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NOVEL SYNTHESIS OF 2-SUBSTITUTED BENZIMIDAZOLE BY RING CONTRACTION REARRANGEMENT OF 1, 5-BENZODIAZEPINES

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ABSTRACT

The interaction of aromatic ketones with aldehydes allowed accessing α, β-unsaturated ketones (chalcones) **9**. Subsequently, these chalcones **9** were reacted with orthophenylenediamine to give the corresponding 1H-1, 5-benzodiazepines 11. Treatments of benzodiazepine under basic or acid condition give respectively 2-substituted benzimidazole 12 or 14 via Ring Contraction Rearrangement. All compounds were characterized by means of ^{1}H, ^{13}C NMR and mass spectroscopy. To explain the formation of benzimidazole, we have made theoretical calculations.

KEYWORDS: Benzimidazole, chalcones, benzodiazepines, orthophenylenediamine.

INTRODUCTION

Parasitic diseases are a real public health problem. These diseases are One of the main causes of infant mortality every year, millions of children die from diarrhea where intestinal nematode infections play an important role in the etiology of acute diarrhea. Intestinal nematodes favor the penetration of the causative agent of diarrhea in children and weaken the body dangerously. Especially the amoebiasis[1-4] and the giardiasis[5-7] have high morbidity and mortality indexes due to the severe diarrhea and invasive infections. The consequences of the various pathologies, although benign in the developed countries, are cruelly dramatic in least developed and developing countries. In the chemotherapy of intestinal helminthiasis, the most determining discovery is undoubtedly that relating to the biologically active chemical

class of compounds which contain the benzimidazole nucleus in their skeleton. These include: Thiabendazole, albendazole, mebendazole, flubendazole (Figure1) which are commonly used to treat intestinal worms.

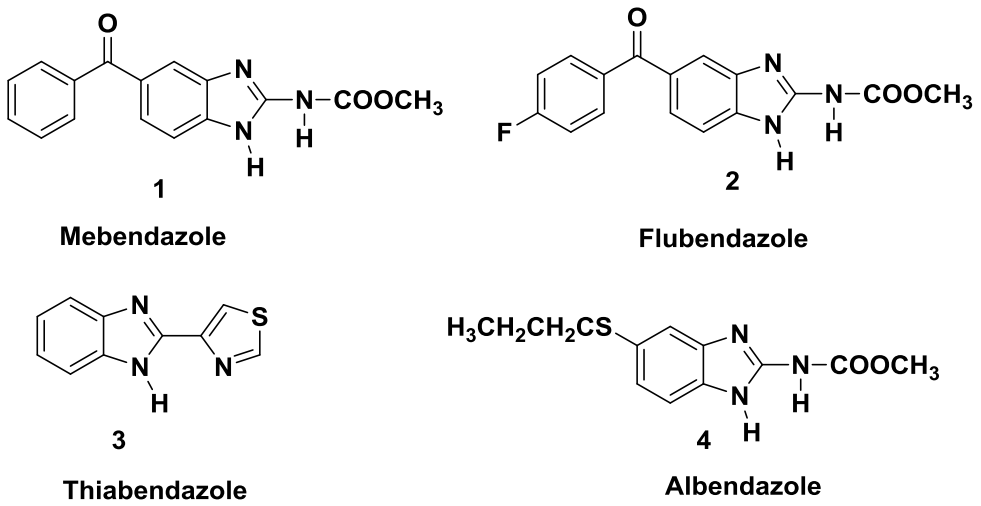


Figure 1

In recent years much attention has been given to the substituents at 1 and 2 position of the benzimidazole ring which gave good antiviral activities.[8] Many reports have revealed that the influence of the substitution at 1, 2 and 5 position of benzimidazole ring was very important for their pharmacological effect.[9] Benzimidazole derivatives have played an important role in chemotherapy with excellent biological activities. Indeed, the optimization of the biological properties depends on the nature of the substituents on these positions.

Recent studies have shown that 2-substituted benzimidazole derivatives exhibit important anti-infectious activities.[10,11] including antiprotozoal,[12] antileishmaniose[13] and antibacterial.[14-17]

The development of new molecules that inhibited resistant strains revived interest in the search for novel bioactive compounds. In the search for new anti-infectious molecules, we have been interested in substituted benzimidazole derivatives in position 2 by aryl groups. The choice of chains linked at the C-2 was made in view of their presence in other classes of antiviral compounds. These molecules are generally synthesized using Phillips method.[18] This method was expensive and the yields obtained were low. In recently work, Timotou et al,[19] were developed an original methodology to synthetize 2-benzimidazole. We used 1, 5-

benzodiazepines as intermediaries which were converted to benzimidazole under basic conditions.

In this paper, we take back Timotou report and we expanded our research of synthesis of 2-substituted benzimidazole derivatives by studied the comportment of the 1,5-benzodiazepines in acid or basic medium and theoretical calculations were made with the benzodiazepines in order to determine their reaction ability, stability and to understand the mechanism of the reaction.

MATERIALS AND METHODS

General

All reagent-grade chemicals were obtained from commercial suppliers and were used as received. Characterizations of known compounds were in accordance with literature. ^{1}H NMR and ^{13}C NMR were recorded on a Bruker Avance 300 and 400 MHz spectrometer instrument using TMS as an internal standard. The proton and carbon signal assignments were determined from decoupling experiments, COSY spectra and HSQC spectra. TLC were performed on Silica F_{254} and detection by UV light at 254 nm. Column chromatography was performed on Silica Gel 60 (230 mesh). Melting points were determined with a Kofler hot-stage apparatus and are uncorrected. Mass spectrometric measurements were performed using HP5989X instrument. All spectrometers analysis were realized at the laboratories LG2A of Jules Verne Picardie University and CEISAM of Nantes University

General method to synthesis of benzodiazepines 11

To a solution of chalcone **9** (4.8 mmol) in 20 ml of methanol, are added o-phenylenediamine (un or substitued) (7.2 mmol) and 2 ml of triethylamine a few drops. The mixture was heated under reflux for 8 hours in the dark under agitation. The mixture was cooled at room temperature and then put in the freezer overnight. The solid product (benzodiazepines) was filtered and recrystallized in ethanol.

7-methyl-2,4-diphenyl-2,3-dihydro-1H-1,5-benzodiazepine 11a

From 1,3-diphenylprop-2-en-1-one **9a** (4g, 19.23 mmol) and 4-methyl-o-phenylenediamine (2.58g, 21.15 mmol) was obtained compound **11a** (3g, 50%) as yellow crystals; Rf : 0.3 (hexane/dichloromethane v/v: 50/50); mp: 116°C.

^{1}H NMR ($CDCl_3$, 300 MHz**)** δ: 2.42 (s, CH_3); 3.05-3.08 (m, 2H, H_3); 5.22 (d, 1H, NH); 5.60-5.78 (m, 1H, H_2); 7.2-8.10 (m, 13H, aromatic protons).

^{13}C NMR ($CDCl_3$, 75 MHz) δ: 20.2 (CH_3); 37.7 (C_3); 62.3 (C_2); 120.3 (C_9); 124.6 (C_7); 126.2 (C_6); 128.4 (C_{17}, C_{21}); 130.2 (C_8); 131.5 (C_{18}, C_{20}); 132.3 (C_{19}); 132.8 (C_{12}, C_{14}); 134.1 (C_{11}, C_{15}); 134.8 (C_{13}); 135.5 (C_{10}) ; 136.1 (C_{5a}); 137.6 (C_{16}); 138.8 (C_{9a}); 153.6 (C_4).

Mass (m/z) = 312. M+ = 312 (28); m/z (%) = 235.25 (31); 208.20 (100); 235.25 (31).

4-(o-hydroxyphenyl)-2-(4-chlorophenyl)-2, 3-dihydro-1H-1,5-benzodiazepine 11b

From 1-(o-hydroxyphenyl)-3-(4-chlorophenyl) prop-2-en-1-one 9b (4g, 15.47 mmol) and o-phenylenediamine (1.84g, 17.02 mmol) was obtained compound 11b (4.6g, 78%) as yellow crystals; Rf: 0.55 (hexane/ethyl acetate v/v : 90/10); mp: 176 °C.

^{1}H NMR ($CDCl_3$, 400 MHz**)** δ: 2.98 (dd, 1H, H_A, $^{2}J_{AM}$ = 16Hz, $^{3}J_{AX}$ = 8Hz); 3.21 (dd, 1H, H_M; $^{2}J_{AM}$ = 16 Hz, $^{3}J_{MX}$ = 4 Hz); 3.73 (s, 1H, NH); 5.15 (dd, 1H, H_X, $^{3}J_{AX}$ = 8 Hz, $^{3}J_{MX}$ = 4 Hz); 6.88-7.32 (m, 12H, aromatic protons).

^{13}C NMR ($CDCl_3$, 101 MHz) δ: 35.9 (C_3); 69.5 (C_2); 117.9 (C_9); 118.1 (C_{12}); 118.8 (C_{10}); 120.6 (C_{14}); 121.7 (C_7); 127.2 (C_{17}, C_{21}); 127.3 (C_6); 127.8 (C_8); 128.0 (C_{18}, C_{20}); 128.9 (C_{13}) 132.8 (C_{15}); 133.7 (C_{19}); 135.4 (C_{16}); 138.6 (C_{9a}); 142.4 (C_{5a}); 162.3 (C_4); 170.9 (C_{11}).

Mass (m/z) = 348.5. M+ = 348 (10); m/z(%) = 210 (85); 182 (40); 181 (45) ; 140 (30); 138 (100); 119 (25); 103 (60); 91 (65); 89 (58); 77 (45); 65 (45); 63 (33).

4-(o-hydroxyphenyl)-2-(4-isopropylphenyl)-2, 3-dihydro-1H-1,5-benzodiazepine 11c

From 1-(o-hydroxyphenyl)-3-(4-isopropylphenyl) prop-2-en-1-one 9c (4g, 15.04 mmol) and o-phenylenediamine (1.8g, 16.54 mmol) was obtained compound 11c (3g, 56%) as yellow crystals; Rf : 0.87 (hexane/ethyl acetate v/v : 90/10); mp: 126 °C.

^{1}H NMR ($CDCl_3$, 400 MHz**)** δ: 1.28 (d, 6H, $2CH_3$, J = 8Hz), 2.91-2.98 (m, 1H, CH); 3.06 (dd, 1H, H_A, $^{2}J_{AM}$ = 16Hz, $^{3}J_{AX}$ = 8Hz); 3.36 (dd, 1H, H_M; $^{2}J_{AM}$ = 16Hz, $^{3}J_{MX}$ = 4Hz); 3.88 (s, 1H, NH); 5.07 (dd, 1H, H_X, $^{3}J_{AX}$ = 8Hz, $^{3}J_{MX}$ = 4Hz); 6.77-7.38 (m, 12H, aromatic protons).

^{13}C NMR ($CDCl_3$, 101 MHz) δ : 23.8 (CH_3) 33.7 (CH); 36.6 (C_3); 69.3 (C_2); 117.8 (C_9); 118.1 (C_{12}); 118.9 (C_{10}); 120.5 (C_{14}); 121.1 (C_7); 125.7 (C_{17}, C_{21}); 126.8 (C_{18}, C_{20}); 127.2

(C_6); 127.9 (C_8); 128.2 (C_{15}); 132.6 (C_{13}); 134.8 (C_{16}); 138.9 (C_{5a}); 141.6 (C_{9a}); 149.0 (C_{19}); 162.4 (C_4); 170.9 (C_{11}).

Mass (m/z) = 356. M+ = 356 (10); m/z (%); 341 (15); 211 (29); 210 (82); 209 (26); 182 (37); 181 (32); 146 (39); 131 (88); 130 (30); 129 (26); 115 (33); 105 (24); 104 (25); 103 (33); 92 (24); 91 (100); 90 (30); 89 (24); 78 (23); 77 (29); 65 (34).

2-(2,4-dichlorophenyl)-4-(o-hydroxyphenyl)-2,3-dihydro-1H-1,5-benzodiazepine 11d

From 3-(2,4-dichlorophenyl)-1-(o-hydroxyphenyl)prop-2-en-1-one 9d (4g, 13.65 mmol) and o-phenylenediamine (1.6g, 15.02 mmol) was obtained compound 11d (3.45g, 66%) as maroon crystals; Rf : 0.5 (hexane/ethyl acetate v/v : 90/10); mp: 152 °C.

^{1}H NMR ($CDCl_3$, 400 MHz**)** δ: 3.21 (d, 2H, H_3; J = 8Hz); 3.80 (s, 1H, NH); 5.76 (t, 1H, H_2, J = 8Hz); 6.88-7.65 (m, 11H, aromatic protons).

^{13}C NMR ($CDCl_3$, 101 MHz) δ: 32.9 (C_3); 66.3 (C_2); 117.9 (C_9); 118.0 (C_{12}); 118.9 (C_{10}); 120.5 (C_{21}); 121.7 (C_{14}); 127.3 (C_7); 127.4 (C_6); 127.8 (C_{20}); 128.0 (C_8); 128.6 (C_{17}); 129.1 (C_{15}); 131.8 (C_{13}); 132.7 (C_{19}); 133.9 (C_{16}); 135.6 (C_{5a}); 138.7 (C_{9a}); 139.5 (C_{18}); 162.1 (C_4); 171.1 (C_{11}).

Mass (m/z) = 383. M+= 383 (50); m/z (%); M+2 = 385 (16); M+1 = 384 (33); 382 (49); 369 (22); 367 (34); 347 (20); 237 (20); 211 (35); 210 (100); 195 (19); 182 (18); 181 (20); 119 (43); 91 (20); 65 (16).

4-(o-hydroxyphenyl)-2-(4-methoxyphenyl)-2,3-dihydro-1H-1,5-benzodiazepine 11e

From 1-(o-hydroxyphenyl)-3-(4-methoxyphenyl)-prop-2-en-1-one **9e** (4g, 15.75mmol) and o-phenylenediamine (1.8g, 17.32 mmol) was obtained compound **11e** (4.3g, 80%) as yellow crystals; Rf: 0.5 (hexane/ethyl acetate v/v: 80/20); mp: 138 °C.

^{1}H NMR ($CDCl_3$, 400 MHz**)** δ: 2.97 (dd, 1H, H_A, $^2J_{AM}$ = 16Hz, $^3J_{AX}$ = 8Hz); 3.25 (dd, 1H, H_M; $^2J_{AM}$ = 16Hz, $^3J_{MX}$ = 4Hz); 3.75 (s, 3H, OCH_3); 3.76 (s, 1H, NH); 5.08 (dd, 1H, H_X, $^3J_{AX}$ = 8Hz, $^3J_{MX}$ = 4Hz); 6.69-7.29 (m, 12H, aromatic protons).

^{13}C NMR ($CDCl_3$, 101 MHz) δ: 36.5 (C_3); 55.2 (OCH_3); 69.1 (C_2); 114.0 (C_{18}, C_{20}); 117.8 (C_9); 118.1 (C_{12}); 118.9 (C_{10}); 120.5 (C_{14}); 121.2 (C_7); 126.8 (C_{17}, C_{21}); 127.2 (C_6); 127.9

(C_8); 128.1 (C_{15}); 132.6 (C_{13}); 134.9 (C_{16}); 136.4 (C_{5a}); 138.8 (C_{9a}); 159.3 (C_{19}); 162.4 (C_4); 170.9 (C_{11}).

Mass (m/z) = 344. M+ = 344 (5); m/z (%); 329 (5); 210 (28); 182 (21); 181 (24); 134 (100); 119 (37); 91 (73); 89 (23); 77 (25); 65 (39); 63 (16); 51 (10).

4-(o-hydroxyphenyl)-2-(4-toluyl)-2, 3-dihydro-1H-1, 5-benzodiazepine 11f

From 1-(o-hydroxyphenyl)-3-(4-toluyl) prop-2-en-1-one 9f (4g, 16; 80 mmol) and o-phenylenediamine (2g, 18.49 mmol) was obtained compound 11f (4.1 g, 75%) as orange crystals. Rf: 0.3 (hexane/ethyl acetate v/v: 60/40); mp: 120 °C.

^{1}H NMR ($CDCl_3$, 400 MHz**)** δ: 2.40 (s, 3H, CH_3); 3.07 (dd, 1H, H_A, $^2J_{AM}$ = 8Hz, $^3J_{AX}$ = 4Hz); 3.35 (dd, 1H, H_M; $^2J_{AM}$ = 8Hz, $^3J_{MX}$ = 4Hz); 3.87 (s, 1H, NH); 5.16 (dd, 1H, H_X, $^3J_{AX}$ = 4Hz, $^3J_{MX}$ = 4Hz); 6.79-7.38 (m, 12H, aromatic protons).

^{13}C NMR ($CDCl_3$, 101 MHz) δ: 20.9 (CH_3); 36.5 (C_3); 69.2 (C_2); 117.8 (C_9); 118.1 (C_{12}); 118.9 (C_{10}); 120.5 (C_{14}); 121.1 (C_7); 125.5 (C_{17}, C_{21}); 127.2 (C_6); 127.8 (C_8); 128.2 (C_{15}); 129.4 (C_{18}, C_{20}); 132.6 (C_{13}); 134.8 (C_{19}); 137.8 (C_{16}); 138.9 (C_{5a}); 141.2 (C_{9a}); 162.4 (C_4); 170.9 (C_{11}).

Mass (m/z) = 344. M+ = 344 (5); m/z (%); 329 (5); 210 (30); 181 (25); 134 (100); 119 (37); 91 (73); 77 (25); 65 (40); 63 (17); 51 (10).

4-(4-toluyl)-2-thienyl-2, 3-dihydro-1H-1,5 benzodiazepine 11g

From 1-(4-toluyl)-3-(2-thiényl)prop-2-en-1-one **9g** (4g, 17.54 mmol) and o-phenylenediamine (2.1g, 19.3 mmol) was obtained compound **11g** (2.5 g, 45%) as yellow crystals; Rf : 0.4 (hexane/ethyl acetate v/v : 95/5); mp: 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, $^3J_{MX}$ = 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, H-aromatic and thienyl).

^{13}C NMR ($CDCl_3$, 75 MHz) δ: 21.4 (CH_3); 37.7 (C3); 66.8 (C2); 121.5 (C9); 125.4 (C_7); 128.7 (C_6); 128.9 (C_{18}); 132.2 (C_{20}); 133.4 (C_{16}); 134 (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 (%); M+1 = 319 (5); 208 (100); 110 (20.15); 91 (21.26); 77 (11.91); 63 (12.25); 39 (25.1).

2-(4-methoxyphenyl)-4-phenyl-2, 3-dihydro-1H-1, 5-benzodiazepine 11h

From 3-(4-methoxyphenyl)-1-phenylprop-2-en-1-one **9h (**4g, 16,80 mmol) and o-phenylenediamine (2g, 18.8 mmol) was obtained compound **11h** (3.9 g, 71%) as yellow crystals; Rf : 0.27 (hexane/ethyl acetate v/v : 90/10); mp: 122 °C.

^{1}H NMR ($CDCl_3$, 400 MHz**)** δ: 3.05 (dd, 1H, H_A, $^{2}J_{AM}$ = 16Hz, $^{3}J_{AX}$ = 8Hz); 3.23 (dd, 1H, H_M, $^{2}J_{AM}$ = 16Hz, $^{3}J_{MX}$ = 4Hz); 3.73 (s, 1H, NH); 3.81 (s, 3H, OCH_3); 5.14 (dd, 1H, H_X, $^{3}J_{AX}$ = 8Hz, $^{3}J_{MX}$ = 4Hz); 6.80-7.88 (m, 13H, H-aromatic).

^{13}C NMR ($CDCl_3$, 101 MHz) δ: 37.8 (C_3); 55.2 (OCH_3); 69.8 (C_2); 114.0 (C_{18}, C_{20}); 120.4 (C_9); 121 (C_7); 126.2 (C_6); 126.8 (C_{17}, C_{21}); 126.9 ($C_{11,}$ C_{15}); 128.2 (C_8); 128.8 (C_{12}, C_{14}); 129.9 (C_{13}); 137.1(C_{16}); 138 (C_{5a}); 138.9 (C_{10}); 139 (C_{9a}); 159.2 (C_{19}); 166.9 (C_4).

Mass (m/z) = 328. M+ = 328,3 (8,5); m/z (%); 195 (18.5); 194 (100); 193 (25); 134 (79); 119 (17); 91 (29); 77 (20).

2-(4-chlorophenyl)-4-phenyl-2, 3-dihydro-1H-1, 5-benzodiazepine 11j

From 3-(4-chlorophenyl)-1-phenylprop-2-en-1-one **9j** (4g, 16.53mmol) and o-phenylenediamine (2g, 18.18 mmol) was obtained compound **11j** (4g, 73%) as yellow crystals; Rf: 0.46 (hexane/ethyl acetate v/v: 90/10); mp: 144 °C.

^{1}H NMR ($CDCl_3$, 400 MHz**)** δ: 3.03 (dd, 1H, H_A, $^{2}J_{AM}$ = 12Hz, $^{3}J_{AX}$ = 8Hz); 3.20 (dd, 1H, H_M, $^{2}J_{AM}$ = 12Hz, $^{3}J_{MX}$ = 4Hz); 3.70 (s, 1H, NH); 5.20 (dd, 1H, H_X, $^{3}J_{AX}$ = 8Hz, $^{3}J_{MX}$ = 4Hz); 6.82-7.81 (m, 13H, aromatic protons).

^{13}C NMR ($CDCl_3$, 101 MHz) δ: 37.2 (C_3); 69.9 (C_2); 120.5 (C_9); 121.5 (C_7); 126.3 (C_6); 126.8 (C_{17}, C_{21}); 127.2 (C_8); 128.2 ($C_{11,}$ C_{15}); 128.7 (C_{18}, C_{20}); 128.8 (C_{12}, C_{14}); 130.1 (C_{13}); 133.5 (C_{19}); 137.8 (C_{16}); 138.8 (C_{5a}); 139.3 (C_{10}); 143.1 (C_{9a}); 166.9 (C_4).

Mass (m/z) = 332, 5. M+ = 332 (8, 5); m/z (%); 195 (17.5); 194 (100); 193 (33,4); 140 (20); 138 (55); 104 (18.5); 103 (55); 102 (26); 91 (30); 89 (23); 77 (50); 65 (15).

7-methyl-2-(o-chlorophenyl)-4-phenyl-2, 3-dihydro-1H-1, 5-benzodiazepine 11k

From 3-(o-chlorophenyl)-1-phenylprop-2-en-1-one 9k (4g, 16.5mmol) and 4-methyl o-phenylenediamine (2.2g, 18.14 mmol) was obtained compound 11k (3.7 g, 65%) as yellow crystals; Rf: 0.66 (hexane/ethyl acetate v/v: 90/10); mp: 123 °C.

^{1}H NMR ($CDCl_3$, 300 MHz**)** δ: 2.25 (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}); 166.4 (C_4).

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

2-(2-chloro-5-nitrophenyl)-7-methyl-4-phenyl-2-3-dihydro-1H-1,5 benzodiazepine 11i

From 3-(2-chloro-5-nitrophenyl)-1-phenylprop-2-en-1-one 9i (4g, 13.9 mmol) and 4-methyl-o-phenylenediamine (1.86g, 15.3 mmol) was obtained compound 11i (77%) as yellow crystals; Rf: 0.62 (hexane/ethyl acetate v/v: 80/20); mp: 200 °C.

^{1}H NMR ($CDCl_3$, 300 MHz**)** δ: 2.22 (s, 3H, CH_3); 3.12-3.14 (m, 2H, H_3); 3.71 (s, 1H, NH); 5.70-5.77 (m, 1H, H_2); 6.88-8.70 (m, 14H, aromatic protons).

^{13}C NMR ($CDCl_3$, 75 MHz) δ: 20.2 (CH_3); 32.1 (C_3); 65.8 (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}); 135.3 (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) = 318. M+ = 318 (10); m/z (%) ; M+1 = 319 (5); 208 (100); 110 (20,15); 91 (21.26); 77 (11.91); 63 (12.25); 39 (25.31).

General method to synthesis of benzimidazole 14

To a solution of 2-3-dihydro-1H-1, 5-benzodiazepines 11 (1g, 1 eq.) in 5 ml of anhydrous dimethylformamide (DMF), was added 1 ml of acetic acid. The mixture was heated under reflux during 2 hours. After cooling under ambient temperature, 10 ml of water are added. The aqueous phase was extracted three times with dichloromethane and the combined organic

phases were dried over magnesium sulfate. After evaporation under reduced pressure, the solid residue was purified by silica-gel column chromatography.

2-parachlorophenyl-1H-benzimidazole 14a

From 2-parachlorophenyl-4-phenyl-2, 3-dihydro-1H-1,5-benzodiazepine 11j (1g, 3 mmol) and 1 ml of acetic acid was obtained the compound 14a (459.3 mg, 67%) as yellow crystals. Rf: 0.3 (hexane/ethyl acetate 66/33); mp: > 266°C.

Or from compound 4-orthohydroxyphenyl-2-parachlorophenyl-2,3-dihydro-1H-1,5-benzodiazepine 11b (1g, 3 mmol) and 1 ml of acetic acid was obtained compound 14a (527.8 mg, 77%). Rf: 0.4 (hexane/ethyl acetate 75/25); mp: > 266°C.

^{1}H NMR (DMSO; 400Mhz**)** δ: 7.20-7.25 (m, 2H, H_6, H_7); 7.54 (d, 1H, H_5, J = 8Hz); 7.63 (d, 2H, H_{12}, H_{14}, J = 8Hz); 7.67 (d, 1H, H_8, J = 8Hz); 8.19 (d, 2H, H_{11}, H_{15}, J = 8Hz); 12.97 (s, 1H, NH).

^{13}C NMR (DMSO; 101 Mhz) δ: 111.8 (C_4, C_7); 119.4 (C_5); 122.2 (C_6); 123.2 (C_8); 128.5 (C_9, C_{13}); 129.5 (C_{10}, C_{12}); 134.9 (C_{3a}); 135.4 (C_{7a}); 144.1 (C_{11}); 150.5 (C_2).

Mass (m/z): 228.5 M+ = 228 (100); M+1 = 229 (22); M+2 = 230 (34); m/z (%): 227 (20); 193 (21.43); 114 (21); 91 (21); 90 (24); 64 (26); 63 (32,58).

2-paramethoxyphenyl-1H-benzimidazole 14b

From 2-paramethoxyphenyl-4-phenyl-2,3-dihydro-1H-1,5-benzodiazepine 11h (1g, 3.05 mmol) and 1 ml of acetic acid was obtained compound 14b (410 mg, 60%) as yellow crystals. Rf: 0.15 (hexane/ethyl acetate 75/25); mp: > 266°C.

Or from compound 4-orthohydroxyphenyl-2-paramethoxyphenyl-2,3-dihydro-1H-1,5-benzodiazepine 11e (1g, 2.9 mmol) and 1 ml of acetic acid was obtained compound 14b (454.7 mg, 70%). Rf: 0.15 (hexane/ethyl acetate 75/25); mp: > 266°C.

^{1}H NMR (DMSO; 300Mhz) δ: 3.84 (s, 3H, OCH_3); 7.11 (d, 2H, H_{12}, H_{14}, J = 6Hz); 7.16 (dd, 2H, H_6, H_7 J = 3Hz); 7.54 (d, 1H, H_5, J = 3Hz); 7.56 (d, 1H, H_8, J = 3Hz); 8.11 (d, 2H, H_{11}, H_{15}, J = 6Hz); 12.74 (s, 1H, NH).

^{13}C NMR (DMSO; 75 Mhz) δ: 55.7 (OCH3); 114.2 (C_8); 114.8 (C_{10}, C_{12}); 122.1 (C_5, C_6); 123.1 (C_4, C_7); 128.4 (C_9, C_{13}); 129.5 (C_{3a}); 130.0 (C_{7a}); 151.7 (C_2); 161.0 (C_{11}).

Mass (m/z): 224 M+ = 224 (43.30); m/z (%): 181 (34.80); 149 (76.76); 121 (98.80); 105 (64); 104 (40.27); 103 (41); 91 (67.49); 90 (49); 89.2 (43); 78 (34.18); 77 (100); 76 (68.33); 65 (45); 64 (48.82); 62.9 (73.86); 51 (39.29); 50 (35.38); 29.1 (63.68); 27.9 (59.02).

2-thienyl-1H benzimidazole 14c

From 4-paratoluyl-2-thienyl-2,3-dihydro-1H-1,5 benzodiazepine 11g (1g, 3.14 mmol) and 1 ml of acetic acid was obtained compound 14c (452.2 mg, 72%) as marron crystals. Rf: 0.37 (hexane/ethyl acetate 70/30); mp: 178°C.

^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.18-7.84 (m, 7H, aromatic and thienyl protons); 12,94 (1H, NH).

^{13}C NMR **(**$CDCl_3$**;** 75 Mhz**)** δ: 22.0 (C_4, C_7); 125.6 (C_5, C_6); 128.7 (C_{10}); 130.4 (C_{12}); 130.8 (C_{11}); 133.7 (C_{3a}, C_{7a}); 147.0 (C_2); 151.5 (C_8).

Mass (m/z): 200 M+ = 200; M+1 = 201 (14.92); m/z (%): 200 (100); 91 (41.93); 64 (35.73); 63 (35.71).

2-paramethylphenyl-1H-benzimidazole 14d

From 2-paramethylphenyl-4-orthohyfroxyphenyl-2,3-dihydro-1H-1,5-benzodiazepine 11f (1g, 3.2 mmol) and 1 ml of acetic acid was obtained compound 14d as beige crystals. Rf: 0.28 (hexane/ethyl acetate 75/25); mp: 264°C.

^{1}H NMR (DMSO; 300Mhz) δ: 2.38 (s, CH_3); 7.16-7.20 (m, 2H, H_6, H_7); 7.35 (d, 2H, H_{12}, H_{14}, J = 9Hz); 7.50 (d, 1H, H_8, J = 9Hz); 7.64 (d, 1H, H_5, J = 9Hz); 8.06 (d, 2H, H_{11}, H_{15}, J = 9Hz); 12.81 (s, 1H, NH).

^{13}C NMR (DMSO**;** 75 Mhz**)** δ: 21.0 (CH_3); 111.2 (C_4); 118.7 (C_7); 121.6 (C_5); 122.3 (C_6); 126.4 (C_9, C_{13}); 127.5 (C_{11}); 129.51 (C_{12}, C_{14}); 135.0 (C_8); 139.6 (C_{7a}); 143.8 (C_{3a}); 151.4 (C_2).

2-(2, 4-dichlorophenyl)-1H-benzimidazole 14f

From 2-(2,4-dichlorophenyl)-4-o-hydroxyphenyl-2,3-dihydro-1H-1,5-benzodiazepine **11d (**1g, 2.61 mmol) and 1 ml of acetic acid was obtained compound **14f** (494.2 mg, 72%) as marron crystals. Rf: 0.6 (hexane/ethyl acetate 75/25); mp: 118°C.

^{1}H NMR (DMSO; 300Mhz) δ: 7.24-7.25 (m, 2H, H_6, H_7); 7.58 (d, 1H, H_{14}, J= 9hz); 7.62 (d, 1H, H_{15}, J= 6hz); 7.64 (s, 1H, H_{12}); 7.84 (d, 1H, H_8, J=6Hz); 7.94 (d, 1H, H_5, J=6 Hz); 12.78 (s, 1H, NH).

^{13}C NMR (DMSO; 75 Mhz) δ: 111.8 (C_4); 119.2 (C_7); 121.9 (C_5); 123.0 (C_6); 127.7 (C_{12}); 128.9 (C_{13}); 129.9 (C_{10}); 132.6 (C_9); 133.3 (C_{11}); 134.7 (C_8); 135.0 (C_{7a}); 143.2 (C_{3a}); 148.1 (C_2).

Mass (m/z): 263 M+ = 263 (20); M+1 = 264 (70.15); M+2 = 265 (10.40); m/z (%): 262 (100); 257 (55); 227 (13); 210 (80).

2-paraisopropylphenyl-1H-benzimidazole 14g

From 4-orthohydroxyphenyl-2-paraisopropylphenyl-2,3-dihydro-1H-1,5-benzodiazepine 11c (1g, 2.81 mmol) and 1 ml of acetic acid was obtained compound 14g (591.2 mg, 80%) as marron crystals. Rf: 0.5 (hexane/ethyl acetate 75/25); mp: 250°C.

^{1}H NMR (DMSO; 400Mhz) δ: 1.23 (d, 6H, $2CH_3$); 2.93-2.96 (m, 1H, CH); 7.18 (d, 2H, H_6, H_7, J = 9Hz); 7.41 (d, 2H, H_{12}, H_{14}, J = 8Hz); 7.56 (d, 1H, H_5, J= 4Hz); 7.58 (d, 1H, H_8, J = 4Hz); 8.09 (d, 2H, H_{11}, H_{15}, J= 4Hz); 12.81 (s, 1H, NH).

^{13}C NMR (DMSO; 101 MHz) δ: 24.1 (CH_3); 33.8 (CH); 122.3 (C_4, C_7); 125.5 (C_5, C_6); 126.4 (C_8); 126.9 (C_9, C_{13}); 127.3 ($C_{10,}$ C_{12}); 128.2 (C_{3a}, C_{7a}); 150.7 (C_{11}); 151.8 (C_2).
Mass (m/z): 263 M+ = 263 (10.74); m/z (%): 237 (20.43); 210 (100); 119 (17.61); 91 (26.85).

2-orthochlorophenyl-5-methyl-1H-benzimidazole 14h

From 7-methyl-2-orthochlorophenyl-4-phenyl-2,3-dihydro-1H-1,5-benzodiazepine 11k (1g, 2.89, mmol) and 1 ml of acetic acid was obtained compound 14h (434.5 mg, 62%) as yellow crystals. Rf: 0.5 (hexane/ethyl acetate 80/20); mp: 227°C.

^{1}H NMR (DMSO; 300 Mhz) δ: 2.43 (s, 3H, CH_3); 7.02-8.18 (m, 7H, aromatic protons); 12.84 (s, 1H, NH)

^{13}C NMR (DMSO; 75 MHz) δ: 21.3 (CH_3); 110.8 (C_7); 114.2 (C_4); 122.6 (C_6); 128.2 (C_8); 132.2 (C_{11}, C_{13}); 133.5 (C_{10}, C_{12}); 135.2 (C_5); 136.5 (C_9); 138.1 (C_{7a}); 141.7 (C_{3a}); 146.0 (C_2).

Mass (m/z): 242.5 M+ = 242; M+2 = 244 (36.29); M+1 = 243 (17.86); m/z (%): 242 (100); 97 (16.20); 63 (27.43).

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.[20,21]

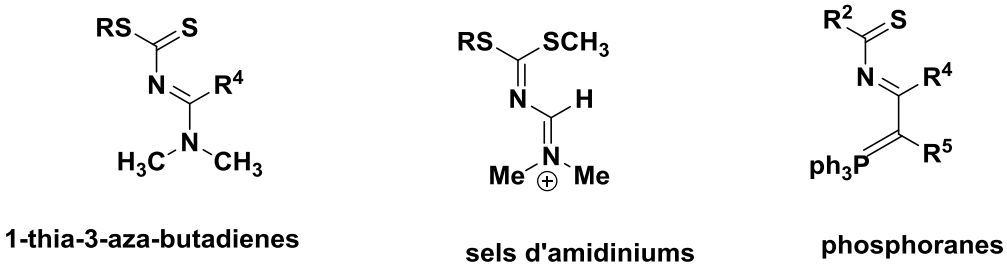
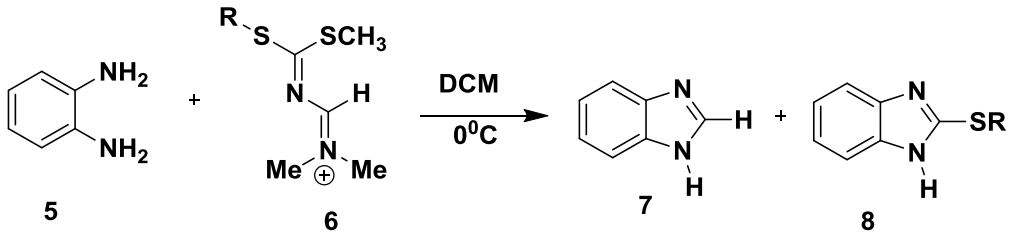


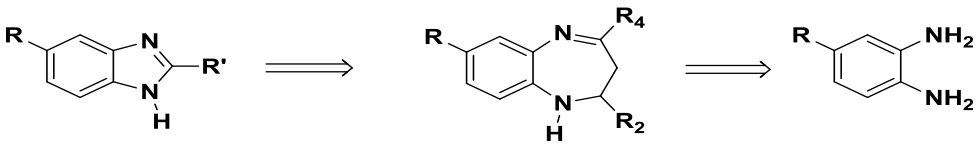
Figure 2: The heteroatomic chains of N'thioacylamidines

Recently, we developed in our laboratory, a study of the reactivity of amidinium salts against binucleophiles like o-phenylenediamine. Sissouma et al[22] have initiated an original method for synthesis of benzimidazole derivatives by using amidinium salts. In this study thiosubstituted amidinium salts derivatives in position-2 were using (Scheme 1).



Scheme 1

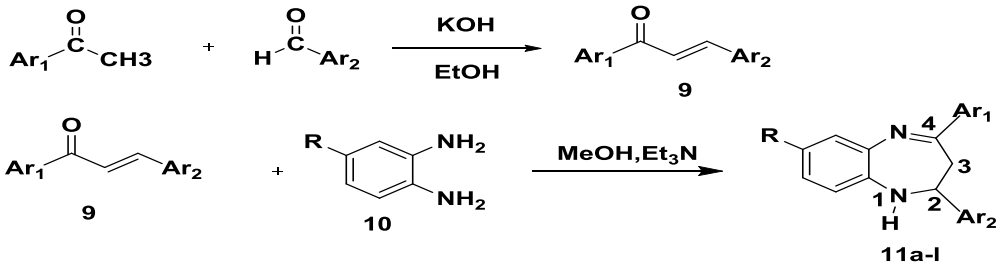
In this paper, we will describe the synthesis of the 2-substituted benzimidazole derivatives by using an original method developing by Timotou et al.[19] We allowed study, the comportment of benzodiazepines in a basic or an acid medium. Our approach methodology for the synthesis of benzimidazole derivatives is illustrated by the following retrosynthetic scheme: (Retrosynthetic Scheme).



Retrosynthetic scheme

To attempt our object, we have previously synthetize benzodiazepines. Generally, benzodiazepines were synthesized by condensation of orthophenylenediamine with α,β-unsaturated carbonyl compounds, halogenoketones or ketones. In our synthesis process, we used method developed by Ricaurte Rodriguez.[23] Chalcones were used as starting material. Thus chalcones 9 were prepared by using Claisen-Schmidt condensation with appropriate substituted benzaldehydes and substituted aromatic ketones (acetophenones) in KOH/EtOH solution.

The reaction of binucleophiles like o-phenylenediamine with α,β-unsaturated carbonyl compounds 9 under reflux in the presence of triethylamine in ethanol afforded compounds 11 in moderate to good yields (45-80%). The reaction was carried out in dark in order to exclude any influence of light with a possible oxidation of o-phenylenediamine.[24] Benzodiazepine was isolated as only reaction product (Scheme 2).



Scheme 2

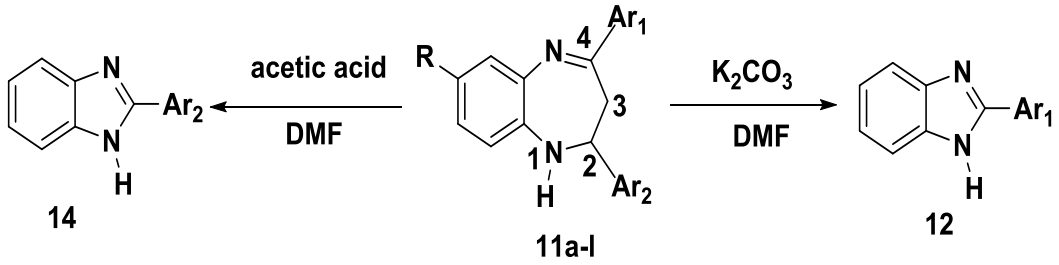
The yields of the reaction were improved by using methanol as solvent instead of ethanol. The structure of compounds 11 were confirmed by NMR (1H, 13C) and SDM spectroscopic analyzes. The ^{1}H NMR analysis of compounds 11f showed that H_3 proton were appeared as doublet dedoublet (dd) at 3.07 ppm. They were coupled with H_2 proton (5.16ppm). The H_3protons were not equivalent. These protons H_A: 3.07 ppm (dd); H_M: 3.35 ppm (dd) were coupled with the H_X proton: 5.16 ppm (dd) ($^{2}J_{AM}$= 8Hz, $^{3}J_{AX}$ = 4Hz), $^{3}J_{MX}$ = 4Hz), therefore, they formed an AMX system. Physical characteristics and yields of compound 11 were summarized in Table 1.

Table 1: Physical characteristics, ^{1}H chemical shifts (ppm) and ^{1}H-^{1}H coupling constants (J in Hz) of compounds 11 in $CDCl_3$ or DMSO.

Compounds	R	Ar_1	Ar_2	Yield	MP °C	δ (ppm)	J (Hz)
11a	CH_3	phenyl	phenyl	50	116	3.08-3.05 (m, H_3); 5.60-5.78 (m, H_2)	
11b	H	o-hydroxyphenyl	p-chlorophenyl	78	176	2.98 (dd, $H3_\alpha$) 3.215(dd, $H_{3\beta}$) 5.155 (dd, H_2)	$^{2}J_{H3\alpha,H3\beta}$=16Hz, $^{3}J_{H3\alpha,H2}$= 8Hz); $^{2}J_{H3\alpha,H3\beta}$=16 Hz, $^{3}J_{H3\beta,H2}$=4 Hz) $^{3}J_{H3\alpha,H2}$ = 8 Hz, $^{3}J_{H3\beta,\ H2}$ = 4 Hz
11c	H	o-hydroxyphenyl	p-isopropylphenyl	56	126	3.06 (dd, $H_{3\alpha}$); 3.365 (dd, $H_{3\beta}$); 5.07 (dd, H_2)	$^{2}J_{H3\alpha,H3\beta}$ = 16 Hz, $^{3}J_{H3\alpha,H2}$ =8Hz $^{2}J_{H3\alpha,H3\beta}$ = 16Hz, $^{3}J_{H3\beta,H2}$ = 4Hz $^{3}J_{H3\alpha,H2}$ = 8Hz, $^{3}J_{H3\beta,H2}$ = 4Hz
11d	H	o-hydroxyphenyl	2,4-dichlorophenyl	66	152	3.21 (d, H_3); 5.762 (t, H_2)	$^{3}J_{H3,H2}$ = 8Hz $^{3}J_{H2,H3}$ = 8Hz
11e	H	o-hydroxyphenyl	p-methoxyphenyl	80	138	2.97 (dd, $H_{3\alpha}$) 3.25 (dd, $H_{3\beta}$) 5.085 (dd, H_2)	$^{2}J_{H3\alpha,H3\beta}$ = 16Hz, $^{3}J_{H3\alpha,H2}$ = 8Hz $^{2}J_{H3\alpha,H3\beta}$ = 16Hz, $^{3}J_{H3\beta,H2}$ = 4Hz $^{3}J_{H3\alpha,H2}$ = 8Hz, $^{3}J_{H3\beta,H2}$ = 4Hz
11f	H	o-hydroxyphenyl	p-methylphenyl	75	120	3.07 (dd, $H_{3\alpha}$) 3.35 (dd, $H_{3\beta}$) 5.16 (dd, H_2)	$^{2}J_{H3\alpha,H3\beta}$ = 8Hz, $^{3}J_{H3\alpha,H2}$ = 4Hz $^{2}J_{H3\alpha,H3\beta}$ = 8Hz, $^{3}J_{H3\beta,H2}$ = 4 Hz $^{3}J_{H3\alpha,H2}$ = 4Hz, $^{3}J_{H3\beta,H2}$ = 4Hz

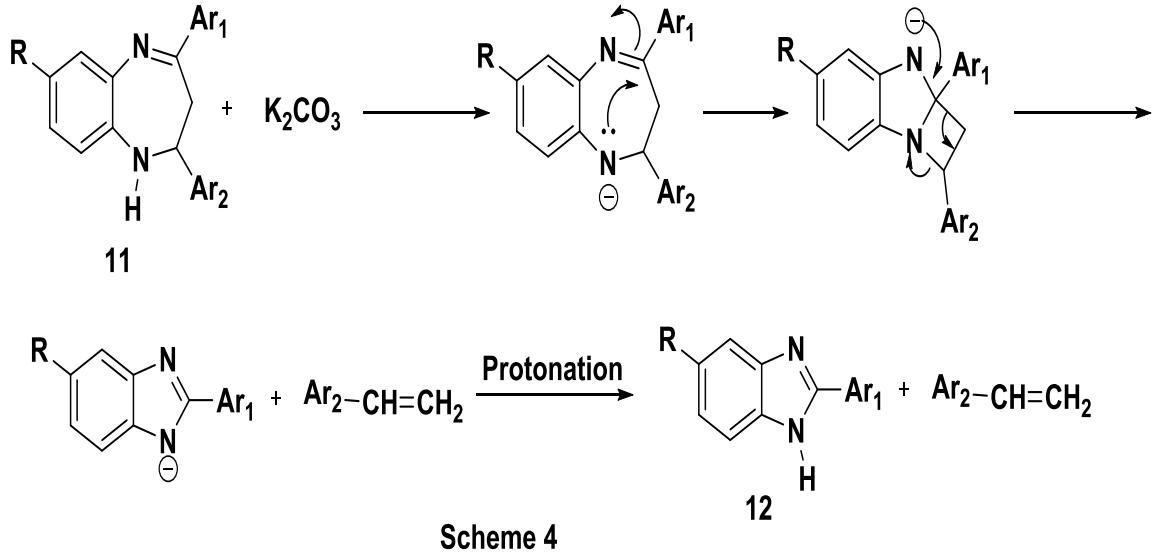
11g	H	p-methylphenyl	thienyl	45	126	2.99 (dd, $H_{3\alpha}$) 3.26 (dd, $H_{3\beta}$) 5.50 (dd, H_2,	$^3J_{H3\alpha,H2}$=9Hz, $^2J_{H3\alpha,H3\beta}$=13.2 Hz) $^3J_{H3\beta,H2}$=4.2 Hz, $^2J_{H3\alpha,3\beta}$=13.2 Hz) $^3J_{H3\alpha,\ H2}$ = 9 Hz, $^2J_{H3\beta,H2}$ = 4.2 Hz);
11h	H	phenyl	p-methoxyphenyl	71	122	3.045 (dd, $H_{3\alpha}$) 3.225 (dd, $H_{3\beta}$) 5.135 (dd, H_2)	$^2J_{H3\alpha,H3\beta}$ = 16Hz, $^3J_{H3\alpha,H2}$ = 8Hz $^2J_{H3\alpha,H3\beta}$=16Hz, $^3JH_{3\beta,H2}$ = 4Hz $^3J_{H3\alpha,H2}$ = 8 Hz, $^3J_{H3\beta,H2}$ = 4 Hz
11j	H	phenyl	p-chlorophenyl	73	144	3.025 (dd, $H_{3\alpha}$) 3.20 (dd, $H_{3\beta}$, 5.20 (dd, H_2,	$^2J_{H3\alpha,H3\beta}$=12Hz, $^3J_{H3\alpha,H}$ = 8Hz); $^2J_{H3\alpha,H3\beta}$=12Hz, $^3J_{H3\beta,H2}$ = 4Hz) $^3J_{H3\alpha,H2}$ = 8Hz, $^3J_{H3\beta,H2}$ = 4Hz);
11k	CH_3	phenyl	2-chlorophenyl	65	123	2.99-3.13(m,H_3) 5.60-5.63(m,H_2)	
11l	CH_3	phenyl	2-chloro-4-nitrophenyl	77	200	3.12-3.14(m,H_3) 5.70-5.77(m,H_2)	

Treatment of compounds 11 with potassium carbonate in dimethylformamide (DMF) under reflux, afforded 2-substituted benzimidazole 12 in moderate yields (40-60%) (Scheme 3) The spectroscopic analysis of protons showed the disappearance of protons H_2 and H_3 observed in compounds 11. The benzimidazolic structures that we proposed were confirmed by mass spectrometry data.



Scheme 3

To explain the formation of the benzimidazole we proposed the following mechanism: 2,3-dihydro-benzodiazepine 11 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 12 (Scheme 4).



Scheme 4

Treatment of benzodiazepines 11 with acetic acid in diméthylformamide (DMF) under reflux afforded 2-substituted benzimidazole 14a-h (Scheme 3) in good yields (60-80%).

The spectroscopic analysis of protons showed the disappearance of proton H_2 and H_3 observed in compounds 11. We also observed an echo zone in the aromatic area with a decrease of protons. We propose the juxtaposition of the ^1H NMR spectrum of benzodiazepine 11c with that of benzimidazole 14g (Figure 3).

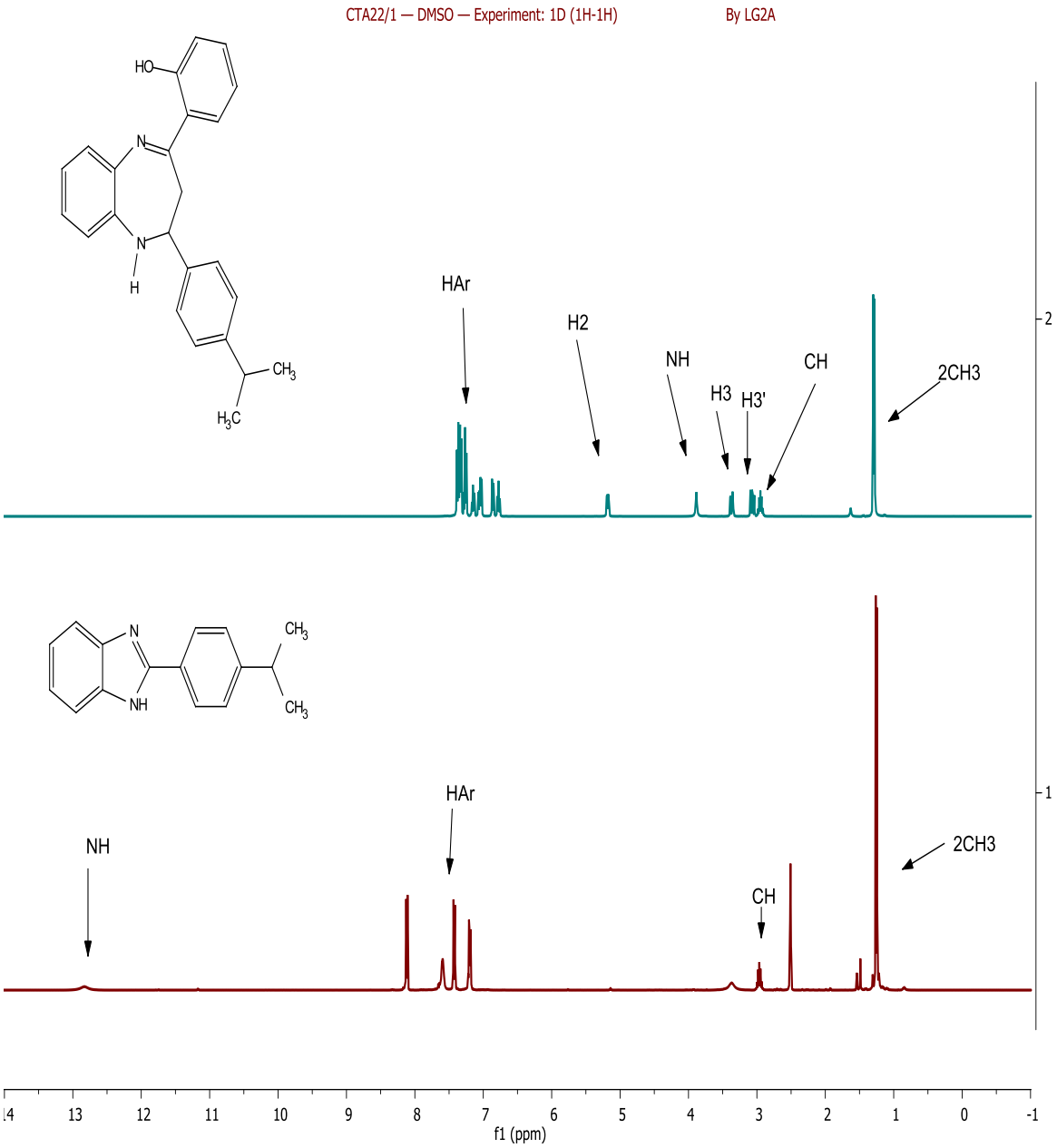
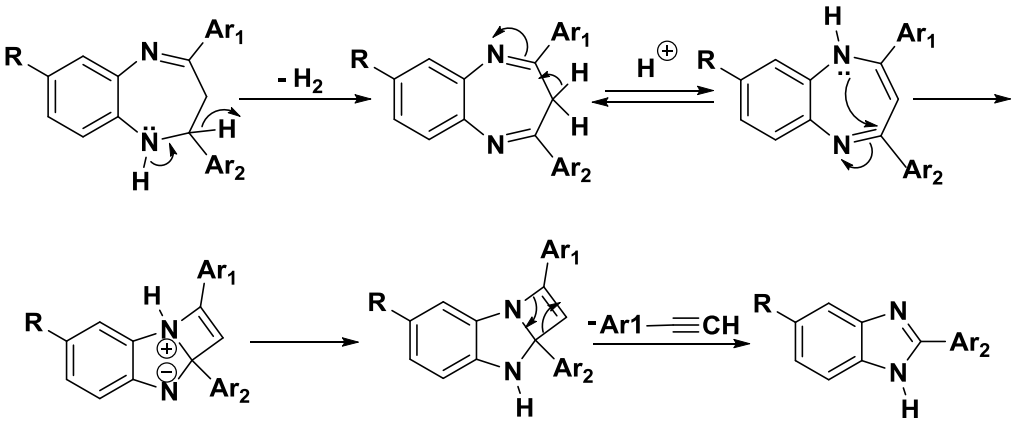


Figure 3:

To explain the formation of the benzimidazoles 14 we proposed the following mechanism: 2,3-dihydro-benzodiazepine 11 could undergo to aromatization following to tautomerization in acid medium. The free doublet of the nitrogen atom attacks iminic carbon affording a

tended cycle. The intermediate formed compound moves in a cyclic regression process to lead to derivative benzimidazoles 14 (Scheme 5).



scheme 5

The benzimidazole structures were confirmed by NMR (1H, 13C) and mass spectrometry data. Physical characteristics and yields of compound **14** were summarized in Table **2.**

Table 2: Physical characteristics and yields of compounds 14.

Compounds	R	Ar_2	Yield	MP °C
14a	H_3	p-chlorophenyl	67	>260
14b	H	p-methoxyphenyl	60	>266
14c	H	thienyl	72	178
14d	H	p-methylphenyl	77	264
14e	H	p-methoxyphenyl	78	>266
14f	H	2,4-dichlorophenyl	72	118
14g	H	p-isopropylphenyl	80	250
14h	CH3	2-chlorophenyl	62	227

After these different reactions, we compared the Rf frontal ratios of these two products by thin layer chromatography. We noted a difference in frontal displacements Rf. In addition, the melting points of the compounds obtained are different. Therefore, we deduce that the products obtained are not the same. To understand the behavior of benzodiazepines in acidic and basic medium we proceeded to a study by making theoretical calculations.

Theoretical calculations were studied to understand the formation of benzimidazoles in acidic and then basic. In order to compare and consolidate our experimental results, we performed theoretical calculations of quantum chemistry. We calculated the Mulliken load of each atom k in the neutral molecule ($q_k(N)$), in its anionic form ($q_k(N+1)$) and in its cationic form

($q_k(N-1)$). From the relationships below, we evaluated the Fukui (and) indices for a k atom of the molecule.

$$f_k^+ = q_k(N+1) - q_k(N)$$
$$f_k^- = q_k(N) - q_k(N-1)$$

These indices give information on a site (atom) k as to a nucleophilic or electrophilic attack respectively. These descriptors therefore make it possible to identify the preferred reaction sites and to predict their relative approach.

Our calculations were performed with the Gaussian 03[25] software at the B3LYP/6-31G theory level (d,p). The results obtained have been simplified. Only the Fukui (f_k^+ and f_k^-) indices of the atoms involved in the cyclic regression of the seven-membered ring are presented. The numbering adopted being indicated in the figure below:

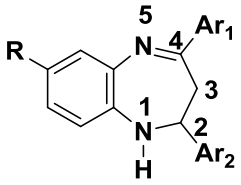


Figure 4: Numbering atoms of the seven-membered ring for quantum chemistry calculations. The calculations are carried out on the 11e, 11g and 11k molecules for which only the values of the descriptors retained for the carbons 2, 3 and 4 and then the nitrogens 1 and 5 are exposed. The indices f_k^+ and f_k^- are descriptors of local reactivity varying from one site to another in the same molecule. These are good descriptors for studying selectivity that have been defined by Yang and Mortier.[26] We also calculated the dual descriptor proposed by Morell et al.[27,28] and defined by the relation: $\Delta f = f_k^+ - f_k^-$.

The values obtained for these different descriptors f_k^+, f_k^- and Δf are reported in the following table 3.

If for each of the five sites (atoms) selected in the molecule, we obtained a value for each of the descriptors f_k^+ and f_k^-, the dual descriptor Δf makes it possible to specify the electrophilic or nucleophilic nature of the site.

It is clear that N1 and N5 are nucleophilic sites. Of the two sites, N1 nitrogen is the most favorable for this interaction. Such an attack seems unlikely on the N5 nitrogen which appears depleted in electron in the molecule 11k.

As for the C3 and C4 carbons, they are exclusively electrophilic sites. The potential of this interaction is at least doubly important for C4. Carbon C2 is rather a site favorable to nucleophilic attacks especially in 11g and 11k compounds. Of the three carbon atoms, C2 is clearly the least prepared for an electrophilic species attack.

Finally, in the basic medium containing nucleophilic species C2 is the preferred site for the reaction. On the other hand, in an acid medium, the C4 carbon will be attacked first by the electrophiles present. Following these first steps, the various mechanisms proposed detail the rest of the reaction according to the nature of the reaction medium.

Table 3: Values calculated at B3LYP/6-31G level (d,p) descriptors f_k^+ and f_k^- for local reactivity and dual descriptor Δf in three molecules.

molecules	11e			11g			11k		
atoms	f_k^+	f_k^-	$\Delta f = f_k^+ - f_k^-$	f_k^+	f_k^-	$\Delta f = f_k^+ - f_k^-$	f_k^+	f_k^-	$\Delta f = f_k^+ - f_k^-$
C_2	-0,006852	0,004991	-0,011843	-0,021941	-0,02202	$7{,}9.10^{-5}$	0,010274	-0,024069	0,034343
C_3	0,021782	0,052162	-0,03038	0,019391	0,057664	-0,038273	0,022571	0,049963	-0,027392
C_4	-0,078432	-0,008082	-0,07035	-0,078727	-0,012358	-0,066369	-0,072291	-0,011459	-0,060832
N_1	0,001948	-0,043381	0,045329	0,001948	-0,043381	0,045329	0,005062	-0,028201	0,033263
N_5	-0,059345	-0,061308	0,001963	-0,059345	-0,061308	0,001963	-0,06383	-0,050307	-0,013523

CONCLUSION

In this work, we developed an original synthesis approach of benzimidazole by cyclic regression of benzodiazepines in acid medium. This method allowed obtaining various substituents in position 2 of the benzimidazole. After analysis of the obtained compounds and in comparison with those of Timotou et al.[19] (2013), we can affirm that the substituent in position 2 of the benzimidazole was selective according to whether it was in a basic or an acid medium. Thus, in a basic medium, the substituent Ar_1 was attached to the 2-position of the benzimidazole, whereas in acid medium it was the substituent Ar_2.

Competing Interests

The authors declare that they have no competing interests.

Authors' Contributions

• Tchambaga Etienne CAMARA

Synthesis of compounds

Spectroscopic analysis

• Siomenan COULIBALI

Contribution the redaction of the manuscript

• Soleymane KONE

Study by theoretical calculations

• Timotou ADÉYOLÉ

Initiator of regression in a basic medium

• Ané ADJOU

Write the manuscript (French and English).

Dean of Thesis of Camara Tchambaga,

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