Nucleophilic Reactions in the Pyrrole Series: Displacement of Halogen as a Tool to Functionalize the Pyrrole Nucleus

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Nucleophilic substitutions on halopyrroles by charged and neutral carbon, nitrogen, oxygen and sulfur nucleophiles are reported. Such reactions represent a valuable and versatile instrument to prepare a wide variety of functionalized pyrroles and to obtain building blocks for the synthesis of polycyclic systems.

The pyrrole, as an electron-rich heteroaromatic nucleus, readily reacts with electrophiles but is less prone to undergo reaction with nucleophiles. However, a few examples of nucleophilic reactions in the pyrrole series are reported.[1] Such reactions can occur on either the protonated pyrrole ring or on the neutral molecule.

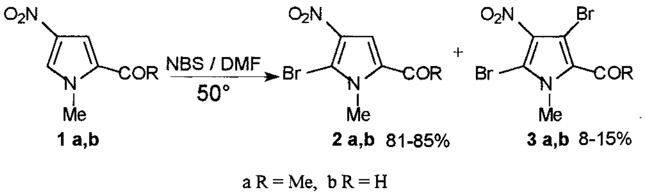
Nucleophiles react with the protonated pyrrole nucleus to give addition products,[2–4] ring-opened products[5,6] or dimerization products.[7] An example of an intramolecular nucleophilic reaction on a protonated pyrrole ring is the formation of substitution products derived from the extrusion of an amino group.[8,9] Nucleophilic reactions on the neutral pyrrole ring involve nucleophilic substitution, with the sole exception in which formation of addition products was observed.[10]

Most of the nucleophilic substitutions involve the displacement of a nitro group assisted by a second nitro group or different electron-withdrawing groups present in a conjugated position of the ring. In particular, displacement of an α-nitro group leads to *ipso*-substitution products,[11] whereas displacement of a β-nitro group leads to *ipso*- or *cine*-substitution products, depending on the reaction conditions.[12] Products derived from a ring-opening/ring-closure mechanism were also observed.[13] Nucleophilic displacement of a halogen, a very common reaction in the aromatic and heteroaromatic series, was verified in the pyrrole series by very effective, charged, polarizable nucleophiles such as sulfide and selenide ions.[14]

In this paper we propose heteroaromatic nucleophilic substitutions on halogenated pyrroles as a useful method to introduce a wide range of functional groups into the five-membered ring.

Bromopyrroles **2a,b** were prepared in high yields (81–85%) by smooth bromination, with *N*-bromosuccinimide in dimethylformamide, of the corresponding pyrrole derivatives **1a,b**. These brominations also led to the formation of a small amount of 2,4-dibromo derivatives **3a,b** (8–15%) (Scheme 1).

The α-bromopyrroles **2a,b** were reacted with stoichiometric amounts of sodium alkoxides in the respective alcohols as the solvent at room temperature. From these reactions compounds **4a–e** were obtained by *ipso*-substitution of the α-bromo group. The yields (80–30%) decreased on increasing the steric bulk of the alcohol.



Scheme 1

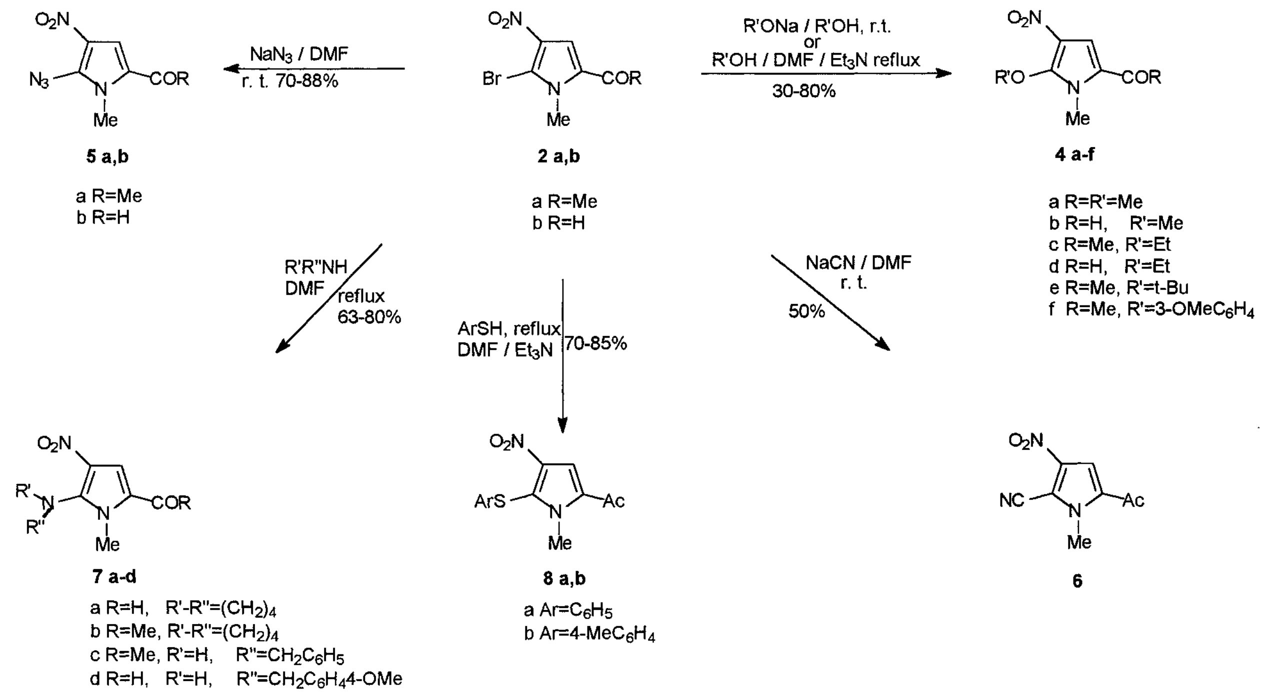
Compounds **2a,b**, upon reaction with sodium azide in dimethylformamide at room temperature, afforded the corresponding azidopyrroles **5a,b** in good yield (70–88%). Sodium cyanide directly substituted the α-bromo group of **2a**, in dimethylformamide at room temperature, affording the corresponding cyanopyrrole **6** in 50% yield. No reaction took place with **2a** and benzylmagnesium chloride in refluxing tetrahydrofuran for 48 hours (Scheme 2).

The α-bromopyrroles **2a,b** were then reacted with less effective neutral nucleophiles such as primary and secondary amines. These reactions, carried out in refluxing dimethylformamide and with excess of amine to neutralize the hydrogen bromide formed during the reaction, gave derivatives **7a–d** in quite good yields (63–80%), as a result of *ipso*-substitution of the α-bromo group (Scheme 2). The observed reactivity differs from that shown in the nucleophilic displacement of a β-nitro group of 1-methyl-3,4-dinitropyrrole by primary amines, in which the formation of 1-substituted 3-alkylamino-4-nitropyrroles was observed. The pyrrole 1-substituent corresponds to that of the primary amine and a ring-opening/ring-closure mechanism was envisaged.[13]

Compound **2a** was reacted with a neutral oxygen nucleophile, such as 3-methoxyphenol, under the same reaction conditions employed in the case of the amines but using stoichiometric amounts of triethylamine to neutralize the hydrogen bromide developed. The 5-phenoxy derivative **4f**, derived from *ipso*-substitution, was isolated in 50% yield.

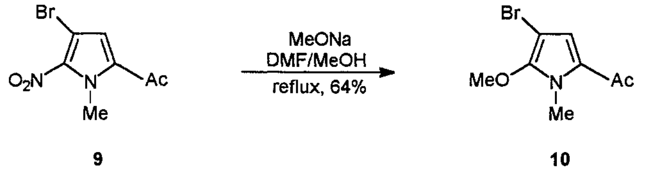
Compound **2a** was also reacted with sulfur nucleophiles. Thus, reaction with thiophenols afforded the corresponding thioethers **8a,b** in good yields (70–85%) using the above mentioned reaction conditions (Scheme 2).

These reactions achieved by the neutral nitrogen, oxygen and sulfur nucleophiles represent the first examples of nucleophilic substitution in the pyrrole series by uncharged nucleophiles.



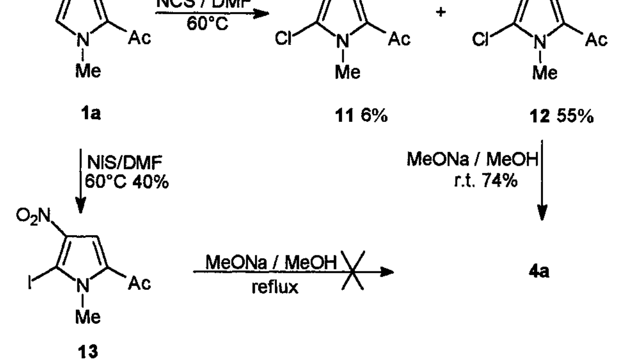
Scheme 2

To verify the reactivity of β-bromopyrroles as substrates for nucleophilic substitution, 2-acetyl-1-methyl-5-nitropyrrole was brominated with *N*-bromosuccinimide in dimethylformamide to give the β-bromo derivative **9** in 60 % yield. Compound **9** reacted with sodium methoxide in refluxing methanol/dimethylformamide (9:1) for 4 hours to give compound **10** by *ipso*-substitution of the nitro in the α-position rather than substitution of the β-bromo group (Scheme 3). Such reactivity can be explained in terms of a combination of the activating effects of the acetyl group in a conjugated position and of the adjacent ring nitrogen on the α-position of the pyrrole ring.



Scheme 3

To verify the behaviour of other halogens as the leaving group in nucleophilic substitution in the pyrrole series, the chloro and iodo derivatives **12** and **13** were prepared by halogenation of **1a** with the corresponding *N*-halosuccinimide in dimethylformamide. The chloro derivative **12** reacted with sodium methoxide under the identical reaction conditions employed for the corresponding bromo derivative **2a** to give the same product **4a** in comparable yield. Contrary to this, the iodo derivative **13** was recovered unchanged, even after reflux with sodium methoxide in methanol for 24 hours (Scheme 4). Such a result seems to be in contrast with the literature reports which state that the substitution rates of chloride, bromide and iodide ions, in aromatic and heteroaromatic series, lies within the same magnitude of order.[15] There is no ready explanation for this anomalous behaviour of the iodo derivative in this type of nucleophilic substitution.



Scheme 4

In conclusion, such nucleophilic reactions in the pyrrole series offer a valuable and versatile instrument to prepare a wide variety of functionalized pyrroles and to obtain building blocks for the synthesis of polycyclic systems.

All melting points were taken on a Büchi-Tottoli capillary apparatus and are uncorrected; IR spectra were recorded with a Jasco FT/IR 5300 spectrophotometer; ^1H and ^{13}C NMR spectra were measured at 200 and 50.3 MHz respectively, using a Bruker AC series 200 MHz spectrometer. Column chromatography was performed with Merck silica gel 230–400 Mesh ASTM.

Table. Spectroscopic Data for Pyrrole Substrates and Nucleophilic Substitution Products

Product[a]	Yield (%)	mp[b] (°C)	IR ($CHBr_3$) ν (cm^{-1})	^1H NMR (DMSO-d_6/TMS) δ, J (Hz)	^{13}C NMR (DMSO-d_6/TMS) δ
2a	85	125–127	1670 (CO), 1510 (NO_2)	2.53 (3 H, s, CH_3), 3.98 (3 H, s, NCH_3), 8.01 (1 H, s, H-3)	27.35 (q, CH_3), 35.97 (q, NCH_3), 114.85 (s, C-5), 115.55 (d, C-3), 130.70 (s, C-4), 133.36 (s, C-2), 188.75 (s, CO)
2b	81	135–138	1682 (CO), 1516 (NO_2)	4.02 (3 H, s, CH_3), 7.93 (1 H, s, H-3), 9.60 (1 H, s, CHO)	35.27 (q, CH_3), 117.00 (s, C-5), 118.97 (d, C-3), 131.30 (s, C-2), 132.22 (s, C-4), 180.94 (d, CHO)
3a	15	117	1668 (CO), 1514 (NO_2)	3.97 (6 H, s, 2 × CH_3)	38.36 (q, CH_3), 41.90 (q, NCH_3), 115.45 (s, C-3), 123.35 (s, C-5), 132.64 (s, C-4), 134.55 (s, C-2), 178.36 (s, CO)
3b	8	158–160	1680 (CO), 1525 (NO_2)	3.78 (3 H, s, CH_3), 12.52 (1 H, s, CHO)	37.30 (q, CH_3), 94.85 (s, C-3), 107.97 (s, C-5), 109.79 (s, C-2), 132.25 (s, C-4), 201.15 (d, CHO)
4a	80	135	1661 (CO), 1512 (NO_2)	2.41 (3 H, s, CH_3), 3.70 (3 H, s, NCH_3), 4.09 (3 H, s, OCH_3), 7.68 (1 H, s, H-3)	26.78 (q, CH_3), 31.58 (q, CH_3), 63.22 (q, CH_3), 113.65 (d, C-3), 121.94 (s, C-4), 122.23 (s, C-2), 148.49 (s, C-5), 188.90 (s, CO)
4b	70	114–115	1674 (CO), 1520 (NO_2)	3.75 (3 H, s, NCH_3), 4.14 (3 H, s, OCH_3), 7.63 (1 H, s, H-3), 9.50 (1 H, s, CHO)	31.05 (q, NCH_3), 63.45 (q, OCH_3), 117.80 (d, C-3), 123.01 (s, C-4), 123.23 (s, C-2), 149.19 (s, C-5), 181.19 (d, CHO)
4c	60	104–105	1662 (CO), 1510 (NO_2)	1.44 (3 H, t, $J = 7.0$, CH_3), 2.47 (3 H, s, CH_3), 3.76 (3 H, s, NCH_3), 4.43 (2 H, q, $J = 7.0$, CH_2), 7.76 (1 H, s, H-3)	15.40 (q, CH_3), 26.84 (q, CH_3), 31.76 (q, CH_3), 72.81 (t, CH_2), 113.76 (d, C-3), 122.17 (s, C-4), 122.35 (s, C-2), 147.68 (s, C-5), 188.92 (s, CO)
4d	63	78	1672 (CO), 1520 (NO_2)	1.41 (3 H, t, $J = 7.0$, CH_3), 3.74 (3 H, s, NCH_3), 4.46 (2 H, q, $J = 7.0$, CH_2), 7.64 (1 H, s, H-3), 9.49 (1 H, s, CHO)	15.40 (q, CH_3), 31.40 (q, NCH_3), 73.06 (t, CH_2), 117.84 (d, C-3), 123.11 (s, C-4), 123.13 (s, C-2), 148.35 (s, C-5), 181.14 (d, CHO)
4e	30	oil	1670 (CO), 1525 (NO_2)	2.46 (3 H, s, CH_3), 2.93 (9 H, s, *t*-C_4H_9), 3.70 (3 H, s, NCH_3), 7.72 (1 H, s, H-3)	26.91 (q, CH_3), 29.21 [s, $C(CH_3)_3$], 33.69 (q, NCH_3), 41.80 [q, $C(CH_3)_3$], 115.41 (d, C-3), 125.14 (s, C-4), 139.31 (s, C-2), 147.02 (s, C-5), 188.65 (s, CO)
4f	50	123–124	1664 (CO), 1510 (NO_2)	2.48 (3 H, s, CH_3), 3.71 (3 H, s, NCH_3), 3.76 (3 H, s, OCH_3), 6.52 (1 H, m, H-4′), 6.64 (1 H, m, H-2′), 6.77 (1 H, m, H-6′), 7.27 (1 H, t, $J = 7.4$, H-5′), 7.86 (1 H, s, H-3)	26.81 (q, CH_3), 32.00 (q, NCH_3), 55.46 (q, OCH_3), 101.76 (d, C-3), 106.78 (d, C-2′), 109.76 (d, C-6′), 113.23 (d, C-4′), 122.44 (s, C-4), 123.40 (s, C-2), 130.73 (d, C-5′), 141.78 (s, C-3′), 156.79 (s, C-5), 160.77 (s, C-1′), 188.19 (s, CO)
5a	88	132	2149 (N_3), 1667 (CO), 1512 (NO_2)	2.49 (3 H, s, CH_3), 3.77 (3 H, s, NCH_3), 7.85 (1 H, s, H-3)	27.20 (q, CH_3), 32.95 (q, NCH_3), 114.50 (d, C-3), 125.44 (s, C-4), 125.97 (s, C-2), 133.98 (s, C-5), 198.02 (s, CO)
5b[c]	70	93–95	2149 (N_3), 1678 (CO), 1518 (NO_2)	3.75 (3 H, s, CH_3), 7.73 (1 H, s, H-3), 9.54 (1 H, s, CHO)	32.30 (q, CH_3), 118.36 (d, C-3), 126.09 (s, C-4), 128.09 (s, C-2), 135.59 (s, C-5), 181.22 (d, CHO)
6	50	115–116	2237 (CN), 1684 (CO), 1521 (NO_2)	2.55 (3 H, s, CH_3), 4.02 (3 H, s, NCH_3), 7.98 (1 H, s, H-3)	28.28 (q, CH_3), 37.03 (q, NCH_3), 108.79 (s, C-5), 109.79 (s, CN), 113.79 (d, C-3), 133.79 (s, C-4), 139.30 (s, C-2), 189.73 (s, CO)
7a[d]	66	75–76	1668 (CO), 1514 (NO_2)	1.98 (4 H, m, 2 × CH_2), 3.37 (4 H, m, 2 × NCH_2), 3.73 (3 H, s, CH_3), 7.64 (1 H, s, H-3), 9.43 (1 H, s, CHO)	25.85 (t, 2 × CH_2), 33.27 (q, CH_3), 50.52 (t, 2 × NCH_2), 120.42 (d, C-3), 125.88 (s, C-4), 126.94 (s, C-2), 145.00 (s, C-5), 180.47 (d, CHO)
7b[d]	63	57	1658 (CO), 1507 (NO_2)	2.03 (4 H, m, 2 × CH_2), 2.46 (3 H, s, CH_3), 3.34 (4 H, m, 2 × NCH_2), 3.70 (3 H, s, NCH_3), 7.73 (1 H, s, H-3)	25.91 (t, 2 × CH_2), 26.89 (q, CH_3), 33.69 (q, NCH_3), 50.47 (t, 2 × NCH_2), 115.56 (d, C-3), 125.39 (s, C-4), 126.44 (s, C-2), 144.22 (s, C-5), 188.56 (s, CO)
7c[d]	80	101–103	3337 (NH), 1653 (CO), 1541 (NO_2)	2.33 (3 H, s, CH_3), 3.69 (3 H, s, NCH_3), 4.70 (2 H, d, $J = 5.9$, CH_2), 7.31 (5 H, s, C_6H_5), 7.58 (1 H, s, H-3), 7.79 (1 H, t, $J = 5.9$, NH)	26.58 (q, CH_3), 34.61 (q, NCH_3), 48.61 (t, CH_2), 115.09 (d, C-3), 124.89 (s, C-4), 127.00 (d, C-3′, 5′), 127.41 (d, C-4′), 128.63 (d, C-2′, 6′), 138.98 (s, C-2, 1′), 147.35 (s, C-5), 187.85 (s, CO)
7d[d]	67	157–158	3320 (NH), 1660 (CO), 1514 (NO_2)	3.73 (3 H, s, NCH_3), 3.80 (3 H, s, OCH_3), 4.69 (2 H, d, $J = 7.4$, CH_2), 6.91 (2 H, d, $J = 8.1$, H-3′, 5′), 7.25 (2 H, d, $J = 8.1$, H-2′, 6′), 7.54 (1 H, s, H-3), 7.90 (1 H, t, $J = 7.4$, NH), 9.27 (1 H, s, CHO)	33.62 (q, NCH_3), 47.45 (t, CH_2), 54.92 (q, OCH_3), 113.97 (d, C-3′, 5′), 120.43 (d, C-3), 125.26 (s, C-4), 128.21 (d, C-2′, 6′), 130.62 (s, C-2), 147.40 (s, C-1′), 148.24 (s, C-5), 158.49 (s, C-4′), 179.48 (d, CHO)

Table. (continued)

Product[a]	Yield (%)	mp (°C)[b]	IR ($CHBr_3$) ν (cm^{-1})	^1H NMR (DMSO-d_6/TMS) δ, J (Hz)	^{13}C NMR (DMSO-d_6/TMS) δ
8a	70	115–117	1670 (CO), 1508 (NO_2)	2.58 (3H, s, CH_3), 3.97 (3H, s, NCH_3), 7.23 (2H, dd, J = 7.6, 1.5, H-2′, 6′), 7.34 (1H, dt, J = 7.6, 1.5, H-4′), 7.41 (2H, dt, J = 7.6, 1.5, H-3′, 5′), 8.05 (1H, s, H-3)	27.86 (q, CH_3), 34.86 (q, NCH_3), 115.45 (d, C-3), 127.39 (d, C-4′), 127.89 (d, C-3′, 5′), 128.37 (s, C-5), 129.94 (d, C-2′, 6′), 131.66 (s, C-2), 131.86 (s, C-4), 133.53 (s, C-1′), 189.28 (s, CO)
8b	85	125–127	1670 (CO), 1508 (NO_2)	2.26 (3H, s, CH_3), 2.52 (3H, s, CH_3), 3.90 (3H, s, NCH_3), 7.07–7.18 (4H, m, C_6H_4), 7.97 (1H, s, H-3)	20.45 (q, CH_3), 27.56 (q, CH_3), 34.64 (q, NCH_3), 115.19 (d, C-3), 128.35 (d, C-3′, 5′), 128.98 (s, C-5), 129.47 (s, C-2), 130.29 (d, C-2′, 6′), 130.29 (s, C-1′), 131.22 (s, C-4), 137.05 (s, C-4′), 188.94 (s, CO)
9	60	120	1670 (CO), 1541 (NO_2)	2.67 (3H, s, CH_3), 3.97 (3H, s, CH_3), 7.47 (1H, s, H-3)	31.73 (q, CH_3), 36.53 (q, NCH_3), 100.51 (s, C-4), 115.13 (d, C-3), 133.31 (s, C-2), 147.70 (s, C-5), 191.18 (s, CO)
10	64	118–119	1628 (CO)	2.47 (3H, s, CH_3), 3.57 (3H, s, NCH_3), 3.88 (3H, s, OCH_3), 5.89 (1H, s, H-3)	30.07 (q, CH_3), 31.54 (q, NCH_3), 58.21 (q, OCH_3), 92.38 (d, C-3), 104.98 (s, C-4), 121.74 (s, C-2), 152.13 (s, C-5), 186.03 (s, CO).
11	6	oil	1667 (CO), 1532 (NO_2)	2.65 (3H, s, CH_3), 3.50 (3H, s, NCH_3)	31.29 (q, CH_3), 34.97 (q, NCH_3), 114.99 (s, C-3), 127.50 (s, C-5), 128.67 (s, C-4), 131.53 (s, C-2), 188.50 (s, CO)
12	55	118	1660 (CO), 1520 (NO_2)	2.47 (3H, s, CH_3), 3.90 (3H, s, NCH_3), 7.92 (1H, s, H-3)	27.21 (q, CH_3), 34.01 (q, NCH_3), 114.70 (d, C-3), 125.29 (s, C-5), 128.44 (s, C-4), 134.25 (s, C-2), 188.69 (s, CO)
13	40	113–115	1653 (CO), 1500 (NO_2)	2.35 (3H, s, CH_3), 3.93 (3H, s, NCH_3), 7.38 (1H, s, H-3)	26.92 (q, CH_3), 40.28 (q, NCH_3), 76.66 (s, C-5), 101.92 (s, C-2), 127.08 (d, C-3), 135.91 (s, C-4), 186.72 (s, CO)

[a] Satisfactory microanalyses obtained: C ± 0.3, H ± 0.2, N ± 0.3.
[b] Solvent for recrystallization: EtOH.
[c] Purified by column chromatography on silica gel [eluent: petroleum ether (bp 40–60 °C)/EtOAc, 7:3].
[d] Reaction time: for **7a,b** = 4 h, **7c** = 10 h, **7d** = 8 h.

Bromination of 2-Substituted 1-Methyl-4-nitropyrroles 1a,b; General Procedure:

To a stirred solution of pyrroles **1a,b**[16] (10 mmol) in anhyd DMF (30 mL) was added a solution of NBS (3.56 g, 20 mmol) in anhyd DMF (30 mL) at r.t. The mixture was heated at 50 °C for 1 h, cooled to r.t. and poured onto crushed ice. The solid precipitated was collected, air dried and chromatographed on a column of silica gel (80 g, eluent: CH_2Cl_2). The products **3a,b** were eluted first. Further elution gave **2a,b** (Table).

Reaction of 2-Substituted 5-Bromo-1-methyl-4-nitropyrroles 2a,b with Alkoxides; General Procedure:

A solution of the sodium alkoxide (2 mmol) in the corresponding anhyd alcohol (30 mL) was added to a solution of the pyrroles **2a,b** (2 mmol) in the same anhyd alcohol (30 mL). The mixture was kept at r.t. for 24 h. The solvent was evaporated under reduced pressure and the residue was purified by chromatography on a column of silica gel (25 g, eluent: CH_2Cl_2) (Table).

Reaction of 2-Substituted 5-Bromo-1-methyl-4-nitropyrroles 2a,b with Sodium Azide; General Procedure:

To a solution of pyrroles **2a,b** (2 mmol) in anhyd DMF (30 mL) was added a solution of NaN_3 (130 mg, 2 mmol) in anhyd DMF (10 mL). The mixture was kept at r.t. for 24 h and then poured onto crushed ice. The solid precipitated was collected and air dried (Table).

2-Acetyl-5-cyano-1-methyl-4-nitropyrrole (6):

To a stirred solution of pyrrole **2a** (494 mg, 2 mmol) in anhyd DMF (20 mL) was added a solution of NaCN (98 mg, 2 mmol) in anhyd DMF (10 mL). The mixture was kept at r.t. for 24 h and poured onto crushed ice. The solid precipitated was collected, air dried and chromatographed on a column of silica gel (25 g, eluent: CH_2Cl_2) to give **6** (Table).

Reaction of 2-Substituted 5-Bromo-1-methyl-4-nitropyrroles 2a,b with Amines; General Procedure:

To a solution of the pyrroles **2a,b** (2 mmol) in anhyd DMF (20 mL) was added the amine (6 mmol). The mixture was refluxed for 4–10 h, cooled to r.t. and poured onto crushed ice. The solid precipitated was collected, air dried and chromatographed on a column of silica gel (25 g, eluent: CH_2Cl_2) (Table).

2-Acetyl-5-(3-methoxyphenoxy)-1-methyl-4-nitropyrrole (4f):

To a solution of pyrrole **2a** (494 mg, 2 mmol) and Et_3N (0.28 mL, 2 mmol) in anhyd DMF (30 mL), was added 3-methoxyphenol (0.44 mL, 4 mmol). The mixture was refluxed for 12 h, cooled to r.t. and poured onto crushed ice. The solid precipitated was collected, air dried and chromatographed on a column of silica gel (25 g, eluent: CH_2Cl_2) to give **4f** (Table).

Reaction of 2-Acetyl-5-bromo-1-methyl-4-nitropyrrole (2a) with Thiophenols; General Procedure:

To a solution of pyrrole **2a** (494 mg, 2 mmol) and Et_3N (0.28 mL, 2 mmol) in anhyd DMF (30 mL), was added the appropiate thiophenol (4 mmol). The mixture was refluxed for 3 h, cooled to r.t. and poured onto crushed ice. The product formed was filtered and dried (Table).

2-Acetyl-4-bromo-1-methyl-5-nitropyrrole (9):

To a stirred solution of 2-acetyl-1-methyl-5-nitropyrrole[16] (336 mg, 2 mmol) in anhyd DMF (30 mL) was added a solution of NBS (712 mg, 4 mmol) in anhyd DMF (20 mL). The mixture was kept at 50 °C for 2 h, cooled to r.t. and poured onto crushed ice. The solid precipitated was collected, air dried and chromatographed on a column of silica gel (25 g, eluent: CH_2Cl_2). The first compound eluted was the unreacted starting pyrrole (8 %). Further elution gave **9** (Table).

2-Acetyl-4-bromo-5-methoxy-1-methylpyrrole (10):
To a solution of pyrrole **9** (247 mg, 1 mmol) in anhyd MeOH/DMF (9:1, 30 mL) was added 1 M NaOMe in anhyd MeOH (1 mL) and the mixture was refluxed for 4 h. The solvent was evaporated under reduced pressure and the residue chromatographed on a column of silica gel (15 g, eluent: CH_2Cl_2) to afford **10** (Table).

2-Acetyl-5-chloro-1-methyl-4-nitropyrrole (12):
To a solution of **1a** (504 mg, 3 mmol) in anhyd DMF (30 mL) was added a solution of *N*-chlorosuccinimide (801 mg, 6 mmol) in anhyd DMF (20 mL). The mixture was heated at 60 °C for 3 h, cooled to r.t. and poured onto crushed ice. The solid precipitated was collected, air dried and chromatographed on a column of silica gel (40 g, eluent: CH_2Cl_2). The first product eluted was **11**. Further elution gave **12** (Table).

2-Acetyl-5-iodo-1-methyl-4-nitropyrrole (13):
To a solution of **1a** (1.68 g, 10 mmol) in anhyd DMF (50 mL) was added a solution of *N*-iodosuccinimide (4.5 g, 20 mmol) in anhyd DMF (50 mL). The mixture was heated at 60 °C for 6 h, cooled to r.t. and poured onto crushed ice. The solid precipitated was collected, air dried and chromatographed on a column of silica gel (80 g, eluent: CH_2Cl_2). The first product eluted was the unreacted starting pyrrole (10%). Further elution gave **13** (Table).

2-Acetyl-5-methoxy-1-methyl-4-nitropyrrole (4a) from 12:
To a solution of pyrrole **12** (405 mg, 2 mmol) in anhyd MeOH (30 mL) was added a solution of 1 M NaOMe in anhyd MeOH (2 mL). The mixture was kept at r.t. for 24 h. The solvent was evaporated under reduced pressure and the residue was chromatographed on a column of silica gel (25 g, eluent: CH_2Cl_2) to give **4a**, which was identical with an authentic sample (TLC, IR, NMR) prepared from **2a**; yield: 74%.

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