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Microwave assisted synthesis of novel 3-mercapto-4, 5-disubstituted 1, 2, 4-triazole derivatives

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Abstract
A series of 3-Mercapto-4, 5-disubstituted 1, 2, 4-triazole derivatives (T1-T8) has been synthesized under conventional and microwave irradiation and the results were compared. The reaction time decreases hours to minutes along with yield enhancement. The structures of these compounds were characterized by means of FT-IR, ^{1}H-NMR.

Keywords: 1, 2, 4-triazole, Conventional, Microwave

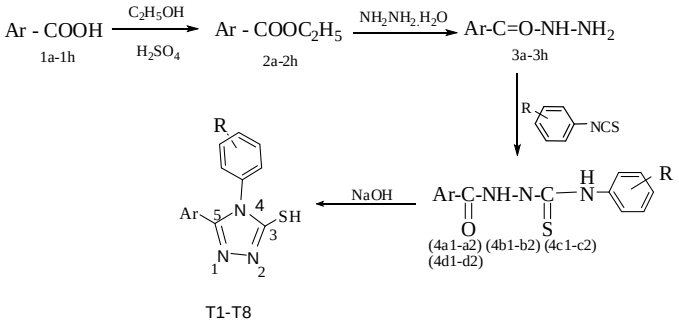
1. Introduction
Over the past few years, scientists show interest in the synthesis of organic compounds under microwave irradiation. The feasibility of microwave-assisted synthesis has been demonstrated in various transformations such as condensation [1], cycloaddition [2], alkylation [3], oxidation [4]. Synthesis of various heterocyclic compounds [5-7] and many other chemical reactions. Microwave irradiation produces efficient internal heat transfer (in situ heating), resulting in even heating throughout the sample as compared with the wall heat transfer that occurs when a water/oil bath is applied as an energy source [8]. The microwave assisted reactions occur more rapidly, safely and with the highest chemical yields. A large number of 1, 2, 4-triazole ring systems, have been incorporated into a wide variety of therapeutically interesting drug candidates having anti-inflammatory, CNS-stimulant, sedative, antianxiety and antimicrobial activities [9-11], antimycotic activity such as fluconazole, in traconazole, and voriconazole [12-13]. Drugs containing 1, 2, 4-triazole moiety are triazolam, alprazolam, etizolam and furacilin [14].

2. Materials and methods
2.1 General
Starting materials were obtained from commercial sources and were used without further purification. Solvents were dried by standard procedures. Reaction progress was observed by thin layer chromatography. Melting points were determined by automated melting point apparatus (model 51142501) and are uncorrected. ^{1}H and ^{13}C NMR spectra were determined by Agilent 400 MHz NMR spectrometer ulventsing DMSO-d6 solvent and are expressed in parts per million (δ, ppm). NMR data are given as multiplicity (s, singlet; d, doublet; t, triplet; m, multiplet) and number of protons. IR spectra were recorded on Brucker 12060280, spectrophotometer in a KBr disc.

2.2. Chemistry
In the present work eight novel derivatives of 1, 2, 4-triazole were synthesized by using conventional and microwave methods, following the synthetic route given in scheme1.The starting material benzoic acid ester derivatives (2a- 2h), for the synthesis of desired compounds were obtained by Esterification of benzoic acid derivatives (1a-1h) with ethanol in the presence of sulphuric acid as catalyst using both reflux and microwave methods. Then the compounds (2a-2h) on the treatment with aromatic hydrazine hydrate provided aryl carbonyl hydrazide derivatives (3a-3h). In the next step (3a-3h) reacts with aryl thiocyanate gave 1-(aryl carbonyl)-4-arylthiocarbazides ($4a_1$-a_2) ($4b_1$-b_2) ($4c_1$-c_2) ($4d_1$-d_2). Finally cyclization of 1-(aryl carbonyl)-4 arylthiocarbazides derivatives with NaOH provided the desired products 3-Mercapto-4, 5-disubstituted 1, 2, 4-triazole (Table1).

The synthesized compounds were purified and recrystallized using ethanol and acetone. The characterization of these new derivatives were done by spectroscopy (FT-IR, ^{1}H NMR).

Scheme 1. Synthetic scheme for 3-Mercapto-4, 5-disubstituted -1, 2, 4-triazole derivatives (T1-T8).



2.2.1. Synthesis of aryl carboxylic acid ester (2a- 2h)

Conventional method: A mixture of pure aryl carboxylic acid (0.1 mol) and absolute ethanol (0.4 mol) were taken in a round bottom flask and refluxed for 4 h in the presence of 2-3 drops of conc. Sulphuric acid. After refluxing the resulting product was kept at room temperature and then poured into about 250 ml of water in a separating funnel. Lower layer of ester was collected at the bottom. Ester of aryl carboxylic acid shook with a strong solution of potassium hydrogen carbonate until all free acid was neutralized. Washed once with water, and dried by pouring into a dry china dish containing about 2 gm of magnesium sulphate.

Microwave method: Aryl carboxylic acid (0.01mol), ethanol (0.025mol) and 1-2 drops of sulfuric acid were mixed in a glass vessel with Teflon stopper. The reaction was performed in the microwave at an engaged power of 360 W for 5 min. The alcohol was removed in a rota evaporator, the obtained product dissolved in ether and extracted with an aqueous solution of sodium hydroxide (pH 9). The ether extract was washed with water to neutralize and dried over anhydrous Na_2SO_4. The m. p., IR and ^{1}HNMR data are in agreement with those obtained for the products synthesized by other reported method [15].

Table 1: Comparative data of esters of different benzoic acids by conventional and microwave method.

Comp	Name of compounds	Reaction Time		Yield (%)		B.P.(^{0}C)
		Conv. (h)	Micro.(sec)	Conv.	Micro.	Conv.
2a.	Ethyl 4-nitro benzoate	5.0	60	72	88	194-196
2b.	Ethyl 4-hydroxy benzoate	4.5	90	75	90	215-217
2c.	Ethyl 2-methylbenzoate	5.0	100	69	87	198-200
2d.	Ethyl 3-methylbenzoate	5.5	95	75	86	194-195
2e.	Ethyl 4- methoxybenzoate	5.0	95	70	87	255-257
2f.	Ethyl 2,4-dimethoxybenzoate	5.5	97	72	85	240-242
2g.	Ethyl 4- chlorobenzoate	5.0	99	64	89	230-233
2h.	Ethyl 4-bromobenzoate	4.5	125	65	87	265-267

2.2.2. Synthesis of aryl carbonyl hydrazide (3a-3h) hydrazinolysis

Conventional method: In this step the compounds (2a-2h) (0.1mol) and hydrazine hydrate (0.116mol) were refluxed in the presence of 25.5 ml of ethanol for 6 h. Excess of ethanol was distilled off, the reaction mixture was cooled. The solid thus separated out was dried and recrystallized from ethanol.

Microwave method: Compounds (2a-2h) (0.01 mol) and hydrazine hydrate (0.012 mol) in a glass vessel with Teflon stopper at 900 W for 1-2 min. After completion, excess of ethanol was distilled off under reduced pressure and residue poured into ice cold water. The solid obtained was filtered and recrystallized from ethanol. The m. p., IR and ^{1}HNMR data are in agreement with those obtained for the products synthesized by other reported method.

Table 2. Comparative data of different aryl carbonyl hydrazide by conventional and microwave method.

Comp	Name of compounds	Reaction Time		Yield (%)		M.P. (^{0}C)
		Conv (h)	Micro (Sec)	Conv	Micro	
3a.	4-nitrobenzohydrazide	5.0	170	72	86	116-118
3b.	4-hydroxy benzohydrazide	4.5	120	75	90	178-180
3c.	2- methyl benzohydrazide	5.0	100	69	85	121-122
3d.	3-methyl benzo hydrazide	5.5	30	75	85	99-100
3e	4- methoxy benzohydrazide	5.0	40	70	82	160-163
3f.	2,4-dimethoxybenzo hydrazide	5.5	30	72	87	152-153
3g.	4- chloro benzohydrazide	5.0	30	64	70	161-162
3h.	4-bromo benzohydrazide	4.5	30	65	74	112-115

2.2.3. Synthesis of aryl carbonyl hydrazinecarbothioamide ($4a_1$-a_2) ($4b_1$-b_2) ($4c_1$-c_2) ($4d_1$-d_2)

Conventional method: Mixture of compounds (3a-3h) (0.1mol) and aryl thiocyanate (0.12 mol) were taken in a of round bottom flask, 20 ml of 10% HCl solution was added drop wise to this mixture and refluxed for 3-4 h. The solid crude product was separated by filtration, washed twice with cold water. Then the product was recrystallized from acetone.

Microwave method: Mixture of compounds (3a-3h) (0.1mol) and arylthiocyanate (0.12mol) were mixed thoroughly in a mortar. Then two drops of ethanol was added and the reaction mixture was irradiated with microwave at 900 W for 2-5 minutes. The solid crude product was purified by recrystallization from ethanol. The m. p., IR and ^{1}HNMR data are in agreement with those obtained for the products synthesized by other reported method [16].

Table 3: Comparative data of different aryl hydrazinecarbothioamide by conventional and microwave method

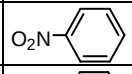
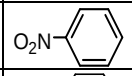
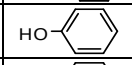
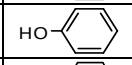
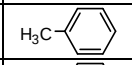
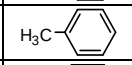
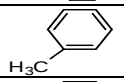
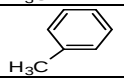
Comp	Name of compound	Reaction Time		Yield (%)		Melting Point (^{0}C)	
		Conv. (h)	Micro. (Sec)	Conv.	Micro.	Conv.	Micro.
$4a_1$	2-(4-nitrobenzoyl)-N-phenylhydrazinecarbothioamide	5.0	120	84	95	200-202	200-202
$4a_2$	2-(4-nitrobenzoyl)-N-p-tolylhydrazinecarbothioamide	4.5	90	88	82	221-222	221-223
$4b_1$	2-(4-hydroxybenzoyl)-N-phenylhydrazinecarbothioamide	5.0	120	80	95	228-229	226-228
$4b_2$	2-(4-hydroxybenzoyl)-N-p-tolylhydrazinecarbothioamide	5.5	125	85	90	230-232	230-231
$4c_1$	2-(2-methylbenzoyl)-N-phenylhydrazinecarbothioamide	5.0	125	84	97	209-210	210-212
$4c_2$	2-(2-methylbenzoyl)-N-(4- ethylphenyl)hydrazinecarbothioamide	5.0	120	75	87	287-289	287-289
$4d_1$	2-(3-methylbenzoyl)-N-phenylhydrazinecarbothioamide	5.0	120	84	95	225-226	224-226
$4d_2$	2-(3-methylbenzoyl)-N-(4-ethylphenyl)hydrazinecarbothioamide	4.5	90	88	82	226-228	227-228

2.2.4. Synthesis of 3-Mercapto- 4, 5-aryl substituted -1, 2, 4-triazole (T1-T8)

Conventional method: 5 ml solution of 2M NaOH (8%solution) was added portion wise to solid aryl carbonyl thiosemicarbazide derivatives (0.01mol) and refluxed for 4 h. After the completion of the reaction, the reaction mixture was treated with activated charcoal and filtered. Then filtrate was acidified with hydrochloric acid for pH 9. The resulting precipitate was filtered and recrystallized from ethanol to obtain the final derivatives.

Microwave method: 2M NaOH added to solid aryl carbonyl thiosemicarbazide (0.004mol) and kept in the microwave for 2-5 minutes. After completion of the reaction, cool the mixture and acidified with 2M HCl. The precipitate obtained was recrystallized from acetonitrile.

Table 4: A comparative study of compounds synthesized by conventional and microwave methods.

Compound	AR	R	Molecular Formula	Mol. Wt.	Reaction Time		Yield (%)		Melting Point (^{0}C)
					Conv. (h)	Micro. (Sec)	Conv.	Micro.	
T1		H	$C_{14}H_{10}N_4O_2S$	298.05	5.0	130	75	88	232-234
T2		CH3	$C_{15}H_{12}N_4O_2S$	312.35	4.5	140	78	90	231-233
T3		H	$C_{14}H_{11}N_3OS$	296.32	5.0	130	80	87	188-189
T4		CH3	$C_{15}H_{13}N_3OS$	283.35	5.0	130	72	84	189-190
T5		H	$C_{15}H_{13}N_3S$	267.35	4.5	130	85	89	210-212
T6		CH3	$C_{16}H_{15}N_3S$	281.38	5.0	200	83	89	211-213
T7		H	$C_{15}H_{13}N_3S$	267.38	5.0	130	70	88	234-236
T8		CH3	$C_{16}H_{15}N_3S$	281.38	4.5	120	70	80	235-237

(4-nitrophenyl)-4-phenyl-4H-1, 2, 4-triazole-3-thiol (T1): IR v_{max} cm^{-1} (KBr): 3067.12 (C-H str., aromatic), 1255.34 (C-N str., aromatic), 1625.44 (C=N str., aromatic), 1507.48 (C=C str., aromatic), 1345.31 (N-O sym. str., aromatic). ^{1}H NMR (DMSO) δ; 6.06-7.87 (9H, m, ArH), 3.35 (1H, s, SH).

4-(4-methylphenyl)-5-(4-nitrophenyl)-4H-1, 2, 4-triazole-3-thiol (T2): IR v_{max} cm^{-1} (KBr): 3098.77 (C-H str., aromatic), 1345.77 (C-N str., aromatic), 1407.22 (C=C str., aromatic), 1531.94 (N-O sym. str., aromatic), 2904.11 (C-CH3 sym.). ^{1}H NMR (DMSO) δ; 6.55-7.95 (8H, m, ArH), 4.15 (1H, s, SH), 2.31 (3H, s, $ArCH_3$).

5-(4-hydroxyphenyl)-4-phenyl-4H-1, 2, 4-triazole-3-thiol (T3): IR v_{max} cm^{-1} (KBr): 3067.12 (C-H str., aromatic), 1255.34 (C-N str., aromatic), 1625.44 (C=N str., aromatic), 1507.48 (C=C str., aromatic), 1311.84 (N-O sym. str., aromatic). ^{1}H NMR (DMSO) δ; 6.63-8.05 (9H, m, ArH), 3.35 (1H, s, SH), 5.0 (IH, s, OH).

4-(4-methylphenyl)-5-(4-hydroxyphenyl)-4H-1, 2, 4-triazole-3-thiol (T4): IR v_{max} cm^{-1} (KBr): 3045.86 (C-H str., aromatic), 1250.88 (C-N str., aromatic), 1688.98 (C=N str., aromatic), 1588.96 (C=C str., aromatic), 3538.45 (O-H str.). ^{1}H NMR (DMSO) δ; 6.64-8.26 (8H, m, ArH), 3.35 (1H, s, SH), 2.37 (3H, s, $ArCH_3$), 4.90 (IH, s, OH).

5-(2-methylphenyl)-4-phenyl-4H-1, 2, 4-triazole-3-thiol (T5): IR v_{max} cm^{-1} (KBr) 3015.00(C-H str., aromatic), 1250.69 (C-N str., aromatic), 1664.96 (C=N str., aromatic), 1507.66 (C=C str., aromatic), 2963.966 (C-CH3 str.). ^{1}H NMR (DMSO) δ; 6.11-8.66 (9H, m, ArH), 3.35 (1H, s, SH), 2.35 (3H, s, $ArCH_3$).

4-(4-methylphenyl)-5-(2-methylphenyl)-4H-1, 2, 4-triazole-3-thiol (T6): IR v_{max} cm^{-1} (KBr): 3015.00 (C-H str., aromatic), 1284.72 (C-N str., aromatic), 1664.98 (C=N str., aromatic), 1507.66 (C=C str., aromatic), 2963.96 (C-CH3 str). ^{1}H NMR (DMSO) δ; 7.49-8.02 (8H, m, ArH), 3.35 (1H, s, SH), 1.45 (6H, s, $ArCH_3$).

5-(3-methylphenyl)-4-phenyl-4H-1, 2, 4-triazole-3-thiol (T7): IR v_{max} cm^{-1}(KBr): 3015.00 (C-H str., aromatic), 1284.72 (C-N str., aromatic), 1664.98 (C=N str., aromatic), 1507.66(C=C str., aromatic), 2963.96 (C-CH3 str.). ^{1}H NMR (DMSO) δ; 7.49-8.02 (8H, m, ArH), 3.35 (1H, s, SH), 1.40 (3H,s, $ArCH_3$).

4-(4-methylphenyl)-5-(3-methylphenyl)-4H-1, 2, 4-triazole-3-thiol (T8): IR ν_{max} cm^{-1} (KBr): 3038.36 (C-H str., aromatic), 1284.12 (C-N str., aromatic), 1624.80 (C=N str., aromatic), 1589.40 (C=C str., aromatic), 2941.93 (C-CH3 str.). ^{1}H NMR (DMSO) δ; 6.71-8.74 (8H, m, ArH), 3.35 (1H, s, SH), 2.34 (6H, s, $ArCH_3$).

4. Conclusion

The short reaction time, easy experimental procedure, quantitative yield and expanded reaction range offered by microwave assisted synthesis is demand of today's industry and should be encouraged in institutes. It will be very helpful for searching novel compounds against the diseases like tuberculosis, which shows resistance and having a long duration of treatment. Structures, we believe that the number of applications of microwaves will only increase in the future.

5. References

1. Villemin D, Martin B. Solvent free organic synthesis. J Chem. Res., 1994; 35(D):146-147.
2. Budiati T, Stephanie DA, Elisabeth C. Rapid solvent-free microwave assisted synthesis of some n-benzylidene salicylic acid hydrazides. Indo. J Chem., 2012; 12(2):163-166.
3. Soriente A, Spinella A, DeRosa M, Giordano M, Seettri A. Michael addition of 1,3-dicarbonyl Compounds. *Tetrahedron Lett*. 1997; 38(2):289-90.
4. Chakraborty V, Bordoloi M. Microwave-assisted oxidation of alcohols by pyridinium chlorochromate. J Chem. Res., 1999; 29(14):118-19.
5. Suarez M, Loupy A, Salfran E, Moran L, Rolando E. Synthesis of decahydroacridines under microwaves using ammonium acetate supported on alumina. Heterocycles, 1999; 51(1):21-27.
6. Goncalo P, Roussel C, Melot JM, Vebrel J. Microwave chemistry: Magic or a bunch of hot air-MSU Chemistry-michigan. J Chem. Soc., Perkin Trans., 1999; 2(10):2111-115.
7. Danks TN. Microwave assisted synthesis of pyrroles. Tetrahedron Lett 1999; 40(20):3957-960.
8. Larhed M, Hallberg A. Microwave assisted high-speed chemistry: a new technique in drug discovery. Drug Discovery Today, 2001; 6(8):406-416.
9. Heindel ND, Reid JR. 4-Amino-3-Mercapto-4H- 1,2,4-Triazoles and propargyl aldehydes: A new route to 3-R-8-Aryl-1,2,4-Triazolo[3,4-b]-1,3,4-Thiadiazepines. J Heterocyclic Chem., 1980; 17(5):1087-1088.
10. Holla BS, Kalluraya B, Sridhar KR, Drake EL, Thomas MK, Bhandary K *et al*. Synthesis, structural characterization, crystallographic analysis and antibacterial properties of some nitrofuryl triazolo [3, 4-b]-1,3,4-thiadiazines. Eur. J. Med. Chem., 1994; 29(4):301-308.
11. Haber J. Present status and perspectives on antimy coties with systematic effects. Cas. lek, cesk, 2001; 140(19):596-604.
12. Brucato A, Coppola A, Gianguzza S, Provenzan PM. Triazolam: characteristics of its depressive action. Boll. Soc. Ital. Biol. Sper., 1978; 54(11):1051-1057.
13. Shaker RM. The chemistry of mercapto- and thione substituted 1, 2, 4-triazoles and their utility in heterocyclic synthesis. *ARKIVOC*. 2006; 9(14):59-112.
14. Mazzone G, Bonina FR, Arrigo R, Blandino G. Synthesis of 1-aroyl-4H(R)-thiosemicarbazides, the corresponding 5-Aryl 4H (R) -1,2,4-triazolin-3-thiones and some derivatives of pharmaceutical interest. Farmaco Sci., 1981; 36(3):181-196.
15. Ozturk G, Gumgum B, Akba O. Synthesis of esters under microwave irradiation using heteropoly acids as catalyst. Catal. Lett, 2002; 82(3-4):233-235.
16. Zamani K, Faghihi K, Bagheri S, Kalhor M. Microwave-assisted synthesis of thiosemicarbazide derivatives. Indian J. Chem., 2004; 43B:2716-2718.