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A facile synthesis of some indolylazetidinones and substituted indolylthiazolidinones

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ABSTRACT

The synthesis of 4-thiazolidinones can be achieved from 2-phenyl-3-substituted benzalamino- indole with thioglycolic, thiolactic, at high temperatures. Elemental analysis, IR, ^{1}H-NMR, and mass spectral data established identification of the compounds. Products were evaluated for their antimicrobial activity using cup plate method[1]. Some of the obtained compounds showed the interesting antimicrobial activity.

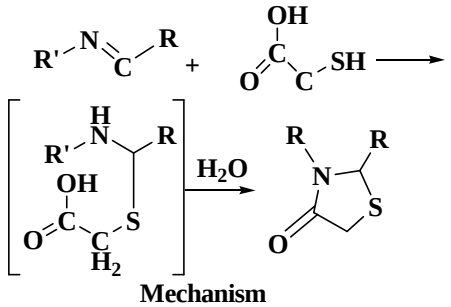
KEYWORDS

4-Thiazolidinones;
Antimicrobial activity;
Indolylazetidinones;
Indolylthiazo-lidinones.

INTRODUCTION

In the family of heterocyclic compounds, nitrogen-containing heterocycles with a sulfur atom are an important class of compounds in medicinal chemistry. There has been considerable interest in the development of preparative method for the production of 4-thiazolidinones. Indoles[2] and 4-thiazolidinones[3] possess a wide spectrum of biological activities. The reaction of β-lactum moiety is greatly influenced by substituted or fused rings[4,5]. 2-Azetidinones are also known to possess a variety of therapeutic activities[5,6]. The present communication reports the synthesis of bi-heterocyclic derivatives of 4-thiazolidinones and 2-azetidinones. These Compounds have been tested for their antibacterial and antifungal activities using cup plate method.

2-phenyl-3-amino indole[7] on condensation with different aromatic aldehydes yielded 2-phenyl-3-substituted benzolamino indoles **2(a-e)**, which on cyclocon densation with thioglycolic acid/thiolactic acid yielded the 4-thiazolidinones **(3Tg-Tl)**. The four member β-lactum ring is introduced in **2(a-e)** by the cycloaddition of chloroacetyl chloride in the presence of triethylamine to yield 2-azetidinones **4(o-s)**(SCHEME 1). The other compounds were prepared in similar manner.



Mechanism

EXPERIMENTAL

All the melting points were determined routinely in an open capillary tube and are uncorrected. Completion of reaction was routinely checked by TLC on silica gel-G plates of 0.5mm thickness and the spots were

TABLE 1 : Physical and analytical data

Sr. no.	R	X	Molecular formula	M.P. °C	Yield %	Nitrogen	
						Calculated	Found
(2a)	4-chlorophenyl	-	$C_{21}H_{15}ClN_2$	151	75	8.47	8.43
(2b)	2-chlorophenyl	-	$C_{21}H_{15}ClN_2$	131	79	8.47	8.51
(2c)	2,4-Dichlorophenyl	-	$C_{21}H_{14}Cl_2N_2$	218	80	7.67	7.61
(2d)	3-hydroxyphenyl	-	$C_{21}H_{16}N_2O$	135	60	8.97	8.99
(2e)	3,4-Dichlorophenyl	-	$C_{21}H_{14}Cl_2N_2$	150	74	7.67	7.70
(3(Tg)f)	4-chlorophenyl	H	$C_{23}H_{17}ClN_2OS$	215	60	6.92	6.90
(3(Tg)g)	2-chlorophenyl	H	$C_{23}H_{17}ClN_2OS$	198	59	6.92	6.95
(3(Tg)h)	3-Nitrophenyl	H	$C_{23}H_{17}N_3O_3S$	202	65	10.12	10.10
(3(Tg)i)	3-hydroxyphenyl	H	$C_{23}H_{18}N_2O_2S$	277	78	7.25	7.20
(3(Tg)j)	4-hydroxyphenyl	H	$C_{23}H_{18}N_2O_2S$	215	81	7.25	7.28
(3(Tl)k)	2,4-Dichlorophenyl	CH_3	$C_{24}H_{18}Cl_2N_2OS$	291	69	6.18	6.11
(3(Tl)l)	2-Chlorophenyl	CH_3	$C_{24}H_{19}ClN_2OS$	166	75	6.69	6.65
(3(Tl)m)	4-Chlorophenyl	CH_3	$C_{24}H_{19}ClN_2OS$	185	56	6.69	6.67
(3(Tl)n)	3-hydroxyphenyl	CH_3	$C_{24}H_{20}N_2O_2S$	360	63	7.00	7.06
(3(Tl)o)	4-hydroxyphenyl	CH_3	$C_{24}H_{20}N_2O_2S$	211	68	7.00	6.98
(4p)	2,4-Dichlorophenyl	-	$C_{23}H_{15}Cl_3N_2O$	251	78	6.34	6.31
(4q)	3,4-Dimethoxypheny	-	$C_{25}H_{21}ClN_2O_3$	198	68	6.48	6.43
(4r)	3-Nitrophenyl	-	$C_{23}H_{16}ClN_3O_3$	198	60	10.07	10.01
(4s)	3-hydroxyphenyl	-	$C_{23}H_{17}ClN_2O_2$	281	77	7.21	7.24
(4t)	4-hydroxy-3-methoxy-phenyl	-	$C_{24}H_{19}ClN_2O_3$	107	67	6.48	6.43

located by iodine. The PMR spectra were recorded in $CDCl_3$ on a Brucker DRX-300 at 300 MHz. The IR spectra were recorded on a Shimadzu-8400 FT-IR spectrometer in KBr (γ in cm^{-1}). Elemental analyses of the newly synthesized compounds were carried out on a Carlo Erba-1108 analyzer and result within the range of the theoretical value was found. Mass spectra were scanned on a GCMS-QP200 instrument,

Synthesis of 2-phenyl-3-p-methoxybenzalaminoin dole (2a)

A mixture of 3-amino-2-phenyl indole (0.01 mol) and 2-methoxy benzaldehyde (0.01 mol) in methanol (20 ml) was refluxed for 8hrs. The resulting solid was washed with 30% sodium bi-sulphate solution; a solid material separated which was recrystallized from 1,4-dioxane-ethanol. Similarly other compounds were also prepared. (TABLE 1)

Synthesis of 2-aryl-3-(2'-phenylindol-3'-yl)-5-H-methyl-4-thiazolidinones [3(Tg)f]:

A mixture of **(2a)** (0.01 mol) and thioglycolic acid (0.015 mol) was heated at 115-120 ^{0}C for 11 hours. The resulting material was triturated with 2N sodium bicarbonate and resulting solid was washed with excess of water dried and crystallized from methanol water. Similarly the other compounds were also prepared. (TABLE 1)

Synthesis of 2-Aryl-3-(2'-phenylindol-3'-yl)-5-methyl-4-thiazolidinones [3(Tl)k]

A mixture of **(2a)** (0.01 mol) and thiolactic acid (0.02 mol) was heated at 120^{0}C for 9-10hr. The reaction mixture was then cooled and triturated with 2N sodium bicarbonate, a solid separated. Which was recrystllized from 1,4-dioxan-ethanol. Similarly the other compounds were also prepared. (TABLE 1)

Synthesis of 4-Aryl-1-(2'-phenyindol-3'-yl)-3-chloroazetidines (4p)

To a stirred solution of **(2a)** (0.01 mol) and triethylamine (0.02 mol) in dry 1,4-dioxan (50 ml) was added chloroacetyl chloride (0.01 mol) drop wise at room temperature. The reaction mixture was stirred for 24hr. and kept for 2 days at room temperature. The precipitates of triethylamine hydrochloride was filtered ad washed with dioxane was distilled off and the contents were poured on crush ice. The resulting solid was dried and crystallized from 99% ethanol. Similarly the other compounds were prepared. (TABLE 1)

Antimicrobial activity

The purified products were screened for its antibacterial activity. The nutrient agar broth prepared by the usual method was inoculated especially with 0.5 ml

TABLE 2 : Antibacterial and antifungal activity (Concentration in µg/ml)

Sr. no.	R	X	Molecular formula	Antifungal activity Zones of inhibition in mm				
				S.aureus	*S.pyogens*	*E.coli*	*K.arogens*	*A.niger*
(2a)	4-Chlorophenyl	-	$C_{21}H_{15}ClN_2$	15	16	17	14	13
(2b)	2-Chlorophenyl	-	$C_{21}H_{15}ClN_2$	16	15	14	16	17
(2c)	2,4-Dichlorophenyl	-	$C_{21}H_{14}Cl_2N_2$	20	14	17	14	13
(2d)	3-Hydroxyphenyl	-	$C_{21}H_{16}N_2O$	14	12	15	14	13
(2e)	3,4-Dichlorophenyl	-	$C_{21}H_{14}Cl_2N_2$	17	18	18	10	18
(3(Tg)f)	4-Chlorophenyl	H	$C_{23}H_{17}ClN_2OS$	18	17	17	13	14
(3(Tg)g)	2-Chlorophenyl	H	$C_{23}H_{17}ClN_2OS$	19	17	15	17	13
(3(Tg)h)	3-Nitrophenyl	H	$C_{23}H_{17}N_3O_3S$	15	18	19	11	19
(3(Tg)i)	3-Hydroxyphenyl	H	$C_{23}H_{18}N_2O_2S$	19	19	18	18	19
(3(Tg)j)	4-Hydroxyphenyl	H	$C_{23}H_{18}N_2O_2S$	18	19	18	17	17
(3(Tl)k)	2,4-Dichlorophenyl	CH_3	$C_{24}H_{18}Cl_2N_2OS$	17	19	11	18	13
(3(Tl)l)	2-Chlorophenyl	CH_3	$C_{24}H_{19}ClN_2OS$	15	11	11	14	12
(3(Tl)m)	4-Chlorophenyl	CH_3	$C_{24}H_{19}ClN_2OS$	17	19	14	13	11
(3(Tl)n)	3-Hydroxyphenyl	CH_3	$C_{24}H_{20}N_2O_2S$	14	14	17	12	19
(3(Tl)o)	4-Hydroxyphenyl	CH_3	$C_{24}H_{20}N_2O_2S$	19	13	19	12	11
(4p)	2,4-Dichlorophenyl	-	$C_{23}H_{15}Cl_3N_2O$	13	19	14	11	15
(4q)	3,4-Dimethoxypheny	-	$C_{25}H_{21}ClN_2O_3$	11	10	11	13	11
(4r)	3-Nitrophenyl	-	$C_{23}H_{16}ClN_3O_3$	10	17	15	12	17
(4s)	3-Hydroxyphenyl	-	$C_{23}H_{17}ClN_2O_2$	11	15	18	19	19
(4t)	4-Hydroxy-3-methoxy-phenyl	-	$C_{24}H_{19}ClN_2O_3$	13	17	13	10	11

for 24 hrs. Old subculture of *S.aureus, S.pyogens, E.coli,* and *K.arogens* in separate conical flask at 40-50^{0}C and mixed well by gentle shaking. About 25 ml of the contents of the flask were poured and evenly spread in a petridish (13 cm in diameter) and allowed to set for two hrs. The cups (10 mm in diameter) were formed by the help of borer in agar medium and filled with 0.10 ml (1 mg/ml) solution of a sample in dimethyl formamide. The plates ere incubated at 37^{0}C for 24 hrs and the control was also maintained with 0.1 ml of dimethyl formamide in similar manner, and the zones of inhibition of the bacterial growth are measured in mm diameter and are recorded in TABLE 2.

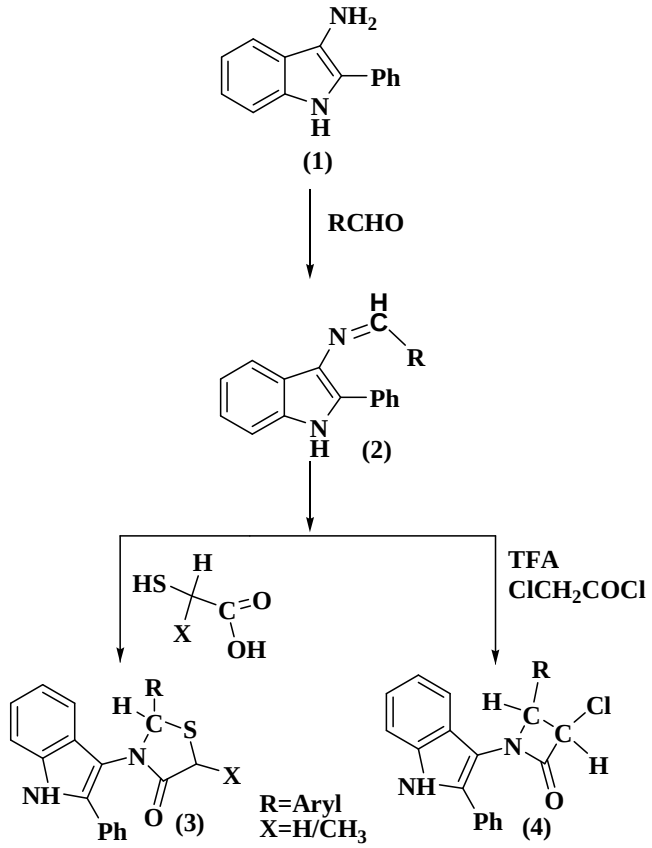
Antifungal activity

A.niger was employed for testing fungicidal activity using cup-plate method. The cultures were maintained on Sabouraud's agar slants. Purified compounds were used for testing the fungicidal activity. Sterilized sabouraud's agar medium was inoculated with 72 hrs old, 0.5 ml suspensions of fungal spores, in separate flask. About 25 ml of the inoculated medium was evenly spreaded in a sterilized petridish and allowed to set for 2 hrs. The cups (10 mm in diameter) were punched in petridish and loaded with 0.1 ml (1.0 mg/ml) of solution of a sample in dimethyl formamide. The plates were incubated at room temperature (30^{0}C) for 48 hrs. After the completion of incubation period the zones of inhibition of growth in the form of diameter in mm was measured. Along the test solution in each petridish one cup was filled up with solvent, which acts as a control. The zones of inhibition are recorded in TABLE 2.

RESULT AND DISCUSSION

The physical data for compound **(3(Tg)f**)are as follows; Yield 73%, m.p.199^{0}C, Anal. Calculated for $C_{22}H_{18}N_2O$; Required: C (62.88%), H (3.67%), N (6.37%); Found: C (62.81%), H (3.62%), N (6.31%); IR (KBr) Vmax Cm^{-1}: 3300 (N-H str.), 2950 (C-H str., asym.), 2880 (C-H str., sym.), 3000, 1500, 1460, 1100, 800, 1330 (=C-N str., C=C-H, C=C, aromatic + indole moiety), 1240 (C-O-C asym., str.), 1060 (C-O-C sym.); PMR δ/ppm (DMF) : 3.8 (s,3H,-OCH_3), 3.4 (s,2H, S-CH_2), 7.25 (s, 1H, -N-CH-R), 7.3-7.7 (m,13H, Ar-H), 9.5 (s,1H, NH-indole) ; Mass spectrum of the compound exhibited a molecular ion peak at m/z 439 (M^+).

The physical data for compound **(3(Tl)m)** are as follows; Yield 73%, m.p.103^{0}C, Anal. Calculated for $C_{24}H_{19}N_3O_3S$; Required: C (67.12%), H (4.46%), N (9.79%) ; Found: C (67.08%), H (4.40%), N (9.72%); IR (KBr) Vmax Cm^{-1} : 3350 (N-H str.), 2820 (C-H str., sym.), 1610, 1250, 1100, 830, 1340, 3350 (=C-



Reaction scheme

N str., C=C-H, C=C, aromatic + indole moiety), 1240 (C-O-C asym., str.), 1025 (C-O-C sym.), 1650, 1170, 695, (C=0 Str., C-N Str., C-S-C Str., Thiazolidinone); PMR δ/ppm (DMF) : 3.5 (s,3H,-OCH_3), 1.7 (d,3H,-CH-CH_3), 2.5 (q,1H,-CH-CH_3), 6.8-7.6 (m, 13H, Ar-H), 7.8 (s,1H,-N-CH-R), 9.5 (s, 1H, -NH Indole); Mass spectrum of the compound exhibited a molecular ion peak at m/z 429 (M^+).

The physical data for compound **(4q)** are as follows; Yield 79%, m.p. 200^{0}C, Anal. Calculated for $C_{24}H_{19}ClN_2O_2$; Required: C (71.55%), H (4.75%), N (6.96%); Found: C (71.50%), H (4.71%), N (6.92%); IR (KBr) Vmax Cm^{-1}: 3050, 1540, 830, (=C-H Str., C=C Str., C-H o.o.p def. Aromatic moiety), 3000 (C-H Str. Asym.-CH_2-), 2900 (C-H Str. Sym.-CH_2), 1455 (C-H def.-CH_2), 1180,1150, 623, 3490 (C=N Str., C-S-C Str., N-H Str., Thiazolidinone), 1640 (C=N Str., Benzal group), 1710 (C=O Str., β-lactum), 760 (C-Cl Str., Halide) ; PMR δ/ppm (DMF) : 3.41 (s, 2H, S-CH_2), 3.59 (d, 1H, -CH-R), 3.93 (d, 1H, -CH-Cl), 7.48-7.74 (m, 5H, Ar-H), 8.44 (s, 1H, -CO-NH-); Mass spectrum of the compound exhibited a molecular ion peak at m/z 402 (M^+).

Antimicrobial activity

The MIC values of the test solution are recorded in TABLE 2, which are recorded in zones of inhibition in mm for the bacteria and fungi.

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