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Synthesis of benzimidazol-2-thiones from dimedone : An unexpected cyclisation into a five-membered ring

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Abstract: When enaminones **9** obtained from dimedone were used instead of furanone **3** and pyranone **4** in the reaction with carbon disulfide in presence of pyridine, a crystalline product was formed whose spectral data and X-Ray structure were inconsistent with the benzodiazepine-thiones **5-6** but agreed with the structure of benzodimidazol-2-thione **11** which is expected to possess a notable pharmacological activities. Theoretical calculations, with DFT/B3LYP method, have been carried out to rationalize the experimental results.

Keywords: Dimedone; enaminones; benzimidazol-thiones; benzodiazepines; carbon disulfide.

1. Introduction

Benzimidazole–derivatives belong to a crucial structural motif that is seen in many pharmaceutically and biologically interesting molecules. They have been intensively used in medicinal chemistry as drugs such as antihistaminic[1], antiulcerative[2], antihelmentic[3], and antipsychotic.[4] Some of their analogous show an array of biological activities, including non-nucleoside HIV-1 reverse transcriptase inhibitors[5] and they are selective inhibitors of

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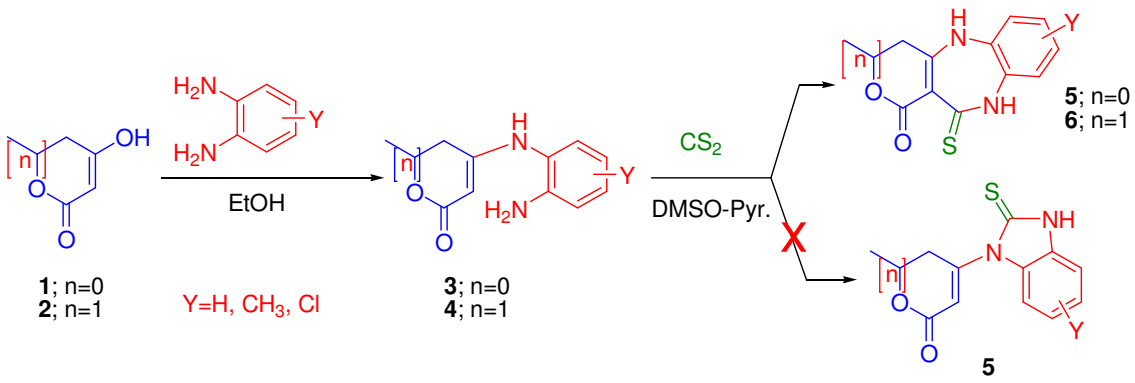
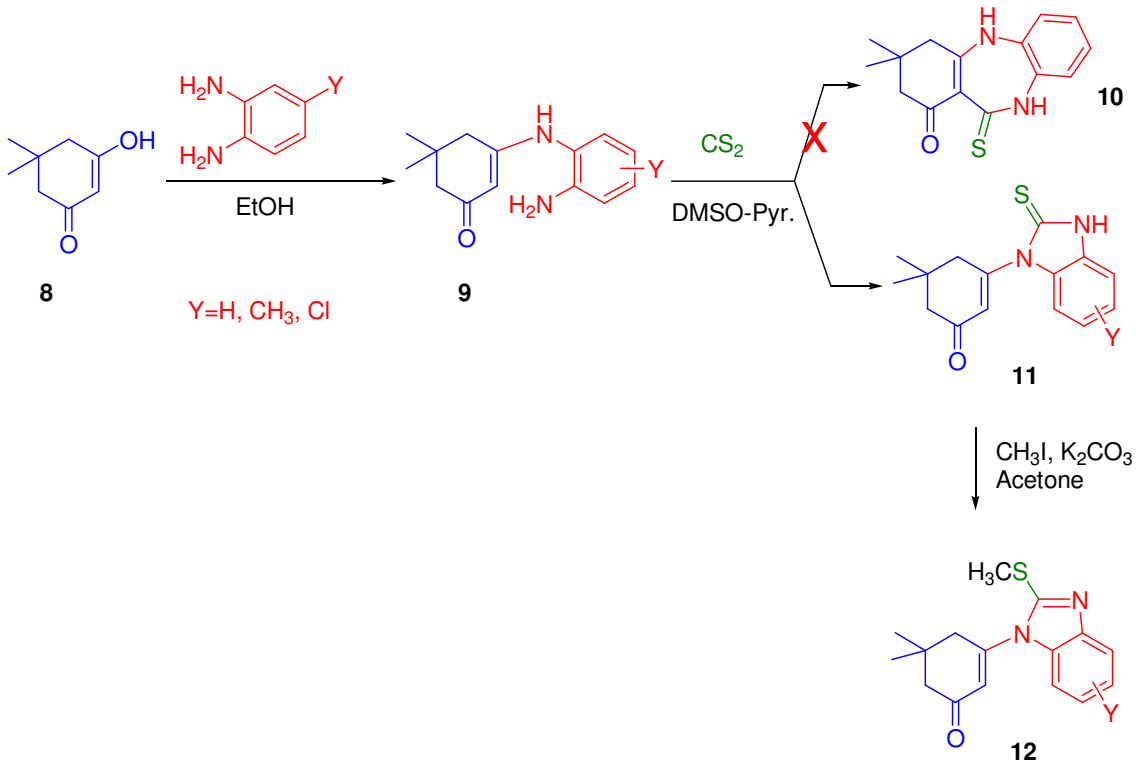
cyclooxygenase-Cox-2.[6] Several benzimidazoles have been reported as antiviral[7], anticoagulant[8], anti-inflammatory[9], antibacterial[10] and anticancer agents.[11] Moreover benzimidazol-thione and alkyl-thio substituted benzimidazoles systems have been tested as potential antimicrobial[12], antibacterial[13] and antitumor agents.[14] Therefore, the widespread importance of benzimidazole structure has prompted extensive studies for practical synthetic methods to access to this class of heterocycles.[15-18]

The preparation and investigation of bioactive nitrogen, oxygen and sulfur containing heterocycles is one of our ongoing projects. We have already developed some procedures to gain access to diverse structures as benzodiazepines[19], benzimidazoles, benzimidazolones[20] and oxazinones.[21] Recently, our research team[22] has described the reaction products from enaminones **3** or **4** derived from furanone **1** and pyrone **2** respectively, with carbon disulfide. In this case, corresponding seven membered benzodiazepine **5** and **6** were exclusively isolated and characterised (Scheme 1)



Scheme 1. Intramolecular cyclisations of enaminones **3** and **4**.

These results prompted us to extend this methodology for a similar synthesis of enaminones **9** starting from 5,5-dimethyl cyclohexan-1,3-dione (dimedone) **8** as precursor, and examined their transformation into benzodiazepin-2-thione **10**. Surprisingly, during this work, we found unexpected cyclisation into a five membered ring benzimidazol-2-thiones **11** instead of benzodiazepin- thiones derivatives (Scheme 2).



Scheme 2. Intramolecular cyclisations of enaminones 9.

In this paper, we report the synthesis and characterisations of this five membered ring benzimidazol -2-thiones **11**.

Theoretical study of the main intermediate has been realized, in order to explain the N-selective reaction. In continuation of our work, we also studied the alkylation reaction of compounds **11** (Table 1).

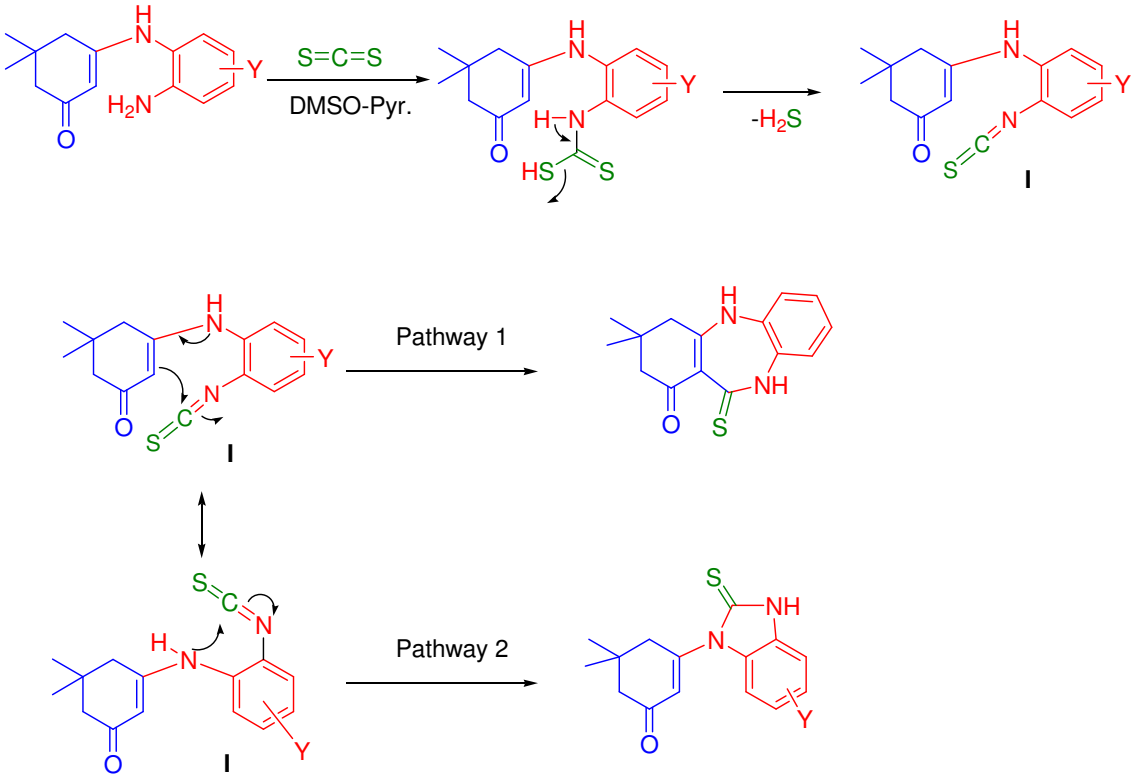
Table 1. Physical data of **11a**-**11c** and **12a**-**12c**

Compounds	Y	yield [%]	m.p. (°C)	Time (h)
11a	H	74	200-202	24
11b	CH_3	80	206-208	16
11c	Cl	76	218-220	16
12a	H	60	192-194	2
12b	CH_3	70	198-200	2
12c	Cl	78	213-215	2

2. Results and Discussion

In the first step, key intermediates **9** were prepared according to known procedure[22] by treatment of **8** with o-phenylene diamine derivatives in ethanol. Taking into account the data of previous work we conducted the reaction of the resulting enaminones **9** with carbon disulfide in dimethylsulfoxide in the presence of pyridine as catalyst (scheme-2). Only one type of product was obtained, namely benzimidazol-2-thione **11** having a dimedone moiety at the N_a nitrogen. As shown in scheme-3, formation of compounds **11** can be explained assuming that the –N=C=S group of isothiocyanate intermediate **I**, undergoes selectively nucleophilic attack by the nitrogen of secondary amine (pathway 1), not by a double bond of the dimedone moiety that would furnish benzodiadepine-thione system (pathway 2).

It should be noted that replacing the starting precursors **1** and **2** with dimedone **8** changed the course of cyclisation reaction of **I**. It seems that the presence of the keto group $–CH_2-C=O$ in the intermediate **I** instead of lactone –O-C =O in alkaline medium can decrease the nucleophility of C_2 carbon of the adjacent double bond favouring the formation of five membered cycle over the seven- membered ring. [23]



Scheme 3. Postulated mechanism for the formation of benzimidazole compounds 11.

In order to access to a best comprehensive explanation on the mechanism of this reaction; we carried out a quantum-chemical calculations on cyclization of intermediate **I** to determine the most nucleophilic of the two previous sites.

The structural assignments of **11a-c** were made on the basis of elemental analysis ^1H, ^{13}CNMR combining with DEPT and mass spectral data. Moreover the structure was unambiguously confirmed by X-ray diffraction analysis of single crystal of **11b**, ORTEP drawing of the molecular structure as well as selected bond lengths are displayed in Figure-1.[24]

The ^{1}H NMR spectrum of **11** exhibited for all compounds a signal at 109.4 – 109.8 ppm assigned to the tertiary carbon in the dimedone moiety at position 2. On the other hand, the vinylic proton at position 2 was clearly visible in the ^{1}H NMR, and its upfield shift of the resonance from 4.6 ppm to 6.2 ppm provided evidence of cyclisation occurred through the nitrogen over the double bond. Moreover, the spectra contain a signal at higher frequencies region 13.0 - 13.2 ppm typical of the NH group in the benzimidazol-thione ring. Furthermore, no signals at 9 ppm and 11 ppm corresponding to the two NH groups of compound **5-6** were found. In addition, ^{13}C NMR spectra revealed in particular a signal at 167.1 -168.3 ppm confirming the presence of the thiocarbonyl function of the five membered cycles **11**.

Compouds **11** were readily alkylated with methyl iodide to afford the desired S-methylated derivatives **12a-c** in good yields. In the NMR spectra of compounds **12a-c** an additional signal appear around 2.7 ppm(^{1}H NMR) and 14.6 ppm (^{13}C NMR) corresponding to S-CH_3 wile signals belonging to –NH and C=S groups disappeared.

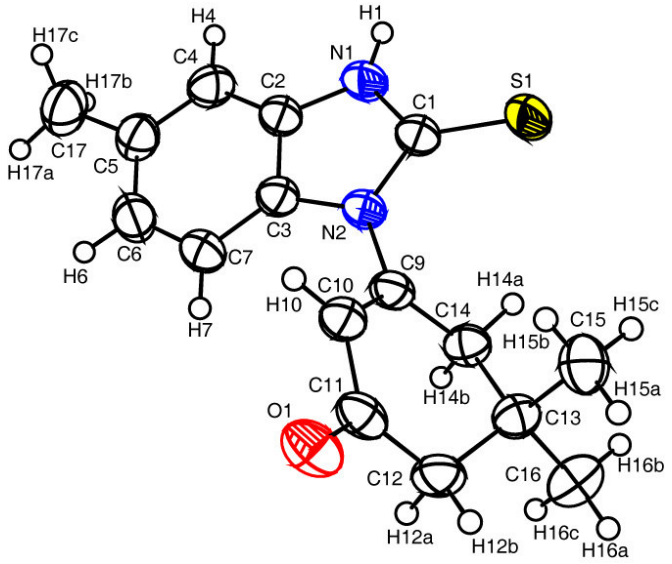
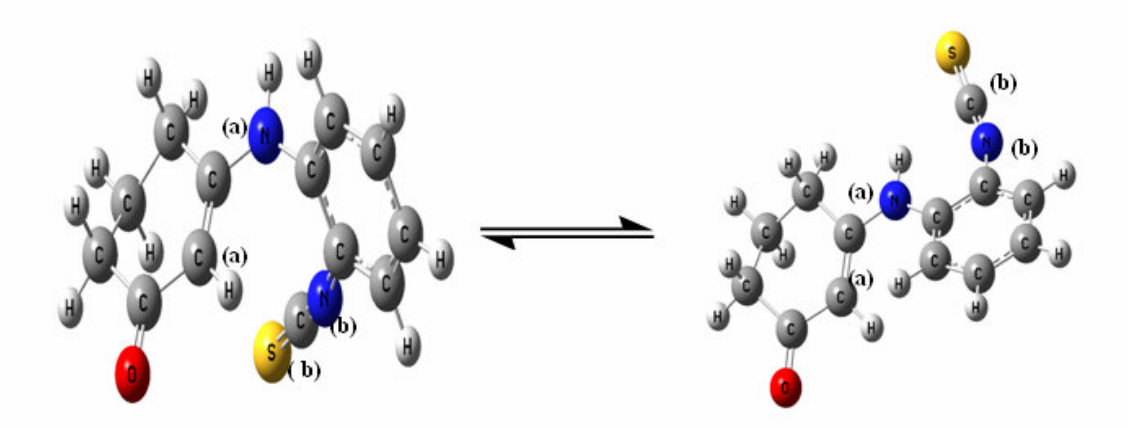


Figure 1. The molecular structure of compound **11b**: Selected bond lengths (Å) C1-S1: 1.672(2); N1-C1: 1.355(3); N1-C2: 1.387(3); N2-C1: 1.379(3); N2-C3: 1.406(3); N2-C9: 1.428(3); C9-C10: 1.331(3); C9-C14: 1.495(3); C10-C11: 1.468(3); C11-C12: 1.499(3); C12-C13: 1.532(3); C13-C14: 1.527(3); O1-C11: 1.219(3).

Computational study; A qualitative theoretical study was performed at the DFT/B3LYP (23) level of theory, using 3-21G** basis set and GAUSSIAN 98-03 suite of programme.[25] The optimized structures of all the species like products and intermediates have been generate. The main reaction is an intramolecular cyclisation one, with two pathways which seem possible but only one has been chosen. In this matter, we considerate the intermediate **I** reactivity, using Mulliken[26] and NPA[27] atomic charges. However, the sites involved in this reaction are hard and the atomic charges should be elected as better condensed hard-hard interaction Descriptors.[28-30]

The intramolecular cyclisation could be lead to the product **11**, via the two intermediates conformations, according scheme 4.



Scheme 4. Intermediate conformations of product 11

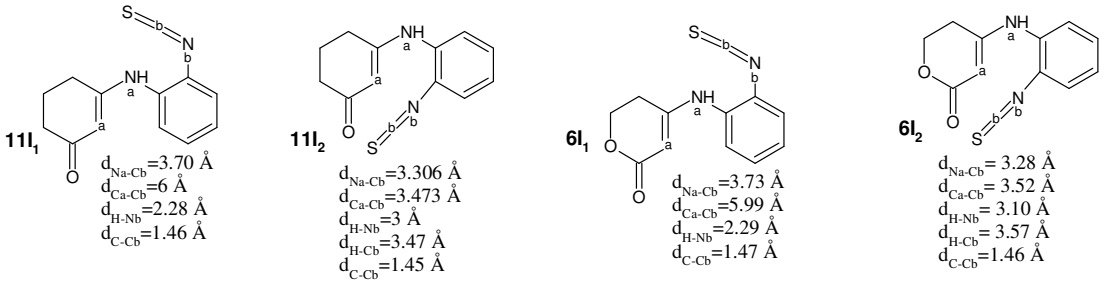
We noted that in **$11I_1$** the distance C_b-N_a is shorter than C_b-C_a. This conformation is the precursor for the observed product **11**.

We have considered two different conformations, noted **$11I_1$** and **$11I_2$**, associated to rotation around the Na- phenyl bond, in intermediate **11I** (case CH_2-C=O). To compare with case O-C=O, we study the intermediate **6I** which leads to product **6**. Scheme 4, presents their structures with selected interatomic distances.

The table 2 presents the computed energies, and atomic charges of selected atoms, of the structures intermediates. Conformers **$11I_1$** and **$11I_2$** are the most stable ones. In all the conformers, the N_a atom has the most important negative charge, it is the privileged nucleophilic centre and the C_b carbon is the electrophilic one, not only for **$11I_1$** and **$11I_2$** but also for **$6I_1$** and **$6I_2$**.

Table 2. Atomic charges of selected atoms in intermediates (**$11I_1$**, **$11I_2$**, **$6I_1$** and **$6I_2$**).

Energy (Hartree)		Atoms	N_a	C_a	C_b	H-N_a	H-C_a
$11I_1$	-1079.953077	Mulliken	-0.7682	-0.1746	0.3033	0.2420	0.1334
		NPA	-0.5710	-0.4125	0.1817	0.4202	0.2542
$11I_2$	-1079.947565	Mulliken	-0.7301	-0.1774	0.3300	0.2334	0.1276
		NPA	-0.6151	-0.4226	0.2030	0.4174	0.2530
$6I_1$	-1115.6532061	Mulliken	-0.7313	-0.2154	0.3271	0.2354	0.1372
		NPA	-0.6155	-0.4601	0.2016	0.4195	0.2620
$6I_2$	-1115.6485558	Mulliken	-0.771	-0.2119	0.3030	0.2431	0.1414
		NPA	-0.5708	-0.4494	0.1829	0.4217	0.2615



Scheme 5. Structures of **$11I_1$**, **$11I_2$**, **$6I_1$** and **$6I_2$**, and selected interatomic distances an Å.

In all the intermediates, charges of the implied atoms are practically the same ones, but the C_a atom in the **$6I_2$** becomes more nucleophilic than in **$11I_2$**. In the same way the N_a atom in the **$11I_1$** becomes more nucleophilic than in **$6I_1$**. However, it is possible that the reaction leads to the **6** product, where the C_a attack is supporting by the proton transfer (from C_a to N_b). In this case, the reaction will be kinetically favored because the products given by the N_a attack are the most thermodynamically stable ones, that it shows in Table 2.

So this selectivity of the attack is due of the difference of the degree of involved proton transfer (in the transition states) occuring in intramolecular cyclisation.

In summary, we have found that when enaminones **9** obtained from dimedone **8** were used in the reaction with carbon disulfide in presence of pyridine, a five membered ring cyclisation take place yielding benzidimidazol-2-thione **11** instead of benzodiazepine-thiones **10**. The present results indicate that the intramolecular cyclisation prefers the N_a site as nucleophilic centre leading to benzimidazoles **11** in the case of enaminone **9** and the C_a one giving benzodiazepines **6** in the case enaminones **3-4**. The computational calculation have explained the mechanism formation of the title products.

3. Experimental

(Melting points were measured on a Stuart Scientific SMP1 melting point apparatus and were uncorrected. FTIR were taken in KBr pellets on a Perkin-Elmer Paragon 1000 PC spectrometer. The ^{1}H NMR spectra (400 MHz) and ^{13}C NMR (100.6 MHz) were run on a Bruker Avance II spectrometer in DMSO-d6 using tetramethyl silane as internal standard. The positive-mode electrospray ionisation (ESI) mass spectra were recorded on a Perkin–Elmer SCIEX API 300 spectrometer. The elemental analysis data were obtained on a Thermo Electron Flash EA 1112. Chemicals were purchased from Aldrich and Acros Organics and used without further purification. X-Ray data were collected at 293 K on single crystal mounted on a Nonius four circle diffractometer equipped with a CCD camera and a graphite monochromated MoK_α radiation source (λ = 0.71073 Å), from the Centre de Diffractométrie (CDFIX), Université de Rennes 1, France. Complete crystal structure results as a CIF file including bond lengths, angles, and atomic coordinates are deposited in the Cambridge Crystallographic Data Center.[23LO]

3.1. General procedure for the preparation of compounds 11.

Appropriate enaminones **9** (1 mmol, 1 eq) was dissolved in a minimum of dimethylsulfoxide, then pyridine (2 mL) and carbon disulfide (20 mL) were successively added, and the mixture was stirred at room temperature for 24 h the progress of the reaction was monitored by TLC. The reaction was

poured into cold water (40 mL), the insoluble solid which separated was filtered, washed well with cold water. The crude product were then recrystallized from ethanol to give **11a-c** as yellow crystals

5,5-dimethyl-3-(2-thioxo-2,3-dihydro-benzimidazol-1-yl)cyclohex-2-en-1-one (11a): Yield: 74 %; IR (film, cm^{-1}) 1211 (C=S), 1630 (C=O); ^{1}H NMR (400 MHz, DMSO-d_6) (δ/ppm) 1.14 (s, 6H), 2.42 (s, 2H), 2.82 (s, 2H), 6.22 (s, 1H), 7.23 -7.29 (m, 4H), 13.08 (s, 1H); ^{13}C NMR (100.6 MHz, DMSO-d_6) (δ/ppm) 27.7, 33.5, 41.1, 50.5, 109.8, 110.0, 122.7, 123.6, 127.3, 131.5, 132.1, 153.7, 167.4, 198.5. MS (ESI) m/z 273.0 ([M+H] $^+$, 100 %). Anal. Calcd. for $C_{15}H_{16}N_2OS$: C, 66.15; H, 5.92; N, 10.29; S, 11.77. Found: C, 65.98; H, 5 .71; N, 10.15; S, 11.47.

5,5-dimethyl-3-(5-methyl-2-thioxo-2,3-dihydro-Benzimidazol-1-yl)cyclohex-2-en-1-one(11b): Yield: 80 %; IR (film, cm^{-1}) 1214 (C=S), 1632 (C=O); ^{1}H NMR (400 MHz , DMSO-d_6) (δ/ppm) 1.13 (s, 6H), 2.37 (s, 3H), 2.41 (s, 2H), 2.82 (s, 2H), 6.19 (s, 1H) , 7.01-7.15 (m, 3H), 12.99 (s, 1H); ^{13}C NMR (100.6 MHz, DMSO- d_6) (δ/ppm) 20.8, 27.6, 33.5, 41.1, 50.5, 109.4, 110.0, 123.5, 126.9, 130.1, 131.6, 133.2, 153.8, 167.1, 198.5. MS (ESI) m/z 287.0 ([M+H]$^+$, 100 %). Anal. Calcd. for $C_{16}H_{18}N_2OS$: C, 67.10; H, 6.33; N, 9.78; S, 11.20. Found: C, 66.88; H, 6.09; N, 9.61; S, 10.80.

3-(5-chloro-2-thioxo-2,3-dihydro-Benzimidazol-1-yl)-5,5-dimethylcyclohex-2-en-1-one (11c): Yield: 76 %; IR (film, cm^{-1}) 1215 (C=S), 1636 (C=O). ^{1}H NMR (400 MHz, DMSO-d_6) (δ/ppm) 1.13 (s, 6H), 2.41 (s, 2H), 2.79 (s, 2H), 6.22 (s, 1H), 7.23-7.28 (m, 3H), 13.20 (s, 1H); ^{13}C NMR (100.6 MHz, DMSO-d_6) (δ/ppm) 27.7, 33.4, 41.0, 50.5, 109.5, 111.0, 122.5, 127.4, 127.9, 131.1, 132.41, 153.3, 168.3, 198.5. MS (ESI) m/z 307.5 ([M+H]$^+$, 100 %). Anal. calcd. for $C_{15}H_{15}ClN_2OS$: C, 58,72; H, 4.93 ; N, 9.13 ; S , 10.45. Found: C, 58.59; H, 4.75; N, 8.88; S, 10.12.

3.2. General procedure for the preparation of compounds 12.

To a solution of **11** (2 mmol, 1 eq) in acetone (20mL) containing potassium carbonate (4 mmol, 2eq) and tetrabutylammonium bromide (30 mg) was added methyl iodide (2.2 mmol, 1.1 eq) and the mixture was stirred at room temperature for 2 hours .The inorganic solid was filtered and washed with acetone The filtrate was concentrated to dryness in vacuum, water (3x25 mL) was added and extracted with chloroform (3×20 mL). After evaporation under reduced pressure ethanol (5 mL), was added, the formed precipitate was collected, washed with water, and recrystallized from ethanol to afford compounds **10a-c** as colourless crystals.

5,5-dimethyl-3-[2-(methylthio)-1H-Benzimidazol-1-yl]cyclohex-2-en-1-one (12a): Yield: 60 %; mp; IR (film, cm^{-1}) 1624(C=O); ^{1}H NMR (400 MHz, DMSO-d_6) (δ/ppm) 1.14 (s, 6H), 2.43 (s, 2H), 2.72 (s, 3H), 2.78 (s, 2H), 6.23 (s, 1H), 7.22-7.62 (m, 4H); ^{13}C NMR (100.6 MHz, DMSO-d_6) (δ/ppm) 14.6, 27.3, 33.8, 41.6, 50.3, 110.5, 117.9, 122.5, 122.6, 124.6, 135.5, 143.8, 151.6, 152.5, 198.2. MS (ESI) m/z 287.5 ([M+H]$^+$, 100 %). Anal. Calcd. for $C_{16}H_{18}N_2OS$: C, 67.10; H, 6.33; N, 9.78; S, 11.20. Found: C, 67.40; H, 6.12; N, 9.56; S, 11.58.

5,5-dimethyl-3-[5-methyl-2-(methythio)-1H-Benzimidazol-1-yl]cyclohex-2-en-1-one (12b): Yield: 70 %; IR (film, cm^{-1}) 1631 (C=O); ^{1}H NMR (400 MHz, DMSO-d_6) (δ/ppm) 1.14 (s, 6H), 2.41 (s, 3H), 2.43 (s, 2H), 2.72 (s, 3H), 2.78 (s, 2H), 6.21 (s, 1H), 7.05-7.41 (m, 3H); ^{13}C NMR (100.6 MHz, DMSO-d_6) (δ/ppm) 14.6, 20.9, 27.3, 33.9, 41.6, 50.3, 110.2, 117.8, 123.6, 124.0, 131.8, 133.2, 143.6, 151.4, 152.6, 198.1. MS (ESI) m/z 301.5 ([M+H]$^+$, 100%). Anal. Calcd. for. $C_{17}H_{20}N_2OS$: C, 67.97; H, 6.71; N, 9.32; S, 10.67. Found: C, 67.73; H, 6.46; N, 9.72; S, 11.07.

3-[5-chloro-2-(methylthio)-1H-Benzimidazol-1-yl]-5,5-dimethylcyclohex-2-en-1-one (12c): Yield: 78 %; IR (film, cm^{-1}) 1632 (C=O); ^{1}H NMR (400 MHz, DMSO-d_6) (δ/ppm) 1.14 (s, 6H), 2.43 (s, 2H),

2.73 (s, 3H), 2.76 (s, 2H), 6.26 (s, 1H), 7.24-7.70 (m, 3H); ^{13}C NMR (100.6 MHZ, DMSO-d_6) (δ/ppm) 14.6, 27.3, 33.8, 41.5, 50.2, 111.7, 117.4, 122.4, 125.1, 127.0, 134.1, 144.2, 152.1, 153.6, 198.2. MS (ESI) m/z 321.0 ([M+H]$^+$, 100%). Anal. Calcd. for. $C_{16}H_{17}ClN_2OS$: C, 59.9; H, 5.34; N, 8.73; S, 9.99. Found: C, 60.18; H, 5.19; N, 9.10; S, 10.37.

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