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Synthesis and Biological evaluation of some of N-alkylidine/ Arylidene-5-Alkyl/Aryl - 1, 3, 4-Thiadiazol- 2 -Amines

Agarwal Alka*[1], Bele D. [2], Singhvi I. [1], Gupta S.K. [1]
[1]Pacific College of Pharmacy, Pacific hills, Pratap nagar extn., Airport road, Debari, Udaipur-313003 (Raj) India
[2]Charak Institute of Pharmacy, Mandleshwar, Khargone (M.P.)

Abstract

A series N-Alkylidine/Arylidene-5- Alkyl/Aryl-1, 3, 4-Thiadiazol-2-Amines have been synthesized *via* multistep reaction sequence. The 5-alkyl/aryl-1, 3, 4-thiadiazol-2-amine derivatives were prepared by the reaction of different aliphatic/ aromatic carboxylic acids with thiosemicarbazide in presence of catalytic amount of concentrated sulfuric acid. These derivatives were treated with different aldehydes and ketones to afford the titled compounds. Structures of synthesized compounds were assigned on the basis analytical and spectral data. All the synthesized compounds were subjected to preliminary *in-vitro* antibacterial activity against Gram-positive bacterial strains *Bacillus Subtillis and* Gram-negative bacterial strains *Klebsiella Pneumoniae, Escheria coli* and *Pseudomonas aeruginasa*. The antifungal activity of the synthesized derivatives was evaluated against *Candida albicans* and *Aspergillus fumigates*. The synthesized compounds were found to possess comparable antimicrobial activity to the standard drug.

*Corresponding author, Mailing address:
Agarwal Alka
E-Mail: alkaagarwal2007@rediffmail.com

Key words:
Synthesis, Antibacterial, Antifungal, Thiadiazole, Antitumor, Anti-HIV.

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INTRODUCTION

The exploitation of a simple molecule with different functionalities for the synthesis of heterocyclic is a worthwhile contribution in the chemistry of heterocyclic. The 1, 3, 4-thiadiazole emerged as a versatile pharmacophore with wide range of biological activities which includes antibacterial [1-2], antifungal [3], phosphodiesterase inhibition [4], anti-inflammatory [5], platelate aggregation inhibition [6] and antihypertensive action [7-8]. A number of 1, 3, 4-thiadiazoles showed antibacterial activity similar to those of well-known sulfonamide drugs [9]. The thiadiazole nucleus with N-C-S linkage exhibits a large number of biological activities [10]. Owing to the importance and established

physiological activity of these compounds, it was thought to synthesize and investigate compounds with comparable structures. The shiff bases are reported to possess antitubercular [11] fungicidal [12] and agrochemical [13] activities. The biological activity of shiff bases is attributed to presence of C=N linkage. Therefore an attempt was made to synthesize and evaluate antibacterial activity of some new Schiff bases of 5-alkyl/ aryl-1, 3, 4-thiadiazol-2-amines.

The synthesis of the titled compounds was affected as outlined in the scheme. These were prepared by the reaction of different carboxylic acids with thiosemicarbazide in presence of catalytic amount of concentrated sulfuric acid. These amine derivatives were treated with aliphatic / aromatic aldehydes and ketones to afford the titled derivatives.

EXPERIMENTAL WORK

Standard procedure or reported methods were followed with or without modification appropriately as and when required. All chemical and solvents used were of analytical grade. The melting points of synthesized compounds were determined by open capillary tube method and are uncorrected. The purity and homogeneity of the titled compounds was routinely ascertained by using TLC. The absorption maxima of the synthesized compounds were measured on shimadzu UV spectrophotometer. The IR absorption spectra of the compounds were recorded on FTIR Bruker Tensor-27 model. The ^1H NMR absorption spectra of the compounds were recorded on Bruker Spectrospin 300 model. Physical characteristics and spectroscopic interpretation data are presented in Table 1-2.

SYNTHESIS

Step 1: Synthesis of 5-alkyl/aryl-1, 3, 4-thiadiazol-2-amine. 1(a-c)

Different aliphatic or aromatic carboxylic acid (0.01 mol), thiosemicarbazide (0.01 mol), and concentrated sulphuric acid (4.0 ml) in 250 ml round bottom flask were heated on water bath. The reaction mixtures were cooled and poured into crushed ice and neutralized with ammonia solution. The separated solids were then filtered, washed with saturated sodium bicarbonate solution and water, dried & recrystallized with ethanol.

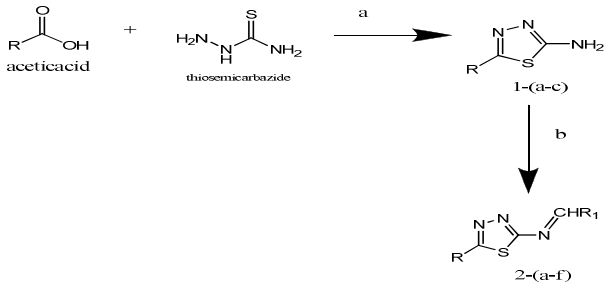
Step 2: Synthesis of N- alkylidine /arylidine - 5-alkyl/aryl-1, 3, 4-thiadiazol-2-amines 2(a-f)

Compounds 1(a-c) (0.01 mol) & aliphatic / aromatic aldehydes/ ketones (0.01 mol) were dissolved in sufficient amount of methanol with addition of some drops of glacial acetic acid in 250ml round bottom flask. The reaction mixtures were refluxed on heating mental for about 3-5h. The resultant mixtures were cooled and evaporated. The separated solid were then filtered, washed with water, dried & recrystallized with ethanol.

ANTIMICROBIAL ACTIVITY:

All the synthesized compounds were subjected to antimicrobial screening [14] by cup plate method for zone of inhibition. All the derivatives were screened against the pathogenic fungi *B. subtilis, K. pneumoniae, E. coli, P. aeruginosa, C. albicans* and *A. fumigatus*. Ciprofloxacin and Fluconazole were used as standard drugs in evaluation of antibacterial and antifungal activity respectively. The solutions of the synthesized compounds and standard drugs were prepared in dimethyl formamide (DMF). The concentration of the prepared solutions was 100 µg/ml. The results of antimicrobial activity are shown in Table 3 and Table 4.

SYNTHETIC SCNEME:



a= Concentrated H_2SO_4
b=R_1CHO
R = -H, $-CH_3$, $-C_6H_5$
R_1= $-CH_3$, $-C_6H_5$

Compound No.	R	R_1
2a	H	CH_3
2b	CH_3	CH_3
2c	C_6H_5	CH_3
2d	H	C_6H_5
2e	CH_3	C_6H_5
2f	C_6H_5	C_6H_5

Table 1: Physical characteristic of synthesized compounds

Comp. No.	Mol. Formula	Mol. Wt.	% Yield	M.P. (°C)	R_f	λ_{max} (nm)
2a	$C_4H_5N_3S$	127.17	75	190-192	0.24	297.6
2b	$C_9H_7N_3S$	189.24	59.2	204-205	0.26	327
2c	$C_5H_7N_3S$	141.19	61.5	186-189	0.82	333.6
2d	$C_{10}H_9N_3S$	203.26	53.6	210-214	0.89	314.5
2e	$C_{10}H_9N_3S$	203.26	73.9	247-249	0.71	243.3
2f	$C_{15}H_{11}N_3S$	265.33	79	214-220	0.58	325.9

Table 2: Absorption spectra of synthesized compounds

Comp. No.	Wave Number (cm^{-1})	Chemical shift δ (ppm)
2a	-NH (3450.00),-CH_3 (2940.65),-C=N (1645), -N=N (1516.74), C-N (1236.12), C-S (715.41).	s, 1H, CH (7.50); s, 3H, CH_3 (1.06).
2b	-NH (3322.92), Ar –CH (2978.4), - CH_3 (2944.67), -C=N (1651.67), N=N (1512.72), C-N (1234.15), C-S (715.41).	s, 1H, CH (7.50); m, 5H, Ar-H (7.23-7.35); s, 1H, CH (7.83).
2c	-NH (3326.91), -CH_3 (2944.67), -C=N (1650.81), N=N (1512.72), C-N (1234.15), C-S (715.41).	s, 1H, CH (7.50); s, 3H, CH_3 (1.06); s, 3H, CH_3 (2.64).
2d	-NH (3327.60), Ar –CH (2980.17), - CH_3 (2924.58), -C=N (1659.72), N=N (1512.72), C-N (1234.15), C-S (715.41).	s, 1H, CH (7.50); s, 3H, CH_3 (2.64); m, 5H, Ar-H (7.23-7.35).
2e	-NH (3324.07), Ar –CH (2963.07) , -C=N (1615.05), N=N (1512.72) , C-N (1234.15), C-S (715.41).	s, 1H, CH (7.50); s, 3H, CH_3 (1.06); m, 5H, Ar-H (7.41-8.03).
2f	-NH (3301.03), Ar –CH (2978.4),-C=N (1594.38), N=N (1512.72), C-N (1234.15), C-S (715.41).	s, 1H, CH (7.50); m, 5H, Ar-H (7.41-8.03); m, 5H, Ar-H (7.52).

Table 3: *In Vitro* Antibacterial activity of the synthesized compounds 2(a-f):

Comp. No.	*Bacterial strain*											
	Bacillus Subtillis			*Klebsiella Pneumoniae*			*E.coli*			*Pseudomonas aeruginasa*		
	Z.O.I	% Inhi.	Activity Index	Z.O.I	% Inhi.	Activity Index	Z.O.I	% Inhi.	Activity Index	Z.O.I	% Inhi.	Activity Index
2a	10	32.25	0.32	8	25.80	0.25	13	41.93	0.41	-	-	-
2b	-	-	-	-	-	-	13	41.93	0.41	-	-	-
2c	-	-	-	-	-	-	14	45.16	0.45	8	25.8	0.25
2d	4	12.90	0.12	-	-	-	19	61.29	0.61	-	-	-
2e	-	-	-	-	-	-	20	64.51	0.64	9	32.14	0.32
2f	-	-	-	18	58.06	0.58	-	-	-	9	32.14	0.32
Standard *	29	100		31	100	1	31	100	1	28	100	1

*Ciprofloxacin
- Denotes no activity.

Table 4: *In vitro* antifungal activity of the synthesized compounds 2(a-f):

Comp. no.	*Candida albicans*			*Aspergillus fumigatus*		
	Z.O.I	% Inhi.	Activity index	Z.O.I	% Inhi.	Activity Index
2a	21	84.00	0.84	25	92.59	0.92
2b	14	56.00	0.56	26	96.29	0.96
2c	24	96.00	0.96	23	85.18	0.85
2d	17	68.00	0.68	-	-	-l
2e	-	-	-	26	96.29	0.96
2f	19	76.00	0.76	14	51.85	0.51
Standard *	25	100	1	27	100	1

* Fluconazole
- Denotes no activity.

RESULTS AND DISCUSSION

The IR and ^{1}H-NMR data indicates the successful synthesis of the titled compounds. All the compounds i.e. 2(a-f) showed mild to moderate antibacterial activity against the tested organisms with maximum activity exhibited against *E. coli*. Compounds 2e showed good activity, amongst the synthesized derivatives, which is attributed to presence of electron releasing groups i.e. $-CH_3$ and $-C_6H_5$. All the compounds exhibited excellent activity against the fungal strains *C. albicans* and *A. fumigatus*. Compound 2c exhibited highest antifungal activity against *C. albicans* while 2b and 2e showed highest activity against *A. fumigatus*. Amongst the tested compounds, 2e emerged as potential antimicrobial agent. Further exploration on this molecule may results into potent therapeutic agent.

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