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Research Article

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Synthesis and antimicrobial elucidation of [1,2,4]-triazole-3-thione derivatives

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ABSTRACT

*4-Methyl benzoyl isothiocyanate **2** is prepared by a reaction of 4-methyl benzoyl chloride **I** and ammonium isothiocyanate. Compound **2** reacts with phenyl hydrazine in the presence of acetone to form 1-phenyl-5-p-tolyl-1,2-dihydro-[1,2,4]triazole-3-thione **3**. Compounds **3** on reaction with formaldehyde and different aromatic amines in 1,4-dioxane yielded 2-(substituted-amino)methyl-5-(p-tolyl)-1-phenyl-1H-1,2,4-triazole-3(2H)-thione **4a-j** respectively. The synthesized compounds **4a-j** were screened for their antibacterial and antifungal activities and were characterized by spectroscopic techniques like IR & NMR.*

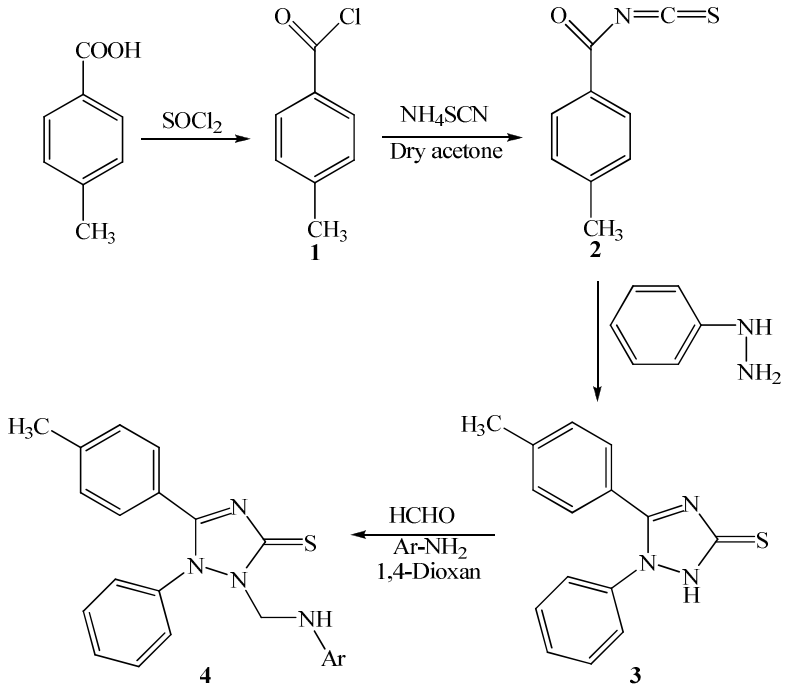
Key words: Acid chloride, Aryl hydrazine, Ammonium thiocynate, 1,2,4-Triazole-3-thione, Mannich reaction, Anyimicrobial activity.

INTRODUCTION

Triazoles have been reported to possess antimicrobial [1-5], anti-inflammatory [6-8], anticonvulsant [9], diuretic [10], antihypertensive [11], anti HIV [12], antitubercular [13], anti cancer [14-16], CNS depressant [17-19] activities, etc. In the synthesis of biologically active heterocyclic compounds, it was considered worthwhile to synthesize some more 1,2,4-triazoles and evaluate them antibacterial and antifungal activities. In the present article, we describe the synthesis of various triazole derivatives. Consideration, 4-methyl benzoyl chloride and ammonium thiocyanate in dry acetone gave 4-methyl benzoyl isothiocyanate **2**. The compound **2** on reaction with phenyl hydrazine produced 1-phenyl-5-p-tolyl-1,2-dihydro-[1,2,4]triazole-3-thione **3**. Compound **3** contains one active hydrogen atom and therefore, Mannich reaction is suitable for further synthesis [20]. Compound **3** is reacted with formaldehyde and aniline in the presence of 1,4-dioxan, yielded Mannich base 1-phenyl-2-phenylaminomethyl-5-p-tolyl-1,2-dihydro-[1,2,4]triazole-3-thione **4a**. All the synthesized compounds were characterized by infrared and ^{1}H nuclear magnetic resonance spectroscopy. The compounds were screened for their in vitro antibacterial activity towards gram positive and gram-negative bacterial strains data.

Biological Activity

Ten compounds of [1,2,4]-triazole-3-thione derivatives were screened for their antibacterial and antifungal activities. The antimicrobial activity was assayed by using the Broth Dilution Method [21-22] by measuring the Minimal Bactericidal Concentrations (MBC) and Minimal Fungicidal Concentrations (MFC) in µg/ml. The antibacterial activity was carried out against *E. coli*, *P. auroginosa*, *S. aureus* and *S. pyogenus*. The standard drug used was Gentamycin. The antifungal activity against *C. albicans*, *A. niger* and *A. clavatus*, the standard antifungal Nystatin was used for a comparison of results and are presented in table-II.



Reaction Scheme

EXPERIMENTAL SECTION

TLC was used to monitor the reaction and to check the purity of the compounds synthesized and the compounds are purified by column chromatography using silica gel (60-120 mesh). The melting points were taken in open capillaries and are uncorrected. IR spectra (KBr disk) were recorded on FT-IR-thermonicolate IR-200 spectrophotometer and ^{1}H NMR spectra on a Brucker DRX 300 in $CDCl_3$ at 200MHz using TMS as an internal standard.

1-Phenyl-5-p-tolyl-1,2-dihydro-[1,2,4]triazole-3-thione 3

A solution of 4-methyl-benzoyl chloride **1** (0.01mole) in dry acetone (50mL), ammonium thiocyanate (0.015mole) was added with constant stirring at room temperature followed by stirring the reaction mixture for an hour. The phenyl hydrazine (0.014mole) was added in the reaction mixture, then the reaction mixture was refluxed for 5hrs, the resulting slurry was filtered and washed with water and cold acetone to get compound **3**. m.p.: 165°C, yield: 64%, Anal. Obs.: C-67.35%, H-4.84%, N-15.70%. Calc. for $C_{15}H_{13}N_3S$: C-67.39%, H-4.90%, N-15.72%. IR: (KBr cm^{-1}) 3450 (-NH str. of secondary amine), 3040 (-CH str. of aromatic ring), 1610 (-C=N str. of triazole ring), 1320 (-CH ben. Ar-CH_3), 1240 (-C=S str. of triazole ring); ^{1}H NMR: δ 2.0 (1H, s), 2.35 (3H, s), 6.9 (1H, t), 7.3-7.4 (6H, m), 7.7 (2H, d).

Table I Characterization of Compounds 3a-j

Compd.	Ar	Yield (%)	M.P. °C	Molecular Formula	Found(%)(Caled)		
					C	H	N
4a	-C_6H_5	65	230	$C_{22}H_{20}N_4S$	70.91 (70.94)	5.39 (5.41)	15.03 (15.04)
4b	3-Cl-C_6H_4	60	265	$C_{22}H_{19}ClN_4S$	64.91 (64.93	4.66 (4.71)	13.75 (13.77)
4c	4-Cl-C_6H_4	65	272	$C_{22}H_{19}ClN_4S$	64.90 (64.93)	4.68 (4.71)	13.73 (13.77)
4d	3-CH_3-C_6H_4	62	238	$C_{23}H_{22}N_4S$	71.42 (71.47)	5.73 (5.74)	14.46 (14.50)
4e	4-CH_3-C_6H_4	60	203	$C_{23}H_{22}N_4S$	71.45 (71.47)	5.69 (5.74)	14.47 (14.50)
4f	4-F-C_6H_4	63	312	$C_{22}H_{19}FN_4S$	67.65 (67.67)	4.85 (4.90)	14.31 (14.35)
4g	3-Br-C_6H_4	62	292	$C_{22}H_{19}BrN_4S$	58.51 (58.54)	4.22 (4.24)	12.38 (12.41)
4h	2,4-$(Cl)_2$-C_6H_3	63	283	$C_{22}H_{18}Cl_2N_4S$	59.82 (59.87)	4.07 (4.11)	12.66 (12.69)
4i	2,6-$(CH_3)_2$-C_6H_3	60	243	$C_{24}H_{24}N_4S$	71.96 (71.97)	6.01 (6.04)	13.96 (13.99)
4j	3-Cl,4-F-C_6H_3	58	274	$C_{22}H_{18}ClFN_4S$	62.15 (62.18)	4.26 (4.27)	13.15 (13.19)

Table II Antibacterial and antifungal activity of compounds 4a-j

	Antibacterial activity is expressed in the form of Minimal Bactericidal Concentrations (MBC) in µg / mL				Antifungal activity is expressed in the form of Minimal Fungicidal Concentrations (MFC) in µg / mL		
Compd.	*E. coli* MTCC 443	*P. aeruginosa* MTCC 1688	*S. aureus* MTCC 96	*S. pyogenus* MTCC 442	*C. albicans* MTCC 227	*A. niger* MTCC 282	*A. clavatus* MTCC 1323
4a	250	100	500	250	1000	1000	>1000
4b	100	250	**50**	100	**200**	500	500
4c	100	**50**	250	100	**200**	1000	500
4d	100	100	100	100	500	500	500
4e	250	200	250	500	>1000	500	1000
4f	**50**	250	200	500	>1000	500	500
4g	100	**50**	250	250	500	**200**	>1000
4h	200	100	250	500	500	500	>1000
4i	200	500	500	1000	500	>1000	1000
4j	100	150	100	200	>1000	500	500

1-Phenyl-2-phenylaminomethyl-5-p-tolyl-1,2-dihydro-[1,2,4]triazole-3-thione 4a

A mixture of compound **3** (0.01mole), formaldehyde (0.01mole) and aniline (0.01mole) in 1,4-dioxan (50mL) was stirred for 24 hrs. After a completion of the reaction, neutralized it with liquor ammonia solution, and extract with ethyl acetate to get the compound **4a**, crystallized it with 1,4-dioxan. m.p.: 230°C, yield: 65%, Anal. Obs.: C-70.91%, H-5.39%, N-15.03%. Calc. for $C_{22}H_{20}N_4S$: C-70.94%, H-5.41%, N-15.04%. IR: cm^{-1} 3310 (-NH str. of secondary amine), 2920 (-CH str. of $–CH_2$ group), 1330 (-CH ben. Ar-CH_3), 1600 & 1510 (C=C- str. of aromatic ring), 1300 (C-N str. of secondary amine), 1090 (-C=S str. of thioketone), 760 (C-H ben. m-substituted benzene ring); ^{1}H NMR: δ 2.3 (3H, s) 4.4 (2H, s), 6.1 (1H, s), 6.7-6.9 (4H, m), 7.2-7.4 (8H, m), 7.7 (2H, d).

Other compounds **4b-j** were synthesized similarly from compound **3** and their characterization data are presented in table-I.

RESULTS AND DISCUSSION

In antibacterial study, the Minimal Bactericidal Concentration (MBC) indicates that the value of MBC 12.5, 25 and 50 show excellent, good and moderately active respectively. Antibacterial screening of above-mentioned compounds indicated that a compound **4f** is moderately active against *E.coli*. Compound **4c** & **4g** are moderately active against *P. auruginosa*. A compound 4b is moderately active *S. aureus.*

The antifungal results that Minimal Fungicidal Concentration (MFC) 100, 150-200 and 250 indicate excellent, good and moderate active respectively. Antifungal activity results indicate that compounds **4b** & **4c** are good active against *C. albicans*. Compound **4g** is good active against *A. niger*.

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