A Simple Synthesis of 4-Amino-6-aryl-2-thioxotetra- and -hexahydropyrimidines

Antonio LORENTE*, José L. GARCIA NAVIO, José C. LOPEZ PEREZ

Departamento de Química Orgánica, Universidad de Alcalá de Henares, Madrid, Spain

José L. SOTO*

Departamento de Química Orgánica, Facultad de Química, Universidad Complutense, Madrid-3, Spain

Although the synthesis of 2-thioxopyrimidines from thioureas is well documented[1-8], no general route to 4-amino-2-thioxopyrimidine-5-carboxamides is known. In a recent pubication we reported on the synthesis of 6-aryl-2-thioxopyrimidines from different benzylidene compounds[9].

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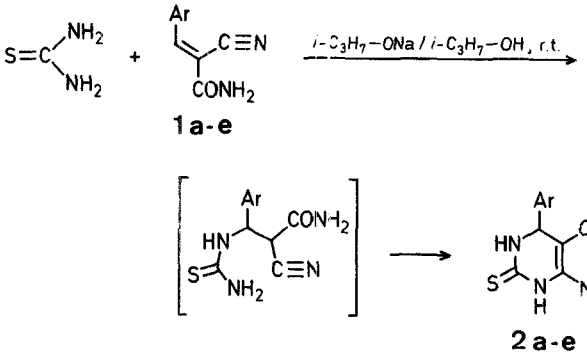
We now describe the synthesis of the hitherto unknown 4-amino-5-aminocarbonyl-6-aryl-2-thioxo-1,2,3,6-tetrahydropyrimidines **2**. The readily accessible (*E*)-3-aryl-2-cyanopropenamides **1** were selected as starting materials.

Compounds **2** were formed by stirring equimolar amounts of **1** and thiourea in isopropanol at room temperature in the presence of 2 equivalents of sodium isopropoxide. The products were isolated by removal of the solvent and precipitation with dilute acetic acid.

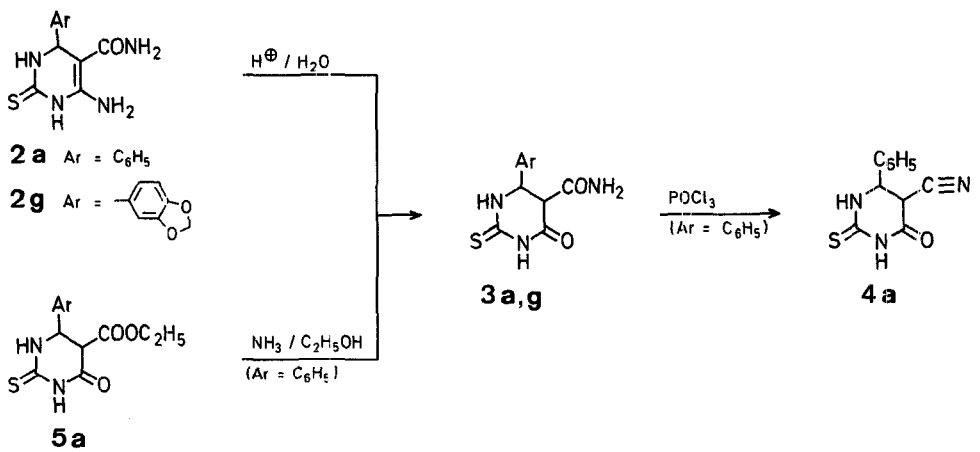


Scheme **A**

As shown in Scheme **A**, it is assumed that the reaction involves addition of thiourea to **1** and subsequent intramolecular attack at the cyano group to form the cyclized products **2**.

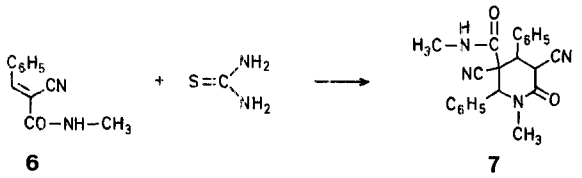
2-Cyano-3-(3′-nitrophenyl)-propenamide (**1f**) did not lead to the corresponding tetrahydropyrimidine and 2-cyano-3-(3′,4′-methylenedioxyphenyl)-propenamide (**1g**) under the same conditions gave, after acidification with 5% acetic acid, 5-aminocarbonyl-6-(3′,4′-methylenedioxyphenyl)-4-oxo-2-thioxohexahydropyrimidine (**3g**), probably originating from hydrolysis of the primarily formed 4-amino-2-thioxopyrimidine (**2g**).

Chemical confirmation of the structure **2** was obtained by acidic hydrolysis of **2a** to 5-aminocarbonyl-4-oxo-6-phenyl-2-thioxohexahydropyrimidine (**3a**). Compound **3a** was indepently prepared by reaction of 5-ethoxycarbonyl-4-oxo-6-phenyl-2-thioxohexahydropyrimidine (**5a**) with an ethanolic solution of ammonia. Furthermore, treatment of **3a** with phosphoryl chloride in refluxing xylene gives 5-cyano-4-oxo-6-phenyl-2-thioxohexahydropyrimidine (**4a**) which is identical with an authentic sample obtained from sodium ethoxide-mediated condensation of ethyl 2-cyano-3-phenylpropenoate and thiourea in ethanol[9] (Scheme **B**).

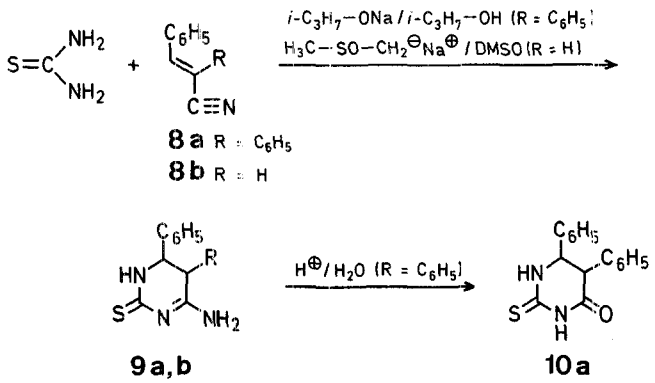


Scheme **B**

Reaction of *N*-methyl-2-cyano-3-phenylpropenamide (**6**) with thiourea under the same conditions as in the preceding cases did not lead to the formation of the corresponding pyrimidine derivatives. 3,5-Dicyano-1-methyl-5-(*N*-methylaminocarbonyl)-4,6-diphenyl-2-piperidone (**7**), resulting from dimerization of the *N*-methylpropenamide **6**, was isolated instead. Similar results have been reported previously[10].



The base-catalyzed condensation of (*Z*)-2,3-diphenylpropenenitrile (**8a**) and (*E*)-3-phenylpropenenitrile (**8b**) with thiourea have also been investigated. As shown in Scheme **C**, 4-amino-5,6-diphenyl-2-thioxo-1,2,5,6-tetrahydropyrimidine (**9a**) and 4-amino-6-phenyl-2-thioxo-1,2,5,6-tetrahydropyrimidine (**9b**) were obtained, respectively. The acid hydrolysis of **9a** afforded the 4-oxo-2-thioxohexahydropyrimidine **10a**.



Scheme **C**

Melting points were determined on a Büchi SMP-20 and are uncorrected. Infrared spectra were obtained using a Perkin-Elmer 700. ^{1}H-N.M.R. spectra were recorded on a Varian FT-80A. Mass spectra were obtained on a Varian MAT 711.

(*E*)-3-Aryl-2-cyanopropenamides **1a–f**[11], **1g**[12], *N*-methyl-2-cyano-3-phenylpropenamide (**6**)[10], 5-ethoxycarbonyl-4-oxo-6-phenyl-2-thioxohexahydropyrimidine (**5a**)[9], (*Z*)-2,3-diphenylpropenenitrile (**8a**)[13] were prepared according to reported procedures. (*E*)-3-Phenylpropenenitrile (**8b**) was purchased from Aldrich and used without further purification.

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Table. 4-Amino-5-aminocarbonyl-6-aryl-2-thioxo-1,2,3,6-tetrahydropyrimidines **2a–e** prepared

Product No.	Ar	Yield [%]	m.p. [°C] (solvent)	Molecular formula[a]	I.R. (KBr) ν [cm^{-1}]	^{1}H-N.M.R. (DMSO-d_6) δ [ppm]
2a[b]	C_6H_5	40	234–236° (C_2H_5OH)	$C_{11}H_{12}N_4OS$ (248.3)	3460, 3360, 3320, 3140, 1645	5.21 (d, 1H, J = 3.2 Hz, H-6); 6.21 (br. s, 2H, NH_2); 6.98 (br. s. 2H. $CONH_2$); 7.25 (s, 5H_{arom}); 9.66 (br. s, 2H, H-1, H-3)
2b	4-H_3C—C_6H_4	35	249–250° (C_2H_5OH)	$C_{12}H_{14}N_4OS$ (262.3)	3460, 3360, 3320, 3160, 1650	2.24 (s, 3H, CH_3); 5.18 (br. s, 1H, H-6); 6.23 (br. s, 2H, NH_2); 6.99 (br. s, 2H, $CONH_2$); 7.11 (s, 4H_{arom}); 9.67 (br. s, 2H, H-1, H-3)
2c	4-H_3CO—C_6H_4	48	254–255° (C_2H_5OH)	$C_{12}H_{14}NO_2S$ (278.3)	3460, 3360, 3340, 3160, 1655	3.69 (s, 3H, OCH_3); 5.14 (d, 1H, J = 3.2 Hz, H-6); 6.22 (br. s, 2H, NH_2); 6.97 (br. s, 2H, $CONH_2$); 6.83–7.17 (A_2B_2, 4H_{arom}); 9.67 (br. s, 2H, H-1, H-3)
2d	4-Cl—C_6H_4	22	245–246° (C_2H_5OH)	$C_{11}H_{11}ClN_4OS$ (282.8)	3460, 3360, 3320, 3150, 1655	5.24 (br. s, 1H, H-6); 6.32 (br. s, 2H, NH_2); 7.01 (br. s, 2H, $CONH_2$); 7.10–7.51 (m, 4H_{arom}); 9.75 (br. s. 2H, H-1, H-3)
2e	2,4-di-H_3C—C_6H_3	50	221–222° (C_2H_5OAc)	$C_{13}H_{16}N_4OS$ (276.4)	3390, 3250, 3130, 1650	3.71, 3.79 (2s, 6H, 2CH_3); 5.28 (d, 1H, J = 3.2 Hz, H-6); 5.91 (br. s, 2H, NH_2); 6.52 (br. s, 2H, $CONH_2$); 6.77–7.14 (m, 3H_{arom}); 9.01 (d, 1H, J = 3.2 Hz, H-1); 9.64 (br. s, 1H, H-3)

[a] Satisfactory microanalyses obtained: C ±0.31, H ±0.23, N ±0.42, S ±0.28, Cl ±0.23.
[b] M.S.: m/e (relative intensity, %) = 248 (M^+, 10); 205 (71); 170 (100).

(*E*)-2-Cyano-3-(2′,4′-dimethylphenyl)propenamide (1e):
Following the general procedure[11], **1e** was obtained from 2,4-dimethylbenzaldehyde and cyanoacetamide in methanol with some drops of potassium hydroxide; yield: 73%; m.p. 208–209°C (methanol).

$C_{12}H_{12}N_2O$ (200.2) calc. C 71.97 H 6.04 N 13.99
found 71.74 6.15 13.75

I.R. (KBr): ν = 3470, 3360, 2220, 1670 cm^{-1}.

^{1}H-N.M.R. (DMSO-d_6): δ = 8.32 (s, 1H, =C—H); 8.06 (d, J = 9.6 Hz, 1H_{arom}); 7.64 (br. s, 2H, $CONH_2$); 6.85–6.52 (m, 2H_{arom}); 3.88, 3.86 ppm (2s, 6H, 2CH_3).

4-Amino-5-aminocarbonyl-6-aryl-2-thioxo-1,2,3,6-tetrahydropyrimidines 2; General Procedure:
Thiourea (760 mg, 10 mmol) and the corresponding propenamide **1** (10 mmol) are added to a solution of sodium *i*-propoxide (20 mmol) in dry *i*-propanol (40 ml). The mixture is stirred at room temperature for 48 h and the solvent removed *in vacuo*. By addition of water (60 ml) and acidification with 5% acetic acid a precipitate is formed, that is collected and washed with water. The product thus obtained is recrystallized to afford the tetrahydropyrimidine **2** (Table).

5-Aminocarbonyl-6-(3′,4′-methylenedioxyphenyl)-4-oxo-2-thioxohexahydropyririmidine (3g):
To a solution of sodium (92 mg, 4 mmol), in dry *i*-propanol (20 ml), thiourea (152 mg, 2 mmol) and 2-cyano-3-(3′,4′-methylenedioxyphenyl)-propenamide (**1g**; 444 mg, 2 mmol) are added. The mixture is stirred at room temperature for 72 h, and then is concentrated to dryness. The resulting residue is dissolved in water (60 ml) and precipitated with 5% acetic acid.The crude product obtained is recrystallized from acetic acid; yield: 350 mg (60%); m.p. 282–283°C.

$C_{12}H_{11}N_3O_4S$ (293.3) calc. C 49.14 H 3.78 N 14.33 S 10.93
found 49.43 3.64 14.07 10.97

I.R. (KBr): ν = 3380, 3250, 1700, 1660 cm^{-1}.

^{1}H-N.M.R. (DMSO-d_6): δ = 11.22 (br. s, 1H, 3-H); 9.90 (br. s, 1H, 1-H); 7.61, 7.26 (2s, 2H, $CONH_2$); 7.01–6.52 (m, 3H_{arom}); 5.98 (s, 2H, —CH_2—); 4.83–4.80 (m, 1H, 6-H); 3.64 ppm (d, J = 5.6 Hz, 1H, 5–H).

Hydrolysis of 2a to 5-Aminocarbonyl-4-oxo-6-phenyl-2-thioxohexahydropyrimidine (3a):
To a suspension of **2a** (390 mg, 1.57 mmol) in ethanol (20 ml), some drops of trifluoroacetic acid are added. The mixture is stirred at room temperature for 36 h, and the resulting precipitate is collected and washed several times with water. The filtrate is concentrated to dryness affording an additional amount of product. The solid is recrystallized from ethanol; yield: 356 mg (97%); m.p. 245–246°C.

$C_{11}H_{11}N_3OS$ (233.3) calc. C 56.63 H 4.75 N 18.01 S 13.74
found 56.51 4.60 18.37 13.52

I.R. (KBr): ν = 3480, 3450, 3240, 3160, 1700, 1670 cm^{-1}.

^{1}H-N.M.R. (DMSO-d_6): δ = 11.23 (br. s, 1H, 3-H); 9.95 (br. s, 1H, 1–H); 7.663, 7.28 (2s, 2H, $CONH_2$); 7.29 (s, 5H_{arom}); 4.87–4.84 (m, 1H, 6-H); 3.64 ppm (d, J = 4.8 Hz, 1H, 5-H).

Ammonolysis of 5a to 5-Aminocarbonyl-4-oxo-6-phenyl-2-thioxohexahydropyrimidine (3a):
To a saturated solution of ammonia in dry ethanol (50 ml), **5a**[9](460 mg, 1.65 mmol) is added. The mixture is kept at room temperature for 12 h and the solvent is removed. The solid thus obtained by removal of the solvent is chromatographed on preparative silicagel thin layer plates using chloroform/ethanol (3:1) as the eluentt. The product obtained is recrystallized from ethanol; yield: 193 mg (50%); m.p. 243–244°C.

Dehydration of 3a to 5-Cyano-4-oxo-6-phenyl-2-thioxohexahydropyrimidine (4a):
Compound **3a** (200 mg, 0.86 mmol) is suspended in dry xylene (20 ml) and phosphoryl chloride (0.2 ml) is added. The mixture is refluxed for 1 h and then the solvent removed in vacuo. The resulting residue is treated with water and the solid obtained is collected, washed several times with water, and recrystallized from ethanol; yield: 159 mg (80%); m.p. 239–240°C (Lit.[9] m.p. 239–240°C).

3,5-Dicyano-1-methyl-5-(*N*-methylaminocarbonyl)-4,6-diphenyl-2-piperidone (7):
To a solution of sodium (92 mg, 4 mmol) in dry *i*-propanol (60 ml), thiourea (152 mg, 2 mmol) and *N*-methyl-2-cyano-3-phenylpropenamide (**6**; 372 mg, 2 mmol) are added. After stirring at room temperature for 48 h the solvent is removed and the residue dissolved in

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water. The solution is acidified with 5% acetic acid and the resulting precipitate is collected, washed with water, and recrystallized from ethanol; yield: 171 mg (46%); m.p. 250–251 °C (Lit[10], m.p. 251–252 °C).

$C_{22}H_{20}N_4O_2$	calc.	C 70.95	H 5.41	N 15.05
(372.4)	found	71.20	5.30	15.25

I.R. (KBr): ν = 3360, 2240, 1660, 1645 cm^{-1}.

^{1}H-N.M.R. (DMSO-d_6): δ = 7.36 (br. s, 11H, $1OH_{arom}$ + NH); 5.35 (s, 1H, 6-H); 5.22, 4.30 (AB, J = 14.4 Hz, 2H, 3-H + 4-H); 2.64 (s, 3H, $N-CH_3$); 2.19 ppm (d, J = 3.2 Hz, 3H, $CONHCH_3$).

M.S.: m/e (rel. int. %) = 372 (M^+, 11), 185 (100).

4-Amino-5,6-diphenyl-2-thioxo-1,2,5,6-tetrahydropyrimidine (9a):
Thiourea (950 mg, 12.5 mmol) and (*Z*)-2,3-diphenylpropenenitrile (**8a**; 2.05 g, 10 mmol) are added to a solution of sodium *i*-propoxide (10 mmol) in dry *i*-propanol (40 ml). The mixture is stirred at room temperature for 5 days and then poured into water. The precipitate formed is collected and recrystallized from acetone; yield: 1.98 g (70%); m.p. 231–232 °C.

$C_{16}H_{15}N_3S$	calc.	C 68.29	H 5.37	N 14.93
(281.4)	found	67.90	5.77	15.20

I.R. (KBr): ν = 3150 (br), 1695 cm^{-1}.

^{1}H-N.M.R. (DMSO-d_6): δ = 9.33, 9.27 (d, J = 4.8 Hz, 1H, 1-H); 7.55–6.93 (m, 12H, $10H_{arom}$ + NH_2); 4.53 (d, J = 4.8 Hz, 1H, 6–H); 3.86 ppm (s, 1H, 5-H).

M.S.: m/e (rel. int. %) = 281 (M^+, 87), 176 (46), 148 (70), 118 (83), 106 (100).

4-Oxo-5,6-diphenyl-2-thioxohexahydropyrimidine (10a):
A suspension of **9a** (281 mg, 1 mmol) in ethanol (20 ml) is acidified with 10% hydrochloric acid. The reaction mixture is stirred at room temperature for 24 h and then the solvent is removed in vacuo. The product obtained is recrystallized from ethanol; yield: 231 mg (82%); m.p. 183–184 °C.

$C_{16}H_{14}N_2OS$	calc.	C 68.05	H 5.00	N 9.92	S 11.36
(282.4)	found	68.20	4.82	10.11	11.01

I.R. (KBr): ν = 3290, 3160, 3050, 1700 cm^{-1}.

^{1}H-N.M.R. (DMSO-d_6): δ = 11.37 (br. s, 1H, 3-H); 10.07 (br, 1H, 1-H); 7.26 (s, $10H_{arom}$); 4.91 (d, J = 5.6 Hz, 1H, 6-H); 4.13 ppm (d, J = 5.6 Hz, 1H, 5-H).

M.S.: m/e (rel. int. %) = 282 (M^+, 98), 118 (100), 106 (50).

4-Amino-6-phenyl-2-thioxo-1,2,5,6-tetrahydropyrimidine (9b):
To a suspension of dimsyl sodium in dimethyl sulfoxide (20 ml; prepared from 25 mmol of sodium hydride), thiourea (760 mg, 10 mmol) and (*E*)-3-phenylpropenenitrile (**8b**; 1.29 g, 10 mmol) are added. The mixture is stirred at room temperature for 20 h and then is poured into water. The precipitate thus obtained is collected and recrystallized from *i*-propanol, yield: 0.87 g (42%); m.p. 248–249 °C.

$C_{10}H_{11}N_3S$	calc.	C 58.51	H 5.40	N 20.47
(205.3)	found	58.17	5.16	20.68

I.R. (KBr): ν = 3180, 1695 cm^{-1}

^{1}H-N.M.R. (DMSO-d_6): δ = 9.9 (br, 1H, 1–H); 7.5 - 7.0 (m, 7H, $5H_{arom}$ + NH_2); 4.77 (part X of ABX system, J_{AX} = 6.3 Hz, J_{BX} = 4.5 Hz, 6-H); 2.8 ppm (part AB of ABX system, J_{AB} = 16.2 Hz, 5-H).

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* Address for correspondence.

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