A CONVENIENT APPROACH TO NOVEL N-SUBSTITUTED BENZIMIDAZOLES

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ABSTRACT: A series of new *N*-pyrazoyl-benzimidazoles **4** have been synthesized through a two-steps reaction using 5,2-aminophenylamino-3-(2-hydroxyphenyl)-1H-pyrazole **2** as a useful precursor. All prepared compounds have been fully characterized by mass spectrometry, ^{1}H, ^{13}C and 2D NMR techniques.

Keys words: 1H-pyrazole, condensation reaction, *N*-pyrazoyl-benzimidazoles

INTRODUCTION

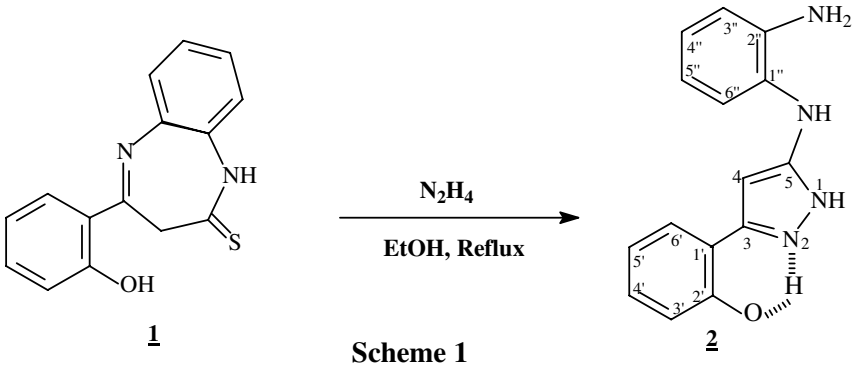
The benzimidazole derivatives are classified under several kinds of drugs [1]. In fact, many of these structures are bioactive and have anticancer, antimicrobial and antihelmintic effects [2-3] some of them exhibited activities against several viruses including HIV, influenza and human cytomegalovirus [4]. Accordingly, the synthesis of benzimidazoles has received much attention and several studies have been developed in recent years to uncover a variety of synthetic methods and new reagents for the preparation of novel benzimidazolic derivatives [5-11]. Among the already known methodologies, we recently described an efficient route to a novel heterocyclic scaffold incorporating the benzimidazole nucleus.

RESULTS AND DISCUSSION

We have previously described the synthesis of 5-(2-aminophenylamino)-3-(2-hydroxyphenyl)-1*H*-pyrazole **2** *via* the condensation of the thiolactam **1** with hydrazine monohydrate in refluxing ethanol [12]. So far as structure **2** possess several reactive sites, we were prompted to use it as a useful key intermediate towards other heterocycles.

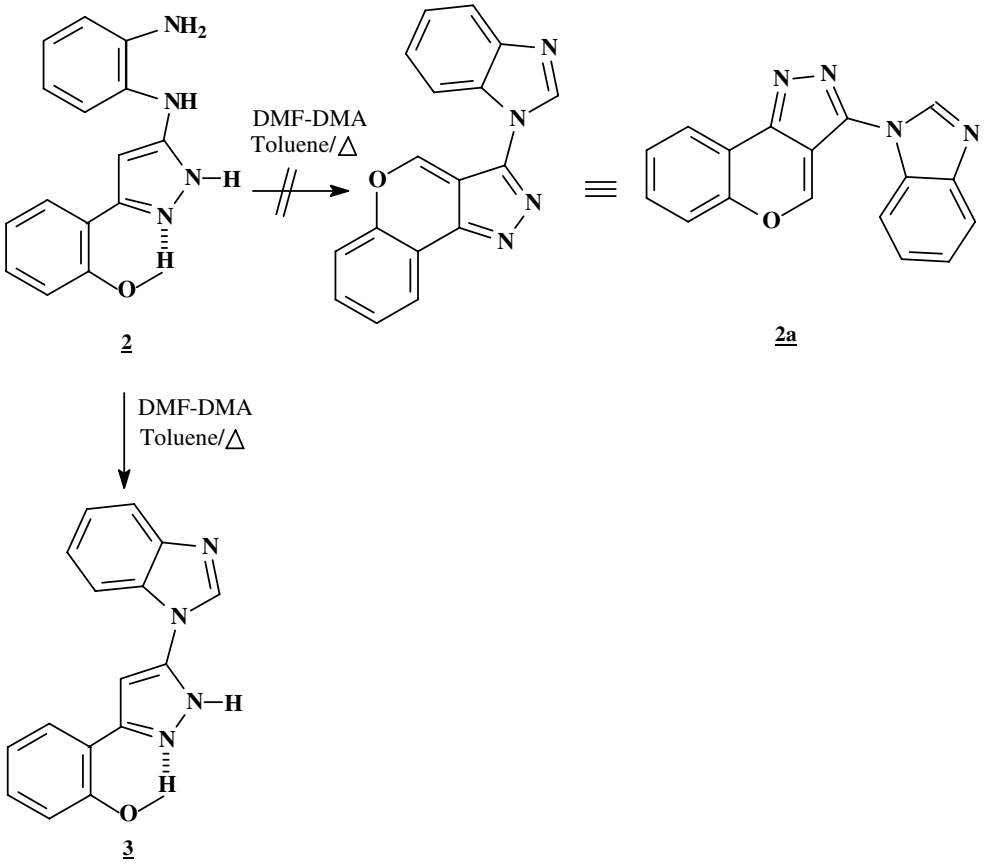
In particular we have previously demonstrated that treatment of 2 with excess DMFDMA resulted in the conversion of both the 4- position and the free amino group into the corresponding *N,N*-dimethylaminoformylidene and *N,N*-(dimethylaminomethylene)amino functionalities, respectively followed by subsequent intramolecular cyclizations should be expected to generate the 7-(1*H*-benzimidazol-1-yl)benzopyrano-[4,3-c]pyrazole **2a** revealed unsuccessful and 5-(2-hydroxyphenyl-2*H*-pyrazol-3-yl)-1*H*-benzimidazole **3** was always recovered as major specie whatever the reaction conditions we have tested (Scheme 1 and 2).

This failure prompted us to investigate other synthetic possibilities. So as a first stage we have managed to build the benzimidazole moiety. For this purpose, compound **2** was firstly treated for twenty minutes with a slight excess of N,N-dimethylformamide dimethylacetal in hot dry toluene to perform the ring closure into the benzimidazole **3**. It is of notice that preparation of a series of alkylated analogs was achieved by using some orthoesters (trietylorthoacetate and triethylorthopropionate) (Scheme 3).



1 **2**

Scheme 1



2 **2a** **3**

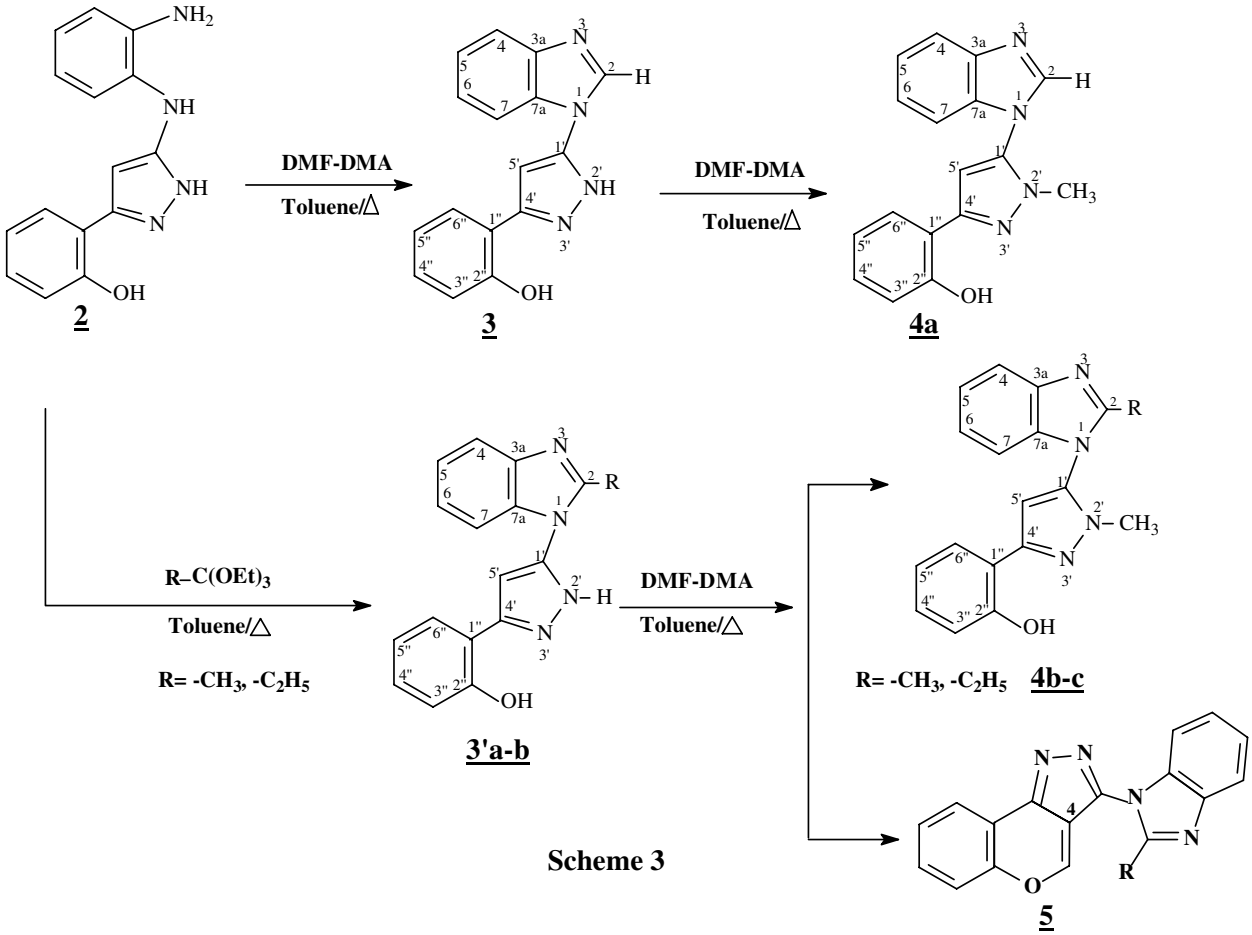
Scheme 2

Trials have then been tested in order to perform the second ring closure into benzopyran (target **5**). Nevertheless and upon treatment of derivatives **3** with DMF-DMA in hot dry toluene, the targeted polyheterocycle could not reached and methylation of the nitrogen atom at the pyrazolic moiety took place exclusively leading to the compound **4** as a sole product (Scheme 3).

In mass spectra, all the compounds **4** gave correct molecular ion peaks and were fully characterized on the basis of their 1 and 2D NMR spectra. Total NMR spectral assignments for all protons and carbons were performed by means of 2D experiments. Thus, ^{1}H NMR spectra of compounds **4a-c** exhibited set of signals attributable to alkyl groups and aromatic protons, for which chemical shifts and multiplicities were in good agreement with the proposed structures.

Unambiguous proofs for the obtained products aroused from their ^{13}C data (see experimental section), particularly the high shift-values attributed to quaternary carbons C_2 (δ 152.2; compound **4b** and δ 156.5; compound **4c** were in agreement with the strong deshielding effects caused by

nitrogen proximity, comparing with anteriorly described *N*-substituted benzimidazoles [12]. On the other hand, Molecular skeletons were deduced from HMBC spectra. In fact, significant long range correlations H_{CH3}-C_2, H_{CH2}-C_2 and H_{CH3}-$C_{1'}$ were sufficient to approve the correct enhancement of the proposed structures (Scheme 2).



2 **3** **4a** **3'a-b** **4b-c** **5**

Scheme 3

CONCLUSION

To summarize, the synthesis described above illustrates a simple and efficient new method leading to the construction of novel 1-[(2''-hydroxyphényl)-2'-méthyl--2-alkyl-pyrazol-1-yl]-1*H*-benzimidazole **4** in good yield from 5-(2-aminophénylamino)-3-(2-hydroxyphényl)-1H-pyrazole **2**.

EXPERIMENTAL

^{1}H, ^{13}C NMR spectra as well as 2D experiments were recorded at 500 *MHz* with Avance AMX Bruker machines. Mass spectra were performed using an Automass Multi Thermo Finnigab (electron impact mode, 70 eV) spectrometer. All the reactions were followed by TLC using aluminium sheets of Merck silica gel 60 F254, 0.2 mm. The starting materials **1** and **2** were prepared according to the literature [13].

General procedure for the synthesis of compound 3: 1.4 eq of orthoesters were solved in 30 mL of toluene, added to 1.2 mmole of pyrazolic derivative **2** and then heated under reflux during 20 minutes. The reaction mixture was cooled to afford solids **3**.

1-[(2-hydroxyphényl)-2H-pyrazol-1-yl]-1H-benzimidazole 3: white solid, yield 40%, ^{1}H NMR (500 *MHz*, DMSO-d_6) δ (ppm) 6.91 (dd, 1H, H-5''), 7.01 (d, 1H, H-3''), 7.15 (s, 1H, H-5'), 7.22 (dd, 1H, H-4''), 7.31 (dd, 1H, H-5), 7.37 (dd, 1H, H-6), 7.71 (d, 1H, H-6''), 7.75 (d, 1H, H-4), 8.07 (d, 1H, H-7), 8.73 (s, 1H, H-2), 10.50 (bs, 1H, NH), 13.16, (bs, 1H, OH). ^{13}C NMR (125 *MHz*, DMSO-d_6) δ (ppm) 95.1 (C-5'), 112.6 (C-7), 115.5 (C1''), 116.4 (C3''), 129.7 (C-4), 122.5 (C-5), 123.6 (C-6), 127.6 (C-6''), 119.7 (C-4''), 132.2 (C-7ª), 141.1 (C-4'), 142.1 (C-2), 143.5 (C-3ª), 145.7 (C-1'), 154.3 (C-2''). (EI): m/z 276 [$M^{+\cdot}$]

1-[(2-hydroxyphényl)-2 méthyl-pyrazol-1-yl]-1H-benzimidazole 3'a: white solid, yield 60% ^{1}H NMR (500 *MHz*, DMSO-d_6) δ (ppm) 2.62 (s, 3H, CH_3), (6.92 t, *J*=7.1 *Hz* 1H, $H_{5''}$), (7.02, m, 2H, $H_{3''}$, $H_{5'}$), (7.22, m, 3H, H_5, H_6, $H_{4''}$), (7.45, d, 1H, H_4), (7.61, d, 1H, H_7), (7.74, d, *J*=7.3 *Hz*, $H_{6''}$). ^{13}C NMR (125 *MHz*,

DMS-d_6) δ (ppm) 14.5 (C_{CH3}), 99.4 ($C_{5'}$), 110.7 (C_4), 115.5 ($C_{1''}$), 116.4 ($C_{3''}$), 118.4 (C_7), 119.3 ($C_{5''}$), 122.0 (C_5), 122.4 (C_6), 128.1 ($C_{6''}$), 129.6 ($C_{4''}$), 135.3 (C_{7a}), 141.2 ($C_{4'}$), 142.3 ($C_{1'}$), 144.2 (C_{3a}), 151.4 (C_2), 154.3 ($C_{2''}$). MS (EI): m/z 290 [$M^{+\cdot}$]

1-[(2-hydroxyphényl)-2éthyl-pyrazol-1-yl]-1H-benzimidazole 3'b: white solid, yield 50% ^{1}H NMR (500 *MHz*, DMSO-d_6) δ (ppm) 1.29 (t, J=7.4 Hz, 3H, CH_3), 2.92 (m, 2H, CH2-8), 6.91 (t, J=7.5 Hz, H5''), (7.01, m, 2H, $H_{3''}$, $H_{5'}$), (7.22, m, 3H, H5, H6, $H_{4''}$), (7.38, d, 1H, H_4), (7.64, d, 1H, H_7), (7.73, d, J=7.6 Hz, $H_{6''}$), 10.44 (s, 1H, NH), 13.22 (s, 1H, OH). ^{13}C NMR (125 *MHz*, DMS-d_6) δ (ppm) 11.8 (C_{CH3}), 20.9 (C_{CH2}), 99.7 ($C_{5'}$), 110.6 (C_4), 115.5 ($C_{1''}$), 116.4 ($C_{3''}$), 118.6 (C_7), 119.4 ($C_{5''}$), 122.0 (C_5), 122.5 (C_6), 127.5 ($C_{6''}$), 129.7 ($C_{4''}$), 135.6 (C_{7a}), 141.2 ($C_{1'}$), 144.2 (C_{3a}), 154.3 ($C_{2''}$), 156.0 (C_2).

Procedure for the synthesis of compound 4a: 0.2 mL (2 eq) of DMFDMA was added to 200 mg (0.75 mmole) of pyrazole 3 solved in Toluene. The mixture was heated under reflux during 20 min. After filtration 100 mg of a benzimidazole precipitate were obtained.

1-[(2-hydroxyphényl)-2H-pyrazol-1-yl]-1H-benzimidazole 4a: white solid, yield 46%, RMN ^{1}H (500 *MHz*, DMSO-d_6) δ (ppm) 3, 73 (s, 3H, NCH_3), 6,90 (t, *J*=7,1 *Hz*, 1H, $H_{5''}$), (6,95, d, *J*=6,85 *Hz*, 1H, $H_{3''}$), (7,20, m, 1H, $H_{5'}$), (7,21, m, 1H, $H_{4''}$), (7,36, m, 1H, H_5), (7,37, m, 1H, H_6), (7,43, m, 1H, H_4), (7,82, m, H_7), (7,83, m, 1H, $H_{6''}$), (8,58, s, 1H, H_2), 10,25 (s, 1H, OH).

RMN ^{13}C (125 *MHz*, DMS-d_6) δ (ppm) 35,9 (CCH3-8),101,7 (C5'), 110,6 (C4), 116,5 ($C_{3''}$), 117,3 ($C_{1''}$), 119,3 ($C_{5''}$), 120,0 (C_7), 123,0 (C_6), 124,2 (C_5), 126,9 ($C_{6''}$), 129,2 ($C_{4''}$), 134,1 (C_{3a}), 135,0 ($C_{1'}$), 142,8 (C_{7a}), 143,9 (C_2), 148,4 ($C_{4'}$), 155,0 ($C_{2''}$). MS (EI): m/z 304 [$M^{+\cdot}$]

Procedure for the synthesis of compound 4b: 0.09 mL (2 eq) of DMF-DMA was added to a solution of 100 mg (0.34 mmole) of 3'a in Toluene. The mixture was heated 20 minutes under reflux. Crude product was then separated and purified on silica gel preparative plates (CH_2Cl_2/AcOEt: 8/2) to give 60 mg of 4b as a white solid.

1-[(2-hydroxyphényl)-2-éthyl-pyrazol-1-yl]-1H-benzimidazole 4b: white solid, yield 58% RMN ^{1}H (500 *MHz*, DMSO-d_6), δ (ppm) 2,43 (s, 3H, CH_3), 3,61 (s, 3H, CH_3-9), 6,90 (t, *J*=6,3 *Hz*, 1H, $H_{5''}$), (6,96, d, *J*=6,85 *Hz*, 1H, $H_{3''}$), (7,21, m, 2H, H_4, $H_{5'}$), (7,22, m, 1H, $H_{4''}$), (7,24, t, *J*=6,5 *Hz*, 1H, H_5), (7,28, t, *J*=6 *Hz*, 1H, H_6), (7,67, d, J=6,25 *Hz*, H_7), (7,82, dd, J_1=13,5 *Hz*, J_2=6,45 *Hz*, $H_{6''}$), 10,25 (s, 1H, OH), RMN ^{13}C (125 *MHz*, DMSO-d_6), δ (ppm) 13.6 (C_{CH3}-8), 35.6 (C_{CH3}-9), 102.8 ($C_{5'}$), 109.9 (C_4), 116.6 ($C_{3''}$), 117.3 ($C_{1''}$), 118.8 (C_7), 118.9 ($C_{5''}$), 122.7 5 (C_6), 123.2 (C_5), 126.8 ($C_{6''}$), 129.2 ($C_{4''}$), 134.1 ($C_{1'}$), 135.7 (C_{3a}), 142.4 (C_{7a}), 148.6 ($C_{4'}$), 152.2 (C_2), 154.9 ($C_{2''}$). MS (EI): m/z 304 [$M^{+\cdot}$]

Procedure for the synthesis of compound 4c: To a solution of benzimidazole 3'b (0.83 mmole) in toluene, was added 0.25 mL of DMF-DMA. The mixture was heated under reflux during 20 minutes and then a white solid was separated and purified using silica gel preparative plates to afford 60 mg of 4c as a white solid.

1-[(2-hydroxyphényl)-2-éthyl-pyrazol-1-yl]-1H-benzimidazole 4c: white solid, yield 25% RMN ^{1}H (500 *MHz*, DMSO-d_6) δ (ppm) 1.27 (t, *J*=6,25 *Hz*, 3H, CH_3), 2.48 (q, 2H, CH_2-8), 3,59 (s, 3H, NCH_3), 6,90 (t, *J*=6.45 *Hz* , 1H, $H_{5''}$), (6,96, d, *J*=6,35 *Hz*, 1H, $H_{3''}$), (7,21, m, 2H, $H_{4''}$, $H_{5'}$), (7,25, t, *J*=6,65 *Hz*, 1H, H_5), (7,29, t, *J*=6,7 *Hz*, 1H, H_6), (7,71, d, *J*=6,5 *Hz*, 1H, H_7), (7,82, dd, J_1=1,25 *Hz*, J_2=6,45 *Hz*, $H_{6''}$), 10,44 (s, 1H, OH). RMN ^{13}C (125 *MHz,* DMSO-d_6) δ (ppm) 11,2 (C_{CH3}-9), 20,3 (CH_2), 35,5 (C_{CH3}-10), 103,0 ($C_{5'}$), 109,8 (C_4), 116,5 ($C_{3''}$), 117,3 ($C_{1''}$), 119,1 (C_7), 119,3 ($C_{5''}$), 122,7 (C_6), 123,3 (C_5), 126,8 ($C_{6''}$), 129,2 ($C_{4''}$), 134,0 ($C_{1'}$), 135,7 (C_{3a}), 142,3 (C_{7a}), 148,6 ($C_{4'}$), 155,0 ($C_{2''}$), 156,5 (C_2). MS (EI): m/z 318 [$M^{+\cdot}$]

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