A Versatile and Convenient Method for the Syntheses of Pyrimido[4,5-*b*][1,4]-thiazine and -thiazepine Ring Systems

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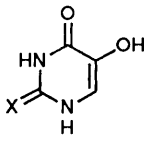
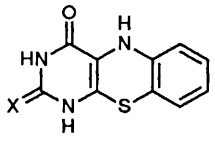
Treatment of 5-hydroxyuracil **1** and 5-hydroxyisocytosine **2** with *N*-bromosuccinimide in ethanol followed by the thermal condensation with β- and γ-amino thiols such as 2-aminothiophenol, cysteamine, L-cysteine and D,L-homocysteine resulted in the formation of the corresponding pyrimido[4,5-*b*][1,4]thiazin-4(3*H*)-ones, **3**–**8**, and pyrimido[4,5-*b*][1,4]thiazepin-4(3*H*)-ones, **9** and **10**. The new method for the construction of pyrimido[4,5-*b*][1,4]thiazine and -thiazepine ring systems was shown to involve the condensation of 5,6-diethoxy-5-hydroxy-5,6-dihydropyrimidin-4(3*H*)-one intermediates, **11** and **12**, with the β- and γ-amino thiols which is accelerated in the presence of an acid-catalyst.

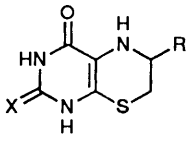
Pyrimido[4,5-*b*][1,4]thiazin-4(3*H*)-ones are of chemical and biological interest as thia analogues of isoalloxazines and pteridines which constitute physiologically important substances such as flavins, biopterin and folic acid. Two methods for the preparation of the pyrimido[4,5-*b*][1,4]thiazine ring system [1] have been reported: (*a*), the photochemical cyclisation of 6-(2-azidophenyl)thiouracils to give 1,5-dihydro-10-thiaisoalloxazines (*cf.* **3**);[2] and (*b*), the condensation of 5-amino-6-mercaptopyrimidin-4(3*H*)-ones with various α-haloketones leading to the pyrimidol[4,5-*b*][1,4]thiazin-4(3*H*)-ones.[3–7] These methods, however, are somewhat troublesome particularly in the preparation of the starting pyrimidines.



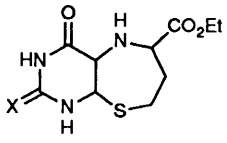
1 X = O
2 X = NH



3 X = O
4 X = NH



5 X = O, R = H
6 X = O, R = CO_2Et
7 X = NH, R = H
8 X = NH, R = CO_2Et



9 X = O
10 X = NH

This paper † describes in full detail a versatile and convenient method for the syntheses of pyrimido[4,5-*b*][1,4]thiazin-4(3*H*)-ones, **3**–**8**, and its homologues, **9** and **10**.

The present method involves the condensation of 5-hydroxyuracil **1** [8] and 5-hydroxyisocytosine **2** [9]‡ with β- and γ-amino thiols for which the reaction with *N*-bromosuccinimide in ethanol is requisite as an activation step.

The special features of the present reaction are its versatility and the formation of the reduced systems corresponding to the pyrimido[4,5-*b*][1,4]thiazin-4(3*H*)-ones and -thiazepin-4(3*H*)-ones in a one-pot procedure. The reaction also has interesting mechanistic implications.

Table 1 Synthetic data of pyrimidol[4,5-*b*][1,4]thiazin-4(3*H*)-ones and -thiazepin-4(3*H*)-ones

Starting material	β- or γ-Amino thiol	Reaction time (h)	Product (yield, %)[a]
1	2-aminothiophenol	1	**3** (82)
1	cysteamine	1	**5** (90)
1	cysteine	1	**6** (80)
2	2-aminothiophenol	4	**4** (81)
2	cysteamine	4	**7** (42)
2	cysteine	12	**8** (47)
1	homocysteine	16	**9** (61)
2	homocysteine	16	**10** (11)

[a] Isolated yield.

To a suspension of **1** in ethanol, a slightly excess of *N*-bromosuccinimide was added and then the mixture was stirred at room temperature. After the disappearance of **1**, 2-aminothiophenol was added and the mixture was heated under reflux. The resulting crystalline mass was collected and recrystallised to give 1,5-dihydro-10-thiaisoalloxazine **3** in 82% yield. The structure of **3** was confirmed by identification with an authentic sample prepared by the photocyclisation of 6-(2-azidophenyl)thiouracil.[2]

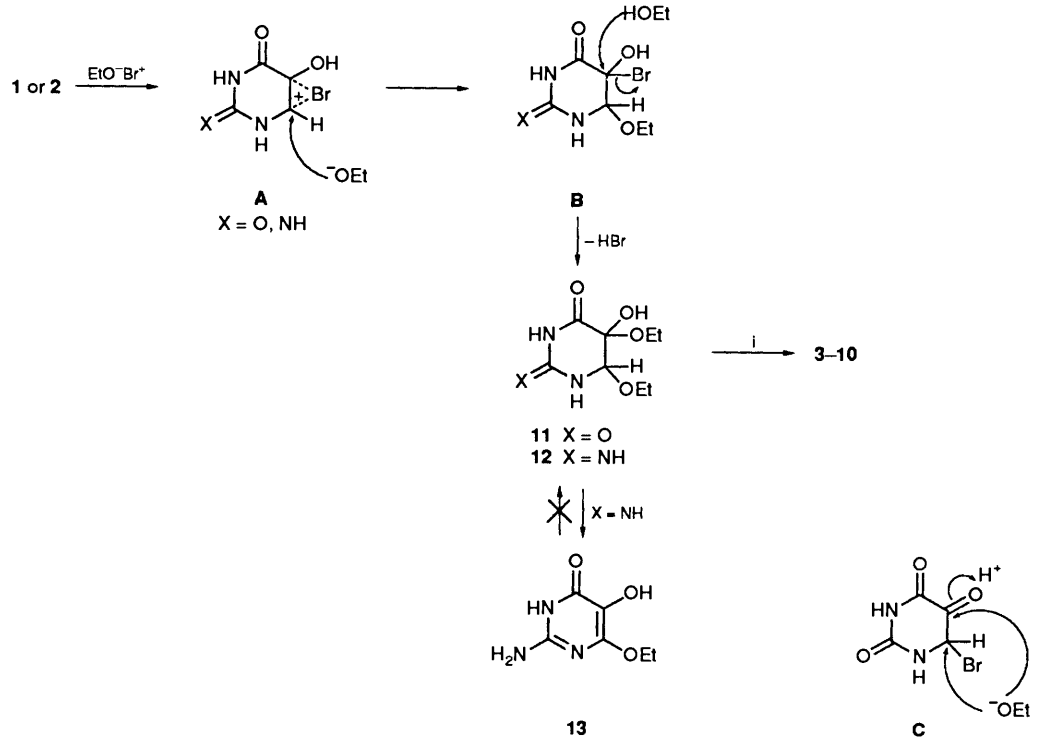
This one-pot procedure was also applicable to preparation of 5,6,7,8-tetrahydro-8-thialumazine **5**, 6-ethoxycarbonyl-5,6,7,8-tetrahydro-8-thialumazine **6**, and 6-ethoxycarbonyl-5,6,7,8-tetrahydropyrimido[4,5-*b*][1,4]thiazepine-2,4(1*H*,3*H*)-dione **9** by the use of cysteamine, L-cysteine, and D,L-homocysteine in place of 2-aminothiophenol.

During the synthesis of **6** using L-cysteine, epimerisation at the C(6)-position of the product occurred to some extent; the specific optical rotation of **6** was variable in several experiments. The 6-ethoxycarbonyl derivatives, **6** and **9**, were obtained as the result of acid-catalysed esterification during the reaction in spite of employment of free L-cysteine and D,L-homocysteine.

Analogously, bromination of **2** with *N*-bromosuccinimide in ethanol followed by treatment with 2-aminothiophenol, cysteamine, L-cysteine, and D,L-homocysteine resulted in the formation of 2-aminopyrimido[4,5-*b*][1,4]benzothiazin-4(3*H*)-one **4**, 5,6,7,8-tetrahydro-8-thiapterin **7**, 6-ethoxycarbonyl-5,6,7,8-tetrahydro-8-thiapterin **8**, and 2-amino-6-ethoxycarbonyl-5,6,7,8-tetrahydro[4,5-*b*][1,4]thiazepin-4(3*H*)-one **10**.

† A part of this account has been reported in a preliminary form (M. Sako, T. Niwa, K. Hirota and Y. Maki, *Chem. Pharm. Bull.*, 1984, **32**, 2474).

‡ For convenience in drawing, the compounds **2**, **4**, **7**, **8**, **10** and **12** are presented as an imino tautomeric form at the C(2)-position.



Scheme 1 *Reagents:* i, H^+, β- and γ-amino thiols

Table 1 summarises the results in the preparation of the pyrimido[4,5-*b*][1,4]thiazin-4(3*H*)-ones, **3**–**8**, and -thiazepin-4(3*H*)-ones, **9** and **10**.

When a suspension of **1** in ethanol was treated with *N*-bromosuccinimide at room temperature, 5,6-diethoxy-5-hydroxy-5,6-dihydrouracil **11** was isolated in 78% yield as a crystalline product. The structural proof of **11** rests upon its microanalytical results and spectral data. For example, the ^1H NMR spectrum of **11** showed a broad doublet signal (δ 4.34, *J* 5.0 Hz), which is assignable to a proton at the C(6)-position because of its coupling with a proton at the N(1)-position (δ 8.52, brd, *J* 5.0 Hz), together with signals arising from two amide groups, a hydroxy group and two ethoxy groups.

Refluxing an equimolar mixture of **11** and 2-aminothiophenol in ethanol containing a catalytic amount of hydrogen bromide gave **3** smoothly in 96% yield. This fact clearly indicates that **11** is a crucial intermediate leading to **3**, **5**, **6** and **9**. We tentatively propose that the reaction pathway for the formation of the intermediate **11** proceeds *via* intermediates **A** and **B**, as depicted in Scheme 1.[10] The alternative route *via* the 6-bromo intermediate **C**, however, is not eliminated.

As in the case of **1**, an unstable intermediate **12** was isolated in an impure state (δ_H 4.58, d, *J* 4.4 Hz, 6-H) when **2** was treated with *N*-bromosuccinimide in ethanol. The major product isolated in this reaction was 6-ethoxy-5-hydroxyisocytosine **13** which can be produced from **12** by elimination of ethanol under the conditions employed.

Contrary to the case of **12**, coupling of **13** with 2-aminothiophenol was not observed even in the presence of the acid catalyst. Thus, the intermediate **12** is responsible for the formation of **4**, **7**, **8** and **10**.

As shown in Table 1, the yields in the preparation of **4**, **7**, **8** and **10** starting from **2** are not satisfactory in comparison with those of **3**, **5**, **6** and **9** from **1**. This difference may be due to the activated intermediate **12** being less stable than **11** because the isocytosine ring possesses more aromatic character than the uracil ring.[11] The preparations of thia analogues of biologically important tetrahydrofolic acid, tetrahydrobiopterin, and dihydroflavin based on the present strategy are now under investigation and will be reported in a forthcoming paper.

Experimental

M.p.s (uncorrected) were determined on a Yamagimoto micro hot-stage apparatus. Elemental analyses were performed by the microanalytical laboratory of our university. Spectroscopic measurements were performed with the following instruments: IR spectrum with Hitachi Model 215 spectrometer; UV absorption spectrum with Shimadzu-260 spectrophotometer; ^1H NMR spectra with a JEOL JNM-GX 270 (270 MHz) FT-NMR spectrometer using tetramethylsilane as an internal standard and $(CD_3)_2SO$ as a solvent; mass spectrum with JEOL JMS-D 300 machine operating at 70 eV. TLC analyses were performed on silica gel plates (Merck, Art 5715).

General Procedure for the Syntheses of Pyrimido[4,5-*b*][1,4]-*thiazin*-4(3H)-*ones* **3**–**8**, *and -thiazepin*-4(3H)-*ones* **9** *and* **10**.—To a suspension of 5-hydroxyuracil **1** (128 mg, 1.0 mmol) or 5-hydroxyisocytosine **2** (127 mg, 1.0 mmol) in ethanol (10 cm^3), *N*-bromosuccinimide (196 mg, 1.1 mmol) was added and the mixture was stirred at room temperature until the disappearance of the pyrimidines was complete (TLC; 0.5–1.0 h). After the addition of the corresponding β- and γ-amino thiols, the mixture was refluxed (for 1–16 h, see Table 1). The resulting precipitate was collected and recrystallised from methanol or ethanol. After evaporation of these filtrates, the resulting residue was subjected to column chromatography (chloroform–methanol) to isolate the respective product in a pure state. The total yields are summarised in Table 1. Microanalytical results and spectral data of the products, **4**–**10**, are as follows.

5H-2-*Aminopyrimido*[4,5-b][1,4]*benzothiazin*-4(3H)-*one* **4**. M.p. >300 °C (from methanol) (Found: C, 51.85; H, 3.55; N, 24.05. $C_{10}H_8N_4OS$ requires C, 51.72; H, 3.47; N, 24.13); *m*/*z* 232 (M^+, 100%), 162 (20), 161 (20) and 135 (30); ν_{max}(KBr)/cm^{-1} 3360 (NH), 3300 (NH) and 1650 (C=O); λ_{max}(ethanol)/nm 265 (ε/dm^3 mol^{-1} cm^{-1} 1.8 × 10^4) and 227 (1.2 × 10^4); δ_H 6.27 (2 H,

br, NH_2), 6.5–7.0 (4 H, m, ArH), 7.17 (1 H, br, NH) and 11.00 (1 H, br, NH).

6,7-*Dihydro*-5H-*pyrimido*[4,5-b][1,4]*thiazine*-2,4(1H,3H)-*dione* **5**. M.p. 291–293 °C (from methanol) (Found: C, 38.9; H, 3.7; N, 22.7. $C_6H_7N_3O_2S$ requires C, 38.92; H, 3.81; N, 22.70); *m/z* 185 (M^+, 100%), 170 (M^+ − NH, 10) and 114 (12); ν_{max}(KBr)/cm^{-1} 3150 (NH), 3100 (NH), 1700 (C=O) and 1660 (C=O); λ_{max}(ethanol)/nm 327 (ε/dm^3 mol^{-1} cm^{-1} 4 × 10^3) and 227 (6.5 × 10^3); δ_H 2.90–3.50 (4 H, m, 6- and 7-H_2), 4.58 (1 H, br, NH), 10.55 (1 H, br, NH) and 10.90 (1 H, br, NH).

6-*Ethoxycarbonyl*-6,7-*dihydro*-5H-*pyrimido*[4,5-b][1,4]-*thiazine*-2,4(1H,3H)-*dione* **6**. M.p. 238–240 °C (from ethanol) (Found: C, 42.2; H, 4.3; N, 16.3. $C_9H_{11}N_3O_4S$ requires C, 42.03; H, 4.31; N, 16.34); *m/z* 257 (M^+, 20%) and 184 (M^+ − CO_2Et, 100); ν_{max}(KBr)/cm^{-1} 3260 (NH), 1725 (C=O), 1690 (C=O) and 1660 (C=O); λ_{max}(ethanol)/nm 323 (ε/dm^3 mol^{-1} cm^{-1} 9.3 × 10^3) and 225 (1.5 × 10^4); δ_H 1.27 (3 H, t, OEt), 3.25–3.42 (2 H, m, 7-H_2), 4.20 (2 H, q, OEt), 4.45 (1 H, br t, 6-H), 5.01 (1 H, br d, *J*/Hz 3.75, NH), 10.75 (1 H, br, NH) and 11.17 (1 H, br, NH).

2-*Amino*-6,7-*dihydro*-5H-*pyrimido*[4,5-b][1,4]*thiazin*-4(3H)-*one* **7**. M.p. 175–177 °C (Found: C, 25.45; H, 4.25; N, 19.65. $C_6H_8N_4OS$·HBr·H_2O requires C, 25.45; H, 3.92; N, 19.79); *m/z* 184 (M^+, 100%) and 169 (M^+ − NH, 20); ν_{max}(KBr)/cm^{-1} 3320 (NH), 3200 (NH) and 1665 (C=O); λ_{max}(methanol)/nm 311 (ε/dm^3 mol^{-1} cm^{-1} 1.2 × 10^4) and 231 (1.5 × 10^4); δ_H 3.08 (2 H, q, 6-H_2), 3.21 (2 H, t, 7-H_2), 6.15 (2 H, b, 2 × NH) and 8.15 (2 H, br s, NH_2).

5H-2-*Amino*-6-*ethoxycarbonyl*-6,7-*dihydropyrimido*[4,5-b]-[1,4]*thiazin*-4(3H)-*one* **8**. M.p. 187–189 °C (from methanol) (Found: C, 41.4; H, 4.8; N, 21.55. $C_9H_{12}N_4O_3S$·5/18H_2O requires C, 41.38; H, 4.74; N, 21.45); *m/z* 256 (M^+, 22%) and 183 (M^+ − CO_2Et, 100); ν_{max}(KBr)/cm^{-1} 3350 (NH), 1720 (C=O) and 1680 (C=O); λ_{max}(ethanol)/nm 329 (ε/dm^3 mol^{-1} cm^{-1} 8.4 × 10^3) and 235 (1.6 × 10^4); δ_H 1.27 (3 H, t, OEt), 3.20–3.40 (2 H, m, 7-H_2), 4.19 (2 H, q, OEt), 4.38 (1 H, br t, 6-H), 4.86 (1 H, br, NH), 5.95 (2 H, br, NH_2) and 10.96 (1 H, br, NH).

6-*Ethoxycarbonyl*-5,6,7,8-*tetrahydropyrimido*[4,5-b][1,4]-*thiazepine*-2,4(1H,3H)-*dione* **9**. M.p. 229–232 °C (from methanol) (Found: C, 44.0; H, 4.75; N, 15.35. $C_{10}H_{13}N_3O_4S$ requires C, 44.28; H, 4.83; N, 15.49); *m/z* 271 (M^+, 12%) and 198 (M^+ − CO_2Et, 100); ν_{max}(KBr)/cm^{-1} 3300 (NH), 1740 (C=O), 1700 (C=O) and 1640 (C=O); λ_{max}(methanol)/nm 319 (ε/dm^3 mol^{-1} cm^{-1} 5 × 10^3) and 233 (8 × 10^3); δ_H 1.22 (3 H, t, OEt), 2.01 and 2.38 (each 1 H, each m, 7-H_2), 2.90 and 3.28 (each 1 H, each m, 8-H_2), 4.00 (1 H, m, 6-H), 4.17 (2 H, q, OEt), 4.88 (1 H, br s, NH), 10.68 (1 H, br, NH) and 11.31 (1 H, br, NH).

2-*Amino*-6-*ethoxycarbonyl*-5,6,7,8-*tetrahydropyrimido*-[4,5-b][1,4]*thiazepin*-4(3H)-*one* **10**. M.p. 235–241 °C (from methanol) (Found: C, 39.05; H, 4.75; N, 18.2. $C_{10}H_{14}N_4O_3S$·1/3 HBr·2/3H_2O requires C, 38.84; H, 5.11; N, 18.12); *m/z* 270 (M^+, 21%) and 197 (M^+ − CO_2Et, 100); ν_{max}(KBr)/cm^{-1} 3300 (NH), 1730 (C=O) and 1680 (C=O); λ_{max}(methanol)/nm 332 (ε/dm^3 mol^{-1} cm^{-1} 7 × 10^3) and 243 (1.4 × 10^4); δ_H 1.19 (3 H, t, OEt), 1.93 and 2.27 (each 1 H, each m, 7-H_2), 2.82 and 3.52 (each 1 H, each m, 8-H_2), 4.14 (2 H, q, OEt), 4.23 (1 H, m, 6-H), 4.65 (1 H, br s, NH) and 6.01 (2 H, br, NH_2).

Reaction of **1** *or* **2** *with* N-*Bromosuccinimide in Ethanol*.—To a suspension of **1** (128 mg, 1.0 mmol) in ethanol (10 cm^3), *N*-bromosuccinimide (196 mg, 1.1 mmol) was added and the mixture was stirred at room temperature for 0.5 h. The resulting crystalline mass (170 mg, 78%) was collected and recrystallised from ethyl acetate to give 5,6-diethoxy-5-hydroxy-5,6-dihydrouracil **11**, m.p. 213–215 °C (Found: C, 44.0; H, 6.35; N, 12.85. $C_8H_{14}N_2O_5$ requires C, 44.03; H, 6.47; N, 12.84); *m/z* 219 (M^+ + 1, 8%), 189, 172 (M^+ − EtOH, 32), 144 (100) and 100 (79); ν_{max}(KBr)/cm^{-1} 3370 (NH), 3280 (NH), 1730 (C=O) and 1710 (C=O); δ_H 1.08 (3 H, t, OEt), 1.10 (3 H, t, OEt), 3.20–3.96 (4 H, m, 2 × OEt), 4.34 (1 H, d, *J*/Hz 5, 6-H, collapsed to singlet on addition of D_2O), 6.95 (1 H, s, OH), 8.52 (1 H, br d, *J*/Hz 5, NH) and 10.25 (1 H, br, NH).

In a similar manner, the reaction of **2** with *N*-bromosuccinimide was carried out. After being stirred at room temperature for 1 h, a clear solution was obtained. The NMR spectrum of the reaction mixture showed the presence of a significant amount of 5,6-diethoxy-5-hydroxy-5,6-dihydroisocytosine **12** [δ_H 1.17 (6 H, t, 2 × OEt), 3.50–3.80 (4 H, m, OEt), 4.58 (1 H, d, *J*/Hz 4.4, 6-H) and 9.98 (1 H, br d, *J*/Hz 4.4, NH)]. Column chromatographic separation (chloroform–ethanol) of the reaction mixture allowed the isolation of 6-ethoxy-5-hydroxyisocytosine **13** (61%) [m.p. 262 °C (from ethanol)] (Found: C, 41.95; H, 5.25; N, 24.35. $C_6H_9N_3O_3$ requires C, 42.10; H, 5.30; N, 24.55); *m/z* 171 (M^+, 56%), 143 (M^+ − CO, 78), 115 (M^+ − 56, 14), and 43 (100); λ_{max}(methanol)/nm 295; ν_{max}(KBr)/cm^{-1} 3300 (NH) and 1650 (C=O); δ_H 1.31 (3 H, t, OEt), 4.25 (2 H, q, OEt), 6.19 (2 H, br s, NH_2), 7.04 (1 H, br s, OH) and 10.73 (1 H, br, NH)], but **12** was not isolated as a pure state. The compound **12** was gradually converted into **13** during reflux in ethanol.

Thermal Reaction of **11** *or* **12** *with* 2-*Aminothiophenol*.—A mixture of **11** (109 mg, 0.5 mmol) and 2-aminothiophenol (67 mm^3, 0.6 mmol) in ethanol (5 cm^3) containing a trace amount of hydrogen bromide was heated under reflux for 1 h. The resulting precipitate (112 mg, 96%) was collected. The product was identical in every respects with the authentic **3**.

In a similar manner, the thermal reaction of **12** (containing a small amount of **13**) with 2-aminothiophenol was carried out. The formation of a significant amount of **4** in this reaction was confirmed by TLC analysis and ^{1}H NMR spectrum of the reaction mixture. Employment of **13** in place of **12** in this reaction resulted in no formation of **4** and recovery of the starting **13**.

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Paper 1/03392A
Received 5*th July* 1991
Accepted 15*th July* 1991