Microwave Assisted Synthesis of Some 4-Carbothioamide-1,2,4-Triazine Derivatives

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Abstract

A rapid , sufficiency and economic with no pollution method was adopted to synthesized several 3,5,6-triayl-4-carbothioamide-3,5,6-trihydro-1,2,4-triazine derivatives (10-16) and (17-23) respectively using solid phase one-pot two component reaction between hetero dienophile represented by Schiff bases (1-7) and hetero diene represented by diarylidene hydrazine (8 and 9) accelerated by grinding for (15-30 minutes) and microwave irradiation using appropriate time and energy in presence of catalytic amounts of tri ethyl amine.

All prepared compounds were illustrated by the available physical and spectral methods .

Key words : 1,2,4-Triazine ,Diels-Alder reaction , Schiff bases , Microwave irradiation , Grinding .

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Introduction

Thioamide and it`s derivatives received a great deals of attention in the recent decades as good synthon in organic chemistry[1] and industrial field[2].Also these compounds were evaluated to possess active anticancer[3],anti-tubercular[4],anti-fungi [5],anti-malarial[6],anti-inflammatory[7] and also it used in treatment at acute nervous convulsions and intestinal worms[8]. on the other hand , the 1,2,4-triazine (which prepared in this presentation) it is one of the most important six-membered heterocyclic compounds, due to it`s wide applications in medical field as anti-cardiovascular disease [9] ,anti-cancer[10] , anti-inflammatory[11],anti-fungal[12],anti-bacterial [13] and anti-viral[14]. Whereas, they used widely in agricultural field as high efficiency insecticide [15] . According to the all mentioning above , therein in this work anew series of 1,2,4-triazine derivatives represented by compounds(10-16) and(17-23) through . one-pot solid phase two component reaction between Schiff bases (1-7) and diarylidene hydrazine (8 & 9) in basic media and also accelerated by grinding for(15-30 minutes) and microwave irradiation with appropriate time and energy . Actually , Schiff base (1-7)(as hetro dienophile) were prepared through . direct condensation reaction . between thioamide represented by N-phenyl thiourea and substituted benzaldehyde in acidic media form acetic acid . Whereas , the diarylidene hydrazine as hetero diene were attended in the some way but in ratio(1:2) of hydrazine hydrate: substituted benzaldehyde .

Experimental

Synthesis of 1-benzylidene-3-phenl urea (Schiff bases)(1-7)[16] :-

In round bottomed flask (100 ml) dissolved with stirring (0.001 mole) of substituted benzaldehyde in (5ml) abs .ethanol in presence of glacial acetic acid (2-3 drops) followed by gradually adding of (5ml) alcoholic solution of phenyl thiourea (0.001 mole/0.152 g) . The stirring was continued for (3hrs) at room temperature until the reaction have been completed which traced by using thin layer chromatography with solvent system (benzene : methanol) in ratio(8:2) . The reaction mixture

then poured into ice-water (10 ml), filtration and washed thoroughly with cold water (4x5 ml) followed by drying to afford the Schiff bases (1-7) with physical properties listed in Table (1) .

Table (1): The physical properties for compounds (1-7)

Comp. No.	X	M.P (°C)	Yield (%)	Molecular Formular	Colour	T.L.C Benzen:Meth (8:2)anol
1	H	122-124	50	$C_{14}H_{12}N_2S$	Yellow	0.650
2	p-NO_2	52-55	70	$C_{14}H_{11}N_3O_2S$	Yellow	0.662
3	p-N,N- diMe-amino	100-102	70	$C_{16}H_{17}N_3S$	Yellow	0.618
4	p-OH	132-135	54	$C_{14}H_{12}N_2OS$	White	0.641
5	o-OMe	130-133	54	$C_{15}H_{14}N_2OS$	Black	0.581
6	p-OMe	122-125	59	$C_{15}H_{14}N_2OS$	Yellow	0.626
7	p-CH_3	135-138	66	$C_{15}H_{14}N_2S$	White	0.600

Synthesis of diarylidene hydrazine(8&9):-

These two compounds have been prepared according to the literature [17]. In ratio (1:2) between hydrazine hydrate :substituted benzaldehyde and it has conformity to the literature in all it's physical constants .

synthesis of 3,5,6-triaryl -4-carbothioamide-3,5,6-trihydro-1,2,4-triazine (10-16)and (17-23)[18] :-

In small mortar equimolar (0.0005 mole) of Schiff bases (1-7) and diarylidene hydrazine (8 & 9)were well grinding in presence of (3 drops) of tri ethyl amine for (15-30 minutes) followed by irradiation via microwave oven by using appropriate time and energy Table(2) . Cooling these adding (5 ml) acetone to separate the un reactant compounds . filtration and washed thoroughly with cold water (4x5 ml) then dried to afford 1,2,4-triazines with physical properties listed in Tables (3 & 4) respectively .

Table(2) : Appropriate time and energy in microwave irradiation

Comp.No.	X	y	Tim.(min.)	energy(watt)
10	H	2,4-diOMe	8	600
11	p-NO_2	2,4-diOMe	8	600
12	p-N,N- diMe-amino	2,4-diOMe	8	600
13	p-OH	2,4-diOMe	10	700
14	o-OMe	2,4-diOMe	10	700
15	p-OMe	2,4-diOMe	10	700
16	p-CH_3	2,4-diOMe	20	700
17	H	p-N,N-diMe amino	10	700
18	p-NO_2	p-N,N-diMe amino	5	700
19	p-N,N- diMe- amino	p-N,N-diMe amino	3	700
20	p-OH	p-N,N-diMe amino	3	700

21	o-OMe	p-N,N-diMe amino	3	700
22	p-OMe	p-N,N-diMe amino	10	700
23	p-CH_3	p-N,N-diMe amino	10	700

Table (3): The physical properties for compounds (10-16)

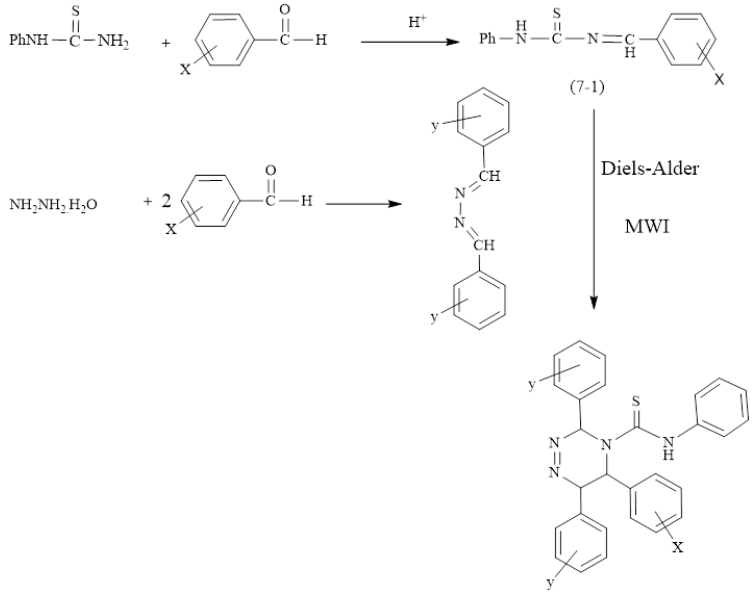
Comp. No.	X	M.P (°C)	Yield %	Molecular. Formular	Colour	T.L.C Benzene: Methanol (8:2)
10	H	189-192	71	$C_{32}H_{32}N_4O_4S$	Yellow	0.700
11	p-NO_2	184-187	67	$C_{32}H_{31}N_5O_6S$	Yellow	0.800
12	p-N,N- diMe-amino	188-190	69	$C_{34}H_{37}N_5O_4S$	Brown light	0.500
13	p-OH	dec.243	74	$C_{32}H_{32}N_4O_5S$	Brown Dark	0.530
14	o-OMe	187-190	71	$C_{33}H_{34}N_4O_5S$	Brown	0.500
15	p-OMe	180-183	71	$C_{33}H_{34}N_4O_5S$	Brown	0.400
16	p-CH_3	185-188	74	$C_{33}H_{34}N_4O_4S$	Brown	0.460

Table (4): The physical properties for compounds (17-23)

Comp. No.	X	M.P (°C)	Yield (%)	Molecular. Formular	Colour	T.L.C Benzene: Methanol (8:2)
17	H	173-177	80	$C_{32}H_{34}N_6S$	Brown	0.750
18	p-NO_2	287-290	70	$C_{32}H_{33}N_7O_2S$	Brown Dark	0.760
19	p-N,N- diMe-amino	288-290	74	$C_{34}H_{39}N_7S$	Brown	0.750
20	p-OH	243-245	74	$C_{32}H_{34}N_6OS$	Brown	0.770
21	o-OMe	280-283	71	$C_{33}H_{36}N_6OS$	Brown	0.780
22	p-OMe	dec-228	71	$C_{33}H_{36}N_6OS$	Brown	0.430
23	p-CH_3	279-282	74	$C_{33}H_{36}N_6S$	Brown	0.760

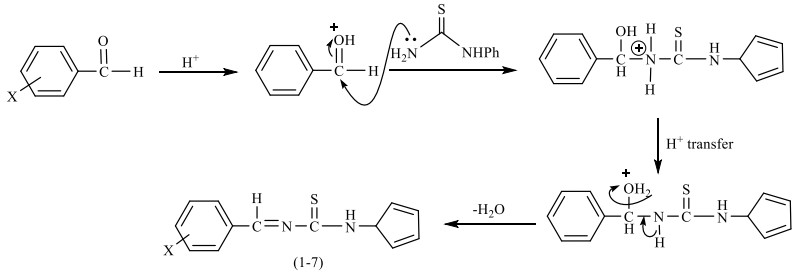
Results and Discussion

1,2,4-triazine derivatives (10-23) have been achieved via green chemistry techniques represented by grinding and microwave irradiation and also through aza Diels-Alder reaction as shown in the following synthetic pathway :-



Scheme(1):synthetic pathway for compounds(1-23)

First of all , Schiff bases(1-7) was prepared through the following mechanism between N-phenyl thiourea and substituted benzaldehyde [19]:



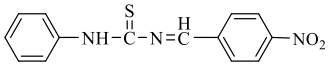
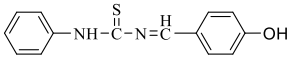
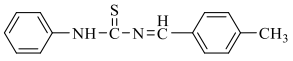
Scheme(2):synthetic mechanisum for compounds(1-7)

Actually , these Schiff base shown different physical properties by comparing with that for starting material and also by using thin layer chromatography (T.L.C) as (R_f value) Table(1) . while, in spectroscopic methods , they gave absorption bond in U.V spectra at λ_{max} (nm):287-347 and (220-289) refer to the n π^* and π π^* respectively . whereas, in FT-IR they gave stretching vibration at (υcm^{-1}): (1543-1593) and (3273-3422) refer to the (C=N)and (N=C-H) functional groups respectively in addition to the other absorption bonds listed in Table (5) which gave an indication for the suggested structure . On the other hands, in ^{1}H-NMR spectroscopy , compounds (2,4 and 7) where shown characteristic peaks at (δ ppm): (1.18 and 2.60) refer to the imine proton(HC=N) and at (5.8 and 7.10) refer to the NH functional group as well as to the other absorption peaks listed in Table (6), which came in agreement with the suggested structure.

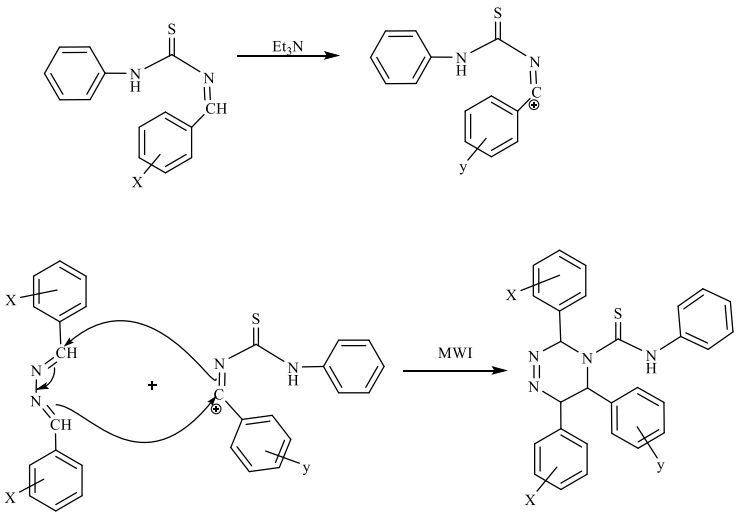
Table (5):Spectral data for compounds (1-7)

Comp. No.	X	FT-IR.V cm^{-1}						
		H-C=N	NH	C=C	C=N	C=S	others	U.V MeOH or EtOH λ_{max} nm
1	H	3424	3181	1614	1526	1443	---	295,289
2	p-NO_2	3422	3179	1615	1536	1443	NO_2 asym1463 sym1352	298,244
3	p-N.N-diMe amino	3310	3150	1634	1593	1443	CH_3 asym2994 sym2822	347,276
4	p-OH	3273	3179	1615	1524	1441	OH 3424	289,220
5	o-OMe	3422	3181	1615	1524	1443	C-O-C asym1262 sym1061	292,243
6	p-OMe	3422	3179	1613	1526	1443	C-O-C asym1262 sym1059	293,243
7	p-CH_3	3424	3179	1615	1524	1443	----	294,244

Table (6):^{1}H-NMR data for compounds (2,4 and 7)

Comp. No.	Structure	^{1}H-NMR, DMSO-d6, δ(ppm)
2		NH-C=S(s,7.10,1H); phenyl ring (m,7.11-7.63,5H); p-NO_2-phenyl(AB system)(d-d,7.40-7.50,4H); CH=N (s,2.60,1H).
4		NH-C=S(s,7.10,1H); phenyl ring (m,7.11-7.39,5H); p-OH-phenyl(AB system) (d-d,7.41-7.50,4H); CH=N (s,2.60,1H);OH(s,9.81,1H)
7		CH_3(s,1.13,3H);NH-C=S(s,5.8,1H); phenyl ring (m,7.12-7.93,5H); p-CH_3-phenyl(AB system) (d-d,8.34-8.70,4H); CH=N (s,1.18,1H).

Finally , a mixture of Schiff bases (1-7) as hetero dienophile and diarylidene hydrazine (8 and 9) as hetero diene were underwent aza Diels-Alder reaction through green chemistry techniques represented by grinding for (15-30 minutes) and microwave irradiation by using appropriate time and energy for each adduct in presence of catalytic amounts of tri ethyl amine as shown in the following mechanism[18]:



[y= H,NO_2,OH,o-CH_3,p-OCH_3,p-CH_3,p.N,N-diamine- amino]
[X=CH_3O,N,N-diamine-amino]

Scheme(3):synthetic mechanism of compounds (10-23)

According to the mechanism in Scheme (3) it was assumed that the mechanism proceeded through sequential addition resulting from using microwave irradiation and grinding which started by forming the carbon anion followed by cycloaddition reaction to afford the tetra substituted 1,2,4-triazine represented by compounds (10-16) and (17-23) respectively . All these compounds were gave in FT-IR spectroscopy a stretching vibration bonds at (υ cm^{-1}):(1253-1289)and (1362-1364) refer to the (N=N)functional group in addition to the other absorption bonds listed in Tables (7 and 8). Actually, the absence of stretching vibration of (C=N) and the appearance of (N=N) gave clear evidence for the suggested structure . Whereas, in ^{1}H-NMR spectroscopy compounds (10,12)and(19-21)shown significant peaks refer to the triazine protons as well as all compounds with para substituent shown clear AB-system as(d-d)peaks as shown in Table(9) which came in agreement with suggested structure.

Table (7):Spectral data for compounds (10-16)

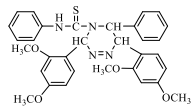
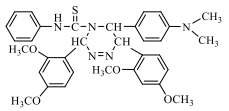
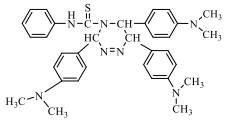
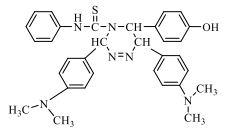
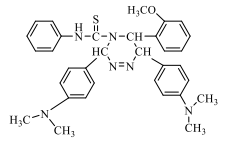
Comp. No.	X		FT-IR.V cm^{-1}							U.V MeOH or EtOH λ_{max} nm
		NH	CH_3		C=C	C=S	N=N	C-O-C	others	
			asym.	sym.						
10	H	3412	2930	2839	1624	1464	1266	asym1266 sym1019	---	363,339
11	p-NO_2	3132	2981	2849	1621	1593	1252	asym1234 sym1016	NO_2 asym1508 sym1338	359,302
12	p-N,NdiMe-amino	3412	2945	2837	1613	1502	1287	asym1269 sym1034	---	358,299

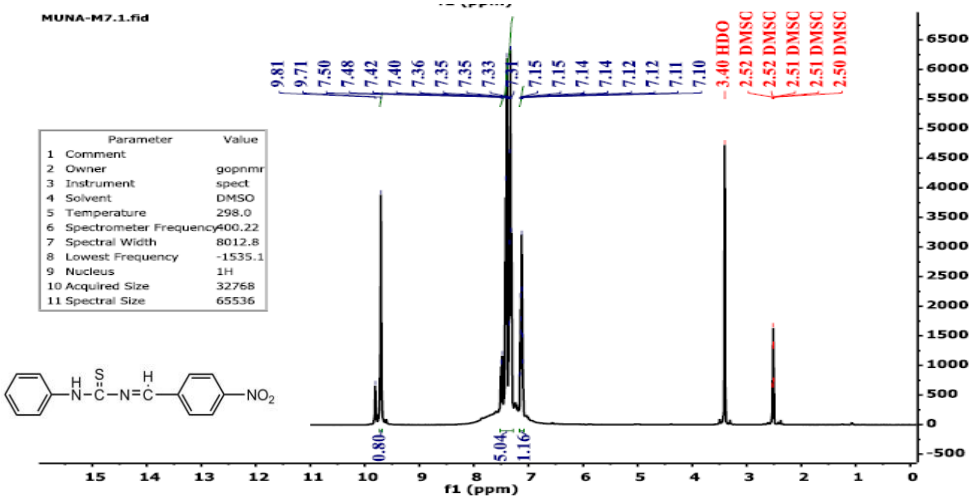
13	p-OH	3235	2930	2837	1615	1505	1279	asym1208 sym1030	OH-3414	362,319
14	o-OMe	3132	2906	2774	1612	1584	1253	asym1234 sym1016	---	358,259
15	p-OMe	3406	2933	2836	1611	1504	1275	asym1208 sym1030	---	352,292
16	p-CH_3	3133	2906	2830	1612	1573	1289	asym1235 sym1130	---	352,299

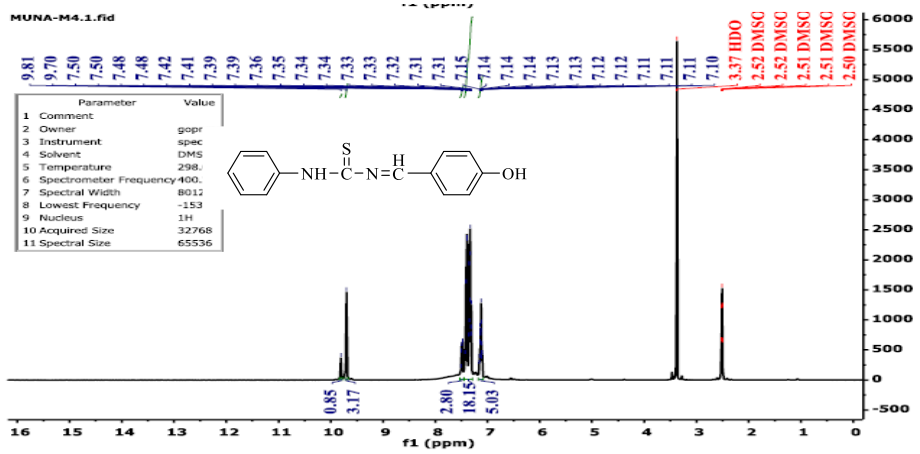
Table (8):Spectral data for compounds (17-23)

Comp. No.	X		FT-IR.V cm^{-1}						
		NH	CH_3		C=C	C=S	N=N	others	U.V MeOH or EtOH λ_{max} nm
			asym.	sym.					
17	H	3132	2906	2793	1600	1552	1363	---	363,252
18	p-NO_2	3416	2920	2853	1605	1526	1364	NO_2 asym1436 sym1175	244,221
19	p-N,N-diMe-amino	3428	2920	2855	1607	1520	1364	---	326,244
20	p-OH	3416	2917	2855	1603	1522	1364	OH-3473	327,244
21	o-OMe	3407	2917	2855	1603	1522	1364	C-O-C asym1229 sym1061	244,218
22	p-OMe	3414	2920	2890	1611	1522	1362	C-O-C asym1321 sym1059	253,228
23	p-CH_3	3416	2918	2890	1611	1520	1364	---	326,246

Table (9):^{1}H-NMR data for compounds (10,12,19-21)

Comp. No	Structure	^{1}H-NMR, DMSO-d6, δ(ppm)
10		H-triazin(m,0.84-3.35,3H); 4CH_3(s,3.36, 12H); H-aromatic (m,7.07-7.50,16H);NH-C=S (s,8.65,1H)
12		H-triazin(m,3.60-3.80,3H); 6CH_3(b,3.83, 18H); p-N,N-diMe amino phenyl (AB system)(d-d,7.07-7.39,4H); H-aromatic (b,7.44-7.50,11H); NH-C=S (s,8.65,1H)
19		H-triazin(m,2.42-2.88,3H); 6CH_3(s,2.99, 18H); p-N,N-diMe amino phenyl (AB system)(d-d,6.58-6.78,12H);phenyl ring (m,7.56-7.66,5H); NH-C=S (s,8.50,1H)
20		H-triazin(m,0.86-1.25,3H); 4CH_3(b,3.05, 12H); p-N,N-diMe amino phenyl (AB system)(d-d,6.76-6.78,8H); p-OH phenyl (AB system)(d-d,7.64-7.66,4H);phenyl ring (b,7.67-8.00,5H); NH-C=S (s,8.48,1H);OH(s,8.50,1H)
21		H-triazin(m,2.41-2.75,3H); 4CH_3(b,3.00, 12H); OCH_3(s,3.21,3H),m-OCH_3-phenyl(m,6.59-6.68,4H);p-N,N-diMe aminophenyl (AB system) (d-d,7.64-7.66,8H); phenyl ring(m,8.46-8.48,5H); NH-C=S (s,8.50,1H).

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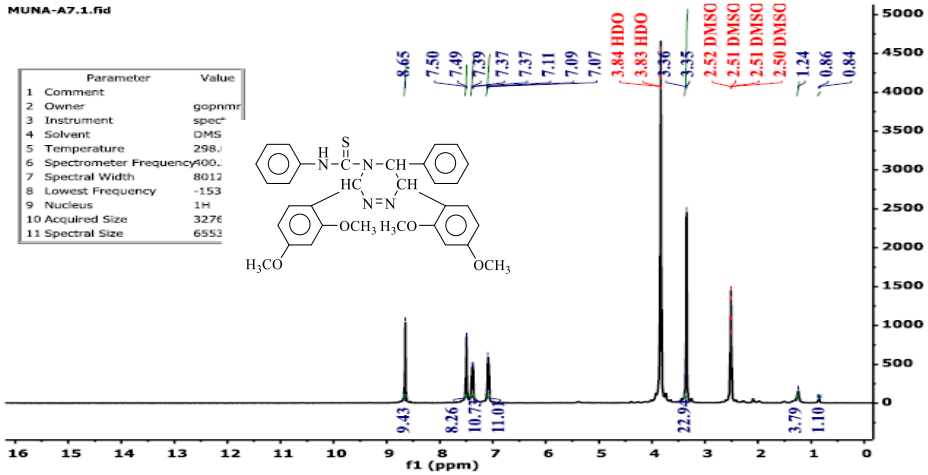
NH
OH
f1 (ppm)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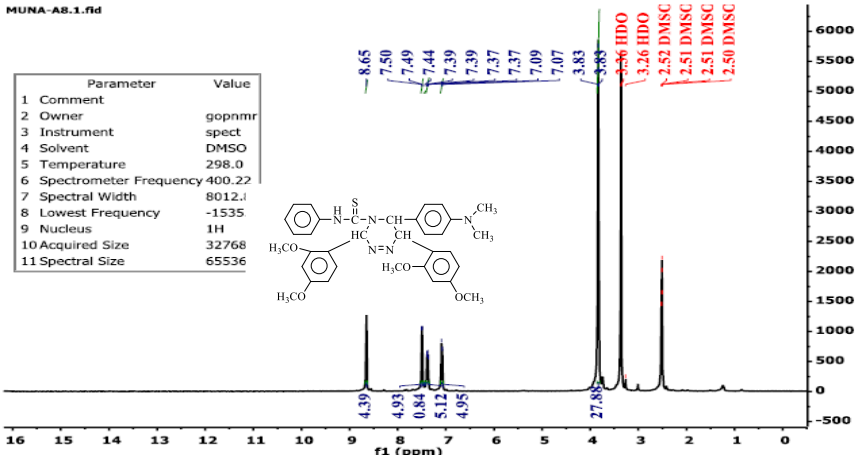
11 Spectral Size 6553
f1 (ppm)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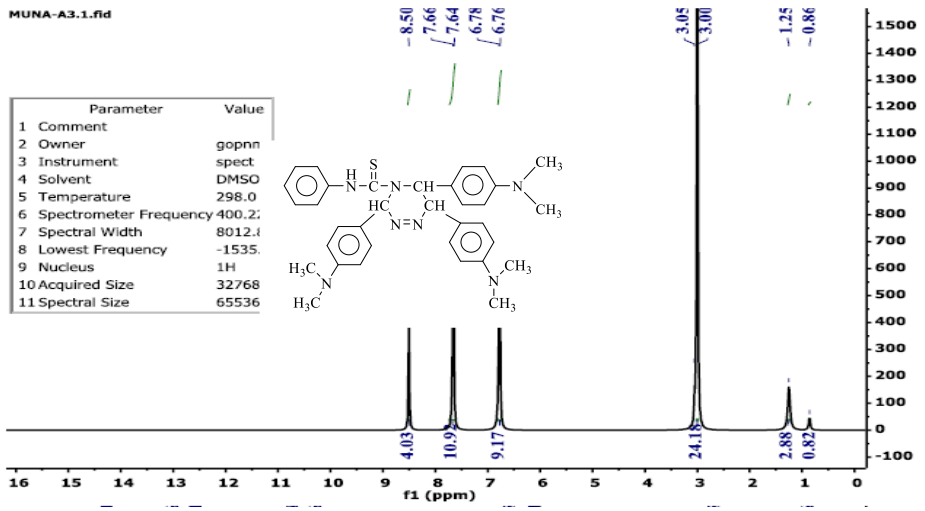
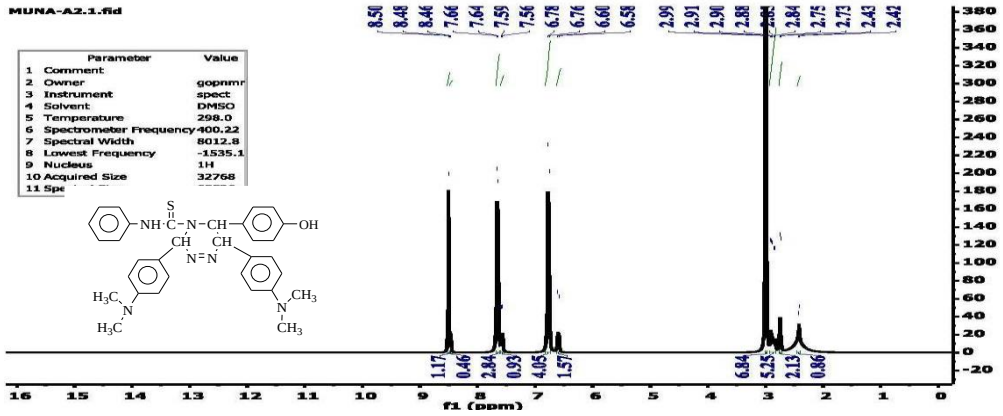
2 Owner gopnmr
3 Instrument spect
4 Solvent DMSO
5 Temperature 298.0
6 Spectrometer Frequency 400.22
7 Spectral Width 8012.
8 Lowest Frequency -1535
9 Nucleus 1H
10 Acquired Size 32768
11 Spectral Size 65536
f1 (ppm)





Conclusion

The reaction time has been brought down from hours to few minutes by using efficient , fast ,simple technique (grinding and microwave irradiation)compared with the conventional methods . As well as the using of tri ethyl amine as catalyst led to yield enhancement for all prepared compounds .

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