SYNTHESIS AND REACTIONS OF 6(4)-(P-BENZYLPHENYL)-4(6)-PHENYLPYRIMIDINE-2(1*H*) THIONE

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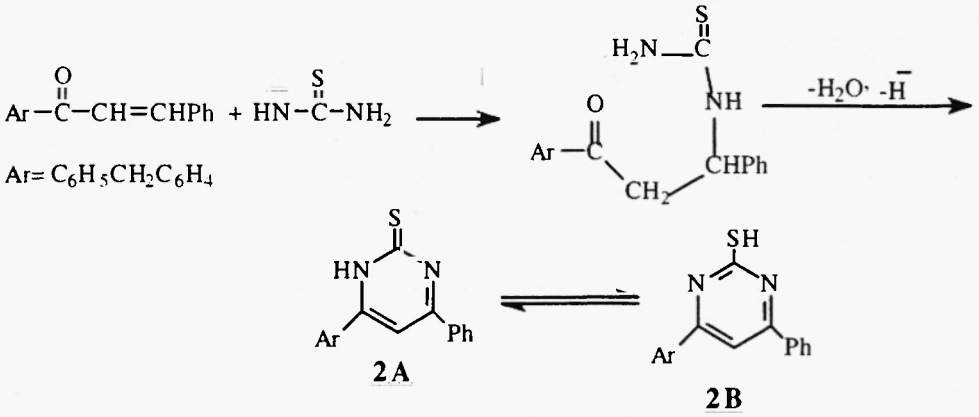
Abstract: 1,3-Diaryl-2-Propen-1-one **1** reacted with thiourea in the presence of sodium ethoxide to furnish 4,6-diarylpyrimidine-2(1*H*) thione **2**. The behaviour of **2** towards nitrogen nucleophiles, and carbon electrophiles under Michael reaction conditions have been investigated. The oxidation of the thione **2** gave the corresponding disulphide derivative **12.** Acylation of **2** yielded the corresponding S-acetyl-**13** and N-benzoyl-**14** derivatives, respectively .

New communications appeared in the last decade describing the synthesis of pyrimidines(1) and their hydrazine derivatives(2) which show important diverse biological activities . In continuation of our studies on the chemistry of diazines(3-5), we have undertaken the synthesis of some interesting heterocyclic systems hitherto unreported derived from the title compound.

The target 4(6)-phenyl-6(4)-(p-benzylphenyl) pyrimidine-2(1*H*) thione **2** was produced from the interaction of p-benzyl-β-arylacrylophenone**1** and thiourea in presence of sodium ethoxide in boiling ethanol. The reaction appears to proceed *Via* Michael addition of the anion derived from thiourea, to p-benzyl-β-arylacrylophenone followed by cyclization of the intermediate **2**. The structure of the thione **2** was established by spectroscopic evidence. The i.r. data indicate that this compound exist in **2A** thiolactam ⇌ thiol **2B** dynamic equilibrium, Scheme (I) .



Scheme (I)

In the present study, hydrazinolysis of 6(4)-(p-benzylphenyl)-4-(6) phenylpyrimidine-2(1*H*)thione **2** was investigated. Thus, when compound **2** was allowed to react with hydrazine derivatives namely, hydrazine hydrate, phenylhydra-

zine and/or 6(4)-(p-benzylphenyl)-2-hydrazino-4(6)-phenylpyrimidine in n-butanol afforded the corresponding 2-hydrazino-,2-(2`-phenylhydrazino)-, and 2-(2`-pyrimidinylhydrazino) pyrimidine derivatives **3a-c** , respectively, Scheme (II) .

On the other hand, subjecting compound **2** to the action of semicarbazide hydrochloride in refluxing acetic acid furnished the corresponding 1-(2-pyrimidinyl)semicarbazide **4**. Compound **4** was also obtained by an independent synthesis on mixing aqueous solutions of potassium cyanate and of the hydrazine hydrochloride(6) .

The author has now found that the reaction of the thione **2** with a weak nitrogen nucleophile such as anthranilic acid by fusion afforded the pyrimidoquinazolinone **5**. However, with a secondary amine such as piperidine in boiling n-butanol furnished 6(4)-(p-benzylphenyl)-2-piperidinyl-4(6)-phenylpyrimidine **6**.

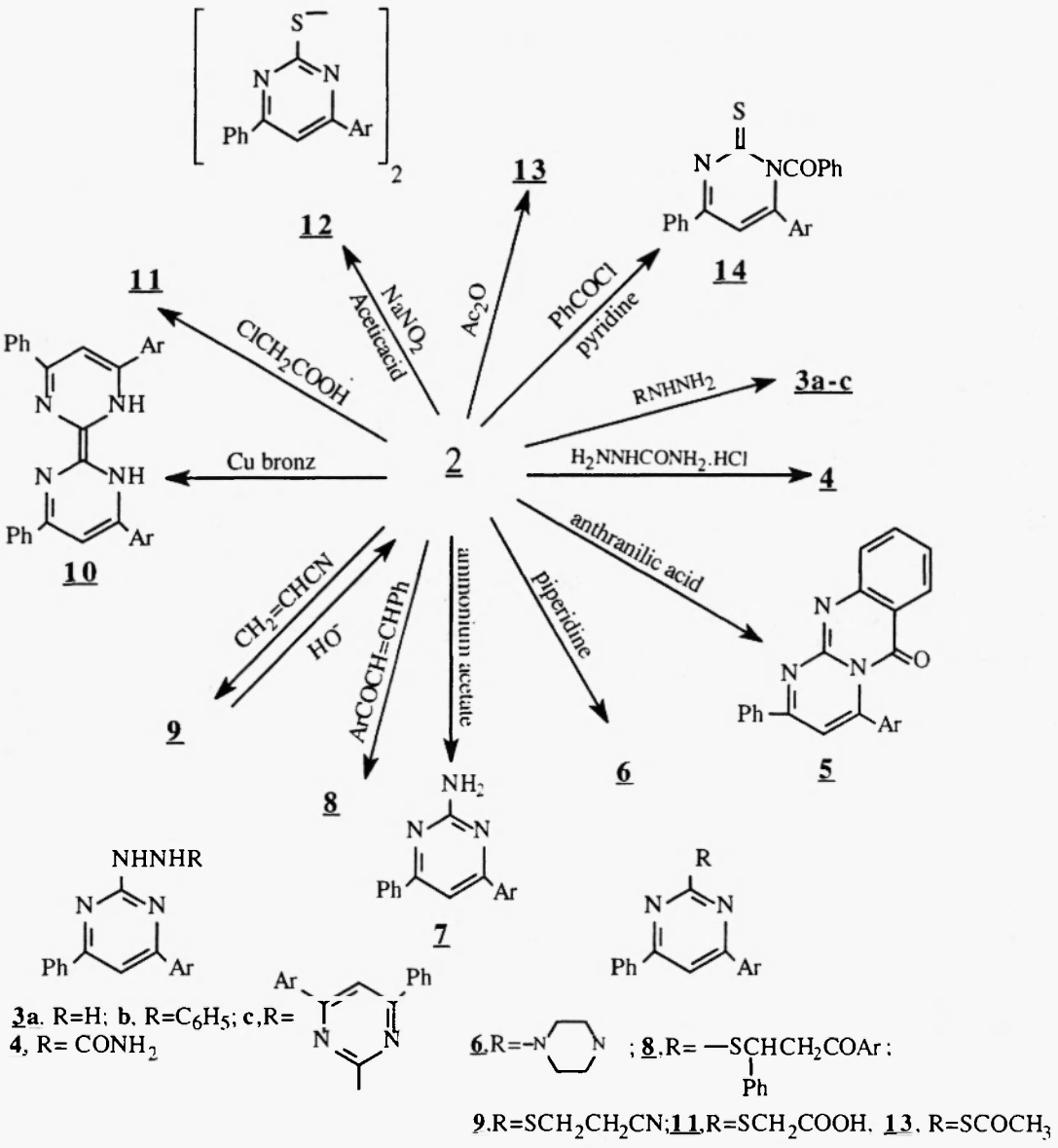
The author has also now attempted to convert compound **2** into the 2-aminopyrimidine derivative **7**. This conversion has been successfully accomplished by refluxing in acetic acid containing ammonium acetate. The structure of **7** was established chemically by independent synthesis *Via* the reaction of chalcone **1** with guanidine hydrochloride in the presence of an alcoholic solution of potassium hydroxide(7) .

The behaviour of **2** as sulphur nucleophile towards some activated unsaturated system under Michael conditions was also studied. Thus , the base catalysed condensation of compound **2** with p-benzyl-β-phenylacrylophenone in boiling benzene in the presence of piperidine as catalyst yielded the Michael-type adduct, viz; 2-(α-aroyl-β-phenyl)ethylmercapto-4,6-diarylpyrimidine **8**. However, treatment of **2** with acrylonitrile in pyridine gave Michael-type adduct, viz; 2-S-cyanoethyl-4,6-diarylpyrimidine **9** . Alkaline hydrolysis of the S-cyanoethyl derivative **9** not led to the formation of the corresponding acid but resulted in cleavage of the cynoethyl group to give **2** .

The action of copper bronz in refluxing xylene on **2** was now found to yield the bis compound **10**. On the other hand, S-alkylation of compound **2** with aqueous chloroacetic acid yielded the corresponding 2-carboxymethylmercapto-4,6-diarylpyrimidine **11**.

In agreement with the reported results(8), oxidation of the thione **2** with sodium hydrogen sulphate and sodium nitrite gave the corresponding 2,2`-bis(4,6-diarylpyrimidinyl)disulphide **12**.

Furthermore, 4,6-diarylpyrimidine-2(1*H*)thione **2** reacted with some acylating agents in different reaction conditions to give S-acyl-and N-acyl derivatives. Thus, S-acetylpyrimidine derivative **13** was formed when **2** was acylated with acetic anhydride but benzoylation of **2** furnished N-benzoylpyrimidine-2-thione derivative **14** .



Scheme (II)

Biological Screening

List of all the synthesised compounds has been forwarded to American Cyanamide, USA through Cyanamide India Limited. Only compounds **4** , **10** and **12** have been chosen by ARD princeton are under testing.

Experimental

All melting points are uncorrected. IR spectra were recorded (KBr) with a Pye Unicam SP_3-200 spectrophotometer. ^1H NMR were measured in DMSO on a Joel Fx

90 Q9 MHz (Fourier transform NMR spectrometer) using TMS as internal reference (chemical shifts are expressed as δ,ppm.) . Mass spectrum was recorded on HP MODEI : Ms 5988.

6(4)(p-Benzylphenyl)-4(6)-phenylpyrimidine-2(1H)thione **2** .

1,3-Diaryl-2-propen-1-one **1** (0.01 mole) and thiourea (0.01 mole) were added successively to a solution of sodium ethoxide (0.04 mole) in absolute ethanol (100ml) . The reaction mixture was heated under reflux for 8hr, the solvent was evapourated and the residue was dissolved in water (150ml) . The alkaline solution was acidified with acetic acid (20 ml) and the precipitated solid was filtered, dired and recrystallized from ethanol, yield 70%, m.p. 170 - 72° (Found: C, 77.7; H, 5.4; N, 8.2. $C_{23}H_{18}N_2S$ requires C,77.9 ; H, 5.0 ; N, 7.9%); IR: 3250 (NH) , 2100(SH) , 1560 (C=N), 1250cm^{-1} (C=S) , ^{1}H NMR : δ 2.4 (s, 2H, 4`-CH_2-Ar) , 6.9 - 7.8 (m, 15H , Ar-H) , 8.5 (s, 1H, NH, exchangeable with deuterium oxide) . MS, m/z (relative abundance %) $M^{+\cdot}$ (unstable),263 (27.1), 205 (2.8) , 204 (5.9) , 103 (12.1), 102 (12.6) , 91 (3.3),77 (45.2),76 (10.5), 65 (2.0) , 58 (1.0), 59 (3.6).

Condensation of the thione **2** *with hydrazines*

A mixture of **2** (0.01mole) and hydrazine derivatives namely, hydrazine hydrate, phenylhydrazine and/or 6(4)-(p-benzylphenyl)-2-hydrazino-4(6)-phenylpyrimidine (0.01mole) in n-butanol (40ml) was heated under reflux for 8hr, the solid separated after cooling was recrystallized from the proper solvent to furnish **3a-c** .

6(4)-(p-Benzylphenyl)-2-hydrazino-4(6)-phenylpyrimidine **3a**; yield 67% , m.p. 218-20 (from ethanol) (Found : C, 78.5; H,5.8; N, 15.5. $C_{23}H_{20}N_4$ requires C, 78.4; H, 5.6; N,15.9%) ; IR : 3300 - 3170($NHNH_2$), 1550cm^{-1} (C = N).

6(4)-(p-Benzylphenyl)-2-(2`-phenylhydrazino) -4(6)-phenylpyrimidine **3b**: yield 64% , m.p. 188-90°(from n-butanol) (Found : C , 81.5 ; H, 5.7 ; N,13.2 . $C_{29}H_{24}N_4$ requires C, 81.3 ; H, 5.6; N, 13.0%) ; IR : 3220 (NH), 1520 cm^{-1} (C= N) .

6(4)-(p-Benzylphenyl)-2-[2`-(4.6-diarylpyrimidinyl)hydrazino]-4(6)-phenylpyri midine **3c**; yield 63%, m.p. 125-27° (from ethanol) (Found : C, 82.3; H, 5.4; N, 12.8. $C_{46}H_{36}N_6$ requires C, 82.1; H,5.3;N, 12.5%); IR : 3270 (NH), 1560 cm^{-1} (C=N) .

1-*(2-Pyrimidinyl) semicarbazide* **4**

A solution of **2** (0.01 mole), semicarbazide hydrochloride (0.01 mole) and sodium acetate (0.02 mole) in acetic acid (25 ml) was heated under reflux for 4 hr. after cooling the resulting pale yellow precipitate was collected and recrystallized

from n-butanol to give pale yellow crystals; yield 58%; m.p. 200-20°; the same compound is readily obtained in 54% when 2-hydrazinopyrimidine **3a**, dissolved in sufficient dilute hydrochloric acid to form the monohydrochloride, is treated with an equivalent quantity of potassium cyanate in aqueous solution and the mixture is warmed on the water bath for Ihr, on cooling, the semicarbazide derivative **4** was separated; (Found : C,72.7; H,5.6; N, 17.9. $C_{24}H_{21}N_5O$ requires C,72.9; H,5.3; N,17.7%); IR : 3250-3160 (NH and NH_2), 1680 (amidic CO), 1540 cm^{-1} (C=N); ^1H NMR : δ 2.3 (s 2H, 4`-CH_2-Ar), 6.4(br s, 2H, NH_2 , exchangeable with deuterium oxide); 6.9-7.7 (m, 15H, Ar-H), 8.5 and 9.3 (2 x s, 2H, 2 x NH, exchangeable with deuterium oxide) .

Pyrimidoquinazolinone **5**

A mixture of pyrimidine-2(1 *H*) thione **2** (0.01 mole) and anthranilic acid (0.01 mole) was heated on an oil bath at 180°C for 3 hr, after cooling water was added and the solid obtained, filtered off and recrystallized from ethanol to yield white crystals; yield 59%, m.p. 113-115° (Found : C, 82.3; H,4.9; N,9.8. $C_{30}H_{21}N_{30}$ requires C, 82.0; H, 4.7, N, 9.5%); IR : 1680 (amidic CO), 1615 cm^{-1} (C=N); ^1H NMR : δ 2.3 (s, 2H, 4`-CH_2-Ar), 6.8-7.9 (m, 19 H, Ar-H) .

6-(4) (P-Benzylphenyl)-2-piperidinyl-4(6)-phenylpyrimidine **6**

A mixture of the thione **2** (0.1 mole) and a secondary amine such as piperidine (0.01 mole) in n-butanol (30 ml) was heated under reflux for 6 hr, the product obtained after concentration and cooling was filtered and recrystallized from ethanol to afford **6** ; yield 54%, m.p. 162° (Found :C, 79.8; H, 6.4; N, 13.6. $C_{27}H_{25}N_4$ requires C, 80.0; H, 6.2; N, 13.8%); IR : 2990 (aliphatic CH), 1620 cm^{-1} (C=N) .

2- *Amino-6(4)-(P-benzylphenyl) -4(6)-phenylpyrimidine* **7**

A mixture of the thione **2** (0.01 mole) and ammonium acetate (0.02 mole) in acetic acid (25 ml) was heated under reflux for 4 hr, the precipitate obtained upon cooling was collected and recrystallized from acetic acid to give white crystals; yield 64%, m.p. 130-32°, an authentic sample of **7** was prepared as described in literature(7), m.p. and m.m.p. determination showed no depression; yield 60% (Found : C,81.5; H, 5.8; N,12.7 . $C_{23}H_{19}N_3$ requires C, 81.8; H, 5.6; N, 12.4%); IR : 3300-3200 (NH_2), 1600 cm^{-1} (C=N) .

2-(α-Aroyl-β-phenyl)ethylmercapto-4,6-diarylpyrimidine **8**

A solution of **2** (0.01 mole) and p-benzyl-β-phenylacrylophenone (0.01 mole) in benzene (40 ml) and (4 drops) of piperidine was refluxed for 3 hr, the reaction

mixture was concentrated, the solid that separated after cooling was recrystallized from ethanol to furnish pale yellow crystals; yield 59%, m.p. > 360° (Found : C, 82.9; H, 5.5; N, 4.4 . $C_{45}H_{36}N_2OS$ requires C, 82.8; H, 5.5; N, 4.2%); IR : 1685 (Ketonic CO), 1630 cm^{-1} (C= N); ^1H NMR : δ 2.3 and 2.5 (2 x s, 4H, 2x4`-CH_2-Ar), 3.2 (m, 2H, non-equivalent -CH_2CO), 4.8 (m, 1H, methine), 6.8-7.8 (m, 29 H, Ar-H) .

2- S-Cyanoethyl-4,6-diarylpyrimidine **9**

It was prepared according the published procedure(9). The crude solid, gave, on recrystallzation from ethanol white crystals; yield 67%, m.p. 199-202° (Found : C, 76.7; H, 5.5; N, 10.6. $C_{26}H_{21}N_3S$ requires C, 76.6; H, 5.1; N, 10.3%); IR : 2960 (aliphatic CH), 2180 (C≡ N), 1580 cm^{-1} (C=N) .

Hydrolysis of **9**

A solution of **9** (1gm) in ethanol (30 ml) was treated with sodium hydroxide solution (1 gm in 5 ml water) and then refluxed for 3 hr . Subsequently, the solution was a cidified with dilute hydrochloric acid . The crystalline product obtained to be **2** by melting point and mixed melting point determination .

Action of Copper Bronz on 4,6-diarylpyrimidine-2(1 H)thione **2** *: Formation of* **10**

A mixture of **2** (0.01 mole) and (2.0 gm) of copper bronz in 100 ml dry xylene was heated under reflux for 10 hr. The reaction mixture was filtered upon hot to get red of excess copper bronz, and the filterate was concentrated, the product that separated was recrystallized from xylene to give yellow needles; yield 55%, m.p. 275-77° (Found : C, 85.5; H, 5.6; N, 8.9 . $C_{46}H_{36}N_4$ requires C, 85.7; H,5.5; N, 8.6%); IR : 3250 (NH), 1630 cm^{-1} (C=N) .

2- Carboxymethylmercapto-4,6-diarylpyrimidine **11**

Compound **2** (0.01 mole) was dissolved in a solution of sodium carbonate (0.01 mole), the chloroacetic acid (0.01 mole) as a sodium salt was added portionwise while stirring, the reaction mixture warmed for 30 minutes, the crystalline solid that separated was recrystallized from toluene to give **11** as white crystals; yield 62%, m.p. 143-45° (Found : C, 72.6; H,4.5; N,6.4 . $C_{25}H_{20}N_2O_2S$ requires C, 72.8; H, 4.8; N,6.7%); IR: 3480 (OH), 1715 (carboxylic CO), 1600 cm^{-1} (C=N); ^1H NMR : δ 2.2 (s, 2H, 4`-CH_2 -Ar), 4.5 (s, 2H, CH_2CO), 6.8-7.9 (m, 15H, Ar-H), 10.6 (s, 1 H, OH) .

2,2`-bis (4,6-Diarylpyrimidinyl)disulphide **12**

It was prepared by the method of Baddar, et al.(8); Recrystallization from pet. ether (60-80°)-benzene gave orange crystals; yield 68%, m.p. 100-01° (Found : C,

78.2; H,4.9; N,8.2 . $C_{46}H_{34}N_4S_2$ requires C, 78.1; H,4.8; N,7.9%); IR :1570, 1525 cm^{-1} (pyrimidine ring) .

2-Acetylmercapto-4,6-diarylpyrimidine **13**

The thione **2** (1.0 gm) was heated with acetic anhydride (8 ml) on a boiling water-bath for 2 hr. The product, which preciptated on addition of cold 50% ethanol (15 ml), was crystallized from ethanol to give **13** as white needles; yield 61%, m.p. 155-57° (Found : C,75.3; H,5.4; N,7.4 . $C_{25}H_{20}N_2OS$ requires C,75.7; H,5.0; N,7.0%); IR : 1720-1715 ($SCOCH_3$),1575 and 1515 cm^{-1}(pyrimidine system); ^1H NMR : δ 2.1 (s, 2H,4`-CH_2-Ar), 2.6(s, 3H, $SCOCH_3$),6.8-7.9 (m; 15H, Ar-H) .

3-(N-Benzoyl)-4,6-diarylpyrimidine-2-thione **14**

A mixture of **2** (0.01 mole) and benzoyl chloride (0.01 mole) in pyridine (40 ml) was refluxed for 3 hr. Allowed to cool, poured on water, the solide obtained was filtered off and recrystallized from benzene to give pale yellow crystals; yield 57%, m.p. 280-82° (Found : C,78.3; H,4.5; N, 6.4 . $C_{30}H_{22}N_2OS$ requires C, 78.6; H,4.8; N,6.1%); IR : 1665-1650 (NCOPh), 1410 cm^{-1} (C=S) .

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