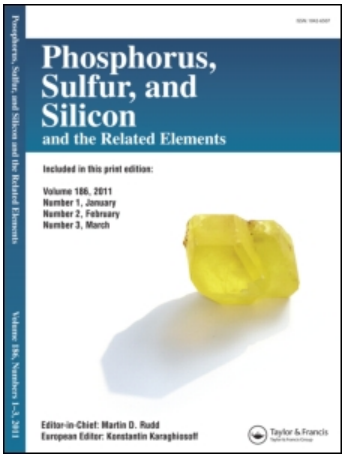

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The title compounds were synthesised by condensation of 3-alykl/aryl-4-amino-5-mercaptotriazole (II) and 5-substituted 2-aminothiophenols (IV) with appropriate 2-phenyl-1H-indole-3-carboxaldehyde (I) under microwave irradiation in the presence of piperidine/p-toluenesulphonic acid using ethanol/DMF as energy transfer media. The considerable increase in reaction rate with improved yield has been observed, using microwave as compared to classical method.

Keywords: Sulfur-containing indole derivatives; 4-amino-5-mercaptotriazole; 2-aminothiophenol; benzothiazole; triazolothiadiazoles; microwave irradiation; antifungal activity

INTRODUCTION

Application of microwave irradiation in organic synthesis is of recent origin.[1,2] There have been few reports[3–10] of the use of commercial unmodified domestic microwave ovens for carrying out organic synthesis in either sealed vessels or in open vessels,[11] using organic solvents like ethanol, N-N-Dimethylformamide, acetic acid, o-dichlorobenzene. 1,2-dichloroethane (DCE) etc. as energy

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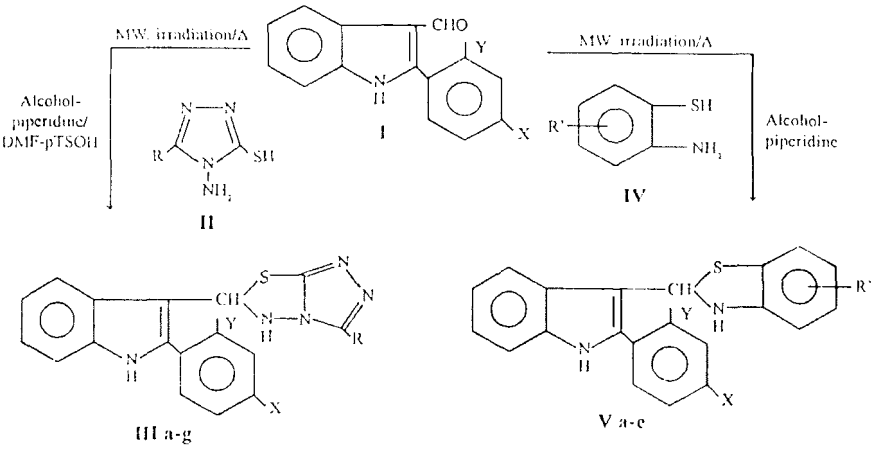

	X	Y
a	H	H
b	F	H
c	F	Cl

S. No.	X	Y	R
a	H	H	CH_3
b	H	H	C_2H_5
c	H	H	C_3H_7
d	F	H	CH_3
e	F	H	C_2H_5
f	4F	3Cl	CH_3
g	4F	3Cl	C_6H_5

S. No.	X	Y	R
a	H	H	OC_2H_5
b	H	H	OCH_3
c	H	H	CH_3
d	H	H	Br
e	H	H	Cl

transfermedia which absorb microwave energy efficiently through dipole rotation. The method offers new vistas directed towards simplification of laboratory technique without the use of reflux condensers, stirrers, water separators (Dean. Stark), etc.

The sulfur containing heterocycles like triazolo-thiadiazoles and benzothiazoles possess diverse biological activities, viz., antibacterial,[12,13] CNS,[14] fungicidal,[15] anthelmintic,[16] antimicrobial,[17] analgesic,[18] and anti-inflammatory.[19] 1,3,4-Thiadiazole ring is associated with broad spectrum of biological activities by virtue of incorporating toxophoric N=C S linkage. A triazolo-thiadiazole system may be viewed as a cyclic analogue of two very important components, thiosemicarbazides and biguanide which, often display diverse biological activities.

Likewise the indole nucleus also has been the subject of extensive studies due to the wide variety of biological activities. Indoles are also used as drug inter-

mediates,[20,21] antirheumatic[22] and antitumor agents.[23] Indole-3-carboxaldehyde derivatives[24,25] are commonly used as intermediates for pharmaceuticals and as agrochemicals.[26] In continuation to our earlier interest on the syntheses of sulfur and nitrogen containing biodynamic-indole derivatives[27–36] and guided by the observation that, many a time the combination of two or more heterocyclic nuclei enchances the biological profile many fold than its parent nuclei, we have synthesized the novel compounds 2-substituted phenyl-3-(3-alkyl/aryl-5,6-dihydro-*s*-triazolo-[3,4-b] [1,3,4]thiadiazol-6-yl] indol (IIIa-g) bearing 1,3,4-thiadiazole and indole moieties for the first time and extended our studies to the conventional and microwave induced synthesis of a series of 2-phenyl-3-[2-substituted benzothiazole] indoles (Va-e), using substituted aminothiophenols (OC_2H_5, OCH_3, CH_3, Br, Cl as substitutent) (IV) and 2-phenyl-1H-indole-3-carboxaldehyde (I).

The classical approach for the synthesis of IIIa-g involves the fusion of I and II in oil bath for 2–6 hrs or stirring in DMF at 60–80°C for 14 hrs. In contrast, when the analogus reaction was performed under microwave irradiation required 5/8 minutes in alcohol/DMF and improvement in yield was also observed. For the classical synthesis of $V_{a\text{-}e}$ the cyclocondensation of $IV_{a\text{-}e}$ with I required 3–5 hrs fusion time in oil-bath, while same reaction under microwave irradiation using ethanol as energy transfer-media required 3–6 minutes. The BPL SANYO Microwave oven manufactured by BPL SANYO Utilities and Appliances Limited, INDIA, has been used. It has a range of microwave out put energy from 140–1200 watts.

DISCUSSION

The comparative results obtained by two synthetic approaches demonstrate the versatility of the process, as considerable reaction rate enhancement has been observed bringing down the reaction time from hours to minutes. The products obtained under microwave irradiation have improved yields. The reaction time and yields obtained have been compared with the standard reaction time and yield, which are given in Table I. The identity of the products was established by their melting points, spectral data and physical data, given in Table I. The synthesized compounds have been screened for antifungal activity against *Alternaria alternata* at 1000 and 500 ppm. Results of antifungal activity are reported in Table IV. All the compounds tested were found effective in reducing the growth at 1000 ppm. The percent inhibition observed was 55–78%. The most effective compounds were Vc and Ve at both 500 and 1000 ppm concentrations.

TABLE I Physical and analytical data of compounds III_{a-g} and V_{a-e}

S. No.	Reaction Time		yield (%)		Molecular Formula	M.P (°C)	Anals % Found/(Calcd)			
	Standard (hrs)	M.W. (min)	Standard	M.W.			C	H	N	S
III*c	4.0[c]/14[d]	5.0[b]/8.00[a]	45[c]/60[d]	[b]85/62[a]	$C_{23}H_{17}N_5S$	231	69.43 (69.87)	4.36 (4.30)	17.40 (17.72)	7.8 (8.10)
IIIa	2.0	4.0	68	80	$C_{18}H_{15}N_5S$	225	64.40 (64.86)	4.00 (4.50)	20.92 (21.02)	9.00 (9.60)
IIIb	4.0	5.0	72	82	$C_{19}H_{17}N_5S$	195	66.83 (65.70)	4.80 (4.89)	20.60 (20.17)	8.80 (9.22)
IIId	5.0	12.0	60	75	$C_{18}H_{14}N_5FS$	257	61.00 (61.53)	4.20 (3.98)	19.52 (19.94)	8.81 (9.11)
IIIe	3.0	10.0	62	70	$C_{19}H_{16}N_5FS$	230	62.20 (62.46)	4.18 (4.38)	19.10 (19.17)	8.46 (8.76)
IIIf	4.0	13.0	61	72	$C_{18}H_{13}N_5FClS$	235	55.63 (56.03)	3.10 (3.37)	17.80 (18.15)	8.10 (8.30)
IIIg	4.0	14.0	64	73	$C_{23}H_{15}N_5FClS$	239	61.30 (61.67)	3.20 (3.35)	15.34 (15.64)	6.85 (7.15)
Va	3.0	3.0	64	82	$C_{23}H_{20}ON_2S$	210	74.00 (74.19)	5.10 (5.37)	7.20 (7.52)	8.30 (8.60)
Vb	3.5	3.0	62	80	$C_{22}H_{18}ON_2S$	180	73.30 (73.74)	4.72 (5.02)	7.30 (7.82)	8.40 (8.93)
Vc	4.0	4.0	61	84	$C_{22}H_{18}N_2S$	205	76.79 (77.19)	5.06 (5.26)	8.10 (8.18)	9.10 (9.35)
Vd	5.0	6.0	57	81	$C_{21}H_{15}N_2BrS$	190	61.41 (61.91)	3.40 (3.68)	6.40 (6.87)	7.20 (7.86)
Ve	4.5	5.0	59	80	$C_{21}H_{15}N_2ClS$	130	69.21 (69.51)	4.0 (4.13)	7.22 (7.72)	8.50 (8.82)

*Reaction, time and yield by method a, b, c and d.

TABLE II IR and ^{1}HNMR data of the compounds IIIa-g

Compound No.	*X*	*Y*	*R*	*IR (cm^{-1})*	*^{1}HNMR (δ ppm)*			
					$-CH$	*$Ar\text{-}N=CH$*	*NH (indole)*	*NH*
IIIa	H	H	CH_3	3280–3180, 1605, 1575, 1470, 1275, 1055, 695	6.00 (s, 1H)	7.05–8.4 (m, 13h)	9.75 (s, 1H)	5.56–5.58 (bs, 1H)
IIIb	H	H	C_2H_5	3390–3350, 1620, 1680, 1480 1270, 1050, 695	6.12 (s, 1H)	7.10–8.2 (m, 13h)	9.75 (s, 1H)	5.56–5.57 (bs, 1H)
IIIc	H	H	C_6H_5	3250–3150, 1610, 1580, 1470, 1275, 1055, 695	6.00 (s, 1H)	6.9–7.20 (m, 13h)	9.75 (s, 1H)	5.58–6.00 (bs, 1H)
IIId	H	F	CH_3	3250–3120, 1605, 1575, 1480, 1275, 1055, 695	5.80 (s, 1H)	7.10–8.2 (m, 13h)	9.75 (s, 1H)	5.57–5.59 (bs, 1H)
IIIe	H	F	C_2H_5	3380–3250, 1620, 1580, 1480, 1270, 1055, 695	6.00 (s, 1H)	7.08–8.8 (m, 12h)	9.75 (s, 1H)	5.55–5.57 (bs, 1H)
IIIf	4F	3Cl	CH_3	3280–3180, 1605, 1580, 1470, 1270, 1055, 695	6.02 (s, 1H)	7.05–8.5 (m, 11h)	9.75 (s, 1H)	5.56–5.59 (bs, 1H)
IIIg	4F	3Cl	C_6H_5	3390–3350, 1610, 1575, 1470, 1275, 1055, 695	6.14 (s, 1H)	7.09–8.8 (m, 11h)	9.90 (s, 1H)	5.54–5.57 (bs, 1H)

TABLE III IR and ^{1}HNMR data of the compounds V_{a-e}

Compound No.	*X*	*IR (cm^{-1})*	*^{1}HNMR (δ ppm)*				
			$-C\underline{H}$	*Ar-H and $=C\underline{H}$*	*$N\underline{H}$ (indole)*	*$N\underline{H}$*	*C-X*
Va	OC_2H_5	3320, 1580, 1520, 1470, 1420, 1350, 1290, 1220, 1170, 1080, 850, 720	4.35 (s, br, 1H)	6.60–8.10 (m, 13H)	(8.29) (s, 1H)	8.75 (s, 1H)	1.35 (t, 3H) 3.92 (2H, q)
Vb	OCH_3	3310, 1600, 1520, 1470, 1420, 1350, 1280, 1210, 1160, 1090, 860, 730	435 (s, br, 1H)	6.63–8.04 (m, 13H)	8.38 (s, 1H)	8.25 (s, 1H)	3.50 (s, 3H)
Vc	CH_3	3320, 1610, 1550, 1460, 1420, 1350, 1290, 1220, 1170, 1080, 840, 720	4.39 (s, br, 1H)	6.64–8.12 (m, 13H)	8.57 (s, 1H)	8.95 (s, 1H)	2.01 (s, 3H)
Vd	Br	3310, 1610, 1520, 1470, 1410, 1360, 1300, 1210, 1160, 1070, 850, 720	4.37 (s, br, 1H)	6.62–8.10 (m, 13H)	8.38 (s, 1H)	8.90 (s, 1H)	– –
Ve	Cl	3320, 1600, 1550, 1460, 1410, 1360, 1300, 1220, 1160, 1080, 840, 720	4.39 (s, br, 1H)	6.65–815 (m, 13H)	8.40 (s, 1H)	8.75 (s, 1H)	–

TABLE IV Antifungal activity of compounds III_{a-g} and V_{a-e}

Compounds	Radial Growth (cm)		Percent inhibition	Radial Growth (cm)	Percent inhibition
	Check (Av)	500 ppm		1000 ppm	
IIIa	5.35	2.4	55.14	1.5	71.96
IIIb	5.35	2.35	56.07	1.8	66.35
IIIc	5.35	2.7	49.53	2.05	61.68
IIId	5.35	1.9	64.48	1.3	75.70
IIIe	5.35	2.2	58.87	1.4	73.83
IIIf	5.35	2.3	57.00	1.2	77.57
IIIg	5.35	3.0	43.92	1.5	71.96
Va	6.00	4.0	33.33	2.55	57.5
Vb	6.00	5.2	13.33	2.65	55.83
Vc	6.00	3.6	40.00	2.55	57.55
Vd	6.00	2.8	53.33	1.30	78.33
Ve	6.00	2.5	58.33	1.25	79.16

IR Spectra

The compounds III_{a-g} and V_{a-e} were characterised by the appearance of characteristic absorption bands at (3150–3300) cm^{-1} (NH), 700–600 (C-S linkage) and 1615 cm^{-1} (C=N).

The bands that appeared at 1630 cm^{-1} (C=O), 3210, 3150 (NH_2) and 1130 cm^{-1} (C=S) respectively, for the starting aldehyde (I), triazole (II) and 2-amino benzenethiol (IV), were absent in the newly formed compounds III and V indicating the cyclocondensation in one step instead of formation of anil derivatives.

^1H and ^{19}F NMR Spectra

The ^{1}HNMR spectra of $III_{(a-g)}$ exhibited broad peaks at δ 5.54–5.58 ppm and δ 9.7–9.9 ppm exchangeable with D_2O due to 5-NH and the indole NH protons. A singlet at δ 5.8–6.1 ppm was assigned to 6-CH proton where as aromatic protons showed a multiplet at δ 6.9–8.4. ppm.

In ^{1}HNMR spectra of compounds V_{a-e} characteristic signals were observed at δ 2.2 (s, 3H, C*H*$_3$), δ 4.35–4.39 (s br-1H, C*H*), δ 6.60–8.12 ppm (m, Ar, H), δ 8.29–8.57 (s, 1H, NH), δ 8.25–8.95 (s, 1H, NH) ppm which confirmed the proposed structure.

The presence of fluorine in the compounds III_{d-g} has been confirmed on the basis of ^{19}FNMR spectra. A sharp signal at -104.19 ppm appeared due to fluorine at 4-position of phenylring.

EXPERIMENTAL

Melting points were determined on a Toshniwal melting point apparatus (capillary method) are uncorrected. The purity of the synthesized compounds was tested by thin layer chromatography on silica gel in various non-aqueous solvents. IR spectra were recorded in KBr on a Perkin Elmer 577 grating spectrometer (ν max in cm^{-1}).

^{1}H and $^{19}FNMR$ were recorded on Jeol (Model-FX 90Q) using $CDCl_3$ as solvent at 89.55 and 84.25 MHz respectively. TMS was used as internal reference for ^{1}H NMR and hexafluorobenzene as external reference for $^{19}FNMR$.

(i) 2-Aryl-1H-indole-3-carboxaldehyde (I), 3-aryl/alkyl-4-amino-5-mercapto-1,2,4-triazole (II) and 5-substituted 2-aminothiophenols (IV), were synthesized by literature methods.[37-39]

A. 3-phenyl-6-(2-phenyl indol-3yl)-5,6-dihydro-s-triazolo-(3,4-b) [1,3,4] thiadiazole (III_c)

This compound has been synthesized by the following four methods. The progress of reaction was checked by tlc and identity of compounds was established by mixed mps. and spectral data.

I. Synthesis Under Microwave Irradiation

The compound III_c has been synthesized using either DMF and p-toluenesulphonic acid or alcohol and piperidine under microwave irradiation.

(a) A mixture of I_a (0.01 mole) and IIc (0.01 mole) with a catalytic amount of p-toluenesulphonic acid (20 mg) in dry DMF (15 ml) taken in a 100 ml borosil beaker was zapped inside a microwave oven for a duration of 8 minute at 240 watts i.e. 20% microwave power. The progress of reaction was monitored by tlc. It was cooled and poured over crushed ice and the solid separated was filtered, washed with water, dried and recrystallized from benzene as white crystals, yield 62% M.P. = 231°C.

(b) The analagous reaction of I_a (0.01 mol) and II_c (0.01 mole) was carried out with a catalytic amount of piperidine (3 drops) in ethanol (20 ml) under microwave irradiation for a duration of 5 minute at 240 watts i.e. 20% microwave power. The mixture was cooled, separated solid was dried and recrystallized from benzene to give white crystals, yield 85% M.P. 231°C.

II. Classical synthesis

The compound has been synthesized by following two classical methods.

(c) An equimolar mixture of I_a (0.01 mol) and II_c (0.01 mol) was fused for 4 hours at 130–150°C in an oil-bath in the presence of 3-drops of piperidine. After heating, the mixture was cooled and extracted with 20 ml of ethanol. The extract was kept overnight. The solid separated was filtered, dried and recrystallized from benzene yield = 45% M.P. = 231°C.

(d) An equimolar mixture of I_a (0.01 mole). IIc (0.01 mol) and p-toluenesulphonic acid (20 mg) in dry DMF (15 ml) was stirred at 70–80°C for 14 hrs. It is cooled and poured over crushed ice and the solid was recrystallized from benzene yield = 60% M.P. 231°C.

Comparision of all the methods indicated the easy work up and better yield by method (b) under microwave irradiation.

Hence the other compounds IIIa-g have been synthesized by method (b) under both microwave irradiation and thermal heating for comparative studies.

(B) 2-phenyl-3 [2-substituted-benzothiazole] indoles (V_{a-e})

These compounds have been synthesized by following two methods.

(i) Synthesis under microwave irradiation

A mixture of I (0.01 mole), IV (0.01 mole) and 2 drops of piperidine in ethanol (20 ml) taken in a borosil beaker was zapped inside a microwave oven for a duration of 3–6 minutes at 240 watts i.e. 20% microwave power. The reaction mixture was kept overnight. The product thus obtained was filtered, washed with 10% NaOH solution followed by water, dried and recrystallized from benzene to give V_{a-e}.

(ii) Classical Synthesis

An equimolar mixture of I and IV was fused for 3–5 hours at 130–150°C in an oil bath in the presence of 2–3 drops of piperidine.[40] After heating the mixture was cooled and was extracted with 20 ml of ethanol. The mixture was kept over night. The product thus obtained after filtration, was dried and recrystallized from benzene to give V_{a-e}.

Antifungal Activity

The synthesized compounds have been screened for antifungal activity against *Alternaria Alternata* in five replications by "Food Poison Technique".[41] Each of the compound was dissolved in 20% acetone at 1000 and 500 ppm concentrations, which then incorporated in required quantities to Potato Dextrose Agar Medium (PDA), before dispersing into petri plates. Saturated checks were also prepared by inoculating fungi in PDA media for comparison. After 7-days of incubation at 25°C, radial growth of the colony was measured.

The effectiveness of the compounds were calculated using following formula.

$$\text{Percent inhibition} = \frac{\text{Radial growth in check (cm)} - \text{Radial growth in treatment (cm)}}{\text{Radial growth in check (cm)}} \times 100$$

All the compounds tested were found effective in reducing the growth at 1000 ppm. The percent inhibition observed was 55–78%.

The most effective compounds were V_c and V_c at both 500 and 1000 ppm concentrations.

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