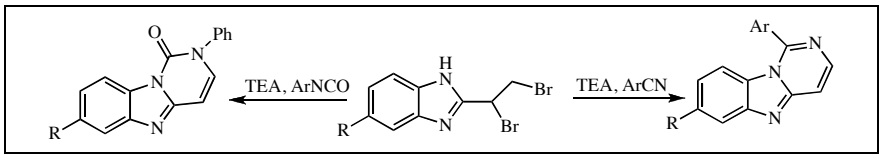
M. Bakavoli[a,b*], M. Nikpour[c], A. R. Ebrahimi[a], A. Taghizadeh[b], M. Rahimizadeh[a] and A. Davoodnia[b]

a:Department of Chemistry, School of Sciences, Ferdowsi University, Mashhad 91775-1436, Iran
b:Department of Chemistry, School of Sciences, Islamic Azad University, Mashhad , Iran
c: Department of Chemistry, School of Sciences, Islamic Azad University, Ahvaz Branch, Ahvaz, Iran
*Corresponding author: email:mbakavoli@yahoo.com
Received June 26, 2007



Cyclocondensation of orthophenylendiamines with 3-bromopropionic acid in PPA afforded 2-vinyl-benzimidazoles which were subsequently converted to their corresponding 2-(1,2-dibromoethyl)-1*H*-benzimidazoles on treatment with bromine. Reaction of these compounds with aryl nitriles or aryl isocyanates in basic chloroform yielded 1-arylpyrimido[1,6-*a*]benzimidazoles and 2-arylpyrimido[1,6-*a*]-benzimidazol-3-ones respectively.

J. Heterocyclic Chem., **45**, 1465 (2008).

INTRODUCTION

Pyrimido[1,6-*a*]benzimidazoles are a class of fused heterocycles with a wide spectrum of biological activities. These compounds have been described as being DNA cleaving agents [1], DNA gyrase inhibitors [2-7], anti-inflammatory [8-10], antiamoebic and analgesic [8,9], herbicidal [11], antimicrobial and antifungal [12], antiulcer [13], polymer dye additive [14], variolin alkaloids analogues [15-17], and nucleoside analogues agents [18,19]. Studies on benzene carcinogenesis and mutagenesis showed that *p*-benzoquinone which is the oxidation product of benzene reacts with deoxycitidine in the human body [20-27] to produce a pyrimido[1,6-*a*]benzimidazole structure as shown in Figure 1.

In view of all these activities we were intrigued by the possibility of preparing various pyrimido[1,6-*a*]-benzimidazole derivatives. These derivatives can be prepared by cyclocondensation of 1-(2-aminoaryl) urea with diethyl malonate, 2-substituted benzimidazolyl-acetates with carbonate esters [1-6], condensation of ketoisothiocyanates with orthophenylenediamines [8-10] and methyl 2-(bromomethyl)-1*H*-benzimidazole-1-carboxylate with tosylmethylisocyanides [15-17], reaction of 4-*O*-[(triisopropylphenyl)sulfonyl]-pyrimidine nucleosides with orthophenylenediamine [18-19] and direct or biomedia reaction of deoxycytidine with *p*-benzoquinone [20-27]. Other routes include condensation of 2-(3-aminopropyl)-benzimidazole with carbon disulfide [28], 2-(2-benz-imidazolyl)acetonitrile and 2-(2-benzimidazolyl)ethyl-acetate [29-36], ring construction of pyrimido[4,5-*b*]-[1,5]benzodiazepines [37-39], reaction of 6-chloro[1,3]-oxazine-2,4-diones with orthophenylenediamine [40] and cyclocondensation of (benzimidazol-2-ylmethyl)-triphenylphosphonium chloride [41-43].

In connection with our work on the synthesis of heterocyclic compounds with potential biological activities [44] and exploration of their synthetic pathways [45], we report herein a general methodology for the preparation of pyrimido[1,6-*a*]benzimidazoles **4** through heterocyclization of 2-(1, 2-dibromoethyl)-1*H*-benzimida-zoles **3a,b** with aromatic nitriles and isocyanates.

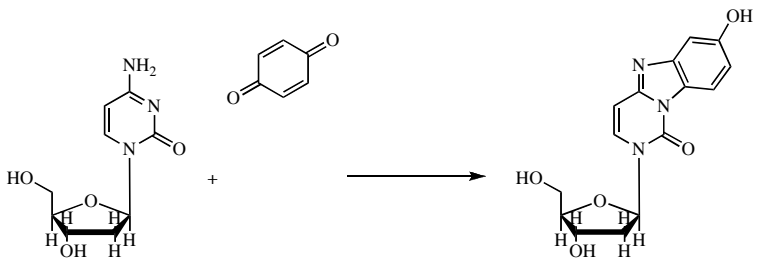
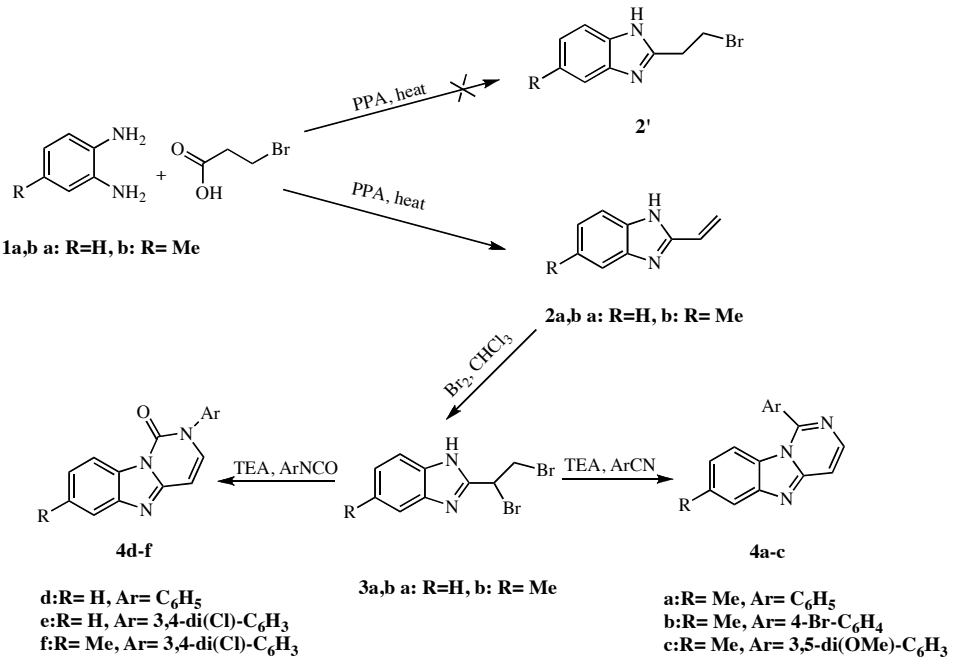


Figure 1

Scheme 1

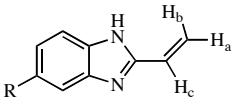


RESULTS AND DISCUSSION

As shown in Scheme 1, reaction of orthophenylenediamines **1a,b** with 3-bromopropionic acid in PPA failed to produce the bromobenzimidazole derivatives **2'** as have been claimed by an earlier worker [46] but instead afforded their corresponding 2-vinylbenzimidazoles **2a,b**. The structures assigned to these compounds were substantiated by their spectral and analytical data. For example, the IR spectrum of **2a** exhibited two vibrational bands at 1650 cm^{-1} and 3300cm^{-1} due to C=C and NH bonds respectively. The ^1H NMR spectrum of this compound showed four signals at δ 5.6, 6.0, 6.7 and 8.5 ppm due to H_a (^3J= 10Hz, ^2J= 2Hz), H_b (^3J= 18Hz, ^2J= 2Hz), H_c ($^3J_{HbHc}$= 18Hz, $^3J_{HaHc}$= 10Hz) and NH respectively (Scheme 2). The mass spectrum showed a molecular ion peak at m/z 144, which confirms the proposed structure.

Bromination of the 2-vinylbenzimidazoles **2a,b** with Br_2/$CHCl_3$ afforded the dibromo derivatives **3a,b** on the basis of their spectral and microanalytical data (data in the experimental section). The latter compounds were

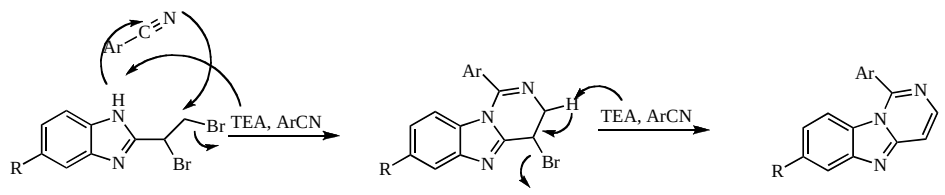
Scheme 2



subjected to base catalyzed heterocyclization with aryl nitriles or aryl isocyanates and gave the desired 1-arylpyrimido[1,6-*a*]benzimidazoles **4a-c** and 2- arylpyrimido-[1,6-*a*]benzimidazol-3-ones **4d-f** respectively. A plausible mechanism is depicted for the formation of selected compounds **4a-c** (Scheme 3). Heterocyclization seems to start with the base catalyzed nucleophilic attack of the benzimidazole ring nitrogen onto the nitrile functionality of the arylnitrile with subsequent nucleophilic attack on the bromomethylene moiety which was followed by dehydrobromination to furnish the tricyclic structure.

The structures of compounds **4a-f** were confirmed from analytical data. For example, the IR spectra of compounds **4a-c** were devoid of the stretching vibration

Scheme 3



bands at 3300cm^{-1} and 2250 cm^{-1} due to NH and CN functional groups while compounds **4d-f** only exhibited a vibrational band for C=O group at 1650 cm^{-1}.The ^{1}H NMR spectra of compounds **4a-f** did not exhibit signals attributed to protons of CH_2Br, CHBr and NH groups of their precursors but instead the appearance of two signals for the representative compounds **4c,f** around δ, 8.0 and 9.0 ppm for C_4H and C_3H respectively is a good indication of the cyclization process. Further proof came from the mass spectra of compounds **4a-f** which showed their expected molecular ion peacks with the exclusion of isotopic pattern for two bromine atoms but in case of **4b** and **4e,f** isotopic patterns were observed for one bromine and two chlorine atoms respectively.

In conclusion, treatment of 2-(1,2-dibromoethyl)-1*H*-benzimidazoles **3a,b** with aromatic nitriles and isocyanates in basic chloroform is a new, efficient and general access to 1-arylpyrimido[1,6-*a*]benzimidazole derivatives.

EXPERIMENTAL

Melting points were recorded on an Electrothermal type 9100 melting point apparatus. The IR spectra were obtained on a 4300 Shimadzu Spectrometer. The ^{1}H NMR (100 MHz) spectra were recorded on a Bruker AC 100 spectrometer. The mass spectra were scanned on a Varian Mat CH-7 instrument at 70 eV. Elemental analysis was obtained on a Thermo Finnigan Flash EA microanalyzer.

General procedure for the preparation of 2-vinylbenzimidazoles. A mixture of orthophenylenediamine or 4-methylorthophenylendiamine (10 mmol), 3-bromopropionic acid (10 mmol) in PPA (5 mL) was heated with stirring for 4 hours at 100-120 °C. Then the mixture was poured onto ice and neutralized with concentrated ammonia solution and kept over 8 hours at 5-10 °C. The yellow residue was recrystallized from ethanol.

2- Vinylbenzimidazole (2a). This compound was obtained as a yellow powder in 40% yield , mp 159 °C; IR:3280 cm^{-1} (NH) ;^{1}H NMR: ($CDCl_3$) δ, 5.6 (dd,1H, H_a) (^{3}J= 10Hz, ^{2}J= 2Hz), 6.0 (dd, 1H, H_b) (^{3}J= 18Hz, ^{2}J= 2Hz), 6.7 (dd, 1H, H_c) (^{3}J= 18Hz, ^{3}J= 10Hz), 7.1-7.6 (m, 4H, aromatic), 8.5 (broad,1H, NH); ms: m/z, 144. *Anal*. Calc. for $C_9H_8N_2$ (%):C, 74.98; H, 5.59; N, 19.43. Found (%): C, 75.20; H, 5.79; N, 19.23.

5- Methyl- 2- vinylbenzimidazole (2b). This compound was obtained as a yellow powder in 46% yield , mp 125 °C; IR:3300 cm^{-1} (NH) ;^{1}H NMR: ($CDCl_3$) δ, 2.3 (s, 3H, CH_3), 5.6 (dd,1H, H_a) (^{3}J = 10Hz, ^{2}J = 2Hz), 6.2 (dd, 1H, H_b) (^{3}J = 17Hz, ^{2}J = 2Hz), 6.8 (dd, 1H, H_c) (^{3}J = 17Hz, ^{3}J = 10Hz), 7 -7.45 (m, 3H, aromatic), 9.1 (broad,1H, NH); ms: m/z, 158. *Anal*. Calc. for $C_{10}H_{10}N_2$ (%):C, 75.92; H, 6.37; N, 17.71. Found (%): C, 76.22; H, 6.18; N, 17.53.

General procedure for the bromination of 2-vinylbenzimidazoles. To a solution of 2-vinylbenzimidazoles **2a** or **2b** (10 mmole) in chloroform (10 mL), bromine (10 mmol) was added dropwise and stirred for half an hour. Then the solvent was removed under reduced pressure and the residue was recrystallized from ethanol.

2-(1,2-Dibromoethyl)-1*H*-benzimidazole (3a). This compound was obtained as a red powder in 65% yield , mp 174 °C; IR: 3300 cm^{-1} (NH) ;^{1}H NMR: ($CDCl_3$) δ, 4.2 (d, 2H, CH_2Br), 6.5 (t, 1H, CHBr), 7.0-7.4 (m, 4H, aromatic), 13.6 (broad,1H, NH); ms: m/z, 284 (100%), 302 (25%), 304 (49%), 306 (24%). *Anal*. Calc. for $C_9H_8Br_2N_2$ (%):C, 35.56; H, 2.65; N, 9.22. Found (%): C, 35.24; H, 2.71; N, 9.43.

2-(1, 2-Dibromoethyl)- 5- methyl-1*H*-benzimidazole (3b). This compound was obtained as a red powder in 65% yield, mp 153 °C; IR: 3320 cm^{-1} (NH) ;^{1}H NMR: ($CDCl_3$) δ, 2.3 (s, 3H, CH_3), 3.7 (d, 2H, CH_2Br), 6.0 (t, 1H, CHBr), 6.5- 7.1 (m, 3H, aromatic), 14.0 (broad, 1H, NH); ms: m/z, 298 (100%), 316 (20%), 318 (39%), 320 (19%). *Anal*. Calc. for $C_{10}H_{10}Br_2N_2$ (%):C, 37.77; H, 3.17; N, 8.81. Found (%): C, 38.04; H, 2.95; N, 9.03.

General procedure for the reaction of 2-(1,2-dibromoethyl)- 5- methyl-1*H*-benzimidazole with nitriles. A solution of 2-(1,2-dibromoethyl)-5-methyl-1*H*-benzimidazole **3b** (10 mmol), aromatic nitrile (20 mmol) and triethylamine (3mL) in chloroform (20mL) was heated under reflux for 6 hours. The solvent was removed under reduced pressure and the residue was washed with water and then recrystallized from ethanol to give compounds **4a-c**.

7-Methyl-1-phenylpyrimido[1,6-*a*]benzimidazole (4a). This compound was obtained as a yellow powder in 75% yield , mp 275 °C; IR: 2850, 2900 cm^{-1} (CH_3); ^{1}H NMR: ($CDCl_3$) δ, 2.4 (s, 3H, CH_3), 7.0- 7.8 (m, 9H, aromatic), 8.2 (d, 1H, C_3H); ms: m/z, 259. *Anal*. Calc. for $C_{17}H_{13}N_3$ (%):C, 78.74; H, 5.05; N, 16.20. Found (%): C, 78.56; H, 5.24; N, 16.41.

1-(4-Bromophenyl)-7-methylpyrimido[1,6-*a*]benzimidazole (4b). This compound was obtained as a brown powder in 85% yield , mp 282 °C; IR: 2850, 2900 cm^{-1} (CH_3); ^{1}H NMR: ($CDCl_3$) δ, 2.2 (s, 3H, 7-CH_3), 7.1- 7.85 (m, 8H, aromatic), 8.25 (d, 1H, C_3H); ms: m/z, 172 (100%) , 337 (55%), 339 (54.3%). *Anal*. Calc. for $C_{17}H_{12}BrN_3$ (%):C, 60.37; H, 3.58; N, 12.42. Found (%): C, 60.12; H, 3.72; N, 12.34.

1-(3,5-Dimethoxyphenyl)-7-methylpyrimido[1,6-*a*]benzimidazole (4c). This compound was obtained as a brown powder in 72% yield , mp 215-217 °C; IR: 2900, 2950 cm^{-1} (CH_3); ^{1}H NMR: ($CDCl_3$) δ, 2.4 (s, 3H, 7-CH_3), 3.8 (s, 6H, 2OCH_3), 6.8- 7.7 (m, 8H, aromatic),; ms: m/z, 319. *Anal*. Calc. for $C_{19}H_{17}N_3O_2$ (%):C, 71.46; H, 5.37; N, 13.16. Found (%): C, 71.27; H, 5.21; N, 12.95.

General procedure for the reaction of 2-(1,2-Dibromoethyl)-5-methyl-1*H*-benzimidazole with aryl isocyanates. A solution of each 2-(1,2-dibromoethyl)-1*H*-benzimidazoles **3a,b** (10 mmol), aromatic isocyanate (20 mmol) and triethylamine (3mL) in chloroform (30mL) was heated under reflux for 5 hours. The solvent was removed under reduced pressure and the residue was washed with water and then crystallized from ethanol to give compounds **4d-f**.

2-Phenylpyrimido[1,6-*a*]benzimidazole-1-one (4d). This compound was obtained as an orange powder in 67% yield , mp 235 °C; IR: 1650 (C=O), 2850, 2900 cm^{-1} (CH_3); ^{1}H NMR: (d^6-DMSO) δ, 7.0 - 7.8 (m, 9H, aromatic), 7.87 (d, ^{3}J = 12Hz, 1H, C_4H), 8.2 (d, ^{3}J = 12Hz, 1H, C_3H); ms: m/z, 261. *Anal*. Calc. for $C_{16}H_{11}N_3O$ (%):C, 73.55; H, 4.24; N, 16.08. Found (%): C, 73.37; H, 4.13; N, 15.89.

2-(3,4-Dichlorophenyl)-pyrimido[1,6-*a*]benzimidazole-1-one (4e). This compound was obtained as an orange powder in 80% yield , mp 220 °C; IR: 1600 (C=O), 2880, 2950 cm^{-1} (CH_3); ^{1}H NMR: ($CDCl_3$) δ, 7.2- 7.7 (m, 7H, aromatic), 7.9 (d, ^{3}J =

13Hz, 1H, C_4H), 8.15 (d, ^3J = 13Hz, 1H, C_3H); ms: m/z, 158 (100%), 329 (9%), 331 (6%), 333 (1%). *Anal*. Calc. for $C_{16}H_9Cl_2N_3O$ (%):C, 58.20; H, 2.75; N, 12.73. Found (%): C, 57.92; H, 2.89; N, 12.94.

2-(3,4-Dichlorophenyl)-7-methylpyrimido[1,6-*a*]benzimidazole-1-one (4f). This compound was obtained as an orange powder in 70% yield , mp 278 °C; IR: 750 (C-Cl), 1600 (C=O), 2850, 2900 cm^{-1} (CH_3); ^{1}HNMR: ($CDCl_3$) δ, 2.4 (s, 3H, 7-CH_3), 7.3- 7.6 (m, 6H, aromatic), 7.9 (d, 1H, C_4H), 9.2 (d, 1H, C_3H); ms: m/z, 173 (100%), 343(12%), 345(8%), 347(1%). *Anal*. Calc. for $C_{17}H_{11}Cl_2N_3O$ (%):C, 59.32; H, 3.22; N, 12.21. Found (%): C, 59.12; H, 2.96; N, 12.41.

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