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Synthesis and Characterization of 2, 2'-Alkyl/Aryl-Bis(Quinoline-8-Ol-5-Azobenzimidazole)

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Amine Ouaket*[1], Souad Hamdouch[1], Fatiha Moughaoui[1], Zoubida Anbaoui[1], Mohamed Berrada[1], Ahmed Bennamara[1], Noureddine Knouzi[1]

[1]Biomolecules and Organic Synthesis Laboratory, Faculty of Sciences Ben M'sick, University Hassan II of Casablanca, Morocco

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ABSTRACT

In the context of our research on substituted benzimidazoles, we are interested in the synthesis of novel heterocyclic molecules, 2,2'-Alkyl/Aryl-bis(quinoline-8-ol-5-azobenzimidazole). This novel organic molecule is a subclass of quinolines with a large variety of biological properties. In order to affect the binding of quinoline to our bis-benzimidazole derivatives, we have chosen the "azo" bond as a fixing means. To achieve our goal, we studied different parameters for the reactions in order to determine the conditions for obtaining the best results. This article deals with the synthesis and characterization of derivatives Bisbensimidazole. A series of 2,2'-Alkyl/Aryl-bis(6-substituted benzimidazole) were synthesized using HCl solution or PPA (Polyphosphoric Acid).

INTRODUCTION

Amongst heterocyclic pharmacophores, the benzimidazole (Figure 1) ring system is quite common. These substructures are often called ˈprivileged' due to their wide recurrence of bioactive compounds.

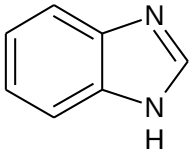


Figure 1: 1H-benzimidazole

Although there is great interest in benzimidazole ligands and structural chemistry, the main interest is in their biological activities.[1]

Benzimidazole and bis-benzimidazole (Figure 2) derivatives are key components in a great many bioactive compounds of natural and synthetic origin [2].

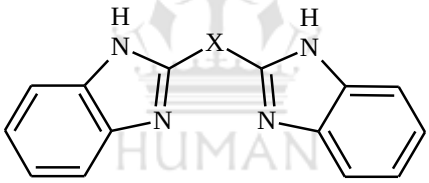


Figure 2: Bis(1H-benzimidazole)

These nitrogenous heterocycles can be prepared by different synthesis methods [3–8]. Many studies carried out very recently have shown that benzimidazoles have several applications in chemistry [9] and in biology [10, 11].

Therefore, benzimidazoles appear quite frequently in pharmaceutical products such as Astemizole [12], Candesartan [13], Omeprazole [14], and Pradaxa [15]. The heterocycle is commonly built up by condensation of ortho-phenylenediamine with carboxylic acids, esters, or imido esters under Brønsted or Lewis conditions [16].

In general, the synthesis of bis(benzimidazoles) is performed by the condensation of derivatives of the 1,2-phenylenediamine with di acids aliphatic or aromatic in a solution acids. This method has been used by Shriner and Upson [17], to prepare for the 2,2'-

bis(benzimidazole) (Figure 2). The use of polyphosphoric acid, as the agent of condensation, for the synthesis of benzimidazoles has been described for the first time by Hein [18].

MATERIALS AND METHODS

2.1. Preparation of the unsubstituted bis(1H-benzimidazoles)

✓ 2,2'-Octane-1,8-diyl-bis(1*H*-benzimidazole) **1b**

A mixture of O-phenylenediamine (0.02 mol) and 1a (0.01 mol) in 30 ml of hydrochloric acid is brought to reflux for 24 hours. After cooling, the medium is neutralized with an ammonia solution (pH 7.5-8). The precipitate obtained is washed, drained and then dried in an oven at a temperature of 65 °C and finally recrystallized from ethanol; $C_{22}H_{26}N_4$; MW : 346.48; (74.88% yield); m.p : 275-280°C; IR (KBr V_{max} /cm^{-1} includes) : 3419 (NH); 2852,2929 (CH); 1625 (C=N); 1450,1483 (C=C); 1271 (C-N); 1027 (C-C); 744 (CH ArH); RMN (DMSO-d_6 / δ / ppm) ^{1}H : 1.3 (s, 8H); 1.8 (s, 4H); 2.9 (s, 4H); 7.35 (s, 4H); 7.56 (s, 4H), ^{13}C : 30.1; 30.3; 31; 32.6; 116.4; 123; 138; 142.5

✓ 2,2'-Benzene-1,4-diyl-bis(1*H*-benzimidazole) 2b

O-phenylenediamine (0.02 mol) is added to 20 g of polyphosphoric acid in a beaker. The mixture is stirred mechanically before adding terephthalic acid **2a** (0.01 mol). The mixture was slowly heated to 160 °C for 4hrs. The solution is cooled to 100 ° C. and poured into a water/ice mixture. The precipitate suspended on water is neutralized with sodium carbonate, and then it is filtered and washed several times with water and filtered. Finally recrystallized from ethanol; $C_{20}H_{14}N_4$; m.w: 310.36; (72.86% yield); m.p: greater than 300°C; IR (KBr V_{max} /cm^{-1} includes) : 3419 (NH); 1630 (C=N); 1438-1473 (C=C); 1275 (C-N); 1024,1124 (C-C); 739 (CH ArH)

2.2. Preparation of the bis (5-nitro-1H-benzimidazoles)

A mixture of 2.25 ml of nitric acid (60%) and 1 ml of sulfuric acid (92%) was added dropwise to the taste with magnetic stirring at 0-5 ° C. To a solution of 0.015 mol of our bisbenzimidazole in 18 ml of sulfuric acid. The solution is maintained at 0-5 ° C for one hour. The mixture is then poured into ice water and then 10 g of NaCl are added while cooling to between 0 and 10 ° C. A solid is obtained which will be drained, washed and then dissolved

in hot water. The pH of the solution is brought to 7.5-8 by an ammonia solution. The precipitate obtained is again drained and recrystallized from methanol.

✓ 2,2'-Octane-1,8-diyl-bis(5-nitro-1*H*-benzimidazole) 3a

$C_{22}H_{24}O_4N_6$; m.w : 436.47; (80.92% yield); m.p : 220-223 °C ;IR (KBr V_{max} /cm^{-1} includes) : 3453 (NH); 3854 (CH); 1630 (C=N); 1426,1454 (C=C); 1384,1503 (NO); 1286 (C-N); 1073-1120 (C-C); 734 (CH ArH); RMN (DMSO-d6 / δ / ppm) : ^{1}H : 1.32 (s, 4H); 1.75 (q, 4H); 2.88 (t, 8H); 8.45 (s, 2H); 7.51 (d, 2H); 8.05 (d, 2H), ^{13}C : 161.23; 112.22; 142.90; 117.94; 114.65, 143.64; 139.81; 29.39; 28.03.

✓ 2,2'-Benzene-1,4-diyl-bis(5-nitro-1*H*-benzimidazole) 3b

$C_{20}H_{12}O_4N_6$; m.w : 400.36; (81.67% yield); m.p : greater than 300 °C; IR (KBr V_{max} /cm^{-1} includes) : 3432 (NH); 3842 (CH); 1625 (C=N); 1469-1501 (C=C); 1348-1561 (NO); 1290 (C-N); 1069,1127 (C-C); 735 (CH ArH); RMN (DMSO-d6 / δ / ppm) : ^{1}H : 8.67 (s, 2H); 8.53 (s, 4H); 8.31 (d, 2H); 7.97 (d, 2H), ^{13}C : 111.3; 120.05; 124.99; 128.29; 130.28; 145.13; 146.11; 147.53; 156.17.

2.3. Preparation of the bis(5-amino-1H-benzimidazoles)

0.005 moles of bisbenzimidazole derivative are added to 150 ml of glacial acetic acid. 14 g of tin chloride are dissolved in 16 ml of concentrated hydrochloric acid and the two solutions are boiled separately. These two solutions are mixed; it is stirred for 30 minutes and then cooled to 5 ° C, to obtain a precipitate. The solid is then neutralized with sodium carbonate before being filtered and recrystallized from ethanol.

✓ 2,2'-Octane-1,8-diyl-bis(5-amino-1*H*-benzimidazole) 4a

$C_{22}H_{28}N_6$; m.w : 376.51; (94.11% yield); m.p : greater than 300 °C;IR (KBr V_{max} /cm^{-1} includes) : 3423 (NH); 2851 (CH); 1636 (C=N); 1414 (C=C); 1339 (C-N); 1022 (C-C); 700 (CH ArH); RMN (DMSO-d6 / δ / ppm) : 1.3 (s, 4H); 1.66 (q, 4H); 2.67 (t, 4H) 4.94 (s, 4H); 6.38 (d, 2H); 6.57 (s, 2H); 7.08 (d, 2H), ^{13}C : 27.59; 28.59; 96.59; 110.34; 115.56; 132.41; 137.89; 143.7; 152.49.

✓ 2,2'-Benzene-1,4-diyl-bis(5-amino-1*H*-benzimidazole) 4b

$C_{20}H_{16}N_6$; m.w : 340.40; (47% yield); m.p : greater than 300 °C; IR (KBr V_{max} /cm^{-1} includes) : 3432 (NH); 2860 (CH); 1635 (C=N); 1448 (C=C); 1339 (C-N); 1066,1130 (C-C); 736 (CH ArH).

2.4. Preparation of the bis(quinolin-8-ol-5-azo-1H-benzimidazoles)

0.004 mol of sodium nitrite dissolved in 8 ml of ice-water at 3 °C. 0.002 mol of our compounds e1-e4 dissolved in hydrochloric acid and water 50/50 at 3 °C. 0.004 mol of the 8-hydroxyquinoline dissolved in a low concentration sodium hydroxide solution. After the various solutions are mixed and allowed to act for 3h, then water is added to precipitate, the product, which has been drained, is recrystallized from methanol.

✓ 2,2'-Octane-1,8-diyl-bis(quinolin-8-ol-5-azo-1*H*-benzimidazole) 5a

$C_{40}H_{36}O_2N_{10}$; m.w : 688.80; (64.51% yield); m.p : greater than 300 °C; IR (KBr V_{max} /cm^{-1} includes) : 3467 (NH); 2834 (CH); 1635 (C=N); 1464,1500 (C=C); 1323,1381 (C-N); 1105 (C-C); 744,787,824 (CH ArH).

✓ 2,2'-Benzene-1,4-diyl-bis(quinolin-8-ol-5-azo-1*H*-benzimidazole) 5b

$C_{38}H_{24}O_2N_{10}$; m.w: 652.70; (45.20% yield); m.p: greater than 300 °C; IR (KBr V_{max} /cm^{-1} includes) : 3445.67 (NH); 1632.07 (C=N); 1463.9,1500.93 (C=C); 1326.74 (C-N); 737.98 (CH ArH).

RESULTS AND DISCUSSION

Before starting the substitution of our bisbenzimidazoles two unsubstituted bisbenzimidazole molecules 2 were synthesized with the condensation of o-phenylenediamine and aliphatic/aromatic diacids 1 in the presence of hydrochloric or polyphosphoric acid (**Figure 3**).

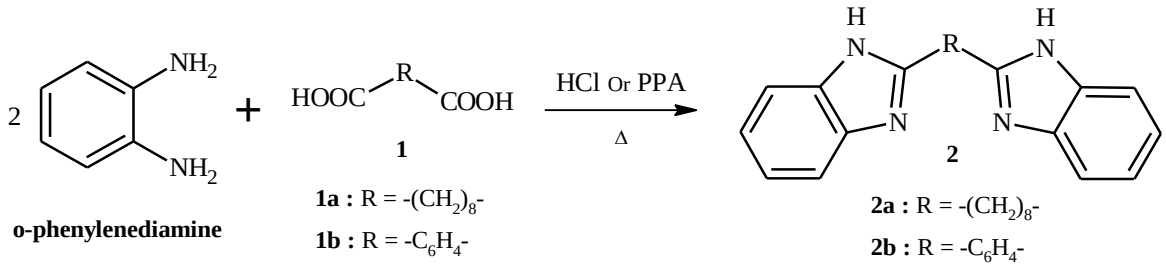
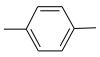


Figure 3: Preparation of the bis(1H-benzimidazole) molecules

We used the Philips [19] method which uses two moles of o-phenylenediamine with one mole of the corresponding diacid, concerning 1b the Thomson [20] process which includes condensing orthodiamine with the aromatic diacid in polyphosphoric acid. The operating conditions are summarized in the table below.

Compounds	R	Reaction conditions			
		T (°C)	Time (h)	Solvent	Yield (%)
2a	-$(CH2)_8$-	100 - 120	24	HCl (5N)	75
2b		160 - 170	4	PPA	73

The literature reports a number of works concerning the nitration of benzimidazole. Maron et al. [21] have described a nitration method of 2,6-dimethylbenzimidazole A and obtained 5-nitro-2,6-dimethylbenzimidazole B, while Fries [22] indicated that the nitration of benzimidazole and its derivatives affect position 5 (or 6). However, according to this method, 7-nitrobenzimidazoles are not obtained.

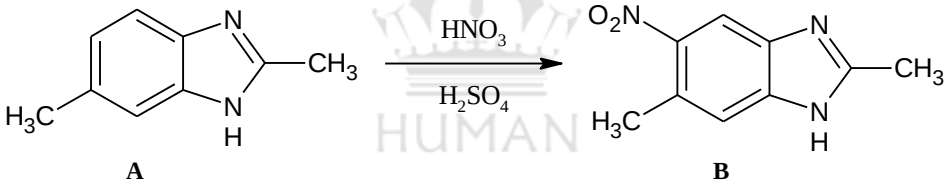


Figure 4: The nitration of 2,6-dimethylbenzimidazole

The nitration of our molecules is carried out according to the procedure described in the experimental part. By nitrating the unsubstituted bisbenzimidazoles (Figure 5) such that this nitration reaction is carried out at 0-5 ° C, with HNO3 (65%) in solution with (92%) H2SO4.

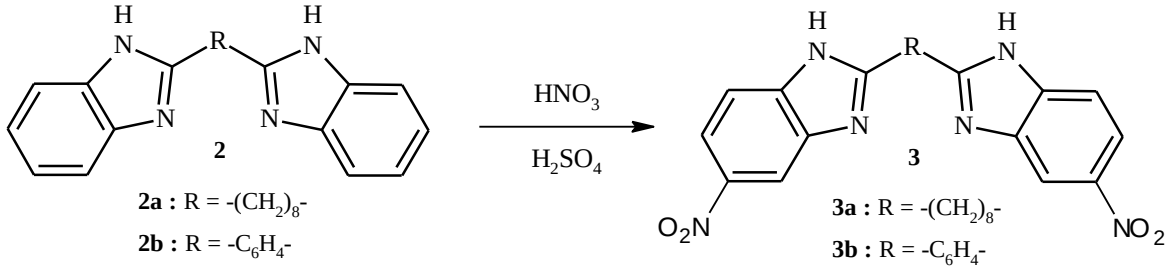


Figure 5: Preparation of the bis(5-nitro-1H-benzimidazole) molecules

It is interesting to note that nitration mainly gives a substituted product in the 6 (or 5) position. We thus obtained the bis(nitrobenzimidazoles) with very good yield.

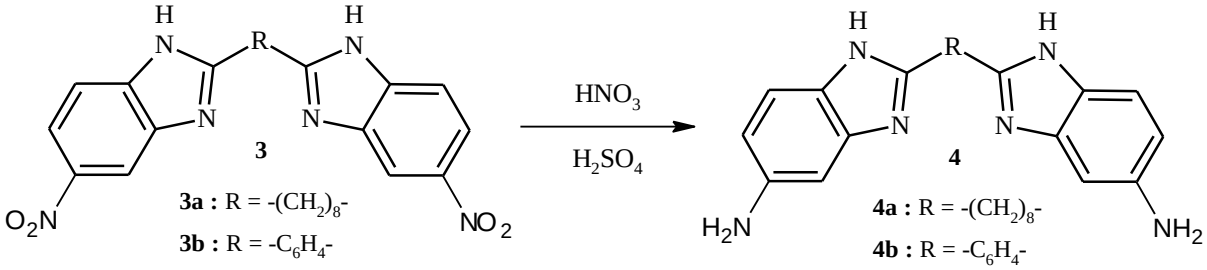


Figure 6: Preparation of the bis(5-amino-1H-benzimidazole) molecules

Mononitrate derivatives are reduced in two ways. The first is a catalytic reduction using hydrogen in the presence of palladium on carbon. The second is a chemical reduction using tin chloride, hydrochloric acid, and acetic acid. We adopted the second process (Figure 6) which gave better yields.

These compounds are excellent synthetic precursors of other multicyclic heterocycles of imidazo benzodiazepine and imidazoquinoline type.

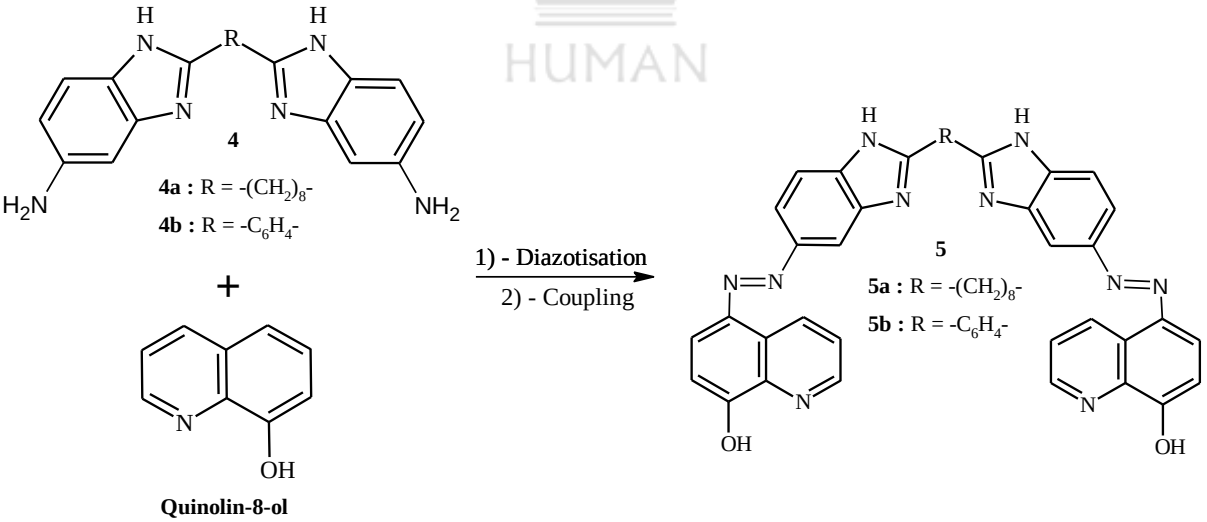


Figure 7: Preparation of the bis(quinoline-8-ol-5-azo-1H-benzimidazoles) molecules

Quinolines are part of the most important compounds among N-heterocycles and have broad application in both the pharmaceutical and agrochemical industries [23]. They have been discovered in a number of natural products and have attracted considerable attention due to their biological activities [24]. In order to affect the binding of 8-hydroxyquinoline to our bis-

benzimidazole derivatives, we have chosen the "azo" bond as a fixing means such that the preparation requires two synthesis steps, diazotization and coupling.

CONCLUSION

Benzimidazoles and bisbenzimidazoles have very important biological activities. Such as anti-inflammatory, anti-anxiety and antimicrobial.

The methods we have used are efficient and economical synthesis of bisbenzimidazole by condensation reaction between ortho-phenylenediamine and dibasic acids in the presence of various conditions presented in this article. this area, to develop protocols for the large production of benzimidazoles and this can be developed from year to year to produce new clean and economical protocols for the large scale production of important pharmacophores based on benzimidazoles synthesized in the future.

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