REACTION OF 1,2-DIAMINOBENZIMIDAZOLE WITH 1-ARYL-2-BROMO-3-PHENYLPROPANONE. SYNTHESIS OF 2-ARYL-3-BENZYL-9-AMINOIMIDAZO[1,2-A]BENZIMIDAZOLES.

Braulio Insuasty[1]*, Fernando Fernández[1], Jairo Quiroga[1], Roberto Martinez[2], Rubén Gavino[2], Enrique Angeles[3]

[1]Grupo de Investigación de Compuestos Heterociclicos, Departamento de Quimica, Universidad del Valle, A. A. 25360, Cali, Colombia. [2]Instituto de Quimica, Universidad Nacional Autónoma de México, Circuito Exterior, Ciudad Universitaria, Coyoacán 04510, México. [3]Laboratorio de Quimica Medicinal, Facultad de Estudios Superiores Cuautitlán, Universidad Nacional Autónoma de Mexico, Cuautitlán, Estado de México, México.

Abstract. – The reaction of 1,2-diaminobenzimidazole **1** with one equivalent of 1-aryl-2-bromo-3-phenylpropanones **2**, in methanol, leads to the formation of 2-Aryl-3-benzyl-9-aminoimidazo[1,2-a]benzimidazoles **3**. The structure elucidation of the products is based on detail nmr analysis of experiments such as ^{1}H.COSY, NOESY, ^{13}C, DEPT, HETCOR and COLOC.

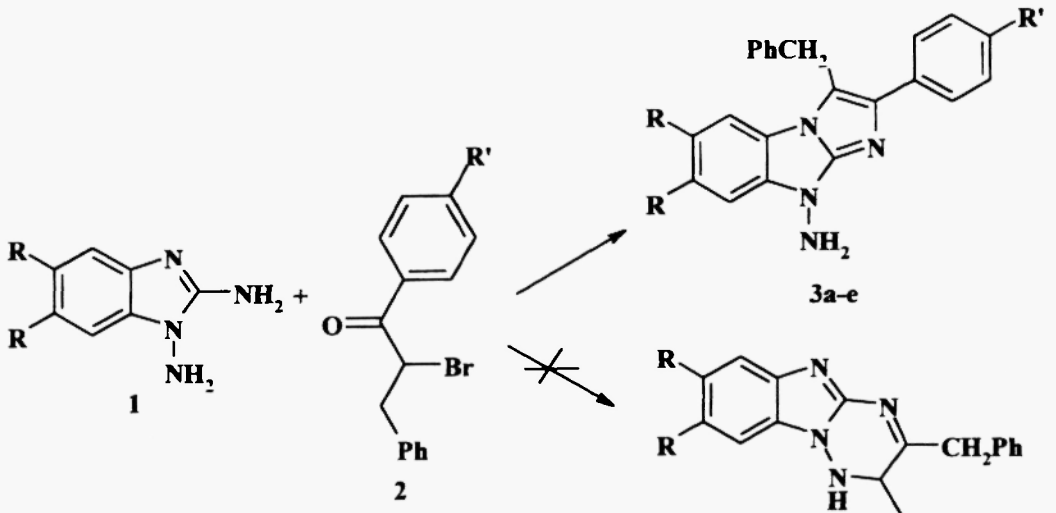
Introduction

The incorporation of an imidazole nucleus, a biologically accepted pharmacophore in the benzimidazole molecule has made it a versatile heterocycle possessing a wide spectrum of biological activities. As benzimidazole are associated with antiparasitic [1-3], CNS depressant and anti-inflammatory activity [4-6] and pharmacological activities [7-10], one may well expect the imidazobenzimidazole to display potent biological activity against different parasites and physiological disorders.

Cyclization reactions of 1,2- diaminobenzimidazole with α-bielectrophile reagents afforded five- or six-membered rings [11-13]. In previous works [14-17] we have shown that reaction of ortho-diamines with α-bromoketones is a good synthetic procedure in order to obtain condensed pyrazine systems. Additionally, the reaction of heterocyclic amines with α-bromocarbonyl compounds is a versatile method for the synthesis of fused imidazole ring [18-21].

Results and Discussion

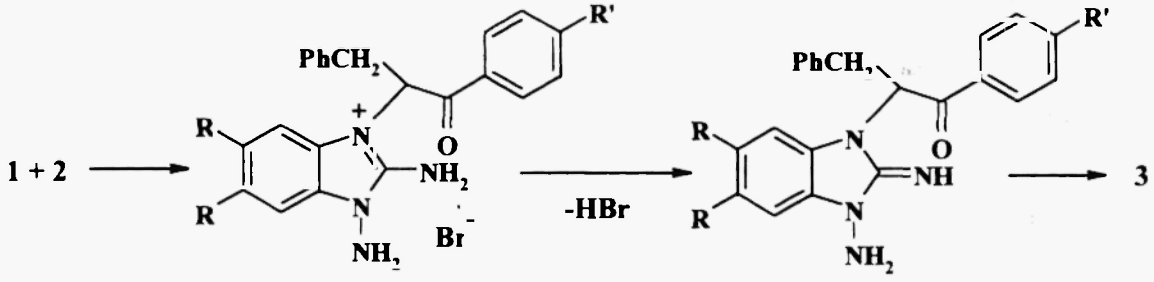
In the present work, we studied the reaction of 1,2-diaminobenzimidazole with α-bromodihydrochalcones **2** (2-bromo-1-aryl-3-phenylpropanones). A solution of equimolar amounts of diamine **1** and **2** were refluxed in methanol. After cooling the generated precipitate was filtered off, to give the corresponding imidazo[1,5-a]benzimidazole **3a-e** (Scheme 1).



Comp.	R	R_1	Mp.,°C	Yield, %
3a	H	H	211	28
3b	H	CH_3	220	37
3c	H	Cl	221	39
3d	CH_3	H	169	23
3e	CH_3	Cl	194	28

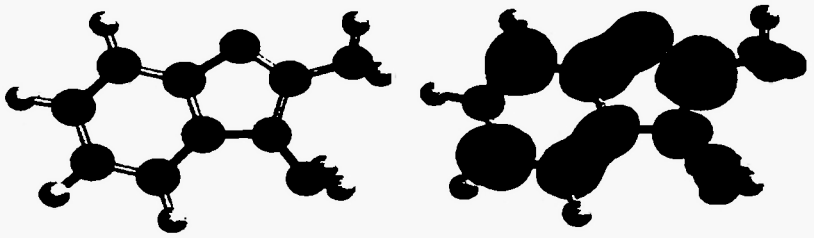
Scheme 1

Because of diamine **1** contains non-equivalent amino groups at the ortho-position and additional nucleophilic nitrogen atom at the position 3. the regioisomeric cyclization products **3** and **4** were expected. However. the formation of a single product was observed in all cases. We assume that reaction is believed to proceed via initial displacement of HBr by nucleophilic reaction (SN_2 via) of ring nitrogen atom followed by the facile closure of the intermediate (Scheme 2). as is described in papers [18-19].



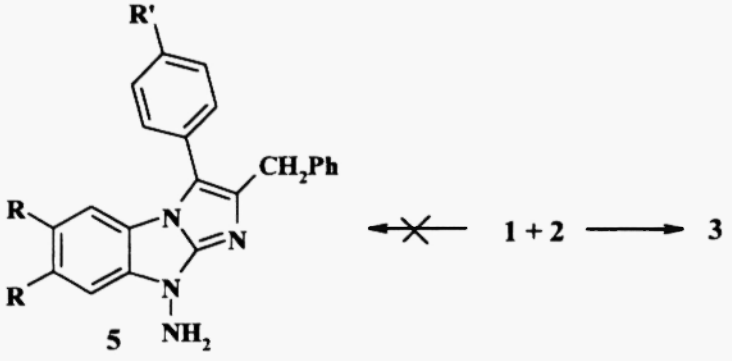
Scheme 2

In order to confirm it. we made a theoretical studies [22] on compound **1**. We determinate the HOMO contribution in nitrogen atoms involved in this step. We found that the imino nitrogen had 15.8 % meanwhile the amino nitrogen had only ca 1% in orbital HOMO contribution [23]. this confirm that the nitrogen in imino group is much nucleophilic than the amino group (graphic 1).



Grafic 1. HOMO CONTRIBUTION OF COMPOUND 1

In the same way we purpose that the structure of compound from the reaction of **1** with **2** is **3** instead **5** (Scheme 3).



Scheme 3

This is supported in COLOC studies in witch we can observed that in the structure 3 the interaction of the methylene is first with C3 and then C2. meanwhile in the structure 5 the interaction of this methylene change firstly with C2 and then C3 as shown in figure 1.

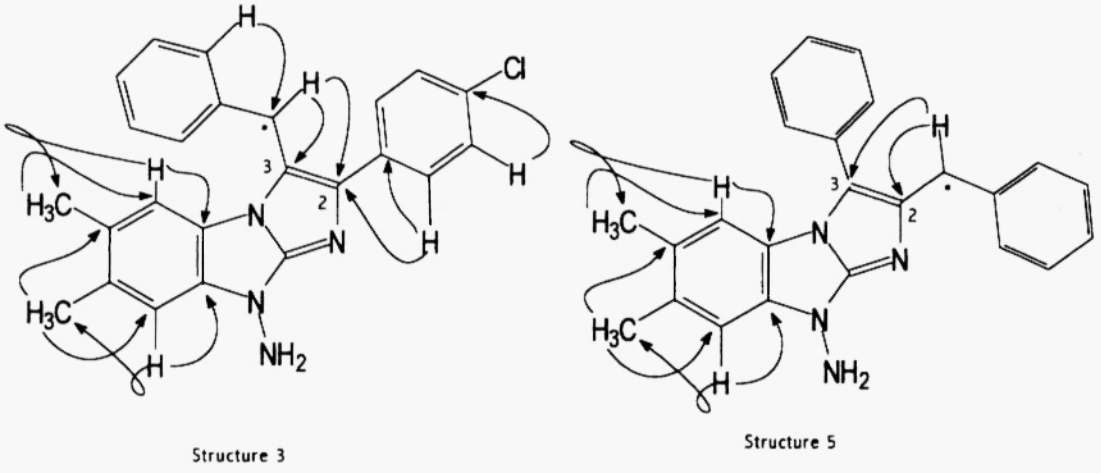


Figure 1. Coloc studies

Structural assignment of compound **3** was made on spectroscopic grounds. The infrared spectrum of **3a-e** showed typical absorption between 3318-3115 cm^{-1} (NH_2). and 1640-1619 cm^{-1} (C=N).

The ^{1}H-nmr spectra of compounds **3a-e** showed the geminal protons joined to benzyl methylene group at δ 4.65-454 ppm. The protons of the NH_2 group appear as a singlet at δ 5-84-5.59 ppm. In addition, a multiplet signal is observed in the spectra of **3a-e** related to aromatic protons (δ 7.95-6.80 ppm). The alternative structure 4 could be ruled out, because in the ^{1}H-nmr of new obtained compounds appears the signal corresponding to NH_2 group at position 9 of tricyclic system. The ^{1}H-nmr data for all products are summarized at the Table 1.

Table 1. ^{1}H-NMR Chemical Shift (δ) for Compounds **3a-e** (DMSO-d_6, 300 MHz)

Comp.	CH_3	CH_2	NH_2	Aromatic
3a	---	4.57	5.84	6.80-7.82
3b	2.27	4.54	5.74	6.92-7.78
3c	---	4.57	5.79	6.83-7.95
3d	2.15; 2.32	4.65	5.59	7.02-7.90
3e	2.19; 2.34	4.58	5.61	7.05-7.86

In the ^{13}C-nmr spectra (DEPT) the number of signals belonging to tertiary, secondary and primary carbons atoms for **3a-e** compounds could be determined (Table 2).

Table 2. ^{13}C-NMR Chemical Shift (δ) for Compounds **3a-e** (DMSO-d_6, 300 MHz)

	3a	**3b**	**3c**	**3d**	**3e**
CH_3	---	20.6	---	19.0, 19.9	18.9, 19.3
CH_2	30.1	30.2	30.1	30.0	29.9
C-2	138.5	138.6	138.2	138.8	134.2
C-3	115.9	115.5	116.4	115.6	116.0
C-4a	137.2	137.2	137.3	135.5	135.4
C-5	109.7	109.6	109.7	110.1	110.1
C-6	119.5	119.4	119.6	127.3	127.7
C-7	122.9	122.4	123.1	130.8	130.9
C-8	110.7	110.6	110.7	110.1	111.1
C-8a	122.1	122.2	122.1	120.4	120.3
C-9a	148.4	148.3	148.0	148.4	148.3
C_i	135.4, 139.8	137.2, 140.0	130.9, 138.6	127.1, 139.3	130.4, 138.0
C_o	126.5,127.5	126.5,127.5	127.5,128.0	125.8, 126.0	127.2, 127.7
C_m	128.4,128.8	128.7,129.0	128.4,128.8	127.9, 128.3	127.9, 128.3
C_p	126.4, 127.5	126.4, 135.5	126.5, 134.4	126.8, 127.3	126.0, 134.2

Conclusion

We have described in this paper the preparation of 2-Aryl-3-benzyl-9-aminoimidazo[1,2-a]benzimidazoles in the reaction of 1,2-diaminobenzimidazole with one equivalent of 1-aryl-2-bromo-3-phenylpropanones in methanol. The orientation of reaction was determined by COLOC experiments. The results demostrate the versatility and a high regioselectivity of this process.

Experimental

All melting points are uncorrected. The ir spectra were recorded on a ATI-Mattson spectrophotometer. The uv-vis spectra were recorded on a Shimadzu UV-160 A spectrophotometer

on ethanol solution. The 1D and 2D nmr spectra were determined in Varian Gemini 200 and Varian Unity 300 spectrometers instrument. All spectra were determined in deuteriochloroform solution containing tetramethylsilane as internal reference with chemical shifts expressed downfield from TMS. Mass spectra were obtained with Jeol SX-102 mass spectrometer. Elemental analysis were determined on a LECO CHNS-900 analyzer.

2-Aryl-3-benzyl-9-aminoimidazo[1,2-a]benzimidazoles 3.

General Procedure

A solution of 1,2-diaminobenzimidazole **1** (2.0 mmol) y 1-aryl-2-bromo-3-phenylpropanone **2** (2.0 mmol) was refluxed in 30 ml anhydrous methanol for 6 hours. The precipitate was collected by filtration. The solid obtained was recrystallized from ethanol to give the compounds **3a-e**. The yields and the melting points were summarized in Scheme 1.

2-Benzyl-3-phenyl-9-aminoimidazo[1,2-a]benzimidazoles (3a).

This compound had ms. EI m/z (relative abundance). 339 (26). 338(**M**$^+$. 100). 323 (18). 322(60). (52). 261(22). 220(13). 161(11).103(14).

Anal. Calcd. For $C_{22}H_{18}N_4$. C. 78.08. H. 5.36. N. 16.56. Found. C.78.20. H. 5.28. N. 16.42.

2-Benzyl-3-(4-methylphenyl)-9-aminoimidazo[1,2-a]benzimidazoles (3b).

This compound had ms. EI m/z (relative abundance). 352 (**M**$^+$.100). 337 (19). 275 (18). 161 (15).

Anal. Calcd. For $C_{23}H_{20}N_4$. C. 78.38. H. 5.72. N. 15.90. Found. C. 78.34. H. 5.68. N. 15.85.

2-Benzyl-3-(4-chlorophenyl)-9-aminoimidazo[1,2-a]benzimidazoles (3c).

This compound had ms. EI m/z (relative abundance) 374 (36).373 (28). 372 (**M**$^+$.100). 358 (18). 357(15). 356 (52). 295 (16). 160 (10). 137 (11).

Anal. Calcd. For $C_{22}H_{17}N_4Cl$. C. 78.87. H. 4.60. N. 15.03. Found. C. 78.67. H. 4.68. N. 15.12.

2-Benzyl-6,7-dimethyl-3-phenyl-9-aminoimidazo[1,2-a]benzimidazoles (3d).

This compound had ms. EI m/z (relative abundance). 366 (**M**$^+$.100). 351 (15). 289 (20). 160 (20).

Anal. Calcd. For $C_{24}H_{22}N_4$. C. 78.66. H. 6.05. N. 15.29. Found. C. 78.55. H. 6.10. N. 15.35.

2-Benzyl-6,7-dimethyl-3-(4-chlorophenyl)-9-aminoimidazo[1,2-a]benzimidazoles (3e).

This compound had ms. EI m/z (relative abundance). 402 (34). 400 (**M**$^+$.100).. 385 (17). 323 (15). 161 (12).

Anal. Calcd. For $C_{24}H_{21}N_4Cl$. C. 71.90. H. 5.28. N. 13.97. Found. C. 71.85. H. 5.15. N. 14.01.

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REFERENCES AND NOTES

1. Loewe, H., Urbanietz, J., . Kirsch and D. Duewel. German Patent (DOS) 2332487 (1975) : Chem. Abstr. **82**. 156301 (1975).

2. H. Loewe, J. Urbanietz, D. Duewel and R. Kirsch. German Patent (DOS) 2541741 (1977) : Chem. Abstr., **87**. 39485 (1977).

3. H. Loewe, J. Urbanietz, R. Kirsch and D. Duewel. German Patent (DOS) 1031780 (1978) Chem. Abstr., **90**. 72183 (1979).

4. H. L. Yale and J. A. Bristol. U. S. Patent 4004016 (1977) : Chem. Abstr., (1977), **86**. 171450

5. T. Denzel and H. Hoehn. U. S. Patent 4109087 (1978). Chem. Abstr., **90**. 87510 (1979).

6. T. Denzel and H. Hoehn. U. S. Patent 4072679 (1978) : Chem. Abstr., **89**. 109553 (1978).

7. L. G. Mendzneritskaya, A. A. Krichovskaya, S. A. Lisovskaya, *Kosm. Biol. Aviakos. Med.*, **12**. 68 (1978) : Chem. Abstr., **89**. 123832 (1978).

8. S. S . Berg and E. W. Parnell, *J. Chem. Soc.*, (1961), 5275.

9. C. J. Paget, K. Kisner, R. L. Stone and D. C. DeLong, *J. Med. Chem.*, **12**, 10110 (1969).

10. C. J. Paget, J. W. Chamberlin and J. H. Wikel. British Patent 1568 542 (1982) : Chem. Abstr., **94**. 30754 (1981).

11. I. Ho and A. Day, *J. Org. Chem.*, **38**. 3084 (1973).

12. A. Zieger and M. Joullie, *J. Org. Chem.*, **42**. 542 (1977).

13. T. Kuzmenko, V. Kuzmenko and A. Pozharskii, *Khim. Geterosikl. Soedin.*, 1071 (1989).

14. N. N. Kolos, B. Insuasty, J. Quiroga and V. D. Orlov, *Khim. Geterosikl. Soedin.*, 1127 (1986).

15. V. D. Orlov, B. Insuasty and N. N. Kolos, *Khim. Geterosikl. Soedin.*, 830 (1987).

16. V. D. Orlov, M. Tueni, N. N. Kolos, N. V. Getmanskii and J. Quiroga, *Khim. Geterosikl. Soedin.*, 787 (1988).

17. B. Insuasty, F. Fernández, J. Quiroga, R. Moreno, R. Martinez, E. Angeles, R. Gaviño and R. H. Almeida, *J. Heterocyclic Chem.*, **35**, 977 (1998).

18. V. A. Anisimova, A. M. Simonov and A. F. Pozharskii, *Khim. Geterosikl. Soedin.*, 797 (1973).

19. A. J. Elliott, H. Guzyk and J. R. Soler, *J. Heterocyclic Chem.*, **19**, 1437 (1982).

20. W. C. Lumma, W. C. Randall, E. L. Cresson, J. R. Huff, R. D. Hartman and T. F. Lyon, *J. Med. Chem.*, **26**. 357 (1983).

21. L. Pentimalli, G. Milani and F. Biavati, *Gazz. Chim. Ital.*, **105**. 777 (1975); L. Pentimalli and L. Greci, *Gazz. Chim. Ital.*, **98**. 1360 (1968); L. Pentimalli and V. Passalacqua, *Gazz. Chim. Ital.*, **100**. 1106 (1970); L. Pentimalli and G. Cogo, *Gazz. Chim. Ital.*, **97**. 488 (1967); L. Pentimalli and M. Guerra, *Gazz. Chim. Ital.*, **97**. 145 (1961).

22. PM3 Method in Spartan Ver 5.0. Wavefunction Inc.

23. The porcentual contibutions were calculated from the addition of the square of the contribution of p_x, p_y and p_z orbitals on the nitrogen atom.

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