SYNTHESIS OF SUBSTITUTED 1,2,3,4-TETRAHYDRO-6-METHYL-2-THIOXO-5-PYRIMIDINECARBOXYLIC ACID ESTERS

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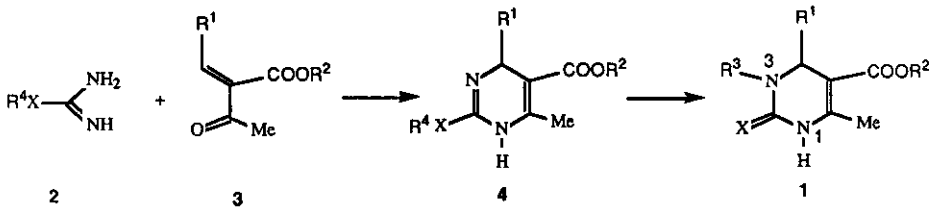
Abstract- Substituted 1,2,3,4-tetrahydro-6-methyl-2-thioxo-5-pyrimidinecarboxylic acid esters are prepared in high overall yield from 2-methylene-3-oxobutanoic acid esters and 2-(4-methoxybenzyl)-2-thiopseudourea hydrochloride.

It has been reported that 1,2,3,4-tetrahydro-6-methyl-2-thioxo-5-pyrimidinecarboxylic acid esters **1** (X = S)[1] can be prepared *via* the Biginelli condensation[2] or by the condensation of thiourea with 2-phenylmethylene-3-oxobutanoic acid esters **3** (R^1 = phenyl) [3]. In our hands both of these methods gave low yields and furthermore, neither method could be used for the synthesis of N-3 substituted pyrimidinethiones **1** (X = S). In the preceding communication we reported a simple method for the synthesis of pyrimidinones **1** (X = O) from readily available starting materials, **2** (X = O, R^4 = Me) and **3** (Scheme 1) [4]. We reasoned that the use of properly protected thiourea in a very similar process might provide a general method for the synthesis of pyrimidinethiones **1** (X = S). Consequently, we prepared 2-(4-methoxybenzyl)-2-thiopseudourea hydrochloride **2** [X = S, R^4 = p-methoxybenzyl (PMB)] [5]. In the present communication we wish to report its utility for a high yield synthesis of substituted 1,2,3,4- tetrahydro -6-methyl-2-thioxo-5-pyrimidinecarboxylic acid esters **1** (X = S).

Scheme 1



2 3 4 1

2-(4-Methoxybenzyl)-2-thiopseudourea hydrochloride **2** (X = S, R^4 = PMB), prepared by the reaction of 4-methoxybenzyl chloride with thiourea[5], was treated with unsaturated ketoester (**3**)[6] in the presence of sodium acetate (or sodium bicarbonate) to provide 1,4-dihydropyrimidine **4** (X = S, R^4 = PMB)[7] in excellent yield (Scheme 1). On reaction with trifluoroacetic acid/ethanethiol, **4** underwent smooth deprotection to provide 1,2,3,4-tetrahydro-6-methyl-2-thioxo-5-pyrimidinecarboxylic acid ester (**1**, X = S, R^3 = H)[8] in good overall yield (see Table 1). This method is fairly general and the products are conveniently isolated by crystallization. It is applicable for the synthesis of pyrimidinethiones **1** (X = S, R^3 = H) from unsaturated ketoester (**3**) derived

from hindered aromatic (entries 2-4) and nonaromatic aldehydes (entry 5). Preparation of some of these compounds by the published methods gave poor yields; for comparison, see table 1 footnote c. The scope of our method is further illustrated by the preparation of N-3 substituted pyrimidinethiones **1** (X = S). Thus, the treatment of 1,4-dihydropyrimidine **4** (X = S, R^1 = 3-nitrophenyl, R^2 = Et, R^4 = PMB) with benzyl bromide/potassium carbonate followed by deprotection with trifluoroacetic acid/ethanethiol provided regiospecifically the N-3 alkylated pyrimidine **1** (X =S, R^1 = 3-nitrophenyl, R^2 = Et, R^3 = benzyl) (mp 182-184°C) in 78% yield [9]. The oxidation (m-chloroperoxybenzoic acid, MeOH) of the alkylated intermediate provided the corresponding pyrimidinone (X = O, R^1 = 3-nitrophenyl, R^2 = Et, R^3 = benzyl) [4].

Attempted synthesis of **1** (X = S, R^1 = 3-nitrophenyl, R^2 = Et, R^3 = benzyl) by the Biginelli condensation (1-benzylthiourea, ethyl acetoacetate, 3-nitrobenzaldehyde, EtOH/HCl) was unsuccesful. Moreover, the reaction [1-benzylthiourea, **3** (R^1 = 3-nitrophenyl, R^2 = Et), EtOH/HCl] reported by Alkasaby[3] to yield **1** (X = S, R^1 = 3-nitrophenyl, R^2 = H, R^3 = Benzyl) led instead to 4-methyl-6-(3-nitrophenyl)-2-(benzylamino)-6H-1,3-thiazine-5-carboxylic acid ethyl ester **5** (85%, mp 117°C from isopropanol), the structure of which was confirmed by X-ray crystallography (Figure 1) [10]. In this connection it is interesting to note that the treatment of pyrimidine **1** (X = S, R^1 = 3-nitrophenyl, R^2 = Et, R^3 = H) with benzyl bromide/potassium carbonate gave the 1,4-dihydropyrimidine **4** (X = S, R^1 = 3-nitrophenyl, R^2 = Et, R^4 = benzyl), mp 129-130°C [11].

In summary, we have shown that 1,4-dihydropyrimidine **4** (X = S, R^4 = PMB) which is readily available from 2-(4-methoxybenzyl)-2-thiopseudourea hydrochloride **2** (X = S, R^4 = PMB) and 2-methylene-3-oxobutanoic acid ester **3**, can be utilized for the synthesis of a variety of substituted pyrimidinethiones **1** (X = S). Some of these compounds are unaccessible by the previously reported methodology.

Typical procedure: 2-[(3-Nitrophenyl)methylene]-3-oxobutanoic acid ethyl ester (1.05 g, 4.0 mmol) (prepared from 3-nitrobenzaldehyde and ethylacetoacetate) in DMF (5 ml) was treated with 2-(4-methoxybenzyl)-2-thiopseudourea hydrochloride (1.12 g, 4.8 mmol) and sodium acetate (410 mg, 5.0 mmol). The reaction mixture was stirred at r. t. for 30 min and then at 65°C overnight. It was cooled to ambient temperature, diluted with water and extracted with ether. The combined extracts were washed (water, brine), dried ($MgSO_4$) and evaporated. The resulting 1,4-dihydropyrimidine was dissolved in THF (6 ml) and treated with trifluoroacetic acid (2 ml) and ethanethiol (2 ml). The reaction was heated at 70°C until completion. Most of the solvent was evaporated and the residue was crystallized from absolute ethanol.

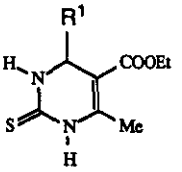
REFERENCES AND NOTES

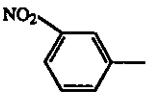
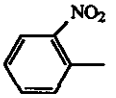
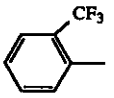
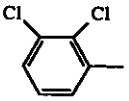
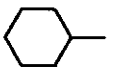
1: a) For biological importance of pyrimidines, see for example: a) R. Hull and G. Swain, British Patent, 868,030, 1961; b) E. L.Khania, G. O. Silinietse, Ya. Ya. Ozol, G. Ya. Dabur and A. A. Kimenis, Khim. Farm. Zh., 1978, **78**, 1321.

2: a) K. Folkers, H. J. Harwood and T. B. Johnson, J. Am. Chem. Soc., 1932, **54**, 3751; b) V. N. Konyukhov, G. S. Sakovich, L. V. Krupova and Z. V. Pushkareva, J. Org. Chem. (USSR), 1965, 1505.

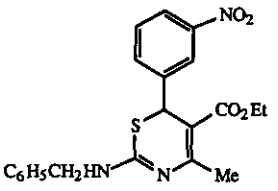
3: M. A. Elkasaby, Pak. J. Sci. Ind. Res., 1978, **21**, 58.

Table 1: Synthesis of 1,2,3,4-tetrahydro-6-methyl-2-thioxo-5-pyrimidine-carboxylic acid esters.



Entry	R^1	Yield[a]	MP (°C)[b]
1		81% (24%)[c]	206-7 (ethanol)
2		60% (10%)[c]	213-215[d]
3		62% (19%)[c]	196-7[d]
4		60%	224-6[d]
5		54%	207-8[d]

[a] Yield is based on the crystalline product isolated; the actual yield is higher. [b] All products gave satisfactory microanalysis. [c] The figure in parenthesis indicates the yield obtained via the Biginelli condensation. [d] Crystallized from isopropyl ether.



5

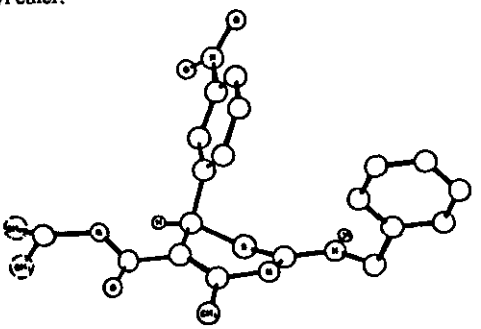


Figure 1: The solid state structure of **5**

4: B. C. O'Reilly and K. S. Atwal, preceding communication in this issue.

5: Preparation of 2-(4-methoxybenzyl)-2-thiopseudourea hydrochloride: A suspension of thiourea (3.8 g, 50.0 mmol) in anhydrous THF (30 ml) at 0°C was treated dropwise with 4-methoxybenzyl chloride (8.0 g, 50.0 mmol). The reaction was stirred at r.t. for 2 h and then at 65°C for 4 h. It was cooled to ambient temperature and diluted with anhydrous ether. The resulting solid was filtered and washed with anhydrous ether to give a colorless solid (10.9g, 94.4%), mp 161-163°C.

6: The unsaturated ketoester (3) is prepared in high yield from an aldehyde and ethyl acetoacetate by standard Knoevenagel condensation.

7: The 1,4-dihydropyrimidine 4 (X = S, R^4 = PMB) can be isolated and stored as its hydrochloride salt.

8: The products were identified by IR, ^{1}H NMR, ^{13}C NMR and Mass spectrometry. Spectral data for 1,2,3,4-tetrahydro-6-methyl-4-(3-nitrophenyl)-2-thioxo-3-pyrimidinecarboxylic acid ethyl ester (entry 1) ^{1}H NMR (Acetone-d_6): δ 9.40 (br s, 1H, N_1-H), 8.8 (br s, 1H, N_3-H), 8.17 (s, 1H, aromatic), 8.14 (d, J = 7.9 Hz, 1H, aromatic), 7.76 (d, J = 7.4 Hz, 1H, aromatic), 7.63 (t, J = 7.9 Hz, 1H, aromatic), 5.52 (d, J = 3.0 Hz, 1H, methine), 4.0 (dq, J = 7.0 and 2.6 Hz, 2H, ethyl ester), 2.40 (s, 3H, methyl) and 1.17 (t, J = 7.0 Hz, 3H, ethyl ester) ppm; IR (KBr): 3183, 1716, 1661, 1595, 1532, 1346, 1326, 1276, 1189, 1104 and 901 cm^{-1}.

9: ^{1}HNMR ($CDCl_3$): δ 8.32 (s, 1H, N_1-H), 8.15 (d, J = 7.9 Hz, 1H, aromatic), 8.11 (s, 1H, aromatic), 7.64 (d, J = 7.9 Hz, 1H, aromatic),7.51 (t, J = 7.9 Hz, 1H, aromatic), 7.32 (m, 5H, aromatic), 5.98, 4.18 (ABq, J = 5.29 Hz, 2H, benzylic), 6.00 (s, 1H, methine), 4.11 (m, 2H, ethyl ester), 2.39 (s, 3H, methyl) and 1.18 (t, J = 7.38 Hz, 3H, ethyl ester) ppm; IR (KBr): 3314, 1651, 1529, 1344, 1252, 1215 and 1127 cm^{-1}; ^{13}CNMR ($CDCl_3$) shows a thiocarbonyl at 176.3 ppm.

10:For λ = 1.5418A, a = 12.063 (2), b = 19.882 (4), c = 8.836 (1) A, α = 99.91 (1), β = 99.26 (1), γ = 95.46(1)°, V = 2044 (1) A^3; Dobs = 1.32 g cm^{-3} (Dcal = 1.34 for Z = 4, $C_{21}H_{21}N_3O_4S$), Space group $P\bar{1}$. A total of 5578 reflections were measured on a Syntex $P2_1$ diffractometer at 23°C with the θ - 2θ variable scan technique and were corrected only for Lorentz-polarization factors. The structure was solved by direct methods and refined by full matrix least squares analysis on the basis of 3042 "observed" reflections with $I \geq 3\sigma(I)$. Some site disorder was found for the methyl of the ethyl ester. Although most hydrogen positions were evident on difference maps, they were introduced in idealized positions and their scattering taken into account in the later stages of refinement. The least squares weights, $w = \sigma^{-2}(F_o)$ were calculated with the assumption that $\sigma^2(I) = e^2 + (pI)^2$ where e is a statistical counting error and p = .04. The refinements (assuming isotropic motion for the disordered methyl, and anisotropic motion for all other C, N, O, S atoms) converged at R = 0.059, Rw = 0.072. The final difference map contained no significant features. The conformations of the two independent molecules of the asymmetric unit differ significantly only in the degree of rotation (Δ= 34°) about the CH-Ar bonds to the phenyl rings. The hydrogen on the exocyclic nitrogen atom is intermolecularly hydrogen bonded (N---O, 2.86, 2.84 A) to the carbonyl oxygen of the ester group.

11: ^{1}HNMR ($CDCl_3$): δ 8.11 (s, 1H, aromatic), 8.09 (d, J = 7.9 Hz, 1H, aromatic), 7.62 (d, J = 7.4 Hz, 1H, aromatic), 7.42 (t, J = 7.9 Hz, 1H, aromatic), 7.18 (br s,5H, aromatic), 6.25 (br s, 1H, N_1-H), 5.80 (s, 1H, methine), 4.24 (ABq, J = 13.2 Hz, 2H, benzylic), 4.13 (q, J = 6.8 Hz, 2H, ethyl ester), 2.34 (s, 3H, methyl) and 1.21 (t, J = 6.8 Hz, 3H, ethyl ester) ppm; IR (KBr): 3328, 1678, 1652, 1627, 1584, 1412, 1204, 1032, 931, 902, 871, 784 and 770 cm^{-1}. This compound was identical with the product obtained by the direct condensation of 2-benzyl-2-thiopseudourea hydrochloride with 3 (R^1 = 3-nitrophenyl, R^2 = Et).

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