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

\[
\begin{align*}
R^1-\text{CHO} + H_{2}N^{\text{NH}_{2}} + \text{Me} - \text{O} \rightarrow & R^{4}N^{3} \text{N}^{1} \text{CO} \text{OR}^{2} \\text{Me} \\
\end{align*}
\]

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\(^6\) is condensed with commercially available O-methylisourea hydrogen sulfate.
sulfate\(^3\) in the presence of sodium bicarbonate and the resulting methoxypyrimidine \(^2\) is hydrolyzed with hydrochloric acid (Scheme 2). The resulting pyrimidines \(^1\) \((R^3 = R^4 = \text{H})\) are obtained in high overall yield, see Table 1. The reaction \((3 + 4 \rightarrow 2)\) always proceeds to completion and the products \(^1\) \((R^3 = R^4 = \text{H})\), 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 \(^2\) \((R^1 = 3\text{-nitrophenyl}, R^2 = \text{Et})\) with benzyl bromide/K\(_2\text{CO}_3\) followed by acid treatment affords the N\(_3\)-alkylated pyrimidine \(^1\) \((R^1 = 3\text{-nitrophenyl}, R^2 = \text{Et}, R^3 = \text{H}, R^4 = \text{CH}_2\text{C}_6\text{H}_5\) (mp 153-155\(^\circ\)C) (50%) along with the N\(_1\)-alkylated pyrimidine \(^1\) \((R^1 = 3\text{-nitrophenyl}, R^2 = \text{Et}, R^3 = \text{CH}_2\text{C}_6\text{H}_5, R^4 = \text{H}\) (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\(^\circ\)C overnight. It was cooled to ambient temperature, diluted with water and extracted with ether. The combined extracts were washed (water, brine), dried (K\(_2\)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.

![Chemical structure](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>R¹</th>
<th>R²</th>
<th>Yield&lt;sup&gt;a&lt;/sup&gt;</th>
<th>MP (°C)&lt;sup&gt;b&lt;/sup&gt;</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>NO₂</td>
<td>Et</td>
<td>80%</td>
<td>227-228&lt;sup&gt;c&lt;/sup&gt; (ethanol)</td>
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<tr>
<td>2</td>
<td>NO₂</td>
<td>t-Bu</td>
<td>58%</td>
<td>218-220&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td>CF₃</td>
<td>Et</td>
<td>69%</td>
<td>198-200&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>4</td>
<td>Cl</td>
<td>Et</td>
<td>63%</td>
<td>212-214&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>Et</td>
<td>66%</td>
<td>233-234&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<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


6:  The unsaturated ketoester (4) is prepared in high yield from an aldehyde and ethyl acetoacetate by standard Knoevenagel condensation.

7:  o-Methyloisourea 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, 1H NMR, 13C NMR and Mass spectrometry. Spectral data for 1,2,3,4-tetrahydro-6-methyl-4-(3-nitrophenyl)-2-oxopyrimidinecarboxylic acid ethyl ester (entry 1) 1H NMR (DMSO-d6): δ 9.33 (s, 1H, N1-H), 8.11 (d, J = 7.4 Hz, 1H, aromatic), 8.09 (s, 1H, aromatic), 7.86 (s, 1H, N3-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 C4-H which comes as a singlet (δ 5.33) when R4 = CH2C6H5 and a doublet (δ 5.52, J = 3.2 Hz) when R4 = H. For a regiospecific synthesis of N3-substituted pyrimidine, see our accompanying communication.

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