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Novel synthesis of benzimidazole by Ring Contraction Rearrangement of benzodiazepine

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ABSTRACT

Condensation of substituted aromatic ketones (acetophenone) and substituted aldehydes give unsaturated ketones **14** (chalcones) which react with *o*-phenylenediamine **7** to afford the corresponding benzodiazepines **15**. Treatments of benzodiazepines under basic conditions give benzimidazole derivatives. Structures of all synthesized compounds have been characterized by their NMR and mass spectral data.

Keywords: *N'*-Thioacylamidines, Chalcone, *o*-phenylenediamine, benzodiazepine, benzimidazole.

INTRODUCTION

The antihelmintic drugs derived from benzimidazole are the largest chemical family used to treat endoparasitic diseases in domestic animals and humans, characterized by their high therapeutical index in the different helmintosis, polyvalent effect, and low toxicity. Specifically, it has been estimated that 10 million people worldwide could be infected, and in the past 10 years an increase of the infection has been reported among domestic animals (pigs, horses), and wildlife, with a consequent increase among humans.

In recent years, much attention has been given to the substituents at the 1- and 2-position of the benzimidazole ring which gave good antiviral activities. Many reports have revealed that the influence of the substitution at the 1,2 and 5-positions of the benzimidazole ring was very important for their pharmacological effects (Ashnagar et al., 2009; Patel and Singh, 2009). It is well known that several 1,2-disubstituted benzimidazoles **1** (DeLong, 1984; Miller et al., 1985), **2** (Porcari et al., 1998), **3** (Victor et al., 1997), **4** (Garuti et al., 1998), **5** (Swayze et al., 1993), **6** (Gardiner et al., 1995) were potent inhibitors of RNA viruses. Thus, this let us to prepare and evaluate other derivatives (Figure 1). Benzimidazole derivatives have been intensively used as drugs in medicinal chemistry such as antihelmentic (Hazelton et al., 1995), antihistaminic (Al-Muhaimeed, 1997) and antiulcerative (Richter, 1997), Facing the resistance phenomena, the development of new molecules that inhibited resistant strains revived interest in the search for novel bioactive compounds. Therefore we decided to develop novel structural analogs of benzimidazole. We expanded our research in the substitution at the 2-position. The choice

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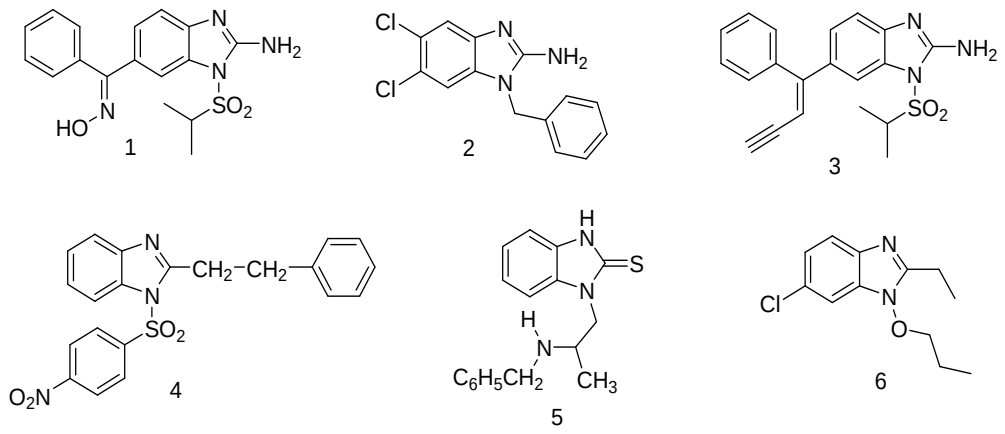


Figure 1: 1,2-disubstituted benzimidazoles.

of chains linked at the C-2 was made in view of their presence in other classes of antiviral compounds. In this paper, we describe the synthesis of benzimidazole. As strategy approach, we used 1,5-benzodiazepines as intermediaries which were converted to benzimidazole under basic conditions.

MATERIALS AND METHODS

General

Melting points were determined with a Kofler hot-stage apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR were recorded on a Bruker Avance 300 MHz spectrometer instrument using TMS as an internal standard. Mass spectrometric measurements were performed using HP5989X instrument. Column chromatography was carried out over silica gel 60 (0.04-0.06 mm) (Merck AG Darmstadt, Germany). All spectrometers analysis were realized at laboratory CEISAM of Nantes University.

General method to synthesis of benzodiazepine

To a solution of chalcone **14** (35 mmol) in ethanol (30 mL), a few drops of triethylamine and *o*-phenylenediamine (un or substituted) (42 mmol) were added. The mixture was heated under reflux for 10 hours in the dark. The mixture was cooled at room temperature and then put in the freezer overnight. The solid product **15** was separated, filtered, and washed with cold ethanol. The residue was purified by column chromatography on silica gel.

***4-diphenyl-2,3-dihydro-1,5-benzodiazepine* 15a**

From 1,3-diphenylpropenone **14a** (7.29 g, 35 mmol) and o-phenylenediamine **7a** (4.54 g, 42 mmol) was obtained **15a** (5.32 g; 51%) as yellow crystals; R_f : 0.4 (hexane/dichloromethane v/v: 70/30); mp: 155-156 °C.

^{1}H NMR ($CDCl_3$, 300 MHz) δ: 3.05-3.08 (m, 2H, CH_2); 5.22 (d, 1H, NH); 5.87-5.88 (m, 1H, H_2); 6.80-7.80 (m, 14H, aromatic protons).

^{13}C NMR ($CDCl_3$, 75 MHz) δ: 37.7 (C_3); 64.4 (C_2); 118.3 (C_9); 121.7 (C_7); 125.3 (C_6);128.6 (C_{17}, C_{21}); 131.1 (C_8); 131.9 (C_{18}, C_{20}); 132.2 (C_{19}); 132.3 (C_{12}, C_{14}); 133.1 (C_{11}, C_{15}); 133.8 (C_{13}); 135.5 (C_{10}); 138.8 (C_{5a}); 143.5 (C_{16}); 146.6 (C_{9a}); 165.8 (C_4).

Mass (m/z) = M^+ = 298 (26); m/z (%) = 221.25 (25); 194.20 (100); 91(21.26); 77 (20.25); 63 (12.25).

(4-methoxyphenyl)-4-(o-hydroxyphenyl)-2,3-dihydroxy-1,5-benzodiazepine 15b

From 1-(o-hydroxyphenyl)-3-(4-methoxyphenyl)propenone **14b** (8.90 g, 35 mmol) and o-phenylenediamine **7a** (4.54 g, 42 mmol) was obtained **15b** (6.74 g; 56%) as yellow crystals; R_f : 0.5 (hexane/ethyl acetate v/v : 80/20); mp: 140-141 °C.

^{1}H NMR ($CDCl_3$, 300 MHz) δ: 3.04 (dd, 1H, $H_{3\alpha}$, J = 9 Hz, and 15 Hz), 3.32 (dd, 1H, $H_{3\beta}$, J = 6 Hz, and 15 Hz), 3.83 (s, 4H, OCH_3 et NH), 5.15 (dd, 1H, H_2, J = 6 Hz and 9 Hz); 6.76-7.37 (m, 12H, aromatic protons); 15.30 (s, 1H, OH). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 36.7 (CH_3); 55.4 (C_2); 69.3 (C_3); 114.3 (C_{18}, C_{20}); 114.8 (C_9); 116.2 (C_{12}); 120.4 (C_7); 120.8 (C_{10}); 124.2 (C_{14}); 127.1(C_6); 132.7 (C_{17}, C_{21}); 133.6 (C_8); 135.7 (C_{15}); 136.5 (C_{13}); 136.8 (C_{16}); 137.1 (C_{5a});145.0 (C_{9a}) ; 150.5 (C_{19}); 162.0 (C_{11}) ; 171.2 (C_4). Mass-(m/z) = 344. M^+ = 344; m/z (%); M+ 2 = 346 (16.41); M+1 = 345 (72.32); 240 (100); 119 (32.96); 91 (35.85) 77 (11.40).

Thienyl-4-tolyl-2,3-dihydro-1,5-benzodiazepine 15c

From 1-tolyl-3-thienyl propenone **14c** (7.99 g, 35 mmol) and o-phenylenediamine **7a** (4.54 g, 42 mmol) was obtained **15c** (5.01 g; 45%) as yellow crystals; R_f: 0.4 (hexane/ethyl acetate v/v: 80/20); mp: 125-126 °C.

^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.38 (s, 1H, CH_3); 2,99 (dd, 1H, H_A, $^3J_{AX}$ = 9 Hz, $^2J_{AM}$ = 13.2 Hz); 3.26 (dd, 1H, H_M, $^3J_{BX}$ = 4.2 Hz, $^2J_{AM}$ = 13.2 Hz); 3,72 (m, 1H, NH); 5.50 (dd, 1H, H_X, $^3J_{AX}$ = 9 Hz, $^2J_{MX}$ = 4.2 Hz); 6.78-7.78 (m, 11H, aromatic and thienyl protons).

^{13}C NMR ($CDCl_3$, 75 MHz) δ: 21.4 (CH_3); 37.7 (C_3); 66.8 (C_2); 121.5 (C_9); 125.4 (C_7); 128.7 (C_6); 128.9 (C_{18}); 132.1 (C_{20}); 133.4 (C_{16}); 134.0 (C_8); 134.9 (C_{19}); 135.2 (C_{11}, C_{15}); 136.2 (C_{12}, C_{14}); 138.2 (C_{10}); 140.5 (C_{5a}); 142.6 (C_{13}); 148.4 (C_{9a}); 167.2 (C_4).
Mass (m/z) = 318. M^+ = 318 (10); m/z (%); 319 (5); 208 (100); 110 (20.15); 91 (21.26); 77 (11.91); 63 (12.25); 39 (25,1).

Phenyl-2-Thienyl-2,3-dihydro-1,5-benzodiazepine 15d

From 1-phenyl-3-thienyl propenone **14d** (7.50 g, 35 mmol) and o-phenylenediamine **7a** (4.54 g, 42 mmol) was obtained **15d** (5.53 g; 52%) as blackish crystals; R_f : 0.4 (hexane/ethyl acetate v/v: 95/5); mp: 120-121 °C.

^{1}H NMR ($CDCl_3$, 300 MHz), δ: 3.06 (dd, 1H, H_A, $^3J_{AX}$ = 9 Hz, $^2J_{AM}$ = 12 Hz); 3.32 (dd, 1H, H_M, $^3J_{MX}$ = 6 Hz, $^2J_{AM}$ = 12 Hz); 3.79 (s, 1H, NH): 5.55 (dd, 1H, H_X, $^3J_{AX}$ = 9 Hz, $^2J_{MX}$ = 6 Hz); 6.83 – 7.92 (m, 12H, aromatic and thienyl protons).

^{13}C NMR ($CDCl_3$, 75 MHz) δ: 37.9 (C_3); 66.7 (C_2); 121.5 (C_9); 124.2 (C_7); 128.7 (C_6); 128.9 (C_{18}); 131.2 (C_{20}); 132.2 (C_{16}); 134.5 (C_8); 134.9 (C_{19}); 136.8 (C_{11}, C_{15}); 137.2 (C_{12}, C_{14}); 139.2 (C_{10}); 141.5 (C_{5a}); 142.2 (C_{13}); 148.4 (C_{9a}); 167.2 (C_4). Mass (m/z) = 304.4. M^+ = 304; m/z (%): 306 (5); 305 (15); 304 (75.76); 77 (100); 52 (48.44); 39 (67.26).

(o-chlorophenyl)-4-phenyl-2,3-dihydroxy-1,5-benzodiazepine 15e

From 1-phenyl-3-(o-chlorophenyl)propenone **14e** (8.49 g, 35 mmol) and o-phenylenediamine **7a** (4.54 g, 42 mmol) was obtained **15e** (8.81 g; 75%) as yellow crystals; R_f : 0.5 (hexane/ethyl acetate v/v: 90/10); mp: 150-151 °C.

^{1}H NMR ($CDCl_3$, 300 MHz) δ: 3.12-3.28 (m, 2H, H_3), 3.79 (s, 1H, NH), 5.79-5.83 (m, 1H, H_2), 6.89-7.76 (m, 13H, H aromatic protons). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 36.7 (CH_3); 55.4 (C_2); 69.3 (C_3); 114.3 (C_{18}, C_{20});114.8 (C_9); 116.2 (C_{12}); 120.4 (C_7); 120.8 (C_{10}); 124.2 (C_{14}); 127.1(C_6); 132.7 (C_{17}, C_{21}); 133.6 (C_8); 135.7 (C_{15}); 136.5 (C_{13}); 136.8 (C_{16}); 137.1 (C_{5a}); 145.0 (C_{9a}); 150.5 (C_{19}); 162.0 (C_{11}); 171.0 (C_4). Mass (m/z) = 335. M^+ = 335 (35.61); M+1 = 336 (35.61); m/$_Z$ (%); 219 (100); 218 (76); 91 (32.53); 77 (25.4); 52 (41.77).

(o-chlorophenyl)-4-phenyl-7-methyl-2,3-dihydroxy-1,5-benzodiazepine 15f

From 1-phenyl-3-o-chlorophenyl-propenone **14e** (8.49 g, 35 mmol) and 4-methyl-o-phenylenediamine **7b** (5.13 g, 42 mmol) was obtained **15f** (7.95 g; 65%) as yellow crystals; R_f : 0.7 (hexane/ethyl acetate v/v: 90/10); . mp: 122-123 °C.

^{1}H NMR ($CDCl_3$, 300 MHz); δ: 2.23 (s, 3H, CH_3), 2.99-3.13 (m, 2H, H_3), 3.64 (s, 1H, NH), 5.60-5.63 (m, 1H, H_2); 6.56-7.60 (m, 12H, aromatic protons). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 21.1 (CH_3); 34.9 (C_3);

67.1 (C_2); 120.8 (C_9); 124.6 (C_6); 128.1 (C_7);128.4 (C_8, C_{21}); 132.2 (C_{19}); 132.7 (C_{18}); 134.7 (C_{20}); 136.6 (C_{12}, C_{14}); 138.1 (C_{11}, C_{15}); 138.6 (C_{13}); 138.8 (C_{17}); 139.2 (C_{10}); 140 (C_{5a}); 141.2 (C_{16}); 142.1 (C_{9a}); 166,40(C_4).

Mass (m/z) = 346. M^+ = 346 (46); M +2 = 348 (15); m/Z (%): 232 (100); 231 (65.81); 77 (38.32).

(2-chloro-5-nitrophenyl)-4-phenyl-2,3-dihydroxy-1,5-benzodiazepine 15g

From 1-phenyl-3-(2-chloro-5-nitrophenyl)propenone (10.07 g, 35 mmol) and o-phenylene diamine **7a** (4.54 g, 42 mmol) was obtained **15g** (8.70 g; 72%) as yellow crystal; R_f 0.7 (hexane/ethyl acetate v/v: 80/20); mp: 166-167 °C.

^{1}H NMR ($CDCl_3$, 300 MHz) δ: 3.16 (d, 2H, H_3, J = 6 Hz), 3.71 (s, 1H, NH), 5.74-5.79 (m, 1H, H_2), 6.85-7.88 (m, 12H, aromatic protons).

^{13}C NMR ($CDCl_3$, 75 MHz) δ: 33.3 (C_3); 67.5 (C_2); 120.8 (C_9); 124.1 (C_6); 128.2 (C_7); 128.7 (C_{19}); 129.1 (C_{21}); 132.7 (C_8); 133.2 (C_{12}, C_{14}); 134.2 (C_{11}, C_{15}); 138.2 (C_{13}); 139.2 (C_{10}); 139.8(C_{5a}); 140.3 (C_{17}); 143.2 (C_{16}); 143.7 (C_{9a}); 146.7 (C_{20}); 167.1 (C_4). Mass (m/z) = 377. M^+ = 377(29.67); M+2 = 379 (10.24); M+1 = 378.1 (10.10); m/ z (%) : 194 (100); 118,9 (33.21); 91 (16.41); 77 (14.88).

(2-chloro-5-nitrophenyl)-4-phenyl-7-methyl-2,3-dihydroxy-1,5-benzodiazepine 15h

From 1-phenyl-3-(2-chloro-5-nitrophenyl)propenone (10.07 g, 35 mmol) and 4-methyl-o-phenylenediamine **7b** (5.13 g, 42 mmol) was obtained **15h** (10.55 g; 77%) as yellow crystals; R_f: 0.6 (hexane/ethyl acetate v/v: 80/20); mp: 200-201 °C.

^{1}H NMR ($CDCl_3$, 300 MHz, δ: 2.23 (s, 3H, CH_3); 3.13 (d, 2H, H_3, J = 6 Hz); 3.69 (s, 1H, NH); 5.70-5.67 (m, 1H, H_2); 6.85-7.88 (m, 11H, H aromatic protons). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 20.1 (CH_3); 32.1 (C_3); 65.7 (C_2); 118.7 (C_9); 126.1 (C_{19}); 127.3 (C_6); 129.1 (C_{21}); 129.8 (C_7); 129.9 (C_8); 131.2 (C_{12}, C_{14}); 132.6 (C_{11}, C_{15}); 135.2 (C_{13}); 138.2 (C_{10}); 140.1 (C_{17}); 141.6 (C_{5a}); 143.6 (C_{9a}) ; 145.2 (C_{16}); 145.6 (C_{20}); 167.1 (C_4).

Mass (m/z) = 391. M^+ = 391 (29.74); M+2 = 393 (9.15); M+1 = 392 (8.16); m/z (%): 208 (100); 207 (48.95); 133 (24.59); 91 (6.22); 77 (20.69).

Benzimidazoles 16 - General method

A solution of 2,3-dihydro-1,5-benzodiazepine **15** (1 g) and potassium carbonate (3 g) in 10 mL of dry dimethylformamide (DMF) was refluxed for 24 h. After cooling to room temperature, 20 mL of water was added. The organic layer was extracted with ethyl acetate (2×50 mL), dried with magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel.

phenyl-1H-benzimidazole 16a

From 2-(2-chloro-5-nitrophenyl)-4-phenyl-2,3-dihydroxy-1,5-benzodiazepine **15g (**1 g, 2.6 mmol) and potassium carbonate (1.8 g, 13 mmol) was obtained **16a** (0.25 g; 50%); R_f : 0.5 (hexane/ethyl acetate v/v: 50/50); mp: 250-251 °C.

Or from 2,4-diphenyl-2,3-dihydro-1,5-benzodiazepine **15a** (1 g, 3.3 mmol) and potassium carbonate (2.28 g, 16.5 mmol) was obtained **16a** (0.29 g; 45%); R_f : 0.5 (hexane/ethyl acetate v/v: 50/50); mp: 250-251 °C Or from 4-Phenyl-2-Thienyl-2,3-dihydro-1,5-benzodiazepine **15d** (1 g, 3.29 mmol) and potassium carbonate (2.27 g, 16.45 mmol) was obtained **16a** (0.38 g; 60%); R_f : 0.5 (hexane/ethyl acetate v/v: 50/50); mp: 250-251 °C.

^{1}H NMR ($CDCl_3$, 300 MHz); δ: 7.10-7.92 (m, 15H, aromatic protons); 12.80 (s, 1H, NH). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 111.4 (C_4); 113.1 (C_7); 124.3 (C_6); 127.7 (C_{13}); 128.1 (C_9);128.8 (C_{11}); 130.1 (C_5); 130.9 (C_{10}, C_{12}); 131.7 (C_8); 138 (C_{3a}); 143.8 (C_{7a}); 151.3 (C_2). Mass (m/z) = 194. M^+ =194 (100); M+1 = 195 (15.16); m/z (%): 193 (27.21); 102.9 (11.39); 91 (16.41); 77 (16.75); 51 (10.85).

phenyl-5-méthyl-1H-benzimidazole 16b

From 7-methyl-2,4-diphenylbenzo-diazepine (1 g, 3.2 mmol) and potassium carbonate (2.21 g, 16 mmol) was obtained 16b (0.27 g; 40%); Rf: 0.2 (hexane/ethyl acetate 95/5); mp : 220-221 °C.

Or from 7-methyl-4-phenyl-2-(2-chlorophenyl) benzodiazepine (1 g, 2.88 mmol) and potassium carbonate (1.99 g, 14.40 mmol) was obtained 16b (0.33 g; 55%); Rf: 0.2 (hexane/ethyl acetate 95/5); mp : 220-221 °C.

^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.42 (s, CH_3); 7.01–8.17 (m, 8H, aromatic protons); 12.80 (s, 1H, NH). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 21.4 (CH_3); 123.6 (C_7); 124.5 (C_4); 124.5 (C_6); 126.9 (C_{13}); 127.6 (C_9);128.8 (C_{11}); 128.9 (C_5); 130.2 (C_{10}, C_{12}); 130.6 (C_8); 130.9 C_{3a}); 150.9 (C_{7a}); 162.3 (C_2). Mass (m/z): 208 M^+ = 208 (29.68); M+1 = 209 (73.85); M+2 = 210 (12.09); m/z (%) : 191 (45.78); 189 (100); 145 (45.22); 131 (11); 40 (30.95).

2-(paratolyl)-1H-benzimidazole 16c

From 2-thienyl-4-(p-tolyl) benzodiazepine (1 g, 3.14 mmol) and potassium carbonate (2.17 g, 15.70 mmol) was obtained 16c (0.23 g; 35%); Rf: 0.5 (hexane/ethyl acetate 25/75);mp: 180-181 °C.

^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.45 (s, 3H, CH_3); 6.80–8.15 (m, 8H, aromatic protons); 12.80 (s, 1H, NH). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 20.3 (CH_3) ; 112.7 (C_4, C_7); 118.6 (C_5, C_6); 124.2 (C_9, C_{13}); 128.5 (C_8); 130.5 (C_{10}, C_{12}); 136.5 (C_{11}); 143.6 (C_{3a}, C_{7a}); 154.2 (C_2). Mass (m/z): 208 M^+= 208 (30.25); M+1 = 209 (67.63); M+2 = 210 (13.20); m/z (%): 191 (40.48); 189 (100); 145 (45.72); 131 (15.12); 40 (26.35).

orthohydroxyphenyl-1H-benzimidazole 16d

From 4-(o-hydroxyphenyl-2-(p-methoxyphenyl) benzodiazepine (1 g, 2.9 mmol) and potassium carbonate (1.8 g, 13 mmol) was obtained 16c (0.21 g; 35%); Rf: 0.5 (hexane/ethyl acetate 80/20); mp: 198-199 °C.

^{1}H NMR ($CDCl_3$, 300 MHz) δ: 6.79 - 7.70 (m, 8H, aromatic protons); 9.80 (s, 1H, OH); 12.80 (s, 1H, NH). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 115.2 (C_4, C_7); 118.5 (C_{10}); 120.1 (C_8); 122.6 (C_{12}); 124 (C_5, C_6) ; 128 (C_{13}); 132.8 (C_{11}); 138.4 (C_{3a}, C_{7a}); 152.9 (C_2); 155.2 (C_9). Mass (m/z): 210 M^+ = 210 (35.21); M+1 = 211 (70.15); M+2 = 212 (10.40); m/z (%): 191 (55.66); 189 (100); 145 (40.25); 131 (14); 40 (28.24).

RESULTS AND DISCUSSION

For several years, our research team is interested in the study of the heteroatomic chains of *N'*-thioacylamidines (Figure 2) and the synthesis of benzimidazole derivatives. The synthesis of *N'*-thioacylamidine intermediaries are widely established. These compounds are easily accessible (Téa et al., 1986) and are subjected of several physico-chimique studies (Chehna et al., 1989).

The obtained results are highlighted as follow: dienic (Téa et al., 1983, 1985, 1986a, 1986b; Chehna et al., 1987), nucleophilic (Meslin et al., 1974, 1975) electrophilic (Meslin et al., 1974, 1975; Guemas et al., 1982) and dipolaroplic characters (De Boer et al., 1967).

Theoretical calculations were made with the imidinium salts in order to determine their reaction ability and stability. The results of the theoretical calculations MNDO, AM1 and PM3 conducted on various imidinium salts confirmed their electrophilic character. The values of the orbital coefficients 2 Pz and the calculated loads using the method AM1 were indicated in the Figure 3.

These results showed that carbons C1 and C3 would be subjected to nucleophilic attacks.

In our search for new benzimidazole derivatives, two main synthetic approaches were used for the preparation of benzimidazole derivatives. In first previous works, we used amidinium salts as starting material. Recently, we developed in our laboratory, a study of the reactivity of amidinium salts against binucleophiles like *o*-phenylenediamine. Thus, *o*-phenylenediamine **7** and amidinium salt **8** were condensed at 5 °C in ethanol. The reaction afforded 2-phenyl-1,3-benzimidazole **9** and 2-phenyl-1,3,5-benzotriazepine **10** (Scheme 1).

The 2-phenyl-1,3-benzimidazole **9** resulted from a double attack of *o*-phenylenediamine to the C3 of amidinium salt and the 2-phenyl-1,3,5-benzotriazepine **10** from a double attack of *o*-phenylenediamine to the C3 and C1 of amidinium salt. At this temperature, the 2-phenyl-1,3-benzimidazole **9** was formed as the major product which was isolated in moderate yield (60%).

Attempt to conduct the same reaction between *o*-phenylenediamine and 3-thioalkyl or 3-thioarylamidinium salt was unsuccessful. Surprisingly, Sissouma et al. (2004) obtained the 1,3-benzimidazole **11** and the 2-thiosubstituted benzimidazole **12** (Scheme 2).

The yield of compounds **11** and **12** depended on the temperature. By raising the temperature, the yield of compound **11** increased while that of compound **12**

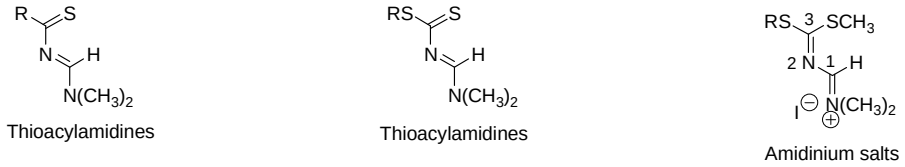


Figure 2: The heteroatomic chains of *N'*-thioacylamidines.

decreased. At room temperature, the yield of **11** became important. We expected to obtain the benzotriazepine ring but we did not in spite of our numerous attempts. The formation of 1,3-benzimidazole could be explained by the formation of a seven member ring, 2-thiosubstituted-1,3,5-benzotriazepine intermediate resulting by double attack on C1 and C3 (Scheme 3).

The 2-thiosubstituted-1,3,5-benzotriazepine must evolve by intermolecular nucleophilic attack. This mechanism was similar to that proposed by Ugi et al. (1986) in the synthesis of β-lactams (Scheme 3).

The second original method was based on the use of benzodiazepine as intermediate compounds. Although many methods for synthesizing benzodiazepine ring systems they continued to receive a great deal attention (Kidwai et al., 2004; Kusanur et al., 2004; Kumar and Joshi, 2007; Sanghetti et al., 2007).

Generally, benzodiazepines are synthesized by the condensation of *o*-phenylenediamine with α,β-unsaturated carbonyl compounds, haloketones or ketones. In the synthesis process, we used chalcone as starting material. Thus, chalcones **14** were prepared by using Claisen-Schmidt condensation with appropriate substituted benzaldehydes and substituted aromatic ketone (acetophenone) in KOH/EtOH solution (Scheme 4). Physical characteristics and yields of compounds **14** were summarized in Table **1**. Indeed, the reaction of binucleophiles like *o*-phenylenediamine with α,β-unsaturated carbonyl compounds **14** under reflux in the presence of triethylamine in ethanol or methanol afforded compounds **15** in moderate to good yields (36 - 77%). The reaction was carried out in dark in order to exclude any influence of light with a possible oxidation of *o*-phenylenediamine (Braulio et al., 1997). Benzodiazepine was isolated as only reaction product (Scheme 4).

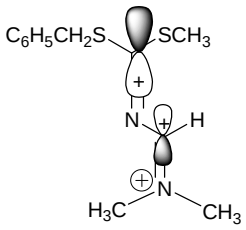
The yields of the reactions were improved by using methanol as solvent instead of ethanol.

The main features of ^{1}H NMR spectra in $CDCl_3$ of the isolated compounds **15** are reported in Table **2**. The ^{1}H NMR analysis of compounds **15b, 15c** and **15d** showed that H3 protons were not equivalent. In compound **15b**, these protons were appeared as doublet dedoublet (dd) at 3.04 and 3.32 ppm; they were coupling with H2 proton (5.15 ppm, dd). The constants coupling were: $^2J_{H3\alpha-\ H3\beta}$ = 15 Hz, $^3J_{H3\alpha-H2}$ = 9 Hz and $^3J_{H3\beta-H2}$ = 6 Hz. This spectrum is characteristic of AMX system which is shown in Figure 4. The yields of benzodiazepines, 1H chemical shifts (ppm) and 1H-1H coupling constants (J in Hz) of compounds **15** in $CDCl_3$ were summarized in Table 2.

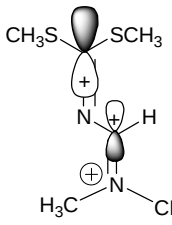
The analysis of the AMX system corresponding to the protons H2 and H3 gave the couplings represented in Figure 4. To confirm the structure of compounds **15**, we realized the X-ray structure analysis (Bibila et al., 2010) of compound **15b** which is shown on Figure 5 and the crystal data is summarized

in Table 3. The molecular of benzodiazepine is crystallized in monoclinic system. The ring system of benzodiazepine adopted a distorted boat conformation. The benzene ring of this system formed dihedral angles of 89.69 (12) and 48.82 (12) with those of the phenol and methoxyphenyl substituent respectively. The dihedral angle between the benzene rings was 49.61 (11). An intramolecular O—H-----N hydrogen bond generated an S(6) ring. Treatment of compounds **15** with potassium carbonate in dimethylformamide (DMF) under reflux, afforded 2-substituted benzimidazole **16** in moderate yields (40-60%) and quinoxaline **17** (Scheme 4).

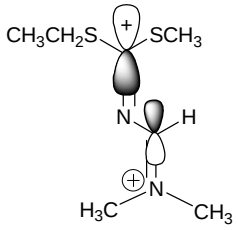
The spectroscopic analysis of protons showed the disappearance of protons H2 and H3 observed in compounds **15**. We also noted an echo zone concentrated in the aromatic area with a decrease of protons. The benzimidazolic structures that we proposed were confirmed by mass spectrometry data. To explain the formation of the benzimidazole we proposed the following mechanism: 2,3-dihydro-benzodiazepine **15** underwent K_2CO_3 attacked to give an amidure ion which, by intramolecular reaction, reacted on the carbon C4 of the imine function. The loss of styrene afforded the benzimidazole **16** (Scheme 5).



C_1 = 0.491 , q_1 = 0.387
C_3 = -0.593 , q_3 = -0.015



C_1 = 0.389 **,** q_1 = 0.483
C_3 = -0.588 , q_3 = -0.012



C_1 = -0.485 , q_1 = 0.388
C_3 = 0.590 , q_3 = -0.012

q_i is the charge and C_i the orbital coefficients in the vacant orbital

Figure 3: Values of the orbital coefficients 2 Pz.

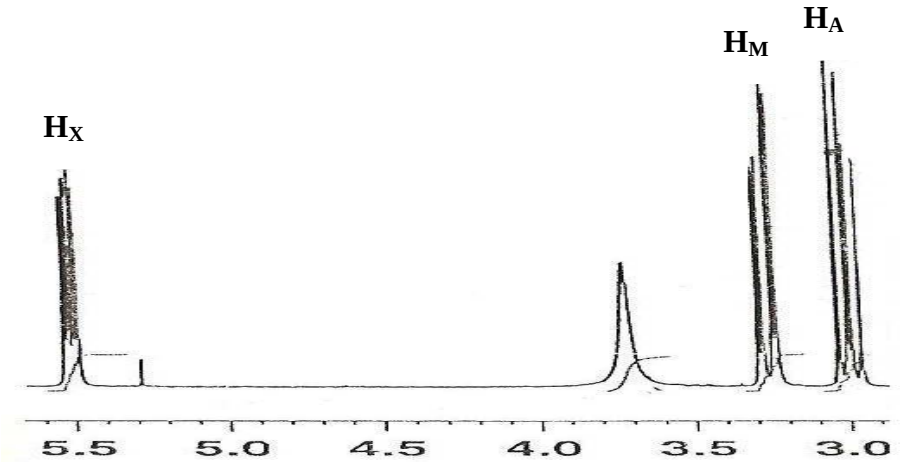


Figure 4: AMX spectrum of compound 15c.

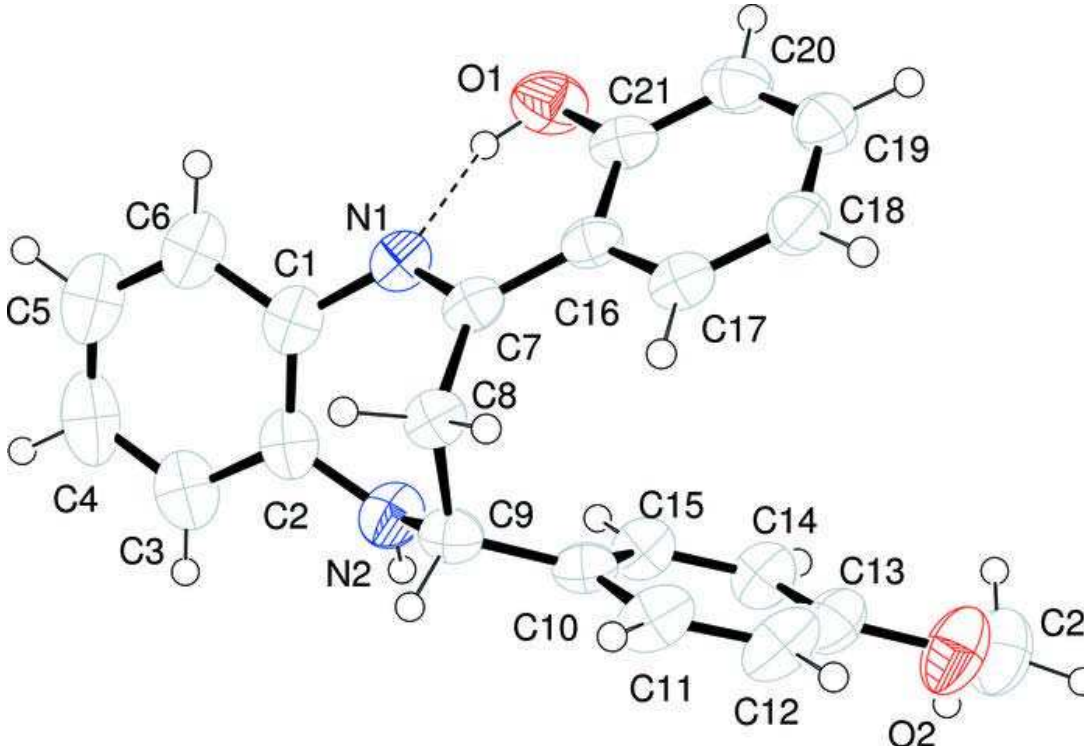
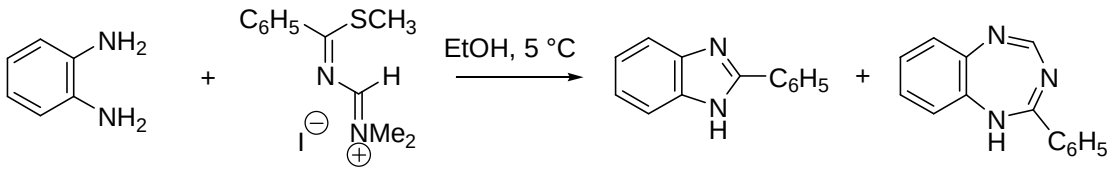


Figure 5: X-ray crystal structure of compound 15b.

Table 1: Physical characteristics and yields of compounds 14.

Compounds	R^2	R^3	Yields (%)	mp. (°C)
14a	Phenyl	Phenyl	71	56-57
14b	*p*-Methoxyphenyl	*o*-Hydroxyphenyl	85	118-119
14c	Thienyl	*p*-Tolyl	72	81-82
14d	Thienyl	Phenyl	78	121-122
14e	*o*-chlorophenyl	Phenyl	70	111-112
14f	2-Chloro-5-nitrophenyl	Phenyl	68	96-97



7 8 9 10

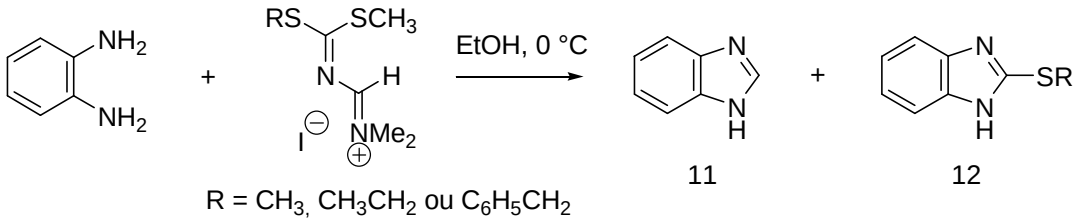
Scheme 1

Table 2: Physical characteristics, ^{1}H chemical shifts (ppm) and ^{1}H-^{1}H coupling constants (J in Hz) of compounds **15** in $CDCl_3$.

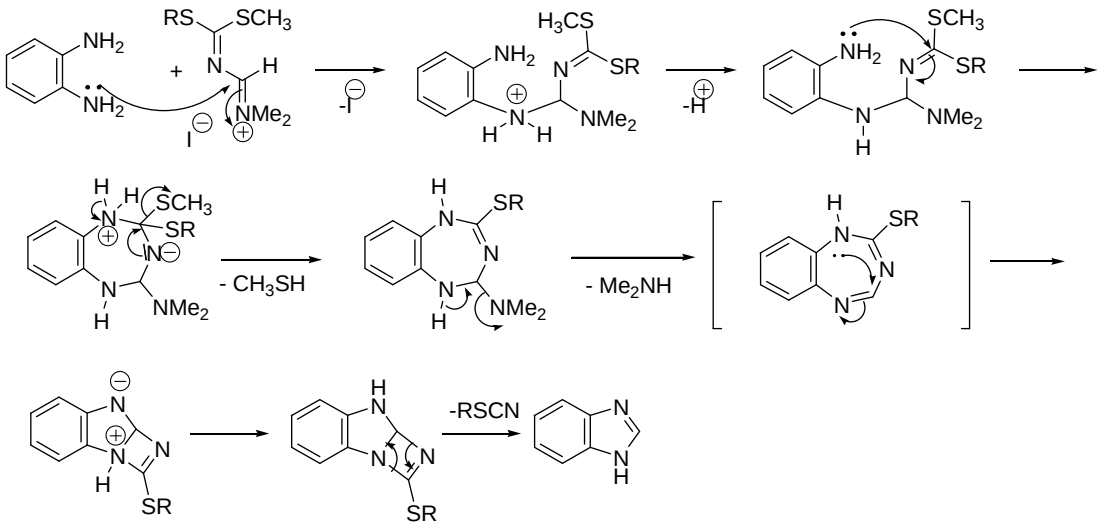
Compounds	R	R^2	R^3	Yields (%)	PF °C	δ (ppm)	J (Hz)
15a	H	Phenyl	Phenyl	41		3.06-3.08 (m, H3) 5.87-5.88 (m, H2)	
15b	H	*p*-Metoxyphenyl	*o*-Hydroxyphenyl	36	141-142	3.04 (dd, H3α) 3.32 (dd, H3β) 5,15 (dd, H2)	$^{3}J_{H3\alpha\text{-}H2}$ = 9, $^{2}J_{H3\alpha\text{-}H3\beta}$ = 15 $^{3}J_{H3\beta\text{-}H2}$ = 6
15c	H	Thienyl	*p*-Tolyl	45	125	2.99 (dd, H3α) 3.26 (dd, H3β) 5,51 (dd, H2)	$^{3}J_{H3\alpha\text{-}H2}$ = 9, $^{2}J_{H3\alpha\text{-}H3\beta}$ = 13.2 $^{3}J_{H3\beta\text{-}H2}$ = 4.2
15d	H	Thienyl	Phenyl	52	133-134	3.06 (dd, H3α) 3.32 (dd, H3β) 5.55 (dd, H2)	$^{3}J_{H3\alpha\text{-}H2}$ = 9, $^{2}J_{H3\alpha\text{-}H3\beta}$ = 12 $^{3}J_{H3\beta\text{-}H2}$ = 6
15e	H	*o*-Chlorophenyl	Phenyl	75	150-151	3.12-3.28 (m, H3) 5.79-5.83 (m, H2)	
15f	CH_3	*o*-Chlorophenyl	Phenyl	65	122-123	2.99-3.13 (m, H3), 5.60-5.63 (m, H2)	
15g	H	2-Chloro-5-nitrophenyl	Phenyl	71	167-168	3.16 (d, H3) 5.74-5.79 (m, H2)	J = 6
15h	CH_3	2-Chloro-5-nitrophenyl	Phenyl	77	223-224	3.13 (d, H3) 5.70-5.67 (m, H2)	J = 6

Table 3: Crystal data of compound 15b.

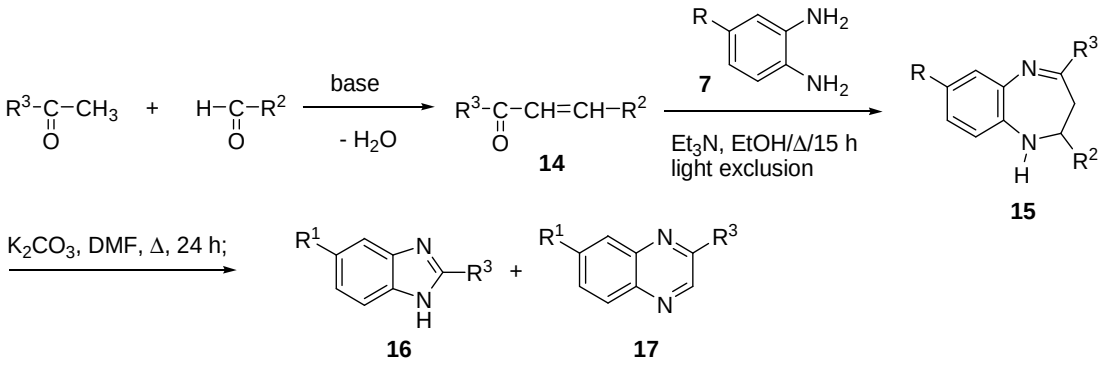
$C_{22}H_{20}N_2O_2$	V = 3506.02 (15) Å^3
Mr = 344.41	Z = 8
Monoclinic, C2=c	Mo Kα radiation
a = 27.5064 (5) Å	μ = 0.08 mm^{-1}
b = 7.3811 (2) Å	
c = 19.5038 (4) Å	T = 223 K
β = 117.699 (2)	0.30 × 0.20 × 0.15 mm
Data collection	2836 reflections with I > 3σ(I)
Nonius Kappa CCD diffractometer	Rint = 0.06
19187 measured reflections	
2507 independent reflections	
Refinement	235 parameters
R[F2 > 2σ(F2)] = 0.055	H-atom parameters constrained
wR(F2) = 0.065	Δρmax = 0.25 e Å^{-3}
S = 1.04	Δρmin = - 0.25 e Å^{-3}
2507 reflections	



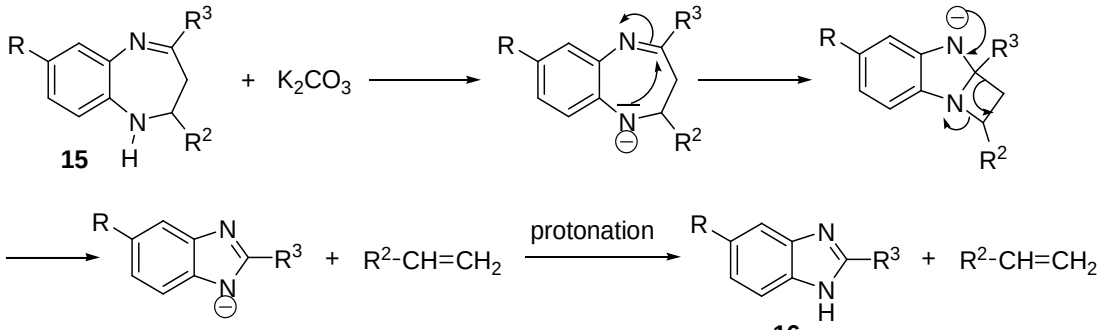
Scheme 2



Scheme 3



Scheme 4



Scheme 5

Conclusion

Through this work, we have shown the synthesis of substituted benzimidazoles by an original method *via* regression (Ring Contraction Rearrangement**)** of 1*H*-1,5-benzodiazepine under basic conditions. Structure elucidation of benzodiazepine and benzimidazole was made possible by NMR and mass spectrometry methods. We have also confirmed the benzodiazepine structure by realizing X-ray crystal structure analysis.

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