REACTIONS OF 4-PYRIMIDINONE DERIVATIVES WITH METHYL ISOCYANATE: FORMATION OF PYRIMIDO[1,2-a][1,3,5]TRIAZINE-2,4-DIONE RING SYSTEM

Masami Sawada,* Yoshiro Furukawa, Yoshio Takai, and Terukiyo Hanafusa*
The Institute of Scientific and Industrial Research, Osaka University, 8-1, Mihogaoka, Ibaraki-shi, Osaka, 567 Japan

Abstract—Base-catalysed reactions of 4-pyrimidinone and 4-quinazolinone with methyl isocyanate gave the compounds with a pyrimido[1,2-a][1,3,5]triazine-2,4-dione ring system (3 and 5, respectively; 1:2-cyclic adducts). In contrast, some uracil derivatives afforded the 1-methylcarbamoyl compounds (7, 1:1-adducts).

Recently, we reported that the reactions of 4-pyridinone or 4-quinolinone with various alkyl isocyanates give condensed ring-1,3-dialkyl-1,3,5-triazine-2,4-dione derivatives (1:2-cyclic adducts). The reaction proceeds via a stepwise addition of two alkyl isocyanates followed by an intramolecular Michael addition to the 4-pyridinone or 4-quinolinone skeleton; a new sequence from 4-pyridinones to form a six-membered ring. In the course of studying general applicability of this cyclization, the reactions of diaza heterocyclic compounds such as 4-pyrimidinone and 4-quinazolinone with methyl isocyanate were investigated. It has been well known that substances having an annelated pyrimidine ring and/or triazine ring play a very important part in organic chemistry of biological compounds. We now communicate the easy formation-reaction of the ring system, pyrimido[1,2-a][1,3,5]triazine-2,4-dione.

To a solution of 4-quinazolinone (1) (1.00g, 0.68mmol) in DMF (23ml) containing 1,1,3,3-tetramethylguanidine (78mg, 0.68mmol) was added two equivalent of methyl isocyanate (0.80g, 14.0mmol) at room temperature under nitrogen atmosphere. The solution was stirred for 2 h. After evaporation of the solvent, the residue was chromatographed on silica gel (elution with chloroform [97]/ethanol [3]) to give 2,4-dimethyl-1,2,3,4,4a,5,6,11-octahydro-quinazolino[1,2-a][2,4,11]triazine-1,3,6-trione (3) (1:2-cyclic adduct; 32% yield) as a main product and 5-methylcarbamoyl-2,4-dimethyl-1,2,3,4,4a,5,6,11-octahydroquinazolino[1,2-a][2,4,11]triazine-1,3,6-trione (5) (1:2-cyclic adduct; 15% yield) as a minor product.
trione (4)(1:3-adduct; 2% yield) and 1-methylcarbamoyl-4-oxo-1,4-dihydro-
quinoxaline (2)(1:1-adduct; 14% yield) as by-products. 4

Similarly, 4-pyrimidinone reacted with methyl isocyanate under similar conditions to afford 1,3-dimethyl-1,2,3,4,5,8,9,9a-octahydro-pyrimido[1,2-a][1,3,5]triazine-2,4,8-trione (5)(1:2-cyclic adduct; 19% yield) and 9-methylcarbamoyl-1,3-dimethyl-1,2,3,4,5,8,9,9a-octahydropyrimido[1,2-a][1,3,5]triazine-2,4,8-trione (6)(1:3-adduct; 25% yield). 5 The structures of these products were determined on the basis of elemental analytical, mass spectral, and 1H-nmr, and 13C-nmr spectral data (Table 1).

![General Scheme 1](image)

It is reasonably understood that 4 was obtained by the further addition of methyl isocyanate to 3, and 2 was isolated on the way of the formation of 3 (Scheme 1). 1 In order to get more mechanistic information, general reversibility of the reactions was tested under relatively higher base-concentrations: a small amount of each component compound of the Scheme 1 was stirred with a drop of 1,1,3,3-
tetramethylguanidine in DMF or CHCl₃ (without methyl isocyanate), and the progress of the reaction was monitored by TLC, independently.
The results were (i) $\frac{1}{2}$ was mostly converted into $\frac{1}{2}$ for a short time (less than 3 min, base-catalysed decomposition), (ii) $\frac{1}{2}$ did not change at least for 20 h (no base-catalysed decomposition), (iii) $\frac{1}{2}$ was mostly converted into $\frac{1}{2}$ (base-catalysed decomposition), but not into $\frac{1}{2}$. The same behavior was observed for $\frac{1}{2}$. These results indicate that the reaction step from $\frac{1}{2}$ to $\frac{1}{2}$ is generally irreversible under such basic conditions. This is in contrast with the fact that in the case of 1:2-cyclic adduct of 4-quinolinone, the corresponding step has generally reversible nature, and must reflect certain effects of the nitrogen atom on the ring-closing and ring-opening steps. It is the important observation that the cyclization occurs only in one way at the C-2 (not at the C-6) position of the 4-pyrimidinone ring. The selectivity may be caused by electron deficiency at the C-2 position which results from electronegative nitrogen atom adjacent to the reaction center. As reported by Oine et al., electron deficiency at the C-2 position of the 4-quinazolinone accelerates such a ring-closing step.

Under the similar conditions, uracil (1.00g, 8.9mmol) was stirred for 2 h with methyl isocyanate (2.62g, 45.9mmol) in DMF (20ml) containing 1,1,3,3-tetramethylguanidine (1.03g, 0.90mmol) at room temperature under nitrogen atmosphere. In this case, only the 1:1-adduct ($\frac{1}{2}$) was obtained in a 33% yield (mp 173°C, dec). Both 5-fluorouracil and 5-bromouracil bearing electron-withdrawing groups, and further 3-methyluracil where an acidic proton is protected by a methyl group, gave the corresponding 1:1-adducts in 46% (mp 171°C, dec), 41% (mp 197.5°C, dec), and 63% yields (mp 133-134.5°C), respectively. Further studies of these reactions are now in progress.

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REFERENCES


4. Recovered 4-quinazolinone, 52% yield.
5. Recovered 4-pyrimidinone, 45% yield. In this case, the corresponding 1:1-adduct could not be isolated.

6. The starting material, 4-quinolinone, was observed after a short time under the same basic conditions as the case of (ii).


8. The more fundamental step is the ring-closing one from the 1:2-acyclic adduct (not isolated in this case, not shown in the general scheme 1, chain-form) to the 1:2-cyclic adduct (ring-form).


Table 1. Physical Data of Some Pyrimido[1,2-a][1,3,5]triazine-2,4-dione and Its Related Derivatives

<table>
<thead>
<tr>
<th>Compound</th>
<th>Yield (%)</th>
<th>mp (°C)</th>
<th>M.S. (Nujol)</th>
<th>$^{13}$C-NMR $\delta_{CO}$ (ppm)</th>
<th>$^{1}H$-NMR $\delta$ (ppm)</th>
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<td>2</td>
<td>4$^a$</td>
<td>194-196</td>
<td>1740</td>
<td>163.1$^{d}$</td>
<td>9.64 (1H, brd, NH)$^{d}$, 9.15 (1H, s, CH$_2$), 8.39-7.47 (4H, m, ArH), 3.07 (3H, d, J=4.5 Hz, CH$_3$)</td>
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<td>1660</td>
<td>152.3</td>
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<td>3</td>
<td>21$^b$</td>
<td>271-274</td>
<td>1740</td>
<td>163.2$^{e}$</td>
<td>9.31 (1H, brd, NH)$^{e}$, 7.96-7.00 (7H, m, ArH), 6.31 (1H, s, CH$_3$), J=1 Hz, CH, 3.12 (3H, s, CH$_3$), 3.07 (3H, s, CH$_3$)</td>
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<td>1680</td>
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<td>4</td>
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<td>1730</td>
<td>164.1$^{d}$</td>
<td>8.52 (1H, brd, NH)$^{d}$, 8.03-7.12 (4H, m, ArH), 6.67 (1H, s, CH), 3.11 (3H, s, CH$_3$), 3.03 (3H, s, CH$_3$), 2.70 (3H, d, J=4.9 Hz, CH$_3$)</td>
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<td>5</td>
<td>8$^c$</td>
<td>198-199</td>
<td>1740</td>
<td>163.2$^{d}$</td>
<td>8.66 (1H, brd, NH)$^{d}$, 7.61 (1H, d, J=7.8 Hz, CH), 6.04 (1H, brd, CH$_2$), 5.42 (1H, dd, J=7.8 and 1.3 Hz, CH), 3.08 (3H, s, CH$_3$), 2.98 (3H, s, CH$_3$)</td>
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<td>6</td>
<td>18$^a$</td>
<td>148(dec)</td>
<td>1740</td>
<td>163.3$^{d}$</td>
<td>8.96 (1H, brd, NH)$^{d}$, 7.42 (1H, dd, J=6.0 and 0.7 Hz, CH), 7.23 (1H, d, J=0.7 Hz, CH), 5.33 (1H, d, J=8.0 Hz, CH), 3.17 (3H, s, CH$_3$), 2.93 (3H, d, J=4.6 Hz, CH$_3$), 2.85 (3H, s, CH$_3$)</td>
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* a) Recryst. from CHCl$_3$-hexane. b) Recryst. from acetonitrile. c) Recryst. from ACOEt. d) CDCl$_3$/TMS. e) DMSO-d$_6$/TMS. f) EI/MS (70 eV); M$^+$-value. g) EI/MS (20 eV); M$^+$-value.

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