SYNTHESIS OF 1,3-DIARYL-1,3-DIHYDRO-4,5-DIOXO-2-THIOXOFURO[2,3-d]-PYRIMIDINES AND 1,3-DIARYL-1,3-DIHYDRO-2-THIOXO-5-(THIAZOL-4-YL)-2H,5H-PYRIMIDINE-4,6-DIONES

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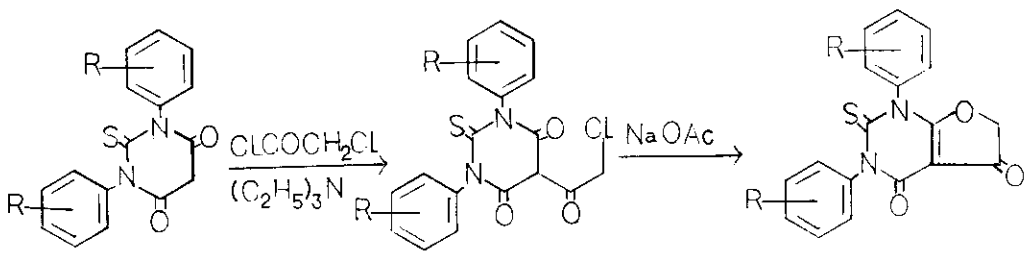
Abstract - The reaction of thiobarbituric acids with chloroacetyl chloride in presence of triethylamine afforded 5-chloroacetyl derivatives which on cyclisation with ethanolic sodium acetate gave the corresponding furo[2,3-d]pyrimidines. Further the 5-chloroacetyl derivative on reaction with ammonium dithiocarbamate and thioacetamide gave 1,3-diaryl-1,3-dihydro-2-thioxo-5-(thiazol-4-yl)-2H,5H-pyrimidine-4,6-diones.

The association of pyrimidine and thiazoles alone or in combination, with a wide range of biological activities,[1-10] is well known. Further the furopyrimidine derivatives are also associated with a number of physiological activities.[11-12] In continuation of our earlier works[11,13] on such compounds, we herein report a facile synthesis of furo[2,3-d]pyrimidine derivatives using thiobarbituric acids as starting compounds. Thus the reaction of 1,3-di-(3-methylphenyl)thiobarbituric acid (1a) with chloroacetyl chloride in presence of triethylamine in benzene at reflux temperature for 30 minutes afforded a compound (A). This compound contained chlorine and its mass spectrum showed molecular ion peaks at 400 (M^+, 49%), 402 (M+2, 16%); in its ^{1}H-nmr spectrum a singlet of two protons at δ 4.94 was observed, which was assigned to CH_2 protons of chloroacetyl moiety. On the basis of the above data the compound (A) was assigned the structure 1,3-di-(3-methylphenyl)-1,3-dihydro-2-thioxo-5-chloroacetylpyrimidine-4,6-dione (2a). Similar reaction of thiobarbiturates (1b-f) with chloroacetyl chloride gave the corresponding 5-chloroacetyl derivatives (2b-f). The chloroacetyl derivative (2a) on refluxing in ethanolic sodium acetate gave a product (B). It gave a positive DNP test and chlorine was found to be absent. The mass spectrum gave a

molecular ion peak at 364 (M^+). Its ^{1}H-nmr spectrum showed a singlet of two protons at δ 4.70 attributed to O-CH_2-C(=O)- of the furanone moiety. Thus the product (B) was assigned the structure 1,3-di-(3-methylphenyl)-1,3-dihydro-4,5-dioxo-2-thioxofuro[2,3-d]pyrimidine (3a). Similarly compounds (2b-f) on cyclization gave the corresponding dihydrofuropyrimidines (3b-f). The furo[2,3-d]pyrimidine (3a-f) could also be obtained in single step by the reaction of thiobarbituric acids (1a-f) with chloroacetyl chloride in presence of triethylamine in benzene at reflux temperature for 12 hours.

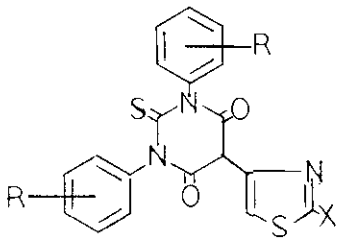


1a-f		2a-f		3a-f	
	R		R		R
(a)	CH_3(m)	(c)	CH_3(p)	(e)	Cl(p)
(b)	H	(d)	OCH_3(o)	(f)	Br(p)

Since the 5-haloacetyl compounds are useful synthons for the synthesis of thiazoles[14] (Hantzch synthesis), the intermediate chloroacetyl compounds (2a-f) have been used for the construction of thiazole ring giving rise to systems containing pyrimidine as well as thiazole rings. Thus the reaction of the chloroacetyl derivative (2a) with ammonium dithiocarbamate in ethanol afforded 1,3-di-(3-methylphenyl)-1,3-dihydro-2-thioxo-5-(2-mercaptothiazole-4-yl)-2H,5H-pyrimidine-4,6-dione (4a). Its structure was in agreement with its ^{1}H-nmr spectral data. Similarly compounds (4b-f) were prepared. Further the reaction of (2a-f) with thioacetamide gave 1,3-di-(3-methylphenyl)-1,3-dihydro-2-thioxo-5-(2-methylthiazole-4-yl)-2H,5H-pyrimidine-4,6-diones (5a-f). The structure of these compounds were in agreement with their ^{1}H-nmr spectra.

All the compounds synthesised have been screened for their in-vitro antifungal and antibacterial activities. Compounds (2e, 4b, 4e, 4f, 5c and 5f) have shown

remarkable activity against S. *aureus* and E. *coli* at 50 µg/ml and compounds (4f and 5c) have shown maximum inhibition of about 86% at 50 µg/ml against A. *niger*.



	R
(a)	CH_3(m)
(b)	H
(c)	CH_3(p)
(d)	OCH_3(o)
(e)	Cl(p)
(f)	Br(p)

4, X = SH

5, X = CH_3

EXPERIMENTAL

All melting points are uncorrected. ^{1}H-Nmr spectra were recorded on Perkin-Elmer R-32 (90 MHz) instrument using TMS as the internal standard chemical shift in δ, ppm).

1,3-Di-(3-methylphenyl)-1,3-dihydro-2-thioxo-5-chloroacetylpyrimidine (2a)

Typical procedure

A mixture of 1,3-di-(3-methylphenyl)thiobarbituric acid (1a, 0.4 g; 1 mmol), triethylamine (0.1 ml) and chloroacetyl chloride (0.11 ml; 1 mmol) in dry benzene (25 ml) is refluxed for 30 min. The solvent is removed under reduced pressure and the residue is recrystallised from chloroform - methanol to give (2a) as light yellow needles (0.40 g, yield 95%), mp 175-177°C; ^{1}H-nmr ($CDCl_3$) δ : 2.35(s, 6H, CH_3), 4.94(s, 2H, $-\overset{O}{\overset{\|}{C}}-CH_2-Cl$), 6.81-7.50(m, 8H, H-Ar). Ms m/z (%) : 400 (M^+, 49), 402 (M+2, 16). Anal. Calcd for $C_{20}H_{17}N_2O_3ClS$: C, 60.0; H, 4.2; N, 7.0. Found : C, 59.8; H, 3.8; N, 6.8. Compounds 2b to 2f were obtained in a similar way.

1,3-Di-(3-methylphenyl)-1,3-dihydro-4,5-dioxo-2-thioxofuro[2,3-d]pyrimidine (3a)

A mixture of 2a (0.40 g, 1 mmol) and sodium acetate (2 g) in ethanol (100 ml) is refluxed for 30 min and water (20 ml) is added to it. Solid separated is filtered and recrystallised from chloroform-methanol. (0.35 g, yield 97%), mp 210-212°C; ^{1}H-nmr($CDCl_3$) δ : 2.42(s, 6H, 2 x-CH_3), 4.70(s, 2H, H-6), 6.8-7.5(m, 9H, H-Ar). Ms m/z : 364 (M^+), 336 (M-28). Anal. Calcd for $C_{20}H_{16}N_2O_3S$: C, 65.99; H, 4.4; N, 7.7. Found : C, 65.4; H, 4.3; N, 7.5.

1,3-Di-(3-methylphenyl)-1,3-dihydro-2-thioxo-5-(2-mercaptothiazol-4-yl)-2H-5H-pyrimidine-4,6-dione(4a)

A mixture of 2a (0.40 g, 1 mmol) and ammonium dithiocarbamate (0.11 g, 1 mmol) in absolute ethanol (50 ml) is refluxed for 4 h. Solvent is distilled off and the residue is treated with crushed ice, filtered, washed with water and recrystallised from chloroform-methanol; (0.31 g, yield 72%), mp 180-182°C. ^{1}H-Nmr ($CDCl_3$) δ : 2.45(s, 6H, 2 x-CH_3), 5.30(s, 1H, exchanged with D_2O, -SH), 7.35-7.55(m, 10H, H-Ar, 5-H, 5'-H). Anal. Calcd for $C_{21}H_{17}N_3O_2S_3$: C, 57.4; H, 3.8; N, 9.5. Found : C, 57.2; H, 3.7; N, 9.6.

1,3-Di-(3-methylphenyl)-1,3-dihydro-2-thioxo-5-(2-methylthiazol-4-yl)-2H,5H-pyrimidine-4,6-dione (5a)

A mixture of 2a (0.40 g, 1 mmol) and thioacetamide (0.09 g, 1 mmol) in absolute ethanol (50 ml) is refluxed for 4 h, solvent is distilled off and the residue is treated with crushed ice, filtered, washed with water and recrystallised from chloroform - methanol; (0.27 g, yield 65%), mp 260-261°C. ^{1}H-Nmr($CDCl_3$) δ : 2.50(s, 6H, 2 x-CH_3), 2.90(s, 3H, 2'-CH_3), 7.40-7.90(m, 9H, H-Ar, 5-H), 8.50(s, 1H, 5'-H). Anal. Calcd for $C_{22}H_{19}N_3O_2S_2$: C, 62.7; H, 4.5; N, 10.0. Found : C, 62.6; H, 4.4; N, 9.9.

Compound No.	Reaction time (min)	Yeald (%)	mp(°C)	Molecular Formula	Elemental Analysis % Calcd/Found C	H	N	^{1}H-Nmr($CDCl_3$) δ (ppm), J in Hz
2b	30	80.2	220-221	$C_{18}H_{12}N_2O_3ClS$	58.0 57.8	3.5 3.4	7.5 7.2	4.9(s, 2H, $-\overset{O}{\overset{\|}{C}}-CH_2Cl$); 6.8-7.3(m, 11H, H_{arom} and 5-H).
2c	30	82.7	161-163	$C_{20}H_{16}N_2O_3ClS$	58.0 57.8	3.5 3.4	7.5 7.2	2.35(s, 6H, 2x CH_3); 4.85(s, 2H, CH_2); 7.3(m, 9H, H_{arom} and 5-H).
2d	30	75.5	230-231	$C_{20}H_{16}N_2O_3ClS$	55.5 55.3	3.9 3.5	6.4 6.1	3.8(m, 6H, 2 x OCH_3); 4.9(s, 2H, CH_2); 7.2(m, 9H, H_{arom} and 5-H).
2e	30	80.9	280 (decomp.)	$C_{18}H_{10}N_2O_3Cl\ S$	49.0 48.7	2.5 2.2	6.3 6.1	4.9(s, 2H, CH_2); 7.2(m, 9H, H_{arom} and 5-H).
2f	30	75.2	280-281(decomp.)	$C_{18}H_{10}N_2O_3Br_2ClS$	40.7 40.6	2.0 1.8	5.2 5.1	4.9(s, 2H, CH_2); 7.3(m, 9H, H_{arom} and 5-H).
3b	30	72.2	281-283	$C_{18}H_{12}N_2O_3S$	65.9 65.5	4.4 4.3	7.7 7.4	4.8(s, 2H, CH_2); 7.3(m, 10H, H_{arom}).
3c	30	72.5	220-222	$C_{20}H_{16}N_2O_3S$	60.6 60.5	4.0 3.8	7.0 6.8	2.35(s, 6H, 2 x CH_3); 4.8(s, 2H, CH_2); 7.2(m, 8H, H_{arom}).
3d	30	80.0	245-248	$C_{20}H_{16}N_2O_5S$	60.6 60.3	4.1 3.8	7.0 6.7	3.9(m, 6H, 2 x OCH_3); 4.7(s, 2H, CH_2); 7.2(m, 8H, H_{arom}).
3e	30	70.5	284-285(decomp.)	$C_{18}H_{10}N_2O_3Cl_2S$	53.3 53.1	2.4 2.1	6.9 6.7	4.7(s, 2H, CH_2); 6.9-7.3(m, 8H, H_{arom}).

3f	30	71.2	290-291 (decomp.)	$C_{18}H_{10}N_2O_3Br_2S$	43.7 43.4	2.0 2.0	5.6 5.6	4.7(s, 2H, CH_2); 6.9 and 7.4 (each d, J = 9.5 Hz, 8H, H-Ar).
4b	3 h	80.4	180-181 (decomp.)	$C_{19}H_{13}N_3O_2S_3$	55.4 53.3	3.1 3.0	10.2 10.3	5.4(s, 1H, exchanged with D_2O, -SH); 7.5-7.8(m, 12H, H_{arom}, 5-H and 5'-H of thiazole).
4c	3 h	75.3	210-212 (decomp.)	$C_{21}H_{17}N_3O_2S$	57.4 57.3	3.8 3.9	9.5 9.6	2.45(s, 6H, 2 x CH_3), 5.1(s, 1H, exchanged with D_2O, -SH); 7.2-7.6(m, 10H, H_{arom}, 5-H and 5'-H of thiazole).
4d	3 h	55.2	180-182	$C_{21}H_{17}N_3O_4S$	53.5 53.4	3.6 3.5	8.9 8.9	3.9(s, 6H, 2 x OCH_3); 5.2(s, 1H, exchanged with D_2O, -SH), 7.2-7.8(m, 10H, H_{arom}, 5-H and 5'-H of thiazole).
4e	3 h	50.3	183-185 (decomp.)	$C_{19}H_{11}N_3O_2Cl_2S_3$	47.5 47.6	2.3 2.3	8.8 8.7	5.4(s, 1H, exchanged with D_2O, -SH), 7.4-7.9(m, 10H, H_{arom}, 5-H and 5'-H of thiazole).
4f	3 h	70.0	195-197	$C_{19}H_{11}N_2O_2Br_2S_3$	43.6 43.6	2.1 2.0	8.0 7.9	5.32(s, 1H, exchanged with D_2O, -SH); 7.3-7.9(m, 10H, H_{arom}, 5-H, and 5'-H of thiazole).
5b[(a)]	4 h	70	300 (decomp.)	$C_{20}H_{15}N_3O_2S_2$	61.0 61.1	3.8 3.6	10.7 10.6	3.1(s, 3H, 2' CH_3); 7.4-7.8 (m, 11H, H_{arom} and 5-H); 8.6(s, 1H, 5'-H of thiazole).

5c	4 h	65	252-254	$C_{22}H_{19}N_3O_2S_2$	62.7 62.5	4.5 4.6	10.0 10.1	2.3(s, 6H, 2 x CH_3); 2.7(s, 3H, 2' CH_3); 7.35(d, J=9 Hz, 4H, 2 x 2"-H, 2 x 6"-H, 2 x 5"-H); 8.3(s, 1H, 5'-H of thiazole).
5d	4 h	70	300 (decomp.)	$C_{22}H_{19}N_3O_4S_2$	58.3 58.2	4.2 4.0	9.2 9.1	2.8(s, 3H, 2' CH_3); 3.95(s, 6H, 2 x OCH_3); 7.2-7.8(m, 9H, H_{arom} and 5-H); 8.5(s, 1H, 5'-H of thiazole).
5e	4 h	60	300 (decomp.)	$C_{20}H_{13}N_3O_2Cl_2S_2$	51.9 51.8	2.8 2.8	10.1 10.0	2.95(s, 3H, 2' CH_3); 7.55(d, J=9 Hz, 4H, 2 x 3"-H and 2 x 5"-H), 7.60(s, 1H, 5-H); 7.9(d, J=9 Hz, 4H, 2 x 2"-H and 2 x 6"-H), 8.5(s, 1H, 5'-H of thiazole).
5f	4 h	67	250-251(decomp.)	$C_{20}H_{13}N_3O_2Br_2S_2$	43.7 43.4	2.0 2.0	5.6 5.3	3.05(s, 3H, 2'CH_3); 7.3(d, J=9 Hz, 4H, 2 x 3"-H and 2 x 5"-H); 7.5(s, 1H, 5-H); 7.8(d, J=9 Hz, 4H, 2 x 2"-H and 2 x 6"-H); 8.55(s, 1H, 5'-H of thiazole).

[a] ^{1}H-nmr recorded in ($CDCl_3$+TFA/TMS).

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