Pyrrolo[3,2-*c*][1,2,5]benzotriazocine: A New Ring System [1]

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A nucleophilic substitution reaction in the pyrrole series, achieved by a neutral nucleophile, led to the key intermediate **7** which by reduction and successive diazotization afforded the new ring system pyrrolo[3,2-*c*][1,2,5]benzotriazocine **9** in good yield.

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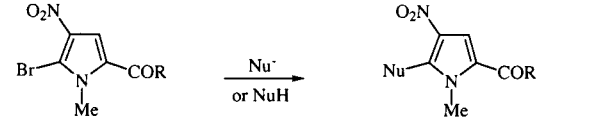
We recently described several examples of nucleophilic reactions on halopyrroles either by charged and neutral carbon, nitrogen, oxygen and sulfur nucleophiles [2]. The nucleophilic reactions achieved by neutral nitrogen, oxygen and sulfur nucleophiles constitute the first examples of direct nucleophilic substitution in the pyrrole series by uncharged nucleophiles. These types of reactions represent a valuable and versatile route to prepare a wide variety of functionalized pyrroles and to obtain building blocks for the synthesis of polycyclic systems.

Scheme 1



1a,b

a R = Me, **b** R = H

2-6

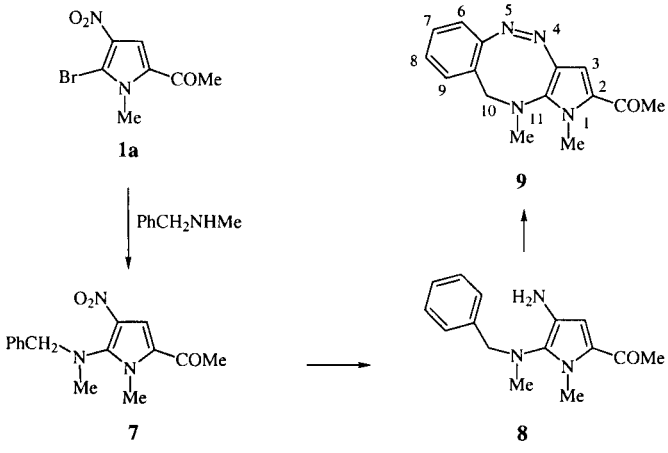
2a	Nu = OMe, R = Me
b	Nu = OMe, R = H
c	Nu = OEt, R = Me
d	Nu = OEt, R = H
3a	Nu = N_3, R = Me
b	Nu = N_3, R = H
4	Nu = CN, R = Me
5a	Nu = Pyrrolidinyl, R = Me
b	Nu = Pyrrolidinyl, R = H
6a	Nu = C_6H_5S, R = Me
b	Nu = 4-MeC_6H_5S, R = Me

As an example of the wide potential of nucleophilic substitution in the pyrrole series and in connection with our studies on polycondensed nitrogen heterocycles of biological importance, we now report an efficient method for the preparation of the new ring system pyrrolo[3,2-*c*][1,2,5]benzotriazocine **9**. In fact, despite the importance of eight membered heterocycles containing at least two nitrogen atoms in a 1-4 relationship, which are structurally related to the class of potent CNS-acting benzodiazepines, only a small number of benzotriazocines is known. In particular, of the ten benzotriazocine systems that are theoretically possible, only four are known [3]. These are 1,3,4- [4], 1,3,6- [5], 1,4,5- [6] and 2,3,5-benzotriazocine systems [7]. Among the isomers known, only derivatives of the 1,4,5-benzotriazocine system have shown biological activities such as analgesic and sedative [6], and psychotropic agents [8]. Only very few condensed benzotriazocine derivatives have been reported. In fact only pyrrolobenzotriazocine [9,10] and pyrazolobenzotriazocine [10,11] are known. Neither pyrrolo-1,2,5-benzotriazocine nor 1,2,5-benzotriazocine systems have been reported to date.

The synthesis of the title ring system was accomplished starting from the bromo derivative **1a** which was allowed to react with the *N*-methyl-*N'*-benzylamine to give the corresponding product of direct nucleophilic substitution **7** in 90% yield. The reaction was carried out in refluxing dimethylformamide with an excess of amine to neutralize the hydrogen bromide developed during the reaction. The structure of compound **7** was confirmed on the basis; of the ^1H and ^{13}C nmr spectra. The ^1H nmr spectrum, beside the signals also present in the starting material, exhibited a singlet for three protons at 3.68 ppm due to the benzylic *N*-methyl group, a singlet for two protons at 4.23 ppm attributable to the methylene group and a singlet at 7.30 ppm for five protons of the phenyl group. The ^{13}C nmr spectrum showed, with respect to that of the starting bromo derivative **1a**, a marked downfield shift of the pyrrole C-5 resonances (*ca* 31 ppm) and a smaller but significant upfield shift of the pyrrole C-4 signals (*ca* 3 ppm) [12]. Such shifts are justified by the effects that the amino and the bromo groups exert on the *ipso* carbon and on the *ortho* position. In fact the presence of the amino group causes a strong downfield shift of the *ipso* carbon and a nearly equal upfield shift of the *ortho* carbon [13]. The bromo group exerts opposite but smaller effects on the above carbon [14].

Nitro compound **7** was reduced to the corresponding amino derivative **8** with hydrogen and palladium on charcoal at room temperature (yield 77%). The formation of the 3-amino group was confirmed by the appearance in the ir spectra of a very broad absorption band centered at 3310 cm^{-1} and, in the ^1H nmr spectrum, of an exchangeable signal for two protons at 3.78 ppm. Moreover, in the

Scheme 2



^{13}C nmr spectrum, the upfield shift of the C-5 resonance (*ca* 7 ppm) gives account of the different effects on the ortho carbon C-5 exerted by the nitro and amino groups present in position 4 in compounds **7** and **8** respectively.

Diazotization of derivative **8** in acetic acid afforded the pyrrolo[3,2-*c*][1,2,5]benzotriazocine ring system **9**, following the intramolecular coupling reaction of the diazonium group with the *ortho* position of the benzylamino moiety, in 75% yield. The structure was confirmed in the ir spectra, by the disappearance of the very broad NH_2 absorption and by the appearance of a band, at 1493 cm^{-1}, due to the stretching of the N=N group. In the ^1H nmr spectrum, the methylene group of compound **9**, bonded to the N-11 nitrogen, appeared as a singlet at 4.52 ppm, the H-3 proton appeared at 6.98 ppm, and the four benzene protons were a multiplet in the range 7.21-7.38 pm.

EXPERIMENTAL

All melting points were taken on a Buchi-Tottoli capillary apparatus and are uncorrected; ir spectra were determined with a Jasco FT/IR 5300 spectrophotometer; ^1H and ^{13}C nmr spectra were measured in dimethyl-d_6 sulfoxide solutions, (tetramethylsilane as internal reference), 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.

Preparation of 2-Acetyl-5-(*N*-benzyl-*N*'-methylamino)-1-methyl-4-nitropyrrole (**7**).

To a solution of the pyrrole **1** [2] (2 mmoles) in anhydrous dimethylformamide (20 ml), the *N*-benzyl-*N*'-methylamine (6 mmoles) was added. The reaction mixture was refluxed for 3 hours, cooled to room temperature and poured onto crushed ice. The solid precipitate was collected, air dried and purified by chromatography on column (25 g, eluent: dichloromethane). The only compound eluted was 2-acetyl-5-(*N*-benzyl-*N*'-methylamino)-1-methyl-4-nitropyrrole (**7**), yield 90%, mp 68°; ir: 1660 (CO), 1506 (NO_2) cm^{-1}; ^1H nmr: ppm 2.40 (3H, s, CH_3), 2.79 (3H, s, NCH_3), 3.68 (3H, s, CH_2NCH_3), 4.23 (2H, s, CH_2), 7.30 (5H, s, C_6H_5), 7.68 (1H, s, H-3); ^{13}C nmr: ppm 26.8 (q, CH_3), 33.1 (q, NCH_3), 39.3 (q, CH_2NCH_3), 57.7 (t, CH_2), 114.8 (d, C-3), 124.8 (s, C-2), 127.5 (s, C-4), 127.6 (d, C-4'), 128.5 (d, C-2', C-6', C-3' and C-5'), 137.3 (s, C-1'), 145.4 (s, C-5), 188.5 (s, CO).

Anal. Calcd. for $C_{15}H_{17}N_3O_3$: C, 62.70; H, 5.96; N, 14.63. Found: C, 62.86; H, 5.68; N, 14.78.

Preparation of 2-Acetyl-4-amino-5-(*N*-benzyl-*N*'-methylamino)-1-methylpyrrole (**8**).

A solution of the nitro derivative **7** (5 mmoles) in ethanol was reduced over 10% Pd on charcoal in a Parr apparatus at 60 psi at room temperature for 24 hours. Removal of the catalyst and evaporation of the solvent under reduced pressure gave a residue which was purified by chromatography on column (25 g; eluent: dichloromethane:ethyl acetate 8:2). The first product eluted was the unreacted, nitro derivative **7** (yield 4%). Further elution gave 2-acetyl-4-amino-5-(*N*-benzyl-*N*'-methylamino)-1-methylpyrrole (**8**), yield 77%; mp 100°; ir: 3310 (NH_2), 1630 (CO) cm^{-1}; ^1H nmr: ppm 2.18 (3H, s, CH_3), 2.67 (3H, s, NCH_3), 3.59 (3H, s, CH_2NCH_3), 3.78 (2H, s, NH_2), 4.16 (2H, s, CH_2), 6.39 (1H, s, H-3), 7.23-7.34 (5H, m, C_6H_5); ^{13}C nmr: ppm 26.3 (q, CH_3), 31.4 (q, NCH_3), 39.9 (q, CH_2NCH_3), 57.9 (t, CH_2), 109.3 (d, C-3), 122.5 (s, C-4), 126.1 (s, C-2), 127.0 (d, C-4'), 128.2 (d, C-3' and C-5'), 128.5 (d, C-2' and C-6'), 135.2 (s, C-1'), 138.8 (s, C-5), 185.5 (s, CO).

Anal. Calcd. for $C_{15}H_{19}N_3O$: C, 70.01; H, 7.44; N, 16.33. Found: C, 70.02; H, 7.31; N, 16.55.

Preparation of 1-(10,11-Dihydro-1,11-dimethyl-1*H*-pyrrolo-[3,2-*c*][1,2,5]benzotriazocin-2-yl)ethanone (**9**).

To a solution of the amine **8** (1.6 mmoles) in acetic acid (30 ml) at 0°, a stoichiometric amount of sodium nitrite (1.6 mmoles), dissolved in water (2 ml), was added. The reaction mixture was allowed to stand at 4° overnight, poured onto crushed ice and extracted with diethyl ether (3 x 50 ml). The organic layer, evaporated under reduced pressure, gave a residue which was purified by chromatography on a column (25 g, eluent, dichloromethane:ethyl acetate 9:1) to give 1-(10,11-dihydro-1,11-dimethyl-1*H*-pyrrolo-[3,2-*c*][1,2,5]triazocin-2-yl)ethanone (**9**), yield 75%, mp 130-132°; ir: 1641 (CO), 1493 (N=N) cm^{-1}; ^1H nmr: ppm 2.35 (3H, s, CH_3), 2.93 (3H, s, NCH_3), 3.75 (3H, s, CH_2NCH_3), 4.52 (2H, s, CH_2), 6.98 (1H, s, H-3), 7.21-7.38 (4H, m, H-6, H-7, H-8 and H-9); ^{13}C nmr: ppm 26.7 (q, CH_3), 31.1 (q, NCH_3), 41.9 (q, CH_2NCH_3), 60.6 (t, C-10), 105.6 (d, C-3), 126.9 (s, C-11a), 127.4 (d, C-9), 128.4 (s, C-2), 128.4 (d, C-6), 128.5 (d, C-7 and C-8), 135.4 (s, C-5a), 138.1 (s, C-3a), 148.5 (s, C-9a), 188.7 (s, CO).

Anal. Calcd. for $C_{15}H_{16}N_4O$: C, 67.13; H, 6.01; N, 20.89. Found: C, 66.94; H, 6.12; N, 21.00.

Acknowledgements.

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REFERENCES AND NOTES

[1] An account of this work was presented at the First Swiss-Italian Joint Meeting on Medicinal Chemistry, Torino, Italy, September 1997, Abstract B62.

[2] G. Cirrincione, A. M. Almerico, A. Passannanti, P. Diana and F. Mingoia, *Synthesis,* 1169 (1997).

[3] The theoretically possible benzotriazocines are the 1,2,3-, 1,2,4-, 1,2,5-, 1,2,6-, 1,3,4-, 1,3,5-, 1,3,6-, 1,4,5-, 2,3,4-, and 2,3,5-benzotriazocine systems. J. K. Daniel and N. P. Peet erroneously reported in *J Heterocyclic Chem.,* **15**, 1309 (1978) that the theoretically possible benzotriazocine systems were eight neglecting the 1,2,4- and 1,2,5-benzotriazocine systems and mentioning the 1,2,6- system as the 1,5,6-benzotriazocine system.

[4] B. M. Adger, C. W. Rees and R. Storr, *J. Chem. Soc., Perkin Trans. I,* 45 (1975).

[5] F. Bertha, G. Hornyak, K. Zauer, A. Feller, K. Lempert, E. Pjeczka, and G. Toth, *Tetrahedron,* **41**, 2855 (1985) and references cited therein.

[6] See for example: M. Shindo, M. Kakimoto, H. Nagano, Y. Fujimura and C. Yasuo, German Offen. 2,308,064 730906; *Chem Abstr.,* **79**, 126537 (1973).

[7] K. Galewicz-Walesa, *Acta Pol. Pharm.,* **51**, 77 (1994); *Chem Abstr.,* **122**, 81340 (1995).

[8] Chugai Pharmaceutical Co., Japan Patent 56 001,313 B4 810113; *Chem. Abstr.,* **95**, 7363 (1981).

[9] D. Korakas, A. Kimbaris and G. Varvounis, *Tetrahedron,* **52**, 10751 (1996).

[10] A. Costanzo, F. Bruni, G. Guerrini, S. Selleri, P. Malmberg Aiello and C. Lamberti, *J. Heterocyclic Chem.,* **29**, 1499 (1992).

[11] S. Plescia, E. Aiello and V. Sprio, *J. Heterocyclic Chem.,* **12**, 199 (1975).

[12] Reported ^{13}C nmr chemical shifts for C-4 and C-5 for **1a** are 130.7 and 114.9 ppm respectively, (see reference 2).

[13] G. Cirrincione, A. M. Almerico, E. Aiello and G. Dattolo, Aminopyrroles in the Chemistry of Heterocyclic Compounds, Vol **48**, Pyrroles, Part II, R. A. Jones, ed, J. Wiley & Sons, Inc., Publisher, 1992, p. 424.

[14] E. Pretsch, T. Clerc, J. Seibl and W. Simon, in Tables of Spectral Data for Structure Determination of Organic Compounds, Springer-Verlag, 1989, p C 120.