# β-Aminomethylation of N-aryl- and N-azaheteroaryl-substituted methyl 2,5-dimethylpyrrole-3-carboxylates. Kinetic effect of the N-pyrrole substituent

**Mariangela Biava[a]*, Giulio Cesare Porretta[a], Giorgio Giorgi[a], and Giancarlo Sleiter[b]**

[a] *Dipartimento di Studi di Chimica e Tecnologia delle Sostanze Biologicamente Attive, Università "La Sapienza", P.le A Moro 5, 00185 Rome, Italy*
*E-mail: Mariangela.Biava@uniroma1.it*
[b] *Dipartimento di Chimica and Centro CNR di Studio sui Meccanismi di Reazione, Università "La Sapienza", P.le A Moro 5, 00185 Rome, Italy*

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**Abstract**

Preliminary kinetic investigations[1,2] on substituted *N*-azaheteroaryl-substituted 2,5-dimethylpyrroles, showed that the relative reactivities of the pyrroles investigated are dependent on the nature of the *N*-substituent. In order to quantitatively study this influence, we synthesized methyl 2,5-dimethylpyrrole-3-carboxylates, containing as *N*-substituents a phenyl **9,** a 2-pyridyl **10** and a 3-pyridyl **11** group; the β-methoxycarbonyl group was introduced in order to render the pyrrolic substrates amenable to the kinetic measurements. The obtained results support one of the proposed hypotheses.

**Keywords:** Pyrroles, kinetic study, β-aminomethylation reaction, Mannich bases

## Introduction

In previous papers[1,2] we reported an unusual effect in the β-aminomethylation of a series of *N*-aryl- (phenyl and *p*-chlorophenyl) and *N*-azahetero-aryl-(2-pyridyl, 2-pyrimidinyl, and 2-thiazolyl)substituted 2,5-dimethylpyrroles. Their reactions with Mannich reagents, formed from formaldehyde and morpholine or *N*-methylpiperazine or piperidine in aqueous acetic acid under different experimental conditions, afforded, in all cases, the single Mannich bases in satisfactory

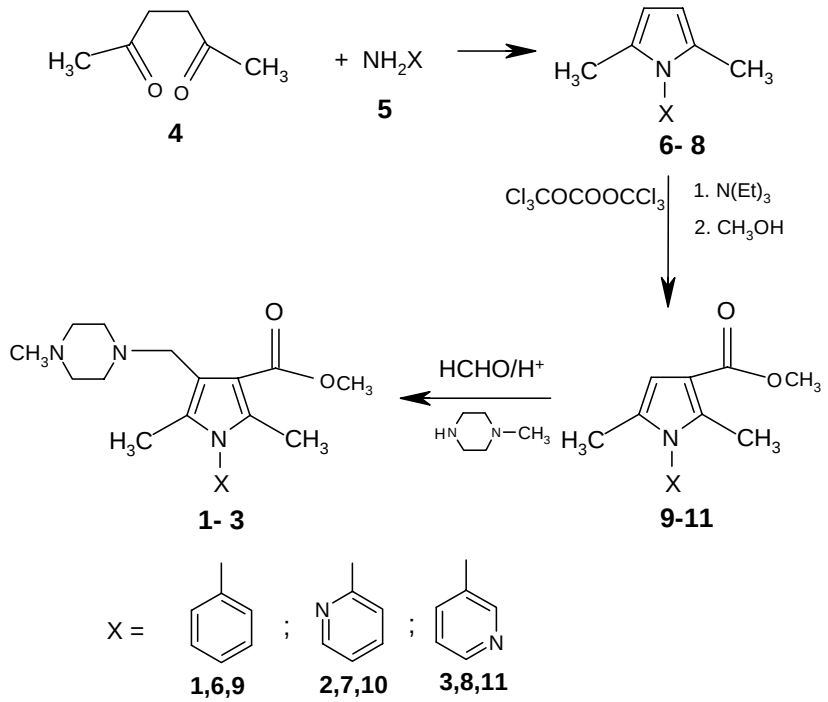
isolated yields (see refs. 1 and 2). The only notable exception was the behaviour of the pyrrole bearing as *N*-substituent the 2-pyrimidinyl group, which in its reaction with the morpholine Mannich reagent always afforded the 3,4-bis(morpholinomethyl)- substituted derivative, even when a 1:1 pyrrole/Mannich reagent was used (of course, accompanied by an equivalent amount of unreacted material). Exclusive β-monosubstitution could be achieved (with very low yields) only when the reaction was quenched at a very early stage. Since the electrophilicity of the morpholine Mannich reagent is, of course, independent of the substrate involved, this unexpected result ought to be related with a special structural feature of the substrate: it can be recognized in the presence of the *N*-(2-pyrimidinyl) substituent. Since the (inductive) electronic effect of a π-deficient heteroaryl group should be a deactivating one, two hypotheses have been put forward in order to explain the overall activating effect of the *N*-(2-pyrimidinyl) group: in the first one, the latter is attributed to a favourable effect on the reaction rate by the activation entropy; the second one justifies the enhancement of the reaction rate by a decrease in the activation enthalpy of the process. Preliminary kinetic investigations did show that the relative reactivities of the pyrroles investigated are indeed dependent on the nature of the *N*-substituent and decrease in the order: *N*-(2-pyrimidinyl)- > *N*-(2-pyridyl)- > *N*-phenyl- > *N*-(2-thiazolyl)-2,5-dimethylpyrrole. In order to settle the question of which effect should be held responsible for the observed reactivity order, a kinetic investigation was performed of the β-(4-methylpiperazino)methylation in a mixture of acetonitrile and aqueous acetic acid at different temperatures of a series of three *N*-substituted 3-methoxycarbonyl-2,5-dimethylpyrroles (*N*-substituent = phenyl, **9**, 2-pyridyl, **10**, and 3-pyridyl, **11**). A 3-methoxycarbonyl group was introduced with the aim of both lowering the reactivity of the pyrroles and allowing only monosubstitution to occur.

## Results and Discussion

### Chemistry

Compounds **6-8** were prepared, as illustrated in Scheme 1, from 2,5-hexanedione and the amine reagent according to the general procedure of Gillet.[3] The methoxycarbonylpyrroles were obtained by the reaction of the appropriate pyrrole with bis(trichloromethyl)carbonate (triphosgene) in the presence of triethylamine. The Mannich bases were obtained by the procedure previously described by us.[2]

The new compounds **1-3, 7** and **8** were identified and characterized by elemental analyses, IR, $^{1}$H and $^{13}$C NMR, and MS data; they are reported in the experimental part along with the pertinent physicochemical data.




**Scheme 1**

The kinetic runs were performed at 70.0, 80.0, and 90.0 ± 0.1 °C in the dark using equimolar amounts of formaldehyde and amine. It should be noted that reproducible results could be obtained only if the Mannich reagent was prepared at least 12 h before the start of the measurements, i.e., only after the time required for the attainment of the equilibrium represented by eq. (2) had elapsed. Pyrroles **9-11** were shown to afford the corresponding β-(4-methylpiperazino)methyl-substituted products **1-3** as the sole products when stirred for 8 h in the dark at room temperature in aqueous acetic acid with equimolecular amounts of formaldehyde and 4-methylpiperazine; in particular, any incursion of α-side-chain substitution could be excluded. The concentration of the water and the pyrrole/Mannich reagent molar ratio were kept constant. By analogy with other Mannich-type reactions,[4] the kinetic data were treated according to a third-order law,[5] equation (1), for $[\text{pyrrole}]_0 = [CH_2O]_0 = [\text{amine}]_0 = A_0$ , and $x = [CH_2O]$ at time $t$. The fit of the experimental data with this kinetic law was always satisfactory; Table 4 shows the mean values of the kinetic constants obtained for the reactions of pyrroles **9-11** at the temperatures indicated.

$$2kt = (2A_0x - x^2)/A_02(A_0 - x)^2 \qquad (1)$$

$$R_2NH + CH_2O + H^+ \rightleftharpoons [R_2N \cdots CH_2]^+ + H_2O \quad (2)$$

Inspection of the kinetic data reveals that, as expected on the basis of the previous qualitative results,[1,2] the reactivity order of the three pyrrole derivatives is indeed **10** > **9** ≥ **11**, i. e., the N-(2-pyridyl) group has an overall rate-enhancing effect which contrasts with the deactivating effect of the N-(3-pyridyl) group. Worth noting is also that, while in the case of pyrrole **10** the reaction rate, as usual, increases with temperature, the rates of the reactions of both pyrroles **9** and **11** decrease as temperature increases (anti Arrhenius behaviour). These results confirm one of the hypothesis proposed in previous works,[1,2] regarding the *N1* 2-pirimidinyl substituent. Indeed, thanks to the presence of an α-aza group with its electron lone pair on the nitrogen atom, the same situation is possible for pyrrole **10:** there is coplanarity between the pyrrole ring and 2-pyridyl group in the transition state of the reaction, and this reduces the activation energy owing to the delocalization (by inductive and hyperconjugative effects) of the incoming positive charge also on the α-methyl groups (Figure1). In such a way this positive charge can be further stabilized by the favourable electrostatic interaction between the acidic protons of the α-methyl group and the adjacent aza group of the pyridine ring. By way of contrast, the reactions of pyrroles **9** and **11** show an apparently negative activation energy. This is an indication that the reaction occurs step-wise and that the rate-determining step ought to be preceded by at least one fast equilibrium, whereby the expected increase in rate for the slow step with increasing temperature would be compensated by a shift of the preceding equilibrium (or equilibria) toward the reagents. In the present cases, the rate-determining steps are slowed down (with respect to that of the reaction of pyrrole **10**) by the impossibility, for the transition state, to gain additional stabilisation by the effect described above and the formation/decomposition equilibrium of the Mannich reagent becomes responsible for the apparent decrease of rate as the temperatures are increased.

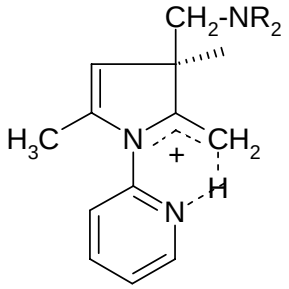



**Figure 1.** The transition state of the electrophilic attack.

## Experimental Section

**General Procedures.** Melting points were taken on a Fischer-Jones apparatus and are uncorrected. Infrared spectra (Nujol mulls) were run on a Perkin-Elmer 297 spectrophotometer. NMR spectra were recorded for all the synthesized compounds on a 400 Brucker spectrometer using deuteriochloroform as solvent and TMS as internal standard. Microanalyses of compounds **1-3, 7** and **8** were performed by the Servizio di Microanalisi dell'Area di Ricerca di Roma del CNR. Fluka aluminium oxide (activity II-III, according to Brockmann) was used for chromatographic purifications. To check the purity of the compounds Fluka Stratocrom aluminium oxide plates with fluorescent indicator were used for thin-layer chromatography (TLC). For use in the kinetic experiments, the compounds were purified chromatographically many times, and stored in a refrigerator into sealed amber-glass ampules under argon.
Formaldehyde was used as commercial aqueous solution. The titer of the 40% formaldehyde solution was determined gravimetrically[6] and found to be 38.5%.

**Synthesis of pyrroles 6-8**
Pyrroles **6-8** were prepared according to the general procedure previously described by us,[1,2] sometimes modifying the general procedure reported by Gillet.[3]

**Synthesis of 2,5-dimethyl-3-methoxycarbonylpyrroles (9-11)**
To a stirred solution of the appropriate pyrrole **6-8** (6 mmol) in 20 ml of anhydrous benzene triethylamine (6 mmol) was added. The mixture was cooled to 0 °C under stirring, then bis(trichloromethyl) carbonate (2 mmol) was added. The mixture was allowed to react for 30 min at room temperature. The mixture was then filtered on anhydrous methanol. To the filtrate water was added, then methanol removed in vacuo, the residue was extracted with ethyl acetate, and the organic extracts were washed with water and dried ($Na_2SO_4$). The residue from the evaporation of the solvent was purified by column chromatography, using aluminium oxide and a 1:3 ethyl acetate/cyclohexane mixture as eluent to give **9** and **11** as yellow crystalline compounds and **10** as an oil. Pertinent physicochemical data are reported in Table 1.

**10.** IR = 1699; $^1$H NMR ($CDCl_3$) δ: 2.00(s, 3H, 5-$CH_3$), 2.36 (s, 3H, pyrrole 2-$CH_3$), 3.81 (s, 3H, 7-CH3), 6.36 (s, 1H, pyrrole 4-H), 7.22 (m, 1H, pyridine 3-H), 7.39 (m, 1H, pyridine 5-H), 7.86 (m, 1H, pyridine 4-H), 8.65 (m, 1H, pyridine 6-H). $^{13}$C ($CDCl_3$) δ: 167.7, 149.3, 138.8, 136.5, 129.6, 125.1, 123.6, 115.1, 112.3, 52.5, 13.7. MS 230 ($M^+$). Anal. ($C_{13}H_{14}N_2O_2$) C, H, N.
**11.** IR = 1699; $^1$H NMR ($CDCl_3$) δ: 1.99 (s, 3H, 5-$CH_3$), 2.31 (s, 3H, pyrrole 2-$CH_3$), 3.82 (s, 3H, 7-CH3), 6.40 (s, 1H, pyrrole 4-H), 7.50 (m, 1H, pyridine 2-H), 7.56 (m, 1H, pyridine 4-H),

8.51 (m, 1H, pyridine 6-H), 8.72 (m, 1H, pyridine 5-H). $^{13}$C ($CDCl_3$) δ: 167.5, 148.3, 138.8, 136.5, 130.3, 124.1, 123.6, 113.1, 111.1, 52.3, 13.4. MS 230 ($M^+$). Anal. ($C_{13}H_{14}N_2O_2$) C, H, N.

**Table 1.** Physicochemical data for compounds **9-11**

| Compd. | X | Mp (°C) | Yield (%) | Formula (MW) |
|---|---|---|---|---|
| **9**[a] | phenyl | 48-49 | 55 | $C_{14}H_{15}NO_2$ |
| **10** | 2-pyridyl | Oil | 12 | $C_{13}H_{14}N_2O_2$ |
| **11** | 3-pyridyl | 44-45 | 20 | $C_{13}H_{14}N_2O_2$ |

[a] See ref. 7.

**Synthesis of pyrrolic Mannich bases 1-3**

To a stirred solution of the appropriate pyrrole **9-11** (5.6 mmol) in 20 ml of acetonitrile, a mixture of *N*-methylpiperazine (5.6 mmol), formaldehyde (5.6 mmol) (40% in water) and 5 ml of acetic acid was added dropwise. After the addition was complete the mixture was stirred at room temperature for 8 hours. The mixture was then treated with a solution of sodium hydroxide (20%, w/v) and extracted with ethyl acetate. The organic extracts were combined, washed with water and dried. After removal of solvent, the residue was purified by column chromatography, using aluminium oxide and chloroform for compounds **1** and **3**, and ethyl acetate for compound **2**. The eluates were combined after TLC control and the solvent was removed to give the pure product **1** and **3** as yellow crystalline compounds and **2** as an oil.

Physicochemical data are reported in Table 2.

**1.** IR = 1694; $^1$H NMR ($CDCl_3$) δ: 1.88 (s, 3H, 5-$CH_3$), 2.16 (s, 3H, pyrrole 2-$CH_3$), 2.20-2.55 (m superimposed, 3H, 2-$CH_3$; 4H, piperazine 2-$CH_2$; 4H, piperazine 3-$CH_2$; 3H, piperazine $CH_3$-N); 3.74 (s, 3H, 7-$CH_3$), 7.04 (m, 2H, phenyl 3-H and 5-H), 7.30 (m, 3H, phenyl 2-H, 4-H and 6-H). $^{13}$C ($CDCl_3$) δ: 166.7, 141.2, 139.8, 138.5, 131.6, 128.1, 127.6, 112.1, 55.1, 52.5, 52.1, 50.3, 45.9, 12.7, 10.6. MS 341 $(M + H)^+$. Anal. ($C_{20}H_{27}N_3O_2$) C, H, N.

**2.** IR = 1694;$^1$H NMR ($CDCl_3$) δ: 2.00(s, 3H, 5-$CH_3$), 2.36 (s, 3H, pyrrole 2-$CH_3$), 2.15-2.54 (m superimposed, 3H, 2-$CH_3$; 4H, piperazine 2-$CH_2$; 4H, piperazine 3-$CH_2$; 3H, piperazine $CH_3$-N); 3.66 (s, 2H, pyrrole CH2-N); 3.79 (s, 3 H, 7-CH3), 7.23 (m, 1H, pyridine 3-H), 7.37 (m, 1H, pyridine 5-H), 7.86 (m, 1H, pyridine 4-H), 8.63 (d, 1H, pyridine 6-H). $^{13}$C ($CDCl_3$) δ: 166.7, 151.2, 149.8, 138.5, 135.6, 128.1, 123.6, 122.9, 112.1, 55.1, 52.5, 52.1, 50.3, 45.9, 12.8, 10.7. MS 343 $(M+ H)^+$. Anal. ($C_{19}H_{26}N_4O_2$) C, H, N.

**3.** IR = 1694; $^{1}$H NMR ($CDCl_3$) δ: 1.99 (s, 3H, 5-$CH_3$), 2.16 (s, 3H, pyrrole 2-$CH_3$), 2.20 (s, 3H, piperazine $CH_3$-N), 2.31-2.55 (m superimposed, 4H, piperazine 2-$CH_2$; 4H, piperazine 3-$CH_2$;); 3.73 (s, 3H, 7-$CH_3$), 7.45-7.55 (2m, 2H, pyridine 2- and 4-H), 8.51 (m, 1H, pyridine 6-H), 8.72 (m, 1H, pyridine 5-H). $^{13}$C ($CDCl_3$) δ: 166.7, 150.1, 140.8, 138.5, 131.5, 126.6, 123.6, 122.1, 109.2, 55.1, 52.5, 52.1, 50.3, 45.9, 12.8, 10.7. MS 343 $(M+H)^+$. Anal. ($C_{19}H_{26}N_4O_2$) C, H, N.

**Table 2.** Physicochemical data for compounds **1-3**

| Compd. | X | Mp (°C) | Yield (%) | Formula |
|---|---|---|---|---|
| **1** | Phenyl | 102-103 | 50 | $C_{20}H_{27}N_3O_2$ |
| **2** | 2-pyridyl | Oil | 66 | $C_{19}H_{26}N_4O_2$ |
| **3** | 3-pyridyl | 122-124 | 35 | $C_{19}H_{26}N_4O_2$ |

**Kinetic Measurements**

The kinetic experiments were performed at 70, 80, and 90 ± 0.1 °C in the dark (conventional dark room, red lamp). Appropriate amounts of the pyrroles **9-11** were weighed in 50 ml volumetric flasks in order to have a final concentration of about 1 M. The aqueous acidic acetonitrile solutions were prepared by weight. The exact amount of water to be weighed was determined after allowance has been made for the amount of water introduced with the aqueous solutions used (*N*-methylpiperazine, formaldehyde and formic acid) and for that produced in the formation of the Mannich reagent. Once prepared, the kinetic solutions were left standing at room temperature for at least 12 h in the dark in order to allow equilibrium (2) to be established. Equal volumes (2 mL) of the kinetic solutions were then filled into amber-glass tubes, which were sealed and immersed at once in the constant temperature bath. As time zero of the reaction the time was taken 10 min after the introduction of the tubes into the thermostatic bath. In no case at $t = t_0$ had the reactions progressed to any appreciable extent. The reaction kinetics were followed up to the attainment of the equilibrium by titrating the unreacted formaldehyde by a mercurimetric method.[8] Blank experiments showed that neither the starting pyrrole nor the reaction product interfered with the determination, which was found to be virtually as precise as the gravimetric one.

The reproducibility of all the values obtained, as ascertained by replicate experiments, was always better than ±4%.

**Table 3.** Observed Third-Order Kinetic Coefficients for the Reactions of Pyrroles 9-11 with 4-methylpiperazine and Formaldehyde in an Aqueous Acetonitrile – Acetic Acid Mixture at 70.0, 80.0, and 90.0 °C[a]

| Pyrrole | $T$, °C | $k_3$,[b] $s^{-1}$ $M^{-2}$ |
|---|---|---|
| **9** | 70.0 | $2.66 \times 10^{-2}$ |
| | 80.0 | $1.27 \times 10^{-2}$ |
| | 90.0 | $2.78 \times 10^{-3}$ |
| **10** | 70.0 | $1.26 \times 10^{-2}$ |
| | 80.0 | $5.25 \times 10^{-2}$ |
| | 90.0 | 0.96 |
| **11** | 70.0 | $1.60 \times 10^{-2}$ |
| | 80.0 | $7.85 \times 10^{-3}$ |
| | 90.0 | $5.07 \times 10^{-3}$ |

[a] $[pyrrole]_0 = [CH_2O]_0 = [4\text{-methylpiperazine}]_0$ = 0,045 M; $[H_2O]$ = 2.77 M; kinetic law, eq. 2.
[b] Mean from triplicate experiments.

## Supplementary Information

See Page 397

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