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Der Chemica Sinica, 2015, 6(1):34-37

Pelagia Research Library
ISSN: 0976-8505
CODEN (USA) CSHIA5

Synthesis and biological studies of triazole-azetidinone containing compounds

Tejas C. Shah and Vipul P. Prajapati

Sheth M. N. Science College, Patan

ABSTRACT

3-(4H-1,2,4-triazol-3-ylthio)-N-arylidene propane hydrazide (2a-f) was prepared good yields by reaction between 3-(4H-1,2,4-triazol-3-ylthio)propane hydrazide (1) with aromatic aldehydes. Cyclo condensation of compounds (4a-f) with chloroacetyl chloride yields 3-(4H-1,2,4-triazol-3-ylthio)-N-(3-chloro-2-oxo-4-substituted phenylazetidin-1-yl)propanamide (3a-f). The structures of these compounds were established on the basis of analytical and spectral data. All the newly synthesized compounds were evaluated for their antibacterial and antifungal activities.

Key words: 3-(4H-1, 2, 4-triazol-3-ylthio) propane hydrazide, azetidinone, antibacterial and antifungal activities.

INTRODUCTION

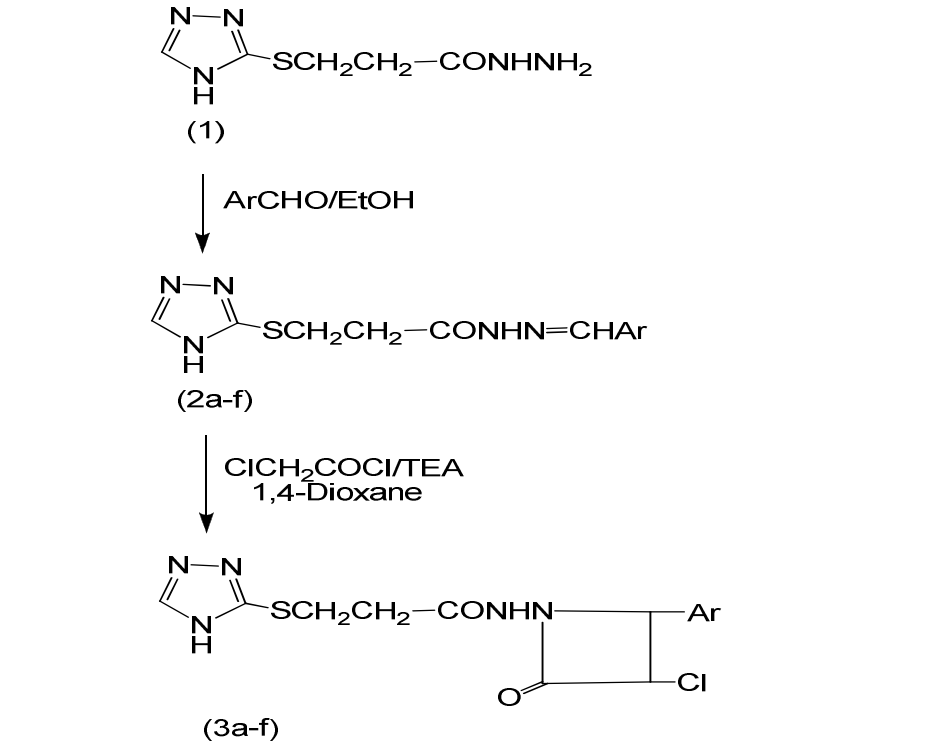
Hydrazide and their heterocyclised products display diverse biological activities including antibacterial, antifungicidal, analgesic, anti-inflammatory properties [1-3]. These heterocyclic systems find wide use in medicine, agriculture and industry. One of the acetohydrazide and their condensed products play a vital role in medicinal chemistry [4-6]. The heterocyclic compound say, triazole derivatives possessing comprehensive bioactivities as antibacterial, antifungal, antimycobacterial, anti-inflammatory, analgesic, anticancer, anti hypertensive, anticonvulsant, antiviral, antidepressant, antiasthmatic, diuretic and hypoglycemic activities[7-15]. Another heterocyclic compound like azetidinones containing β-lactam rings[16,17] are known to exhibit various biological activities like antibacterial, antifungal[18] and antibiotic[19] activities. Hence, it was thought of interest to merge both of azetidinone and hydrazide moieties which may enhance the drug activity of compounds to some extent, or they might possess some of the above mentioned biological activities. From this point of view, the objective of the present work is to prepare new derivatives of triazole containing azetidinone moiety. Hence the present communication comprises the synthesis of 3-(4H-1,2,4-triazol-3-yl thio)-N-(3-chloro-2-oxo-4-substituted phenyl azetidin-1-yl) propanamide. The synthetic approach is shown in scheme-1.

MATERIALS AND METHODS

Melting points were determined in open capillary tubes and were uncorrected. The IR spectra were recorded in KBr pellets on a Nicolet 400D spectrometer and ^{1}H NMR spectra were recorded in DMSO with TMS as internal standard on a Bruker spectrometer at 400 MHz.

***Preparation of* 3-(4H-1, 2, 4-triazol-3-ylthio)-N'-arylidene propane hydrazide (2a-f)**

A mixture of 3-(4H-1, 2, 4-triazol-3-ylthio)propane hydrazide (1) and the aromatic aldehydes (a-f) in ethyl alcohol was refluxed on a water bath for 1.5 hrs. The solid separated was collected by filtration, dried and recrystallized from ethyl alcohol. The yields, melting points and other characterization data of these compounds are given in Table -1.



SCHEME - 1

***Preparation of* 3-(4H-1, 2, 4-triazol-3-ylthio)-N-(4-oxo-2-arylthiazolidin-3-yl) propanamide (3a-f)**

A mixture 3-(4H-1, 2, 4-triazol-3-ylthio)-N'-arylidene propane hydrazide **(2a-f)** in THF (30Ml) and triethyl amine (TEA) (0.004 mole) was dissolved in 1,4-dioxane (50 ml), cooled, and stirred. To this well-stirred cooled solution chloroacetyl chloride (0.004 mole) was added drop wise within a period of 30 minutes. The reaction mixture was then stirred for an additional 3 hours and left at room temperature for 48 hours. The resultant mixture was concentrated, cooled, poured into ice-cold water, and then air-dried. Recrystallization from ether/n-hexane gave 3-(4H-1, 2, 4-triazol-3-ylthio)-N-(4-oxo-2-arylthiazolidin-3-yl) propanamide (3a-f), which were obtained in 58-70% yield. The yields, melting points and other characterization data of these compounds are given in Table -2.

Table:-1 Analytical Data and Elemental Analysis of Compounds (2a-f)

Compd.	Molecular formula (Mol.wt.)	Yield	M.P.* ^{0}C	Elemental Analysis							
				%C		%H		%N		%S	
				Found	Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.
2a	$C_{12}H_{13}N_5OS$ (275)	81	239-241	52.33	52.35	4.75	4.76	25.42	25.44	11.64	11.65
2b	$C_{13}H_{15}N_5OS$ (289)	85	241-243	53.94	53.96	5.21	5.23	24.18	24.20	11.06	11.08
2c	$C_{12}H_{13}N_5O_2S$ (291)	78	233-235	49.45	49.47	4.48	4.50	24.03	24.04	11.00	11.01
2d	$C_{13}H_{15}N_5O_2S$ (305)	83	229-232	51.12	51.13	4.92	4.95	22.93	22.94	10.47	10.50
2e	$C_{13}H_{15}N_5OS$ (289)	77	225-227	53.95	53.96	5.21	5.23	24.19	24.20	11.06	11.08
2f	$C_{13}H_{15}N_5O_2S$ (305)	80	228-230	51.11	51.13	4.93	4.95	22.91	22.94	10.48	10.50

***** *Uncorrected*

Table:-2 Analytical Data and Elemental Analysis of Compounds (3a-f)

Compd.	Molecular formula (Mol.wt.)	Yield	M.P.* ^{0}C	Elemental Analysis							
				%C		%H		%N		%S	
				Found	Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.
3a	$C_{14}H_{14}N_5O_2SCl$ (351)	69	214-216	47.78	47.80	4.00	4.01	19.90	19.91	9.10	9.11
3b	$C_{15}H_{16}N_5O_2SCl$ (365)	66	204-206	49.24	49.25	4.40	4.41	19.12	19.14	8.75	8.76
3c	$C_{14}H_{14}N_5O_3SCl$ (367)	63	200-201	45.71	45.72	3.82	3.84	19.02	19.04	8.70	8.72
3d	$C_{15}H_{16}N_5O_3SCl$ (381)	58	192-194	47.16	47.18	4.20	4.22	18.33	18.34	8.38	8.40
3e	$C_{14}H_{14}N_5O_2SCl$ (363)	67	208-210	49.23	49.25	4.39	4.41	19.13	19.14	8.74	8.76
3f	$C_{14}H_{14}N_5O_2SCl$ (379)	70	199-201	47.16	47.18	4.21	4.22	18.32	18.34	8.39	8.40

***** Uncorrected

Antibacterial activities

The antibacterial activities of all the compounds were studied against gram-positive bacteria (*Staphylococcus aureus and Bacillus subtilis*) and gram-negative bacteria (*E.coli, and klebsiella promioe*) at a concentration of 50µg/ml by agar cup plate method. A methanol system was used as control in this method. Similar conditions using tetracycline as a control was used standard for comparison. The area of inhibition of zone measured in mm. Compounds 3c and 3d were found more toxic for microbes. Other compounds found to be less or moderate active than tetracycline Tables -3.

Table:-3 Antibacterial Activity of Compounds (3a-f)

Compounds	Gram +Ve		Gram -Ve	
	Staphylococcus aureus	Bacillus subtilis	E.coli	Klebsiella promioe
3a	47	46	59	49
3b	51	50	53	53
3c	63	62	74	46
3d	65	64	76	75
3e	60	55	56	60
3f	62	61	68	45
Tetracycline	55	79	74	84

Antifungal Activities

The fungicidal activity of all the compounds was studied at 1000 ppm concentration in vitro. Plant pathogenic organisms used were *Nigrospora Sp, Aspergillus niger, Botrydepladia thiobromine, and Rhizopus nigricum***,** *Fusarium oxyporium*. The antifungal activities of all the compounds (3a-f) were measured on each of these plant pathogenic strains on a potato dextrose agar (PDA) medium. Such a PDA medium contained potato 200g, dextrose 20g, agar 20g and water 1c. Five days old cultures were employed. The compounds to be tested were suspended (1000ppm) in a PDA medium and autoclaved at 120^o C for 15 min. at 15atm. pressure. These media were poured into sterile Petri plates and the organisms were inoculated after cooling the Petri plates. The percentage inhibition for fungi was calculated after five days using the formula given below:

Percentage of inhibition = 100(X-Y) / X

Where, X = Area of colony in control plate
Y = Area of colony in test plate

The fungicidal activity displayed by various compounds (3a-f) is shown in Tables-4.

Table:-4 Antifungal Activity of Compounds (3a-f)

Compounds	Zone of Inhibition at 1000 ppm (%)				
	Nigrospora Sp.	*Aspergillus niger*	*Botrydepladia thiobromine*	*Rhizopus nigricum*	*Fusarium oxyporium*
3a	57	51	59	57	63
3b	58	52	61	62	60
3c	66	67	63	61	69
3d	70	68	70	74	73
3e	65	66	62	61	58
3f	66	63	64	62	61

RESULTS AND DISCUSSION

It was observed that 3-(4H-1, 2, 4-triazol-3-ylthio)propane hydrazide(1), on condensation with various aromatic aldehydes, yields 3-(4H-1,2,4-triazol-3-ylthio)-N'-arylidene propane hydrazide(2a-f). The structures of (2a-f) were confirmed by elemental analysis and IR spectra showing an absorption band at 1620-1640 (C=N), 3030-3080 cm^{-1}(C-H, of Ar.), 1720-1750 cm^{-1} (CO), 2815-2850 cm^{-1}(OCH_3), 2950, 1370 cm^{-1} (CH_3), 3380-3290 cm^{-1}(OH).^{1}H NMR:7.91-9.6 (6H, m, Ar-H), 3.36-2.58(4H, t, -CH_2), 8.43-8.80(1H, s, N=CH), 8.62-8.81(2H, s, NH), 2b; 2.45(3H, s, CH_3), 2c; 5.35(1H, s, OH), 2d; 3.90(3H, s, OCH_3), 2e; 5.37 (1H, s, OH), 2f; 3.92 (3H, s, OCH_3).The C, H, N analysis data of all compounds are presented in Table -1.

The structures assigned to 3-(4H-1,2,4-triazol-3-ylthio)-N-(3-chloro-2-oxo-4-substituted phenylazetidin-1-yl)propanamide (3a-f) were supported by the elemental analysis and IR spectra showing an absorption bands at 1750-1760 (C=O of azetidinone ring), 3030-3080 cm^{-1} (C-H, of Ar.), 3450-3550 cm^{-1} (-OH), 1660-1670 cm^{-1} (-CONH), 2815-2850 cm^{-1} (OCH_3), 2950, 1370 cm^{-1} (CH_3), 3380- 3290 cm^{-1} (OH).^{1}H NMR: 3.36-2.58(4H,t,-CH_2),8.43-8.80(1H,s, N=CH),7.29-7.45 (5H,m,Ar-H),8.20-8.22 (1H,s,CONH),8.62-8.81(2H,s,NH), 5.19 (1H,d,N-C_2H),5.49(1H,d,C_3H),3b; 2.48(3H,s,CH_3),3c;5.38(1H,s,OH),3d;3.92(3H,s, OCH_3), 3e; 5.38(1H,s, OH), 3f; 3.95 (3H, s,OCH_3). The C, H, N, S analysis data of all compounds are presented in Table-2.

CONCLUSION

The examination of elemental analytical data reveals that the elemental contents are consistence with the predicted structure shown in Scheme-1. The IR and NMR data also express for assignment of the predicted structure.

Acknowledgement
The authors are very much thankful to the Dr. Vipul P. prajapati and Dr. Piyush J. Vyas, Sheth M.N.Science College, Patan for providing necessary facility, guidance and motivation during research work.

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