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

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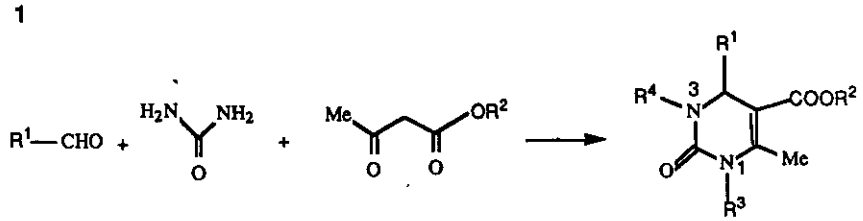
Abstract- A general synthesis of substituted 1,2,3,4-tetrahydro-6-methyl-2-oxo-5-pyrimidinecarboxylic acid esters from 2-methylene-3-oxobutanoic acid esters and O-methylisourea hydrogen sulfate is reported.

The biologically important 1,2,3,4-tetrahydro-6-methyl-2-oxo-5-pyrimidinecarboxylic acid esters (1)[1] are prepared from an aldehyde, acetoacetic acid ester and urea under strongly acidic conditions (Scheme 1) [2]. We have found that this reaction, termed the Biginelli condensation, is not very reliable and often gives low yields [3]. Since the reaction is usually carried out in refluxing ethanolic HCl, acid sensitive functional groups are lost during this reaction [4]. Using N-alkyl urea, N_1-alkylated products are obtained and hence the reaction is inapplicable for the synthesis of N_3-alkylated pyrimidines [5]. We proposed that a synthesis of 1 proceeding via the methoxypyrimidine 2

Scheme 1



1

might provide an effective alternative to the Beginelli 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[6] is condensed with commercially available O-methylisourea hydrogen

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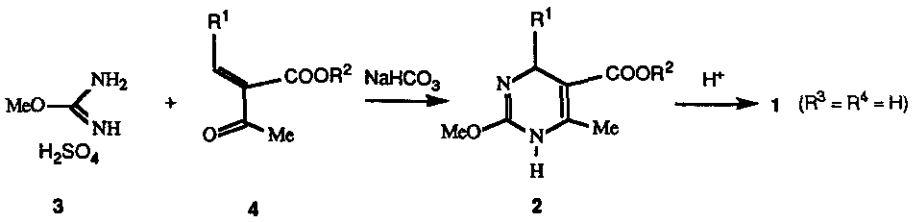
#Dedicated to Professor Gilbert Stork on the occasion of his 65th birthday

sulfate 3[7] in the presence of sodium bicarbonate and the resulting methoxypyrimidine 2[8] is hydrolyzed with hydrochloric acid (Scheme 2). The resulting pyrimidines 1 ($R^3 = R^4 = H$)[9] are obtained in high overall yield , see Table 1. The reaction (3 + 4 -> 2) always proceeds to

Scheme 2

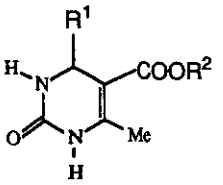


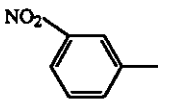
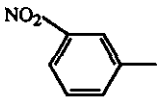
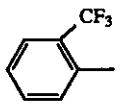
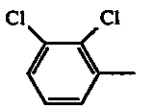
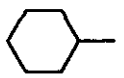
3 4 2

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) [3]. 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 [5]. For example, treatment of 2 (R^1 = 3-nitrophenyl, R^2 = Et) with benzyl bromide/K_2CO_3 followed by acid treatment affords the N_3-alkylated pyrimidine 1 (R^1 = 3-nitrophenyl, R^2 = Et, R^3 = H, $R^4 = CH_2C_6H_5$) (mp 153-155°C) (50%) along with the N_1-alkylated pyrimidine 1 (R^1 = 3-nitrophenyl, R^2 = Et, $R^3 = CH_2C_6H_5$, R^4 = H) (20%) [10].

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 $NaHCO_3$ (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 (K_2CO_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^1	R^2	Yield[a]	MP (°C)[b]
1		Et	80%	227-228[c] (ethanol)
2		t-Bu	58%	218-220[d]
3		Et	69%	198-200[d]
4		Et	63%	212-214[d]
5		Et	66%	233-234[d]

[a] Yield is based on the crystalline product isolated; the actual yield is higher.

[b] All products gave satisfactory microanalysis.

[c] Literature mp 226-227.5°C (see reference 3).

[d] 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, ^{1}H NMR ,^{13}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) ^{1}H NMR (DMSO-d_6): δ 9.33 (s, 1H, N_1-H), 8.11 (d, J = 7.4 Hz, 1H, aromatic), 8.09 (s, 1H, aromatic), 7.86 (s, 1H, N_3-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^{-1}.

10:The two products, separable by flash chromatography, were identified by NMR spectroscopy [5a]. The most distinct signal is due to C_4-H which comes as a singlet (δ 5.33) when $R^4 = CH_2C_6H_5$ and a doublet (δ 5.52, J = 3.2 Hz) when R^4 = H. For a regiospecific synthesis of N_3-substituted pyrimidine, see our accompanying communication.

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