An Analysis upon Various Varsatile Heterocyclic Thiazepines Substituted Quinoline Derivatives

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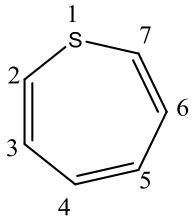
INTRODUCTION

The Chemistry of 1,3,4-thiadiazepine derivatives have been reviewed in last few years. The thiadiazepine ring system have one sulphur atom and two nitrogen atom at 1,3,4-position in seven membered heterocyclic ring. The interesting biological activities of these novel heterocyclic have stimulated considerable research work in recent years leading to the synthetic utility of the derivatives of this ring system.



Different methods for the synthesis of these derivatives have been documented in literature1-3. Sandhu et al.4 have prepared thiadiazepine derivatives by condensation of thiodiacetophenones with hydrazine hydrate in ethylene glycol. A symmetric pyrrolo thiadiazepine derivatives have also been prepared by Bolos et al.5 Synthesis and characterization of zinc(II) and cadmium(II) halide complexes with 3,6-disubstituted-2,7-dihydro-1,4,5-thiadiazepine derivatives have been reported by Sandhu et al.6 Corral and coworkers7 have investigated a new method for the synthesis of chlorosubstituted dibenzo thiadiazepines and their 5,6-dihydro derivatives. The synthesis of triazolo thiadiazepines have been carried out by using phase transfer catalysts8. Brukstus et al.9 have synthesized triazole [1,3,4] thiadiazepine by the reaction of 4,6-dichloro-2-methyl thio pyrimidine-5-carboxyldehyde with 3-substituted -4-amino -1,2,4-triazole-5-thiones.

Synthesis of quinolinethiadiazepine derivatives by condensation of 2-chloro-6-substituted quinoline-3-carboxaldehyde with thiocarbohydrazide in pyridine have been studied by Gururaja et. al.10 Aly and his co-workers11 have synthesized some new thiadiazepines by the reaction of N-imidoylthioureas with dimethyl acetylenedicarboxylate.

From the literature survey, it was revealed that 1,3,4-thiadiazepine are better therapeutic agents due to the presence of the -N=C-S group12. Various workers have been reported their various biological activities such as antitumor13, antimicrobial14, antidepressant15, anti psychotic16, antibacterial17, anticonvulsant18, CCK antagonists19, gastrin receptor antagonists20 etc. These derivatives are also known to be found as potent drug in pharmaceutical industries. These derivatives are not only known for their potent antimicrobial activities21 but they also act as excellent charge generating agent22

Wei et al.23 have synthesized 1,2,5-benzothiadiazepine 1,1-dioxides and tested their antidepressant, anticonvulsant, and hypoglycemic activity.

New dibenzothiadiazepine derivatives with antidepressant activities have been described by Giannotti et al.24 Rao and Sastry25 have reported biological activity of some other 1,3,4-thiadiazepines. The antibacterial26 and anti-HIV27 activity of some other 1,3,4-thiadiazepines have also been reported. Non-nucleoside reverse transripatase activity of some thiadiazepines have been described by Artico et al.28 Vice Susan29 have prepared di-indolo thiadiazepine compounds as inflammation inhibitors, neoplasm inhibitors and pharmaceuticals for Psoriasis treatment., Swati has reported anticancer activity of thiadiazepine derivatives30 whereas Lebegue et al.31 have evaluated their antiproliferative activity toward the murine L1210 leukemia cell line. Ammar et al.32 have

discovered thiadiazepine derivatives as possible potential drug for fungal infection. Kalluraya B et al.33 have synthesized thiadiazepines and screen for their antibacterial activities. Anthelmintic activity of 1,3,4-thiadiazepine have documented by Gururaja et al.10 Ashutos singh and nizamudin34 have prepared thiadiazepines and reported their molluscicidal activity. Antifungal activity of thiadiazepines have been studied by Anshu Dandia et al.35 Kamble and Sudha36 have discovered some 1,3,4-thiadiazepines as cardiovascular agent.

Thus, significant biological properties associated with thiadiazepine derivatives have aroused considerable interest to design the compounds in which therapeutically active triazole nucleus is incorporated and to study their biological activity.

EXPERIMENTAL

Synthesis of 3-(4-methoxyphenyl)8,9-substituted pyrido [3,2-f] [1,2,4] triazolo [3,4-*b*][1,3,4] thiadiazepine.

[A] Synthesis of 4-methoxy benzoate: A solution of 4-methoxy benzoic acid (0.01M) in methanol (20 ml) and 0.5 ml conc. sulfuric acid was refluxed for 12 hrs. The content was cooled and poured on crushed ice. The product was filtered and treated with saturated sodium bicarbonate solution.

[B] Synthesis of 4-methoxy benzoic acid hydrazide:

A solution of 4-methoxy benzoate (0.01 M) in absolute ethanol was refluxed with 95% hydrazine hydrate (0.01M) for 8 hrs. in a water bath. The product was isolated and crystallized from ethanol.

[C] Synthesis of potassium 4-methoxy benzoic acid hydrazide dithiocarbamate:

An alcoholic solution of potassium hydroxide (0.015 M), absolute ethanol and the compound [B] was treated with carbon disulfide. This mixture was stirred for 12 hrs. It was then isolated with dry ether and the precipitated solid was filtered, washed with ether and dried.

[D] Synthesis of 4-amino-5-(4-methoxy phenyl)-4H-1,2,4-triazole-3-thiol:

Above synthesized Potassium salt (0.01 M) was mixed with hydrazine hydrate and heated in oil bath for about 5 hrs till the evolution of H2S gas ceases. The reaction mixture was then poured onto crushed ice and treated with glacial acetic acid. The product was filtered and purified by KOH treatment and crystallized from ethanol.

[E] Synthesis of 3-(4-methoxyphenyl) 8,9-substituted-pyrido [3,2-*f*] [1,2,4] triazolo [3,4-*b*] [1,3,4] thiadiazepine (NTD-1):

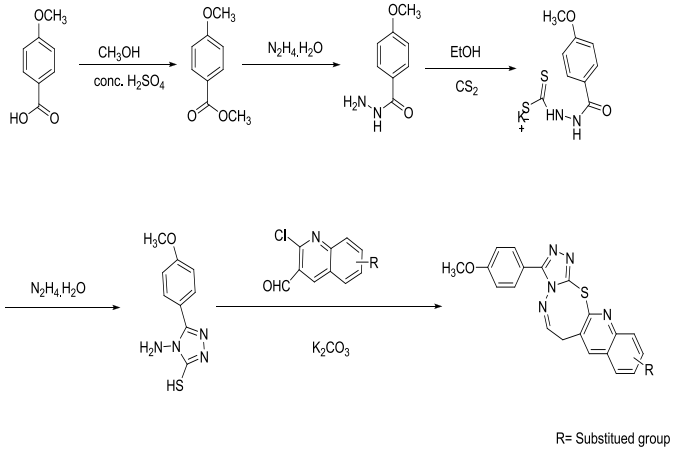
To a mixture of 4-amino-5-(4-methoxy phenyl)-4H-1,2,4-triazole-3-thiol(0.01M) and 2-chloro-6-fluoroquinoline-3-carbaldehyde (0.01 M) in DMF (20ml), anhydrous K2CO3 (2.0 g) was added. The reaction mixture was stirred at 70-80 ^{0}C for 2 hrs. It was then cooled and poured onto crushed ice. The product was isolated and recrystallized from methanol. Similarly, other substituted thiadiazepines were prepared. The physical data for the synthesized compounds are reported in Table 1.

Table 1: Physical constants of thiadiazepines

Sr. No.	Code	R	M.F.	M. Wt. (g/mol)	R_f* Value	M.P. °C	Yield %
1	NTD-1	4-F-	$C_{19}H_{12}FN_5OS$	377.4	0.49	198	50
2	NTD-2	C_4H4-	$C_{23}H_{15}N_5OS$	409.5	0.61	214	55
3	NTD-3	3-NO_2-	$C_{19}H_{12}N_6O_3S$	404.4	0.52	224	45
4	NTD-4	4-NO_2-	$C_{19}H_{12}N_6O_3S$	404.4	0.53	174	40
5	NTD-5	4-CH_3-	$C_{20}H_{15}N_5OS$	373.4	0.50	220	60
6	NTD-6	2,5-diCl-	$C_{19}H_{11}Cl_2N_5OS$	428.3	0.58	241	48
7	NTD-7	H-	$C_{19}H_{13}N_5OS$	359.4	0.59	238	50
8	NTD-8	4-OCH_3-	$C_{20}H_{15}N_5OS$	389.4	0.61	215	60
9	NTD-9	2,4-diCl-	$C_{19}H_{11}Cl_2N_5OS$	428.3	0.52	189	65
10	NTD-10	4-Br-	$C_{19}H_{12}BrN_5OS$	438.3	0.51	211	45

* Acetone:Benzene: 2:8

Reaction scheme



The characterization was done by IR, 1H NMR and mass spectra.

Infrared spectra:

The IR spectra were recorded by SHIMADZU-FTIR-8400 Spectrophotometer in the frequency range of 4000-400 cm-1 by KBr powder method. Figure 1 shows IR spectra of NTD-1. The IR spectral data for NTD-1 is given in Table 2. The spectral data for all other compounds are reported in Table 3.

1H NMR Spectra:

The NMR spectra were recorded by BRUKER Spectrometer (400 MHz) using internal reference TMS and solvent CDCl3/DMSO The spectral data for NTD-4 is given in Table 4.

Figure : IR spectra of 3-(4-methoxyphenyl) 8,9-substituted-pyrido [3,2-f] [1,2,4] triazolo [3,4-b] [1,3,4] thiadiazepine (NTD-1).

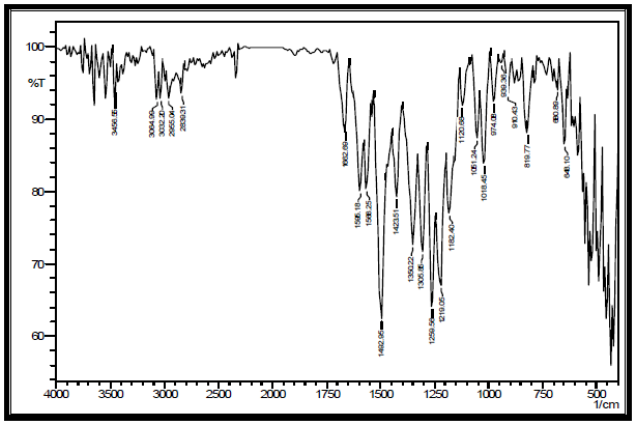


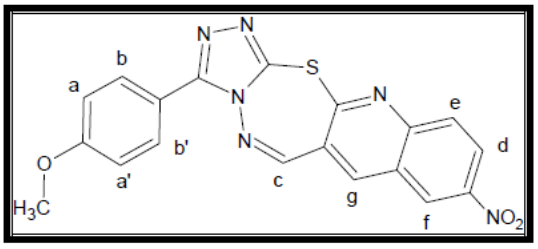
Table 2: IR spectral data of 3-(4-methoxyphenyl) 8,9-substituted-pyrido [3,2-f] [1,2,4] triazolo [3,4-b] [1,3,4] thiadiazepine (NTD-1).

Type	Vibration mode	Frequency in cm^{-1}	
		Observed	Reported[37,38]
Alkane (methyl)	C-H str. (asym.)	2955.04	2975-2920
	C-H str. (sym.)	2839.31	2880-2860
	C-H def. (asym.)	1423.51	1470-1435
	C-H def.(sym.)	1350.22	1395-1370
Aromatic	C-H str.	3064.99	3100-3000
	C=C str.	1566.25	1585-1480
	C-H i.p. def.	1120.68	1125-1090
	C-H o.o.p. def.	819.77	860-810
Triazole+ thiadiazepine ring	C=N str.	1662.69	1690-1640
	C-N str.	1259.56	1350-1200
	N-N str.	1018.45	1050-1010
	C-S-C str.	1182.40	1250-1000
	C-S-C def.	648.10	700-600
ether	C-O-C str. (asym.)	1219.05	1275-1200
	C-O-C str. (sym.)	1051.24	1075-1020
	C-F	1305.85	1400-1000

Table 3: IR spectral data of synthesized thiadiazepines.

Compounds	*IR ν, (cm^{-1})*				
	C=C	N-N	C-S-C	C-O-C	R
NTD-2	1502.32	1023.73	1175.24	1222.54	1144.34
NTD-3	1485.52	1038.12	1170.65	1228.34	-
NTD-4	1498.64	1022.32	1162.35	1227.64	1334.51
NTD-5	1522.31	1042.47	1182.40	1219.05	1321.52
NTD-6	1524.85	1014.84	1195.23	12.08.21	2941.12
NTD-7	1512.32	1032.14	1220.74	1219.05	668.98
NTD-8	1508.12	1027.65	1182.40	1244.42	1244.42
NTD-9	1498.64	1038.12	1225.14	1248.65	712.04
NTD-10	1508.12	1022.32	1162.35	1219.05	572.95

Table 4:1H NMR spectral data of 3-(4-methoxyphenyl) 8,9-substitutedpyrido [3,2-*f*] [1,2,4] triazolo [3,4-*b*] [1,3,4]thiadiazepine (NTD-4)



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