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Utility of Benzimidazoles in Synthesis of New Bases of Nucleoside Moieties, and as Antioxidant in Lubricant Oils

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Abstract

The treatment of 4-(4-Chloro-3-methylphenyl)-4-oxobut-2-enoic acid with benzimidazole, and 2-mercapto benzimidazole afforded aza- and thia-Michael adduct as unnatural α-amino acid 1 and α-thiaacid 6 respectively. Micheal adducts 1 and 6 are used to synthesize some antioxidant heterocycles. TAN study can be confirmed, the fused heterocycles has a lower antioxidant expt that contain sulfur atom. Quantum chemical studies of 2-mercaptobezimidazole, and its amide long chain, confirmed that N-butyl-S-benzimidazol-2-ylthioglycolate at 400 ppm was more effective antioxidant heterocycles.

Keywords: 4-Aryl-4-oxobut-2-enoic acid; Unnatural amino acid; Antioxidant heterocycle; 2-marcapto/1-furo-4-yl/1,3-hiazolo/1,3-thiazinobenzimidazole; 4-benzimidazo-1-ylpyridazine/oxazine; Triazinobenzimidazole

Introduction

Amino acids have proven to play a significant role in the synthesis of novel drug candidate with the use of non-proteinogenic and unnatural amino acids [1-8]. Cytotoxic activity of eight thiazolobenzimidazole derivatives on sensitive HL60 and multidrug-resistant (MDR) (HL60R) leukemia cell lines can be reported [9]. Benzimidazoles have been identified as inhibitors of the microsomal NADPH-dependent lipid peroxidation (LP) levels [10] and anti-proliferative effect to human colorectal cancer cell line HT-29, breast cancer cells MDA-MB-231 [11]. From this point of view the authors try to investigate the reaction of 4-(4-chloro-3-methylpheny) l-4-oxobut-2-enoic acid with benzimidazole, under aza-Michael reaction conditions to afford unnatural α-amino acid derivative. And so, to synthesize some heterocyclic compounds carrying benzimidazole moiety aiming at obtaining some interesting antioxidant materials as additives in lubricant oils.

Experimental Analysis

All melting points are uncorrected. Elemental analyses were carried out at the Micro analytical Center, National Research Center, Cairo, Egypt. By Elementar Viro El Microanalysis IR spectra (KBr) were recorded on infrared spectrometer FT-IR DOMEM Hartman Braun, Model: MBB 157, Canada and ^{1}H-NMR spectra recorded in DMSO-d6 on a Varian Gemini spectrophotometer at 200 MHz (Germany 1999) using TMS as internal standard. The mass spectra were recorded on Shimadzu GCMS-QP-1000 EX mass spectrometer at 70 eV using the electron ionization technique. Homogeneity of all compounds synthesized was checked by TLC.

3(4-chloro-3-methylphenyl)-2-(1H-benzimidazol-1-yl)-4-oxobutanoic acid (1)

A solution of acid 1 (3 g; 0.01 mol) and benzimidazole (1.38 g; 0.01 mol) in 30 ml ethanol and 4 drops piperidine was refluxed for 3 h. The reaction mixture was allowed to cool and the crude product was washed by petroleum ether (b.p 40- 60°C), and then, crystallized from dioxane. Yield 78%, m.p. 154-156°C, IR spectrum υCO(1732-1685) cm^{-1} for carboxylic and ketone groups and 3437-3360, 3175 cm^{-1} attributable to υOH. The ^{1}HNMR spectrum DMSO-d6 for revealed at δ 2.1(s, 1H,CH3), three protons for ABX spin system 2.7-2.9 (2dd, CH_2-C=O, dia stereo topic protons), 3.1-3.3 (dd,CH-CO, stereogenic methine proton), 7.2-7.5 (m, 8ArH aromatic protons), 9.2 (s,1H, acidic proton which exchanged in D_2O. Elemental anal. Found % C 56.55, % H 3.28, % N 7.62, % Cl 9.53, $C_{18}H_{15}N_2O_3Cl$(342.5), Calc. % C 56.943, % H 3.28, % N 7.69, % Cl 9.80 (Figure 1).

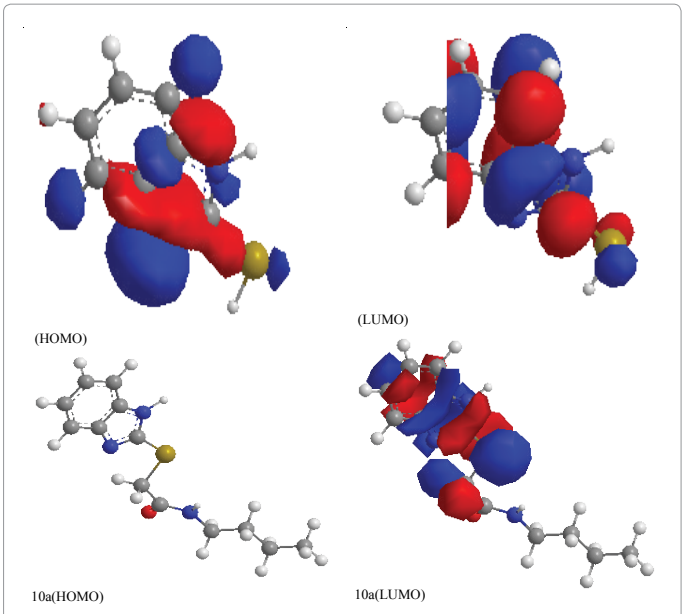

Figure 1: The frontier molecule orbital density distributions of (2-mercaptobenzimidazole) $\Delta E=E_{HOMO}-E_{LOMO}$=9.885 eV.

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5-(4-chloro-3-methylphenyl)-3 (1H-benzimidazol-1-yl)-2- (3H) furanone (2)

A mixture of 1 (3.73 g; 0.01 mol) and acetic anhydride (9.4 mL, 0.1 mol) and then refluxed on water bath for 1h. The reaction mixture was allowed to cool and then pour into ice-H_2O and the separated product was filtered, dried and were re-crystallized from toluene. Yield 82%, m.p. 218-220°C, IR spectrum υCO (lactonic) 1780 cm^{-1}. EIMS m/z: 324.5, 15% (M+) and m/z: 140(2-phenyl furan molecular radical entity as a base peak. The ^{1}HNMR spectrum in DMSO-d6 exhibits Signals at δ 2.1(s, 1H, CH3), 2.7(dd, 1H, the methine proton), 7.0-7.9 (m, 8H, 7ArH and 1H furanone moiety). Elemental anal. Found %C 58.86, %H 3.15, %N 8.09, %Cl 10.53, $C_{18}H_{13}N_2O_2Cl$ (324.5), Calc. %C 58.95, %H 3.17, %N 8.09, %Cl 10.52 (Figure 2).

6-(4-chloro-3-methylphenyl)4-(benzimidazol-1-yl)2,3,4,5-tetrahydro-3(2H)pyridazinone (3)

A solution of 1 and/ or 2 (0.01 mol) in ethanol (40 mL) was treated with hydrazine hydrate 98% (1.5 mL; 0.04 mol) and then refluxed for 3 h. The solid that separated after concentration and cooling was re-crystallized. Yield 77%, m.p. 196-198°C. IR spectrum υCO) 1683 cm^{-1} ^{1}HNMR spectrum DMSO-d6 of revealed singlet at δ 2.1(s, 1H, CH_3), 2.8-3.0 (2 dd,1Ha and 1Hb methylene protons), 3,8-4.2(dd, CH-CO, methine proto), 7.2-7.8 (m, 8 ArH), 11.2 (s,1H, pyridazinone proton), EIMS *m/z*: 338.56% (M^+) and 3410.5%(M^++2), *m/z*: 248 (M^+-benzimidazolyl radical) as a base peak. Elemental anal. Found %C 56.66, %H 3.57, %N 15.56, %Cl 9.67, $C_{18}H_{15}N_4OCl$ (338.5), Calc. %C 56.66, %H 3.61, %N 15.55, %Cl 9.72 (Figure 3).

4-(3,4-dichlorophenyl)-1-phenyl-4-(1H-benzo[d]imidazolo[1,2-c]1,2,4-triazin -3-one (4)

A mixture of 2 (3.7 g; 0.01 mol) and phenyl hydrazine hydrate (1 mL, 0.01 mol) in boiling ethanol and then refluxed on water bath for 2h. The reaction mixture was allowed to cool and then pour into ice-H2O and the separated product was filtered, dried and were re-crystallized from ethylacetate. Yield 64%, m.p. 152-154°C, IR spectrum υ CO 1672 cm^{-1} The ^{1}HNMR spectrum DMSO-d6 revealed δ 2.1(s, 1H, CH3), 3.0-3.3 (2 dd,1Ha and 1Hb methylene protons, CH_2-C=N, J=15.6, J=7.1 diastereotopic protons), 3,8-4.2(dd, CH-CO, methine proton), 6.2(bs,3H, 2NH and CH protons) , 7.2-7.8 (m,12H,ArH). Elemental anal. Found %C 560.86, %H 3.97, %N 12.56, %Cl 8.67, $C_{24}H_{21}N_4O_2Cl$ (433.5), Calc. %C 60.96, %H3.91, %N 12.55, %Cl 8.72 (Figure 4).

6-(4-chloro-3-methylphenyl)-4(benzimidazol-1-yl2,3,4,5 tetrahydro 3(2H) oxazinone (5)

A solution of 1 (0.01 mol) was treated with hydroxyl amine

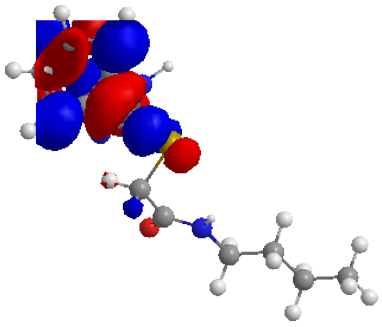


Figure 2: The frontier molecule orbital density distributions of (10a) ΔE=E $_{HOMO}$-E_{LOMO}=9.347 eV.

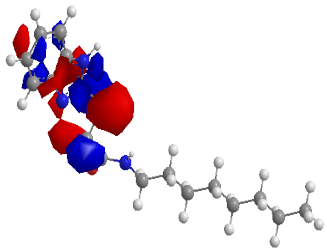


Figure 3: The frontier molecule orbital density distributions of (10b ΔE = E_{HOMO}-E_{LOMO}= 9.377 eV) 10b(HOMO)

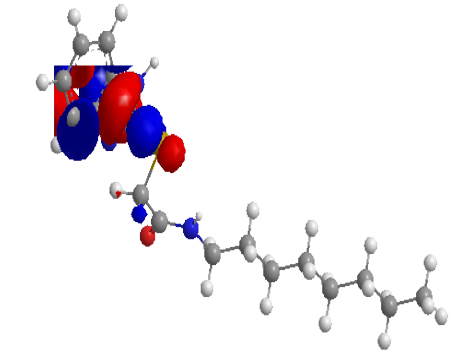


Figure 4: Optimized structure of (10bLUMO).

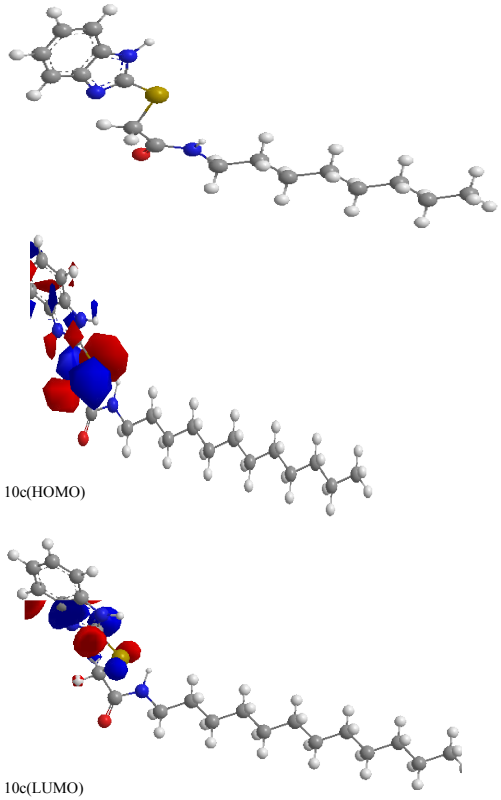


Figure 5: The frontier molecule orbital density distributions of (10c) ΔE = E $_{HOMO}$-E_{LOMO}=9.390 eV.

hydrochloride (1.5 g; 0.04 mol) in boiling pyridine (30 mL) and then refluxed for 3 h. The reaction mixture was pour into ice/HCl and the solid that separated was re-crystallized. Yield 74%, m.p. 174-176°C, IR spectrum υCO (1704 cm^{-1}). ^{1}HNMR spectrum DMSO-d6 of singlet at δ 2.1(s, 1H, CH_3), 2.8-3.0 (2 dd, 2H, diastereotopic protons), 3,8-4.2(dd, CH-CO, methine proton ,), 7.4-7.8 (m, 7ArH). Elemental anal. Found %C 56.50, %H 3.37, %N 11.56, %Cl l0.67, $C_{18}H_{15}N_3O_2Cl_2$ (339.5), Calc. %C 56.56, %H 3.31, %N 11.55, %Cl 10.72 (Figure 5).

4-(4-chloro-3-methylphenyl)-2-(1H-benzimidazol-2-ylmercapto)-4-oxobutanoic acids (6)

A solution of acid 1 (3 g; 0.01 mol) and 2-mercapto benzimidazole (1.70 g; 0.01 mol) in 50 ml benzene and 4 drops piperidine was allowed overnight at r.t. The crude product that formed was washed by petroleum ether (b.p 40-60°C), and then, crystallized from benzene. Yield 80 %, m.p. 122-124°C. IR spectrum υCO 1710, 1686 cm^{-1}, The ^{1}HNMR spectrum DMSO-d6 δ 2.1(s, 1H, CH3), 2.4-2.6 (2 dd, methylene protons, CH_2-C=O), 2,7-3.1(dd ,CH-CO, sterogenic methine proton), 6.9-7.3 (m, 7ArH and 1H of imidazole moiety), 8.2 (s,1H, acidic proton exchanged in D_2O). Elemental anal. Found %C 56.46, %H 3.27, %N 7.56, %Cl 10.67, $C_{18}H_{15}N_2O_3SCl$ (374.5), Calc. %C 56.46, %H 3.28, %N 7.55, % Cl 10.72 (Figure 6).

Formation of compounds 7 and 8

A mixture of 6 (3.73 g; 0.01 mol) and acetic anhydride (9.4 mL, 0.1mol) and then refluxed on water bath for 1h. The reaction mixture was allowed to cool and then pour into ice-H_2O and the separated product was filtered, dried and was fractional crystallized.

2-(4-chloro-3-methylbenzoyl) methyl-3-Oxo-1, 3-thiazolo [3,2-a]benzimidazole (7)

Yield 39%, m.p. 146-148 °C (toluene), IR spectrum υCO 1715, 1681 cm^{-1}. The ^{1}HNMR spectrum in DMSO-d6 exhibits Signals at δ 2.1(s, 1H, CH_3), 2.4-2.6(2dd, 1Ha and 1Hb CH_2-C=O, diastereotopic protons) 2.7(dd, 1H, proton of thiazole moiety), 7.0-7.9 (m, 7ArH). Elemental anal. Found %C 60.66, %H 3.64, %N 6.56, %S 7.32, %Cl 9.17, $C_{18}H_{13}N_2O_2SCl$ (356.5), Calc. %C60.66, %H 3.61, %N 6.55, %S 7.30, %Cl 9.12.

4-(4-chloro-3-methylphenyl)-1,3-thiazinoo[2,3-a]benzimidazole-2-carboxylic acid (8)

Yield 38% , m.p. 178-180°C (ethanol), IR spectrum υCO 1706 cm^{-1}

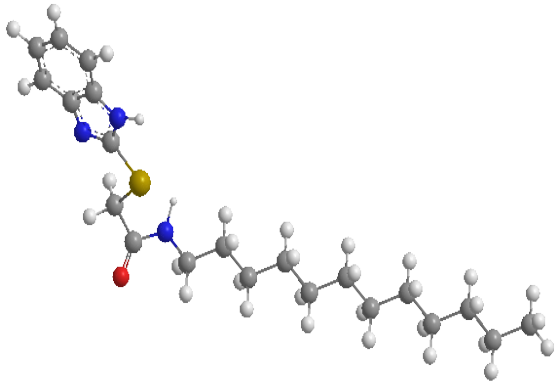


Figure 6: Optimized structure of (10c).

The ^{1}HNMR spectrum in DMSO-d6 exhibits Signals at δ 2.2 (s, 1H, CH_3), 2.7(dd,1H, methine proton), 7.0-7.9 (m, 8H of both 7ArH and 1H thiazine moieties). Elemental anal. Found %C 56.42, %H 3.59, %N 7.56, %S 7.84, %Cl 9.67, $C_{18}H_{13}N_2O_2SCl$ (356.5), Calc. %C 60.46, %H 3.64, %N 7.85, %S 7.80, %Cl 8.72.

Ethyl-2-benzoimidazol-2-ylthioglycolate (9)

A mixture of 16.7 g (0.1 mole) of 2-mercapto-benzoImidazole and 12.25 g of ethyl chloroacetate (0.1mole). This mixture is then refluxed for 3 h in ethanol. The ester is then collected and re-crystallized from n-pentane. 70% yield, m.p. 136-138°C. IR spectrum υCO (ester) 1746 cm^{-1}. The ^{1}HNMR spectrum in DMSO-d6 exhibits Signals at δ 1.23 (t, 3H, CH_3), 2.2 (s, 1H, CH_3), 3.7(q, 2H, CH_2), 4.1(s, 2H, CH_2), 7.4-7.7 (m, 4H, 4ArH). Elemental anal. Found %C 56.66, %H 3.57, %N 15.56, %Cl 9.67, $C_{11}H_{12}N_2O_2S$ (236), Calc. %C 56.66, %H 3.61, %N 15.55, %Cl 9.72.

Formation of additives, ethyl-2-(benzoimidazol-2-ylthio)-*N*-alkyl acetamide] (10a-c)

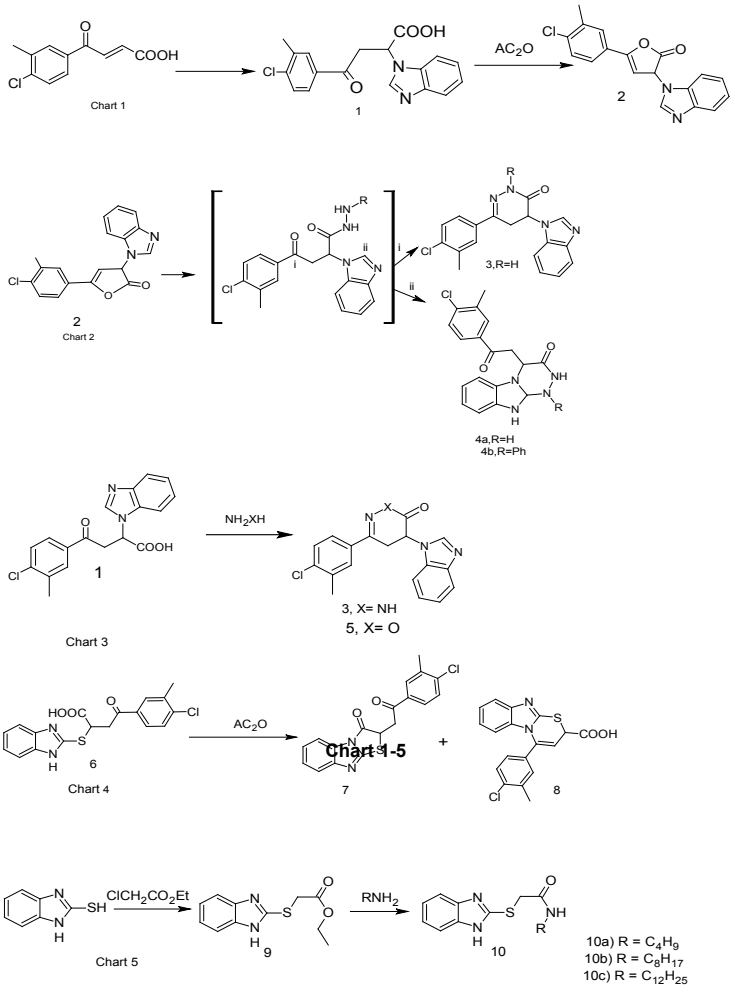
A mixture of 11.05 g (0.05 mole) of ester 9 and (0.05 mole) of N-alkyl amines, [(*N*-butylamine(a), N-octylamine(b) and N-dodecylamine (c)]. The mixture is cooled to zero °C in ethanolic KOH for one hour. The products were filtered and re-crystallized from ethanol. The ^{1}HNMR spectra in DMSO-d6 exhibit Signals at δ 1.33-1.48 (m, alkyl protons), 2.1 (s, 1H, CH_3), 4.0-4.1(s, 2H, CH_2), 7.3-7.8 (m, 4H, 4ArH). Elemental anal. For butyl deriv. Found %C 58.74, %H 7.17, %N 15.66, %S 12.17, $C_{13}H_{19}N_3OS$ (265), Calc. %C 58.86, %H 7.16, %N 15.84, %Cl 12.07.

Results and Discussion

With the aim of broading the synthetic potential of 4-Aryl-4-oxo-but-2-enoic acids [12-22], the authors can be reported the behavior of 4-(4-chloro-3-methylphenyl)-4-oxo-but-2-enoic acid was allowed to react with benzimidazole and 2 mercaptobenzimidazole afforded aza/thia-Michael adducts. The preference of nitrogen and sulfur nucleophiles at C_2 was due to stability of the primary zwitterionic adducts 1 and 6 (Chart 1).

2(3H) Furanone as a new antioxidant and anti-inflammatory agent, Cotelle et al. [23] and Weber et al. [24] synthesized new ascorbic acid analogues have resulted in obtaining antioxidant and anti-tumoral [25]. The most activating furanone when substituted in 2 and 5 positions by activating aryl group [26]. In continuation to our previous works to design and synthesize new furanones substituted in position 2 by 4-chlorophenyl moiety and benzimidazole in 5-position to increase its anti-oxidant activity. The synthesis can be achieved by the lactonization of the acid 1 on heating water bath for 1h with acetic anhydride, afforded 5-(4-chloro-3-methylphenyl)-3-(1H-benzimidazol-1-yl)-2-(3H) furan one (2) (Chart 1). Furthermore, reaction of the furanone 2 with hydrazine hydrate in boiling ethanol, afforded the pyridazinone derivative 3. So, the reaction is favor the route i versus the route ii that afford fused benzimidazolo [1,2-c]triazinone derivative 4a that reflect to us the pyridazinone isomer 3 is more thermodynamic stable. Otherwise, the treatment of furanone 2 with phenylhydrazine afforded benzimidazolo [1,2-c]triazinone derivative 4b. That can be confirmed, the presence of phenyl group increase the stability of fused heterocycle 4 (Chart 2).

A series of 2H-pyridazine-3-one and 1,2-oxazine derivatives have anti-inflammatory activity was tested in vitro on superoxide formation and effects on lipid peroxidation[27], as antioxidants in natural rubber [28,29], pyridazinone PDE inhibitors [30], 1,2-oxazine as PTP 1B inhibitors [31]. An authentic reaction was done by refluxing the acids



Total Acid Numbers, mg KOH / g Sample x 10^2												
	3	2	1	6	5	4	7	8	9	10b	10c	10a
0 ppm	197	197	197	197	197	197	197	197	197	197	197	197
200 ppm	182	101	117	92	51	134	77	102	79	74	86	83
400 ppm	167	99	81	68	70	157	84	99	86	65	82	78
500 ppm	184	121	173	167	133	171	101	150	99	73	74	74
1000 ppm	191	130	171	174	156	174	120	156	101	80	87	90

Table 1: TAN after 72 Hours x 10^2

1 with hydrazine hydrate and/or hydroxylamine hydrochloride in boiling pyridine afforded the pyridazinone, and oxazinone derivatives 3,5 respectively in good yield (Chart 3).

On the other hand, when the 4-(4-dichloro-3-methylphenyl)-4-oxo-but-2-enoic acid was allowed to react with 2-mercaptobenzimidazole in boiling benzene yielded the adduct 6. The charge density localized on the sulfur atom (0.266), was found to be greater than nitrogen atom (0.236). Consequently, the attack preferred via sulfur atom (Thiol tautomer). IR spectra of them reveal strong absorption bonds at (1710-1682 cm^{-1}) for υCO of adduct. Also, treatment of the adduct 6 with acetic anhydride gave the corresponding thiaazolobenzimidazole derivative 7, and 1, 3-thiazinoquinazoline derivative 8 (Chart 4).

An important class of compounds in the field of petroleum chemistry because of their broad spectrum antioxidant and anticorrosive activities [32-36]. The performance of engine oils and industrial lubricants are improved by the addition of specific types of additives. These additives are oil soluble chemicals and usually added to prevent the deposition of insoluble materials, lubricant oxidation and metal corrosion. Most antioxidant functions are either by thermal decomposition via C-C bond chain or reacting with free radical via hydroperoxide radical mechanism. In the present work, the authors can be reported the benzimidazole derivative 10, R=C4 at 400 ppm [37] has a higher stability due to the electron donating nature of the alkyl group butyl > octyl>dodecyl groups that facilitate to generate stable free radical. The results confirm the N-alkyl-S-benzimidazol-2-yl thioglycolamide 10 are better antioxidant than 2-mercaptobenzimidazole itself. Enhancement of the amide 10 as antioxidant prove that the process of thermal

degradation of engine lubricants proceed via thermal decomposition of C-C bond chain (Chart 5).

At higher concentration of the hydrazide 10, gave higher % SO_2 concentration and formation of the diametric structures. The SO_2 moiety will be increased % sulfuric acid and therefore increase TAN that causes competition for antioxidant role and so optimum concentration of antioxidant hydrazine derivatives 10 were 400 ppm . The Correlation between the antioxidant character of the heterocyclic additives and their structure has been investigated, using Ab initio (HF/3-21G) and semi-empirical gas phase AM1(Austin model 1) calculations. Parameters as total energy, HOMO and LUMO energies, dipole moment and dipole-dipole interaction 2-mercaptobenzoimidazole derivatives 10 indicate the importance of the thiol structure as antioxidant and anticorrosive. To investigate the effect of substituent on the inhibition mechanism and efficiency, they computed the E_{-HOMO}, E_{-LUMO} energies and energy gap. According to the frontier molecular orbital theory, the formation of a transition state is due to an interaction between frontier orbital's (HOMO and LUMO) of reacting species [38,39]. Usually the total acid number of the oil increases by increasing the oxidation time. The increment of TAN value is due to oxidation processes which produce peroxides when subjected to heat and air. In presence of additives, the total acid numbers after thermal oxidation of the base oil for 24-72 h. The total acid numbers decrease by increasing the additive dose from 200 part per million to 1000 parts per million (Table 1).

From the Table 1 at 0 ppm, no additive in the oil lubricant, we can notice the total acid number(TAN) can be reflect the oxidation stability of the antioxidant organic materials 1-10, at different concentration that increased in compounds 1,3 and 6 because of the presence of acidic protons.

Conclusion

Cyclization of the acids 1, 6 afforded 2, 7 and 8 respectively that increase the oxidation stability and becomes act as good antioxidants. The presence of sulfur atom in the compounds 6, 7 and 8 can be afforded the higher oxidation stability than corresponding compounds 1 and 2 respectively. Finally, the fused heterocycles e.g. compounds 4, 7 and 8 (although the presence of phenyl group and sulfur atom) has a lower oxidation stability than separated heterocycles 2, and 5, as expected the stability of radicals appear in a large area and size of atom or compound.

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