Communications to the Editor

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A VERSATILE AND CONVENIENT METHOD FOR THE SYNTHESIS OF PYRIMIDO[4,5-b][1,4]THIAZINES

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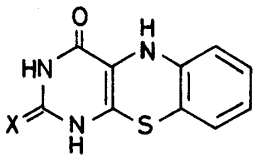
Treatment of 5-hydroxypyrimidines 3 with N-bromosuccinimide in ethanol followed by thermal condensation with β-aminothiols resulted in the formation of pyrimido[4,5-b][1,4]thiazines 1 and 2 in high yields.

KEYWORDS — pyrimido[4,5-b][1,4]thiazine; 5-hydroxypyrimidine; N-bromosuccinimide; β-aminothiol; 1,5-dihydro-10-thiaisoalloxazine; 5,6,7,8-tetrahydro-8-thiapterin

The pyrimido[4,5-b][1,4]thiazines are of chemical and biological interest in view of the thia analogues of isoalloxazines and pterins which constitute physiologically important substances such as flavins, biopterin, and folic acid.

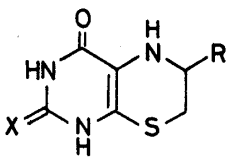
Along this line, only two methods for the preparation of the pyrimido-[4,5-b][1,4]thiazine ring system have been reported,[1] that is, 1) the photochemical cyclization of 6-(2-azidophenylthio)uracils to give 1,5-dihydro-10-thiaisoalloxazines[2] and 2) the condensation of 2,5-diamino-6-mercaptopyrimidines with α-haloketones leading to 7,8-dihydro-8-thiapterins.[3] These methods, however, are somewhat troublesome particularly in the preparation of the starting pyrimidine derivatives.

We now report here a versatile and convenient method for the synthesis of pyrimido[4,5-b][1,4]thiazines 1 and 2 starting from the readily available 5-hydroxypyrimidines 3.[4-6] The present one-pot reaction is in principle applicable to the synthesis of other fused pyrimidine ring systems.



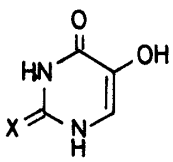
1

a : X=O
b : X=NH



2

a : X=O, R=H
b : X=O, R=COOEt
c : X=NH, R=COOEt



3

a : X=O
b : X=NH

Chart 1

To a suspension of 5-hydroxyuracil (3a)[5] (1.0 mmol) in ethanol (10 ml), N-bromosuccinimide (1.1 mmol) was added by portions at room temperature. After having been stirred until the disappearance of 3a (monitored by TLC, for about 0.5 h) followed by addition of 2-aminothiophenol (1.5 mmol), the mixture was heated under reflux for 1 h. The precipitated crystalline mass was collected and recrystallized from ethanol to give 1,5-dihydro-10-thiaisoalloxazine (1a) in a high yield. In this procedure, employment of methanol as a solvent also gave analogous results. The structure of 1a was confirmed by identification with an authentic sample prepared by photocyclization of 6-(2-azidophenylthio)uracil.[2]

This one-pot procedure can be applied to the preparation of 5,6,7,8-tetrahydro-8-thialumazine (2a)[7] and 6-ethoxycarbonyl-5,6,7,8-tetrahydro-8-thialumazine (2b) by the use of cysteamine and cystein ethyl ester in place of 2-aminothiophenol.

Analogously, bromination of isocytosine (3b)[6] in ethanol with N-bromosuccinimide followed by treatment of 2-aminothiophenol and cystein ethyl ester resulted in the formation of 1,5-dihydro-2-amino-10-thiaisoalloxazine (1b) and 6-ethoxycarbonyl-5,6,7,8-tetrahydro-8-thiapterin (2c), respectively.

Table 1. Preparation of Pyrimido[4,5-b][1,4]thiazines 1 and 2

Starting material	β-Aminothiol	Product	Mp (°C)	Yield (%)
3a	2-Aminothiophenol	1a	310 (lit.[2] 267)	82
3a	Cysteamine	2a	292	90
3a	Cystein ethyl ester	2b	239	83
3b	2-Aminothiophenol	1b	>300	81
3b	Cystein ethyl ester	2c	188	47

When a suspension of 3a (1.0 mmol) in ethanol was treated with N-bromosuccinimide (1.1 mmol) at room temperature for 0.5 h, 5,6-diethoxy-5-hydroxy-5,6-dihydrouracil (5a)(see Chart 2), mp 214°C, was isolated in 78% yield. The structural proof of 5a rests upon its spectral data. For example, the ^{1}H-NMR spectrum of 5a (in DMSO-d_6) 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, broad doublet, J = 5.0 Hz), together with signals arising from two amide groups, a hydroxy group and two ethoxy groups.

Attempts to isolate the expected 6-bromo-5-hydroxyuracil (4a) in a pure state were unsuccessful due to its instability, e.g., bromination of 3a by N-bromosuccinimide in dry acetonitrile gave 4a[8] (detected by NMR) which was not stable enough to purify. Employment of acetonitrile instead of ethanol as a solvent was not advantageous for the preparation of the pyrimido[4,5-b][1,4]-thiazines 1 and 2 because of their formation in low yields (20-60%).

Refluxing an equimolar mixture of 5a and 2-aminothiophenol in ethanol in the presence of a trace amount of hydrogen bromide gave 1a in 96% yield. The above findings clearly indicate that 5 is an intermediate product in the present synthesis of pyrimido[4,5-b][1,4]thiazines 1 and 2.

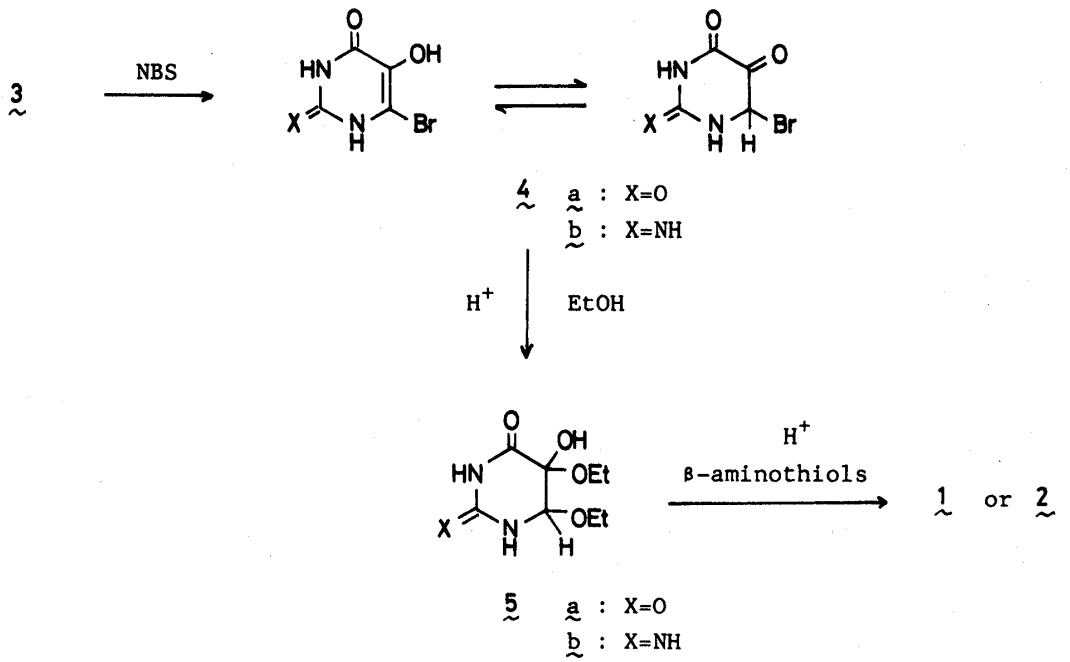


Chart 2

Taking the above facts into consideration, a plausible reaction sequence for the present reaction is outlined as shown in Chart 2. The initially formed 6-bromo-5-hydroxypyrimidine (4) is trapped by ethanol to give the dihydropyrimidine intermediate 5. The dihydropyrimidine 5 could react with β-aminothiols under thermal conditions to produce the pyrimido[4,5-b][1,4]thiazines 1 and 2 in the presence of the acid catalyst.

REFERENCES AND NOTES

1) A number of synthetic methods of the isomeric pyrimido[5,4-b][1,4]thiazine ring system have so far been reported. cf. Y. Maki, M. Sako, M. Tanabe, and M. Suzuki, Synthesis, 1981, 462 and references cited therein ; R.N. Henrie II, R.A. Lazarus, and S.J. Benkovic, J. Med. Chem., 26, 559 (1983).
2) T. Hiramitsu and Y. Maki, J. Chem. Soc., Chem. Commun., 1977, 557.
3) M.G. Nair, L.H. Boyce, and M.A. Berry, J. Org. Chem., 46, 3354 (1981) and references cited therein.
4) For convenience in drawing, the compounds 1b, 2c, and 3b are represented as their imino form at the C(2)-position, respectively.
5) S.Y. Wang, J. Am. Chem. Soc., 81, 3786 (1959).
6) R. Hull, J. Chem. Soc., 1956, 2033.
7) All new compounds gave satisfactory microanalytical results and spectral data consistent with their proposed structures.
8) The NMR spectrum of 4a (in DMSO-d_6) showed a broad signal (δ 4.65), which is assignable to C(6)-H and was collapsed to singlet by the addition of deuterium oxide.

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