Synthesis of (4*S**,5*S**)-diphenyl-1,3,4,5-tetrahydro-2*H*-[1]benzopyrano [4,3-*d*]pyrimidine-2-thiones by base-catalysed cyclocondensation of (*E*)-3-benzylideneflavanones with thiourea, and determination of their monoacetylation site

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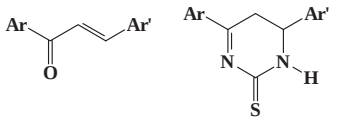
Base-catalysed cyclocondensation of (*E*)-3-benzylideneflavanones with thiourea has been found to be highly stereoselective, producing (4*S**,5*S**)-diphenyl-1,3,4,5-tetrahydro-2*H*-[1]benzopyrano[4,3-*d*]pyrimidine-2-thiones in high yield, the structure of one of which has been determined by X-ray crystallography. Just like 4,6-diaryl-3,4-dihydropyrimidine-2(1*H*)-thiones, the said products also undergo monoacetylation on treatment with Ac_2O. The site of acetylation in both of these classes of compound are established by detailed NMR spectral studies.

Keywords: flavanones, thiourea, fused [1]benzopyrans, fused pyrimidinethiones

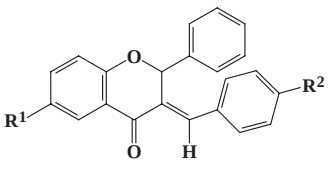
Among the available reports on base-catalysed cyclocondensation of chalcones (**1**) with thiourea, two[1,2] state that the products are 4,6-diaryl-5,6-dihydropyrimidine-2(1*H*)-thiones (**2**), while a third[3] claims that they are 4,6-diaryl-3,4-dihydropyrimidine-2(1*H*)-thiones (**3**). The spectral data of the products, however, gave convincing evidence that the last structure is actually correct.[3] (*E*)-3-Benzylideneflavanones (**4**), the synthesis and reactions of which we have recently studied[4-8], possess a part structure which is similar to the chalcones (**1**). So we endeavoured to synthesise a new type of fused heterocycle possessing a flavonoid and a pyrimidine moiety, both endowed with interesting physiological activities[9-12], by cyclocondensation of **4** with thiourea. Since the target system contains two stereogenic centres, our interest was also to determine the configuration of the major / only product of the reaction (which may be **5** or its diastereomer). Furthermore, on acetylation **3** gives a monoacetyl derivative. Without giving any concrete chemical or spectral evidence, Al-Hajjar *et al.*[3] assigned the structure **6** to this derivative. So, in connection with synthesis of the said new heterocycles, we intended to observe the outcome of their acetylation reaction and to ascertain the acetylation site(s). The results of these studies are presented in this paper.

Results and discussion

When each of the (*E*)-3-benzylideneflavanones **4a–d** was treated with thiourea in methanol in presence of sodium methoxide, a single product was obtained in very good yield. Analytical and spectral data of the products from **4a–d** (see Experimental) definitely showed that one diastereomeric *dl* pair of the desired cyclocondensation product was formed in all cases. The reaction was thus highly stereoselective. All the products formed good quality crystals from methanol. An X-ray crystallographic analysis of the product from **4a** established its stereostructure as **5a**. The other compounds were therefore



1 **2** **3**



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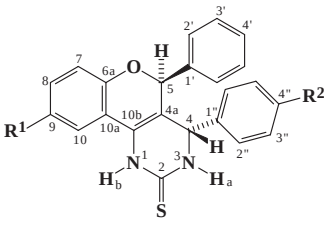
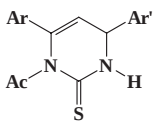


5

a: $R^1 = R^2 = H$; **b**: $R^1 = H$, $R^2 = OMe$

d: $R^1 = H$, $R^2 = Cl$; **d**: $R^1 = Me$, $R^2 = H$



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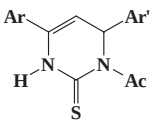


7

* Correspondence.

assigned as **5b–d**. A view of the solid state conformation of **5a** is given in Fig. 1. It is expected that the formation of **5** from **4** follows the same mechanistic path(s) as that of **3** from **1**.[3]

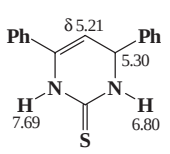
In accordance to our expectation, **5a** formed a monoacetyl derivative on treatment with Ac_2O (100 °C, 1 h). The structure of this monoacetyl derivative (a viscous liquid) was established to be **8** by first determining the site of acetylation of 4,6-diphenyl-3,4-dihydropyrimidine-2(1*H*)-thione (**3a**, **3** with Ar = Ar' = Ph) by detailed NMR spectral studies and then by appropriate comparison as discussed below.

Between the two possible structures **6** and **7** for the monoacetyl derivatives of **3**, the former was chosen by Al-Hajjar *et al.*[3] on the basis that there was no substituent effect on the ^1H and ^{13}C NMR chemical shifts of the $COCH_3$ moiety of these compounds. We felt that the rationale for this choice was not firmly based. So we prepared the monoacetyl derivative of **3a** and studied its routine ^1H and ^{13}C NMR spectra as well as the COSY (^1H–^{13}C, one bond) and homodecoupled spectra. The most significant observation in the COSY spectrum was the correlation: δ 5.91 (^1H)– δ 105.54 (^{13}C) and δ 6.32 (^1H)– δ 54.20 (^{13}C). So the broad doublet at δ 5.91 can be assigned to the olefinic proton. Irradiation at δ 8.94 (the position of the N–H signal) made the δ 5.91 doublet sharper and at the same time more intense than the δ 6.32 doublet. This clearly indicated that the N–H and the olefinic proton interact in an allylic type of coupling which is possible only with the structure **7**.

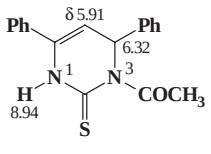
Al-Hajjar *et al.*[3] reported the appearance of H-4 and H-5 of **3a** at δ 5.20 as a multiplet. In the 300 MHz ^1H NMR spectrum, however, these two protons appeared as two separate multiplets at δ 5.21 and 5.30 which could be assigned by by observing the changes on irradiating at the positions of the N-H absorptions. Thus, irradiation at δ 6.80 changed the δ 5.30 signal to a doublet, and irradiation at δ 7.69 decreased the multiplicity of the δ 5.21 signal. So the δ 5.30 signal was due to H-4 and the δ 5.21 signal to H-5. The downfield shift of H-4 of **3a** due to acetylation was therefore 1.02 ppm. This Δδ value was utilised to determine the site of acetylation of **5a**.

In $CDCl_3$ **5a** showed signals for four nonaromatic protons at δ 4.71 (br.s), 5.41 (s), 6.76 (br.s, N–H) and 7.94 (br.s, N–H). Decoupling experiments showed that among these signals the first and the third were due to the >CH-NH- moiety of the molecule. It is evident from the positions of the proton signals of the monoacetyl derivative of **5a** in $CDCl_3$ that on acetylation the δ 4.71 signal shifted to either δ 5.78 or 5.87 (the assignments for H-4 and H-5 could not be made with certainty). This corresponds to a downfield shift of 1.07 or 1.16 ppm for H-4, confirming the structure **8** for the monoacetyl derivative. The alternative structure **9** would not be expected to show downfield shift of such a magnitude.

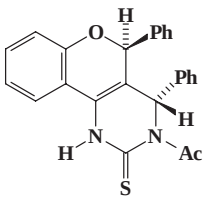
So both **3** and **5** undergo acetylation at the thioamido nitrogen, not at the enethioamido nitrogen.



3a



7a



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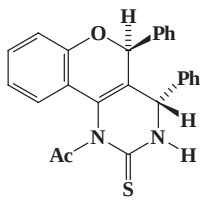

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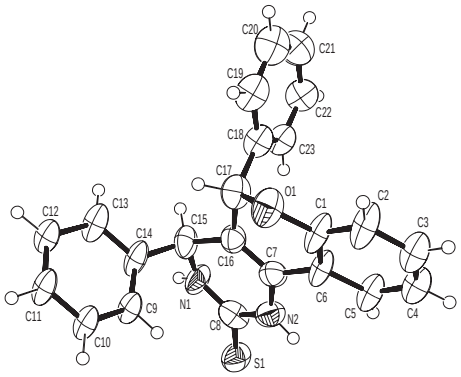

Fig. 1 ORTEP view of compound **5a**.

Experimental

Melting points were recorded on a Köfler block. IR spectra were recorded in $CHCl_3$ or KBr on a Perkin-Elmer 297 spectrophotometer. ^1H NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 on Bruker DPX-300 (300 MHz), Bruker AM-300L (300.13 MHz) and Varian Unity Plus (U^+) 400 (400 MHz) spectrometers. ^{13}C NMR spectra were recorded in DMSO-d_6 or $CDCl_3$ using the above instruments at 75 or 100 MHz. EI mass spectra were recorded on JEOL JMS D-300 and Shimadzu QP-1000 spectrometers.

Analytical samples were routinely dried *in vacuo* at room temperature. Column and thin layer chromatographies were carried out using silica gel (100–200 mesh, Tara Chemicals, Calcutta) and silica gel G (Qualigens Fine Chemicals, Mumbai), respectively. Petrol had the boiling point range 60–80 °C.

4,5-Diaryl-1,3,4,5-tetrahydro-2H-[1]benzopyrano-[4,3-d]pyrimidine-2-thiones by condensation of (E)-3-benzylideneflavanones with thiourea; general procedure

A mixture of thiourea (1 mmol) and sodium methoxide [prepared from sodium (230 mg) and dry methanol (10 ml)] in dry methanol (60 ml) was stirred for 15 minutes. To this mixture the benzylideneflavanone (1 mmol) was added in three equal portions over 10 minutes. The resulting mixture was stirred at room temperature for 6 h and then poured onto ice and the solid thus obtained was filtered off, washed with water, dried, and then crystallised from methanol. The yields, melting points and analytical and spectral data of the compounds **5a–d** were as follows.

4,5-Diphenyl compound **5a:** yield 92 %, m.p. 194–195 °C. IR: ν_{max} (KBr): 3240–3180 (N-H), 1175 (C=S) cm^{-1}. ^1H NMR ($CDCl_3$): δ 4.71 (1H, s, H-4), 5.41 (1H, s, H-5), 6.76 (1H, s, exchangeable with D_2O, N–H_a), 6.76 (1H, d, *J* = 8.4 Hz, H-7), 7.03 (1H, t, *J* = 8.4 Hz, H-9), 7.19–7.39 (12H, m, Ar-H) and 7.94 (1H, s, exchangeable with D_2O, N-H_b). ^1H NMR (DMSO-d_6): δ 4.51 (1H, s, H-4), 5.52 (1H, s, H-5), 6.72 (1H, br.d, *J* = 8.1 Hz, H-7), 6.95 (1H, br.t, *J* = 7.5 Hz, H-9), 7.18 (1H, br.t, *J* = 7.8 Hz, H-8), 7.29-7.46 (10H, m, Ar-H), 7.85 (1H, br.d, *J* = 7.8 Hz, H-10), 9.21 (1H, br.s, exchangeable with D_2O, N-H_b) and 10.26 (1H, s, exchangeable with D_2O, N-H_a). Calc. for $C_{23}H_{18}N_2OS$: C, 74.55; H, 4.90; N, 7.56. Found: C, 74.51; H, 4.85; N, 7.33 %.

4-p-Anisyl-5-phenyl compound ***5b:*** yield 95 %, m.p. 236–238 °C. IR: ν_{max} (KBr): 3220 (N-H), 1188 (C=S) cm^{-1}. ^1H NMR (DMSO-d_6): δ 3.75 (3H, s, OCH_3), 4.43 (1H, br.s, H-4), 5.47 (1H, s, H-5), 6.71 (1H, br.d, *J* = 7.6 Hz, H-7), 6.93 (1H, dt, *J* = 6.6 Hz, H-9), 6.97 (2H, pattern resembles a pair of triplets[13], *J* =6.6 Hz and 2.8 or 1.7 Hz, H-3",5"), 7.16 (1H, dt, *J* = 6.6 and 1.2 Hz, H-7), 7.20 (2H pattern resembles a pair of triplets[13]), *J* = 6.6 Hz and 1.7 or 2.8 Hz, H-2",6"), 7.33-7.36 (5H, m, Ar-H), 7.83 (1H, dd, *J* = 8 and 1.2 Hz, H-10), 9.19 (1H, s, exchangeable with D_2O, N-H_b) and 10.26 (1H, s, exchangeable with D_2O, N-H_a). Calc. for $C_{24}H_{20}N_2O_2S$: C, 75.35; H, 5.28; N, 7.32. Found: C, 75.87; H, 5.18; N, 7.32%.

4-p-Chlorophenyl-5-phenyl compound ***5c:*** yield 85 %, m.p. 208–210 °C. IR: ν_{max} (KBr): 3220 (N-H), 1185 (C=S) cm^{-1}. ^1H NMR (DMSO-d_6): δ 4.54 (1H, s, H-4), 5.52 (1H, s, H-5), 6.73 (1H, br.d, *J* = 8.0 Hz, H-7), 6.94 (1H, br.t, *J* = 7.6 Hz, H-9), 7.17 (1H, br.t, *J* = 8.0 Hz, H-8), 7.30–7.43 (9H, m, Ar-H), 7.85 (1H, br.d, *J* = 8.0 Hz, H-10), 9.28 (1H, s, exchangeable with D_2O, N-H_b) and 10.36 (1H, s, exchangeable with D_2O, N-H_a). ^{13}C NMR (DMSO-d_6): δ 55.13 (C-4), 76.01 (C-5), 105.91 (C-4a), 116.16 (C-10a), 117.20 (C-7), 121.90 (C-9), 123.25 (C-10), 125.87 (C-1"), 128.22 (C-3",5"), 129.53 (C-2",6"), 129.57 (C-2',6'), 129.72 (C-3',5'), 129.84 (C-8), 131.21 (C-4'), 133.68 (C-4"), 138.50 (C-1'), 141.27 (C-10b), 152.63 (C-6a) and 175.44 (C=S). EIMS: *m/z*

406, 404 (M^+). Calc. for $C_{23}H_{17}ClN_2OS$: C, 68.21; H, 4.24; N, 6.91. Found: C, 68.49; H, 3.98; N, 6.43%.

9-Methyl-4,5-diphenyl compound ***5d****:* yield 89 %, m.p. 220–222 °C. IR: ν_{max} (KBr): 3220 (N-H), 1170 (C=S) cm^{-1}. ^1H NMR (DMSO-d_6): δ 2.23 (3H, s, CH_3), 4.51 (1H, br.s, H-4), 5.45 (1H, s, H-5), 6.60 (1H, br.d, *J* = 8.1 Hz, H-7), 6.98 (1H, dd, *J* = 8.1 and 1.5 Hz, H-8), 7.27–7.45 (10H, m, Ar-H), 7.71 (1H, d, *J* = 1.5 Hz, H-10), 9.20 (1H, br.s, exchangeable with D_2O, N-H_b) and 10.19 (1H, s, exchangeable with D_2O, N-H_a). ^{13}C NMR (DMSO-d_6): δ 20.16 (CH_3), 55.31 (C-4), 75.38 (C-5), 105.61 (C-4a), 115.17 (C-10a), 116.11 (C-7), 122.96 (C-10), 124.87 (C-1''), 126.93 (C-2'',6''), 127.48 (C-3'',5''), 128.37 (C-8), 128.80 (C-2',6'), 128.99 (C-3',5'), 129.06 (C-4''), 130.01 (C-4'), 130.67 (C-9), 137.97 (C-1'), 141.81 (C-10b), 149.66 (C-6a), and 174.72 (C=S). EIMS: *m/z* (rel. intensity) 384 (64.4), 307 (100, $[M\text{-}Ph]^+$), 278 (26.7), 248 (33.7), 219 (15.1), 191 (17.2), 165 (14.1), 115 (28.3), 106 (34.7), 91 (33.4) and 77 (35.8, Ph^+). Calc. for $C_{24}H_{20}N_2OS$: C, 74.96; H, 5.25; N, 7.28. Found: C, 74.92; H, 5.17; N, 6.99 %.

3,4-Dihydro-4,6-diphenylpyrimidine-2(1H)-thione (**3a**): This was prepared by the method of Al-Hajjar *et al.*[3] Yield 81 %, m.p. 152–154 °C (lit.[3] 153–154 °C), ^1H NMR ($CDCl_3$): δ 5.21 (1H, m, H-5), 5.30 (1H, m, H-4), 6.80 (1H, br.s, exchangeable with D_2O, N-H), 7.22-7.52 (10H, m, Ar-H) and 7.69 (br.s, exchangeable with D_2O, N-H).

General procedure for acetylation of **3a/5a:** The thione **3a**/**5a** (1 g) was heated with acetic anhydride (1.5 ml) on a boiling water bath for 1 h. After cooling, the reaction mixture was poured into crushed ice (100 g) and extracted with chloroform (3 × 20 ml). The chloroform extract was washed, dried (anhyd. Na_2SO_4) and concentrated. Chromatography of the concentrate over silica gel gave the pure product.

3-Acetyl-3,4-dihydro-4,6-diphenylpyrimidine-2(1H)-thione (**7a**): *acetylation product of* **3a**. Yield 75 %, m.p. 152–154 °C (lit.[3] 153–154 °C). ^1H NMR ($CDCl_3$): δ 2.80 (3H, s), 5.91 (1H, d, *J* = 6.9 Hz), 6.32 (1H, d, *J* = 6.9 Hz), 7.27–7.50 (10H, m, Ar-H) and 8.94 (1H, br.s, N-H). ^{13}C NMR ($CDCl_3$): δ 27.51 ($COCH_3$), 54.20 (C-4), 105.54 (C-5), 125.41 (two carbons, mp), 126.56 (two carbons, mp), 127.95 (mp), 128.68 (two carbons, mp), 128.98 (two carbons, mp), 129.70 (mp), 132.07 (np), 135.67 (np), 139.19 (C-6), 173.56 (C-2) and 178.78 (*C*OCH_3) [mp: monoprotonated, np: nonprotonated].

Compound **8**, *acetylation product of* **5a**: Yield 56 %, viscous liquid. IR: ν_{max} ($CHCl_3$): 3400 (N-H), 1160 (C=S) cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.74 (3H, s, $COCH_3$), 5.78 (1H, s, H-5/H-4), 5.87 (1H, s, H-4/H-5), 6.83 (1H, dd, *J* = 8.1 and 1.2 Hz, H-7), 6.99 (1H, dt, *J* = 8.4 and 1.2 Hz, H-9), 7.19–7.44 (12H, m, Ar-H) and 8.68 (1H, br.s, exchangeable with D_2O, N-H).

X-ray structure determination

X-ray data collection was carried out on an Enraf-Nonius CAD-4 diffractometer[14] using a single crystal with dimension 0.20 × 0.15 × 0.10 mm^3 with a graphite monochromatised MoK_α radiation (λ = 0.71073 Å). Experimental conditions are summarised in Table 1. Precise unit cell dimensions were determined by least-squares refinement on the setting angles of 25 reflections ($3.45° \le \theta \le 13.23°$) carefully centred on the diffractometer. The standard reflections (1 3 0, 2 1 1, 1 1 2) were measured every 7200 s and the orientation of the crystal was checked after every 600 reflections. A total of 5158 reflections was recorded, with Miller indices h_{min}= -19, h_{max}= 17, k_{min}= 0, k_{max}= 12, l_{min}= 0, l_{max}= 23. Data reduction and corrections for absorption and decomposition were achieved using the Nonius Diffractometer Control Software.[14] The structure was solved by SHELXS-97[15] and refined with SHELXL-97.[16] The positions of the H atoms bonded to C atoms were calculated (C-H distance 0.96 Å), and refined using a riding model, and H atom displacement parameters were restricted to be 1.2 U_{eq} of the parent atom.

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Table 1 Crystallographic data for compound **5a**

Molecular formula	$C_{23}H_{18}N_2OS$
f_w (g.mol^{-1})	370.45
Space group	$P2_1/n$
a = 16.338(3) Å	α = 90 °
b = 8.723(3) Å	β = 114.237(12) °
c = 18.012(3) Å	γ = 90 °
Vol [Å^3]	2341(1)
Z	4
D_{calc} (g.cm^{-3})	1.051
μ [cm^{-1}]	0.150
Index ranges	$-19 <= h <= 17$
	$0 <= k <= 12$
	$0 <= l <= 23$
Reflections collected	5158
Independent reflections	4344 [*R*(int) = 0.023]
Data / restraints / parameters	4344 / 0 / 245
Goodness-of-fit on F^2	1.079
Final *R* indices [$I>2\sigma$ (I)]	*R* = 0.0580, *wR* = 0.1237
Largest diff. peak and hole	0.230 and –0.204 e Å^{-3}

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