# About the Synthesis of *N*-1-Substituted 3-Aminopyrroles. A Comparison [1]



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A general method for the preparation of 3-amino-1-methylpyrroles in excellent yields is reported. The key step involves the *N*-methylation of the nitro derivatives **2**, under phase transfer catalysis conditions.

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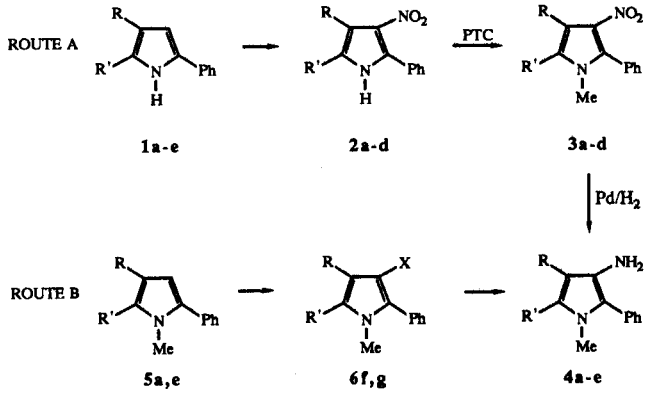
In the course of our investigations on aminopyrrole derivatives as key intermediates for the preparation of biologically interesting molecules as pyrrolyltriazenes and pyrrolylsulfonamides we required a flexible method for the synthesis of 1-methyl-3-aminopyrroles in preparative scale. Although several direct procedures are reported for the preparation of 1-substituted 2-aminopyrroles [2], no simple synthesis appears available for the corresponding 3-amino derivatives.

An approach to 1-substituted 3-aminopyrroles could involve the alkylation of the corresponding 1-unsubstituted derivatives. In fact several two steps routes have been described for the preparation in good yields of 3-aminopyrroles [3,4] and the selective *N*-1 methylation of 2-aminopyrroles has been reported [5].

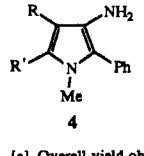
But this method fails to give the desired 1-methyl-3-amino derivatives, in that a substancially reduced nucleophilic character of the *C*-aminopyrroles still remains whereas due to the position of the amino group the electronic effects lower the basicity of the ring nitrogen [6].

Two less straightforward routes could then be considered: A) nitration of the *N*-unsubstituted pyrrole derivatives, the products of which can be alkylated first in the 1-position under phase transfer catalysis conditions [7] and reduced then to the required 3-aminopyrroles **4**; B) conversion of the *N*-alkylpyrroles **5** into nitro or azo derivatives of type **6** which, upon reduction, could give compounds **4**.

A comparison of the overall yields obtained by using route **A** and **B**, made the former synthetic pathway the most advantageous one for the preparation of the title compounds in a preparative scale. In fact the nitration of 1-substituted pyrroles is usually achieved in lower yield than those obtained in the case of NH pyrroles [8], whereas the reduction of the azo derivatives led, during the work-up, to a reaction mixture difficult to handle. On the contrary the alkylation of pyrroles by using TDA-1 as a catalyst gives nearly quantitative conversion of **2** into **3** and the Pd-catalysed reduction of 3-nitro or 3-nitroso-pyrroles to the corresponding 3-amino derivatives is generally achieved in high yield [9]. Route **A** is also more advantageous because it is possible to use an excess of methyl iodide without further alkylation, it is possible to carry out all the steps under mild conditions and the yields are nearly quantitative. Therefore a series of new 3-amino-1-methylpyrroles was prepared according to the route **A** shown in the scheme in excellent overall yield.




a: R = COOEt, R' = Me; b: R = COMe, R' = Me, c: R = CN, R' = Ph; d: R =R' = Ph; e: R = H, R' = Ph; f: R = COOEt, R' = Me, X = 4-$NO_2$-$C_6H_4$-$N_2$; g: R = H, R' = Ph, X = $NO_2$



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| | | Overall Yield (%) |
|---|---|---|
| a, | R = COOEt, R' = Me | 74 [a] |
| b, | R = COMe, R' = Me | 65 |
| c, | R = CN, R' = Ph | 79 |
| d, | R = R' = Ph | 95 |
| e, | R = H, R' = Ph | 45 [b] |

[a] Overall yield obtained by using Route B is 27% (see experimental).
[b] Prepared according to Route B.

Only the 3-amino-2,5-diphenyl-1-methylpyrrole (**4e**) could not be prepared by using route **A**. In fact the nitro compound of type **2** could not be isolated either in the nitration reaction of the pyrrole with isoamylnitrite in excess, or by oxidation of the isolated 3-nitrosopyrrole under the same experimental conditions employed for the oxidation of the 3-nitrosoindoles [10]. Moreover it is impossible

to methylate the ring nitrogen atom of the 3-nitroso compound due to the nitroso-isonitroso equilibrium [11]. Therefore compound **4e** could be synthetized according to route **B**, by nitration of the corresponding 1-methylpyrrole and subsequent catalytic reduction, in 45% overall yield. However another method for the preparation of 1-methyl-3-nitro-2,5-diphenylpyrrole (**6g**) in 35% overall yield has been reported [12].

## EXPERIMENTAL

All melting points were taken on a Buchi-Tottoli capillary apparatus; ir spectra were determined in bromoform with a Perkin-Elmer 299 spectrophotometer; $^1$H nmr spectra were obtained with a JEOL JMN-100FT spectrometer (TMS as internal references); mass spectra were obtained with a JEOL JMS-01 SG-2 double focusing mass spectrometer operating with an electron beam energy of 75 eV and 10 Kv accelerating voltage. The chromatography was performed on silica gel columns.

Route **A**.

4,5-Disubstituted 3-Nitro-2-phenylpyrroles **2a-d**.

The compounds **2** were prepared according to known procedures: **2a** (R = COOEt, R' = Me) [13], **2c** (R = CN, R' = Ph) [14], **2d** (R = R' = Ph) [15].

4-acetyl-5-methyl-3-nitro-2-phenylpyrrole (**2b**).

This compound was synthesized by nitration in nitric acid/acetic anhydride of 3-acetyl-5-methyl-2-phenylpyrrole according to the reported procedure [16]. It was recrystallized from ethanol (yield 70%), mp 167°; ir: 3310 (NH), 1675 (CO) cm$^{-1}$; $^1$H nmr (DMSO-d$_6$): δ 2.39 (3H, s, $CH_3$), 2.42 (3H, s, $CH_3$), 7.47 (5H, s, $C_6H_5$), 12.25 (1H, s, exchangeable NH); ms: M$^+$ = 244.

*Anal.* Calcd. for $C_{13}H_{12}N_2O_3$: C, 63.92; H, 4.95; N, 11.47. Found: C, 64.15, H, 4.80; N, 11.70.

4,5-Disubstituted 1-Methyl-3-nitro-2-phenylpyrroles **3a-d**.

To a cold suspension of 3-nitro-pyrroles **2a-d** (5 mmoles) in benzene (50 ml) potassium *t*-butoxide (6.8 mmoles) was added. The orange reaction mixture was stirred and TDA-1 (1 or 2 drops) was added. After 30 minutes methyl iodide was added dropwise and the reactants were smoothly warmed up with stirring until the colour turned yellow. The benzene was evaporated under reduced pressure, the residue was treated with water and the solid was filtered off and air dried.

1,5-Dimethyl-4-ethoxycarbonyl-3-nitro-2-phenylpyrrole (**3a**).

This compound was recrystallized from ethanol (yield 100%), mp 76°; ir: 1675 (CO) cm$^{-1}$; $^1$H nmr (DMSO-d$_6$): δ 1.23 (3H, t, $CH_3$), 2.42 (3H, s, $CH_3$), 3.32 (3H, s, $CH_3$), 4.23 (2H, q, $CH_2$), 7.48 (5H, s, $C_6H_5$); ms: M$^+$ = 288.

*Anal.* Calcd. for $C_{15}H_{16}N_2O_4$: C, 62.49; H, 5.59; N, 9.72. Found: C, 62.25; H, 5.65; N, 9.97.

4-Acetyl-1,5-dimethyl-3-nitro-2-phenylpyrrole (**3b**).

This compound was recrystallized from ethanol (yield 97%), mp 114-116°; ir: 1675 (CO) cm$^{-1}$; $^1$H nmr (DMSO-d$_6$): δ 2.36 (3H, s, $CH_3$), 2.41 (3H, s, $CH_3$), 3.30 (3H, s, $CH_3$), 7.50 (5H, s, $C_6H_5$); ms: M$^+$ = 258.

*Anal.* Calcd. for $C_{14}H_{14}N_2O_3$: C, 65.10; H, 5.46; N, 10.85. Found: C, 64.97; H, 5.27; N, 10.70.

4-Cyano-2,5-diphenyl-1-methyl-3-nitropyrrole (**3c**).

This compound was recrystallized from ethanol (yield 98%), mp 211°; ir: 2210 (CN) cm$^{-1}$; $^1$H nmr (DMSO-d$_6$): δ 3.31 (3H, s, $CH_3$), 7.59 (5H, s, $C_6H_5$), 7.65 (5H, s, $C_6H_5$); ms: M$^+$ = 303.

*Anal.* Calcd. for $C_{18}H_{13}N_3O_2$: C, 71.27; H, 4.32; N, 13.86. Found: C, 71.45; H, 4.41; N, 14.01.

1-Methyl-3-nitro-2,4,5-triphenylpyrrole (**3d**).

This compound was recrystallized from ethanol (yield 100%), mp 196°; $^1$H nmr (DMSO-d$_6$): δ 3.23 (3H, s, $CH_3$), 7.33 (5H, s, $C_6H_5$), 7.50 (5H, s, $C_6H_5$), 7.55 (5H, s, $C_6H_5$); ms: M$^+$ = 354.

*Anal.* Calcd. for $C_{23}H_{18}N_2O_2$: C, 77.95; H, 5.12; N, 7.91. Found: C, 78.15; H, 5.34; N, 8.08.

4,5-Disubstituted 3-Amino-1-methyl-2-phenylpyrroles **4a-d**.

Compound **3a-d** (10 mmoles) were reduced over 10% palladium on charcoal in methanol in a Parr apparatus at 45 psi. After standing overnight at room temperature, the catalyst was filtered off, the solvent was evaporated under reduced pressure and the solid was recrystallized.

3-Amino-1,5-dimethyl-4-ethoxycarbonyl-2-phenylpyrrole (**4a**).

This compound was recrystallized from ethanol (yield 99%), mp 65°; ir: 3330 and 3300 ($NH_2$), 1680 (CO) cm$^{-1}$; $^1$H nmr (DMSO-d$_6$): δ 1.29 (3H, t, $CH_3$), 2.47 (3H, s, $CH_3$), 3.36 (3H, s, $CH_3$), 4.21 (2H, q, $CH_2$), 4.41 (2H, bs, $NH_2$), 7.28-7.44 (5H, m, $C_6H_5$); ms: M$^+$ = 258.

*Anal.* Calcd. for $C_{15}H_{18}N_2O_2$: C, 69.74; H, 7.02; N, 10.85. Found: C, 69.59; H, 7.00; N, 10.73.

4-Acetyl-3-amino-1,5-dimethyl-2-phenylpyrrole (**4b**).

This compound was recrystallized from ethanol (yield 95%), mp 126°; ir: 3325 and 3315 ($NH_2$), 1675 (CO) cm$^{-1}$; $^1$H nmr (DMSO-d$_6$): δ 2.36 (3H, s, $CH_3$), 2.46 (3H, s, $CH_3$), 3.35 (3H, s, $CH_3$), 4.85 (2H, bs, $NH_2$), 7.32 (5H, s, $C_6H_5$); ms: M$^+$ = 228.

*Anal.* Calcd. for $C_{14}H_{16}N_2O$: C, 73.65; H, 7.06; N, 12.27. Found: C, 73.81; H, 7.03; N, 12.04.

3-Amino-4-cyano-2,5-diphenyl-1-methylpyrrole (**4c**).

This compound was recrystallized from ethanol (yield 95%), mp 149°; ir: 3440 and 3360 ($NH_2$), 2200 (CN) cm$^{-1}$; $^1$H nmr (DMSO-d$_6$): δ 3.38 (3H, s, $CH_3$), 4.28 (2H, s, $NH_2$), 7.44-7.57 (10H, m, $C_6H_5$); ms: M$^+$ = 273.

*Anal.* Calcd. for $C_{18}H_{15}N_3$: C, 79.09; H, 5.53; N, 15.38. Found: C, 79.33; H, 5.33; N, 15.11.

3-Amino-1-methyl-2,4,5-triphenylpyrrole (**4d**).

This compound was recrystallized from ethanol (yield 95%), mp 142°; ir: 3400 and 3330 ($NH_2$), cm$^{-1}$; $^1$H nmr (DMSO-d$_6$): δ 3.29 (3H, s, $CH_3$), 7.16-7.50 (17H, m, $C_6H_5$ and $NH_2$); ms: M$^+$ = 324.

*Anal.* Calcd. for $C_{23}H_{20}N_2$: C, 85.15; H, 6.21; N, 8.64. Found: C, 85.43; H, 6.11; N, 8.45.

Route **B**.

1,2-Dimethyl-3-ethoxycarbonyl-5-phenylpyrrole (**5a**).

This compound was prepared by condensation of ethyl phenacylacetoacetate and aqueous methylamine (40%) in acetic acid. The reaction mixture was poured onto crushed ice, the solid was filtered off, air dried and recrystallized from ethanol (yield 70%), mp 83°; ir: 1690 (CO) cm$^{-1}$; $^1$H nmr (deuteriochloroform): δ 1.20 (3H, t, $CH_3$), 2.44 (3H, s, $CH_3$), 3.36 (3H, s, $CH_3$), 4.18 (2H, q, $CH_2$),

6.44 (1H, s, CH), 7.20 (5H, s, $C_6H_5$); ms: $M^+$ = 243.

*Anal.* Calcd. for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04; N, 5.76. Found: C, 74.08; H, 7.06; N, 5.63.

1,2-Dimethyl-3-ethoxycarbonyl-4-(4-nitrophenylazo)-5-phenylpyrrole (**6f**).

To a stirred solution of 4-nitroaniline (40 mmoles) in 6*N* hydrochloric acid (30 ml), a solution of sodium nitrite in water (30%, 15 ml) was added dropwise at 0-5°. The mixture, cooled at 0°, was treated with the pyrrole **5a** (40 mmoles) dissolved in buffered acetic acid (200 ml with sodium acetate (10 g) added). After being stirred for 1 hour, the mixture was poured onto crushed ice. The solid product was collected, washed with water and ethanol, and recrystallized from ethanol (yield 91%), mp 165°; ir: 1710 (CO) $cm^{-1}$; $^1H$ nmr (deuteriochloroform): δ 1.26 (3H, t, $CH_3$), 2.44 (3H, s, $CH_3$), 3.50 (3H, s, $CH_3$), 4.25 (2H, q, $CH_2$), 7.20-8.34 (9H, m, $C_6H_5$ and $C_6H_4$); ms: $M^+$ = 392.

*Anal.* Calcd. for $C_{21}H_{20}N_4O_4$: C, 64.27; H, 5.14; N, 14.28. Found: C, 64.58; H, 5.32; N, 14.02.

3-Amino-1,5-dimethyl-4-ethoxycarbonyl-2-phenylpyrrole (**4a**).

Method a.

To a stirred suspension of stannous chloride dihydrate (20 g) in acetic acid (20 ml) at room temperature, compound **6f** (10 mmoles) was added in small portions. The reactants were stirred until the mixture became colourless. The mixture was added to an ice cold solution of aqueous potassium hydroxide (20%) with stirring. After 0.5 hour, the solid precipitate was filtered off, air dried and chromatographed. Elution with dichloromethane gave the aminopyrrole **4a** (yield 15%), further elution with ethyl acetate gave the *p*-phenylendiamine (yield 50%).

Method b.

The azo compound was reduced over 10% palladium on charcoal in methanol in a Parr apparatus at 45 psi. Column chromatography gave, in this case the aminopyrrole **4a** (yield 30%) and *p*-phenylendiamine (yield 50%).

3-Amino-2,5-diphenyl-1-methylpyrrole (**4e**).

2,5-Diphenyl-1-methylpyrrole [17] was nitrated with potassium nitrate in concentrated sulphuric acid according to the procedure reported previously [18]. The crude product was chromatographed using dichloromethane as eluant. It was impossible to isolate pure **6g**, therefore the fractions containing the nitro compound **6g** together with two impurities was catalitically reduced and the amino compound **4e** was purified by chromatography. It was obtained in 45% overall yield, mp 193-195°; ir: 3420 and 3380 ($NH_2$) $cm^{-1}$; $^1H$ nmr (DMSO-$d_6$): δ 3.52 (3H, s, $CH_3$), 5.22 (2H, s, $NH_2$), 6.20 (1H, s, CH), 6.62-7.49 (10H, m, $C_6H_5$); ms: $M^+$ = 248.

*Anal.* Calcd. for $C_{17}H_{16}N_2$: C, 82.22; H, 6.50; N, 11.28. Found: C, 81.96; H, 6.65; N, 11.13.

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