4-cyano-3-[2,3-(difluoromethylenedioxy)phenyl]pyrrole (*VIa*)

The compound *IIIa* (5 mmol) was dissolved at 0 °C in a mixture of phosphorus oxychloride (0.5 cm^3) and triethylamine (3.5 cm^3). Reaction mixture was stirred for 30 min at this temperature, water was then added and the organic material was extracted into benzene. The benzene solution was dried (Na_2SO_4), filtered and the solvent was evaporated. The residue was purified on a SiO_2-column using 2-methylpentane—ethyl acetate (φ_r = 2 1). The product *VIa* was isolated in 55 % yield as white crystals, m.p. = 145—147 °C (2-methylpentane—ethyl acetate). For $C_{14}H_7F_2N_3O_2$ (M_r = 287.23) w_i(calc.): 58.54 % C, 2.46 % H, 14.63 % N; w_i(found): 58.01 % C, 2.39 % H, 14.42 % N. ^{1}H NMR spectrum (CD_3COCD_3), δ: 6.00 (s, 2H, CH_2), 7.19—8.82 (m, 5H, H_{arom}).

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