ACADEMIA ROMÂNĂ
Revue Roumaine de Chimie
http://web.icf.ro/rrch/

Rev. Roum. Chim.,
2015, *60*(9), 853-859

EXPERIMENTAL AND THEORETICAL INVESTIGATION OF THE INTRAMOLECULAR CYCLISATION OF *N*-(BENZOXAZOLINON-6-YL)MALEIMIDE DERIVATIVES

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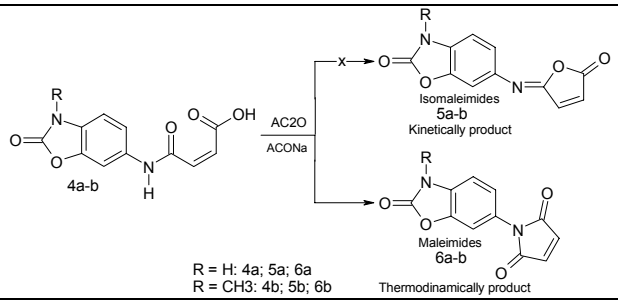
Received March 3, 2014

A new N–H and N–CH_3 2(3*H*)-benzoxazolones substituted at the C_6 position in the aromatic ring by imide group (maleimides) has been synthesized in good yields. The regioselectivity of the cyclisation step has been investigated through DFT calculations at the B3LYP/6-31G (d,p) level of theory. The obtained results indicate that the maleimide is favored both kinetically and thermodynamically as observed experimentally.



INTRODUCTION

In recent years, several structurally interesting compounds with substitute benzoxazolinone (BOA) moiety have gained importance due to their application in pharmaceutical chemistry.[1,2] In addition, benzoxazolone derivatives are widely distributed in plants and are of increasing interest for a variety of pharmacological properties, such as detoxification, antibacterial, antimicrobial, antifungal, anti-HIV, anti-inflammatory, and tranquilizers.[3-7] Nevertheless, most efforts have focused on 6-, 5-, or 3-substituted benzoxazolones.[8] Moreover, *N*-Substituted imides, such as maleimide derivatives have been the subjects of numerous synthetic efforts due to their potential applications in synthetic chemistry.[9-16] They represent an important class of molecules known for a variety of pharmacological properties, which include antiviral, antibacterial, anti-inflammatory, and antitumor properties,[17-21] and a multitude of bioactive natural products have also been prepared by development of *N*-aryl maleimides.[22-25] Recently, it has also been demonstrated that human hemoglobin chemically modified with maleimide-polyethylene glycol is a blood substitute and can be used on any blood type.[26] On the other hand, it has been shown that maleimide have various applications in polymer chemistry.[27] The incorporation of maleimide moiety into various heterocyclic systems was found to increase their biological activities.[28]

In continuation of our work on the synthesis of biologically active benzoxazolone containing heterocycles[29], we present in this paper the synthesis of some new benzoxazolinonic maleamic

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acids and their corresponding maleimide derivatives, and the theoretical investigation of the intramolecular cyclisation of the *N*-(benzoxazolinon-6-yl)maleamic acids to their maleimides derivatives.

A tremendous amount of experimental and theoretical work devoted to the study of the structure-activity relationship of the substituted benzoxazolinone can be found in the literature. Doğruer and co-workers[30] studied the synthesis of some (2-benzoxazolone-3-yl and 2-benzothiazolone-3-yl) acetic acid derivatives. Various anticancer and antimicrobial qualities of benzoxazolone derivatives were described also by Mariola *et al.*;[31] Murty *et al.*[32,33] In other studies, Koksal and co-workers[34] synthesized the 3-(4-substituted benzoylmethyl)-2-benzoxazolinones and screened their antimicrobial activities. Ilieva *et al.*[35] studied through DFT calculations at the B3LYP/6-31G* level the mechanism of the ring opening reaction of 2-benzoxazolinone upon aminolysis with methylamine.

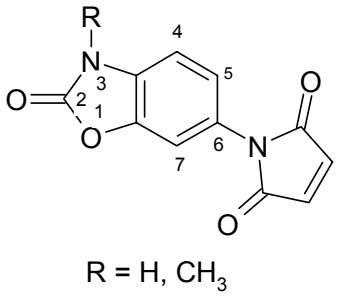


Fig. 1 – Structure of *N*-(benzoxazolinon-6-yl)maleimides.

In this manuscript we report the synthesis of new compounds **(6a-b)** containing imide group at 6-position of the 2(3*H*)-benzoxazolone and 3-methyl-2(3*H*)-benzoxazolone aromatic rings (Fig. 1). We reasoned that the effect of the side maleimide at the C_6 position in the aromatic ring of the benzoxazolone could be able to enhance the antibacterial capacity of these compounds. This prompted us to design some new benzoxazolone analogues in an attempt to improve potency against some bacteria[36] and to find more potent antibacterial compounds. A standard method for maleimides synthesis is the intramolecular cyclisation by dehydration of the corresponding *N*-substituted maleamic acids[37,38] with simple heating or direct fusion of the maleic anhydride and 6-aminobenzoxazolinonic substrates in the presence of acetic anhydride with anhydrous sodium acetate used as dehydrating agent for maleamic acids cyclisation.[39-42] Under certain conditions the reaction mixture has also been found to contain beside maleimide isomer, *N*-substituted isomaleimide in different amounts.[43] Then we have performed a computational investigation of the regioselectivity of the cyclisation step of these maleamic acids using DFT methods. Structure of new compounds was identified by spectroscopic methods using IR, ^{1}H-NMR.

RESULTS AND DISCUSSION

The synthetic routes for the preparation of the respective benzoxazolinonylmaleimide derivatives **(6a-b)** have been realized as illustrated in Scheme 1. Compounds **1a-b, 2a-b** and **3a-b** (Scheme 1) were prepared as described in the literature.[44-48] 2(3*H*)-benzoxazolone **(1a)** was obtained by simple reaction between the commercially available compound 2-aminophenol and urea. The methylation of the benzoxazolinonic nitrogen atom in position **3**, using dimethylsulfate in a basic medium afforded the corresponding 3-methyl-2(3*H*)-benzoxazolone **(1b)** in quantitative yield. The reaction of compounds **1a** and **1b** with nitric acid and acetic anhydride produced the 6-nitro-2(3*H*)-benzoxazolone and 6-nitro-3-methyl-2(3*H*)-benzoxazolone derivatives **(2a-b)**, followed by reduction of the nitro group in the presence of tin chloride dihydrate ($SnCl_2$. $2H_2O$) in refluxing ethanol, afforded the amine substrates **(3a-b)** respectively. Therefore we carried out the next steps of the reaction without any further purifications and analysis. Finally, the reactions of these 6-amino-2(3*H*)-benzoxazolone and 3-methyl-6-amino-2(3*H*)-benzoxazolone **(3a-b)** with maleic anhydride in dichloromethane for 3h at room temperature give the corresponding maleamic acid derivatives **(4a-b)** in acceptable yields (Scheme 2). The last step represented a cyclic dehydration of the corresponding benzoxazolinonic maleamic acids by chemical treatment, using acetic anhydride and sodium acetate as catalyst to obtain the desired benzoxazolinonic maleimide derivatives in good yield.

Spectral characterization

The most FT-IR frequencies of maleamic acids **(4a-b)** and maleimides **(6a-b)** are given in the experimental part. The FT-IR spectrum confirms the total cyclic dehydration and formation of maleimide compounds, and they indicate the formation of the maleamic and maleimide products

by the presence of the characteristic band for the maleamics and imides carbonyl function.

The FT-IR spectra of maleamic acid derivatives in general, showed the disappearance of (NH_2) absorption of primary amine and appearances of the (NH) absorption band at (3263-3294) cm^{-1}. The FT-IR spectrum of maleimide derivatives showed disappearance of (OH) acid and (NH) amide absorption bands and appearance of (C=O) imide at (1708-1717) cm^{-1}. Also, the absorption bands observed around 750 and 1370 cm^{-1} in the maleimide compounds are assigned to the $\nu_{C\text{-}N\text{-}Cimide}$ vibrational modes, confirming the formation of the desired maleimide derivatives. In addition, the absorption bands around 1570 cm^{-1} correspond to the vibrations of the aromatic rings.

All maleimides were characterized by ^{1}H-NMR spectra and confirmed their chemical structure. Analysis of ^{1}H-NMR spectra, allows us to clearly identify the structure of the obtained maleimide compounds. After analysis, we can assign the different observed peaks.

The ^{1}H-NMR spectrum indicate the formation of the maleimide products (**6a-b)** by the presence of a singlet peak ranged from 6.86 ppm to 6.87 ppm assignable to the -CH=CH- imide protons, while the aromatic protons of the maleimide compounds appear in the appropriate region at δ 7.01-8.14 ppm. The signal due to the aliphatic protons of the methyl substituent on the N(3)-substituted benzoxazolone derivatives appear at δ 3.42 ppm. The presence of the imide peak at δ 6.86-6.87 ppm in the spectrum of the maleimide derivatives clearly demonstrate the formation of the desired maleimide compounds. Details of the experimental protocols used are shown in the experimental part.

Theoretical study

Energies

Table 1 reports the energies (a.u) and relative energies (kcal/mol) of the stationary points (reactants, transition structures and products) of the two possible channels of the cyclisation reaction, leading to the formation of the *N*-(benzoxazolinon-6-yl)maleimide and *N*-(benzoxazolinon-6-yl)isomaleimide. The proposed formation mechanism of the two products is illustrated in Scheme 2. The geometries of the TSs are given in Fig. 2 together with the newly forming bond lengths. The cyclisation of the maleamic acid can take place along two reactive channels corresponding to the formation of the benzoxazolinonic maleimide and the isomaleimide derivatives. For each reaction, we studied two TSs and two products.

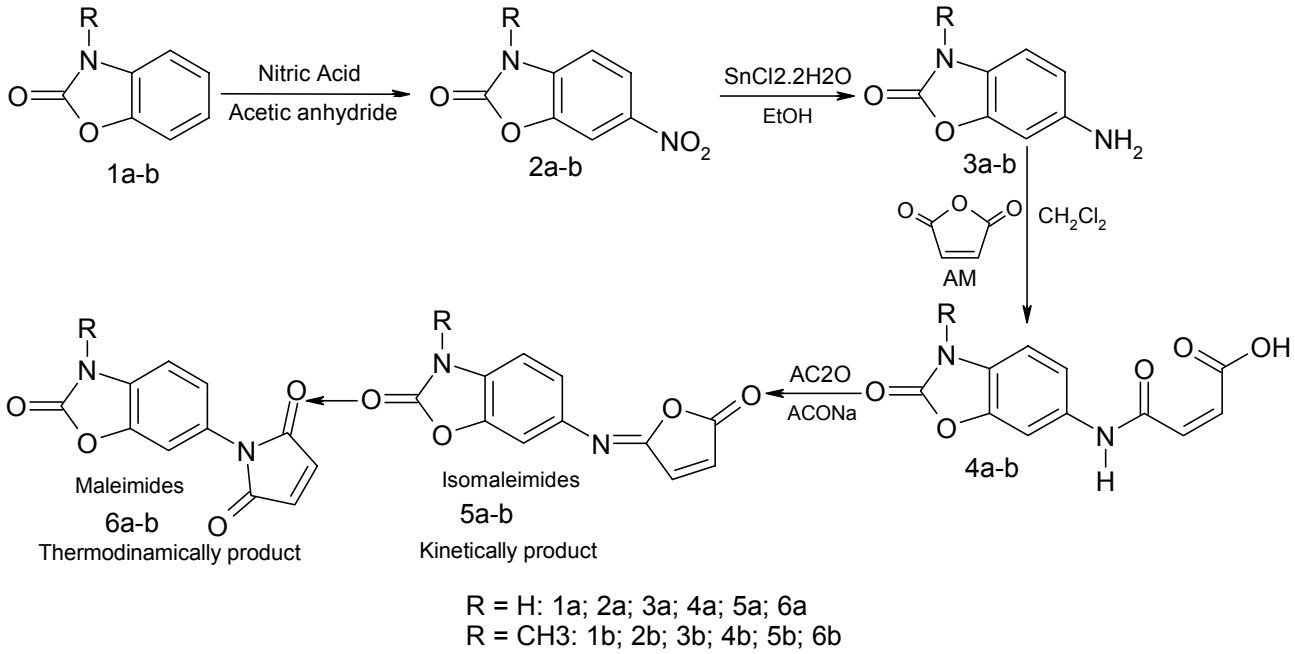
Cyclisation of the maleamic acid (**4a)**: from the calculated relative energies, the transition state TS2 is favored kinetically in comparison with the other transition state TS1, this reveals the formation of the isomaleimide **P1** as the kinetically product. In the other hand, the product **5a** is favored thermodynamically. Consequently, we can obtain a mixture of maleimide and isomaleimide. Experimentally, the maleimide derivative is the sole product obtained.

Table 1

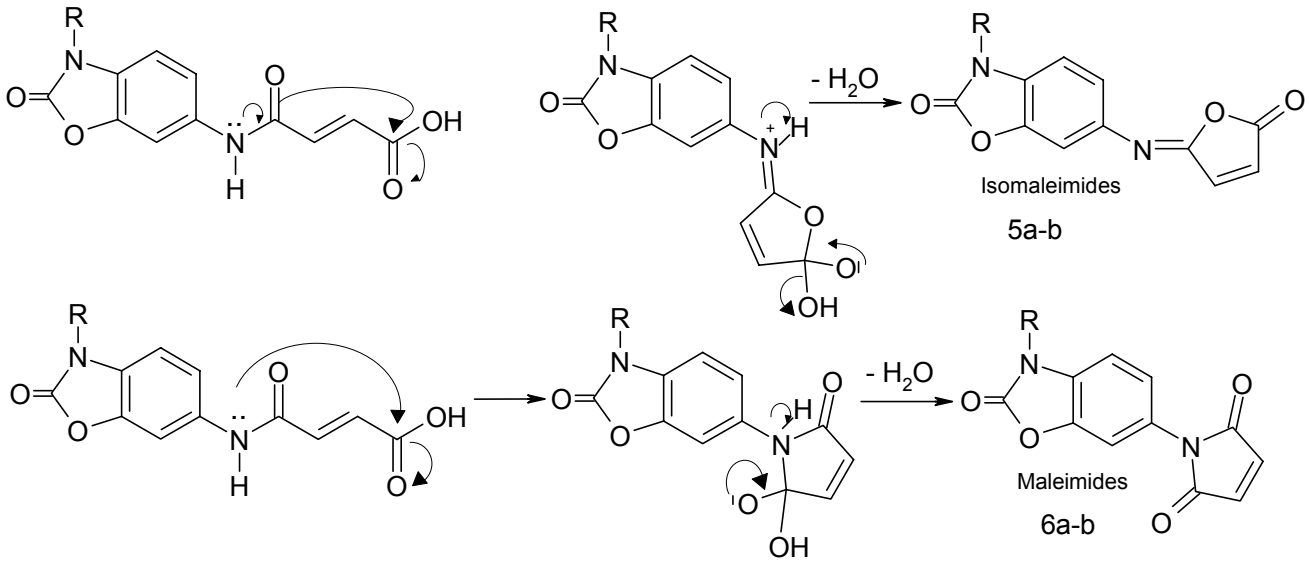
Energies E (a.u.) and relative energies ΔE (kcal/mol) of the maleamic acids cyclisation

Reactant	E(a.u)	ΔE(Kcal/mol)
4a	-909.65622	00.00
TS1	-909.46980	116.98
TS2	-909.48550	107.13
5a	-909.63871	10.98
P1	-909.59158	40.56
4b	-948.96967	00.00
TS3	-948.78618	115.14
TS4	-948.76276	129.84
5b	-948.95546	08.91
P2	-948.93049	24.60

Cyclisation of the maleamic acid (**4b)**: analysis of the relative energies indicates that the pathway corresponding to the formation of maleimide (TS3) possess low activation energy (115.14 kcal/mol) in comparison with TS4 (129.84 kcal/mol), this suggest its formation as the product favored kinetically. In addition the product **5b** is more stable (08.91kcal/mol) than the isomaleimide P2 (24.60kcal/mol). Consequently, the product **5b** is favored both kinetically and thermodynamically.



Scheme 1 – Reactional sequences of the synthesis of *N*-(benzoxazolinon-6-yl)maleimide derivatives.



Scheme 2 – Proposed mechanism of formation of maleimide and isomaleimide derivatives.

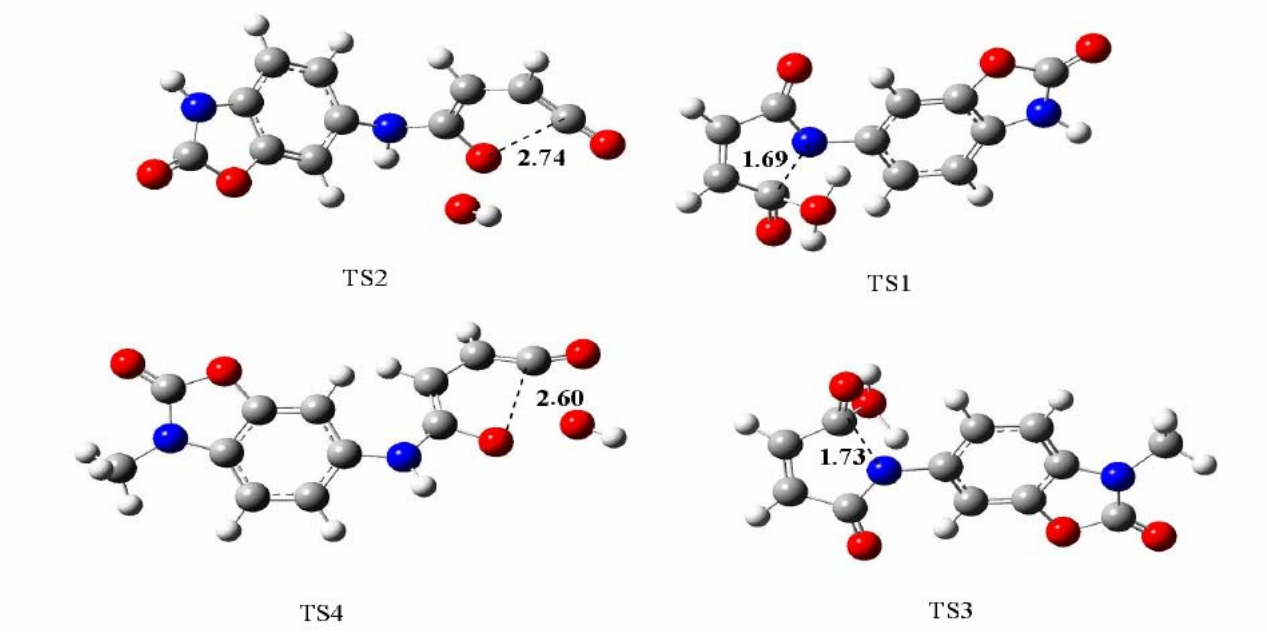


Fig. 2 – Transition structures of the two cyclisation of maleamic acids derivatives **4a** and **4b**.

EXPERIMENTAL

General

All chemicals and solvents that we have used in this study were purchased from Aldrich Chemicals. Melting points have been determined using a BUCHI A 9000 apparatus and are uncorrected. IR spectra (KBr pellets) were performed on a SHIMADZU-FTIR 8400 IR spectrophotometer. The ^{1}H NMR spectra were performed using a Bruker AC 250 spectrometer using dimethylsulfoxide-d_6 with TMS as internal standard, with chemical shifts reported as δ (*ppm*), *J* values are recorded in Hz. The purity of the compounds was established by thin layer chromatography (TLC). The physical and spectral properties of the intermediate derivatives **1a-b**, **2a-b** and **3a-b** were in accordance with the data in the literature. The complete IR and NMR data of the new synthesized compounds **4a-b** and **6a-b** was in agreement with the proposed structures. Analytical thin layer chromatography was performed on a plastic sheet (0.2 mm, silica gel 60 F254, Merck). Silica gel 60 (70–230 mesh, Merck) was used for column chromatography.

General procedure for the synthesis of 6-nitro-2(3*H*)-benzoxazolone and 3-methyl-6-nitro-2(3*H*)-benzoxazolone compounds (2a-b)

Nitric acid (68%, 5.30 cm^3, 80 mmol) cooled to 0–5°C was added dropwise to a solution of benzoxazolinone (10 mmol) in 20 cm^3 of acetic anhydride. The mixture was stirred at 0–5°C for 3 h. The precipitate was filtered, washed with cold H_2O, dried, and recrystallized from suitable solvent to afford the corresponding nitrobenzoxazolones compounds **3a** (67.77%) and **3b** (91%).

General procedure for the synthesis of 6-amino-2(3*H*)-benzoxazolone and 6-amino-3-methyl-2(3*H*)-benzoxazolone compounds (3a-b)

To a mixture of 6-nitro-2(3*H*)-benzoxazolone **2a** (8.1 mmol, 0.145 g) or 3-methyl-6-nitro-2(3*H*)-benzoxazolinone **2b** (8.1 mmol, 0.157 g) and 10% Pd/C (375 mg) in 30 mL of methanol was added ammonium formate (2.55 g, 40.5 mmol, 5equiv), and the reaction was heated to reflux for 3 h until the reaction was complete and the starting material disappeared as indicated by TLC analysis. The reaction mixture was allowed to cool down, filtered through Celite, and evaporated to give the desired amines **3a** (55.39%) and **3b** (73.36%).

General procedure for the synthesis of maleamic acid derivatives (4a-b)

To a stirred solution of maleic anhydride (0.196 g, 2mmol) in dichloromethane CH_2Cl_2 (5 ml) at room temperature under argon, was added dropwise, the appropriate 6-amino-benzoxazolinone derivatives **3a** (0.30 g, 2 mmol) and **3b** (0.32 g, 2mmol), in the same solvent CH_2Cl_2 (10 ml). The resulting suspension was stirred at room temperature during 2 hours. The residue obtained was filtered off, washed with dry DCM, dried, and recrystallized giving the desired benzoxazolinonic maleamic acids compounds **4a** and **4b** respectively. These crude products were purified by column chromatography on silica gel plate using cyclohexane/ethyl acetate (2:8) as eluent.

N-(benzoxazolinon-6-yl)maleamic acid **(4a):** Yellow solid, Yield (0.3g, 71.42%), m.p. 199-201°C (Ethanol). FT-IR (KBr, cm^{-1}): ν_{OH} 3450, ν_{NH} 3263 and 3274 cm^{-1}, ν_{CHar} 3105 cm^{-1}, $\nu_{C=O\ (-\underline{N}\text{-}\underline{CO}\text{-}O\text{-})}$ 1751, $\nu_{CO\ (acide)}$ 1717, $\nu_{CO\ (amide)}$ 1635 cm^{-1}, $\nu_{C=Car}$ 1558 cm^{-1}. ^{1}H-NMR δ_H (400 MHz, DMSO-d_6): 6.32-6.35 (d, *J* = 12 Hz, 1H, -CH=<u>CH</u>-CO_2H), 6.46-6.49 (d, *J* = 12 Hz, 1H, -<u>CH</u>=CH-CO_2H), 7.07-7.09 (d, *J* = 8 Hz, 1H, H_4), 7.29-7.32 (dd, *J* = 8 Hz ; *J* = 4 Hz, 1H, H_{5ar}), 7.73-7.74 (d, *J* = 4 Hz, 1H, H_{7ar}), 10.58 (s, 1H, NH).Anal. Calcd for $C_{11}H_8N_2O_5$: C, 53.23; H, 3.25; N, 11.29. Found: C, 53.78; H, 3.54; N, 11.66.

N-(3-methylbenzoxazolinon-6-yl)maleamic acid **(4b):** The same procedure was used for the preparation of acid **4b:** Brown solid, Yield (3.85g, 77.60%); m.p. 198-200°C (Ethanol). IR (KBr, cm^{-1}): ν_{OH} 3463, ν_{NH}, 3294 cm^{-1}, ν_{CHar} 3124 cm^{-1}, ν_{CH3} 2931 cm^{-1}, $\nu_{C=O\ (-\underline{N}\text{-}\underline{CO}\text{-}O\text{-})}$ 1758, $\nu_{CO\ (acide)}$ 1708, $\nu_{CO\ (amide)}$ 1635 cm^{-1}, $\nu_{C=Car}$ 1557 cm^{-1}. ^{1}H-NMR δ_H (400 MHz, DMSO-d_6): 3.32 (s, 3H, N-CH_3), 6.30-6.34 (d, *J* = 16 Hz, 1H, -CH=<u>CH</u>-CO_2H), 6.43-6.47 (d, *J* = 16 Hz, 1H, -<u>CH</u>=CH-

CO_2H), 7.19-7.22 (d, J = 12 Hz, 1H, H_4), 7.33-7.37 (dd, J = 8 Hz; J = 4 Hz, 1H, H_{5ar}),7.74 (d, J = 2 Hz, 1H, H_7), 10.50 (s, 1H, NH). Anal. Calcd. for $C_{12}H_{10}N_2O_5$: C, 54.97; H, 3.84; N, 10.68. Found: C, 55.03; H, 3.64; N, 10.96.

General procedure for the synthesis of N-(benzoxazolinon-6-yl)maleimide derivatives (6a-b)

Under argon, appropriate benzoxazolinonic maleamic acids **4a** (1.25 g, 5 mmol) or **4b** (1.31 g, 5 mmol) in dichloromethane (10 mL) were added to a mixture of 2 ml of acetic anhydride and 0.2 g of anhydrous sodium acetate. The resulting suspension was heating on a steam bath, and stirring was continued until TLC showed that the reaction is completed. The mixture was cooled and evaporated to dryness under reduced pressure. The residue was dissolved in ethylacetate (AcOEt, CH_3CO_2Et), $_{washed}$ with 2×10 ml of cold saturated bicarbonate solution ($NaHCO_3$), and dried (Na_2SO_4). The solvent was evaporated under reduced pressure to give a brown solid. The residue obtained after removal of solvent was washed with distilled water, dried and the crude products were purified by column chromatography on silica gel plate using cyclohexane/ethyl acetate (2:8) as eluent. The purity of the compounds was checked by thin-layer chromatography (TLC) on silica gel plate using cyclohexane/ethyl acetate (2:8) as eluent.

N-(benzoxazolinon-6-yl)maleimide **(6a):** was obtained after purification as brown powder. Yield (1.2g, 89.13%), m.p. 216-218°C. FT-IR (KBr, cm^{-1}): ν_{NH} 3312-3298 cm^{-1}, ν_{CHar} 3101-3120 cm^{-1}, ν_{CH3} 2927 cm^{-1}, $\nu_{C=O\ (-\underline{N\text{-}CO\text{-}O}-)}$, 1793 cm^{-1}, $\nu_{C=O\ (cyclic\ imide)}$ 1716 cm^{-1}, $\nu_{C=C\ (aromatic)}$ 1558, $\nu_{C\text{-}N\text{-}C}$ 1315 and 1325 cm^{-1}, $\nu_{HC=CH\ (cis)}$, 752 cm^{-1}. ^1H NMR δ_H (400 MHz, $CDCl_3$): 6.87 (s, 2H, -CH=CH-), 7.25-7.26(m, 1H, H_{5ar}), 7.28-7.29 (d, J = 4 Hz, 1H, H_{7ar}), 8.12-8.14 (d, J = 8 Hz, 1H, H_{4ar}). Anal. Calcd for $C_{11}H_6N_2O_4$: C, 57.40; H, 2.63; N, 12.17; O, 27.80. Found: C, 57.13; H, 2.24; N, 12.66; O, 28.

N-(3-methylbenzoxazolinon-6-yl)maleimide **(6b):** Compound **6b** was prepared similarly as compound **6a**, and a yellow-brown solid was obtained, which was filtered and dried at room temperature. The obtained compound is stable at room temperature, insoluble in water, relatively soluble in ethanol, methanol, very soluble in acetone and dimethylformamide (DMF). Yield (78.26%), m.p. 202-204°C (Ethanol). FT-IR (KBr, cm^{-1}): ν_{CHar} 3101 cm^{-1}, ν_{CH3} 2923 cm^{-1}, $\nu_{C=O\ (-\underline{N\text{-}CO\text{-}O}-)}$ 1793 cm^{-1}, $\nu_{C=O\ (cyclic\ imide)}$ 1717 cm^{-1}, $\nu_{C=C\ (aromatic)}$ 1555 cm^{-1}, $\nu_{C\text{-}N\text{-}C}$ 1377 and 1269 cm^{-1}, and $\nu_{HC=CH\ (cis)}$ 750 cm^{-1}. ^1H NMR δ_H (400 MHz, $CDCl_3$): 3.42 (s, 3H, N-CH_3), 6.86 (s, 2H, -CH=CH-), 7.01-7.03 (d, J = 8 Hz, 1H, H_{4ar}), 7.17-7.19 (dd, J = 8 Hz; J = 4 Hz, 1H, H_{5ar}), 7.22-7.23 (d, J = 4 Hz, 1H, H_{7ar}). Anal. Calcd for $C_{12}H_8N_2O_4$: C, 59.02; H, 3.30; N, 11.47; O, 26.21. Found: C, 59.43; H, 3.14; N, 11.76; O, 26.58.

Computational methods

Optimization of the stationary points (reactants, transition structures and products) were carried out using DFT methods[49] with B3LYP functional[50] in conjunction with 6-31G (d,p) basis set.[51] The stationary points were characterized by frequency calculations in order to verify that minima and transition states have zero and one imaginary frequency, respectively. All calculations were carried out with the GAUSSIAN 03 program.[52]

CONCLUSIONS

In the present paper, we describe the synthesis of new maleimide derivatives bearing benzoxazolone ring from the reaction of (benzoxazolinon-6-yl)maleamic acids **4a** and **4b** with maleic anhydride, and characterization by ^1H-NMR and FT-IR spectroscopy. The complete FT-IR and NMR data of the newly synthesized compounds **4a-b** and **6a-b** was in agreement with the proposed structures. The molecular geometry of the observed reaction pathways of the cyclisations of maleamic acids **4a** and **4b** was analyzed by density functional theory. The computational results explain the regioselectivity of the cyclization step observed in the experimental data based on spectroscopic analysis structure determination.

Acknowledgments: This work was financially supported by the Algerian Ministry of Higher Education and Scientific Research (CNEPRU, Project number E01120100062), and Directorate-General for Scientific Research and Technological Development (PNR-27/21-2011).

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