

Cyclic Addition of Acetylene Dicarboxylic Acid to Some New Aldonitrones Containing 1,3,4 Thiadizol Ring

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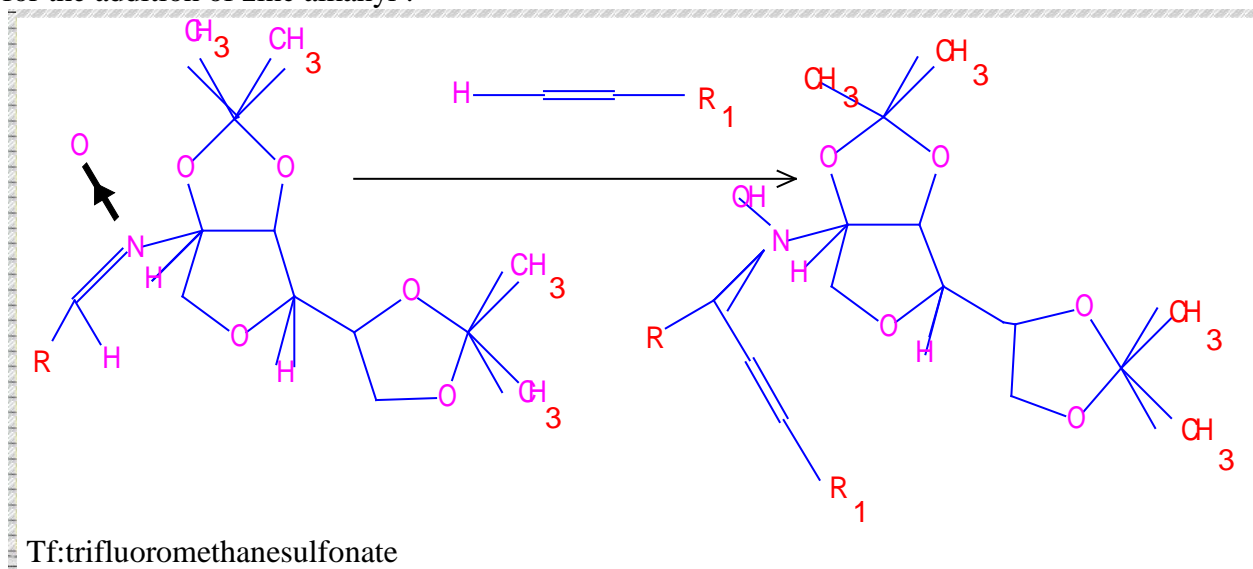
Abstract :

Nine new aldonitrones containing 1,3,4 – thiadizole ring were prepared and characterized by using different spectroscopic methods . Then a cyclic addition reaction with acetylene dicarboxylic acid for nine nitrones was carried out .Only one reaction was succeeded to give the 1,3 –dipolar cyclic addition producing 3- (4 – chloro phenyl (5 – thio – 1,3,4 – thiodizoyl)- 4,5 – dicarboxyl – isoxazoline .

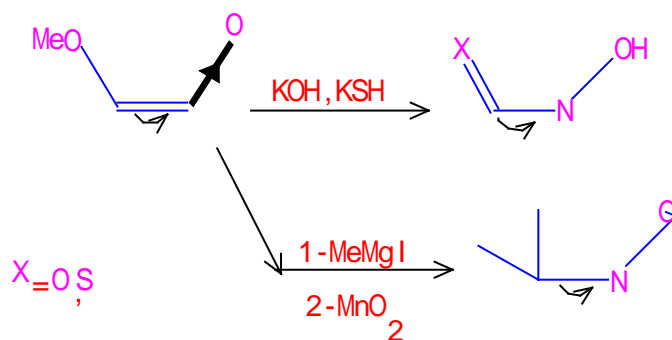
Introduction :

Nitrones⁽¹⁾ means (Nitrogen – Ketone) which involve $C=N \rightarrow O$ group are classified into two types aldo and ketonitrones with alkyl , aryl subsituent on C_{α} instead of hydrogen atoms . Also nitrones have a polar^(2,3) behavior that the nitrogen atom has (+ve) charge and the oxygen has contain (- ve) charge and this induces π - delocalization in the nitrones that give the structure of the dipole and it will give a geomtrical isomers due to the presence of a double bond . This fact was proved by Semper et.al^(4,5). Many reactions for this type of nitrone could be involved. An important one is the cyclic addition to symmetrical and unsymmrtical alkene or alkyne^(6,8). Nucleophilic addition is one of the interesting reaction .

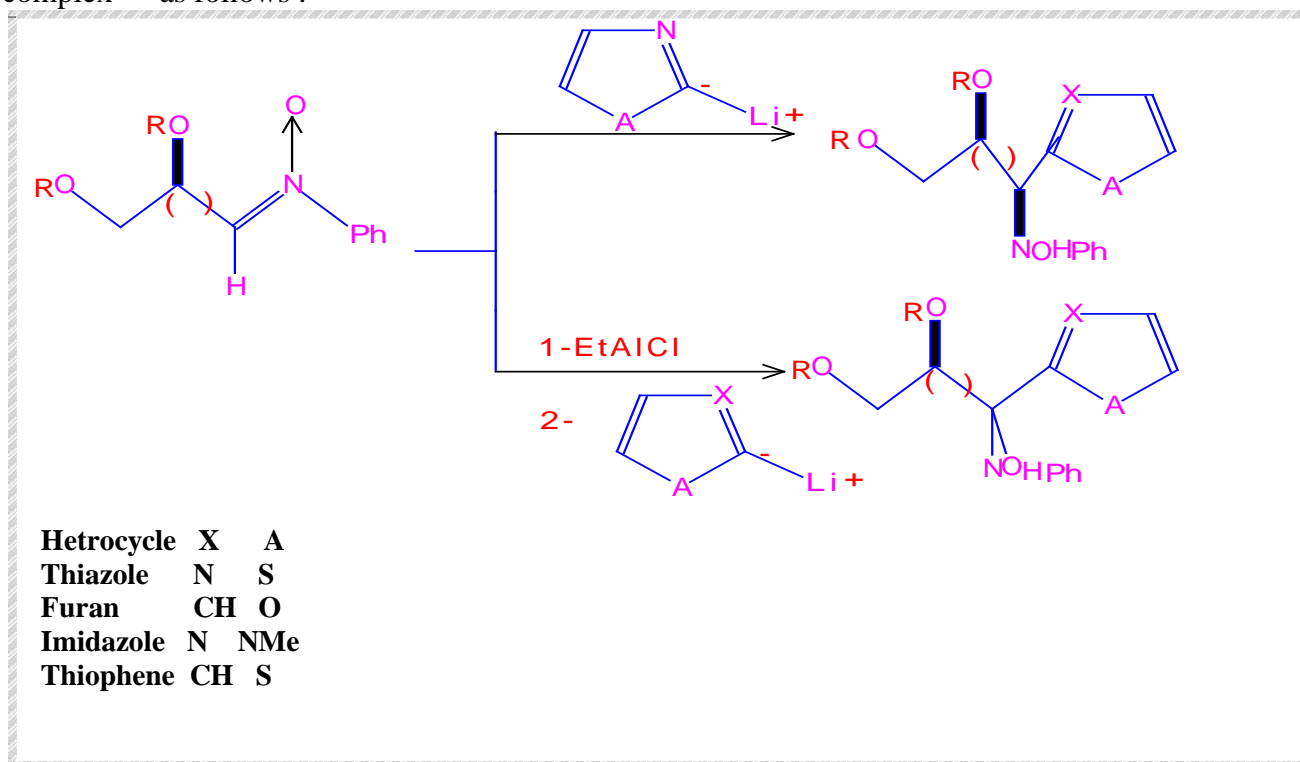
Carreia et.al^(9,10) used the sugar derivative (mannose – derived auxiliary) to prove the anti addition for the addition of zinc alkanyl .



Also Grignard reagent and alkali base (KOH) and sulpha base (KSH) were added to cyclic α -methoxy nitrones⁽¹¹⁾ as follows :



Optically active nitrones derived from aldoses or dialdose could be added to its metallic heterocyclic ring with a stereoselective controlled depends on the kind of Lewis acid used to having the hydroxyl amine this amine was used in the preparation of poly alkoxy α - amino acid which was introduced to synthesis of some natural products like aminosaccarides , aza sugar , and nucleoside complex⁽¹²⁾ as follows :



Vasella et.al^(13,14) were added the dialkyl phosphate anion to the nitrones so with anti stereo selectivity addition . This depends on the nucleophilic type of solvent and nitronone structure . 1,3-dipolar reaction is a common reaction for a dipolar having four electrons (here is the nitronone) with the dipolarophile (alkene or alkyne) which have unsaturated center to give 5- hetro member ring⁽¹⁵⁾ in a high yield , and with highly stereoselectivity⁽¹⁶⁾ . The major line in this project was the dipolar cycloaddition reaction which was our aim .

Experimental :

The NMR spectra were obtained by NMR – 400 MHz Bruker using CDCl_3 as a solvent and TMS as a standard . The Infrared spectra were obtained by FT 8400S type Shimadzu as KBr disk . The Ultraviolet data was recorded by UV -1601 type Shimadzu using quartz cell and the samples were prepared in dry ethanol .

Procedure :***Preparation of 2-amino -5 thio – 1,3,4- thiadiazole^(17,18)***

In a round bottom flask fitted with a condenser , 4.5 g thiosemicarbazide was dissolved in 18 ml dry ethanol . Then a solution of 2.65 g anhydrous sodium carbonate in 3.65 ml carbon disulfide was added to the thiosemicarbazide solution . The resulting mixture was refluxed with stirring for 1 hr.. The mixture was heated on water bath for 6 hrs until the reaction mixture became yellow . The ethanol was removed by rotatory evaporator , 20 ml of H₂O were added to the residue then it was acidified . Then the precipitate was collected and recrystallized from ethanol to give a yellow crystals m .p 226 -228 C^o .

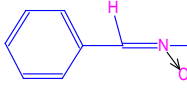
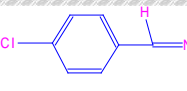
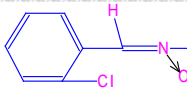
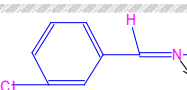
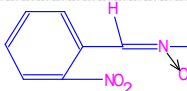
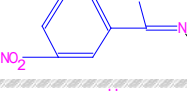
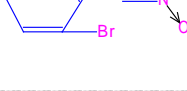
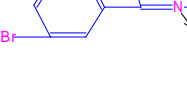
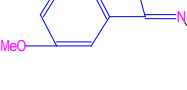
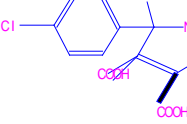
General procedure for preparation of imine

All imines were prepared by reacting of 2- amino – 5 – thio – 1,3,4 – thiadiazole with different benzaldehydes (2- Cl , 3- Cl , 4 –Cl , 2 –NO₂ , 3 – NO₂ , 2 – Br , 3 –Br , and 3 –OMe) as follows : 0.0075 mole substituted benzaldehyde was added to a round bottom flask fitted with a condenser containing 1 gm (0.0075 mole) 2 – amino – 5 – thio – 1,3,4 – thiadiazole dissolved in 20 ml dry ethanol . The mixture was refluxed for about 6 – 8 hours , depending on the type of substituent in the reacted aldehyde , until the reaction mixture became yellow . After evaporation of the ethanol , a yellow viscous product was formed then the product was checked by TLC and recrystallized from ethanol . The products are summarized in Table 1 .

Table 1 : Some physical data for the prepared imines

m .p calc C ^o	m .p lit C ^o	Time	Imines	Symbol
250 -248	254 -252	24	2 –benzylideneamino -5-thio – 1,3,4 – thiadiazole	C ₁
229 -227	228 -226	6	2-(p –chlorobenzylideneamino)- 5 –thio – 1,3,4 –thiadizloe	C ₂
214 -212	–	12	2 –(o –chlorobenzylideneamino) – 5 –thio - 1,3,4 –thiadizole	C ₃
223 -219	–	12	2 –(m –chlorobenzylideneamino) -5 –thio – 1,3,4 –thiadizole	C ₄
210 -207	–	8	2 –(o-nitrobenzylideneamino)- 5 –thio – 1,3,4 – thiadizole	C ₅
217 -215	–	10	2 –(m –nitrobenzylideneamino) -5 –thio -1,3,4 –thiadizole	C ₆
208 –206	–	12	2 –(o –bromobenzylideneamino) -5 –thio - 1,3,4 –thiadizole	C ₇
212 -210	–	12	2 –(m –bromobenzylideneamino) -5- thio – 1,3,4 –thiadizole	C ₈
205 -202	–	48	2 –(m –methoxybenzylideneamino) – 5-thio - 1,3,4 –thiadizole	C ₉

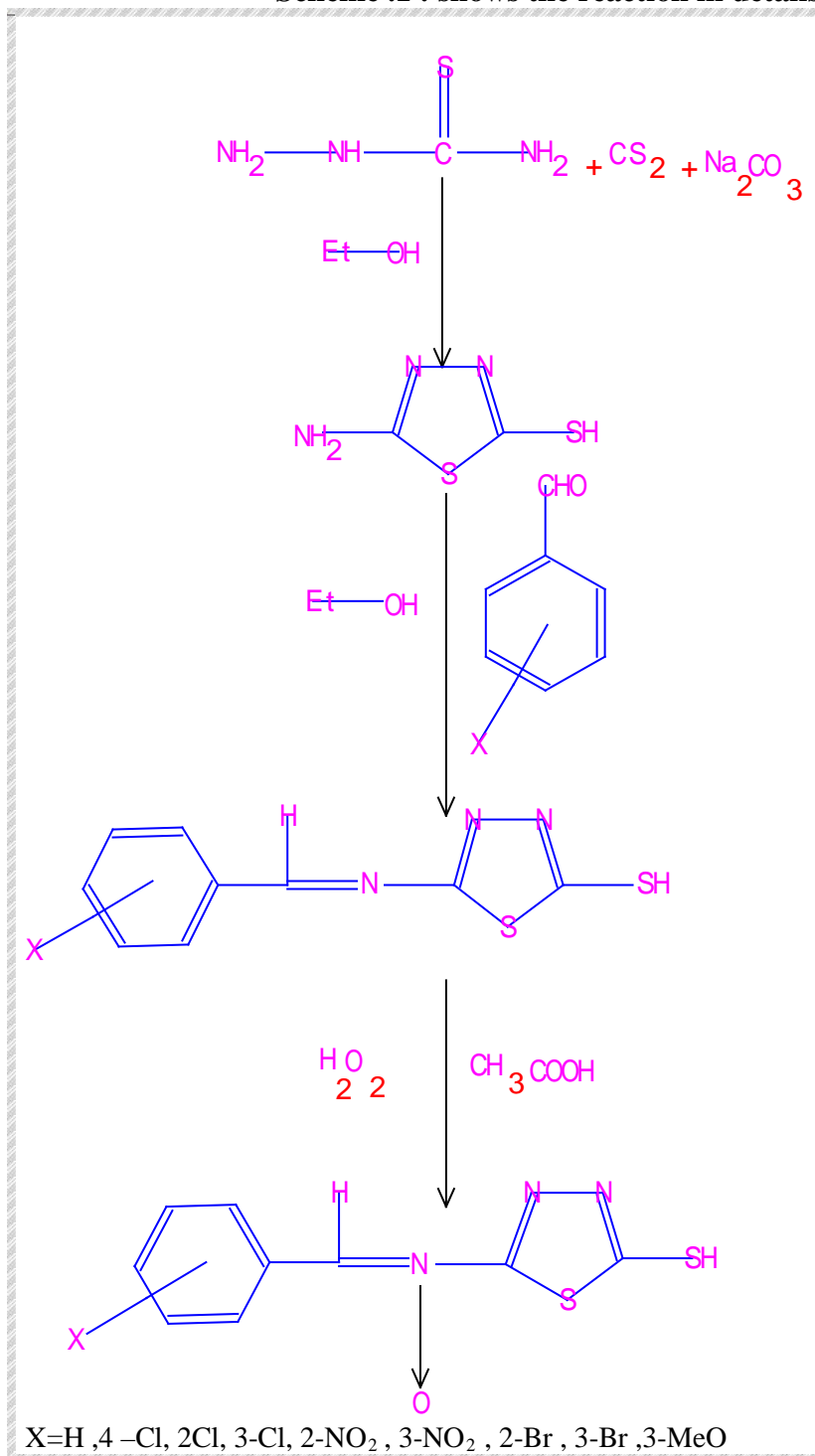
Table 2 : Some physical data of the new aldonitrones

Structure	Name of Compound	Yield %	m.pC ^o	Rec.solvent	state
	α -(phenyl)-N-[2-(5-thio-1,3,4-thiadizoyl)]Nitrone	48	119-121	Hexane	White
	α -(4-chloro-phenyl)-N-[2-(5-thio-1,3,4-thiadizoyl)]Nitrone	73	231-233	CCl ₄	White
	α -(2-chloro-phenyl)-N-[2-(5-thio-1,3,4-thiadizoyl)]Nitrone	65	135	Hexane	White
	α -(3-chloro-phenyl)-N-[2-(5-thio-1,3,4-thiadizoyl)]Nitrone	63	151	Hexane	White
	α -(2-nitro-phenyl)-N-[2-(5-thio-1,3,4-thiadizoyl)]Nitrone	85	155-137	Cyclo_hexane	White
	α -(3-nitro-phenyl)-N-[2-(5-thio-1,3,4-thiadizoyl)]Nitrone	75	131	Cyclo_hexane	White
	α -(2-bromo-phenyl)-N-[2-(5-thio-1,3,4-thiadizoyl)]Nitrone	60	143-145	Hexane	White
	α -(3-bromo-phenyl)-N-[2-(5-thio-1,3,4-thiadizoyl)]Nitrone	50	151-149	Hexane	White
	α -(3-methoxy-phenyl)-N-[2-(5-thio-1,3,4-thiadizoyl)]Nitrone	45	102-104	Hexane	White
	3-(4-chloro-phenyl)-N-[2-(5-thio-1,3,4-thiadizoyl)]-4,5-dicarboxyl-isoxazoline	50	Dec. 233	CCl ₄	White

Preparation of nitrone⁽²⁰⁾ Compounds :

1.141 ml hydrogen peroxide (36%) in 2.54 ml glacial acetic acid were added to 2-benzilidene amino-5-thio-1,3,4-thiadizoyl to each of the following derivatives 2-(4-chloro , 2-chloro , 3-chloro , 2-nitro , 3-nitro , 2-Bromo , 3-Bromo and 3-methoxy)-benzilidene amino-5-thio-1,3,4-thiadizoyl in round bottom flask fitted with a condenser . Then the reaction became vigorous with evolution of high heat , in different cases . Evolution of heat was observed after gentle heating in compound C₁ , while in compounds C₃ , C₄ , C₇ , C₈ and C₉ after the addition had been completed . The

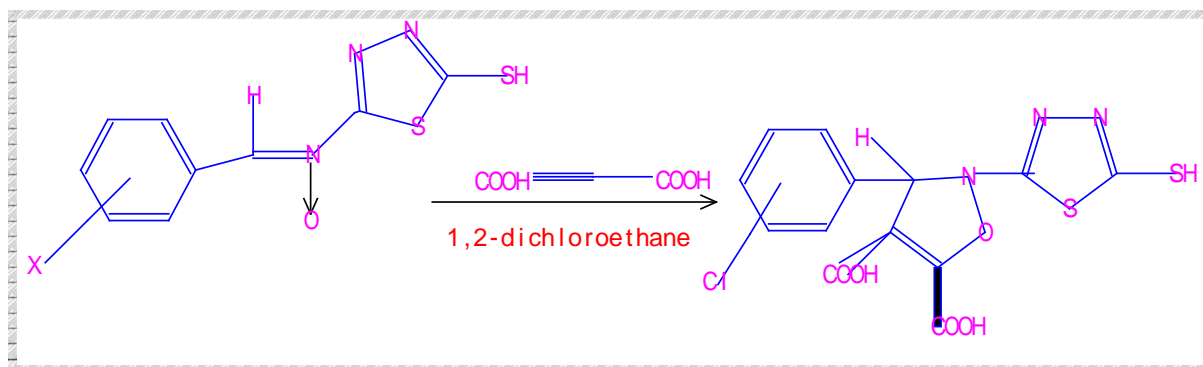
Scheme .1 : shows the reaction in details



Result and Discussion

Two kinds of compounds were prepared in this paper . The first were series A of compounds and the second was compound B. Series A were nine compounds represent the nine aldonitrone formed by a series of reactions of 2- amino- 5-thio-1,3,4 –thiadizole , which was prepared from the reaction of thiosemicarbazide , carbon disulfide and anhydrous sodium carbonate . The nine imines were prepared from the reaction of to amino -5-thio-1,3,4 –thiadizole with nine substituted

benzaldehydes as given in the experimental part . The reactions were done in ethanol and toluene , and the product was purified as in literature . The time of reaction became longer and the yield became lower . So we increased the ratio of benzaldehyde to aminoes , but still the yield was low even when larger amounts of material were used , however , when dry ethanol was used the yield became higher . The aldonitrone were obtained by the oxidation imines H_2O_2/HAC . Compound B which represents isoxazoline derivative was prepared from the 1,3 –dipolar cyclic addition between the nitron and the acetylene dicarboxylic acid in 1,2 –dichloroethane as a solvent . Only the para substituted benzaldehyde derivatives gave yield (50%). This could be attributed to technical reasons or to the type of substituent which are either ortho (steric and ortho factor interfered) or meta (no mesomericinterter here , only the inductive rule in the meta substituent) .



We can explain the geometry of interaction between the nitron (A_2) and the acetylene dicarboxylic acid in terms of endo interaction which involved the HOMO of nitron with the LUMO of acetylene dicarboxylic acid to give a fast primary interaction , due to similarity of the interacted orbitals .

Scheme (2): gives the anti product for 1,3- Dipolar cyclic addition

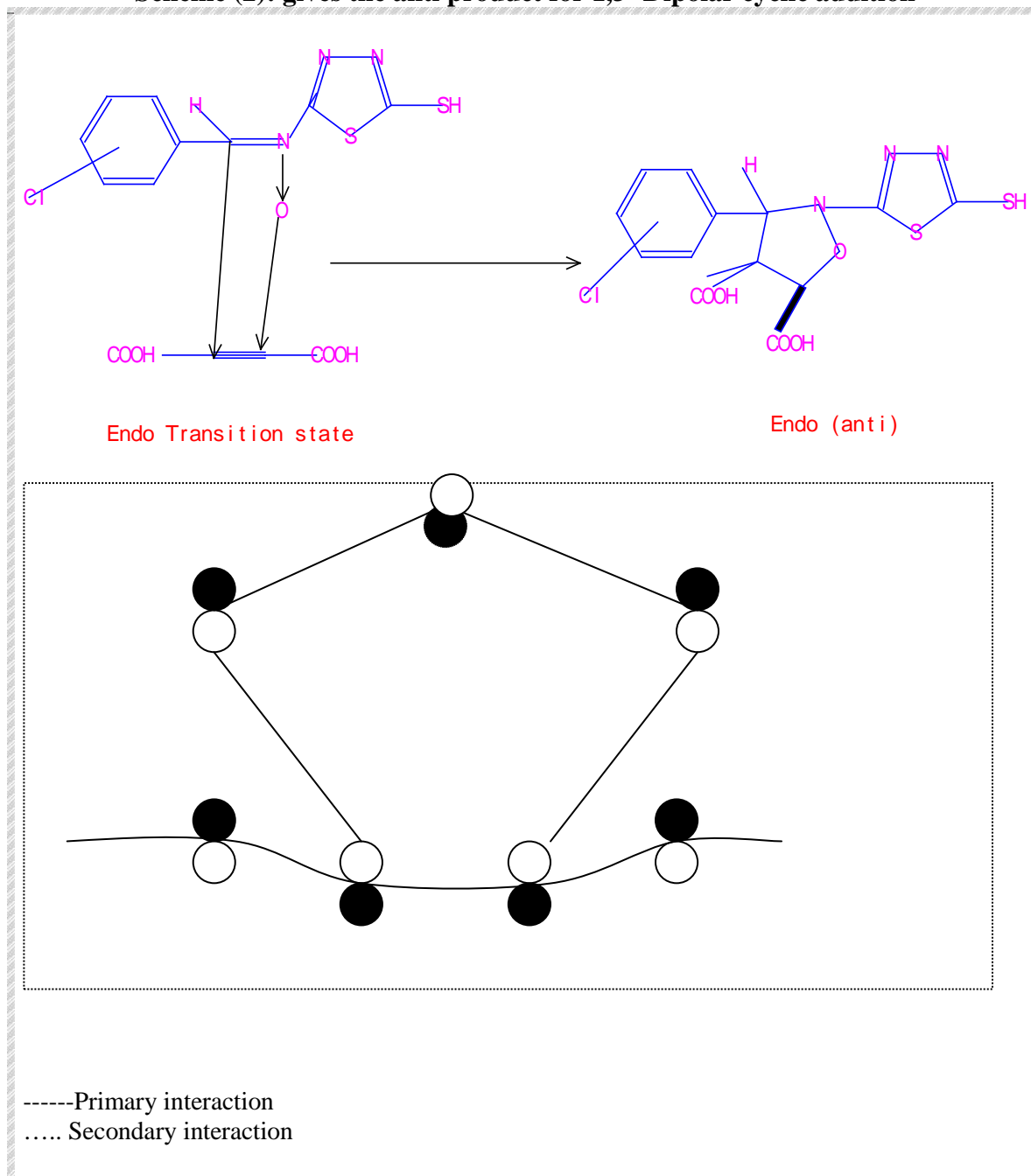


Table 3 : I.R data of the prepared compounds

Comp.	=C-H ben.Ar	=C-H str.Ar	N-O str.	C=N str.	C=C ring	S-H	C=O
A ₁	710(m) 680(m) 745(s)	3025 (w)	1275 (m)	1600 (s)	1575 (s)	2550 (m)	–
A ₂	750(s) 850(m)	3100 (w)	1300 (m)	1600 (s)	1575 (m)	2550 (m)	–
A ₃	750(s)	3090 (w)	1325 (m)	1600 (m)	1575 (m)	2550 (w)	–
A ₄	720 ,80 0,850,900(m)	3080 (w)	1300 (m)	1600 (m)	1575 (m)	2550 (m)	–
A ₅	720(m)	3100 (w)	1350 (m)	1620 (m)	1575 (w)	2550 (m)	–
A ₆	715(m)	3100 (w)	1350 (m)	1620 (m)	1575 (w)	2550 (m)	–
A ₇	740(s)	3075 (w)	1300 (m)	1590 (m)	1565 (m)	2550 (m)	–
A ₈	700(s) 805(m)	3075 (w)	1295 (s)	1600 (m)	1575 (m)	2550 (m)	–
A ₉	750(s) 800(m) 875(m) 900(m)	3010 (w)	1285 (m)	1585 (w)	1580 (w)	2550 (m)	–
B	765(s) 850(m)	3100 (w)	1300 (m)	–	1575 (m)	2550 (m)	1685, 1670(s)
A ₉		A ₇ – A ₈		A ₅ – A ₆		A ₂ _A ₄	Comp.
C –OCH ₃		C -Br		C-NO ₂		C -Cl	group
525 ,575(w) 2825(w)		400 – 500(w)		1555(w) 1350(s)		400 -565 (w– s)	Aromatic ring

Bending :ben ; Stretching (str) ; Weak :(w) ; medium : (m) ; strong :(s)

Charcterization of Compounds :

Infrared Spectra :

Table (3) shows the extensive absorption band for the nine aldonitrones and the cyclic addition product (B). The I.R spectra were measured as KBr disk . Compounds of series A have similar absorption planes at 1275 – 1350 cm⁻¹ , for N – O stretching and C=H stretching planes , for the aromatic (C –H) about 3010 -3100 cm⁻¹ and its out bending 680 -900 cm⁻¹ , and C=C aromatic

stretching at $1425 - 1550 \text{ cm}^{-1}$, S –H stretching at 2550 cm^{-1} and C –S –C stretching $640 - 675$, C – S bending at $1415 - 1440 \text{ cm}^{-1}$, have been observed for all samples .

There is a small difference in the positions and the intensities of the bands due to changing in the kind and the behaviour of the substituent (X) , if it is with drawing group or donor group , it will give an increase or decrease in the frequency . Compound B clearly shows a new band at $1670 - 1685 \text{ cm}^{-1}$ for C =O stretching , and C=C stretching at 1600 cm^{-1} . The O –H stretching band disappears . This could be due to hydrogen bonding . This fact can be taken as evidence that the cyclic addition was occurred .

UV Spectra :

The prepared compounds were studied in dry ethanol .Series A shows a highly intensive band λ_{max} $201.6 - 215.8 \text{ nm}$ for the transitions in the aromatic ring ⁽²²⁾.

Table 4 : UV data of the prepared compounds in ethanol ($1 \times 10^{-5} \text{ M}$)

Compound	λ (nm)		Compound	λ (nm)	
A ₁	201.6	214.0	A ₆	215.8	256.4
A ₂	202.4	236.8	A ₇	202.6	–
A ₃	202.2	–	A ₈	203.2	–
A ₄	202.2	228.4	A ₉	207.2	230.4
A ₅	215.6	256.6	B	201	235

Also compounds A₁ , A₂ , A₄ , A₅ , A₆ and A₉ show a peak $214 - 256.6$ caused by $\text{CH}=\text{N} \rightarrow \text{O}$ which belongs to the electronic transitions ($\pi - \pi^*$) ^(7,23).

This band disappeared in A₃ , A₇ and A₈ due to the low concentration (1×10^{-5}) while in cease the concentration to ($1 \times 10^{-4} \text{ M}$) appears from the spectra , all the compounds give absorption maximum larger than in A₁ (X=H) , which may be due to the type of substituent and its environment (o ,p ,m) on the phenyl ring , since an increase in the conjugation makes the system more stable by lowering it energy and causes a bathochronic shift for the electronic transition ($\pi \rightarrow \pi^*$) .

Table (4) shows the UV data for the prepared compounds in dry ethanol , concentration $1 \times 10^{-4} \text{ M}$, and selective examples are shown in Fig .1 and 2.

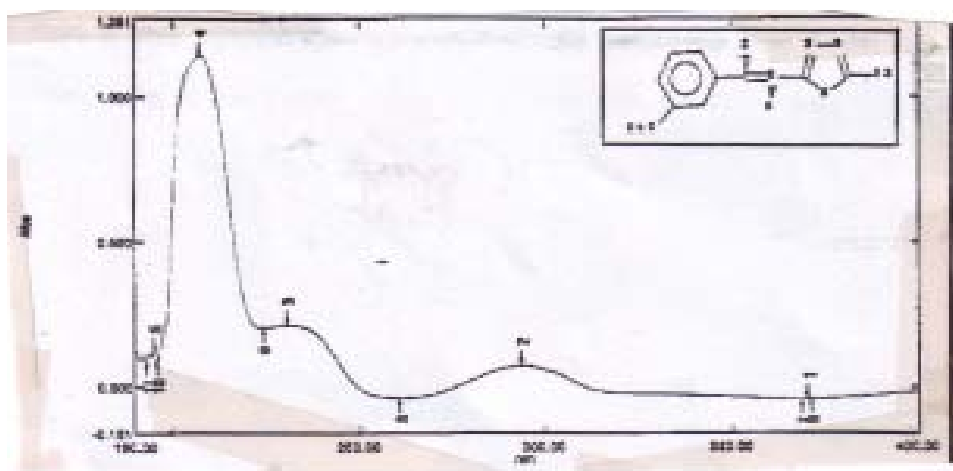


Fig. 1: UV spectrum of A₉

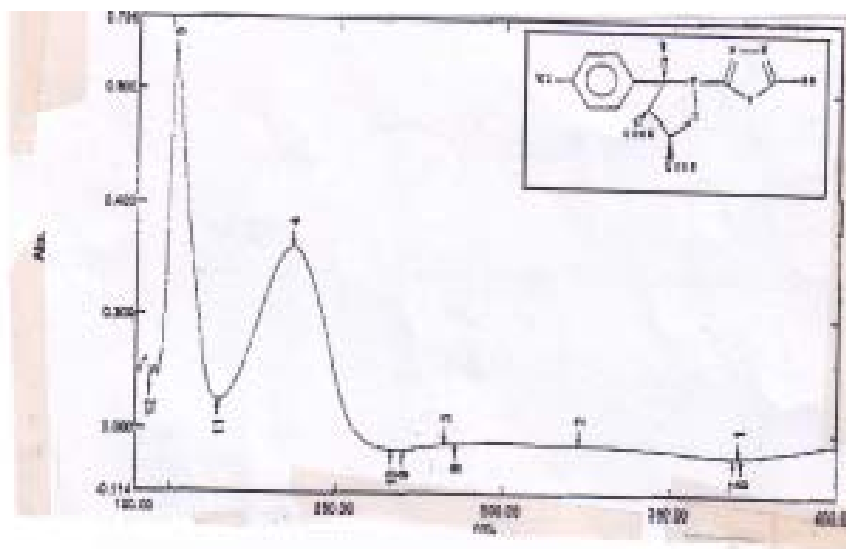


Fig 2: UV spectrum of compound B

^1H - NMR Spectroscopy :

Table (5) shows the chemical shifts , coupling constants and other details for the measured products in CDCl_3 solvent . Fig III and Fig IV are examples of the NMR spectra for compounds A_2 and A_6 . There is a similarity in some peak and differences between different product were smaller ($\text{A}_1 \rightarrow \text{A}_9$) the nitrone proton product ($\text{CH}=\text{N} \rightarrow \text{O}$) ranged from $\delta=7.19 - 7.2$ ppm , for all isomers as singlet which is in agreement with the literature ^(7,22) . The S -H gives singlet at 1.8 - 1.194 ppm .

The NMR spectra show difference is the aromatic region for ortho , meta and p- substituted compounds . Para -substituted phenyl give a simple AB system , Table (5) and Fig. IV .

Table 5 : NMR data for the prepared compounds

Comp.	Functional groups	Chemical shifts (ppm)	Coupling constants (Hz)	Solvents
A ₁	CH=N→O, 1H, S, S-H, 1, S Arom, 1H, tr,H-5 Arom, 2H,tr,H-4,H-6 Arom,2H,q,H-3,H-7	7.194 1.183 7.405 -7.443 7.543 -7.580 8.050 -8.083	7.6 7.6 7.2	CDCl ₃
A ₂	CH=N→O,1H,S S -H,1,S Arom,2H,d,H-3,H-6 Arom,2H,d,H -4,H-5	7.195 1.183 7.382 -7.454 7.991 -7.958	6.8 6.8	CDCl ₃
A ₃	CH=N→O,1H,S S -H,1,S Arom,2H,m,H -4,H-5 Arom,1H,m,H-3 Arom,1H,d,H-6	7.19 1.18 7.26 -7.33 7.40-7.45 7.95 -7.97	4 -8 4 8	CDCl ₃
A ₄	CH=N→O,1H,S S-H,1,S Arom,1H,m,H-5 Arom,1H,m,H-4 Arom,1H,m,H-6 Arom,1H,tr,H-3	7.194 1.182 7.399-7.455 7.673-7.700 7.952-7.999 8.188-8.197	2-1.6 1.032 1.179 -1.225 1.733	CDCl ₃
A ₅	CH=N→O,1H,S S-H,1,S Arom,2h,TR,H-4,H-5 Arom,1H,q,H-6 Arom,1H,tr,H-3	7.2 1.18 7.63-7.67 8.37-8.44 8.89-8.90	8 4-8 4	CDCl ₃
A ₆	CH=N→O,1H,S S-H,1,S Arom,1H,tr,H-5 Arom,1H,m,H-6 Arom,1H,m,H-4 Arom,1H,tr,H-3	7.2 1.18 7.63-7.67 8.37-8.44 8.89-8.90 8.892-8.901	8 8 4 4	CDCl ₃
A ₇	CH=N→O,1H,S S-H,1,S Arom,2h,M,h-4,h-5 Arom,1H,m,H-3 Arom,1H,m,H-6	7.19 1.18 7.30-7.37 7.62-7.68 7.62-7.96	4 4 4	CDCl ₃

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ملخص النتائج

تم تحضير تسعة الدونايترونات جديدة حاوية على حلقة (4,3,1-ثايديازول) وتم تشخيصها بواسطة مختلف الطرق الطيفية وطرق غيرها. ثم أجريت دراسة للأضافة الحلقية لتلك الألدونايترونات مع مركب أستلين_ثنائي حامض الكاربوكسيل ولم تنجح تلك الدراسة إلا لمركب واحد عانى الأضافة الحلقية من نوع 3,1-ثنائي القطب ليعطي مركباً هو 3- (4-كلورو فنيل) -2- (5-ثايو-4,3,1-ثايديازول)-5,4-ثنائي الكاربوكسيل أوكسازولين .

