

Facile and convenient new synthesis of imidazobenzimidazol-2-one and pyrimidobenzimidazol-2,3-dione derivatives

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Abstract: Reaction of epoxides **1** and **2** with 2-aminobenzimidazole led to formation of imidazobenzimidazol-2-ones **4** and pyrimido[1,2-a]benzimidazol-2,3-diones **5**, respectively in good yields. This same compound **5** may be obtained by another route by reacting halohydrin derivatives **3** with 2-aminobenzimidazole. The mechanisms of the studied reactions are discussed.

Keywords: Cyanoepoxides, epoxides cyanoesters, 2-aminobenzimidazole, imidazobenzimidazol-2-ones and pyrimidobenzimidazol-2,3-diones.

Introduction

Benzimidazole derivatives belong to a crucial structural motif that is seen in many pharmaceutical and biologically interesting molecules¹. Some of their analogues show an array of biological activities, including nonnucleoside HIV-1 reverse transcriptase inhibitors², they are selective inhibitors of cyclooxygenase-Cox-2³, and they are resistance in *Trichostrongylus axei* in sheep⁴. Several benzimidazoles have been reported as antiviral⁵, anticoagulant⁶, anti-inflammatory⁷, antibacterial⁸, anticancer⁹ and antiproliferative agents¹⁰.

Moreover heterocycles derivatives of benzimidazoles systems have been tested as a potential antimicrobial¹¹, antibacterial¹², antimalarial¹³, antineoplastic¹⁴, antioxidant¹⁵, antidiabetic¹⁶, anticonvulsant¹⁶ and anti-hepatitis C virus agents¹⁷.

Therefore, the widespread importance of benzimidazole structure has prompted extensive studies for practical synthetic methods to access to this class of heterocycles¹⁸.

The preparation and investigation of bioactive nitrogen, oxygen and sulfur containing heterocycles is one of our ongoing projects. We have already developed some procedures to gain access to diverse structures as benzodiazepines¹⁹, triazoles, triazolopyrimidines, benzimidazoles and imidazoles²⁰.

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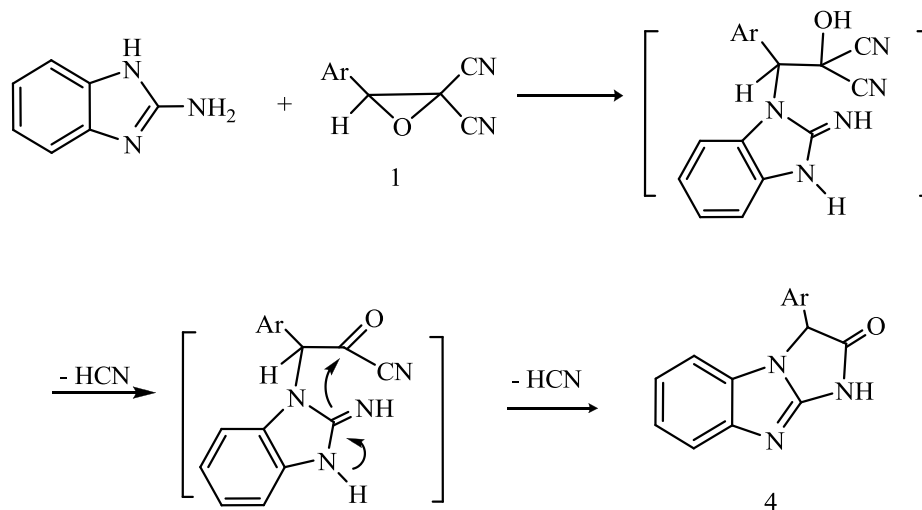
In continuation of our interest in the synthesis of novel polyfunctionalized heterocycles of biological importance, we report here an easy one-pot synthesis of the novel compounds via the reaction of cyanoepoxides **1**, epoxides cyanoesters **2** and halohydrins **3** respectively, with 2-aminobenzimidazole. Thus, corresponding five membered imidazobenzimidazolone and six membered pyrimidobenzimidazolone derivatives were exclusively isolated and characterized.

Results and Discussion

When cyanoepoxides **1** are heated under reflux with 2-aminobenzimidazole in acetonitrile solution for 20 hours, 1,3-dihydro-3-aryl imidazo[1,2-a]benzimidazol-2-ones **4** are formed in good yields (Table 1). The reaction proceeds by the initial attack of the imino ring nitrogen of the 2-aminobenzimidazole to the carbon β to the nitrile groups.

The instable cyanohydrin loses hydrogen cyanide giving intermediate acyl cyanide, leading immediately to imidazobenzimidazol-2-ones **4** through heterocyclization type reaction.

In this reaction, the two carbons of epoxide **1** act as potential electrophilic centers (Scheme 1). The results obtained from the IR, ^1H NMR, and ^{13}C NMR data as well as the mass spectra are in agreement with the assigned structures **4**.



Scheme 1. Mechanism of the formation of imidazo[1,2-a]benzimidazol-2-ones **4**.

Table 1: Prepared imidazo[1,2-a]benzimidazol-2-ones **4**.

Substrate	Ar	Product	Yield (%) ^a	mp (°C)
1a	C ₆ H ₅	4a	80	185-187
1b	4-MeC ₆ H ₄	4b	81	195-197
1c	4-ClC ₆ H ₄	4c	83	240-242
1d	4-NO ₂ C ₆ H ₄	4d	78	224-226

^a Yields of purified products after their recrystallization in EtOH.

Pyrimidobenzimidazoles have been found to be of pharmacological interest. For example pyrimido[1,2-*a*]benzimidazoles have been described as antihypertensives, antidiabetics, antiinflammatory agents, antirheumatics and as antibiotics against staphylococcus and mycobacterium ranae. They have antiarrhythmic effects, herbicidal activity, antidepressant effects, microfilaricidal and macrofilaricidal effects, they act as bactericides, fungicides, virucides and as diuretics²¹.

These findings prompted us to design compounds with near structural relationship to pyrimido[1,2-*a*]benzimidazoles for further pharmacological tests.

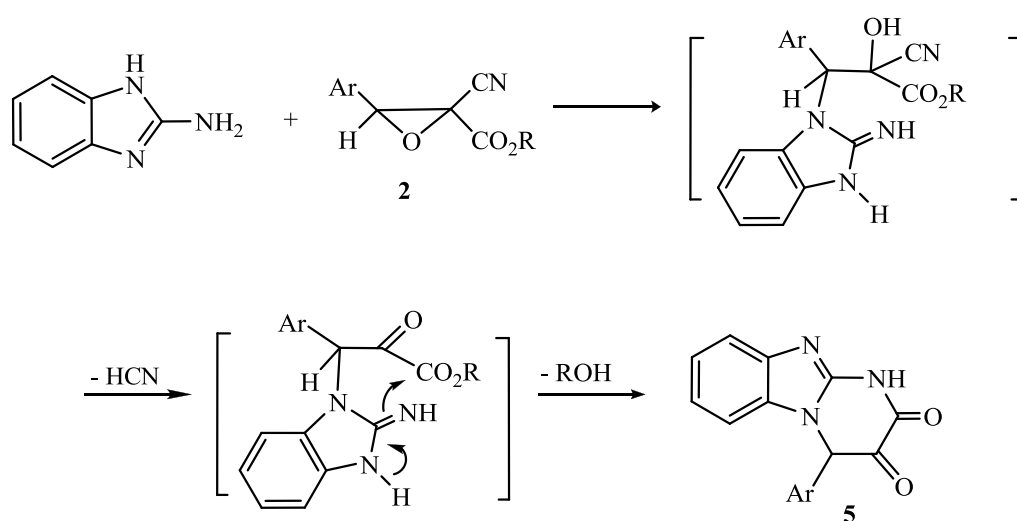
As part of our study using the epoxide as the starting material for the preparation of pyrimidobenzimidazoles, we have designed a simple method for the synthesis of pyrimidobenzimidazol-2,3-diones by the reaction of epoxide cyanoesters **2** with the 2-aminobenzimidazole.

Thus, treatment of **2** with 2-aminobenzimidazole, in equimolecular amounts, in acetonitrile under reflux, afforded products identified as the 1,2-dihydro pyrimido[1,2-*a*]benzimidazol-2,3-diones **5** (Scheme 2, Table 2).

Although the synthetic methods of pyrimido[1,2-*a*]benzimidazoles derivatives are well documented, the methods for the synthesis of 1,2-dihydro pyrimido[1,2-*a*]benzimidazol-2,3-diones **5** are limited.

The scheme 2 proposes a mechanism which shows the formation of pyrimido[1,2-*a*]benzimidazol-2,3-diones **5**.

This reaction was interpreted by an initial opening of the epoxide **2** by a nucleophilic attack of the imino ring nitrogen on the carbon related to the aryl group. The formed intermediate loses a molecule of hydrocyanic acid and leads to cyanoformyl intermediate. The latter undergoes an heterocyclization reaction to give the pyrimido[1,2-*a*]benzimidazol-2,3-diones **5**.



Scheme 2. Route to pyrimido[1,2-*a*]benzimidazol-2,3-diones **5**.

The regioselectivity of the formed product formation was observed on the level of the electrophilic sites of attack which are carbons of epoxide. In effect, carbon related to the grouping aryl is proven to be most electrophilic of the cycle. In our laboratory, it has been demonstrated that the epoxide is acting as a synthon type $R-\overset{\oplus}{C}H-\overset{\oplus}{C}=O$. The strong nucleophilicity of the ring nitrogen imino compared with nitrogen of the amine function explains the selectivity on the level of the nucleophilic attack on epoxide.

Table 2: Preparation of pyrimidobenzimidazol-2,3-diones **5**.

Entry	Ar	R	Product	mp (°C)	Yield ^a % () ^b
a	C ₆ H ₅	Et	5a	> 260	80 (76)
b	4-MeC ₆ H ₄	Et	5b	240-242	84 (81)
c	4-ClC ₆ H ₄	Et	5c	245-247	81 (80)
d	4-MeC ₆ H ₄	Me	5b	234-236	80 (76)
e	4-ClC ₆ H ₄	Me	5c	245-247	82 (80)
f	4-NO ₂ C ₆ H ₄	Me	5d	254-256	70 (75)

^a Yields of purified products after their recrystallization in EtOH.

^b Yields obtained from halohydrins **3**

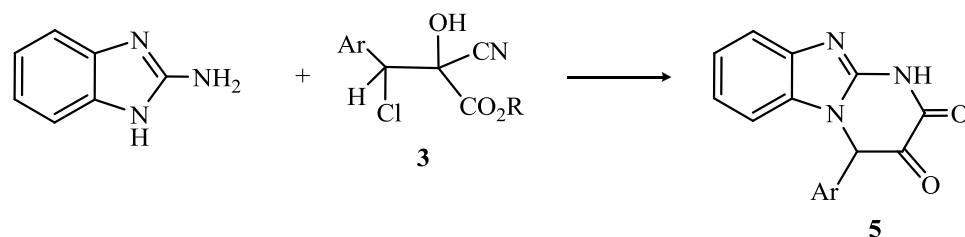
The halohydrins **3**²² are readily accessible in regioselective form, employing the ring opening reaction of epoxides esters **2** by halohydric acids.

Indeed, halohydrins with hydroxy, cyano and ester groups on the same carbon atom have synthetic value because they are interesting starting materials for some useful synthetic transformation²³.

These conditions led us to imagine that the reaction of these halohydrins with the 2-aminobenzimidazole could constitute respectively a new route to pyrimido[1,2-a]benzimidazol-3,4-dione isomer of the pyrimido[1,2-a]benzimidazol-2,3-dione **5**.

However, it is also important to mention that when halohydrins **3** were used in this reaction, under the same conditions described above, the same isomer 1,2-dihydro pyrimido[1,2-a]benzimidazol-2,3-dione **5** was also obtained (Scheme 3, Table 2).

The regioselectivity of the reaction was preserved. We found that this reaction is not efficient (see table 2) that the direct reaction of 2-aminobenzimidazole with epoxides **2**, but it served to compare compounds of type **5** from the two reactions.



Scheme 3. Synthesis of **5** starting from halohydrins **3** as substrate.

The structures of all new compounds **5** were appropriately established by the usual spectroscopic methods.

The determination of the structure **5** was also confirmed in agreement with ^1H NMR data in accord with the results published by Elnagdi and Wamhoff²⁴. Indeed, it has been shown that the hydrogen in position 6 of the core tricyclic benzene system resonates with the downfield (8.33 to 8.52 ppm) when its position is perished from the amide carbonyl. This deshielding is due to the magnetic anisotropy induced by the carbonyl of the pyrimidine ring.

Conclusion

In summary, we have developed a short, practical, and simple method for the synthesis of novel imidazo[1,2-a]benzimidazol-2-ones and pyrimido[1,2-a]benzimidazol-2,3-diones derivatives from epoxides **1** or **2**, resulting in promising substrates for drug design. Moreover, our new route seems of interest to us and compares favorably with existing methods. The biological interest and the study by X-ray of compounds mainly obtained in these experiments are under investigation.

Experimental Section

Melting points were taken on a KOFER hot stage apparatus and are uncorrected. The ^1H NMR spectra were measured in dimethyl sulfoxide- d_6 or (DMSO- d_6) solutions on a Bruker 300 MHz spectrometer using TMS as an internal reference (chemical shift in δ ppm), ^{13}C NMR spectra were recorded at 75 MHz. Infrared spectra were determined with a PERKIN ELMER 1600 Series FT-IR Spectrometer using KBr pellets. Mass spectra were recorded on a Thermo DSQII-Focus mass Spectrometer.

Epoxides **1** or **2** were prepared in a two-step procedure: the first one, a Knoevenagel-Cope condensation. The second step, a stereospecific epoxidation of olefin by sodium hydrochlorite²⁵.

General procedure for synthesis of halohydrin **3**

To a solution of chlorhydric acid (14 mL) in diethyl ether (10 mL), epoxides cyanoesters **2** (10 mmol) dissolved in diethyl ether (10 mL) were added dropwise at 25 °C. The reaction mixture was stirred at this temperature for 5h. The mixture was shaken with cold water (50 mL) and

extracted. The combined organic extracts were washed with water and finally dried over Na_2SO_4 . After evaporation of the solvent, the chlorohydrins **3** were recrystallized from CCl_4 .

General procedure for synthesis of imidazo[1,2-a]benzimidazol-2-ones **4a-d**

To a solution of epoxide **1** (5 mmol) in acetonitrile (20 mL), were added the 2-aminobenzimidazole (5 mmol). The mixture was then refluxed for 24 h. The solvent was removed under reduced pressure and the crude product was treated with a mixture of ether / petroleum ether, the imidazo[1,2-a]benzimidazol-2-ones **4a-d** (Table 1) precipitate slowly and were recrystallized from EtOH.

3-phenyl imidazo[1,2-a]benzimidazol-2-one (4a): Yield: 80%; mp: 185-187 °C.

IR (KBr): 1722, 3320 cm^{-1} . ^1H NMR (DMSO- d_6) δ (ppm): 6.80-7.20 (m, 9H, Ar), 5.47 (s, 1H, CH), 8.22 (s, 1H, NH). ^{13}C NMR (DMSO- d_6) δ 108.1, 111.0, 115.5, 117.2, 120.5, 126.6, 128.4, 129.3, 130.1, 134.7, (Ar-C), 155.2 (C=N), 165.0 (C=O), 55.4 (CH). MS m/z (%): 249 (M^+ , 20), 221 (M^+ -CO, 100), 206 (M^+ -HNCO, 40).

3-(4-methyl phenyl) imidazo[1,2-a]benzimidazol-2-one (4b): Yield: 81%; mp: 195-197 °C.

IR (KBr): 1720, 3319 cm^{-1} . ^1H NMR (DMSO- d_6) δ (ppm): 6.84-7.15 (m, 8H, Ar), 2.20 (s, 3H, CH_3), 5.45 (s, 1H, CH), 8.20 (s, 1H, NH). ^{13}C NMR (DMSO- d_6) δ 109.2, 112.0, 117.5, 119.8, 121.9, 127.8, 129.7, 130.4, 131.1, 138.7, (Ar-C), 155.4 (C=N), 165.1 (C=O), 21.6 (CH_3), 55.4 (CH). MS m/z (%): 263 (M^+ , 23), 235 (M^+ -CO, 100), 220 (M^+ -HNCO, 45).

3-(4-chloro phenyl) imidazo[1,2-a]benzimidazol-2-one (4c): Yield: 83%; mp: 240-242 °C.

IR (KBr): 1715, 3320 cm^{-1} . ^1H NMR (DMSO- d_6) δ (ppm): 7.14-7.40 (m, 8H, Ar), 5.43 (s, 1H, CH), 8.23 (s, 1H, NH). ^{13}C NMR (DMSO- d_6) δ 110.2, 110.1, 118.7, 120.5, 124.9, 128.8, 131.2, 132.3, 134.8, 140.5, (Ar-C), 156.2 (C=N), 165.4 (C=O), 55.6 (CH). MS m/z (%): 283 (M^+ , 20), 255 (M^+ -CO, 100), 240 (M^+ -HNCO, 48).

3-(4-nitro phenyl) imidazo[1,2-a]benzimidazol-2-one (4d): Yield: 78%; mp: 220-222 °C.

IR (KBr): 1720, 3320 cm^{-1} . ^1H NMR (DMSO- d_6) δ (ppm): 7.16-7.44 (m, 8H, Ar), 5.44 (s, 1H, CH), 8.24 (s, 1H, NH). ^{13}C NMR (DMSO- d_6) δ 110.6, 110.5, 118.8, 120.7, 125.2, 129.1, 131.5, 132.7, 135.5, 141.5, (Ar-C), 156.2 (C=N), 165.4 (C=O), 55.6 (CH).

Preparative procedure for synthesis of pyrimido[1,2-a]benzimidazol-2,3-diones **5a-d**

Epoxide **2** or halohydrin **3** (5 mmol) was dissolved in acetonitrile (20 mL), and the 2-amino benzimidazole was added (5 mmol). The mixture was refluxed, stirring constantly for 24 h. After evaporation of the solvent under reduced pressure, the precipitate pyrimido[1,2-a]benzimidazol-2,3-diones **5a-d** were recrystallized from EtOH.

4-phenyl pyrimido[1,2-a]benzimidazol-2,3-diones (5a): Yield: 80%; mp: > 260 °C.

IR (KBr): 1722, 1700, 3260 cm^{-1} . ^1H NMR (DMSO- d_6) δ (ppm): 7.06-7.35 (m, 9H, Ar), 5.41 (s, 1H, CH), 8.54 (s, 1H, NH). ^{13}C NMR (DMSO- d_6) δ 107.4, 115.2, 121.2, 124.5, 127.1, 128.2, 136.1, 137.2, 139.3 (C-Ar) 152.1 (C=N), 165.4 (CO), 175.1 (CO), 61.9 (CH). MS m/z (%): 278 (M^+ +1, 100), 174 (55), 134 (35).

4-(4-methyl phenyl) pyrimido[1,2-a]benzimidazol-2,3-diones (5b): Yield: 84%; mp: 240-242 °C.

IR (KBr): 1720, 1700, 3257 cm^{-1} . ^1H NMR (DMSO- d_6) δ (ppm): 7.12-7.42 (m, 8H, Ar), 5.40 (s, 1H, CH), 8.56 (s, 1H, NH), 2.31 (s, 3H, CH_3). ^{13}C NMR (DMSO- d_6) δ 111.7, 117.5, 123.2,

126.9, 129.4, 130.2, 136.7, 139.1, 140.3 (C-Ar) 152.0 (C=N), 165.8 (CO), 175.5 (CO), 62.0 (CH), 21.3 (CH₃). Ms m/z (%): 292 (M⁺ + 1, 100), 174 (60), 134 (30).

4-(4-chloro phenyl) pyrimido[1,2-a]benzimidazol-2,3-diones (5c): Yield: 81%; mp: 254-256 °C. IR (KBr): 1722, 1700, 3250 cm⁻¹. ¹H NMR (DMSO-d₆) δ (ppm): 7.20-7.53 (m, 8H, Ar), 5.42 (s, 1H, CH), 8.52 (s, 1H, NH). ¹³C NMR (DMSO-d₆) δ 112.3, 118.4, 124.2, 127.2, 130.5, 131.2, 136.2, 139.5, 142.1 (C-Ar), 152.4 (C=N), 165.2 (CO), 168.3 (CO), 62.1 (CH). MS m/z (%): 312 (M⁺ + 1, 100), 174 (50), 134 (40).

4-(4-nitro phenyl) pyrimido[1,2-a]benzimidazol-2,3-diones (5d): Yield: 70%; mp: 250-252 °C. IR (KBr): 1720, 1703, 3253 cm⁻¹. ¹H NMR (DMSO-d₆) δ (ppm): 7.03-7.30 (m, 8H, Ar), 5.42 (s, 1H, CH), 8.52 (s, 1H, NH). ¹³C NMR (DMSO-d₆) δ 106.3, 115.2, 121.1, 123.8, 126.4, 127.8, 135.5, 137.1, 139.1 (C-Ar) 152.2 (C=N), 165.2 (CO), 175.3 (CO), 62.1 (CH). MS m/z (%): 322 (M⁺, 100), 174 (55), 134 (35).

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