

**SYNTHESIS OF SUBSTITUTED 1,2,3,4-TETRAHYDRO-6-METHYL-2-  
OXO-5-PYRIMIDINECARBOXYLIC ACID ESTERS:  
THE BIGINELLI CONDENSATION REVISITED<sup>#</sup>**

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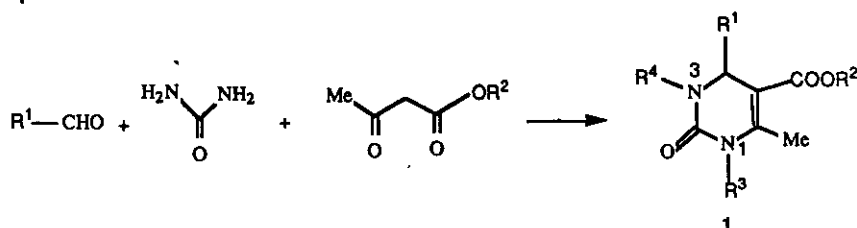
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**Abstract-** A general synthesis of substituted 1,2,3,4-tetrahydro-6-methyl-2-oxo-5-pyrimidinecarboxylic acid esters from 2-methylene-3-oxobutanoic acid esters and O-methylisourea hydrogen sulfate is reported.

The biologically important 1,2,3,4-tetrahydro-6-methyl-2-oxo-5-pyrimidinecarboxylic acid esters (1)<sup>1</sup> are prepared from an aldehyde, acetoacetic acid ester and urea under strongly acidic conditions (Scheme 1)<sup>2</sup>. We have found that this reaction, termed the Biginelli condensation, is not very reliable and often gives low yields<sup>3</sup>. Since the reaction is usually carried out in refluxing ethanolic HCl, acid sensitive functional groups are lost during this reaction<sup>4</sup>. Using N-alkyl urea, N<sub>1</sub>-alkylated products are obtained and hence the reaction is inapplicable for the synthesis of N<sub>3</sub>-alkylated pyrimidines<sup>5</sup>. We proposed that a synthesis of 1 proceeding via the methoxypyrimidine 2

**Scheme 1**



might provide an effective alternative to the Biginelli condensation. In order to prepare 2, we explored the reaction of O-methylisourea hydrogen sulfate 3 with the unsaturated ketoester 4. These studies resulted in a general synthesis of substituted pyrimidines (1) and are the subject of this communication.

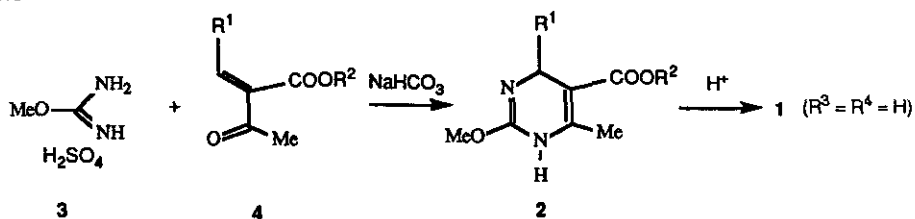
The unsaturated ketoester 4<sup>6</sup> is condensed with commercially available O-methylisourea hydrogen

<sup>#</sup>Dedicated to Professor Gilbert Stork on the occasion of his 65th birthday

sulfate **3**<sup>7</sup> in the presence of sodium bicarbonate and the resulting methoxypyrimidine **2**<sup>8</sup> is hydrolyzed with hydrochloric acid (Scheme 2). The resulting pyrimidines **1** ( $R^3 = R^4 = H$ )<sup>9</sup> are

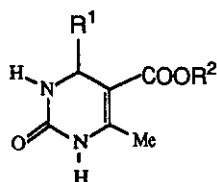
obtained in high overall yield, see Table 1. The reaction (**3** + **4** → **2**) always proceeds to

**Scheme 2**



completion and the products **1** ( $R^3 = R^4 = H$ ), after hydrolysis of **2**, are conveniently isolated by crystallization. This method allows the synthesis of pyrimidines from hindered nonaromatic aldehydes (entry 5)<sup>3</sup>. Pyrimidines containing acid sensitive functional groups (entry 2) can be prepared by careful hydrolysis of the intermediate **2**. Although this method requires prior formation of the unsaturated ketoester **4**, its reliability for the formation of a variety of pyrimidine derivatives (Table 1) makes it an attractive alternative to the Biginelli condensation. An important feature of this method is that methoxypyrimidine **2**, which is prepared during this reaction, can be utilized for selective functionalization of the pyrimidine  $N_3$ -nitrogen which is otherwise difficult<sup>5</sup>. For example, treatment of **2** ( $R^1 = 3$ -nitrophenyl,  $R^2 = \text{Et}$ ) with benzyl bromide/ $\text{K}_2\text{CO}_3$  followed by acid treatment affords the  $N_3$ -alkylated pyrimidine **1** ( $R^1 = 3$ -nitrophenyl,  $R^2 = \text{Et}$ ,  $R^3 = H$ ,  $R^4 = \text{CH}_2\text{C}_6\text{H}_5$ ) (mp 153-155°C) (50%) along with the  $N_1$ -alkylated pyrimidine **1** ( $R^1 = 3$ -nitrophenyl,  $R^2 = \text{Et}$ ,  $R^3 = \text{CH}_2\text{C}_6\text{H}_5$ ,  $R^4 = H$ ) (20%)<sup>10</sup>.

For example, 2-[(3-nitrophenyl)methylene]-3-oxobutanoic acid ethyl ester (500 mg, 1.9 mM), prepared from 3-nitrobenzaldehyde and ethyl acetoacetate, in DMF (5 ml) was treated with *O*-methylisourea hydrogen sulfate (425 mg, 2.47 mM) and  $\text{NaHCO}_3$  (622 mg, 7.4 mM). The reaction was stirred at r. t. for 30 min and then heated 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 ( $\text{K}_2\text{CO}_3$ ) and evaporated. The resulting methoxypyrimidine was dissolved in MeOH-THF (10 ml of 1:1 mix) and treated with 3N HCl (3 ml). The reaction was stirred at r.t. until completion. Most of the solvent was evaporated and the residue was crystallized from absolute ethanol.

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

Entry	R <sup>1</sup>	R <sup>2</sup>	Yield <sup>a</sup>	MP (°C) <sup>b</sup>
1		Et	80%	227-228 <sup>c</sup> (ethanol)
2		t-Bu	58%	218-220 <sup>d</sup>
3		Et	69%	198-200 <sup>d</sup>
4		Et	63%	212-214 <sup>d</sup>
5		Et	66%	233-234 <sup>d</sup>

<sup>a</sup> Yield is based on the crystalline product isolated; the actual yield is higher.

<sup>b</sup> All products gave satisfactory microanalysis.

<sup>c</sup> Literature mp 226-227.5°C (see reference 3).

<sup>d</sup> Crystallized from MeOH-isopropyl ether.

## REFERENCES AND NOTES

- 1: a) R. Hull and G. Swain, British Patent , 1961, 868,030; b) E. W. Hurst and R. Hull, J. Med. Pharm. Chem. , 1961, 3, 215; c) D. McKinstry and E. H. Reading, J. Franklin Inst., 1944, 237, 203; d) H. A. Rutter and L. O. Gustafson, J. Franklin Inst., 1954, 258, 413; e) E. L. Khania, G. O. Silinietse, Ya. Ya. Ozol, G. Ya. Dabur and A. A. Kimenis, Khim. Farm. Zh., 1978, 78, 1321
- 2: a) D. J. Brown, "The Pyrimidines", Wiley, New York, N. Y. 1962, p. 440; b) *ibid.*, Supplement I, 1970, 326.
- 3: The best yields during Biginelli condensation are obtained with unhindered aromatic aldehydes, see for example: K. Folkers, H. J. Harwood and T. B. Johnson, J. Am. Chem. Soc. , 1932, 54, 3751.
- 4: For a study of the pH dependence of this reaction, see A. Ehsan and Karimullah Pak. J. Sci. Ind. Res. , 1967, 10, 83.
- 5: a) T. George, R. Tahilramani and D. V. Mehta, Synthesis , 1975, 405; b) K. Folkers and T. B. Johnson, J. Am. Chem. Soc. , 1934, 56, 1374.
- 6: The unsaturated ketoester (4) is prepared in high yield from an aldehyde and ethyl acetoacetate by standard Knoevenagel condensation.
- 7: o-Methylisourea hydrogen sulfate was purchased from Aldrich Chemical Co..
- 8: The methoxypyrimidine (2) is obtained as a mixture of tautomers with 1,4-isomer being the predominant one; ratio 4:1 approximately.
- 9: The products were identified by IR, <sup>1</sup>H NMR, <sup>13</sup>C NMR and Mass spectrometry. Spectral data for 1,2,3,4-tetrahydro-6-methyl-4-(3-nitrophenyl)-2-oxo-3-pyrimidinecarboxylic acid ethyl ester (entry 1) <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 9.33 (s, 1H, N<sub>1</sub>-H), 8.11 (d, J = 7.4 Hz, 1H, aromatic), 8.09 (s, 1H, aromatic), 7.86 (s, 1H, N<sub>3</sub>-H), 7.68 (t, J = 7.9 Hz, 1H, aromatic), 7.64 (d, J = 7.4 Hz, 1H, aromatic), 5.30 (d, J = 3.2 Hz, 1H, methine), 4.0 (dq, J = 7.4 and 2.6 Hz, 2H, ethyl ester), 2.26 (s, 3H, methyl) and 1.1 (t, J = 7.4 Hz, 3H, ethyl ester) ppm; IR (KBr): 3333, 1710, 1690, 1631, 1526, 1347, 1225, 1088 and 901 cm<sup>-1</sup>.
- 10: The two products, separable by flash chromatography, were identified by NMR spectroscopy <sup>5a</sup>. The most distinct signal is due to C<sub>4</sub>-H which comes as a singlet (δ 5.33) when R<sup>4</sup> = CH<sub>2</sub>C<sub>6</sub>H<sub>5</sub> and a doublet (δ 5.52, J = 3.2 Hz) when R<sup>4</sup> = H. For a regioselective synthesis of N<sub>3</sub>-substituted pyrimidine, see our accompanying communication.

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