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Microwave Assisted Synthesis of Some 4-Amino-5-substituted Aryl-3-mercapto-(4*H*)-1,2,4-triazoles

A. BIJUL LAKSHMAN* and R.L. GUPTA
Division of Agricultural Chemicals, Indian Agricultural Research Institute
New Delhi-110 012, India
E-mail: bijullakshman@gmail.com

The conventional and microwave synthesis of twenty eight 4-amino-5-substituted aryl-3-mercapto-(4*H*)-1,2,4-triazoles (**V**) were studied and compared. Methyl esters of the substituted benzoic acids (**II**) were made to its respective hydrazides (**III**) by treating with hydrazine hydrate. These hydrazides were then treated with alcoholic potassium hydroxide and carbon disulphide to obtain the respective aryl dithiocarbazinic acid salts (**IV**). These salt were cyclized under conventional and microwave condition separately to the corresponding 4-amino-5-aryl-3-mercapto-(4*H*)-1,2,4-triazole. The structures of final compounds (**V**) were confirmed by elemental analysis, IR and ^{1}H NMR.

Key Words: Microwave synthesis, Triazoles, 1,2,4-triazoles, 4-Amino-5-aryl-3-mercapto-(4*H*)-1,2,4-triazoles.

INTRODUCTION

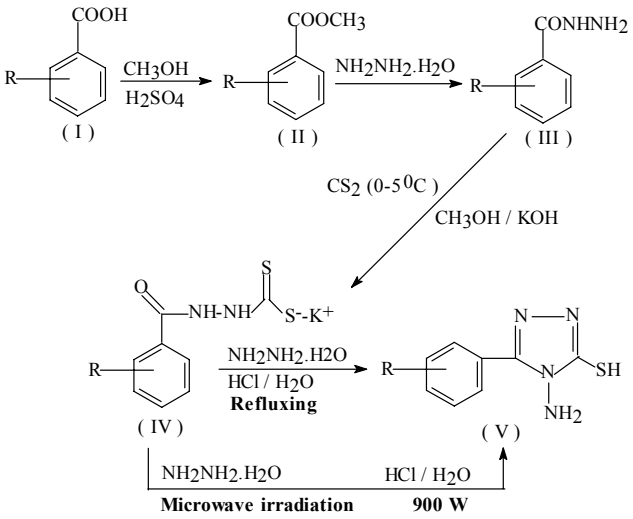
Among heterocyclic compounds, 1,2,4-triazoles and their derivatives show wide spectrum of activity, hence are having good commercial importance. The pharmacological activities are antibacterial, antifungal, hypoglycemic, antihypertensive, analgesic and anti-inflammatory properties[1-5]. In agriculture, this group of compounds have shown wide spectrum of activity as fungicides[6-8], herbicides[8-10], insecticides[11], antialgal[12], antibacterial[13] and nitrification inhibitory[14]. The gaining importance of this group prompted to look forward for a better, faster, efficient and economical way of synthesis using microwave, purification and characterization. The outcome of this study gives an over view of the conventional and microwave synthesis of 4-amino-5-substituted aryl-3-mercapto-(4*H*)-1,2,4-tiazole compounds.

EXPERIMENTAL

The synthesis of the 4-amino-5-aryl-3-mercapto-(4*H*)-1,2,4-triazoles were accomplished according to the reactions shown in **Scheme-I**. First, methyl esters of aryl acids (**II**) were prepared by acid mediated esterification of aryl acids (**I**), from this aryl acid hydrazides (**III**) were prepared which

were converted to potassium salt of aryl dithiocarbazinic acids (**IV**). The 4-amino-5-aryl-3-mercapto-(4*H*)-1,2,4-triazoles (**V**) were obtained in the final step by conventional refluxing and also by neat reaction under microwave irradiation.

No.	R
1	H
2	4-NH_2
3	2-Cl
4	3-Cl
5	4-Cl
6	2-F
7	4-F
8	2-OH
9	4-OH
10	2-SH
11	2-OCH_3
12	4-OCH_3
13	4-OC_2H_5
14	2-CH_3
15	3-CH_3
16	4-CH_3
17	3-NO_2
18	4-NO_2
19	4-CHO
20	4-$C(CH_3)_3$
21	2,4-Cl_2
22	2,4-$(OH)_2$
23	3,5-$(OH)_2$
24	3,4-$(OCH_3)_2$
25	5-Cl, 2-OH
26	5-SO_3H, 2-OH
27	2-Cl, 5-NO_2
28	3,5-$(NO_2)_2$, 2-OH



Scheme-I: Synthesis of 4-amino-5-aryl-3-mercapto-(4*H*)-1,2,4-triazoles

The final compounds (**V_{1-28}**) were characterized by elemental analysis, IR and ^{1}H NMR. The IR spectra of all the compounds (**V_{1-28}**) showed peaks for N-H *str.* (3310-3242 cm^{-1}), C=N (1575-1481 cm^{-1}), S-H (2800-2524 cm^{-1}), C-H aromatic (3100-3000 cm^{-1}) and C-C aromatic (1643-1612 cm^{-1}). The ^{1}H NMR of 4-amino-5-aryl-3-mercapto-4*H*-1,2,4-triazoles (**V_{1-28}**) showed characteristic peaks, singlet for -NH_2 (δ 4.15-5.81 ppm) and singlet for -SH (δ 12.50-14.79 ppm). Elemental analysis for the compounds was done for C, H, N and S and found values were close to the corresponding calculated values.

RESULTS AND DISCUSSION

Melting points were determined by using sulphuric acid bath and are uncorrected. Infrared spectra were recorded on a Nicolet Transform Infrared Spectrophotometer (Model Impact-400) using KBr pellets. The ^{1}H NMR spectra were recorded on a Varian EM 360L, 60 MHz instrument in DMSO-d_6 using TMS as an internal reference. Elemental analysis for the compounds for C, H, N and S was done on Euro-EA, elemental analyzer using sulphanilamide as reference standard.

TABLE-1
COMPARISON OF REACTION TIME AND YIELD IN CONVENTIONAL AND MICROWAVE SYNTHESIS OF 4-AMINO-5-ARYL-3-MERCAPTO-(4*H*)-1,2,4-TRIAZOLES (**V**)

Compd.	R	m.p. (ºC)	Conventional method		MW method	
			Time (h)	Yield (%)	Time (s)	Yield (%)
$\mathbf{V_1}$	H	203-205	4.0	88.57	36	95.06
$\mathbf{V_2}$	4-NH_2	260-261	5.0	74.90	40	85.76
$\mathbf{V_3}$	2-Cl	155-156	4.3	77.15	38	88.34
$\mathbf{V_4}$	3-Cl	124-125	4.3	81.56	42	82.93
$\mathbf{V_5}$	4-Cl	211-212	4.3	77.15	38	87.68
$\mathbf{V_6}$	2-F	127-128	4.3	82.74	45	89.31
$\mathbf{V_7}$	4-F	139-140	4.3	73.28	29	84.91
$\mathbf{V_8}$	2-OH	202-203	5.0	71.07	51	81.88
$\mathbf{V_9}$	4-OH	215-216	5.0	79.65	48	84.16
$\mathbf{V_{10}}$	2-SH	159-160	4.3	85.45	31	90.39
$\mathbf{V_{11}}$	2-OCH_3	218-220	4.0	63.08	29	80.98
$\mathbf{V_{12}}$	4-OCH_3	205-206	4.0	56.32	34	71.99
$\mathbf{V_{13}}$	4-OC_2H_5	158-160	4.0	78.14	38	80.51
$\mathbf{V_{14}}$	2-CH_3	154-155	5.0	67.72	34	78.05
$\mathbf{V_{15}}$	3-CH_3	159-160	5.0	62.88	38	74.17
$\mathbf{V_{16}}$	4-CH_3	210-213	5.3	65.30	43	76.48
$\mathbf{V_{17}}$	3-NO_2	182-183	6.0	82.30	35	89.68
$\mathbf{V_{18}}$	4-NO_2	215-216	6.0	86.52	38	92.73
$\mathbf{V_{19}}$	4-CHO	164-165	7.0	87.33	39	93.19
$\mathbf{V_{20}}$	4-$C(CH_3)_3$	184-185	7.0	76.88	41	80.13
$\mathbf{V_{21}}$	2,4-Cl_2	209-210	8.0	79.26	41	84.09
$\mathbf{V_{22}}$	2,4-$(OH)_2$	95-96	9.0	87.70	58	94.88
$\mathbf{V_{23}}$	3,5-$(OH)_2$	189-190	10.0	71.96	65	83.95
$\mathbf{V_{24}}$	3,4-$(OCH_3)_2$	174-175	10.0	67.48	41	85.32
$\mathbf{V_{25}}$	5-Cl, 2-OH	207-208	8.0	80.57	33	73.14
$\mathbf{V_{26}}$	5-SO_3H, 2-OH	152-154	9.0	66.18	42	76.65
$\mathbf{V_{27}}$	2-Cl, 5-NO_2	115-116	10.0	66.73	39	80.88
$\mathbf{V_{28}}$	3,5-$(NO_2)_2$, 2-OH	174-175	9.0	77.42	45	79.05

Preparation of methyl esters of aryl acids ($\mathbf{II_{1-28}}$): The preparation of methyl esters of aryl acids was carried out following literature methods[15] by reacting aryl acids (**I**) with excess of methanol in presence of concentrated sulfuric acid except the methyl esters of *m*- and *p*-chlorobenzoic acids, which were prepared by reacting the aryl acids with BF_3-methanol complex.

Preparation of aryl hydrazides ($\mathbf{III_{1-28}}$): These were prepared by reaction of corresponding methyl esters with hydrazine hydrate following literature methods[16,17].

Preparation of potassium salt of aryl dithiocarbazinic acids ($\mathbf{IV_{1-28}}$): The aryl acid hydrazides (**III**) (0.1 mol) were dissolved in saturated solution (50 mL) of chilled methanolic potassium hydroxide. Then CS_2 (1.2 mol)

TABLE-2
ELEMENTAL ANALYSIS OF 5-ARYL-4-AMINO-3-MERCAPTO-(4*H*)-1,2,4-TRIAZOLES

Compd.	R	Analysis (%)							
		C		H		N		S	
		Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
1	H	49.98	50.12	4.19	3.98	29.14	28.86	16.68	16.85
2	4-NH_2	46.36	46.30	4.38	4.28	33.79	33.68	15.47	15.41
3	2-Cl	42.39	42.28	3.11	3.09	24.72	24.68	14.15	14.11
4	3-Cl	42.39	41.82	3.11	2.88	24.72	25.12	14.15	14.68
5	4-Cl	42.39	42.25	3.11	3.94	24.72	24.48	14.15	14.21
6	2-F	45.70	44.96	3.36	3.24	26.65	26.97	15.25	14.85
7	4-F	45.70	45.45	3.36	3.30	26.65	26.56	15.25	15.21
8	2-OH	46.14	46.18	3.87	3.79	26.90	26.82	15.40	15.35
9	4-OH	46.14	46.20	3.87	3.91	26.90	26.85	15.40	15.62
10	2-SH	42.84	42.79	3.59	3.50	24.98	24.90	28.59	28.64
11	2-OCH_3	48.63	48.62	4.53	4.46	25.21	25.17	14.43	14.32
12	4-OCH_3	48.63	48.70	4.53	4.49	25.21	25.28	14.43	14.61
13	4-OC_2H_5	50.83	50.76	5.12	5.08	23.71	23.65	13.57	13.59
14	2-CH_3	52.41	52.39	4.89	4.94	27.16	27.10	15.55	16.01
15	3-CH_3	52.41	52.44	4.89	4.96	27.16	27.08	15.55	15.71
16	4-CH_3	52.41	52.35	4.89	4.80	27.16	27.22	15.55	15.65
17	3-NO_2	40.50	39.99	2.97	2.99	29.52	29.49	13.52	13.49
18	4-NO_2	40.50	40.25	2.97	3.24	29.52	29.58	13.52	13.58
19	4-CHO	49.08	49.01	3.66	3.57	25.44	25.34	14.56	14.82
20	4-$C(CH_3)_3$	58.03	58.10	6.49	6.38	22.56	22.51	12.91	12.87
21	2,4-Cl_2	36.80	36.77	2.32	2.30	21.46	21.55	12.28	12.41
22	2,4-$(OH)_2$	42.85	42.99	3.60	3.68	24.99	25.32	14.30	14.21
23	3,5-$(OH)_2$	42.85	42.92	3.60	3.72	24.99	25.01	14.30	14.25
24	3,4-$(OCH_3)_2$	47.61	47.70	4.79	4.99	22.21	22.28	12.71	12.57
25	5-Cl, 2-OH	39.59	39.72	2.91	2.96	23.09	23.01	13.21	13.31
26	5-HSO_3, 2-OH	33.33	33.49	2.80	2.84	19.43	19.54	22.24	22.15
27	2-Cl, 5-NO_2	35.37	35.48	2.23	2.28	25.78	25.84	11.80	11.95
28	3,5-$(NO_2)_2$, 2-OH	32.22	32.34	2.03	2.11	28.18	28.28	10.75	10.53

was added dropwise. After the addition, the reaction mixture was stirred for 0.5 h. The solid obtained (**IV**) was filtered off and washed with acetone, dried and used as such for further reaction[18].

Conventional synthesis of 4-amino-5-substituted aryl-3-mercapto-(4*H*)-1,2,4-triazoles (V_{1-28}): A suspension of potassium salt of aryl dithiocarbazinic acid (**IV**) (0.1 mol), hydrazine hydrate-99 % (0.2 mol) and of water (1.67 mol) was refluxed with stirring for 4-10 h in a round bottom flask kept on hot plate cum magnetic stirrer until the evolution of hydrogen sulfide ceased. The solution becomes light green tinged blue or colourless and homogenous. Dilution with 100 mL of cold water and acidification with concentrated HCl precipitated a white solid which was filtered, washed with 2 × 50 mL of cold water and recrystallized from methanol or methanol-water[19,20].

TABLE-3
INFRARED SPECTRAL DATA (cm^{-1}) OF 5-ARYL-4-AMINO-3-MERCAPTO-(4*H*)-1,2,4-TRIAZOLES

Compd.	R	ν (cm^{-1})				
		ν(N-H)	ν(C=N)	ν(S-H)	ν(C-H), ν(Ar-H)	ν(C-C), ν(Ar-H)
1	H	3250	1483	2575	3053	1615-1618
2	4-NH_2	3111	1605	2580	3026	1615-1620
3	2-Cl	3261	1489	2578	3032	1615
4	3-Cl	3302	1531	2598	3012	1627
5	4-Cl	3250	1531	2590	3000	1630
6	2-F	3300	1504	2600	3062	1618
7	4-F	3300	1560	2524	3047	1616
8	2-OH	3267	1504	2557	3093	1643
9	4-OH	3295	1520	2524	3022	1620
10	2-SH	3274	1555	2600	3000	1618
11	2-OCH_3	3288	1515	2550	3074	1612
12	4-OCH_3	3265	1500	2582	3034	1615-1618
13	4-OC_2H_5	3265	1500	2575	3068	1615
14	2-CH_3	3267	1498	2580	3018	1617
15	3-CH_3	3267	1500	2580	3016	1643
16	4-CH_3	3270	1498	2594	3064	1615-1618
17	3-NO_2	3265	1575	2582	3080	1615-1618
18	4-NO_2	3242	1514	2580	3057	1614
19	4-CHO	3296	1500	2590	3057	1614
20	4-$C(CH_3)_3$	3296	1500	2580	3039	1615-1618
21	2,4-Cl_2	3265	1504	2580	3034	1615-1618
22	2,4-$(OH)_2$	3265	1514	2580	3034	1615-1618
23	3,5-$(OH)_2$	3268	1481	2582	3084	1612.49
24	3,4-$(OCH_3)_2$	3288	1514	2580	3057	1615-1618
25	5-Cl, 2-OH	3309	1558	2590	3091	1615-1618
26	5-HSO_3, 2-OH	3310	1504	2600	3057	1615-1618
27	2-Cl, 5-NO_2	3265	1565	2580	3100	1615-1618
28	3,5-$(NO_2)_2$, 2-OH	3265	1565	2547	3026	1612

Microwave synthesis of 4-amino-5-substituted aryl-3-mercapto-(4*H*)-1,2,4-triazoles (V_{1-28}): Potassium salt of aryl dithiocarbazinic acid (**IV**) (4 mmol) and hydrazine hydrate-99 % (8 mmol) was taken in a 100 mL round bottom flask which was then connected with a specially designed apparatus containing lead acetate. The lead acetate worked as a trap for hydrogen sulfide, that was evolved during the microwave reaction. The microwave irradiation was done at 900 W till a white solid appeared at the bottom or till the carbon disulfide evolution ceased. The solid was taken in 15-20 mL of water and acidified with concentrated HCl. The white precipitate obtained was washed to neutral pH with water to obtain pure triazoles (**V**). The purity of the compounds was checked by TLC using methanol as developing solvent and iodine as visualizing agent and also by melting point.

TABLE 4
^{1}H NMR DATA OF 5-ARYL-4-AMINO-3-MERCAPTO-(4*H*)-1,2,4-TRIAZOLES

Compd.	R	Chemical shift, δ (ppm)			
		s, N_3C_2-Ar-H	m, N_3C_2-NH_2	s, N_3C_2-SH	Aryl substituent Protons (C_6H_5-R)
1	H	7.85-8.15	5.14	13.61	
2	4-NH_2	8.00	5.12	13.92	
3	2-Cl	8.23	4.84	14.00	
4	3-Cl	7.23-7.49	5.10	13.91	
5	4-Cl	8.11-7.62	5.70	13.87	
6	2-F	7.25-7.89	5.83	14.10	
7	4-F	8.00-8.75	5.80	13.26	
8	2-OH	6.80-7.40	5.30	13.82	
9	4-OH	6.80-7.85	5.60	13.02	
10	2-SH	6.90-5.50	4.60	13.40	
11	2-OCH_3	6.83-7.37	4.21	13.78	3.90, s, -OC$\underline{H}_3$
12	4-OCH_3	7.01-7.98	5.48	13.91	3.78, s, -OC$\underline{H}_3$
13	4-OC_2H_5	7.30-8.00	4.45	13.82	3.98, -OC$\underline{H}_2$ & 1.81, -$OCH_2C\underline{H}_3$
14	2-CH_3	7.52	5.51	13.99	2.31, s, -C$\underline{H}_3$
15	3-CH_3	8.02	5.87	14.79	2.31, s, -C$\underline{H}_3$
16	4-CH_3	7.21-8.02	5.49	13.96	2.41, s, -C$\underline{H}_3$
17	3-NO_2	7.60-8.45	5.10	12.50	
18	4-NO_2	7.50-8.30	4.60	12.90	
19	4-CHO	5.20-5.90	4.61	13.68	8.15, s, -C$\underline{H}$O
20	4-$C(CH_3)_3$	7.20-8.35	4.31	13.00	2.58-2.75, s, -$C(C\underline{H}_3)_3$
21	2,4-Cl_2	6.20-6.90	5.60	13.75	
22	2,4-$(OH)_2$	6.20-6.70	5.50	13.46	
23	3,5-$(OH)_2$	5.10-6.51	5.80	13.00	
24	3,4-$(OCH_3)_2$	6.30-8.40	5.65	13.01	
25	5-Cl, 2-OH	6.90-8.00	5.55	13.89	
26	5-HSO_3, 2-OH	6.45-8.10	4.15	13.85	
27	2-Cl, 5-NO_2	7.64-8.40	4.23	13.10	
28	3,5-$(NO_2)_2$, 2-OH	8.05	4.75	13.65	

Conclusion

In this study, a convenient method over the conventional method was devised using microwave. The twenty-eight 4-amino-5-aryl-3-mercapto-(4*H*)-1,2,4 triazoles ($\mathbf{V_{1\text{-}28}}$) were synthesized using both conventional and microwave methods. In conventional method time of reaction varied from 4-10 h and yield from 56.3-88.6 %. The microwave synthesis was carried out in a domestic oven at 900 W, the time of reaction varied from 29-65 s and yield from 72-95 %. The microwave assisted synthesis drastically reduced the time of reaction and have resulted an increase of 2-18 % in yield.

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