A NOVEL ONE POT SYNTHESIS OF 7,9-DISUBSTITUTED 5H-THIAZOLO [2,3-b] QUINAZOLINE-3,5 [2H]-DIONES

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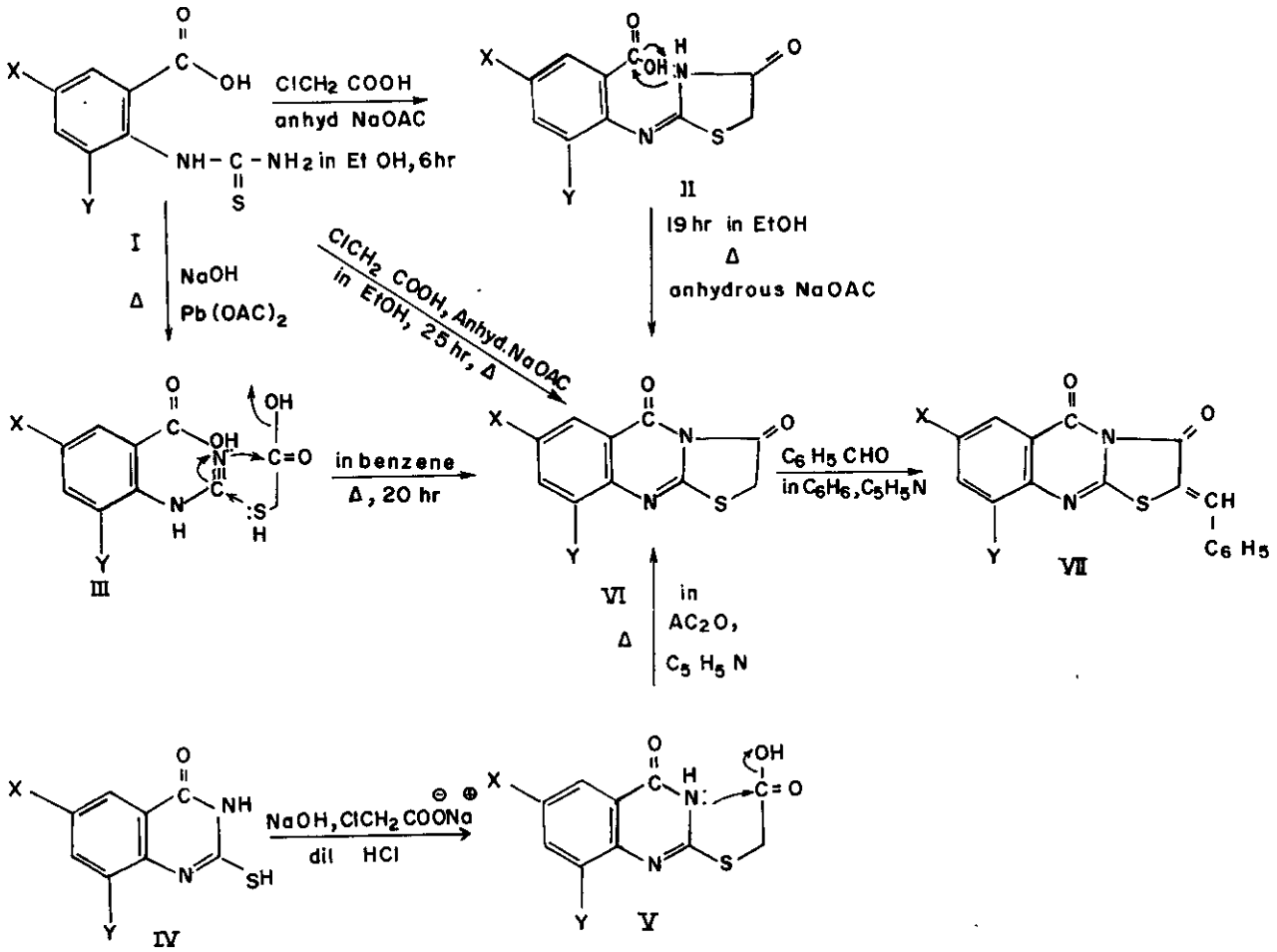
Abstract - Various 7,9-disubstituted 5H-thiazolo[2,3-b]quinazoline-3,5(2H)-diones and 7,9-disubstituted 2-benzylidene-5H-thiazolo[2,3-b] quinazoline-3,5(2H)-diones have been synthesized and screened for various biological activities. Some of the compounds checked fungal growth and also showed significant antibacterial activity.

Several heterocyclic compounds with bridgehead nitrogen atom have acquired considerable importance on account of the diverse biological activities associated with them. Numerous condensed compounds incorporating the quinazolinone and various five membered heterocyclic systems have been prepared[1,2]. Hardtman[3,4] reported the synthesis of several quinazolinones showing bronchodilatory, analeptic, antiinflammatory, analgesic and antihypertensive activities. Joshi et al[5] have recently synthesized some 2,3-dihydrothiazolo[2,3-b]-7 or 8-fluoroquinazolin-5-ones. 5H-Thiazolo[2,3-b]quinazolin-3,5(2H)-dione was recently prepared by Ali et al[6].

Keeping in view these biological properties associated with such compounds, a novel one pot synthesis of 7,9-disubstituted 5H-thiazolo[2,3-b]quinazoline 3,5(2H)-diones have been developed.

7,9-Disubstituted 5H-thiazolo[2,3-b]quinazoline-3,5(2H)-diones (VI) have been prepared by the cyclization of 6,8-disubstituted 2-carboxymethylthio-4(3H)-quinazolinones (V)[7]. However this method is quite elaborate and involves several steps.

3,5-Disubstituted 2-thioureidobenzoic acids (I) were obtained by heating corresponding anthranilic acid hydrochlorides[8-12] with ammonium thiocyanate on a sand bath. On refluxing I with chloroacetic acid and anhydrous sodium acetate in absolute ethanol for 6 hr, 2-[2-carboxy(substituted)phenylnitrilo]-4-thiazolidinones (II) were obtained. Refluxing of I with lead acetate in


ClCH2 COOH
anhyd NaOAC
NH – C – NH2 in Et OH, 6hr
II
19 hr in EtOH
Δ
anhydrous NaOAC
I
Δ
NaOH
Pb(OAC)2
ClCH2 COOH, Anhyd. NaOAC
in EtOH, 25 hr, Δ
in benzene
Δ, 20 hr
C6 H5 CHO
in C6H6, C5H5N
III
VI
Δ
in
AC2O,
C5 H5 N
VII
NaOH, ClCH2 COONa
dil HCl
IV
V

presence of sodium hydroxide gave 3,5-disubstituted N-cyanoanthranilic acids (III) which yield II by cycloaddition with thioglycolic acid in dry benzene. Refluxing of II with anhydrous sodium acetate in absolute ethanol for 19 hr gave 7,9-disubstituted 5H-thiazolo[2,3-b]quinazoline-3,5(2H)-diones (VI). The compound VI was also obtained on refluxing I with chloroacetic acid and anhydrous sodium acetate in absolute ethanol for 25 hr or on refluxing III with thioglycolic acid in dry benzene for 20 hr. Another route for obtaining VI involves the treatment of sodium salt of 6,8-disubstituted 2-mercapto-4(3H)-quinazolinones (IV) with sodium chloroacetate yielding 6,8-disubstituted 2-carboxymethylthio-4-(3H)-quinazolinones (V)[13] and subsequent cyclization with acetic anhydride and pyridine.

Thus, VI have been synthesized directly from compounds I and III by the method described. The procedure involves a single step and dispenses with several reactants used in the other method[7]. 7,9-Disubstituted 2-benzylidene-5H-thiazolo[2,3-b]quinazoline-3,5(2H)-diones (VII) were obtained by condensing VI, benzaldehyde and pyridine in dry benzene for 4 hr.

EXPERIMENTAL

All melting points were taken in open capillary in liquid bath and are uncorrected. Ir spectra were recorded on a Perkin Elmer 621 spectrophotometer. A coleman analyser was used for elemental analysis.

3,5-Disubstituted anthranilic acids were prepared by the known methods[8-12].

5-Chloro 2-thioureidobenzoic acid (Ia) was prepared according to the method of Rout et al[14] in 50% yield, mp 165°.

Similarly, other 3,5-disubstituted 2-thioureidobenzoic acids (Ib-g) were prepared. Their yields, mp and analytical data are listed in Table I.

2-(2-Carboxyphenylnitrilo)-4-thiazolidinones (IIa) A solution of N-cyano-anthranilic acid (0.01 M) and 60% thioglycolic acid (0.015 M) in benzene (30 ml) was refluxed for 6 hr. Excess of the benzene was distilled off and the residue was diluted with water. The resulting precipitate was filtered off, washed with distilled water, dried and recrystalised from ethanol to give IIa in 54% yield, mp 189°.

Similarly, other 2-[2-carboxy(substituted)phenylnitrilo]-4-thiozolidinones (IIb-g) were prepared. Their yields, mp and analytical data are listed in Table II.

N-Cyanoanthranilic acid (IIIa) was prepared according to the method of Krall[15] in 68% yield, mp 261°.

Other 3,5-disubstituted N-cyanoanthranilic acids (IIIb-g) were prepared similarly. Their yields, mp and analytical data are listed in Table III.

2-Mercapto-4-(3H-quinazolinone (IVa) was synthesised according to the method of Dave[16], mp 285° (lit. mp 280°).

Similarly, other 6,8-disubstituted 2-mercapto-4(3H)-quinozolinones (IVb-e) were synthesised. Their yields, mp and analytical data are listed in Table IV.

6,8-Disubstituted 2-carboxymethylthio-4(3H)-quinazolinones (Va-d) were prepared by the method of Bhargava et al[17]. Their yields, mp and analytical data are listed in Table V.

5H-Thiazolo[2,3-b]quinazoline-3,5(2H)-dione[6] (VIa) Method A: A mixture of 2-thioureidobenzoic acid (0.01 M), chloroacetic acid (0.011 M), anhydrous sodium acetate (0.02 M), and absolute ethanol (50 ml) was refluxed on a water bath for 25 hr. The reaction mixture was poured into ice cold water. The resulting precipitate was filtered off, washed with 5% sodium bicarbonate solution and distilled water, and recrystallized from ethanol to give 50% yield of VIa, mp 295°. Anal. Calcd. for $C_{10}H_6N_2O_2S$:C, 55.05; H, 2.75, Found: C, 55.35; H, 2.52%.

IR(nujol): 1710(s), 1680(s), 1620(m), 1580(m), 1370(s), 880(s) cm^{-1}.

B: A solution of N-cyanoanthranilic acid (0.01 M) and 60% thioglycolic acid (0.015 M) in dry benzene (30 ml) was refluxed on a water bath for 20 hr. After excess of benzene was distilled off, the residue was poured into cold water. The resulting precipitate was filtered off, washed with 5% sodium bicarbonate solution and distilled water, and recrystallized from ethanol to give VIa in 50% yield, mp 294°.

C: A solution of 2-(2-carboxyphenylnitrilo)-4-thiozolidinone (0.01 M), anhydrous sodium acetate (0.02 M) in absolute ethanol (30 ml) were refluxed on a water bath for 19 hr. Excess of ethanol was distilled off. The reaction mixture was poured into ice-cold water. The resulting precipitate was filtered off, washed with 5% sodium bicarbonate solution and distilled water, and recrystallized from ethanol to give VIa in 56% yield, mp 295°.

D: A solution of 2-carboxymethylthio-4(3H)-quinazolinone[7] (0.01 M), acetic anhydride (20 ml) and a few drops of pyridine was refluxed for 30 min. The reaction mixture was poured into ice cold water. The resulting precipitate

was filtered off, washed with 5% sodium bicarbonate solution and distilled water and recrystallized from ethanol, to give VIa in 51% yield, mp 193°. Similarly, other 7,9-disubstituted 5H-thiazolo[2,3-b]quinazoline-3,5(2H)-diones (VIb-f) were synthesised by four different routes. Their yields, mp, ir and analytical data are listed in Table VI.

7-Chloro-2-benzylidene-5H-thiazolo[2,3-b]quinazoline-3,5(2H)-dione (VIIa) A solution of 7-chloro-5H-thiazolo[2,3-b]quinazoline-3,5(2H)-dione (0.01 M) benzaldehyde (0.011 M), and a few drops of pyridine in dry benzene (30 ml) was refluxed for 4 hr. Excess of the benzene and pyridine was distilled off under reduced pressure and the residue was washed with a mixture of distilled water and a little of ethanol. Recrystallisation of the crude product with ethanol gave VIIa.

Similarly, other 7,9-disubstituted 2-benzylidene 5H-thiazolo[2,3-b]-quinazoline-3,5(2H)-diones (VIIb-g) were synthesized. Their yields, mp, ir and analytical data are listed in Table VII.

PHARMACOLOGICAL SCREENING

The synthesized compounds were screened for fungicidal action on Aspergillus niger and Alternaria alternata by the agar diffusion technique[18] at two dilutions viz., 1:2800 and 1:6500. The percentage inhibition of growth was determined by comparison with growth in controls. All solutions were prepared in absolute alcohol. The medium in controls and treated plates was potato dextrose agar culture medium and the incubation time was 96 hr at 26 ± 1°C. The compounds VIb,c,d and e inhibit 80-100% spore germination against Alternaria alternata at both the dilutions, while in the case of Aspergillus niger maximum compounds inhibit 50-70% spore germination at both the dilutions.

The compounds VIb and c were screened in vitro against S. aureus and found to be active at 250 g/ml but inactive at 100 g/ml against Streptococcus faccalis, Klebsiella pneumoniae, E. coli, Pseudomonas aeruginose, Candida albicans, Cryptococcus neoformans, Sporotrichum schenekii, Trichophyton mentagrophytes and Aspergillus fumigatus.

Anticancerous activity of compounds VIb and c is in progress in N.I.H. Maryland, U.S.A. and will be reported latter.

Table I

3,5-Disubstituted 2-thioureidobenzolic acids (Ib-g)

No.	Substituents X	Y	Molecular formula	Mp °C	Yield %	Carbon % Found	Carbon % Calcd.	Hydrogen% Found	Hydrogen% Calcd.
Ib	Cl	Cl	$C_8H_6Cl_2N_2O_2S$	228	71	36.02	36.23	2.02	2.26
c	Br	H	$C_8H_7BrN_2O_2S$	214	56	34.78	34.91	2.42	2.55
d	Br	Br	$C_8H_6Br_2N_2O_2S$	134	82	26.98	27.12	1.58	1.70
e	I	H	$C_8H_7IN_2O_2S$	116	70	29.71	29.81	1.99	2.17
f	I	I	$C_8H_6I_2N_2O_2S$	103	86	21.26	21.43	1.12	1.34
g	NO_2	H	$C_8H_7N_3O_4S$	254	74	39.68	39.83	2.81	2.91

Table II

2-[2-Carboxy(substituted)phenylnitrilo]-4-thiazolidinones (IIb-g)

No.	Substituents X	Y	Molecular formula	Mp °C	Yield %	Carbon % Found	Carbon % Calcd.	Hydrogen % Found	Hydrogen % Calcd.
IIb	Cl	H	$C_{10}H_7ClN_2O_3S$	266	58	44.21	44.36	2.49	2.59
c	Cl	Cl	$C_{10}H_6Cl_2N_2O_3S$	206	62	39.31	39.35	1.88	1.97
d	Br	H	$C_{10}H_7BrN_2O_3S$	251	56	37.97	38.10	2.15	2.22
e	Br	Br	$C_{10}H_6Br_2N_2O_3S$	241	69	30.38	30.46	1.42	1.52
f	I	H	$C_{10}H_7IN_2O_3S$	234	58	33.03	33.15	1.84	1.93
g	I	I	$C_{10}H_6I_2N_2O_3S$	218	67	24.52	24.59	1.19	1.23

Table III

3,5-Disubstituted N-cyanoanthranilic acids (IIIb-g)

No.	Substituents X	Y	Molecular formula	Mp °C	Yield %	Carbon % Found	Carbon % Calcd.	Hydrogen % Found	Hydrogen % Calcd.
IIIb	Cl	H	$C_8H_5ClN_2O_2$	327	72	48.74	48.86	2.41	2.55
c	Cl	Cl	$C_8H_4Cl_2N_2O_2$	268	60	41.49	41.56	1.68	1.73
d	Br	H	$C_8H_5BrN_2O_2$	274	62	39.73	39.84	2.01	2.08
e	Br	Br	$C_8H_4Br_2N_2O_2$	261	69	29.88	30.00	1.22	1.25
f	I	H	$C_8H_5IN_2O_2$	332	58	33.19	33.33	1.69	1.74
g	I	I	$C_8H_4I_2N_2O_2$	221	64	23.14	23.19	0.88	0.97

Table IV

6,8-Disubstituted 2-mercapto-4(3H)-quinazolinones (IVb-e)

No.	Substituents X	Y	Molecular formula	Mp °C	Yield %	Carbon % Found	Carbon % Calcd.	Hydrogen % Found	Hydrogen % Calcd.
IVb	Cl	H	$C_8H_5ClN_2OS$	233	61	45.11	45.18	2.22	2.35
c	Cl	Cl	$C_8H_4Cl_2N_2OS$	240	69	38.76	38.87	1.54	1.62
d	I	H	$C_8H_5IN_2OS$	205	65	31.44	31.58	1.54	1.65
e	I	I	$C_8H_4I_2N_2OS$	156	57	23.19	22.33	0.86	0.93

Table V

6-8-Disubstituted 2-carboxymethylthio-4(3H)-quinazolinones (Va-d)

No.	Substituents X	Y	Molecular formula	Mp °C	Yield %	Carbon % Found	Carbon % Calcd.	Hydrogen % Found	Hydrogen % Calcd.
Va	Cl	H	$C_{10}H_7ClN_2O_3S$	160	50	44.28	44.36	2.49	2.59
b	Cl	Cl	$C_{10}H_6Cl_2N_3OS$	227	69	39.19	39.35	1.86	1.97
c	I	H	$C_{10}H_7IN_2O_3S$	204	54	33.01	33.15	1.84	1.93
d	I	I	$C_{10}H_6I_2N_2O_3S$	198	51	24.48	24.59	1.15	1.23

Table VI

7,9-Disubstituted 5H-thiazolo[2,3-b]quinazoline-3,5(2H)-diones (VIb-f)

No.	Substituents X	Y	Molecular formula	Mp °C	Yield %	Found (Calcd.) % C	H	Characteristics IR (nujol) peaks cm^{-1}
VIb	Cl	H	$C_{10}H_5ClN_2O_2S$	229	60	47.78 (47.53)	2.12 (1.98)	1710(s), 1670(m), 1610(w), 1530(m), 1375(s), 830(m)
c	Cl	Cl	$C_{10}H_4Cl_2N_2O_2S$	158	52	42.00 (41.81)	1.60 (1.39)	1710(s), 1690(s), 1610(w), 1580(w), 1380(s), 825(w)
d	I	H	$C_{10}H_5I\ N_2O_2S$	267	64	34.80 (34.88)	1.54 (1.45)	1710(s), 1675(m), 1560(m), 1380(s), 840(m)
e	I	I	$C_{10}H_4I_2N_2O_2S$	221	58	25.48 (25.53)	0.99 (0.85)	1760(s), 1730(s), 1610(s), 1385(s), 820(w)
f	NO_2	H	$C_{10}H_5N_3O_4S$	241	67	45.44 (45.63)	2.06 (1.90)	1700(s), 1680(s), 1670(m), 1380(s), 830(m)

Table VII

7,9-Disubstituted 2-benzylidene-5H-thiazolo[2,3-b]quinazoline-3,5-(2H)-diones (VIIa-f)

No.	Substituents X	Y	Molecular formula	Mp °C	Yield %	Found (Calcd.) % C	H	Characteristic IR (nujol) peaks cm^{-1}
VIIa	Cl	H	$C_{17}H_9ClN_2O_2S$	102	48	59.84 (59.91)	2.53 (2.64)	1710(s), 1670(m), 1630(m), 1370(s), 1180(m), 850(m)
b	Cl	Cl	$C_{17}H_8Cl_2N_2O_2S$	116	59	54.31 (54.4)	2.03 (2.13)	1720(s), 1680(s), 1620(m), 1380(s), 1160(m), 880(m)
c	Br	H	$C_{17}H_9BrN_2O_2S$	97	67	52.86 (52.99)	2.19 (2.34)	1710(s), 1670(m), 1630(m), 1370(s), 1170(m), 850(m)
d	Br	Br	$C_{17}H_8Br_2N_2O_2S$	110	64	43.76 (43.97)	1.68 (1.72)	1700(m), 1680(m), 1620(w), 1385(s), 1160(w), 875(w)
e	I	H	$C_{17}H_9I\ N_2O_2S$	112	42	47.02 (47.22)	2.01 (2.08)	1690(s), 1670(m), 1610(m), 1380(s), 1180(m), 840(m)
f	I	I	$C_{17}H_8I_2N_2O_2S$	100	69	36.42 (36.56)	1.33 (1.43)	1700(s), 1680(s), 1630(m), 1370(s), 1175(m), 830(w)

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