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ACCELERATED SYNTHESIS 3-(N-SUBSTITUTED CARBOXAMIDOMETHYLTHIO)-(4H)-1, 2, 4-TRIAZOLES UNDER MICROWAVE IRRADIATION

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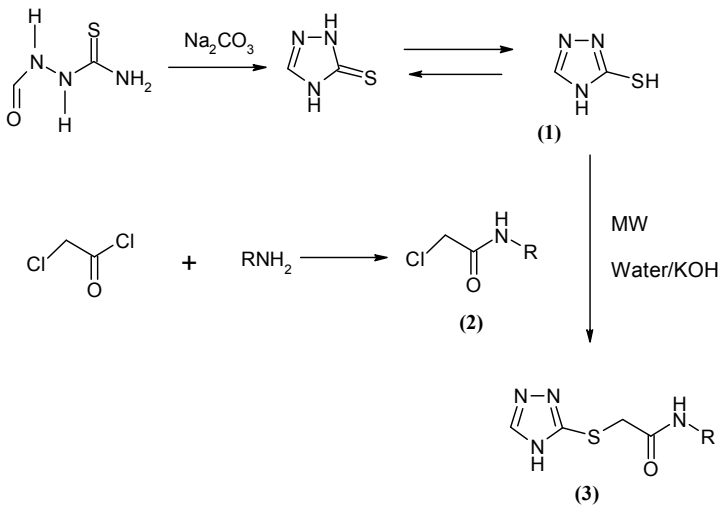
ABSTRACT: Microwave irradiation techniques were used to synthesized a series of 3-(N-substituted carboximidomethylthio)-(4H)-1, 2, 4-triazoles by the reaction of 3-mercapto-(4H)-1, 2, 4-triazole and N-substituted chloroacetamides in aqueous potassium hydroxide. This method appeared to be rapid and economical, with a wide range of applications. The reactions were found to proceed smoothly under microwave irradiation within 2-6 min. The synthesized compounds were confirmed by IR, ^{1}NMR spectra and elemental analysis. All the compounds were screened for their preliminary *in-vitro* antibacterial and antifungal activity.
KEYWORDS: Microwave irradiation, 1, 2, 4-triazole, chloroacetamide, antibacterial, antifungal.

INTRODUCTION

Microwave radiation provides an alternative to conventional heating as it utilizes the ability of liquids or solids to transform electromagnetic energy into heat. Chemical transformation that took hours, or even days, to complete can now be accomplished in minutes; microwave energy offers numerous benefits for performing synthesis including increased reaction rates, yield enhancement, and cleaner chemistries[1]. In view of the utility of microwave irradiation and the biological importance of 3-(N-substituted carboximidomethylthio)-(4H)-1, 2, 4-triazoles, it was thought worthwhile to develop a convenient method for the synthesis of the title compounds. The substituted triazoles are heterocyclic compounds, which serve both as biomimetic and reactive pharmacophores and many are key elements with potential biological activities such as tuberculostatic[2-7], analgesic[8], anti-inflammatory[9-11], antimicrobial[12-18], and can be used as herbicides[19] or fungicides[20].

3-mercapto-(4H)-1, 2, 4-triazole **(1)** was synthesized by cyclization of 1-formylthiosemicarbazide as the essential pharmacophore. Various N-substituted chloroacetamides **(2)** were synthesized by an appropriate method given in the literature[21], by condensing substituted amines with chloroacetyl chloride as acylating agent. These different N-substituted chloroacetamides **(2)** were condensed with **(1)** by conventional as well as microwave irradiation to obtain title compounds **(3)** as shown in **Scheme-1**.

The infrared spectra of the 3-mercapto-(4H)-1,2,4-triazole showed characteristic absorption band at 2585cm^{-1} attributed to SH , which was disappeared by the formation of 3-(N-Substituted carboximidomethylthio)-(4H)-1,2,4-triazoles**(3a-k)**.Similarly the ^{1}H NMR spectra of the synthesized triazoles **(1)** showed one characteristic signal at δ13.8-13.95,which was absent in the ^{1}H NMR spectra of substituted triazoles. The absence of these absorptions due to SH established that the triazoles had been converted to title compounds by both conventional and microwave irradiation method. The products obtained by both the methods were found to be identical by their melting point, mixed melting point, elemental analysis and spectral data. All the novel compounds were evaluated for their preliminary *in-vitro* antibacterial and antifungal activity.



Scheme -1

BIOLOGICAL EVALUATION

ANTIBACTERIAL ACTIVITY

Studies on the antibacterial activity of the synthesized compounds **(3a-k)** by microwave irradiation have been screened using cup-plate agar diffusion method[22] against four pathogenic organisms, viz., *Staphylococcus aureus* (G^+), *Klebsiella pnemoniae* (G^-), *Escherichia coli* (G^-), and *Pseudomonas aeruginosa* (G^-) by measuring the inhibition zone in mm at two concentrations (100 and 150 µg/ml). Streptomycine (100 and 150 µg/ml) was used as a standard and was also screened under similar conditions for comparison. The results of the antibacterial studies are shown in **Table-1**.

Table1. Antibacterial Activity of Synthesized Compounds (3a-k)
Zone of inhibition expressed in mm

Comp.	*Staphylococcus aureus*		*Klebsiella pnemoniae*		*Escherichia coli*		*Pseudomonas aeruginosa*	
	100 µg/ml	**150 µg/ml**	**100 µg/ml**	**150 µg/ml**	**100 µg/ml**	**150 µg/ml**	**100 µg/ml**	**150 µg/ml**
3a	2	5	4	7	3	7	6	9
3b	9	12	13	17	12	16	11	15
3c	-	-	-	-	-	-	-	-
3d	8	11	13	18	11	16	11	16
3e	4	6	5	6	4	5	3	5
3f	6	8	5	7	3	5	2	4
3g	3	6	4	6	4	4	2	4
3h	2	4	5	7	5	6	3	5
3i	5	6	3	6	5	6	3	5
3j	4	6	3	5	6	7	4	5
3k	6	7	4	7	5	6	2	3
std Streptomycin	15	18	16	21	13	16	18	22

ANTIFUNGAL ACTIVITY

The antifungal activity studies of the novel triazoles derivatives synthesized by microwave irradiation have been screened using cup-plate agar diffusion method[22] against the fungi *Aspergillus flavus*, *A.fumigatus, penicillium* and *Trichophyton* by expressing the zone of inhibition in mm at two concentrations (100 and 150 µg/ml). Griseofulvin (100 and 150 µg/ml) was used as a standard and was also screened under similar conditions for comparison. The results of the antifungal studies are shown in **Table-2.**

EXPERIMENTAL

GENERAL

The reactions were carried out under microwave irradiation at 160 watts (LG-make) and by conventional stirring method. TLC was used to monitor the progress of the reaction every after 30sec, on silica gel-G precoated plates by using chloroform and methanol (8:2) as the eluent and observed in UV light. Melting points were taken using microprocessor based melting point apparatus (Veego make) containing liquid paraffin and were uncorrected. IR spectra in KBr were recorded on Shimadzu-8400 FTIR spectrophotometer, ^{1}H NMR Spectra were recorded on Bruker spectrophotometer(400MHz) in DMSO-d6/CDCl3 using TMS as an internal standard (chemical shifts are expressed in δ, ppm).

GENERAL PROCEDURE FOR THE SYNTHESIS 3-(N-SUBSTITUTED CARBOXAMIDOMETHYLTHIO)-(4H)-1, 2, 4-TRIAZOLES (3a-k).

The 3- mercapto-(4H)-1, 2, 4-triazole **(1)** (0.01mole) was dissolved in aqueous potassium hydroxide solution (0.06g in 100ml water) till clear solutions was obtained and filter to remove insoluble impurities. To this aqueous solution N-substituted chloroacetamides**(2)** was added in small portion with constant stirring at room temperature during 3 hr. Some solid remained in the mixture, a few ml of ethanol was added to get clear solution. The reaction mixture was stirred for 36 hr at 60-70^{0}C by conventional method and the reaction mixture was subjected to microwave irradiation at 160 watts for 2-4 min. TLC was run after every 30sec to check the progress of reaction. On completion of the reaction by both the methods, the reaction mixture was left for 24 hr and crystalline product that separated was filtered, dried and recrystallized from 50% ethanol to obtain 3-(N-Substituted carboximidomethylthio)-(4H)-1,2,4-triazoles**(3a-k).** Physicochemical and spectral data of titled compounds **(3a– k)** are shown in **Table 3** and **4.**

Table2. Antifungal Activity of Synthesized Compounds (3a-k)
Zone of inhibition expressed in mm

Comp.	*Aspergillus flavus*		*A.fumigatus*		*Penicillium*		*Trichophyton*	
	100 µg/ml	150 µg/ml	100 µg/ml	150 µg/ml	100 µg/ml	150 µg/ml	100 µg/ml	150 µg/ml
3a	6	7	7	8	6	8	7	8
3b	5	7	7	8	7	8	8	9
3c	9	11	10	11	8	10	11	12
3d	6	8	8	9	7	8	8	9
3e	10	11	9	11	9	11	10	11
3f	5	7	7	8	6	7	7	8
3g	4	5	3	4	2	4	5	6
3h	6	7	7	8	7	8	5	6
3i	7	8	6	7	8	9	6	7
3j	2	3	4	6	6	7	7	7
3k	6	7	7	8	8	9	6	7
Std Griseofulvin	12	15	13	17	11	14	13	16

Table3. Physicochemical data of Synthesized Compounds (3a-k)

Comp.	R	Mol Formula	Mol Wt.	%Yield Conventional	m.p.	Time (sec)	%yield Microwave	R_f (cm)
3a	C_6H_5	$C_{10}H_{10}N_4OS$	234	79.34%	188-190	2.0	87%	0.70
3b	p-Cl-C_6H_4	$C_{10}H_9ClN_4OS$	268	64.00%	145-147	3.5	76%	0.56
3c	p-NO_2-C_6H_4	$C_{10}H_9N_5O_3S$	279	47.00%	156-160	6	68%	0.45
3d	m-Cl-C_6H_4	$C_{10}H_9ClN_4OS$	268	60.12%	138-140	4.5	78%	0.56
3e	m-NO_2-C_6H_4	$C_{10}H_9N_5O_3S$	279	45.14%	169-172	5.5	62%	0.45
3f	o-CH_3-C_6H_4	$C_{11}H_{12}N_4OS$	248	67.34%	147-150	4	79%	0.58
3g	p-CH_3-C_6H_4	$C_{11}H_{12}N_4OS$	248	68.25%	151-154	5	75%	0.61
3h	o-NO_2-C_6H_4	$C_{10}H_9N_5O_3S$	279	45.00%	121-124	5.5	64%	0.48
3i	p-OCH_3-C_6H_4	$C_{11}H_{12}N_4O_2S$	264	69.23%	168-170	4.5	73%	0.35
3j	$CH_2C_6H_5$	$C_{11}H_{12}N_4OS$	248	80.00%	128-132	3.5	89%	0.60
3k	o-Cl-C_6H_4	$C_{10}H_9ClN_4OS$	268	60.00	172-174	4.5	72%	0.52

Table4. Spectral data of Synthesized Compounds (3a-k)

Compd.	IR (KBr)cm^{-1}	^1H NMR ($CDCl_3$)	Elemental analysis (%) Found	Calculated
3a	3304(ArN-HStr),3061(ArC-HStr),1676 (C=OStr), 1600(2^0N-H), 1175(C-NStr),754(ArC-H bend)	4.08(s,2HCH_2),7.2-7.3(m,5H-Ar), 8.8(s,1H CH), 9.65 (s,1H NH)	C, 51.27,H, 4.30 N,23.91	C,51.42,H,4.20 N,23.86
3b	3544(Ar N-H Str), 3073(ArC-H str),1659(C=OStr), 1544(2^0N-H), 1179(C-N Str),824(ArC-H bend)	3.9(s,2H CH_2),7.2-7.4(dd,4H-Ar) ,8.24(s,1H CH),10.3 (s,1H NH)	C, 44.70,H, 3.38 N, 20.85	C,44.63,H,3.45N, 20.77
3c	3570(Ar N-H Str), 3081(ArC-H tr),1629(C=OStr), 1564(2^0N-H), 1110 (C-N Str), 841(ArC-H bend)	5.5 (t,2H CH_2), 7.0-7.3 (m,4H-Ar), 8.05(s,1H CH), 10.4 (s,1H NH)	C, 43.01,H, 3.25 N, 25.08	C,43.10,H,3.18 N, 25.21
3d	3299(ArN-HStr), 3105(ArC-H Str),1666(C=OStr), 1533(2^0N-H),1179(C-Nstr), 779(ArC-H bend)	3.9 (s,2H CH_2), 7.0-7.4 (m,4H-Ar), 7.7 (s,1H CH), 8.2 (s,1H NH)	C, 44.70,H, 3.38 N, 20.85	C,44.64,H,3.39N, 0.87
3e	3243(Ar N-H Str), 3056(ArC-H Str),1685 (C=OStr),1542(2^0N-H),1170(C-N str), 836(ArC-H bend)	3.8 (s,2H CH_2), 7.2-7.4 (m,4H-Ar), 8.2 (s,1H CH), 9.3 (s,1H NH)	C, 43.01,H, 3.25 N, 25.08	C,43.11,H,3.29 N, 25.18
3f	3221(Ar N-H Str), 3091(ArC-H Str),1653 (C=OStr),1546(2^0N-H), 1246(C-N str), 876(ArC-H bend)	3.7(s,2H CH_2), 3.8 (s,3H CH_3), 7.0-7.7 (m,4H-Ar), 8.1 (s,1H CH), 9.4 (s,1H NH)	C, 53.21,H, 4.87 N, 22.56	C,53.28,H,4.77 N, 22.51
3g	3301(Ar N-H Str), 3037(ArC-H Str),1669(C=OStr), 1535(2^0N-H),1174(C-	2.6 (s,2H CH_2), 3.9 (s,3H CH_3) 7.0-7.4(dd,4H-Ar), 8.2 (s,1H CH), 10.1	C, 53.21, H, 4.87 N, 22.56	C,53.23,H,4.81 N, 22.47

	NStr),815(ArC-H bend)	(s,1H NH)		
3h	3317(ArN-HStr),3082(ArC-HStr), 1685(C=OStr), 1491(2^0N-H),1164(C-Nstr), 747(ArC-H bend)	4.0 (s,2H CH_2), 7.2-7.6(q,4H-Ar), 8.5 (s,1H CH), 11.1 (s,1H NH)	C, 43.01,H, 3.25N, 25.08	C,43.11,H, 3.22N, 25.03
3i	3254(Ar N-H Str),3057(ArC-H Str),1667 (C=OStr),1544(2^0N-H),1247(C-N Str),832(ArC-H bend)	3.7 (s,2H CH_2), 4.1 (s,3H OCH_3), 6.8-7.4(m,4H-Ar), 8.2 (s,1H CH), 9.9 (s,1H NH)	C, 49.99,H, 4.58N, 21.20	C,49.89,H, 4.61N, 21.23
3j	3307(ArN-HStr),3058(ArC-H Str),1643(C=OStr), 1542(2^0N-H), 1120(C-NStr),898(ArC-H bend)	3.2 (s,2H CH_2), 3.8 (s,2H CH_2), 7.1-7.3(m,5H-Ar), 8.1 (s,1H CH), 9.9 (s,1H NH)	C, 53.21,H, 4.87,N,22.56	C,53.25,H, 84,N,22.59
3k	3241(ArN-HStr), 3064(ArC-H Str),1659(C=OStr), 536(2^0N-H),1180(C-NStr), 759(ArC-H bend)	3.9 (s,2H CH_2), 7.0-7.2(m,4H-Ar), 8.1 (s,1H CH), 9.7 (s,1H NH)	C, 44.70,H, 3.38,N, 20.85	C, 44.74,H, 3.37,N, 20.85

RESULT AND DISCUSSION

As indicated by TLC analysis, a maximum of 6 min of heating suffices to produce nearly complete conversion. However, in conventional stirring method, poor conversions to triazoles derivatives were realized when the reactions were stirred at 60-70^{0}C for 36 hr. Microwave irradiation method appeared to be rapid and economical with a wide range of applications. The reaction was found to proceed smoothly under microwave irradiation within 2-6 min, whereas under stirring at 60-70^{0}C, 36 hr were required.

Among the compounds tested, **3b** and **3d** showed remarkable activity against the bacteria *E.coli*, *P. aeruginosa* and *K. pneumonae* and moderate activity against *S.aureus*. Among the compounds tested, **3c** and **3e** showed good activity against all the fungi. Remaining compounds tested showed minimum to moderate activity.

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