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Synthesis and Antibacterial Evaluation of Some New Fused Cyclic Sulfoxides

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ABSTRACT

A series of diarylidine cyclohexanones (1_t-12_t) have been prepared via Clasien-Schmidt reaction then condensed with dimethyl sulphoxide through Michael-Claisen condensation to afford the corresponding fused heterocycles (13_t-24_t). The structures of the products were elucidated by the spectrum (UV, IR, ^{1}H-NMR). The suggested mechanisms for these reactions were investigated according to theoretical calculations, heat of formation (H.F.) and the steric energy (S.E.). Furthermore some of the products have been tested for their biological activity (antibacterial).

Keywords: Dimethyl sulfoxide, Diarylidene cyclohexanone, Antibacterial effect, Fused cyclic sulfoxide.

تشييد وتقييم الفعالية المضادة للبكتريا لبعض السلفوكسيدات الحلقية المندمجة الجديدة

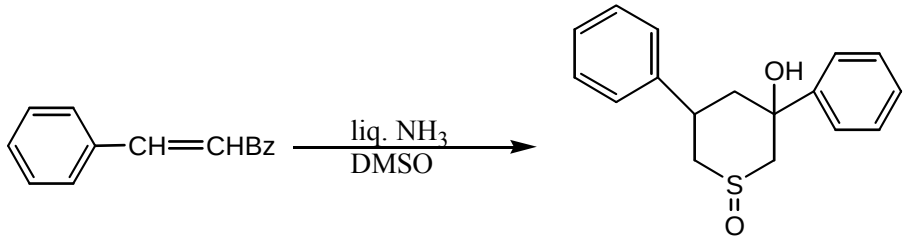
الملخص

تم تحضير سلسلة من ثنائي ارايليدين هكسانون حلقي (1_t - 12_t) من خلال تفاعل كليزن-شميدت حيث ثم تكثيفها مع ثنائي مثيل سلفوكسيد من خلال تفاعل مايكل-كليزن لإعطاء الحلقات غير المتجانسة المندمجة المقابلة (13_t-24_t)، وتم دعم تراكيبها في ضوء الطرائق الطيفية (^{1} H-NMR , I.R , U.V) . وتم التحقق من الميكانيكيات المقترحة لهذه التفاعلات استنادا إلى الحسابات النظرية لحرارة التكوين (H.F.) وطاقـة الإعاقة (S.E) ، إضافة لذلك فإن بعض النواتج قد تم فحصها لبيان فعاليتها البيولوجية المضادة للبكتريا .

INTODUCTION

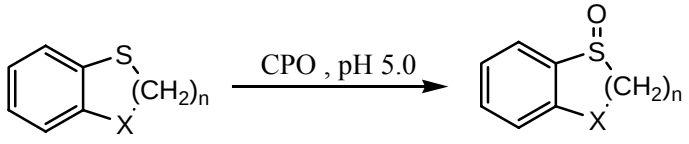
Sulfoxides are compounds that contain a sulfinyl group covalently bonded at the sulfur atom to two carbon atoms and oxygen atom (Segurel *et al*., 2005). The naturally occurring sulfoxides are often accompained by the corresponding sulfides or sulfones (Lake *et al*., 1988). The most commercially important sulfoxide is the simplest member, dimethyl sulfoxide. Sulfoxides occur widely in small concentrations in plant and animal tissues (Wiley and Sons, 2001). Sulfoxides have fascinated organic chemists for a long time owning to their varied reactivity as a functional group for transformation into a variety of organo sulfur compounds. These transformations are ureful for the synthesis of drugs and sulfur – substituted natural products (Musah *et al*., 2009). Optically active sulfoxides continue to deserve much attention as important chiral auxiliaries in asymmetric synthesis and in C-C bond forming reactions (Abbas *et al*., 2005). A novel bioactive sulfoxide like N-acetyl-2-(1-adamantylsulfoxo)-3-acetoxy-4-phenyl-6-hydroxy-1,2,3,6-tetrahydropyridine was tested for anti–microbial action using the agar dilution method against twenty one microorganisms gram – positive and gram – negative bacteria and diploid fungus. It was found that the sulfoxide inhibited the growth of Moraxella catarrhalis and Streptococcus pyogenes with minimum inhibitory concentration.in addition, the growth of Corynebacterium diphtheriae (NCTC) was partially inhibitted (80%) at 256 µg/ml (Prachayasittikul *et al*., 2010).

Different routes were used to afford the cyclic sulfoxides such as the condensation of MeS(O) CH_2^-Na with phCH=CHBz in liquid ammonia which gave 3-hydroxy-3,5-diphenyl -1-thiacyclohexane-1-oxide as shown below (Gautier *et al*., 1970).



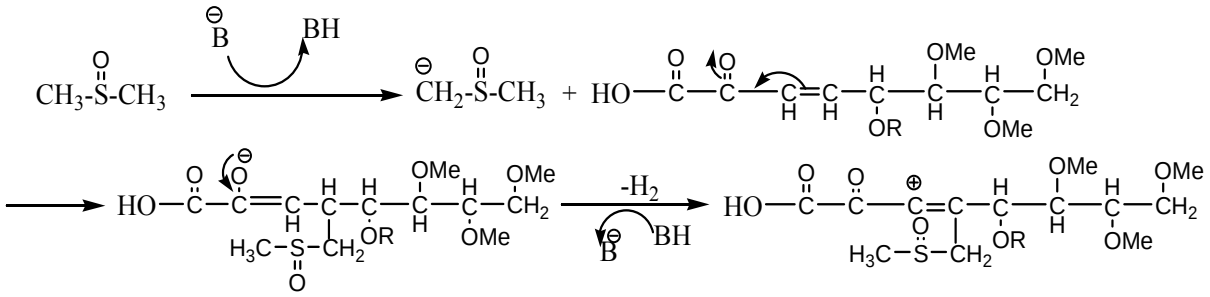
Bz: Benzoyl

Chloroperoxidase was used as catalyst in the synthesis of a series of aromatic cyclic sulfoxides. This have been acheived by the reaction as shown below (Allenmark and Andersson, 1996).



X: CH_2 n: 1,2
C=O 2
S 1

Michael addition of DMSO to permethylated core of oligosaccharides was used in the formation of covalent DMSO products adducts as shown below (Sioud *et al*., 2010).



EXPERIMENTAL

Materials

All chemicals was supplied from Fluka, Sigma and Aldrich company.

Melting points were determined by Electrothermal 1A 9000 Digital – series 1998 apparatus (uncorrected).

UV-visible spectra were recorded using Shimadzu UV-Vissible spectrophotometer 160 (Department of Chemistry - College of Science - University of Mosul).

Fourier-Transform Infrared spectra were recorded on Brucker Tensor spectrophotometer 2003 (Germany) (Department of Chemistry - College of Science - University of Mosul).

Nuclear magnetic resonance (^{1}H-NMR) spectra were recorded using, 500 MHz perkin Elmer spectrometer, using tetramethylsilane (TMS) as an internal standard, $CDCl_3$ as a solvent was used in our investigation.(Department of Chemistry- I. I. T. Roorkee , India).

The theoretical calculations based on the data obtained from the minimized geometry were computed using semi-empirical AM1 module in the CS Chem. Office 2003 version 8.0 molecular modeling package.

Starting materials

I. Diarylidene cyclohexanones (1_t-12_t) (General procedure) (Karthikeyan *et al*., 2009), (Qitto, 2008), (Yonis Mahmood, 2009) and (Al-lewzy , 2011).

These compounds were prepared by stirring (3.7mmol) of the cyclohexanone with 7.5 mmol of the desired benzaldehyde, and 5 ml of 10% ethanolic sodium hydroxide in 25 ml ethanol in a 50 ml round-bottomed flask. After 3 hours the reaction mixture was filtered to obtain the crude precipitate which then washed several times with ethanol. The precipitate was dried and recrystallized from appropriate solvent. The colour for all diarylidene cyclohexanones is distinct yellow. (Table-1 and Table-2).

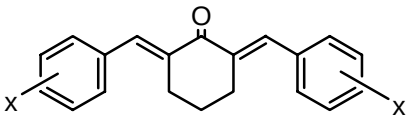
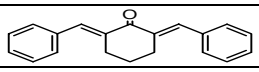
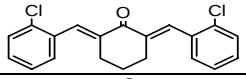
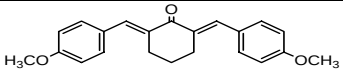
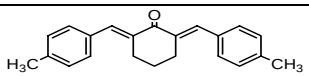
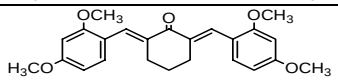
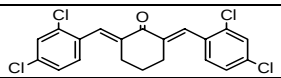
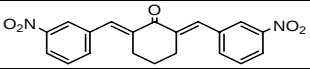
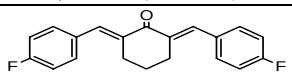
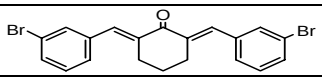
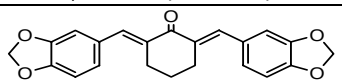
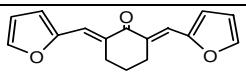
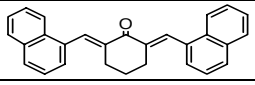


Table1: Names and some physical properties of (1_t-12_t).

Cpd No.	Name	X	Recryst. From	m.p. (^oC)	(Lit.)*	Yield (%)
1_t	2,6 -Dibenzylidene cyclohexanone	H	ethanol	119-120	116-119	24
2_t	2,6-Di(2-chloro benzylidene) cyclohexanone	2-Cl	ethanol	112-113	110-112	22
3_t	2,6-Di(4-methoxy benzylidene) cyclohexanone	4-OMe	ethanol	157-158	156-158	18
4_t	2,6-Di(4-methyl benzylidine) cyclohexanone	4-Me	ethanol	163-165	------	21
5_t	2,6-Di(2,4-dimethoxy benzylidene) cyclohexanone	2,4-diOMe	xylene	170-171	164-166	18
6_t	2,6-Di(2,4-dichloro benzylidene) cyclohexanone	2,4-diCl	carbon tetra chloride	161-163	-------	36
7_t	2,6-Di(3-nitrobenzylidene) cyclo hexanone	3-NO_2	carbon tetra chloride	194	190-192	27
8_t	2,6-Di(4-fluoro benzylidene) cyclohexanone	4-F	ethanol	149-150	154-155	29
9_t	2,6-Di(3-bromo benzylidene) cyclohexanone	3-Br	ethanol	113	111-113	21
10_t	2,6-Di(2-piperonylidene) cyclohexanone	2-piperonyl	carbon tetra chloride	181-183	------	33
11_t	2,6-Di(2-furylidene) cyclo hexanone	2-furyl	ethanol	142-144	143-145	35
12_t	2,6-Di(1-naphthylidene) cyclohexanone	1-Naphthyl	carbon tetra chloride	198-200	-------	22

*(Yonis Mahmood, 2009) and (Al-lewzy, 2011)

Table 2: Spectral data of compounds (1_t-12_t).

Cpd No.	Structure	UV($CHCl_3$) λ_{max},nm , ($\varepsilon \times 10^{-3}$) L.mole^{-1}.cm^{-1}	IR(KBr),ν cm^{-1}				
			C=O	C=C	C=C aromatic	NO_2 Sym., assym	C-O-C Sym., assym
1_t		326 (2.752)	1661	1607	1486, 1573	……..	……..
2_t		336 (2.752)	1664	1602	1469, 1575	……..	……..
3_t		306 (2.683)	1658	1595	1508, 1554	……..	1024,1250
4_t		326 (2.738)	1660	1601	1508, 1565	……..	……..
5_t		308 (2.683)	1662	1597	1468, 1500	……..	1027,1207
6_t		324 (2.767)	1660	1598	1468, 1578	……..	……..
7_t		340 (2.754)	1663	1638	1565, 1615	1347,1534	……..
8_t		328 (2.767)	1662	1608	1507, 1567	……..	……..
9_t		362 (2.696)	1661	1606	1573, 1591	……..	……..
10_t		302 (2.671)	1656	1588	1489, 1555	……..	1028,1262
11_t		328 (2.738)	1643	1591	1547, 1560	……..	1020,1248
12_t		334 (2.768)	1662	1604	1504, 1574	……..	

The sulfoxide compounds:

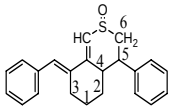
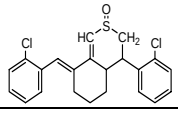
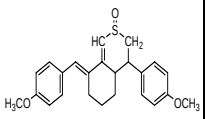
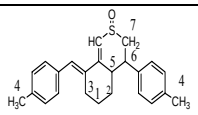
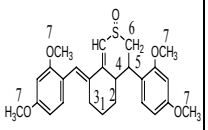
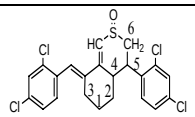
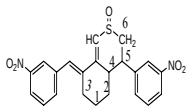
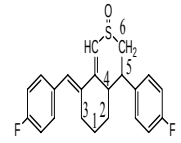
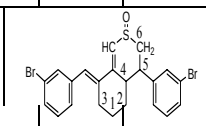
***General procedure*:**(Ghazal, 1997)

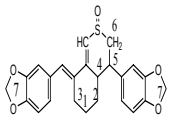
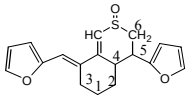
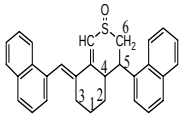
The desired diarylidine cyclohexanone (1 mmole) was allowed to react with 10 ml of dimethylsulphoxide in a 50 ml round-bottomed flask. A drop-wise addition with stirring of 10% ethanolic NaOH cause the colour to be changed. Stirring is continued for 5 hours till the colour became dark brown (in case of no colour change the reaction mixture is refluxed for 10 min). After cooling, water is added to precipitate the corresponding products which then filtered off, washed with water then dried at r.t. and recrystallized from ethanol. (Table-3 and Table-4). It seems that the products were less soluble in DMSO than the reactants hence the reactants remained soluble in the DMSO-H_2O mixture while the product was precipitated .

Table 3: Names and some physical properties of (13_t-24_t).

Cpd No.	Names	X	m.p. (^oC)	Yield (%)	Colour
13_t	3,4-Dihydro-4-phenyl -8-benzylidene cyclohexano [1,2-c]-1-oxo thiapyran	H	106-110	16	Brown
14_t	3,4-Dihydro-4-(2-chloro phenyl) -8-(2-chloro benzylidene) cyclohexano [1,2-c]-1-oxo thiapyran	2-Cl	150-153	12	Light brown
15_t	3,4-Dihydro-4-(4-methoxy phenyl) -8-(4-methoxy benzylidene) cyclohexano [1,2-c]-1-oxo thiapyran	4-OMe	116-120	13	Green
16_t	3,4-Dihydro-4-(4-methyl phenyl) -8-(4-methyl benzylidene) cyclohexano [1,2-c]-1-oxo thiapyran	4-Me	95-98	11	Brown
17_t	3,4-Dihydro-4-(2,4-dimethoxy phenyl) -8-(2,4-dimethoxy benzylidene) cyclohexano [1,2-c]-1-oxo thiapyran	2,4-diOMe	80-83	20	Brown
18_t	3,4-Dihydro-4-(2,4-dichloro phenyl) -8-(2,4-dichloro benzylidene) cyclohexano [1,2-c]-1-oxo thiapyran	2,4-diCl	186-186	17	Light brown
19_t	3,4-Dihydro-4-(3-nitro phenyl) -8-(3-nitro benzylidene) cyclohexano [1,2-c]-1-oxo thiapyran	3-NO_2	158-160	10	Brown
20_t	3,4-Dihydro-4-(4-fluro phenyl) -8-(4-fluro benzylidene) cyclohexano [1,2-c]-1-oxo thiapyran	4-F	104-106	10	Brown
21_t	3,4-Dihydro-4-(3-bromo phenyl) -8-(3-bromo benzylidene) cyclohexano [1,2-c]-1-oxo thiapyran	3-Br	120-123	24	Brown
22_t	3,4-Dihydro-4-(2-piperonyl) -8-(2-piperonylidene) cyclohexano [1,2-c]-1-oxo thiapyran	piperonyl	104-108	5	Orange
23_t	3,4-Dihydro-4-(2-furyl) -8-(2-furylidene) cyclohexano [1,2-c]-1-oxo thiapyran	2-Furyl	182-185	13	Light brown
24_t	3,4-Dihydro-4-(1-naphthyl) -8-(1-naphthylidene) cyclohexano [1,2-c]-1-oxo thiapyran	1-Naphthyl	124-126	16	Distinct brown

Table-4 Spectral data (UV, IR, ^{1}H-NMR) for compounds (13_t-24_t)

Cpd No.	Structure	UV($CHCl_3$) λ_{max} ,nm , ($\varepsilon \times 10^{-3}$) L.mole^{-1}.cm^{-1}	IR(KBr),ν cm^{-1}					^{1}H-NMR ($CDCl_3$) δ ppm
			C=C	C=C Aromatic	S=O	C-O-C	NO_2 Sym. assym	
13_t		338 (2.800)	1598	1446, 1492	1067	……	……	H_1 , H_2 , H_3 , H_4 , H_5 , H_6 1.1 1.35 1.7 2.5 2.7 3.3 2H 2H 2H 1H 1H 2H P q t q q d (Aromatic + olefinic) 6.5-7.7 12H m
14_t		328 (2.752)	1617	1439,1470	1037	……	……	---------
15_t		340 (2.799)	1606	1462,1509	1033	1248	……	----------
16_t		316 (2.737)	1606	1512,1541	1021	……	……	H_1 , H_2 , H_3 , $2CH_3$, H_5 , H_6 , 1.3 1.1 2.25 2.4,2.7 2.8 3.2 2H 2H 2H 6H 1H 1H p q t dd q q H_7 , (Aromatic + olefinic) 3.4 7.1 -7.4 2H 10H d m
17_t		334 (2.737)	1611	1505,1586	1035	1208	……	H_1 , H_2 , H_3 , H_4 , (H_5 , H_6) , 1.15 0.8 2 2.5 3.65 2H 2H 2H 1H 3H P q t q m $4OCH_3$, (Aromatic + olefinic) 4, 4.19 , 4.2 6.4 -6.9 12H 8H s m
18_t		306 (2.709)	1587	1469,1560	1049	……	……	H_1 , H_2 , H_3 , H_4 , H_5 , H_6 , 1 1.2 2.35 2.5 2.65 3.37 2H 2H 2H 1H 1H 2H P q t q q d (Aromatic + olefinic) 6.4-7.6 8H m
19_t		314 (2.767)	1606	1525,1577	1097	……	1350,1525	H_1 , H_2 , H_3, H_4 , H_5 , H_6 , 1.75 1.4 1.9 2.5 2.9 3.3 2H 2H 2H 1H 1H 2H p q t t q d (Aromatic + olefinic) 7.7 - 8.4 10H m
20_t		338 (2.738)	1601	1456,1508	1045	……	……	H_1 , H_2 , H_3 , H_4 , H_5 , H_6 , 1.15 0.8 2.2 2.5 2.85 4 2H 2H 2H 1H 1H 2H P q t q q d (Aromatic + olefinic) 6.5 - 7.9 10H m
				21_t			338 (2.752)	1591 1473,1566 1072 …… …… (Aromatic + olefinic) 6.8-7.75 10H m

22_t		310 (2.767)	1606	1487,1502	1039	1244	……	H_1 , H_2 , H_3 , H_4 , H_5 , H_6 1.1 1.2 2.5 3 3.35 3.8 2H 2H 2H 1H 1H 2H P q t q q d H_7 , (Aromatic + olefinic) 5.9 6.15 -6.9 4H 8H s m
23_t		362 (2.752)	1591	1506,1541	1013	1262	……	H_1 , H_2 , H_3 , H_4 , H_5 , H_6 1.2 0.8 1.43 2.5 2.8 3.9 2H 2H 2H 1H 1H 2H P q t q q d (Furfuryl + olefinic) 7.2-7.6 8H m
24_t		338 (2.723)	1597	1473,1508	1078	……	……	H_1 , H_2 , H_3 , H_4 , H_5 , H_6 1 1.2 2.35 2.5 2.65 3.3 2H 2H 2H 1H 1H 2H P q t q q d (Aromatic + olefinic) 6.8-7.9 16H m

Preliminary biological study:

In the present work, it is decided to investigate final products and study their inhibitory effect on the growth of two kinds of bacteria Grampositive *(staphylococcus aureus)* and Gram-negative *(E. coli)* by using disc diffusion method, (the standard Kirby and Bauer method) (Bauer *et al*., 1966).

The isolates were isolated and identified in the Dept. of Biology, College of Science, Univ. of Mosul.

PROCEDURE

Of each bacterial species a loopful were cultured in a nutrient broth and incubated at 37 ^oC for 14-16 hr, then eventually distributed on the nutrient agar by using a sterile swab. The plates were incubated at 37 ^oC for 30 min.

A Whatmann No. 1 type filter paper discs were distributed on the agar and a certain equal (0.01 mg/ 0.5 ml) of the compound per solvent (DMSO) was added. The controls here were Stryptomycin, Vancomycin and Gentamycin for comparison. The plates were then incubated at 37 ^oC for 18-24 hr. Prescott (Prescott *et al*., 1996) method was used to illustrate the sensitivity of the studied compounds. The results were interpreted according to the report of (W.H.O.). The resistance (R) represent the diameter of inhibition zone <11 mm, while the sensitive (S) was over 16 mm, but moderately sensitive (MS) was regarded when the inhibition zone is (12-16) mm.

Table 5: Inhibition effect of compounds (13_t-24_t) on growth of *Staphylococcus aureus* and *Escherichia coli*.

Compound No.	Test organism	
	E.Coli G(-)	Sta. Aueus G (+)
13_t	R	-Ve
14_t	MS	-Ve
15_t	MS	-Ve
16_t	R	-Ve
17_t	-Ve	-Ve
18_t	R	-Ve
19_t	-Ve	-Ve
20_t	R	-Ve
21_t	-Ve	-Ve
22_t	-Ve	-Ve
23_t	-Ve	-Ve
24_t	MS	-Ve
Control		
gentamycin	S	S
CDz30 (cefodizime)	-Ve	…….
Tetracycline	……..	S

R: Resistant
MS: Moderately sensitive
S: Sensitive

RESULTS AND DISCUSSION

The structures of the starting materials (1_t-12_t) and the products (13_t-24_t) were confirmed by (UV, IR) more over the structure of the final products were confirmed by (^{1}H-NMR) (see Tables 1-4). The biological activities of the final products (13-24_t) had been investigated for two type of bacteria and compared with some common antibiotics like (Gentamycin, Cefodizime and Tetracycline). Compounds number (13_t, 14_t, 15_t, 16_t, 18_t, 20_t and 24_t) showed inhibitory effects towards *E. coli* only, but they showed no effects towards *Sta. Aueus*. Also compounds (17_t, 19_t, 21_t, 22_t, and 23_t) did n't show any inhibitory effects towards *Sta. Aueus* and *E. coli* (Table -5).

According to the spectral data obtained on Tables 1-4, the suggested mechanism for the reaction of diarylidine cyclohexanones with dimethylsulphoxide (Scheme-1) may proceed via Michael or Claisen routes as indicated in the (scheme-1) (Qitto , 2008).

i- Michael route

The anion $H_2^{\ominus}CSOCH_3$ may attack the β -carbon of the cyclohexanone .

Table 6: The heat of formation (H.F.) and steric energy (S.E.) for compounds (13_t-24_t).

Cpd No.	X	Form	Heat of formation H.F. (Kcal/mole)	Steric energy S.E. (Kcal/mole)
13_t	H	a	32.563559	10.1849
		b	36.843252	11.5606
14_t	2-Cl	a	21.395082	11.2858
		b	24.905872	11.9686
15_t	4-OMe	a	-43.286278	21.9422
		b	-39.008496	23.8322
16_t	4-Me	a	18.446187	10.1619
		b	21.341061	11.4784
17_t	2,4-DiOMe	a	-64.28304	36.1100
		b	-113.373465	37.2457
18_t	2,4-DiCl	a	8.262933	15.9798
		b	11.422312	16.0670
19_t	3-NO_2	a	41.012672	2.2045
		b	43.672064	12.5437
20_t	4-F	a	-57.867521	10.2825
		b	-53.948069	11.0288
21_t	3-Br	a	42.539050	11.3248
		b	46.336908	12.2099
22_t	2-Piperonyl	a	-84.607943	29.0593
		b	-80.517700	29.0497
23_t	2-Furyl	a	-3.943829	28.8390
		b	-0.790590	28.7838
$^{\theta 24}{}_t$	1-Naphthyl	a	88.080591	2.4750
		b	77.862936	6.2183

From the values of the heats of formation and steric energy (Table-6) it was found that (a) is more stable than (b) (scheme 1), But experimentally according to the spectral data of ^{1}H-NMR it was found that (b) is more favourable than (a), and hence will predominate. It seems that compounds (a) were the thermodynamically (more stable) product while compound (b) are the kinetically (more stable) product. i.e. the activation energy of path (b) is less than path (a), and hence kinetic products were predominate.

ii-Claisen route

The anion $^{\Theta}CH_2SOCH_3$ may attack the carbonyl carbon via Claisen condensation to afford the intermediate C_1. (C_1) may cyclize via intramolecular Michael condensation to give M_2C_2 or lose a water molecule to afford C_2 which in turn may cyclize via intramolecular Michael condensation to produce b. Theoretically it may be concluded that the better suitable route is $M_1 \rightarrow M_2C_2 \rightarrow$a, rather than $C_1 \rightarrow C_2 \rightarrow$b (Table 5).

Spectroscopic analysis :

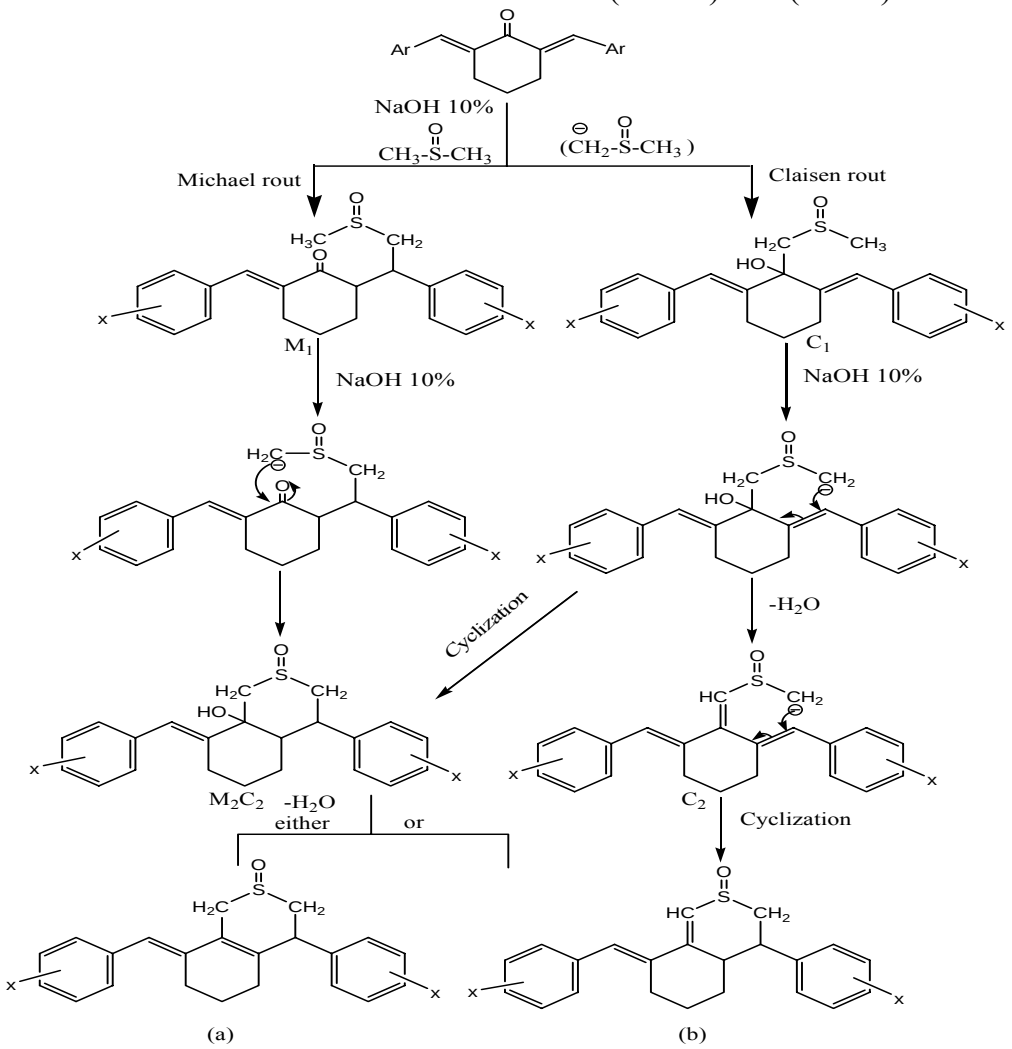
The compound (13_t) is chosen as a representative model for the spectral (^{1}H-NMR and IR) discussion.

The ^{1}H-NMR spectrum of compound (13_t) showed a pentet signal at δ1.1 ppm related to the 2H of H_1 whereas the quartet signal at δ 1.35 ppm is due to the 2H at H_2 . The 2H at

H_3 seemed a triplet signal at δ 1.7 ppm . But the quartet signal at δ 2.5 ppm is due to the 1H at H_4 . Another quartet signal at δ 2.7 ppm it seemed to the 1H at H_5 . The doublet signal at δ3.3 ppm correspond to 2H at H_6 . Finally a multiplet signal at δ 6.5-7.7 ppm related to the 12H of aromatic and olefinic protons. (Table 4)

The IR spectrum of compound (13_t) showed a band at 1598 cm^{-1} related to the stretching vibration of olefinic (C=C). A frequency at 1492 cm^{-1} , 1466 cm^{-1} related to the symmetrical and a symmetrical vibrations of the aromatic (C=C). But the frequency at 1067 cm^{-1} related to the sulfoxide group.

The UV spectrum of the products reflects a wavelength at maximum absorption (λ_{max}) at (306-362) nm and values the molar absorbtivity at range (2.709-2.88 × 10^3) $L.mole^{-1}.cm^{-1}$ that related to the electronic transition ($n\rightarrow\pi^*$) and ($\pi\rightarrow\pi^*$).



Ar = ph , 2-furyl, biphenyl, 2- piperonyl, m-NO_2 C_6H_4, 2-Cl C_6H_4, 2,4-diCl C_6H_3, 2,4-diOMe C_6H_3, p-OMe C_6H_4, p-CH_3 C_6H_4, p-F C_6H_4, m-Br C_6H_4

Scheme 1: The mechanistic route of the condensation of diarylidene cyclohexanone with dimethylsulfoxide.

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