NUCLEOPHILIC SUBSTITUTION AT THE AMINALIC CARBON OF SOME MACROCYCLIC POLYAMINALS

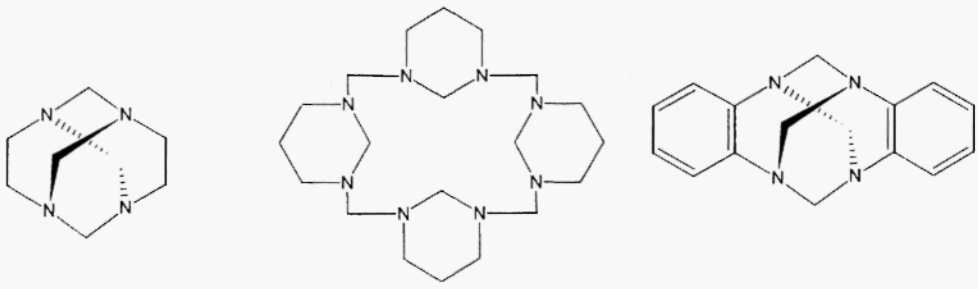
Augusto Rivera[1]*, Mauricio Maldonado, Martin E. Núñez[1] and Pedro Joseph-Nathan[2]

[1]Departamento de Química, Universidad Nacional de Colombia, Apartado Aereo 14490, Ciudad Universitaria, Bogotá, Colombia.
[2]Departamento de Química, Centro de Investigación y de Estudios Avanzados del Instituto Politecnico Nacional, Apartado 14-740, México D.F., 07000, Mexico.

Abstract - Macrocyclic polyaminals 1,3,6,8-tetraazatricyclo[4.4.1.1^{3,8}]dodecane **1**, 1:3,7:9,13:15,19:21-tetramethyleneperhydro pyrimidine **2**, and 6H,13H-5:12,7:14-dimethanedibenzo[d,i] [1,3,6,8]tetrazecine **3** react at room temperature with benzotriazole to give symmetrical imidazolidine, perhydropyrimidine and 2,3-dihydrobenzimidazole, respectively. Such aminals also react with cyanide to produce symmetric 1,3-bis(cyanomethyl)imidazolidine **4b**, 1,3-bis(cyanomethyl)perhydropyrimidine **5b** and 1,3-bis (cyanomethyl)-2,3-dihydrobenzimidazole **6b**.

INTRODUCTION

Benzotriazole (1) is a synthetic aid which has become very useful in obtaining several organic compounds due to the properties it confers on its derivatives. Benzotriazole derivatives can be obtained by displacing a halogen in alkyl or acyl halides, a hydroxyl group in alcohols and an alkoxyl group in acetals or ketals. Other important routes involve adding benzotriazole to aldehydes (and their conjugate analogues), to imines, to iminium salts, and to enamines. Katrytzky *et al* (1,2) reported that benzotriazol derivatives **4a** and **5a** were obtained by ethane-1,2-diamine and propane-1,3-diamine reaction, respectively, with benzotriazole and formaldehyde in water at 20°C. Katritzky et al (3,4) has also reported synthesising 1,3-bis(benzotriazol-yl-methyl)-2,3-dihydrobenzilimidazol **6a** by reacting benzotriazole with formaldehyde and o-phenylenediamine. However, it is well known (5,6) that diamines, such as ethane-1,2-diamine, propane-1,3-diamine and o-phenylenediamine, react easily with formaldehyde in aqueous medium to produce macrocyclic polyaminals 1,3,6,8-tetraazatricyclo[4.4.1.1^{3,8}]dodecane **1**; 1:3,7:9,13:15,19:21-tetramethyleneperhydropyrimidine **2**, and 6H,13H-5:12,7:14-dimethanedibenzo[d,i] [1,3,6,8]tetrazecine **3**, respectively.



1 **2** **3**

Figure 1: Macrocyclic polyaminals studied in this work.

To our knowledge, no benzotriazole derivatives has been obtained from such aminals directly. Katrytzky *et al* (1,2) have also demonstrated the ability of benzotriazole as a synthetic auxiliare for the preparation of 1,3-bis(cyanomethyl)imidazolidine **4b** and 1,3-bis(cyanomethyl) perhydropyrimidine **5b** through nucleophilic substitution reaction by replacing the benzotriazole group by cyanide in 1,3-bis(benzotriazol-yl-methyl)imidazolidine **4a** and 1,3-bis(benzotriazol-yl-methyl)perhydropyrimidine **5a**, respectively.

EXPERIMENTAL

All yields refer to isolated products and all products were characterised by comparing their spectra and physical data with those published (2,4). See Table 1. Melting points are uncorrected and were taken in open capillaries in a Digital Electrothermal IA9100 melting point apparatus. ^{1}H NMR spectra were run at 300 MHz and ^{13}C NMR at 75 MHz on a Varian Mercury spectrometer. Mass spectra were determined at 20 eV on a Shimadzu 9020DF. IR spectra were obtained using a Perkin Elmer 1750 FT-IR. Elemental analysis was done on a Carlo Erba 1106 equipment.

Preparation of 1,3-bis(benzotriazol-yl-methyl)imidazolidine 4a and 1,3-bis(benzotriazol-yl-methyl)perhydro pyrimidine 5a.

A solution of the appropriate aminal **1** or **2** (0.59 mmol) in water (10 ml) was added to a stirred solution of benzotriazole (1.18 mmol) in water (5 ml) at room temperature. After a few minutes, the formed precipitate, was filtered off and washed with cold water. The respective compounds 4a and **5a** were dried and recrystallised from ethanol 96%.

Preparation of 1,3-bis(benzotriazol-yl-methyl)-2,3-dihydrobenzilimidazol 6a.

A solution of **3** (0.59 mmol) in dioxane (10 ml) was added to a stirred solution of benzotriazole (1.18 mmol) in dioxane (5 ml) and the resulting mixture was stirred for 6 hours. The solvent was evaporated and the product was recrystallised from ethanol 96%.

Preparation of 1,3-bis(cyanomethyl)imidazolidine 4b and 1,3-bis(cyanomethyl) perhydropirimidine 5b.

To a solution of aminal **1** or **2** (0.59 mmol) in water (10 ml) was bubbled slowly an excess of hydrogen cyanide gas. The reaction mixture was stirred at room temperature for 1 h and then extracted with chloroform (3x20ml). The organic layer was dried (Na_2SO_4), filtered and evaporated to affords crude **4b**, as an oily liquid which was distilled at reduced pressure, b. p. 144°C (1.5 Torr). Compound **5b**, an amorfous solid, was recrystallised (from ethanol 96%).

Preparation of 1,3-bis(cyanomethyl)-2,3-dihydrobenzimidazole 6b.

To a solution of aminal **3** (0.59 mmol) in an ethanol:water (4:1) mixture (10 ml) was bubbled slowly an excess of hydrogen cyanide. The reaction mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure and purified by column chromatography on silica gel with an 4:1 (benzene-ethyl acetate) mixture as eluent. Yield 40 mg (34 %), mp 120-122°C; IR (KBr) ν_{max}: 3020-2969 (CH-Ar), 2921-2850 (-CH_2-), 2235 (-CN), 1468-1426 (-CH_2-); EIMS m/z (relative intensity): 198(M^+), 197(M-1), 186 (35), 158 (16.5), 146 (53), 119 (100), 92 (19); ^{1}H RMN δ: 4.44 (s, 4H), 4.86 (s, 2H), 7.06 (s, 4H); ^{13}C RMN δ: 39.42, 71.67, 111.17, 117.44, 125.76, 134.98. Anal. Calc. for $C_{11}H_{10}N_4$: C, 66.58; H, 5.04; N, 28.25. Found C, 66.63; H, 5.10; N, 28.18.

RESULTS AND DISCUSSION

Based on the foregoing and since our group of investigation has already developed reactions from **1** and **2** with phenols producing 1,3-bis(2′-hydroxy-5′substituted–benzyl)imidazolidines (7) and 1,3-bis(2′-hydroxy-5′substituted–benzyl) hexahydropyrimidines (8) we supposed that aminals **1**, **2** and **3** react with benzotriazole thus proving the aminalic groups electrophilic capacity. On this account we carried out some reactions between benzotriazole and the above-mentioned aminals employing described reaction conditions (3,4). Our hypothesis was supported by our experiments, because we obtained **4a**, **5a** and **6a**, respectively (Scheme 1). Except 6b which was

not reported previously, all known compounds showed spectroscopical and physical constants ostensibly equals to those reported in the literature (2,4) .

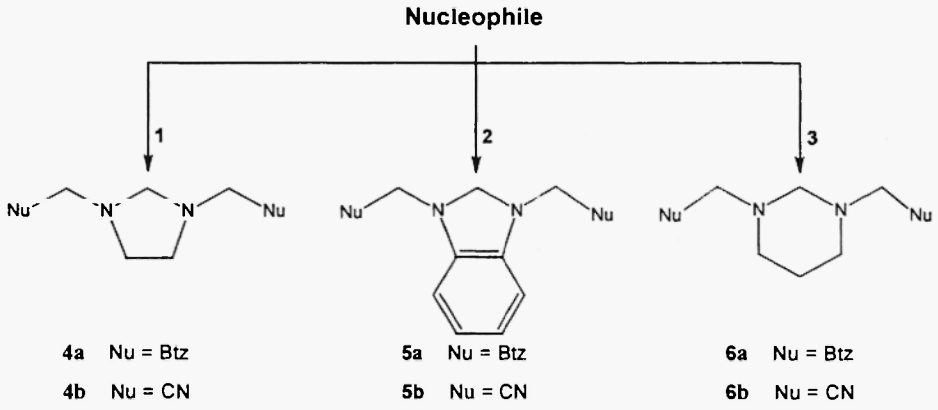


Figure 2: Scheme of reactions between macrocyclic polyaminals with nucleophiles.

As shown in table 1, in our hands the reactions took place with better yield in shorter time than those reported (2,4). In addition, direct nucleophilic substitution reactions on the methylene groups of aminals **1**, **2** and **3** were achieved using cyanide to obtain 1,3-bis(cyanomethyl)imidazolidine **4b**, 1,3-bis(cyanomethyl)perhydropyrimidine **5b** and 1,3-bis(cyanomethyl)-2,3-dihydrobenzimidazole **6b**, respectively (Scheme 1).

Table 1: Comparison of results obtained by using aminals 1, 2 and 3 with those reported (2,4).

Product	Time (h)		Yield (%)		Melting Point (°C)	
	Lit.	Our	Lit.	Our	Lit.	Our
4a	1	0.1	85	86	97-99	98-100
5a	1	0.1	93	95	63-65	62-64
6a	17	2	22	35	177-178	176-178
4b	24	1	88	93	Oil	Oil
5b	24	1	85	90	65-67	66-68

Compound **6b** to our knowledge, is not described in the literature. It was synthesized by direct reaction of the polyaminal **3** with cyanide and its structure was deduced by spectroscopic methods. Since **4a** and **5a** are already known, we can observe that changes in the electronic structure of the imidazoline ring system can easily be detected by means of ^{1}H and ^{13}C RMN. The ^{1}H NMR spectrum of **6b**, show besides the characteristic signals for the aromatic protons, the absorption of the N-CH_2-N methylene group as a singlet at 4.86 ppm, downfield shifted as compared to those of **4a** or **5a** due to nitrogen conjugation with aromatic ring. The methylene protons attached to the nitrile group are easily distinguished near 4.44 ppm. In the ^{13}C NMR spectrum of **6b** the signal for the aminalic carbon

was found at 71.6 ppm almost at same field as the analogous aminals (7). For example **4a** and **5a** which exhibit such signals at 72.5 ppm and 77.8 ppm, respectively. The mass spectrum revealed the M-1 peak with the expected molecular weight and the lost of HCN to give a different M-28. The IR spectrum shows the typical nitrile absorption at 2235 cm^{-1}, aromatic and aliphatic C-H stretch and the scissoring band (CH_2) at 1468 cm^{-1}. In summary, a novel approach to symmetrical imidazolidine, perhydropyrimidine and 2,3-dihydrobenzimidazole, was successfully achieved by the directed nucleophilic attack of macrocyclic polyaminals.

ACKNOWLEDGMENTS

We thank the División de Investigación de Bogotá (DIB), Departamento de Química de la Universidad Nacional de Colombia, CONACYT (México) and COLCIENCIAS (Colombia) for financial support.

REFERENCES

1. A. Katrytzky, X. Lan, J. Yang, and O. Denisko, Chem. Rev. **98**, 409 (1998).

2. A. Katrytzky, B. Pilarsky, and L. Urogdi,, J. Chem. Soc. Perkin Trans. 1 541 (1990).

3. A. Katrytzky, K. Suzuky, and H. He, J. Org. Chem. **67**, 3109 (2002).

4. A. Katrytzky, S. Rachwal, and J. Wu, Can. J. Chem. **68**, 446 (1990).

5. G. Volpp, Chem. Ber. **95**, 1493 (1962).

6. R. Murray, and F. Ridell, Tetrahedron. **32**, 427 (1976).

7. A. Rivera, G. I. Gallo, M. E. Gayón, and P. Joseph-Nathan, Synth. Commun. **23**, 2921 (1993).

8. A. Rivera, M.A. Bejarano. In preparation.

Received on September 27, 2003.