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Synthesis, Characterization and DFT Studies on Some 2,3-Dihydro-4-Methyl-1H-1,5-Benzodiazepinone and N-Isopropenyl Benzimidazolone Derivatives

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ABSTRACT

Benzodiazepinones and benzimidazolones have been synthesized by the reaction of o-phenylenediamine with ethylacetoacetate in boiling xylene. Alkylation of the obtained compounds was carried out by reaction with excess of ethyl iodide. The reaction of alkylated compounds with aromatic aldehyde leads to the formation of aryldinodiazepinone and/or arylidinone derivatives. The prepared compounds were tested for antibacterial and fungicidal activity. Gram-negative bacteria (Bacillus cereus), as well as the fungus was used for this purpose. The newly prepared compounds have been characterized by IR, MS, elemental analysis and 1H NMR spectroscopies and as well as theoretical level (DFT/B3LYP).

Keywords

DFT; Synthesis; Benzimidazoles; Benzodiazepines; Ethylacetoacetate; o-Phenylenediamine.

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1. INTRODUCTION

Benzodiazepines are very important compounds, widely used in the last decades as anticonvulsant, antianxiety, antitumor, psychosis, hypnotic and antipyretic agents [1]. Some benzodiazepine derivatives are also used in industry, such as light-sensitive material [2], and also as anti-inflammatory agents [3]. 1, 5-Benzodiazepines are also used for preparation of some fused ring benzodiazepine derivatives, such as triazole [4], and oxadiazole [5]. Due to their wide range of pharmacological activity, industrial and synthetic applications, many methods for their preparation are reported in the literature. This includes the condensation reaction of o-phenylenediamine with α, β-unsaturated carbonyl compounds [2, 6], and β-haloketones [7]. Benzimidazole derivatives are endowed with different types of biological activities especially antitumor activity [8-10],. The research program on benzimidazole series [11, 12]. The structures of the synthesized compounds were elucidated by IR, NMR spectra and DFT study.

Benzodiazepines and benzimidazoles have found wide-spread clinical use as inhibitors and drugs, these compounds are synthesized by condensing ortho phenylenediamine with ethylacetoacetate, two readily-available commercial chemicals. The chemical background of these classes of precursor compounds and more recent study report was presented in an earlier [13, 14].

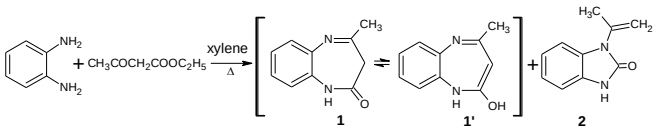
The aim of the present study is to synthesize new benzodiazepine and benzimidazole derivatives which act as antibacterial and antifungal. The prepare compounds were characterized by elemental anaylsis, IR,1H NMR and Mass.

2. EXPERIMENTAL

2.1. Instrumentation

All melting points for the synthesized compounds are (uncorrected) measured on a Gallen-Kamp melting point apparatus with a digital thermometer type MFB-595-010M. The elemental analysis was done on a Perkin-Elmer 240ºC elemental analyzer system GmbH VAR IDEL V2.3 2007 CHNS mode. (Cairo University). IR spectra were measured as KBr discs on a Pye Unicom Sp 1100 infrared spectrophotometer Shimadzu (υ. Cm-1). 1H-NMR spectra were recorded for CDCl3 and DMSO solution on a Varian T-60 NMR spectrometer using TMS as an internal reference (chemical shifts in δ ppm) at 450 MHz (Cairo University). Mass spectra were recorded on a Hp.Ms 5988 spectrometer. Elemental analysis was carried out at the micro analytical of Cairo University. Column chromatography was performed over RP-18 (LiChroprep_ RP-18, 40-63 lm, Merck, 2x50 cm) for separation of the compounds. TLC was performed on both silica gel F254 (Merck) and visualized with Liebermann-Burchard reagent.

2.2. Synthesis of 2,3-dihydro-4-methyl-1H-1,5-benzodiazepine-2-one/or 2,3-dihydro-4-methyl-1H-1,5-benzodiazepine-2-ol and N-isopropenylbenzimidazolone (1, 1', 2).



Khalid et al., 1994; Sultan et al., 1990.

Khodarahmi et al., 2005; Meth-Cohn & Smith 1982.

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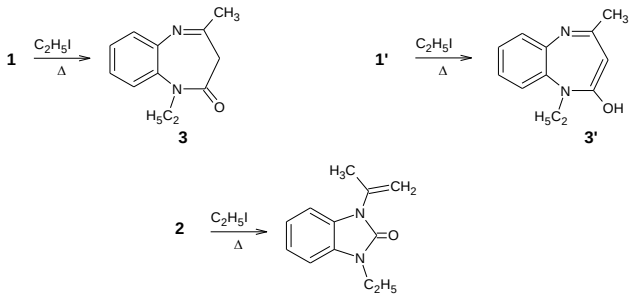
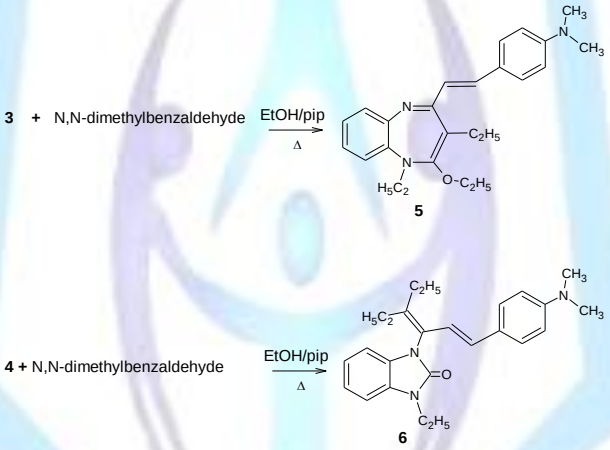
2.3. Synthesis of 1-ethyldiazepinone derivative and 3-ethylimidazolone derivative (3, 3' and 4) :



Meth-Cohn & Smith 1982.

2.4. Synthesis aryldinodiazepinone derivative and arylidinobenzimidazolone derivative (5 and 6):



Compounds **3'** or **4** and N,N-dimethylbenzaldehye in equimolar ratio were dissolved in ethanol and few drops of piperidine as catalyst were added, the reaction mixture was refluxed about 6-8 hours. The formed solid products were separated by filtration and recrystallized from ethanol to yield compounds arylidinobenzodiazepinone derivative (**5**) and arylidinobenzimidazolone derivative (**6**), respectively.

{4-[2-(4-ethoxy-3,5-diethyl-5H-benzo[b][1,4]diazepin-2-yl)-vinyl]-phenyl}-dimethyl-amine (5) :

Colour : Brown crystals.

Yield: 45%.

MP: > 250 °C.

^{1}H NMR(300 MHz, DMSO-d_6) δ 1.5(s, , 6H, 2($N(CH_3)_2$), 1.2(t, J=6.9 Hz, 9H, 3(CH_3)), 2.6(q, J=6.9 Hz, 6H, 3($CH_2 CH_3$)), 6.5(d, 2H, 2CH olefine), 7-8(m, 8H, Ar-H^+).

MS (EI, m/z(%)):389 (M^+, 100).

Anal. Calcd. for $C_{25} H_{31} N_3 O$(389) : C, 77.12 ; H, 8.00 ; N, 10.79 . Found C, 77.10; H, 8.00; N, 10.82.

1-{1-[2-(4-dimethylamino-phenyl)-vinyl]-2-ethyl-but-1-enyl}-3-ethyl-1,3-dihydro-benzoimidazol-2-one (6):

Colour : Brown crystals.

Yield: 80%.

MP: >250 °C.

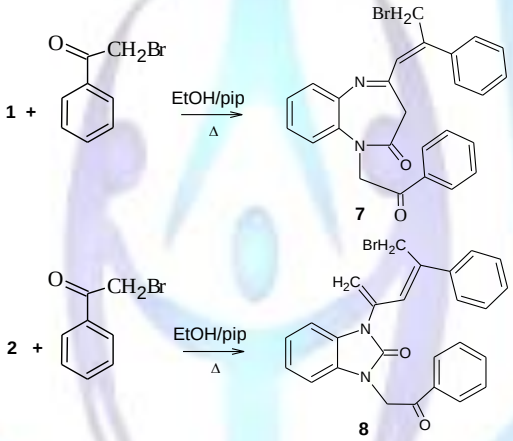
IR : (cm^{-1}), v 1665(`C=O).

^{1}H NMR(300 MHz, DMSO-d_6) δ 1.2(t, J=6.9 Hz, 9H, $3CH_3$), 1.5(s, 6H, $2CH_3$ N), 2.7(q, J=6.9 Hz, 6H, $3CH_2$), 6.6(d, 2H, 2CH olefine), 7-8(m, 8H, Ar-H^+)

MS (EI, m/z(%)):389 (M^+, 100).

Anal. Calcd. For $C_{25}H_{31}N_3O$: C, 77.12 ; H, 7.97 ; N, 10.79 . Found C, 77.16 ; H, 7.95 ; N, 10.74 .

2.5. Synthesis of diphenylbenzdiazepinone derivative and diphenylbenzimidazolone derivative (7 and 8):



A mixture of benzdiazepinone derivative (**1**) (0.01mole) or benzimidazolone derivative (**2**) and phenacylbromide (0.01 mole) were dissolved in 50 mL ethanol and few drops of piperidine as catalyst. The reaction mixture was refluxed for 2 hours. The obtained solid was filtered off, dried and crystallized from ethanol, to yield compounds **7** and **8**, respectively

1-(3-bromo-1-methyl-4-oxo-4-phenyl-but-1-enyl)-3-(2-oxo-2-phenyl-ethyl)-1,3-dihydro-benzoimidazol-2-one (7):

Colour : Pale yellow crystals.

Yield: 25%.

MP: 210-212 °C.

IR : (cm^{-1}), v 1665 (C=O).

^{1}H NMR(300 MHz, DMSO-d_6) δ 3.4(s, 4H overlabed, $2CH_2$ CO), 5.6(s, 1H, CH olifinc), 2.9(s, 2H, CH_2 Br), 7-8(m, 14H, Ar-H^+).

MS (EI, m/z(%)):472 (M^+, 100).

Anal. Calcd. for $C_{26}H_{20}N_2O_2Br$: C, 66.11 ; H, 4.27 ; N, 5.93. Found C, 66.20 ; H, 4.30 ; N, 6.00 .

1-(4-bromo-1-methylene-3-phenyl-but-2-enyl)-3-(2-oxo-2-phenyl-ethyl)-1,3-dihydro-benzoimidazol-2-one (8):

Colour : Yellow crystals.

Yield: 40%.

MP: 218-220 °C.

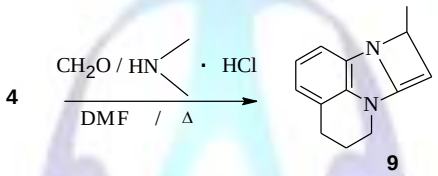
IR : (cm^{-1}), v 1687, 1658, 1665(C=O).

^{1}H NMR(300 MHz, DMSO-d_6) δ 1.8(s, 2H, CH_2Br), 2.2(s, 2H, CH_2 CO), 5.5(s, 1H, CH olifine),6(s, 2H, CH_2 olifine), 7-8(m, 14H, Ar-H^+)

MS (EI, m/z(%)):473 (M^+, 100).

Anal. Calcd. for $C_{26}H_{21}N_2O_2Br$: C, 65.97 ; H, 4.47 ; N, 5.92 . Found: C, 65.92 ; H, 4.45 ; N, 5.85 .

2.6. Synthesis of 8-methyl-5,6,-dihydro-4H,8H-6a,8a-diaza-cyclobuta[a]acenaphthylene(9)



A mixture of benzdiazepinone derivative (**4**) (0.01 mole) and dimethyl amine hydrochloride in dimethylformamide as a solvent. The reaction mixture was refluxed for 2 hours, and evaporated in vacuo. The residue was washed thoroughly with water, filtered off, dried and crystallized from ethanol.

8-methyl-5,6,-dihydro-4H,8H-6a,8a-diaza-cyclobuta[a]acenaphthylene(9)

Colour : White crystals.

Yield: 50%.

MP: 187-189 °C.

IR : (cm^{-1}), v 1600(C=N), 1665(C=O).

^{1}H NMR(300 MHz, DMSO-d_6) δ 1.23 (d, J= 6 Hz, 3H, CH_3 CH sat.), 2.38- 4.70(m, 4H, Lactam-H^+), 1.85-3.35(m, 6H, Trihydropyridine-H^+), 6-7 (m, 3H, Ar-H^+)

MS (EI, m/z(%)):198.27 (M^+, 100).

Anal. Calcd. For $\mathbf{C_{13}H_{14}N_2}$ **:** C, 78.75 **;** H, 7.12 ; N , 14.13 . Found : C , 78.78 ; H , 7.10 ; N , 14.20 .

2.7. DFT STUDIES

To further confirm the structure of the products systematic theoretical treatment of these compounds is performed by using the DFT/B3LYP approach implemented in the Gaussian 09 series of programs [15]. The B3LYP hybrid functional has been used in describing potential energy surfaces (PES). The geometries of compounds (**1**-**9**) are fully optimized using analytic gradients. The harmonic vibrational frequencies of the stationary points of the PES have been calculated at the same level of theory in order to identify the local minima as well as to estimate the corresponding zero-point vibrational energy (ZPE) [16, 17]. For each atom no pseudo potential is used. A 6-311+g(d,p) basis set is employed for each atom. Optimized geometry for compounds (**1**-**9**).

3. RESULTS AND DISCUSSION

We have noted that, in the hot xylene reaction, the variability of yield of rearranged material was directly related to the severity and length of time of reflux. The possibility of a thermally induced transformation of dihydrobenzodiazepinone into isopropenylbenzimidazolone, which this observation suggested, was further enhanced when it was formed that 2,3 –dihydro-4-methyl-1H-1,5-benzodiazopin-2-one, prepared alternately from ethylacetoacetate and ortho phenylene diamine at 185^0 , after 15 minutes, when allowed to continue for 1.5 hours, was partially converted into N-isopropenylbenzimidazolone. Eventually it was found that dihydrobenzodiazepinone was thermally rearranged smoothly into N-isopropenylbenzimidazolone, by dry fusion at 185^0 for 1.5 hours. An equimolar amounts of benzodiazepinone derivative (**1**) and/or benzimidazolone derivative (**2**) and ethyliodide yield to formation of 1-ethylbenzodiazepinone derivative and 3-methylbenzimidazolone derivatives (**3**, **3'** and **4**). The active methyl group in compounds **3**, **3'** and **4** condensed with N, N-dimethylbenzaldehyde in ethanol as solvent under piperidine catalyst yield the corresponding aryldinobenzodiazepinone derivative **5** and arylidinobenzimidazolone derivative **6**. The reaction of benzodiazepinone derivatives and/or benzimidazolone derivatives with phenacylbromide gave diphenylbenzodiazepinone derivative (**7**) and diphenylbenzimidazolone derivative (**8**) respectively. The diaza cyclobuta[a]acenaphthylene (**9**) was prepared through the cycloaddition of diazepine derivative (**1**) p-formaldehyde, dimethylamine hydrochloride and DMF.

The two isomers of diazepine compound $C_{10}H_{12}N_2O$ [2,3-dihydro-4-methyl-1H-1, 5- benzodiazepine-2-one and/or 2,3-dihydro-4-methyl-1H-1, 5- benzodiazepine-2-ol (**1** and **1'** respectively)] were optimized by means of the DFT/B3LYP method and have been identified on the singlet PES. Compound **1** appears to be the most stable isomer, it's calculated to be lower than **1'** by 23.0 kcal mol^{-1}(table 1). Similarly, we optimized the two isomers [ketone (**3**) /enol (**3'**) form] of 1-ethyldiazepine $C_{12}H_{14}N_2O$. Also, they have been identified on the singlet PES. the ketone form **3** are above the enol form **3'** by 26. 4 Kcal mol^{-1} (table 1). Is known experimentally that the ketone form is more stable than enol form isomer. This is due to the strength of the double bond between carbon and oxygen [18]. Our theoretical results are in a good agreement with the experimental data. Furthermore we have limited our studies only for the ketone form. The calculated thermodynamic parameters of compounds **1**,**1'**,**3** and **3'** were listed in table 2.

In the absence of an X-ray determination, a comparison between IR experimental data and theoretical IR spectra can be performed. We have calculated the frequencies of vibration of our compounds in the harmonic approximation. The values of the Experimental and theoretical vibrational frequencies (cm^{-1}) and infrared intensities (km mol^{-1}) of compounds **1 – 9** are listed in the table 3. We know that DFT/B3LYP method overestimate the vibrational frequencies. These discrepancies are corrected either by computing anharmonic corrections explicitly or by introducing scaled field or directly scaling the calculated frequencies with the proper scale factor[19]. In this study, we have used scaling factor of 0.9663, [20]. After scaling with the scaling factor, the deviation from the experimental is less than 4%; consequently the proposed structures were supported by theoretical calculations.

The biological activity of 2,3-dihydro-4-methyl-1H-1,5-benzodiazepine and N-isopropenylbenzimidazolone derivatives were tested for antibacterial and fungicidal activity. Gram-negative bacterial(Serratia sp.), Gram positive bacteria(Bacillus cereus), as well as the fungus(Fusarium oxysporum) were used for this purpose. This biological assay was determined according to the filter paper methods. Assay plates were incubated at 30^0 C for one day for the bacteria and three dayes for the fungus and 3% the concentration of the samples in the dimethylformamide as a solvent. The results are shown in table 4.

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Table 1: DFT/B3LYP relative energies (kcal mol^{-1}) of compounds 1, 1' and 3, 3'.

	1	1'	3	3'
ΔE	0.0	23.0	0.0	26.4
ΔE+ZPE	0.0	22.5	0.0	25.7
ΔH°	0.0	22.8	0.0	26.0
ΔG°	0.0	22.3	0.0	26.0

Table 2. The calculated thermodynamic parameters of compounds 1,1', 3 and 3' employing B3LYP method with 6-311+g(d,p) basis set.

Thermodynamic parameters	1	1'	3	3'
Total energy (Thermal) E_{total} (kcal/mol)	121.953	121.669	159.012	158.530
Heat capacity at const. volume, C_v (cal/mol.K)	42.091	43.569	52.133	53.781
Entropy, S (cal/mol.K)	99.760	101.341	116.098	115.825
Vibrational energy, E_{vib}(kcal/mol)	120.176	119.892	157.235	156.752
Zero-point vibrational energy, E^o (kcal/mol)	115.36911	114.84930	150.62687	149.86914
Rotational constant (GHz)				
X	1.45215	1.28950	0.82422	0.70819
Y	0.67090	0.69618	0.59014	0.64828
Z	0.48135	0.46712	0.41269	0.37049
Dipole moment (Debye)				
μ_x	-1.8327	-1.8197	2.0083	-2.1002
μ_y	-0.8394	2.3613	-0.3973	1.8441
μ_z	1.1481	-0.8152	-0.4791	-0.4356
μ_{Total}	2.3198	3.0906	2.1026	2.8286
Total energy (a.u.)	-571.9844	-571.9476	-650.6239	-650.5818

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Table 3. Experimental and theoretical vibrational frequencies (cm^{-1}) and infrared intensities ($km\ mol^{-1}$) of compounds 1-9.

Compounds	Functional group	Experimental		Theoretical		
		Frequencies	Intensities*	Unscaled Freq.	Scaled Freq.	Intensities
1	CO(azepine)	1655	vs	1761	1702	600
	NH	3370	w	3584	3463	35
1'	OH	3550	w	3822	3693	75
	NH	3350	w	3598	3477	40
2	CO	1675	vs	1802	1741	864
	NH	3450	w	3671	3547	80
3	CO	1661	s	1730	1672	375
3'	OH	3540	w	3812	3684	58
4	CO (imidazole)	1665	vs	1771	1711	725
6	CO (imidazole)	1665	vs	1771	1711	588
7	CO (imidazole)	1652	vs	1758	1699	595
	$CO(CH_2-CO)$	1678	s	1766	1706	173
	CO(CHBr-CO)	1658	s	1745	1686	196
8	CO (imidazole)	1665	vs	1774	1714	610
	$CO(CH_2-CO)$	1650	s	1761	1702	264

*w, weak; s , strong; vs, very strong.

Table 4 : Antibacterial and Fungicidal Activity of the Tested Compounds.

Compound	Serratia sp.	Bacillus cereus	Fusarium oxysporum
5	**+**	**+++**	**++**
6	**N**	**++**	**+**
7	**+**	**+++**	**++**
8	**N**	**++**	**+**
9	**N**	**++**	**+**

N = No effect .

Diameter of the zone of inhibition : + = till 0.5 Cm; ++ = till 1.0 Cm ; +++ = till 2.0 Cm . The solvent was DMF . Concentration of the sample = 3% .

CONCLUSION

Benzodiazepinones and Benzimidazolones have found wide-spread clinical use as inhibitors and drugs, these compounds are synthesized by condensing ortho phenylene diamine with ethylacetoacetate, two readily-available commercial chemicals.

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