Synthesis and biological activity of some novel triazol derivative

K. S. Lamani
C.S.B. Arts, S.M.R.P. Science and G.L.R. Commerce College Ramdurg-591123. India

Abstract

Heterocyclic compounds are considered as the most promising molecules in drug designing. Many drugs are heterocycles which are of synthetic origin and this has resulted in the diversity of synthetic procedures for the heterocyclic rings. The search for useful precursor and the development of simple and concise procedures has become an important goal for organic synthetic chemists.

Keywords: 1,2,4-Triazole, 1,3,4-thiadiazole, Oxadiazole

Introduction: Heterocyclic compounds are considered as the most promising molecules in drug designing. Many drugs are heterocycles which are of synthetic origin and this has resulted in the diversity of synthetic procedures for the heterocyclic rings. The search for useful precursor and the development of simple and concise procedures has become an important goal for organic synthetic chemists.

The therapeutic effects of 1,2,4-triazole and 1,2,4-triazol-3-one containing compounds have been well studied for a number of pathological conditions including inflammation, cancer, pain, tuberculosis or hypertension[1-9]. In addition, it was reported that 1,3,4-thiadiazoles exhibit various biological activities possibly due to the presence of the C=N-C-S moiety[10]. Moreover, synthesis of triazoles fused to another heterocyclic ring has attracted wide spread attention due to their diverse applications as antibacterial-, antidepressant-, antiviral-, antitumorial- and anti-inflammatory agents, pesticides, herbicides dyes, lubricant and analytical reagents[11]. Among these, the commonly known systems are generally triazoles fused to pyridines, pyridazines, pyrimidines, pyrazines and triazines. Although there are not many triazoles fused to thiadiazines or thiadiazoles, a number of them are incorporated into a wide variety of therapeutically important compounds possessing a broad spectrum of biological activities[12-15]. In this connection, some biheterocyclic compounds containing two 1,2,4-triazol-3-one rings or both 1,2,4-triazol-3-one and 1,3,4-thiadiazole rings have been synthesized in our laboratory as antimicrobial compounds[16].

Sydnones are a novel class of meso-ionic compounds with unique chemical and physical properties. A vast array of sydnone derivatives have been found to show varied biological properties,[17] antioxidant activity[18] and liquid crystalline properties[19]. Furthermore, sydnones have been used as precursors in 1,3-dipolar additions,[20] material chemistry[21] and in battery applications[22]. In continuation of our effort to develop benign synthetic methods for sydnone and oxadiazolines[23] we report here a new series of 4-(5-mercapto-1,3,4-thiadiazol-2-yl)-2-phenyl-5-[(*E*)-2-phenylvinyl]-2,4-dihydro-3*H*-1,2,4-triazol-3-one containing 1,3,4-thiadiazole rings. It was interesting to study the influencing biological behaviors with various substituted oxadiazoles. Therefore, we felt it of interest to study the chemical reactivity of these heterocyclic 1,3,4-thiadiazole moieties.

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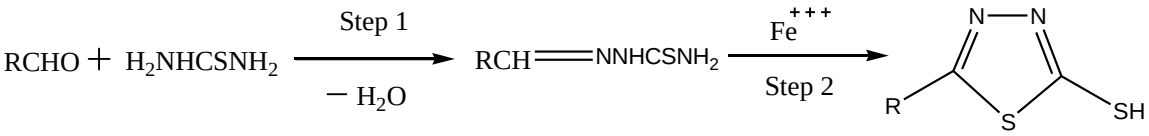
biological properties,[24] antioxidant activity[25] and liquid crystalline properties[26]. Furthermore, sydnones have been used as precursors in 1,3-dipolar additions,[27] material chemistry[28] and in battery applications[29]. In continuation of our effort to develop benign synthetic methods for sydnone and oxadiazolines[30]. We report here a new series of 4-(5-mercapto-1,3,4-thiadiazol-2-yl)-2-phenyl-5-[(*E*)-2-phenylvinyl]-2,4-dihydro-3*H*-1,2,4-triazol-3-one containing 1,3,4-thiadiazole rings. It was interesting to study the influencing biological behaviors with various substituted oxadiazoles. Therefore, we felt it of interest to study the chemical reactivity of these heterocyclic 1,3,4-thiadiazole moieties.

PRESENT WORK

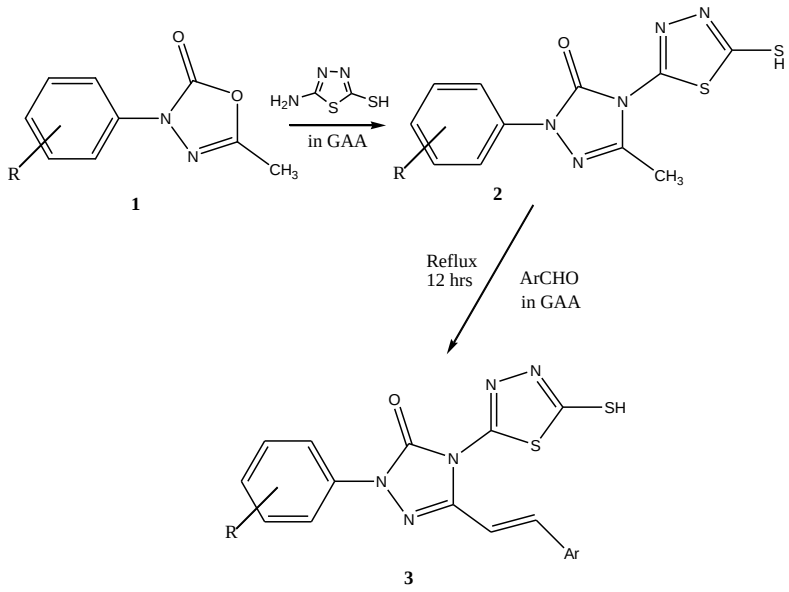
The importance for synthesizing compound came from the observation that 1,3,4-oxadiazolin-2-ones would show a strong affinity towards nucleophilic reagents, due to the presence of a lactone group. One of the most frequently encountered heterocycles in medicinal chemistry is 4(*3H*)-quinazolinone with wide applications including anticonvulsant, sedative, tranquilizer, analgesic, antimicrobial, anesthetic, anticancer, properties. Literature survey revealed that the presence of substituted aromatic ring at position 2 is necessary requirement for the central nervous system (CNS) depression and anticonvulsant activities. The 1,3,4-oxadiazolin-2-ones contains lactone group therefore this on refluxed with the 1,3,4-thiadiazole. The 1,3,4-thiadiazole itself have anticonvulsant activities.

SYNTHETIC OUTLINE

The 5-methyl-3-phenyl-1,3,4-oxadiazol-2(3H)-one **1**, 5-amino-1,3,4-thiadiazole-2-thiol in glacial acetic acid (GAA) was added and refluxed for 4hrs. Obtained reaction mixture is left overnight. The solid **2** which separated out was filtered, washed thoroughly with water. To the compound **2** and opportune benzaldehyde were reacted with glacial acetic acid and refluxed for 12 hrs. The solid **3** which separated out was filtered with suction and recrystallised from dimethylformamide to give pure compound.



Scheme 1: Scheme for the synthesis of 2-amino-5-aryl-1,3,4-thiadiazoles.



1 2 3

Scheme 2

Experimental Procedure:

Synthesis of 2-amino 5-aryl 1,3,4-thiadiazole [31-34]

2-Amino-5-aryl 1,3,4-thiadiazole was synthesized following two steps.

Step 1: synthesis of thiosemicarbazones.

Aromatic aldehyde I (0.2 M) in warm alcohol (300 mL) and thiosemicarbazide II (0.2 M) in warm water (300 mL) were mixed slowly with continuous stirring. The product separated immediately on cooling which was filtered with suction, dried and recrystallised in 75% ethanol to yield III. Physicochemical properties are presented in Table 1.

Table 1

Physico-chemical data of thiosemicarbazone R-CH=NNHCSNH$_2$

S. No.	R	Yield (%)	Solvent recrystallize	M.P. (^{0}C)	Molecular formula	Molecular weight
1	C_6H_5	92%	Aq. ethanol (50%)	159	$C_8H_9N_3S$	179.25
2	p-$OCH_3C_6H_4$	85%	Ethanol	170	$C_9H_4N_3OS$	209.27
3	p-$CH_3C_6H_4$	95%	Aq. ethanol (50%)	160	$C_9H_4N_3S$	193.27
4	p-ClC_6H_4	90%	Ethanol	207	$C_8H_8ClN_3S$	213.69
5	m-ClC_6H_4	90%	Aq. ethanol (50%)	206	$C_8H_8ClN_3S$	213.69
6	-CH=CHC_6H_4	80%	Ethanol	185	$C_{10}H_{11}N_3S$	205.28

IR	NMR
3350 (NH2), 3320 (NH)	2.0 (NH2), 2.0 (NH)
3362 (NH2), 3315 (NH)	2.0 (NH2), 2.0 (NH), 3.73 (CH3)
3294 (NH2), 3140 (NH)	2.0 (NH2), 2.0 (NH), 2.35 (CH3)
3315 (NH2), 3326 (NH)	2.0 (NH2), 2.0 (NH)
3340 (NH2), 3326 (NH)	2.0 (NH2), 2.0 (NH)
3350 (NH2), 3321 (NH)	2.0 (NH2), 5.6 (CH1), 6.6 (CH2)

Step-2: synthesis of 2-amino-5-aryl 1,3,4-thiadiazoles.

Thiosemicarbazone III (0.05 M) was suspended in 300 ml warm water, $FeCl_3$ (0.15 M) in 300 ml water was added quantitatively, slowly with constant stirring. The contents were heated at 80-90 ^{0}C for 45 min. Solution was filtered hot and then citric acid (0.11 M) and sodium citrate (0.05 M) were added. The resulting mixture was divided into 4 parts and each part was neutralized separately with ammonia (10%). The required amine separated out, filtered with suction, dried and recrystallised with appropriate solvent. Physicochemical properties are reported in Table 2.

Table 2

Physico-chemical data of 2-amino-5-aryl 1,3,4-thiadiazole

S. No.	R	Yield (%)	Solvent recrystallize	M.P. (^{0}C)	Molecular formula	Molecular weight
1	C_6H_5	65%	Aq. ethanol (25%)	224	$C_8H_7N_3S$	177.23
2	p-$OCH_3C_6H_4$	60%	Aq. ethanol (50%)	210	$C_9H_9N_3OS$	207.26
3	p-$CH_3C_6H_4$	62%	Aq. ethanol (25%)	215	$C_9H_9N_3S$	191.26
4	p-ClC_6H_4	70%	Aq. ethanol (50%)	227	$C_8H_6ClN_3S$	211.67
5	m-ClC_6H_4	70%	Aq. ethanol (50%)	226	$C_8H_6ClN_3S$	211.67
6	-CH=CHC_6H_4	60%	Aq. ethanol	220	$C_8H_8N_3S$	202.27

IR	NMR
177.23 3496 (NH2)	4.0 (NH2)
207.26 3500 (NH2)	4.0 (NH2), 3.73 (OCH3)
191.26 3450 (NH2)	4.0 (NH2), 2.35 (CH3)
211.67 3452 (NH2)	4.0 (NH2)
211.67 3466 (NH2)	4.0 (NH2)
202.27 3490 (NH2)	4.0 (NH2), 6.9 (CH1), 6.9(CH2)

General procedure for compounds 2a-2h (Scheme-2)

To the 5-methyl-3-phenyl-1,3,4-oxadiazol-2(3H)-one (0.01 M) ***(1)***, 5-amino-1,3,4-thiadiazole-2-thiol (0.01 M) in glacial acetic acid(GAA) was added and refluxed for 4 h. Obtained reaction mixture was poured into crushed ice and left overnight. The solid which separated out was filtered, washed thoroughly with cold distilled water, dried and recrystallised from hot ethanol. The other derivatives are also synthesized by same method. The yield, melting point and other physical properties of synthesized compound are recorded in Table 3.

Table 3

S. No.	2a	2b	2c	2d	2e	2f	2g	2h
R	H	COOH	$COOC_2H_5$	$COOCH_3$	$COCH_3$	p-Cl	m-Cl	p-OCH_3
Molecular weight.	291.35	335.36	363.41	349.38	333.38	325.79	325.79	321.37

All the products gave satisfactory NMR, IR and MS data Isolated yield.

General procedure for compounds 3a-3h (Scheme-2)

The title compounds were synthesized by following the procedure reported earlier [35-40].

The title compounds were synthesized by following the procedure solution of **2** (0.01 M) and opportune benzaldehyde (0.01 M) were reacted with glacial acetic acid (10 ml) and refluxed for 12 h. The solid which separated out was filtered with suction and recrystallised from dimethylformamide to give pure compound. The physical data of the the compound **3** are given in Table 4.

Table 4. Elemental Analysis of the compounds

S. No.	**R**	**Meting Point ^{0}C**	**Yield (%)**	**Molecular formula**	**Elemental analysis Found (Calc) %**			
					C	**H**	**N**	**S**
3a	H	197-98	89	$C_{18}H_{13}N_5OS_2$	56.98 (56.97)	3.46 (3.45)	18.47 (18.46)	16.92 (16.90)
3b	COOH	200-01	87	$C_{19}H_{13}N_5O_3S_2$	53.90 (53.89)	3.10 (3.09)	16.55 (16.54)	15.16 (15.14)
3c	$COOC_2H_5$	211-12	72	$C_{21}H_{17}N_5O_3S_2$	55.87 (55.86)	3.80 (3.79)	15.52 (15.51)	14.21 (14.20)

Table 4. Elemental Analysis of the compounds.

Continued page…

S. No.	R	Meting Point ^{0}C	Yield (%)	Molecular formula	Elemental analysis Found (Calc) %			
					C	H	N	S
3d	$COOCH_3$	232-33	68	$C_{20}H_{15}N_5O_3S_2$	54.93 (54.91)	3.47 (3.46)	16.02 (16.01)	14.67 (14.66)
3e	$COCH_3$	256-57	76	$C_{20}H_{15}N_5O_2S_2$	56.98 (56.99)	3.60 (3.59)	16.63 (16.62)	15.22 (15.21)
3f	p-Cl	223-24	79	$C_{18}H_{12}ClN_5OS_2$	52.24 (52.23)	2.93 (2.92)	16.93 (16.92)	15.48 (15.49)
3g	m-Cl	194-95	82	$C_{18}H_{12}ClN_5OS_2$	52.24 (52.23)	2.93 (2.92)	16.93 (16.92)	15.48 (15.49)
3h	p-OCH_3	211-12	80	$C_{19}H_{15}N_5O_2S_2$	55.72 (55.73)	3.70 (3.69)	17.11 (17.10)	15.65 (15.66)

SPECTRAL CHARACTERISATION

The IR Spectra of compound **3** is showed the C=O peak at 1701 cm^{-1}, C=O stretching at 1580 and C=C stretching (Alkene) vibration at 1630 cm^{-1}.

Biological Activity

All the newly synthesized compounds were screened for their antimicrobial activity by cup plate method at 100 µg/ml concentration in DMF against the Bacterial strains viz., *E. Coli* & *B. Subtilis* and also against Fungal strains viz., *A Niger* and *A. Sereus*. Norfloxacin for bacteria and Griseofulvin as the reference drugs respectively. Some these compounds were less active against the bacterial strains, but some of them showed selective fungal inhibitory activity. The antimicrobial data of synthesized compounds are given in Table 3.

Conclusion

The synthesized compounds were characterized by various spectral studies. Some of compounds (3e, 3f and 3h) were found to be more susceptible towards the fungal strains as well as bacterial strains. (Figure 1 and 2)

Table 3. Anti-microbial activities of compounds.

S. No.	Antibacterial		Antifungal	
	E.coli	*B. subtilis*	*A. niger*	*C. Albicans*
3a	16	18	16	17
3b	15	17	19	20
3c	15	14	14	18
3d	12	11	22	21
3e	20	23	20	21
3f	21	22	22	23
3g	15	14	19	18
3h	23	24	20	21
Norf	24	24	--	--
Gris	--	--	26	26
DMF	04	04	04	04

Figure 1. Antibacterial activity of synthesized compounds.

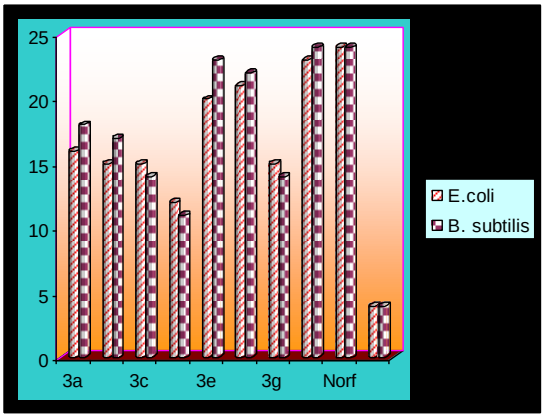
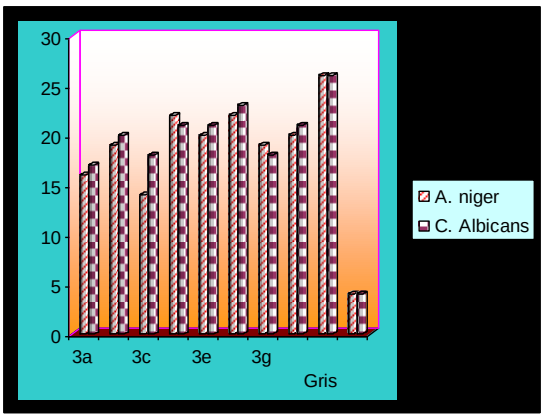


Figure 2. Antifungal activity of synthesized compounds.



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