Microwave-assisted Synthesis of New Isoxazolyl triazinethiones and Isoxazolyl oxadiazinethiones in Dry Media

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Trimolecular condensation of *N*-(3-methyl-5-styryl-isoxazol-4-yl)-*N*'-aryl thioureas (**2**), paraformaldehyde and primary amines using montmorillonite K-10 in dry media under microwave irradiation leads to isoxazolyl triazinethiones (**3**) in high yield. Condensation of **2** with paraformaldehyde alone under similar conditions provide isoxazolyl oxadiazinethiones (**4**) in excellent yield.

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Introduction.

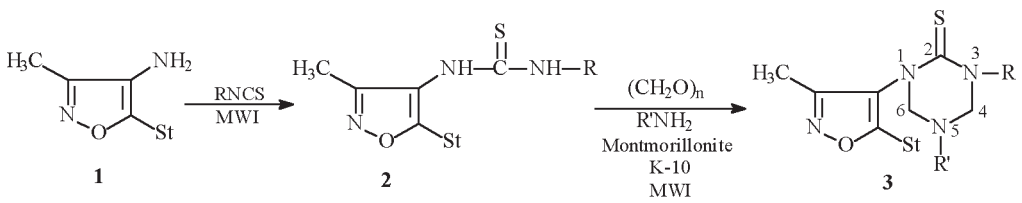
Microwave dielectric heating has been widely exploited for the acceleration of organic reactions during the last decade [1-3]. Microwave irradiation in solvent-free conditions has attracted much significance in organic synthesis [4-6]. K-10 clays as catalysts have received considerable attention and have been employed in several organic reactions [7-9]. As a sequel to our work on isoxazole derivatives synthesis [10-12], we now wish to report an efficient and simple procedure for the synthesis of isoxazolyl triazinethiones through trimolecular condensation of primary amines, isoxazolyl thioureas and paraformaldehyde using montmorrillonite K-10 clay under microwave irradiation in dry media and also isoxazolyl oxadiazinethiones by two component condensation of isoxazolyl thioureas with paraformaldehyde. Very few reports [13] are available in the literature concerning the synthesis of unsymmetrical substituted triazinethiones and oxadiazinethiones under conventional heating conditions.

Results and Discussion.

The reaction of 4-amino-3-methyl-5-styryl isoxazole (**1**) with alkyl/arylisothiocyanates in toluene under microwave irradiation afforded *N*-(3-methyl-5-styryl-isoxazol-4-yl)-*N*'-arylthioureas (**2**) in excellent yields. It is significant to note that the microwave reaction is completed within 1.0 minute compared to 4-6 hours under normal conventional heating mode [14]. The trimolecular condensation of primary amines, N,N'-unsymmetrical substituted thioureas (**2**) and paraformaldehyde supported on montmorillonite K-10 under microwave irradiation in dry media led to the formation of new 1-(3-methyl-5-styryl-isoxazol-4-yl)-3-aryl/alkyl-5-alkyl-hexahydro-1,3,5-triazine-2-thiones (**3**) in high yields within 5 minutes (Scheme 1). When the reaction was conducted under conventional heating mode, it required 4-5 hours and the product yield was poor (Table 1). Similarly, condensation of N,N'-disubstituted thioureas (**2**) and paraformaldehyde supported on montmorillonite K-10 clay under solvent-free conditions using microwave irradiation resulted new 3-(3-methyl-5-styryl-isoxazol-4-yl)-2,3,5,6-tetrahydro-4*H*-5-aryl/alkyl-1,3,5-oxadiazine-4-thiones (**4**) in good yields in 5 minutes (Scheme 2). Conventional heating using ethanol and excess conc. HCl and formalin solution in the same reaction required 4-5 hours and resulted in very low yield of the product (Table 1) and it also involves environmental problem, as disposal of excess catalyst leads to environmental pollution.

Montmorrillonite K-10 has Lewis acid character and it appears that paraformaldehyde is slowly decomposed to formaldehyde, which then reacts with the primary amine to give an amine-formaldehyde adduct which leads to an iminium species, which then reacts with the nitrogen atom of N,N'-disubstituted thiourea (**2**) to form the first N-C-N

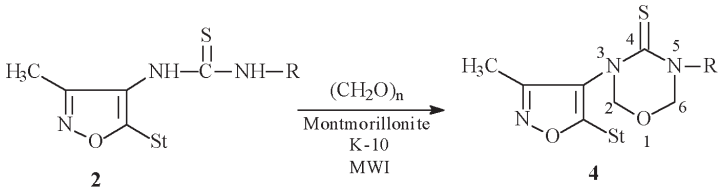
Scheme 1



St = CH=CH-Ph

3a = R = CH_3, R' = CH_3
3b = R = Ph, R' = CH_3
3c = R = CH_3, R' = CH_2CH_3
3d = R = Ph, R' = CH_2CH_3
3e = R = CH_3, R' = $CH_2CH_2CH_3$
3f = R = Ph, R' = $CH_2CH_2CH_3$
3g = R = CH_3, R' = $CH_2CH_2CH_2CH_3$
3h = R = Ph, R' = $CH_2CH_2CH_2CH_3$

Scheme 2



St = CH=CH-Ph

4a = R = CH_3, **4b** = R = Ph, **4c** = R = C_6H_4-Br(*p*), **4d** = R = C_6H_4-CH_3(*p*)

Scheme 3

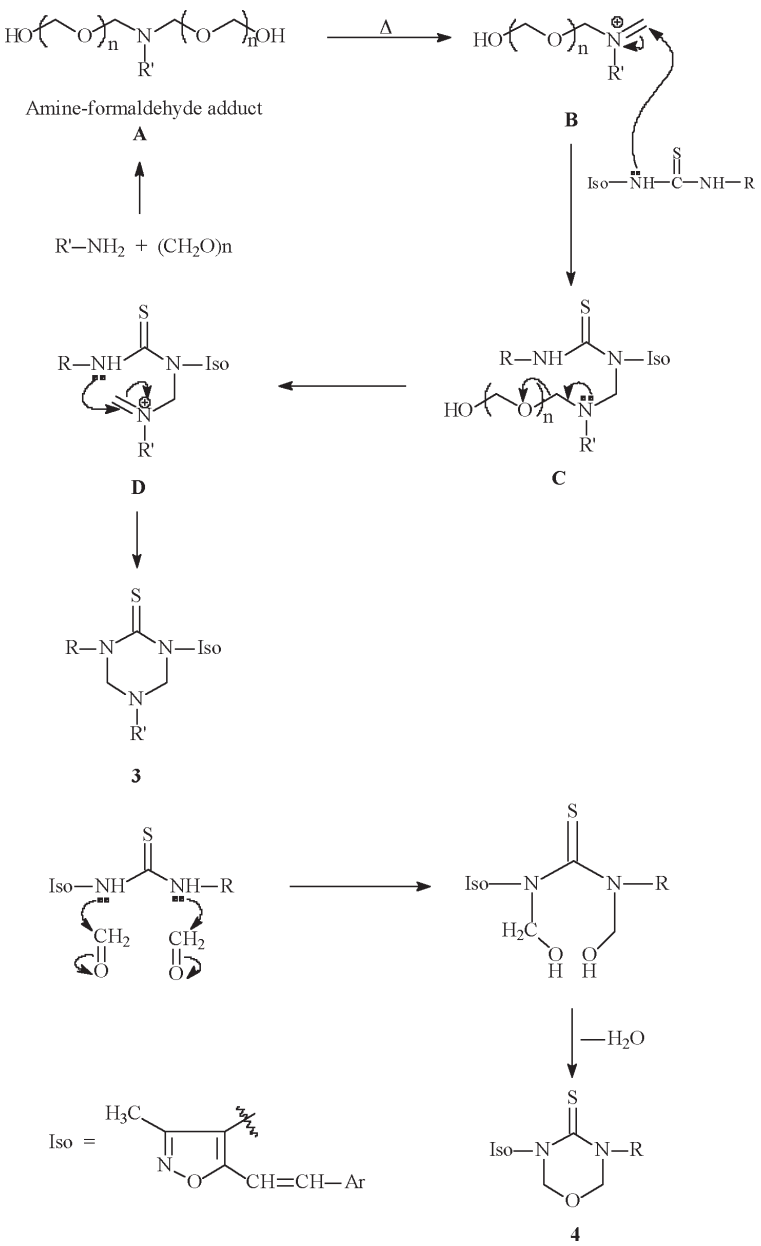


Table 1
Synthesis of Isoxazolyl Triazinethiones **3** and Isoxazolyl Oxadiazinethiones **4**: Comparison Between Conventional Heating and Microwave-assisted Methods

Entry	R	R'	Conventional heating method		Microwave-assisted method	
			Time (hrs)	Yield [a] %	Time (min)	Yield [a] %
3a	CH_3	CH_3	5	40	5	80
3b	Ph	CH_3	5	40	6	90
3c	CH_3	CH_2CH_3	5	40	5	85
3d	Ph	CH_2CH_3	4	40	5	80
3e	CH_3	$CH_2CH_2CH_3$	4	40	4	90
3f	Ph	$CH_2CH_2CH_3$	5	35	5	85
3g	CH_3	$CH_2CH_2CH_2CH_3$	4	35	5	80
3h	Ph	$CH_2CH_2CH_2CH_3$	5	30	4	85
4a	CH_3	--	4	35	4	85
4b	Ph	--	4	30	4	80
4c	*p*-BrC_6H_4	--	5	25	4	80
4d	*p*-$CH_3C_6H_4$	--	4	30	4	85

[a] Isolated yields after column chromatography.

bond. Thermal generation of second iminium electrophile, triggers ring closure to give the triazinethione (**3**) (Scheme 3). Formation of oxadiazinethione (**4**) could occur by the nucleophilic attack of urea nitrogen on formaldehyde followed by dehydration on the surface of the catalyst (Scheme 3). Montmorillonite K-10 besides giving solid support also acts as a catalyst in these processes.

Conclusion.

In summary, we have developed an efficient and high yield procedure for the synthesis of new isoxazolyl triazinethiones (**3**) and isoxazolyl oxadiazinethiones (**4**) in dry media using K-10 clay. To the best of our knowledge this represents the first report on the synthesis of triazinethiones and oxadiazinethiones substituted with isoxazole moiety by using microwave irradiation by trimolecular condensation and two-component condensation respectively.

EXPERIMENTAL

Microwave irradiation was carried out in LG microwave oven, model No. LGMS 257PL (2450 MHz, 900 watts). Analytical TLC was performed on Merck precoated 60 F_{254} silica gel plates. Melting points were determined on a Cintex melting point apparatus and are uncorrected. IR spectra (KBr pellet) were obtained on a Perkin Elmer BX series FT-IR spectrophotometer. ^{1}H NMR spectra were obtained on a Varian Gemini instrument at 300 MHz in $CDCl_3$ using TMS as internal standard. Mass spectra were recorded using JEOL JMC D-300 spectrometer at 70 eV. The silica gel (0.040 x 0.063 mm) used for column chromatography was purchased from Merck. C, H and N analyses were carried out on a Carlo Erba 106 and Perkin-Elmer model 240 analysers.

General Procedure for the Synthesis of 1-(3-Methyl-5-styryl-isoxazol-4-yl)-3-aryl/alkyl-5-alkyl-hexahydro-1,3,5-triazin-2-thiones (**3a-h**).

Method A (Conventional).

A mixture of N,N'-disubstituted thiourea **2** (1 mmol) 30% formaldehyde (1 mmol) and primary amine (1 mmol) in toluene (10 ml) was heated under reflux for 4-5 hours. The solvent was distilled off, the residue was triturated with petroleum ether and the crude product obtained was chromatographed over a silica gel column. Elution with ethyl acetate afforded triazinethione.

Method B(MORE-Microwave-induced Organic Reaction Enhancement).

A mixture of N,N'-disubstituted urea **2** (1 mmol), paraformaldehyde (0.5 g) and primary amine (1 mmol) and 1 g montmorillonite K-10 were irradiated by microwave at 540 watts in a Teflon vessel for 5 minutes. The reaction mixture was extracted with dichloromethane, filtered and washed with water. The organic phase was separated and concentrated by rotary evaporator. The crude product was chromatographed over a silica gel column. Elution with ethyl acetate afforded the products **3**. All the products were characterized by IR, ^{1}H NMR, Mass spectral and elemental analysis data.

1-(3-Methyl-5-styryl-isoxazol-4-yl)-3,5-dimethyl-hexahydro-1,3,5-triazin-2-thione (**3a**).

This compound was obtained as colourless crystals; mp 154 °C; IR: 1232 (C=S) cm^{-1}; ^{1}H NMR: δ 2.32 (s, 3H, isoxazole CH_3), 2.83 (s, 3H, NCH_3-5), 3.54 (s, 3H, NCH_3-3), 4.42 (s, 2H, CH_2-4), 4.62 (s, 2H, CH_2-6), 6.62 (d, J = 15 Hz, 1H, CH_α=CH), 6.75 (d, J = 15 Hz, 1H, CH=CH_β), 7.12-7.53 (m, 5H, H_{arom}); MS: (m/z 328, M$^+$, 20%), (m/z 243, 100%).

Anal. Calcd. for $C_{17}H_{20}N_4OS$: C, 62.19; H, 6.09; N, 17.07. Found: C, 62.18; H, 6.09; N, 17.08.

1-(3-Methyl-5-styryl-isoxazol-4-yl)-3-phenyl-5-methyl-hexahydro-1,3,5-triazin-2-thione (**3b**).

This compound was obtained as colourless cryatals; mp 188 °C; IR: 1225 (C=S) cm^{-1}; ^{1}H NMR: δ 2.30 (s, 3H, isoxazole CH_3), 2.82 (s, 3H, NCH_3-5), 4.61 (s, 2H, CH_2-4), 4.84 (s, 2H, CH_2-6), 6.82 (d, J = 15 Hz, 1H, CH_α=CH), 6.95 (d, J = 15Hz, 1H, CH=CH_β), 7.00-7.62 (m, 10H, H_{arom}); MS: (m/z 390, M$^+$, 100%).

Anal. Calcd. for $C_{22}H_{22}N_4OS$: C, 67.69; H, 5.64; N, 14.35. Found: C, 67.70; H, 5.66; N, 14.39.

1-(3-Methyl-5-styryl-isoxazol-4-yl)-3-methyl-5-ethyl-hexahydro-1,3,5-triazin-2-thione (**3c**).

This compound was obtained as colourless crystals; mp 110 °C; IR: 1220 (C=S) cm^{-1}; ^1H NMR: δ 1.22 (t, J = 7.5Hz, 3H, CH_3), 2.42 (s, 3H, isoxazole CH_3), 3.23 (q, J=7.5Hz, 2H, CH_2), 3.52 (s, 3H, NCH_3-3), 4.54 (s, 2H, CH_2-4), 4.60 (s, 2H, CH_2-6), 6.61 (d, J = 15Hz, 1H, CH_α=CH), 6.80 (d, J = 15 Hz, 1H, CH=CH_β), 7.00-7.42 (m, 5H, H_{arom}); MS: (m/z, 342, M^+, 20%), (m/z 131, 100%).

Anal. Calcd. for $C_{18}H_{22}N_4OS$: C, 63.15; H, 6.43; N, 16.37. Found: C, 63.14; H, 6.44; N, 16.36.

1-(3-Methyl-5-styryl-isoxazol-4-yl-3-phenyl-5-ethyl-hexahydro-1,3,5-triazin-2-thione (**3d**).

This compound was obtained as colourless crystals; mp 175 °C; IR: 1230 (C=S) cm^{-1}; ^1H NMR: δ 1.20 (t, J = 7.5Hz, 3H, CH_3), 2.40 (s, 3H, isoxazole CH_3), 3.22 (q, J= 7.5Hz, 2H, CH_2), 4.52 (s, 2H, CH_2-4), 4.71 (s, 2H, CH_2-6), 6.80 (d, J = 15 Hz, 1H, CH_α = CH), 7.02 (d, J = 15 Hz, 1H, CH=CH_β); 7.11-7.52 (m, 10H, H_{arom}); MS: (m/z 404, M^+, 10%), (m/z 131, 100%).

Anal. Calcd. for $C_{23}H_{24}N_4OS$: C, 68.31; H, 5.94; N, 13.86. Found: C, 68.31; H, 5.95; N, 13.86.

1-(3-Methyl-5-styryl-isoxazol-4-yl)-3-methyl-5-n-propyl-hexahydro-1,3,5-triazin-2-thione (**3e**).

This compound was obtained as colourless crystals; mp 105 °C; IR: 1225 (C=S) cm^{-1}; ^1H NMR: δ 1.02 (t, J = 7.0Hz, 3H, CH_3), 1.32 (m, J = 7.0Hz, 2H, CH_2), 2.35 (s, 3H, isoxazole CH_3), 3.01 (t, J = 7.0Hz, 2H, CH_2), 3.52 (s, 3H, NCH_3-3), 6.67 (d, J = 15 Hz, 1H, CH_α=CH), 6.85 (d, J = 15Hz, 1H, CH=CH_β), 7.00 – 7.35 (m, 5H, H_{arom}); MS: (m/z 356, M^+, 25%), (m/z 131, 100%).

Anal. Calcd. for $C_{19}H_{24}N_4OS$: C, 64.04; H, 6.74; N, 15.73. Found: C, 64.03; H, 6.75; N, 15.70.

1-(3-Methyl-5-styryl-isoxazol-4-yl)-3-phenyl-5-n-propyl-hexahydro-1,3,5-triazin-2-thione (**3f**).

This compound was obtained as colourless crystals; mp 170 °C; IR: 1222 (C=S) cm^{-1}; ^1H NMR: δ 1.12 (t, J = 7.0Hz, 3H, CH_3), 1.40 (m, J = 7.0Hz, 2H, CH_2), 2.35 (s, 3H, isoxazole CH_3), 3.12 (t, J = 7.0Hz, 2H, CH_2), 4.42 (s, 2H, CH_2-4), 4.66 (s, 2H, CH_2-6), 6.80 (d, J = 15Hz, 1H, CH_α=CH), 6.94 (d, J = 15 Hz, 1H, CH=CH_β), 7.05 – 7.44 (m, 10H, H_{arom}); MS (m/z 418, M^+, 10%), (m/z 131, 100%).

Anal. Calcd. for $C_{24}H_{26}N_4OS$: C, 68.89; H, 6.22; N, 13.39. Found: C, 68.90; H, 6.21; N, 13.40.

1-(3-Methyl-5-styryl-isoxazol-4-yl)-3-methyl-5-*n*-butyl-hexahydro-1,3,5-triazin-2-thione (**3g**).

This compound was obtained as colourless crystals; mp 98 °C; IR: 1220 (C=S) cm^{-1}; ^1H NMR: δ 0.92 (t, J = 6.2Hz, 3H, CH_3), 1.30 (m, J = 6.2Hz, 2H, CH_2), 1.55 (m, J = 6.2Hz, 2H, CH_2), 2.32 (s, 3H, isoxazole CH_3), 3.05 (t, J = 6.2Hz, 2H, CH_2), 3.52 (s, 3H, NCH_3-5), 4.60 (s, 2H, CH_2-4), 4.82 (s, 2H, CH_2-6), 6.80 (d, J = 15 Hz, 1H, CH_α=CH), 7.02 (d, J = 15 Hz, 1H, CH=CH_β), 7.22-7.65 (m, 5H, H_{arom}); MS: (m/z 370, M^+, 100%).

Anal. Calcd. for $C_{20}H_{26}N_4OS$: C, 64.86; H, 7.02; N, 15.13. Found: C, 64.89; H, 7.01; N, 15.15.

1-(3-Methyl-5-styryl-isoxazol-4-yl)-3-phenyl-5-*n*-butyl-hexahydro-1,3,5-triazin-2-thione (**3h**).

This compound was obtained as colourless crystal; mp 165 °C; IR: 1225 (C=S) cm^{-1}; ^1H NMR: δ 1.02 (t, J = 6.2Hz, 3H, CH_3), 1.35 (m, J = 6.2Hz, 2H, CH_2), 1.62 (m, J = 6.2Hz, 2H, CH_2), 2.32 (s, 3H, isoxazole CH_3), 3.12 (t, J = 6.2Hz, 2H, CH_2), 4.52 (s, 2H, CH_2-4), 4.75 (s, 2H, CH_2-6), 6.97 (d, J = 15 Hz, 1H, CH_α=CH), 7.12 (d, J = 15Hz, 1H, CH=CH_β,), 7.23 – 7.65 (m, 10H, H_{arom}); MS: (m/z 432, M^+, 10%), (m/z 131, 100%).

Anal. Calcd. for $C_{25}H_{28}N_4OS$: C, 69.44; H, 6.48; N, 12.96. Found: C, 69.45; H, 6.48; N, 12.95.

General Procedure for the Synthesis of 3-(3-Methyl-5-styryl-isoxazol-4-yl)-2,3,5,6-tetrahydro-4*H*-5-aryl/alkyl-1,3,5-oxadiazine-4-thiones(**4a-d**).

Method A (Conventional).

N,N'-Disubstituted thiourea **2** (1 mmol) was added with stirring to 30% formaldehyde solution (1 mmol) and the mixture treated with conc. HCl (1 ml). After heating at 90-95 °C for 4-5 hours, the reaction mixture (monitored by TLC) was cooled and neutralized with NaOH. The solid thus obtained was collected by filtration and chromatographed using silica gel column. Elution with benzene:ethyl acetate (1:1) afforded the oxadiazine thiones.

Method B (MORE).

A mixture of N,N'-disubstituted thiourea **2** (1 mmol) and paraformaldehyde (0.5 g) and montmorillonite K-10 (1 g) was irradiated by microwave at 540 watt in a Teflon vessel for 5 minutes. The reaction was extracted with dichloromethane, filtered and washed with water. The organic layer was separated and vacuum distilled then the crude residue, on passing through silica gel column, afforded the products **4** by elution with benzene:ethylacetate (1:1). All the products were characterized by IR, ^1H NMR, Mass spectral and elemental analysis data.

3-(3-Methyl-5-styryl-isoxazol-4-yl)-2,3,5,6-tetrahydro-4*H*-5-methyl-1,3,5-oxadiazin-4-thione (**4a**).

This compound was obtained as colourless crystals; mp 130 °C; IR : 1120 (C-O-C), 1230 (C=S) cm^{-1}, ^1H NMR: δ 2.30 (s, 3H, isoxazole CH_3), 3.32 (s, 3H, NCH_3), 4.80 (s, 2H, CH_2-6), 5.05 (s, 2H, CH_2-2), 6.72 (d, J = 15 Hz, 1H, CH_α=CH), 6.92 (d, J = 15 Hz, 1H, CH=CH_β), 7.00-7.45 (m, 5H, H_{arom}); MS: (m/z 315, M^+, 20%), (m/z 131, 100%).

Anal. Calcd. for $C_{16}H_{17}N_3O_2S$: C, 60.95; H, 5.39; N, 13.33. Found: C, 60.96; H, 5.38; N, 13.30.

3-(3-Methyl-5-styryl-isoxazol-4-yl)-2,3,5,6-tetrahydro-4*H*-5-phenyl-1,3,5-oxadiazin-4-thione (**4b**).

This compound was obtained as colourless crystals; mp 140 °C; IR: 1125 (C-O-C), 1228 (C=S) cm^{-1}; ^1H NMR: δ 2.25 (s, 3H, CH_3), 4.80 (s, 2H, CH_2-6), 5.12 (s, 2H, CH_2-2), 6.85 (d, J = 15 Hz, 1H, CH_α=CH), 7.02 (d, J = 15 Hz, 1H, CH=CH_β), 7.14-7.55 (m, 10H, H_{arom}); MS: (m/z 377, M^+, 10%), (m/z 131, 100%).

Anal. Calcd. for $C_{21}H_{19}N_3O_2S$: C, 66.84; H, 5.03; N, 11.14. Found: C, 66.85; H, 5.05; N, 11.18.

3-(3-Methyl-5-styryl-isoxazol-4-yl)-2,3,5,6-tetrahydro-4*H*-5-*p*-bromophenyl-1,3,5-oxadiazin-4-thione (**4c**).

This compound was obtained as colourless crystals; mp 100 °C; IR: 1120 (C-O-C), 1225 (C=S) cm^{-1}; ^1H NMR: δ 2.33 (s, 3H, CH_3), 4.90 (s, 2H, CH_2-6), 5.14 (s, 2H, CH_2-2), 6.82 (d, J = 15 Hz, 1H, CH_α=CH), 7.04 (d, J = 15 Hz, 1H, CH=CH_β), 7.34-7.45

(d, J = 8.0 Hz, 2H, *p*-bromophenyl), 7.60 – 7.72 (d, J = 8.0 Hz, 2H, *p*-bromophenyl); MS (m/z 456, M^+, 20%), (m/z 131, 100%).

Anal. Calcd. for $C_{21}H_{18}N_3O_2SBr$: C, 55.26; H, 3.94; N, 9.21. Found: C, 55.29, H, 3.95, N, 9.19.

3-(3-Methyl-5-styryl-isoxazol-4-yl)-2,3,5,6-tetrahydro-4*H*-5-*p*-methylphenyl-1,3,5-oxadiazin-4-thione (**4d**).

This compound was obtained as colourless crystals; mp 126 °C; IR: 1120 (C-O-C), 1232 (C=S) cm^{-1}; ^1H NMR: δ 2.40 (s, 3H, CH_3), 4.82 (s, 2H, CH_2-6), 5.04 (s, 2H, CH_2-2), 6.62 (d, J = 15 Hz, 1H, CH_α=CH), 6.80 (d, J = 15 Hz, 1H, CH=CH_β), 7.02-7.12 (d, J = 7.5 Hz, 2H, *p*-methylphenyl), 7.20-7.55 (d, J = 7.5 Hz, 2H, *p*-methylphenyl); MS: (m/z 432, M^+, 100%).

Anal. Calcd. for $C_{22}H_{21}N_3O_2S$: C, 67.51; H, 5.37; N, 10.74. Found: C, 67.48; H,5.38; N, 10.73.

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