PYRROLO[2,3-*b*][1,4]BENZOTHIAZINE. A NEW RING SYSTEM FROM AZIDOPYRROLES

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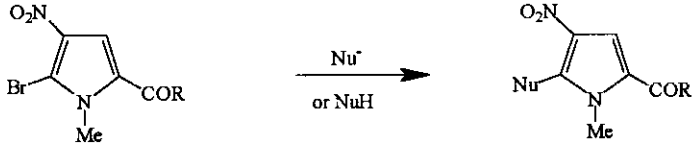
Abstract – Nucleophilic substitutions in pyrrole series by uncharged nucleophiles, represented a valuable and versatile method to synthesize different types of key intermediates such as compounds (**6**), that were used to prepare the corresponding azides (**10**) which by thermal decomposition afforded the title ring system (**11**).

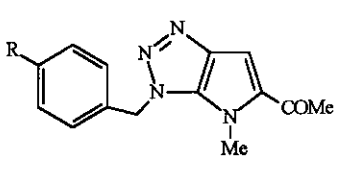
We recently described several examples of direct nucleophilic reactions on halonitropyrroles of type (**1**).[1] These reactions were achieved either by charged and neutral carbon, nitrogen, oxygen and sulfur nucleophiles. Such substitutions constitute a valuable and versatile route to prepare key intermediates of type (**2-6**) for the synthesis of polycyclic systems.



1 a,b **2-6**

2 Nu=OMe, OEt, R=H, Me; **3** Nu=N_3, R=H, Me; **4** Nu=CN, R=Me; **5** Nu=Pyrrolidinyl, R=H, Me; **6** **a** Nu=C_6H_5S, R=Me; **b** Nu=4-MeC_6H_4S, R=Me

As examples of the wide potentiality of nucleophilic substitution in pyrrole series and in connection with our studies on polycondensed nitrogen heterocycles of biological importance, we reported the synthesis of the pyrrolo[2,3-*d*][1,2,3]triazole[2] ring system of type (**7**), potential alkylating agents, and of the pyrrolo[3,2-*c*][1,2,5]benzotriazocine[3] ring system of type (**8**), related to the class of the potent CNS-acting benzodiazepines.



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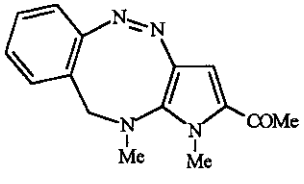

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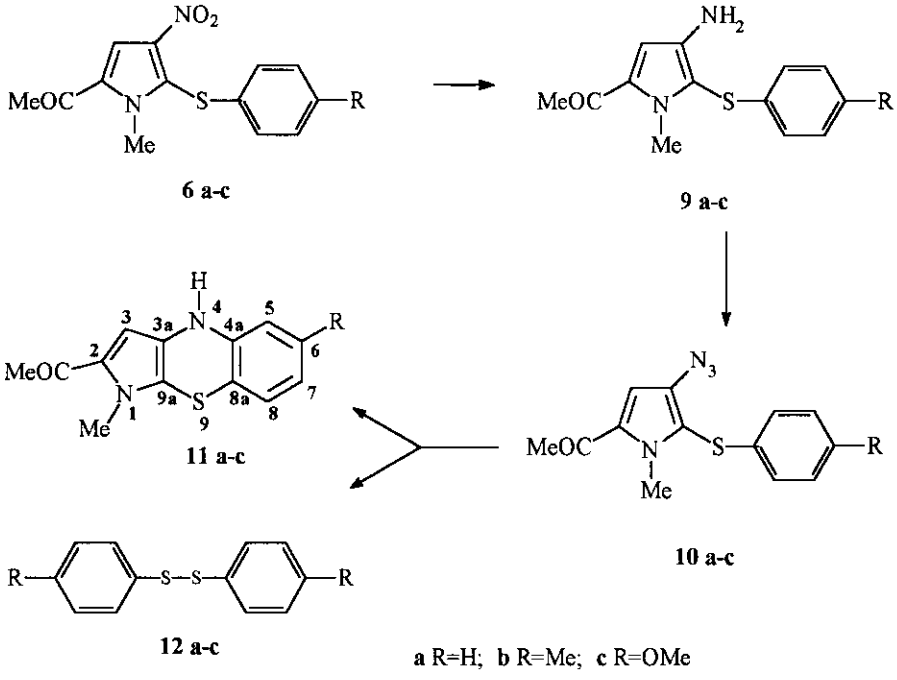
A further example of the versatility of the nucleophilic substitutions in pyrrole series is demostrated by the preparation of the new ring system pyrrolo[2,3-*b*][1,4]benzothiazine of type (**11**) reported below.

This ring system is certainly of pharmacological interest since either 1,4-benzothiazine and annelated 1,4-benzothiazine derivatives possess a wide spectrum of biological activities. In fact 1,4-benzothiazine derivatives are used in pharmaceutical compositions as ciliary muscle relaxants for pseudomyopia and eye fatigue;[4] other derivatives showed cardiotonic, bronchodilator properties,[5] and antifungal activity.[6]



a R=H; **b** R=Me; **c** R=OMe

The annelated 1,4-benzothiazine have much greater importance in therapy. In fact phenothiazine is a veterinary anthelmintic agent and *N*-substituted phenothiazine derivatives, such as promethazine and chlormethazine, due to their powerful depressant effects on the central nervous system, reached the market as antipsycotic agents.[7] Annelation of the pyrrole ring to the 1,4-benzothiazine produced compounds that are active as calcium channel antagonists.[8]

The synthesis started with the reaction of the bromo derivatives (**1a**) with substituted thiophenols to give the corresponding product of direct nucleophilic substitution (**6a-c**) in 70-90% yields. The reaction was carried out in refluxing dimethylformamide with a stoichiometric amount of triethylamine to neutralize the hydrogen bromide developed during the reaction. The nitro compounds (**6a-c**) were reduced catalytically over palladium on charcoal to give the amino derivatives (**9a-c**) in 75-88% yield. The structure of these compounds was confirmed on the basis of the IR as well as the ^{1}H NMR and ^{13}C NMR spectra. In fact the IR spectra showed very broad absorption bands centered at 3427-3425 and 3340-3320 cm^{-1} due to the stretchings of the amino group. The ^{1}H NMR spectra, beside the signals also present in the

starting nitro derivatives, exhibited an exchangeable signal for two protons at 4.39-4.47 ppm due to amino substituent. ^{13}C NMR spectra showed, with respect to that of nitro derivative, an upfield shift of the C-5 resonance (15-18 ppm) due to the different effects on the *ortho* carbon exerted by the nitro and amino groups.[9,10] Amines (**9a-c**) were diazotized in acetic acid and the diazonium salts were directly reacted with an excess of sodium azide to give the azido derivatives (**10a-c**) in excellent yields (80-90%). The azido derivatives (**10**) were identified by IR spectra that showed a strong absorption band at 2116 cm^{-1}. ^{13}C NMR spectra showed with respect to the amino derivative a downfield shift of the pyrrole C-5 resonance (4-7 ppm) and a smaller upfield shift of C-4 resonance (~ 3 ppm) due to the two the different effects on the *ipso* carbon and on the adjacent carbon exerted by the amino and azido groups.[10]

We supposed that decomposition of the azides of type (**10**) by treatment with trifluoromethanesulfonic acid (TFMSA) could produce the intermediate nitrenium ion capable of an aromatic electrophilic substitution on the position of the phenyl ring *ortho* to the sulfur atom, giving the 1,4-thiazine ring, by analogy with the acid assisted decomposition of substituted 1- and 2-azidophenylpyrroles that cyclized to the pyrrolo[1,2-*f*]phenanthridine ring sistem.[11,12] Unfortunately this type of decomposition gave a very complex reaction mixture and extensive formation of tars.

Thermal decomposition of the azido derivatives (**10**) at 15°C above their melting point for 8-10 hours gave a complex mixture from which it was possible to isolate the 6-substituted 2-acetyl-1-methyl-1,4-dihydro-4*H*-pyrrolo[2,3-*b*][1,4]benzothiazines (**11a-c**) (30-40%) and the disulfide derivatives (**12a-c**) (25-30%). It was observed that when the reaction was carried out under argon atmosphere the yields of derivatives (**11**) increased (40-45%), whereas the yields of the disulfide derivatives (**12a-c**) decrease (15-18%). The structure of the derivatives of the new ring system was confirmed by analytical as well as spectroscopic data. In the IR spectra disappeared the characteristic band due to the azido group and appeared a broad absorption band at 3442-3437 cm^{-1} attributable to the NH stretching. In the ^{1}H NMR spectra the exchangeable NH signals were shown at 7.05-7.57 ppm and the H-3 was exhibited at 7.40-7.43 ppm. The phenyl protons confirmed the ring closure showing, in the case of **11a**, an integration for four protons and a pattern typical for a condensed benzene; in the case of **11b,c**, the characteristic pattern for a 1,4 disubstituted benzene of the starting azide was replaced by three signals for one proton each typical for 1,2,4 trisubstituted benzenes.

EXPERIMENTAL SECTION

All melting points were taken on Buchi-Tottoli capillary apparatus and are uncorrected; IR spectra were determined in bromoform with a JASCO FT/IR 410 spectrophotometer; ^{1}H and ^{13}C NMR spectra were measured at 200 and 50.3 MHz respectively in DMSO-d_6 solution, using a Bruker AC series 200 MHz spectrometer (TMS as internal reference). Column chromatography was performed with Merck silica gel

230-400 Mesh ASTM.

Preparation of 2-Acetyl-1-methyl-4-nitro-5-(4-substituted phenylthio)pyrroles (6a-c)

Compounds (**6a-c**) were prepared according to the procedure described previously for **6a,b**.[1]

To a solution of the pyrrole (**1a**) (0.494 g, 2 mmol) and triethylamine (0.202 g, 2 mmol) in anhydrous DMF (30 mL), was added the 4-substituted thiophenols (4 mmol). The mixture was heated under reflux for 3 h, cooled to rt and poured onto crushed ice. The formed precipitate was filtered, air dried and purified by column chromatography using dichloromethane as eluant.

2-Acetyl-5-(4-methoxyphenylthio)-1-methyl-4-nitropyrrole (6c): Yield 90%, mp 144-145°C (ethanol); IR: 1668 (CO), 1493 (NO_2) cm^{-1}; ^1H NMR (ppm): 2.50 (3H, s, CH_3), 3.73 (3H, s, CH_3), 3.91 (3H, s, CH_3), 6.92 (2H, d, J=8.8 Hz, H-3' and H-5'), 7.25 (2H, d, J=8.8 Hz, H-2' and H-6'), 7.93 (1H, s, H-3); ^{13}C NMR (ppm): 27.5 (q, CH_3), 34.7 (q, CH_3), 55.2 (q, CH_3), 115.2 (d, C-3), 115.3 (d, C-3' and C-5'), 122.8 (s, C-1'), 130.3 (s, C-5), 131.0 (s, C-2), 131.5 (d, C-2' and C-6'), 136.7 (s, C-4), 159.1 (s, C-4'), 188.9 (s, CO). Anal. Calcd for $C_{14}H_{14}N_2O_4S$: C, 54.89; H, 4.61; N, 9.15. Found: C, 55.01; H, 4.49; N, 9.16.

Preparation of 2-Acetyl-4-amino-1-methyl-5-(4-substituted phenylthio)pyrroles (9a-c)

A solution of the nitro derivatives (**6a-c**) (4 mmol) in ethanol (80 mL) was reduced over 10% Pd on charcoal (0.1 mg) in a Parr apparatus at 60 psi at rt for 24 h. Removal of the catalyst and evaporation of the solvent under reduced pressure gave a solid, which was purified by column chromatography using dichloromethane:ethyl acetate 98:2 as eluant.

2-Acetyl-4-amino-1-methyl-5- phenylthiopyrrole (9a): Yield 88 %, mp 73-75°C (ethanol); IR: 3425 and 3320 (br, NH_2), 1649 (CO) cm^{-1}; ^1H NMR (ppm): 2.42 (3H, s, CH_3), 3.77 (3H, s, CH_3), 4.46 (2H, s, NH_2), 6.62 (1H, s, H-3), 7.05 (2H, d, J=7.3 Hz, H-2' and H-6'), 7.21 (1H, t, J=7.3 Hz, H-4'), 7.34 (2H, t, J=7.3 Hz, H-3' and H-5'); ^{13}C NMR (ppm): 27.5 (q, CH_3), 33.0 (q, CH_3), 106.2 (d, C-3), 110.7 (s, C-5), 125.7 (d, C-3' and C-5'), 126.0 (d, C-4'), 129.5 (d, C-2' and C-6'), 131.5 (s, C-4), 136.8 (s, C-2), 140.0 (s, C-1'), 188.1 (s, CO). Anal. Calcd for $C_{13}H_{14}N_2OS$: C, 63.39; H, 5.73; N, 11.38. Found: C, 63.48; H, 5.68; N, 11.41.

2-Acetyl-4-amino-1-methyl-5-(4-methylphenylthio)pyrrole (9b): Yield 75 %, mp 82-84°C (ethanol); IR: 3426 and 3340 (br, NH_2), 1649 (CO) cm^{-1}; ^1H NMR (ppm): 2.23 (3H, s, CH_3), 2.35 (3H, s, CH_3), 3.71 (3H, s, CH_3), 4.39 (2H, s, NH_2), 6.65 (1H, s, H-3), 6.91 (2H, d, J=8.8 Hz, H-3' and H-5'), 7.10 (2H, d, J=8.8 Hz, H-2' and H-6'); ^{13}C NMR (ppm): 20.4 (q, CH_3), 27.3 (q, CH_3), 32.9 (q, CH_3), 106.0 (d, C-3), 111.3 (s, C-5), 126.0 (d, C-3' and C-5'), 130.0 (d, C-2' and C-6'), 131.1 (s, C-4), 133.0 (s, C-2), 135.3 (s, C-1'), 139.6 (s, C-4'), 187.8 (s, CO). Anal. Calcd for $C_{14}H_{16}N_2OS$: C, 64.59; H, 6.20; N, 10.77. Found: C, 64.70; H, 6.11; N, 10.61.

2-Acetyl-4-amino-5-(4-methoxyphenylthio)-1-methylpyrrole (9c): Yield 80 %, mp 66°C (ethanol); IR: 3427 and 3340 (br, NH_2), 1647 (CO) cm^{-1}; ^1H NMR (ppm): 2.41 (3H, s, CH_3), 3.76 (3H, s, CH_3), 3.87 (3H, s, CH_3), 4.47 (2H, s, NH_2), 6.52 (1H, s, H-3), 6.80 (2H, d, J=8.8 Hz, H-3' and H-5'), 7.01 (2H, d, J=8.8 Hz, H-2' and H-6'); ^{13}C NMR (ppm): 27.4 (q, CH_3), 33.6 (q, CH_3), 55.3 (q, CH_3), 106.4 (d, C-3), 115.0 (d, C-3' and C-5'), 115.3 (s, C-5), 126.6 (s, C-1'), 128.3 (d, C-2' and C-6'), 131.3 (s, C-4), 137.1 (s, C-2), 158.4 (s, C-4'), 188.4 (s, CO). Anal. Calcd for $C_{14}H_{16}N_2O_2S$: C, 60.85; H, 5.84; N, 10.14. Found: C, 60.77; H, 5.91; N, 10.01.

Preparation of 2-Acetyl-4-azido-1-methyl-5-(4-substituted phenylthio)pyrroles (10a-c)

To a solution of the amines (**9a-c**) (3 mmol) in acetic acid (5 mL) a solution of sodium nitrite (0.207 g, 3 mmol) in water (1 mL) was added at 0°C. After 15 min sodium azide (1.95 g, 30 mmol) in water (5 mL) was added dropwise at 0°C. The solid precipitated was filtered, air dried and recrystallized from ethanol to give the azides (**10a-c**).

2-Acetyl-4-azido-1-methyl-5-phenylthiopyrrole (10a): Yield 80 %, mp 100°C; IR: 2116 (N_3), 1657 (CO) cm^{-1}; ^1H NMR (ppm): 2.46 (3H, s, CH_3), 3.80 (3H, s, CH_3), 7.03 (2H, dd, J=7.8, 1.9 Hz, H-2' and H-6'), 7.22 (1H, dt, J=7.8, 1.9 Hz, H-4'), 7.32 (1H, s, H-3), 7.33 (2H, dd, J=7.8, 1.9 Hz, H-3' and H-5'); ^{13}C NMR (ppm): 27.5 (q, CH_3), 33.4 (q, CH_3), 109.7 (d, C-3), 117.5 (s, C-5), 126.2 (d, C-3' and C-5'), 126.5 (d, C-4'), 128.8 (s, C-4), 129.6 (d, C-2' and C-6'), 132.2 (s, C-2), 135.3 (s, C-1'), 188.5 (s, CO). Anal. Calcd for $C_{13}H_{12}N_4OS$: C, 57.35; H, 4.44; N, 20.58. Found: C, 57.41; H, 4.38; N, 20.70.

2-Acetyl-4-azido-1-methyl-5-(4-methylphenylthio)pyrrole (10b): Yield 80 %, mp 90°C; IR: 2116 (N_3), 1657 (CO) cm^{-1}; ^1H NMR (ppm): 2.24 (3H, s, CH_3), 2.44 (3H, s, CH_3), 3.80 (3H, s, CH_3), 6.96 (2H, d, J=7.8 Hz, H-3' and H-5'), 7.13 (2H, d, J=7.8 Hz, H-2' and H-6'), 7.28 (1H, s, H-3); ^{13}C NMR (ppm): 20.5 (q, CH_3), 27.5 (q, CH_3), 33.4 (q, CH_3), 109.7 (d, C-3), 118.4 (s, C-5), 126.8 (d, C-3' and C-5'), 128.5 (s, C-4), 130.2 (d, C-2' and C-6'), 131.6 (s, C-2), 132.0 (s, C-1'), 136.2 (s, C-4'), 188.4 (s, CO). Anal. Calcd for $C_{14}H_{14}N_4OS$: C, 58.72; H, 4.93; N, 19.58. Found: C, 58.91; H,4.80 ; N, 18.65.

2-Acetyl-4-azido-5-(4-methoxyphenylthio)-1-methylpyrrole (10c): Yield 90 %, mp 45°C; IR: 2116 (N_3), 1657 (CO) cm^{-1}; ^1H NMR (ppm): 2.43 (3H, s, CH_3), 3.72 (3H, s, CH_3), 3.82 (3H, s, CH_3), 6.91 (2H, d, J=8.8 Hz, H-3' and H-5'), 7.12 (2H, d, J=8.8 Hz, H-2' and H-6'), 7.26 (1H, s, H-3); ^{13}C NMR (ppm): 27.5 (q, CH_3), 33.5 (q, CH_3), 55.2 (q, CH_3), 109.6 (d, C-3), 115.3 (d, C-3' and C-5'), 119.7 (s, C-5), 125.0 (s, C-1'), 128.1 (s, C-4), 129.8 (d, C-2' and C-6'), 131.7 (s, C-2), 158.6 (s, C-4'), 188.4 (s, CO). Anal. Calcd for $C_{14}H_{14}N_4O_2S$: C, 55.62; H, 4.67; N, 18.54. Found: C, 55.82; H, 4.77; N, 18.51.

Decomposition of the Azidopyrroles (10a-c)

Compounds (**10a-c**) (2 mmol) were heated under argon atmosphere at 15°C above their mp. The

compounds were kept at the same temperature for 8-10 h. The dark solid was purified by chromatography on column using dichloromethane as eluant. The first products eluted were the disulfide derivatives (**12a-c**):

12a: Yield 15 %, mp 58-59°C (ethanol). **12b**: Yield 15 %, mp 45-47°C (ethanol). **12c:** Yield 18 %, mp 32-35°C (ethanol).

Further elution gave the 6- substituted 2-acetyl-1-methyl-1,4-dihydropyrrolo[2,3-*b*][1,4]benzothiazines (**11a-c**):

2-Acetyl-1-methyl-1,4-dihydro-4*H*-pyrrolo[2,3-*b*][1,4]benzothiazine (11a) Yield 40%, mp 145-146°C (ethanol); IR: 3437 (NH), 1651 (CO) cm^{-1}; ^1H NMR (ppm): 2.73 (3H, s, CH_3), 4.24 (3H, s, CH_3), 7.20 (1H, s, NH), 7.43 (1H, s, H-3), 7.52-7.57 (2H, m, H-6 and H-7), 7.71-7.76 (2H, m, H-5 and H-8); ^{13}C NMR (ppm): 32.0 (q, CH_3), 65.7 (q, CH_3), 107.6 (d, C-3), 112.5 (s, C-9a), 115.8 (s, C-3a), 120.8 (d, C-6), 126.1 (s, C-2), 128.0 (d, C-8), 129.0 (d, C-5), 130.1 (d, C-7), 142.2 (s, C-4a), 145.4 (s, C-8a), 194.0 (s, CO). Anal. Calcd for $C_{13}H_{12}N_2OS$: C, 63.91; H, 4.95; N, 11.47. Found: C, 64.08; H, 4.88; N, 11.31.

2-Acetyl-1,6-dimethyl-1,4-dihydro-4*H*-pyrrolo[2,3-*b*][1,4]benzothiazine (11b) Yield 40%, uncrystallizable oil; IR: 3442 (NH), 1664 (CO) cm^{-1}; ^1H NMR (ppm): 2.29 (3H, s, CH_3), 2.71 (3H, s, CH_3), 4.23 (3H, s, CH_3), 7.05 (1H, s, NH), 7.41 (1H, s, H-3), 7.53 (1H, dd, J=7.8, 2.0 Hz, H-7), 7.69 (1H, d, J=2.0 Hz, H-5), 7.73 (1H, d, J=7.8 Hz, H-8); ^{13}C NMR (ppm): 22.7 (q, CH_3), 31.9 (q, CH_3), 65.6 (q, CH_3), 107.7 (d, C-3), 112.5 (s, C-9a), 115.6 (s, C-3a), 126.0 (s, C-2), 128.8 (d, C-8), 129.8 (s, C-6), 130.3 (d, C-5), 130.9 (d, C-7), 141.0 (s, C-8a), 145.4 (s, C-4a), 194.0 (s, CO). Anal. Calcd for $C_{14}H_{14}N_2OS$: C, 65.09; H, 5.47; N, 10.85. Found C, 64.91; H, 5.31; N, 10.97.

2-Acetyl-6-methoxy-1-methyl-1,4-dihydro-4*H*-pyrrolo[2,3-*b*][1,4]benzothiazine (11c) Yield 45%, uncrystallizable oil; IR: 3437 (NH), 1651 (CO) cm^{-1}; ^1H NMR (ppm): 2.71 (3H, s, CH_3), 4.22 (3H, s, CH_3), 4.27 (3H, s, CH_3), 7.26 (1H, s, NH), 7.40 (2H, br s, H-3 and H-5), 7.48 (1H, dd, J=7.6, 1.9 Hz, H-7), 7.65 (1H, d, J=7.6 Hz, H-8); ^{13}C NMR (ppm): 31.8 (q, CH_3), 56.4 (q, CH_3), 65.6 (q, CH_3), 107.7 (d, C-3), 113.1 (s, C-9a), 115.9 (s, C-3a),126.0 (d, C-5), 126.1 (s, C-2), 126.9 (d, C-7), 130.9 (d, C-8), 136.0 (s, C-6), 138.6 (s, C-8a), 143.4 (s, C-4a), 192.0 (s, CO). Anal. Calcd for $C_{14}H_{14}N_2O_2S$: C, 61.30; H, 5.15; N, 10.21. Found: C, 61.41; H, 5.02; N, 10.42.

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