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Synthesis of Thiadiazole and Azetidinone Derivatives Derived from Triazoles

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A series of novel thiadiazole and azetidinone derivatives of triazole nucleus were synthesized by the sequence of reactions with conventional and microwave techniques. The microwave technique is very useful with excellent yield at less reaction time compare to other conventional methods. The microwave synthesis of titled compound have been successfully performed in these conditions using environmentally friendly method with high atom economy. These compounds identified and characterized by physical and spectral (IR, NMR) techniques. All the synthesized compounds have been evaluated for their antibacterial and antifungal activity against bacteria *Staphylococus aureus* and *Bacillus subtilis* and fungi *Fusarium oxisporum* and *Aspergillus niger* when compared with standard drugs.

Keywords: Thiadiazoles, Azetidinones, Triazole nucleus, Microwave synthesis, Conventional method.

INTRODUCTION

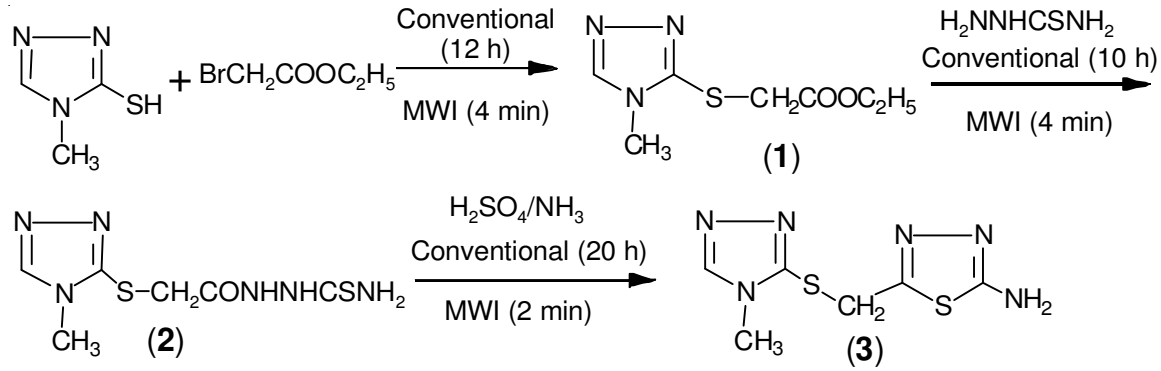
Several chemical classes of heterocycles such as thiazole, triazole, oxazole, 1,3,4-thiadiazole and 2-azetidinone are biological active and have been discovered to have remarkable chemical and geometrical similarties [1-5]. The present paper reports conventional as well as microwave assisted chemical preparation of 1,3,4-thiadiazole and 2-oxoazetidine incorporation with mercapto heterocycles [6-13]. The rapid heating capability of the microwave leads to considerable saving in dissolution time, chemical solvents and environmental pollution [14-16]. The condensation of all the steps have been carried out by both conventional and microwave method to give final products.

4-Methyl-4*H*-1,2,4-triazole-3-thiol on reaction with ethyl bromoacetate gave 4-methyl-3-(methylthio)-4*H*-1,2,4-triazole (**1**), which on reaction with thiosemicarbazide afforded 2-[(4-methyl-4*H*-1,2,4-triazalolyl)thioacetyl]thiosemicarbazide (**2**). The compound **2** on dehydrative annulation by H_2SO_4 followed by NH_3 afforded, 5-[(4-methyl-4*H*-1,2,4-triazolyl)thiomethyl]-1,3,4-thiadiazol-2-amine (**3**) (**Scheme-I**). The compound **3** on condensation with various aromatic aldehyde afforded N-(2-substituted benzylidene)-5-((4-methyl-4*H*-1,2,4-triazolyl)-thiomethyl)-1,3,4-thiadiazol-2-amine (**4**) which on further reaction with chloroacetyl chloride in presence of Et_3N afforded 4-(2-bromophenyl)-3-chloro-N-[5-((4-methyl-4*H*-1,2,4-triazolyl)thiomethyl)-1,3,4-thiadiazolyl]-2-oxo-azetidine (**5**) (**Scheme-II**).

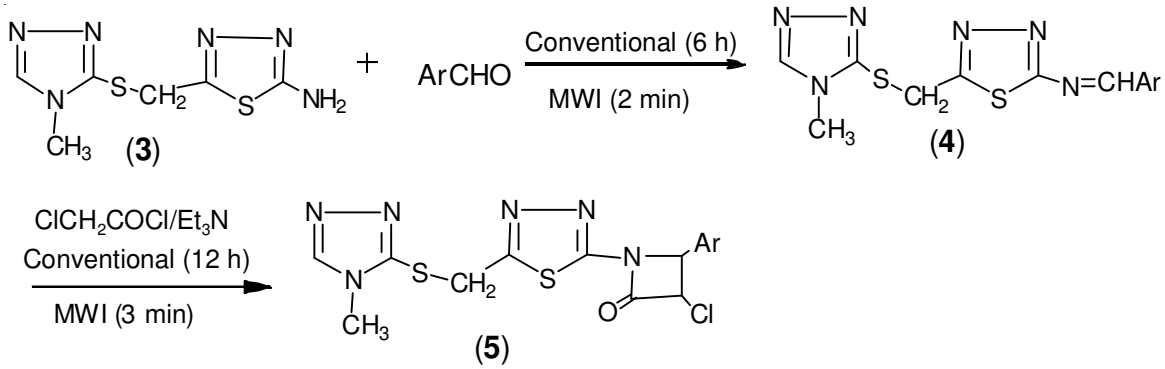
EXPERIMENTAL

All the melting points were taken in open capillary method. The IR spectra in cm^{-1} were recorded in KBr pellets on a Shimadzu 8201 PC spectrophotometer and ^1H NMR spectra on a Brucker DRX 300 spectrophotometer in $CDCl_3$ at 300 MHz using TMS as an internal standard (chemical shift in δ ppm). The purity of the compounds was checked by TLC using silca-gel-G-coated plates and spot were visualizing in iodine vapour. For the microwave irradiation domestic oven was used with temperature control.

Ethyl-(4-methyl-3-mercapto-1,2,4-triazalolyl)acetate (1): Ethyl bromoacetate (0.1 mol) was added to a solution of 4-methyl-4*H*-1,2,4-triazole-3-thiol (0.1 mol) in ethanol (60 mL) and anhydrous K_2CO_3 (5 g). It was refluxed for 12 h. The resulting product was isolated and recrystallized by methanol, yield 69 %, m.p. 108-09 °C; A mixture of both starting material in ethanol (10 mL) and anhydrous K_2CO_3 (1 g) was added and irradiated in domestic microwave oven at 80 watts for 4 min upon completion of reaction (checked by TLC), the reaction mixture was allowed to attain room temperature and treated with cold water. The compound **1** thus separated filtered under suction washed, dried and recrystallized by methanol yield 78 %, m.p. 108-09 °C; IR (KBr, ν_{max}, cm^{-1}): 1688, 1553, 1462, 1349 (1,2,4-triazole nucleus), 2598 (Ar-SH), 2829, 1477, 1210 (N-CH_3), 718 (C-S-C), 1721 (>C=O of ester); ^1H NMR 1.21 (t, 3H, $COOCH_2\underline{CH_3}$), 3.82 (s, 3H, N-CH_3), 4.18 (q, 2H, $COO\underline{CH_2}CH_3$) 4.42 (s, 2H, s-CH_2) and 7.12 (m, 1H, Ar-H).



Scheme-I: Synthesis of 2-(4-methyl-4*H*-1,2,4-triazolyl-thio)methyl)-1,3,4-thiadia- azol-2-amine



Ar = 2-BrC_6H_4, 2-$OCH_3C_6H_4$, 4-ClC_6H_4, 4-$NO_2C_6H_4$, 4-BrC_6H_4, 2-$OCH_3C_6H_4$

Scheme-II: Synthesis of 2-[(4-methyl-4*H*-1,2,4-triazolylthio)methyl]-1,3,4-thiadiaazol-2-azetidinones

2-[(4-Methyl-4*H*-1,2,4-triazaloly)thioacetyl]thiosemicabazide (2): A mixture of compound **1** (0.01 mol) thiosemicarbazide (0.01 mol) was dissolved in methanol (70 mL) was taken in round bottom flask and refluxed on a water-bath for 10 h. It was cooled, concentrated and filtered. The product was recrystallized from chloroform yield 63 % m.p. 133-35 °C. A mixture of compound **1** (0.01 mol) and thiosemicarbazide (0.01 mol) in methanol (10 mL). All these content taken in 100 mL conical flask and placed in a microwave oven and irradiated for 4 min. The completion of reaction was monitored by TLC. The solvent was removed and recrystallized from ethanol to get compound **2** yield 81 %, m.p. 133-35 °C; IR (KBr, ν_{max}, cm^{-1}) 1135 (C=S), 1668 (CONH), 3351 (NH_2); ^1H NMR 3.85 (s, 3H, N-CH_3) 4.46 (S, 2H, S-CH_2), 7.15 (m, 1H, Ar-H) and 8.35 (m, 4H, $NHNHCSNH_2$).

5-[(4-Methyl-4*H*-1,2,4-triazolyl)thiomethyl]-1,3,4-thiadiazol-2-amine (3): Compound **2** (0.02 mol) with H_2SO_4 (8 mL) was kept overnight at room temperature. It was then diluted with 100 mL ice cold water and the excess acid was neutralized with liquid ammonia. The product obtained was recrystallized from chloroform yield 59 %, m.p. 182 °C; compound **2** (0.02 mol) with conc. H_2SO_4 (8 mL) was kept 2 min in microwave irradiation at 80 °C, then 150 mL ice water added to this mixture and the excess acid was neutralized with liquid ammonia. The product obtained was recrystallized by chloroform to get compound **3**. Yield 83 %, m.p. 180 °C; IR (KBr, ν_{max}, cm^{-1}): 3558 (NH_2), 1605, 1439, 1300, 1171 and 705 (C=N and thiadiazole nucleus); ^1H NMR: 4.25 (s, 2H, NH_2), 3.85 (s, 3H, N-CH_3) 4.46 (s, 2H, S-CH_2) and 7.18 (m, 1H, Ar-H).

N-(2-Bromobenzylidene)-5-[(4-methyl-4*H*-1,2,4-triazolyl)thiomethyl]-1,3,4-thiadiazol-2-amine (4a): A mixture of compound **3** (20 mmol), 2-bromobenzaldehyde (20 mmol) and glacial acetic acid (3 mL) was refluxed on a water bath for 6 h. The solvent was removed under reduced pressure and the solid thus obtained was recrystallized from methanol, yield 60 %, m.p. 205 °C. A mixture of compound **3** (20 mmol) and 2-bromobenzaldehyde and 1-2 drops of glacial acetic acid in CH_2Cl_2 (10 mL) was taken in 50 mL conical flask in microwave oven and irradiated for 2 min. The resultant mixture was cooled to room temperature and added cold water. The solid thus obtained was recrystallized from $CHCl_3$ to give compound **4a** yield 85 %, m.p 205 °C; IR (KBr, λ_{max}, cm^{-1}) 688 (Ar-Br), 1605 (N=CH); ^1H NMR: 3.88 (s, 3H, N-CH_3), 4.48 (s, 2H, S-CH_2), 8.55 (s, 1H, N=CH), 7.55 (m, 5H, Ar-H).

A series of compounds **4b-f** were synthesized using same method from compound **3** and different aromatic aldehydes characterization and spectral data presented in (Table-1).

4-(2-Bromophenyl)-3-chloro-N-[5-((4-methyl-4*H*-1,2,4-triazolyl)thiomethyl)-1,3,4-thiadiazolyl]-2-oxo-azetidine (5a): A cold mixture of compound **4a** (0.001 mol) and triethylamine (2 mL) and chloroacetyl chloride (0.001 mol) in methylene chloride was stirred for 12 h. Triethylamine hydrochloride was filtered off. The filtrate was refluxed on steam bath for 3 h and the solvent removed off to get product **5a**. The solid product was filtered, dried and recrystallized from ethanol. Yield 66 %, m.p. 224-25 °C, to a stirred solution of compound **4a** (0.001 mol) in methylene chloride (10 mL) add chloroacetyl chloride (0.001 mol) and triethyl amine (1 mL)

TABLE-1
PHYSICAL AND SPECTRAL DATA OF CONVENTIONAL AND MICROWAVE ASSISTED SYNTHESIZED COMPOUNDS **4a-f** AND **5a-f**

Compd.	R	Reaction time		Yield (%)		m.p. (°C)	IR (cm^{-1})	^1H NMR (δ, ppm)
		Conv. (h)	MWI (min)	Conv.	MWI			
4a	2-BrC_6H_4	06	2	60	85	–	–	–
4b	4-BrC_6H_4	09	3	65	74	202	638 (C-Br), 1609 (N=CH)	3.86 (s, 3H, N-CH_3), 4.40 (s, 2H, S-CH_2), 7.56 (m, 1H, ArH)
4c	4-ClC_6H_4	10	2	68	76	238	758 (C-Cl), 1600 (N=CH)	3.83 (s, 3H, N-CH_3), 4.45 (s, 2H, S-CH_2), 7.52 (m, 1H, ArH)
4d	4-$NO_2C_6H_4$	10	3	59	79	211	1345 (Ar-NO_2), 1600 (N=CH)	3.8 (s, 3H, N-CH_3), 4.49 (s, 2H, S-CH_2), 7.52 (m, 1H, ArH)
4e	4-$OCH_3C_6H_4$	12	4	61	73	210	2866, 1162 (OCH_3), 1598 (N=CH)	3.93 (s, 3H, OCH_3), 4.46 (s, 2H, S-CH_2) 3.85 (s, 3H, N-CH_3), 7.53 (m, 1H, ArH)
4f	2-$OCH_3C_6H_4$	12	3	58	79	198	2865, 1170 (OCH_3), 1590 (N=CH)	3.89 (s, 3H, OCH_3), 4.46 (s, 2H, S-CH_2), 3.87 (s, 3H, N-CH_3), 7.53 (m, 1H, ArH)
5a	2-BrC_6H_4	12	3	66	83	–	–	–
5b	4-BrC_6H_4	09	3	64	73	212	638 (C-Br), 1762 (C=O), 765 (C-Cl)	3.86 (s, 3H, N-CH_3), 4.46 (s, 2H, S-CH_2), 4.12 (d, 1H, N-CH), 5.19 (d, 1H, CH Cl), 7.56 (m, 5H, ArH).
5c	4-ClC_6H_4	11	3	61	72	210	758 (C-Cl), 1761 (C=O), 765 (C-Cl)	3.85 (s, 3H, N-CH_3), 4.48 (s, 2H, S-CH_2), 4.13 (d, 1H, N-CH), 5.21 (d, 1H, CHCl), 7.56 (m, 5H, ArH)
5d	4-$NO_2C_6H_4$	12	4	59	82	230	1345 (Ar-NO_2), 1764 (C=O), 765 (C-Cl)	3.88 (s, 3H, N-CH_3), 4.42 (s, 2H, S-CH_2), 4.14 (d, 1H, N-CH), 5.20 (d, 1H, CHCl), 7.55 (m, 5H, ArH)
5e	4-$OCH_3C_6H_4$	13	6	61	79	235	2865, 1170 (OCH_3), 1765 (C=O), 764 (C-Cl)	3.85 (s, 3H, N-CH_3), 3.90 (s, 3H, OCH_3), 4.44 (s, 2H, S-CH_2), 4.13 (d, 1H, N-CH), 5.20 (d, 1H, CHCl), 7.53 (m, 5H, ArH)
5f	2-$OCH_3C_6H_4$	14	5	59	83	220	1763 (C=O), 766 (C-Cl)	3.86 (s, 3H, N-CH_3), 3.91 (s, 3H, OCH_3), 4.43 (s, 2H, S-CH_2), 4.13 (d, 1H, N-CH), 5.18 (d, 1H, CHCl), 7.58 (m, 5H, ArH)

add slowly. This mixture was stirred for 1 h and then placed inside a microwave oven for about 3 min. It was then diluted with ice-cold water and separated amine hydrochloride was filtered off. The separated solid recrystallized from ethanol to get compound **5a**. Yield 83 %, m.p. 224-25 °C; IR (KBr, ν_{max}, cm^{-1}): 1765 (C=0), 760 (C-Cl); ^1H NMR; 3.86 (s, 3H, N-CH_3), 4.46 (s, 2H, S-CH_2), 4.10 (d, H, N-CH), 5.2 (d, 1H, CHCl) 7.53 (m, 5H, ArH) other compounds **5b-f** were synthesized similar manner from using precursor **4b-f**, respectively. The physical data with spectral data for all the synthesized compounds reaction time by two different methods have been summarized in Table-1.

RESULTS AND DISCUSSION

In conventional method, the reaction is carried out in various solvent system with large quantity and it takes 6-20 h for completion, while under microwave irradiation 2-6 min for completion. In conventional method, the yield is lower as compared to microwave irradiation.

In conclusion, an environmental friendly cyclization and cycloaddition reaction is developed by conventional and microwave irradiation with increase in yield and decrease in reaction time period.

The compounds **4a-f** and **5a-f** were screened for their antibacterial activity against *Bacillus subtilis, Staphylococcus aureus* and antifungal activity against *Aspergillus niger, Fusarium oxisporum* by filter paper disc technique [15-18] at two concentrations (100 and 50 ppm) a standard antibacterial streptomycin and antifungal griseofulvin were also screened for comparison of the activity of synthesized compounds. The result of active compound of both the series **4a-f** and **5a-f** are presented in Figs. 1 and 2.

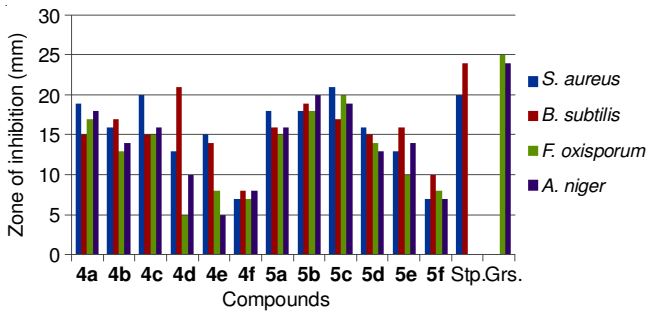


Fig. 1. Antimicrobial activity of synthesized compounds at conc.50 µg/mL

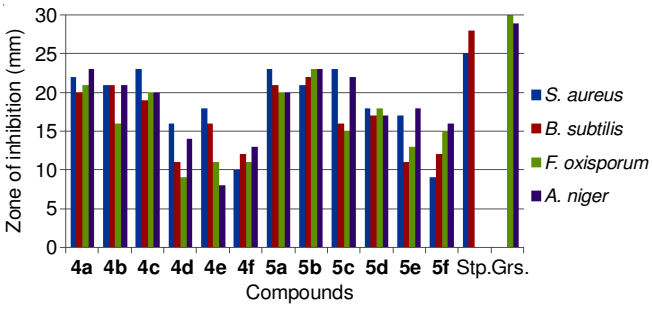


Fig. 2. Antimicrobial activity of synthesized compounds at conc.100 µg/mL

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