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Synthesis of Some new 1,2,4-TriazinesDerived from 4-Amino Antipyrine

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Abstract **- A series of 1,2,4-triazines represented by compounds 3,5,6-triaryl-4-antipyrino-3,4,5,6-tetrahydro-1,2,4-triazine (3a-d) and (4a-e)have been synthesized from 4-aminoantipyrine as useful precursor. 4-Aminoantipyrine was reacted firstly with substituted benzaldehyde to afford schiff bases represented by compounds 4-arylidene antipyrine (1a-e), and later these compounds underwent Diels-Alder reaction with two substituted heterodiene represented by compounds N,N-diarylidenehydrazone (2a,b) under microwave irradiation and dry conditions to obtained the titled compounds (3a-d) and (4a-e) respectively. The structure of the prepared compounds were confirmed by the available physical and spectral methods.**

Keywords **- 4-Aminoantipyrine, 1,2,4-triazines, Diels-Alder reaction, Schiff bases**

I.INTRODUCTION

Nitrogen containing heterocycles have attracted huge interest over the past decades because of their divers pharmacology activities including protein kinase inhibition [1] , protein kinase have become the most important targets of drugs for various indications, such as cancer [2] and antimalarial activity [3]. Herein in this presentation 1,2,4-triazines have been synthesized as good example for the nitrogen containing heterocycles from 4-amino antipyrine which is on the other hand one of the most important biological active classes of heterocyclic nitrogen systems as anti-inflammatory, antipyretic, analgesic, antimicrobial agents [4,5] and active agent in industrial field as corrosion inhibiter [6]. 1,2,4-Triazine and its derivatives have been found to exhibit the variety of biological applications such as , antifungal [7,8], anticancer [9-11], anti-inflammatory [12,13], tuberculosis [14], antimicrobial[15-17], estrogen receptor[18], anti-malarial [19,20],anti-hypertensive [21,22] and as anti-AIDS agents [23]. Additionally to all the above applications, these compounds have been reported to possess a broad spectrum in the field of agriculture, they showed effects such as insecticides, herbicides, plant growth regulators and they are deployed for enhancing crop yield [24-26].

II.EXPERIMENTAL

Melting point were determined using electro thermal 9300 melting point apparatus and are uncorrected. Infrared (FT-IR) spectra were recorded as (KBr) disc using a Bruker, FT-IR, Spectrophotometer Tensor 27. Ultra-Violet (U.V) spectra were performed on Shimadzu UV-Visible Spectrophotometer UV-1650 PC using ethanol as a solvent. NMR spectra were recorded using England- Oxford (AS 400MHz) with TMS as internal standard, and DMSO-d_6 as solvents; [(s) singlet; (d) doublet; (m) multiplet],Turkish -EGE University .The domestic microwave oven(LG,MS,192W)with 750 watt power setting was used for irradiation.

Synthesis of 4-arylideneantipyrine(Schiff bases) (1a-e):- [27]

A solution of 4-amino antipyrine(0.01 mole, 2.03gm) in ethanol was added drop wise to a solution of substitutedbenzaldehyd(0.01 mole in 10 ml ethanol) with stirring at room temperature then refluxed for(30 mints) with stirring. The contents were cooling and the precipitate was filtered off and recrystallized from ethanol to obtain the desired products(1a-e) , the physical and spectral data were listed in Table I & II.

Synthesis of N,N-diarylidenehydrazone (2a, b):[28]

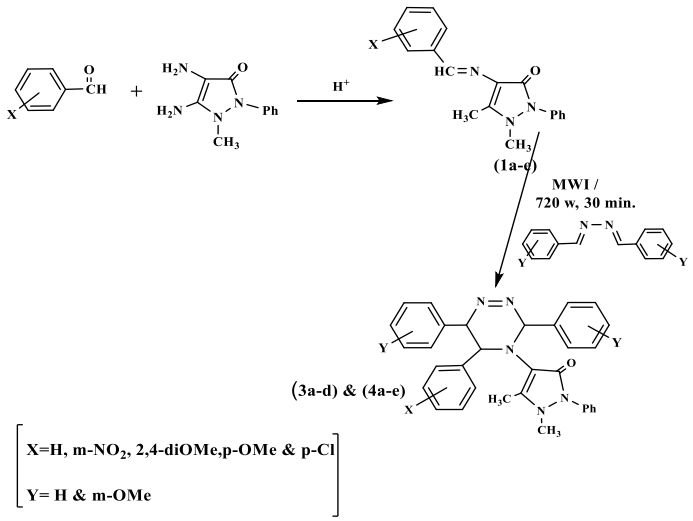
A mixture of appropriate aromatic aldehyde (0.01 mole) and hydrazine hydrate (80%) (0.05 mole, 2.5ml) in the presence of (50%) acetic acid (10 ml) and ethanol (30 ml) was refluxed for (3 hrs.). The excess solvent was distilled off, cooled and the solid product was filtered off, washed with cold water and then recrystallized from ethanol. The physical and spectral data were listed in Table III.

Synthesis of 3,5,6-triaryl-4-antipyrino-3,4,5,6-tetrahydro-1,2,4-triazine (3a-d) and(4a-e):[29]

A mixture of N,N-diarylidenehydrazone(2a,b)(0.002 mole) and 4-arylideneantipyrin (1a-e)(0.002 mole) was irradiated in a microwave oven for(13 mints) at (720 watt), cold water (10ml) was added to the reaction mixture after cooling to obtained the solid product which was filtered off and recrystallized from ethanol-water. The physical and spectral data were illustrated in Table IV, V , VI, VII respectively.

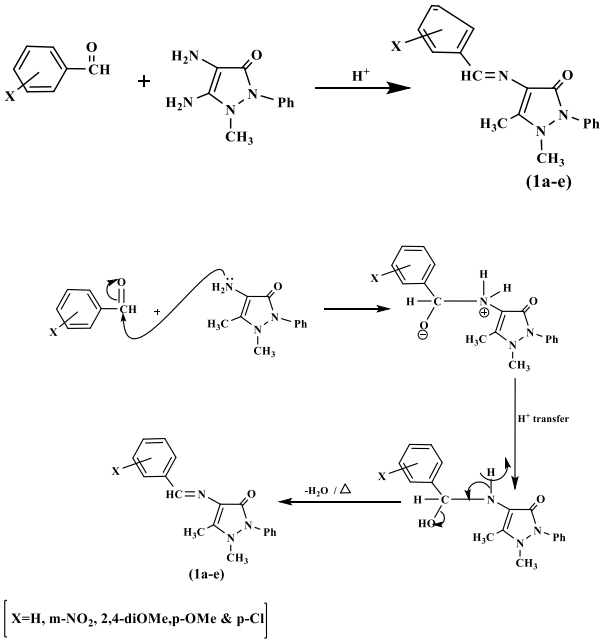
III.RESULTS and DISSCUSION

4-Aminoantipyrine used as good essential group to give the required product represented by compounds 1,2,4-triazines represented by compounds 3,5,6-triaryl-4-antipyrino-3,4,5,6-tetrahydro-1,2,4-triazine (3a-d) and (4a-e) respectively, also this due to the amino group in 4- position. The synthetic pathway is given in Scheme (1).



Scheme (1)

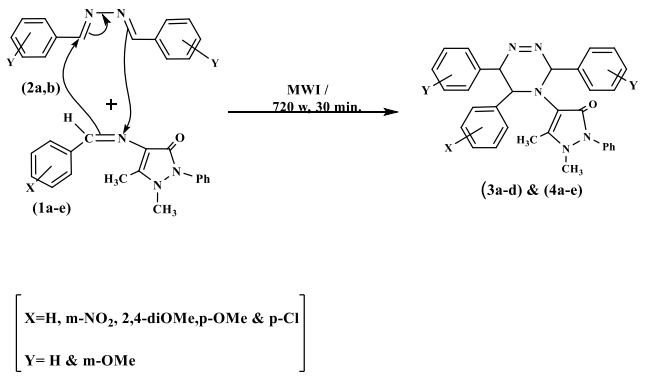
The first stage of the current project involved the synthesis of schiff bases represented by compounds 4-arylidene antipyrine (1a-e)**.**The mechanism is believed to be the condensation between the active amino group with various substituted benzaldehyde in presence of catalaytic amount of glacial acetic acid to afford the schiff bases (1a-e) with loosing of a molecule of water as shown in equation (1) and Scheme (2)[30].



Scheme (2)

The structure of these compounds were confirmed by spectroscopic analysis , FT-IR and U.V , Table (1). Actually, in IR spectra these compounds shown the presence of (C=N) functional group by the appearance of a stretching absorption bands at (1607-1610 cm^{-1}) and stretching absorption bands at (1730-1735 cm^{-1}), (1642-1650 cm^{-1}) and (1071-1075 cm^{-1}) refer to (C=O), (C=C) and (N-N) functional groups respectively [31]. Whereas, in NMR spectra they show sharp singlet band due to (1H,CH=N) additionally to other spectral data as shown in Table (2). Finally, in U.V spectra they shown a maximum absorption bands at λ_{max} (284-340 nm) and (250-266 nm) refer to ($n\rightarrow\pi^*$) and ($\pi\rightarrow\pi^*$) respectively [31], Table (1)& (2).The second and final stage in this presentation involved the reaction between schiff

bases (1a-e) with two different types of diarylidine hydrazine (2a&b) via Diels-Alder reaction in the absence of solvent and accelerated by microwave irradiation in order to synthesis of a new series of substituted 1,2,4-triazines (3a-d) and (4a-e) respectively in good yields. Mechanistically, it is reasonable to assume that the reaction was proceeded directly through sequence addition in solid facereaction without any catalyst just accelerated by microwave irradiation which reduce the reaction time ,economic and gave accepted yield, Scheme (3)[32].



Scheme (3)

These compounds were also confirmed by FT-IR , ^{1}H-NMR and U.V spectroscopic methods. Fortunately, the IR spectra provided a clear evidence about the right structure of these compounds as shown in tables IV, V, VI , VII respectively. Generally, the mean evidence came from the absence of (C=N) functional group at (1607-1610 cm^{-1}) and the appearance of (N=N) functional group which shown stretching absorption bands at (1571-1592 cm^{-1}) and (1547-1575 cm^{-1}) respectively. On the other hand,in NMR spectra the appearance of three singlet bands between (δ8.84-10.51 ppm) due to (3H, CH, triazine ring) [33] came with agreement with the expected formula in Scheme (3) .Also, in U.V spectra they shown different absorption bands at λ_{max} (312-350 nm), (298-350 nm) and (276-278 nm), (224-276 nm) due to the ring system additionally to ($n\rightarrow\pi^*$) and ($\pi\rightarrow\pi^*$) respectively[31] as shown in tables IV,V,VI & VII.

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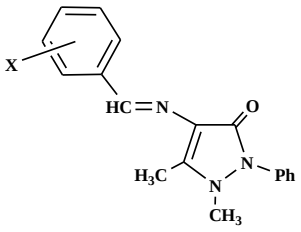
Table I
The physical and spectral data for compounds (1a-e)



Comp. No.	X	M.P (˚C)	Yield (%)	UV (EtOH) λmax (nm)	I.R (KBr) υ (cm^{-1})				
					C=O	C=C	C=N	N-N	others
1a	H	170 - 172	70	340,250	1735	1642	1607	1073	—
1b	m-NO_2	218 -220	78	320,250	1735	1650	1610	1075	NO_2: asym. 1514 , sym. 1381
1c	2,4-di OCH_3	181 -183	65	312,266	1734	1644	1607	1071	C-O-C: asym. 1494, sym. 1342
1d	p- OCH_3	166 - 168	55	300,252	1734	1643	1607	1071	C-O-C: asym. 1454, sym. 1365
1e	p- Cl	250 -251	66	284,252	1730	1644	1607	1071	—

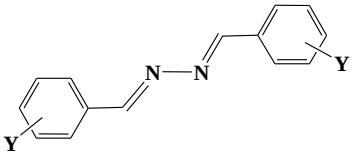
Table II

The ^{1}H-NMR spectral data for compounds (1a-e)

Compd. No.	^{1}H-NMR (δ,ppm, DMSO-d_6)
1a	δ1.98 (s,3H,CH_3), δ2.48 (s,3H,CH_3N) , δ 9.57(s,1H,CH=N), δ7.34-7.81(m, aromatic)
1b	δ2.08(s,3H,CH_3), δ3.16 (s,3H,CH_3N) , δ 9.64(s,1H,CH=N), δ7.35-8.58 (m, aromatic)
1c	δ1.98(s,3H,CH_3), δ3.16 (s,3H,CH_3N) , δ 3.38 (s,6H, 2OCH_3), δ 9.64(s,1H,CH=N), δ7.35-8.58(m, aromatic)
1d	δ1.22(s,3H,CH_3), δ2.48(s,3H,CH_3N) , δ 3.79 (s,3H, OCH_3), δ 9.51(s,1H,CH=N), δ6.98-7.75(m, aromatic)
1e	δ1.22 (s,3H,CH_3), δ2.47 (s,3H,CH_3N) , δ 9.55(s,1H,CH=N), δ7.35-7.82(m, aromatic)

Table III

The Physical and spectral data for compounds (2a,b)

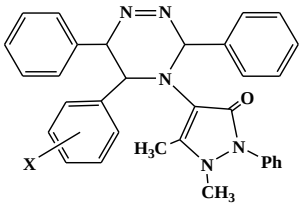


Compd. No.	Y	M.P (˚C)	Yield (%)	UV (MeOH) λmax (nm)	FT-I.R (KBr) υ (cm^{-1})		
					N─N	C═N	C-O-C
2a	H	92-94⋆	80	306, 288	1075	1626	—
2b	m-OCH_3	73-74	74	308,273	1048	1617	asym.1477 sym. 1341

⋆Recorded : [94˚C] [28]

Table IV

The physical properties and spectral data of compounds (3a-d)



Comp. No.	X	M . P (˚c)	Yield %	(MeOH) λmax (nm)	FT-IR νcm^{-1} (KBr)					
					C=O	C=C	N=N	C-N	N-N	Others
3a	H	88 - 87	55	340,276	1707	1618	1583	1352	1076	—
3b	m-NO_2	168 -169	80	330,278	1734	1632	1588	1350	1071	NO_2: asym. 1552 , sym. 1375
3c	2,4-di OCH_3	150 - 151	66	350,278	1734	1643	1592	1347	1075	C-O-C: asym. 1438, sym. 1343
3d	p- OCH_3	130 - 133	66	312,278	1735	1642	1572	1361	1073	C-O-C: asym. 1464,sym. 1352

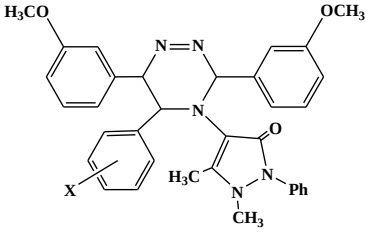
Table V

The ^{1}H-NMR spectral data of compounds (3a-d)

Compd. No.	^{1}H-NMR (δ,ppm, DMSO-d_6)
3a	δ2.01 (s,3H,CH_3), δ2.48 (s,3H,CH_3N) , δ 9.09,9.58 & 10.51 (s,3H,triazine), δ7.35-8.89(m, aromatic)
3b	δ1.97 (s,3H,CH_3), δ2.64 (s,3H,CH_3N) , δ 8.85, 9.56 & 9.65 (s,3H,triazine), δ7.36-8.23(m, aromatic)
3c	δ1.21 (s,3H,CH_3), δ2.48 (s,3H,CH_3N) , δ 3.81 (s,6H, 2OCH_3), δ 8.84, 9.57 & 9.78 (s,3H,triazine), δ6.61-7.51(m, aromatic)
3d	δ1.21 (s,3H,CH_3), δ2.48 (s,3H,CH_3N) , δ 3.79 (s,3H, OCH_3), δ 8.69, 9.51 & 9.57 (s,3H,triazine), δ6.98-7.81(m, aromatic)

Table VI

The physical and spectral data for compounds (4a-f)



Comp. No.	X	M.P (°C)	Yield (%)	U.V (MeOH) λmax (nm)	FT-IR *v*cm^{-1} (KBr)					
					C=O	C=C	N=N	C-O-C	C-N	N-N
4a	H	125 - 127	65	322,276	1732	1620	1562	asym.1520 sym. 1450	1365	1072
4b	m-NO_2	158 - 160	90	298,224	1733	1612	1562	asym.1514 sym. 1381	1365	1051
4c	2,4-di OCH_3	155 - 157	69	316,254	1737	1640	1575	asym.1508 sym. 1390	1340	1085
4d	p- OCH_3	110 - 112	69	350,276	1736	1643	1562	asym.1508 sym. 1421	1365	1091
4e	p- Cl	148 - 150	94	310,254	1735	1620	1547	asym.491 sym. 1381	1367	1090

Table VII

The ^{1}H-NMR spectral data for compounds (4a-f)

Compd. No.	^{1}H-NMR (δ,ppm, DMSO-d_6)
4a	δ1.21 (s,3H,CH_3), δ2.48 (s,3H,CH_3N) , δ 3.74 (s,6H, 2OCH_3), δ 8.70, 9.53 & 9.57 (s,3H,triazine), δ7.07-7.78(m, aromatic)
4b	δ2.01 (s,3H,CH_3), δ2.47 (s,3H,CH_3N) , δ 3.72 (s,6H, 2OCH_3), δ 8.66, 9.64 & 10.36 (s,3H,triazine), δ6.08-8.20(m, aromatic)
4c	δ1.22 (s,3H,CH_3), δ2.48 (s,3H,CH_3N) , δ 3.83 (s,12H, 4OCH_3), δ 8.67, 9.76 & 9.77 (s,3H,triazine), δ6.587-7.95(m, aromatic)
4d	δ1.20 (s,3H,CH_3), δ2.48 (s,3H,CH_3N) , δ 3.81 (s,9H, 3OCH_3), δ 9.08, 9.54&10.05 (s,3H,triazine), δ6.98-7.75(m, aromatic)
4e	δ1.22 (s,3H,CH_3), δ2.47 (s,3H,CH_3N) , δ 3.85 (s,6H, 2OCH_3), δ 8.67, 9.54 & 9.55 (s,3H,triazine), δ7.09-7.82(m, aromatic)