ONE-STEP MULTICOMPONENT SYNTHESIS OF 4-AMINO-2-ARYL-3-CYANO-1,2-DIHYDROPYRIMIDO[1,2-A]BENZIMIDAZOLES

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Abstract: This paper describes the synthesis of a new serie of 4-amino-2-aryl-3-cyano-1,2-dihydropyrimido[1,2-a]benzimidazoles **4a-f** from the reaction of 2-aminobenzimidazole **1** with malonodinitrile **2** and benzaldehydes **3**. The structure elucidation of the products is based on detail nmr analysis of experiments such as ^{1}H-COSY. NOESY. DEPT. HSQC and HMBC.

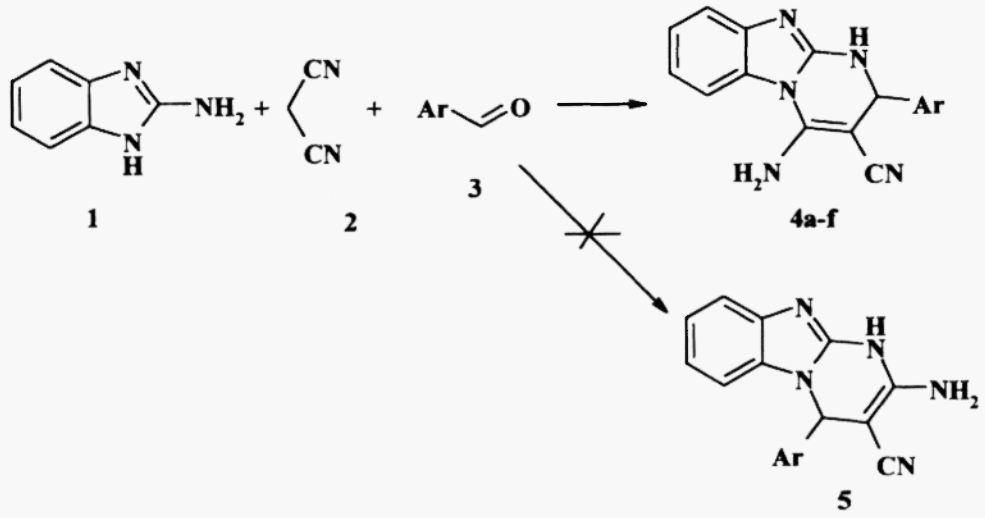
Introduction

A wide variety of benzimidazole derivatives have been described for their chemotherapeutic importance [1-6]. one may well expect the pyrimidobenzimidazoles to display potent biological activity. Multi-component condensations (MCC's) constitute an specially attractive synthetic strategy for rapid an efficient library generation due to the fact that products are formed in a single step and the diversity can be achieved simply by varying the reacting components [7].

This study is a continuation of our earlier works [8-10]. in which we have shown that reaction of heterocyclic amines with benzylidenderivatives of compounds with active methylene group. such as malonodinitrile and ethyl cyanoacetate. is a good synthetic procedure for the obtention of condensed pyridinic and pyrimidinic systems.

Results and Discussion

The aim of this work was the preparation of some new derivatives of 1,2-dihydropyrimido[1,2-a]benzimidazoles in the reaction of 2-aminobenzimidazole **1** with malonodinitrile **2** and benzaldehydes **3**. a process that is adaptable for the assembly of a library of compounds. which has recently gained much attention in pharmaceutical research [11]. Thus. a solution of equimolar amounts of compounds **1**. **2** and **3** in ethanol in the presence of catalytic amounts of triethylamine was heated to reflux for 1-3.5 hours. then reaction mixture was cooled and the precipitate formed was filtrated to give the corresponding 4-amino-2-aryl-3-cyano-1,2-dihydropyrimido[1,2-a]benzimidazoles **4a-f** (Scheme 1).



Scheme 1

The formation of **4** as unique product of reaction was confirmed by their spectroscopy analysis. Thus, the IR spectra of compounds **4** measured in KBr pellets shows a band of the elongation vibrations of the C=N group at 2185-2202 cm^{-1} and three bands for NH_2 and NH-groups at 3215-3420 cm^{-1}.

In the ^{1}H-nmr spectra of compounds **4a-f** measured in $(CD_3)_2SO$ (Table 1) besides the aromatic proton signals at 7.16-7.57 ppm, there were observed three singlets at δ = 5.15-5.25, 8.51-8.61 and 6.78-6.87 ppm with a 1:1:2 relation, corresponding to the protons 2H, 1-NH of pyrimido[1,2-a]benzimidazole system and NH_2 group.

TABLE 1. ^{1}H-NMR Data of **4a-f** (δ values, TMS as the Internal Standard, in DMSO-d_6)

Comp.	NH_2 (s)	NH (s)	2-H (s)	6-H (dd)	7-H (dt)	8-H (dt)	9-H (dd)	2-Ar H_{orto} (d)	2-Ar H_{meta} (d)
4a	6.82	8.61	5.21	7.63	7.12	7.03	7.23	7.26-7.38	
4b	6.79	8.54	5.16	7.63	7.11	7.01	7.21	7.16*	
4c	6.78	8.51	5.15	7.63	7.11	7.02	7.22	7.21	6.91
4d	6.84	8.53	5.19	7.64	7.11	7.03	7.23	6.63	---
4e	6.86	8.60	5.25	7.62	7.11	7.01	7.23	7.30	7.42
4f	6.87	8.61	5.24	7.63	7.12	7.05	7.23	7.25	7.57

* Singlet

CH_3 for **4b**, **4c** and **4d** 3.34, 371 and 3.63 and 3.70 ppm respectively

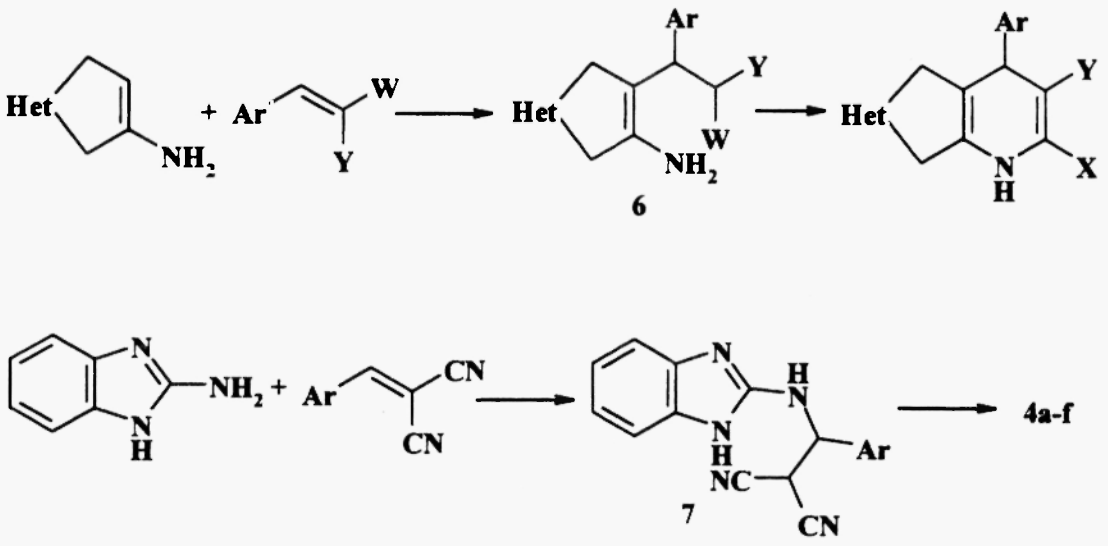
The final elucidation of structure of compounds **4a-f** was carried out by analysis of the ^{13}C-nmr spectra (Table 2). In the ^{13}C-nmr spectra of compounds **4a-f** a carbon signal at δ = 52.5-53.2 ppm was observed. ^{1}H,^{13}C-COSY reveals that the proton signal at belongs to the carbon atom **C-2** at highest field. Additionally information was given by the NOESY experiment carried out on compounds **4**. The NOE interactions between signals 2-H-H_{orto}, 6-H-NH_2 and 2-H-NH for compounds **4** confirm the structure assigned for compounds **4** and discard the formation of structure **5**.

TABLE 2. ^{13}C NMR chemical shifts (δ in ppm) of compounds **4a-f**

Comp.	4a	4b	4c	4d	4e	4f
C-2	53.1	52.9	52.7	53.2	52.5	52.5
C-3	61.8	62.0	62.2	61.7	61.4	61.3
CN	119.1	119.1	119.1	119.1	119.0	118.9
C-4	149.0	149.0	149.0	149.2	149.2	149.1
C-5a	129.2	129.2	129.2	129.2	129.2	129.2
C-6	112.3	112.3	112.3	112.2	112.4	112.4
C-7	119.8	119.7	119.7	119.8	119.9	119.8
C-8	123.2	123.2	123.2	123.2	123.2	123.2
C-9	116.0	115.9	115.9	116.0	116.1	116.0
C-9a	143.5	143.5	143.5	143.4	143.5	143.5
C-10a	151.7	151.7	151.7	151.7	151.8	151.7
C_i	142.8	137.0	134.7	138.0	141.8	142.5
C_o	125.8	125.8	127.2	103.5	127.9	128.2
C_m	128.6	129.1	113.9	152.8	128.7	131.5
C_p	127.7	139.8	158.8	137.1	132.4	120.9

CH_3 for **4a** .**4b** and **4c** 20.5 and 55.1 ppm respectively

In previous works [7-16] on the reaction of pyrazolic and pyrimidinic amines with benzylidene derivatives of compounds with active methylene group we demostrated that this reaction presents a high regioselectivity and we assumed that in the first step occurs the attack from the carbon atom in the α position with respect to the amino group to the β-carbon atom of unsaturated system forming a Michael adduct **6**, the one which later on is cycled. However, the study reaction takes another *via*, being carried out in the first step the attack of the aminogroup on the β-carbon atom of unsaturated system (intermediate 7), followed by cyclization (Scheme 2). This change in the reaction orientation, we consider due to the substitution of highly nucleophilic carbon atom in pyrazole and pyrimidine amines for a nitrogen atom in the 2-aminobenzimidazole, being presented a redestribution of the electronic densities, increasing this on the amino group of amine **1**.



Scheme 2

Conclusion

We have described in this paper the preparation of a novel, one-step procedure, 4-amino-2-aryl-3-cyano-1,2-dihydropyrimido[1,2-a]benzimidazoles from 2-aminobenzimidazole, malonodinitrile and benzaldehydes. The results demostrate the versatility and a high regioselectivity of the process.

Experimental

Melting points were determined in a Buchi Melting Point Apparatus and are uncorrected. The ir spectra were obtained in potassium bromide pellets with a Perkin-Elmer 599B spectrometer. The ^{1}H- and ^{13}C nmr spectra were run on a Bruker DPX 300 spectrometer operating at 300 MHz and 75 MHz respectively, using dimethyl sulfoxide-d_6 as solvent and tetramethylsilane as internal standard. The mass spectra were scanned on a Hewlett Packard HP Engine-5989 spectrometer (equipped with a direct inlet probe) and operating at 70 eV. The elemental analysis have been obtained using a LECO CHNS-900 equipment.

General procedure for the preparartion of the 4-amino-2-aryl-3-cyano-1,2-dihydropyrimido[1,2-a]benzimidazoles 4a-f.

A solution of 2-aminobenzimidazole **1** (2.0 mmoles), malonodinitrile **2** (2.0 mmoles) and benzaldehyde **3** (2.0 mmoles) in ethanol (10 ml) with 1 ml of triethylamine was refluxed during 1-3.5 hours (tlc control), then the reaction mixture was cooled and resulting precipitate was filtered, washed with ethanol, dryed and recrystallized from ethanol.

4-Amino-3-cyano-2-phenyl-1,2-dihydropyrimido[1,2-a]benzimidazole 4a.

This compound was obtained according to general procedure as withe crystals: mp 218 °C, yield 55 %. The mass spectrum shows the following peaks: ms: (70 eV) m/z (%) = 288 (13), 287 (M^{-}, 59), 286 (27), 244 (14), 222 (29), 221 (30), 220 (100), 211 (14), 210 (78), 133 (59), 118 (14), 106 (11), 105 (13), 92 (15), 91 (74), 90 (20), 89 (11), 77 (25), 65 (24), 64 (12), 63 (18), 52 (11), 51 (26), 50 (10), 39 (22).

Anal. Calcd. for $C_{17}H_{13}N_5$: C, 71.08; H, 4.53; N, 24.39. Found: C, 71.15; H, 4.48; N, 24.34.

4-Amino-3-cyano-2-(4-methylphenyl)-1,2-dihydropyrimido[1,2-a]benzimidazole 4b.

This compound was obtained according to general procedure as pale yellow crystals: mp 208 °C, yield 50 %. The mass spectrum shows the following peaks: ms: (70 eV) m/z (%) = 302 (19), 301 (M^{-}, 62), 300 (28), 299 (14), 234 (16), 210 (60), 168 (23), 141 (14), 140 (15), 134 (14), 133 (100), 115 (10), 106 (13), 105 (21), 91 (15), 90 (20), 77 (10), 65 (17), 64 (10), 63 (18), 52 (13), 51 (18), 39 (24).

Anal. Calcd. for $C_{18}H_{15}N_5$: C. 71.76: H. 4.98: N. 23.25. Found: C. 71.71: H. 4.96: N. 23.31.

4-Amino-3-cyano-2-(4-methoxyphenyl)-1,2-dihydropyrimido[1,2-a]benzimidazole 4c.

This compound was obtained according to general procedure as withe crystals: mp 197 °C. yield 50 %. The mass spectrum shows the following peaks: ms: (70 eV) m/z (%) = 318 (27) 317 (M^+. 85). 316 (35). 315 (17). 252 (10). 251 (19). 250 (30). 210 (13). 185 (11). 184 (41). 134 (21). 133 (100). 114 (14). 105 (13). 64 (10). 63 (14). 52 (11). 51 (15). 39 (17).

Anal. Calcd. for $C_{18}H_{15}N_5O$: C. 68.14: H. 4.73: N. 22.08. Found: C. 68.19: H. 4.68: N. 22.12.

4-Amino-3-cyano-2-(3,4,5-trimethoxyphenyl)-1,2-dihydropyrimido[1,2-a]benzimidazole 4d.

This compound was obtained according to general procedure as withe crystals: mp 225 °C. yield 60%. The mass spectrum shows the following peaks: ms: (70 eV) m/z (%) = 377 (M^+. 27). 244 (21). 229 (11). 210 (26). 134 (10). 133 (100). 115 (13). 106 (11). 105 (17). 90 (17). 78 (11). 77 (16). 76 (11). 67 (10). 66 (24). 65 (11). 64 (14). 63 (16). 53 (27). 52 (20). 51 (22). 50 (16). 43 (17). 39 (22). 38 (16).

Anal. Calcd. for $C_{20}H_{19}N_5O_3$: C. 63.66: H. 5.04: N. 15.57. Found: C. 66.61: H. 5.10: N. 15.51.

4-Amino-3-cyano-2-(4-chlorophenyl)-1,2-dihydropyrimido[1,2-a]benzimidazole 4e.

This compound was obtained according to general procedure as pale yellow crystals. mp 238 °C. yield 60 %. The mass spectrum shows the following peaks: ms: (70 eV) m/z (%) = 323/321 (M^+. 1/34). 320 (37). 319 (100). 318 (50). 254 (14). 133 (20). 105 (12). 90 (23). 75 (10). 63 (10). 51 (11).

Anal. Calcd. for $C_{17}H_{12}ClN_5$: C. 63.45: H. 3.73: N. 21.77. Found: C. 63.39: H. 3.78: N. 21.71.

4-Amino-3-cyano-2-(4-bromophenyi)-1,2-dihydropyrimido[1,2-a]benzimidazole 4f.

This compound was obtained according to general procedure as withe crystals. mp 209 °C. yield 60 %. The mass spectrum shows the following peaks: ms: (70 eV) m/z (%) = 367/365 (M^+. 14/16). 234 (23). 232 (19). 210 (53). 171 (17). 169 (17). 153 (40). 134 (10). 133 (100). 126 (14). 106 (15). 105 (19). 90 (15). 75 (12). 63 (12). 51 (16). 50 (13).

Anal. Calcd. for $C_{17}H_{12}BrN_5$: C. 55.74: H. 3.28: N. 19.12. Found: C. 55.82: H. 3.26: N. 19.16.

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