

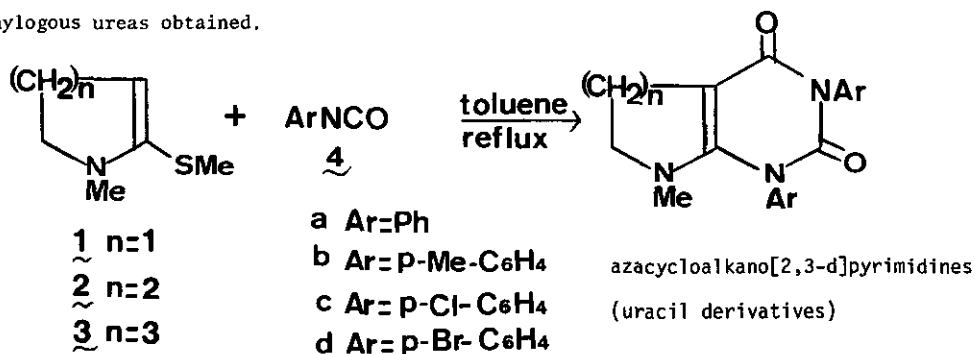
## ACTIVATED LACTAMS: REACTION OF KETENE-S,N-ACETALS WITH ARL ISOCYANATES

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**Abstract** — Reaction of ketene-S,N-acetals (1, 2, and 3) as activated lactams with aryl isocyanates (4a-d) has been described. The vinylogous ureas (6a-d and 7a-d) obtained by this reaction have been utilized as intermediates for the synthesis of some uracil derivatives.

We have been interested in developing a new synthesis of heterocycles using ketene-S,N-acetals<sup>1</sup> (1, 2, and 3) as activated lactams.<sup>2</sup> In the previous paper,<sup>3</sup> we reported a new one-step synthesis of azacycloalkano[2,3-d]pyrimidines (uracil derivatives) by the ring closure of 1, 2, and 3 with aryl isocyanates (4a-d) in boiling toluene. We wish to report in this communication a synthesis of vinylogous ureas and a two-step synthesis of azacycloalkano[2,3-d]pyrimidines via the vinylogous ureas obtained.



Reaction of 2 and 3 with phenyl isocyanate (4a) in ether at room temperature gave the vinylogous ureas (1:1 adducts) (6a and 7a), respectively, in good yields, whereas that of 1 afforded the ring closure product (5a) and the lactam (8a). Similarly, vinylogous ureas (6b-d and 7b-d) were obtained by the reaction using aryl isocyanates (4b-d), and the uracil derivative (5b) and the lactams (8b-d) were also prepared from 1 and 4b-d. However, compounds 5c,d could not be isolated. The results are summarized in Table I.

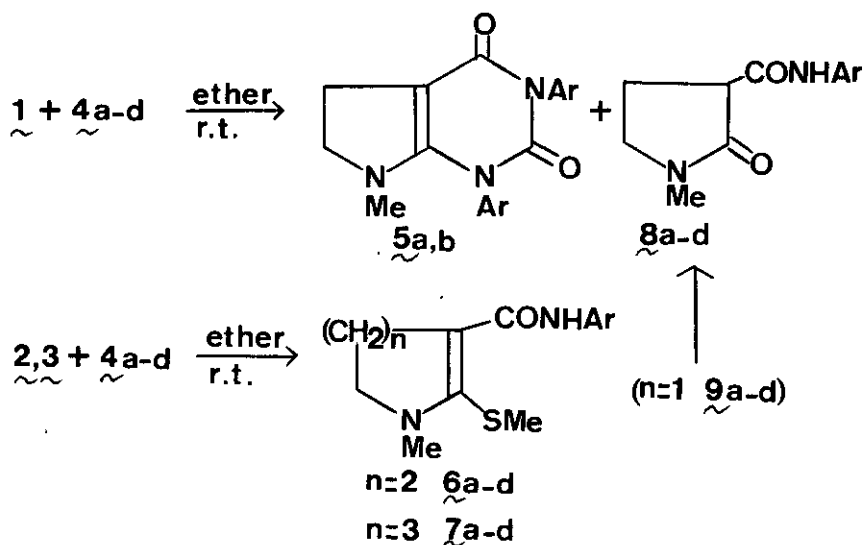


Table I. Reaction of ketene-S,N-acetals ( $\sim 1-3$ ) with aryl isocyanates ( $\sim 4a-d$ )<sup>a</sup>

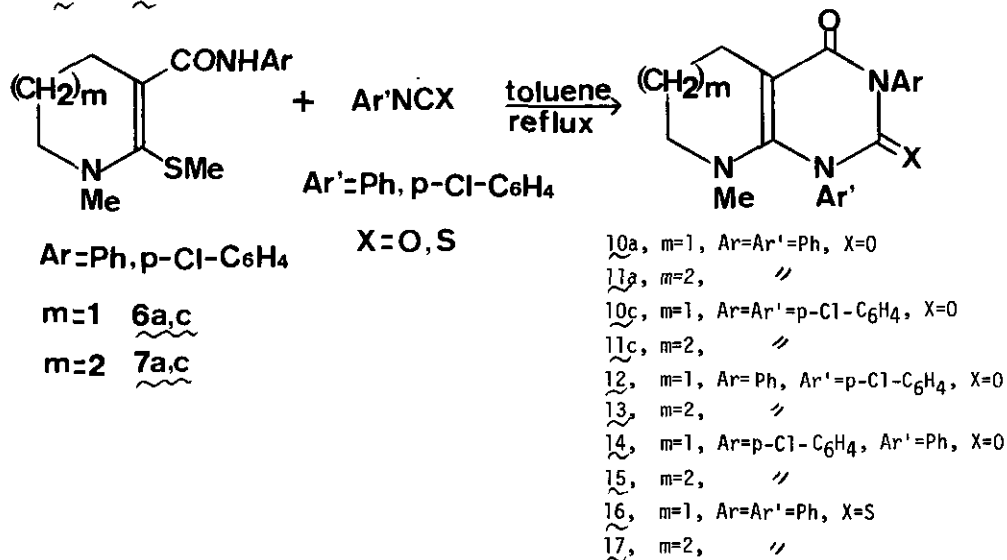
| Product <sup>b</sup> | Yield (%) | mp <sup>c</sup> (°C) | nmr (CDCl <sub>3</sub> ) $\delta$ [ppm] |      |      | ir (Nujol) $\nu$ [cm <sup>-1</sup> ] |                  | MS m/e (M <sup>+</sup> ) |
|----------------------|-----------|----------------------|-----------------------------------------|------|------|--------------------------------------|------------------|--------------------------|
|                      |           |                      | SMe                                     | NMe  | NH   | NH                                   | C=O              |                          |
| $\sim 5a$            | 31        | 234-235              |                                         | 2.17 |      |                                      | 1690, 1650, 1590 | 319                      |
| $\sim 5b$            | 26        | 218-220              |                                         | 2.13 |      |                                      | 1700, 1660, 1600 | 347                      |
| $\sim 6a$            | 100       | 135-137              | 2.33                                    | 3.00 | 9.05 | 3300, 1640                           |                  | 262                      |
| $\sim 6b$            | 95        | 134-136              | 2.25                                    | 3.00 | 9.05 | 3350, 1620                           |                  | 276                      |
| $\sim 6c$            | 92        | 140-142              | 2.30                                    | 3.03 | 9.20 | 3360, 1630                           |                  | 298, 296                 |
| $\sim 6d$            | 93        | 146-147              | 2.30                                    | 3.03 | 9.20 | 3360, 1630                           |                  | 342, 340                 |
| $\sim 7a$            | 60        | 147-149              | 2.20                                    | 3.03 | 8.43 | 3360, 1630                           |                  | 276                      |
| $\sim 7b$            | 66        | 144-146              | 2.27                                    | 2.93 | 8.33 | 3340, 1635                           |                  | 290                      |
| $\sim 7c$            | 57        | 152-154              | 2.30                                    | 3.03 | 8.47 | 3300, 1640                           |                  | 312, 310                 |
| $\sim 7d$            | 53        | 157-159              | 2.30                                    | 3.05 | 8.47 | 3300, 1640                           |                  | 356, 354                 |
| $\sim 8a$            | 32        | 168-170              |                                         | 2.90 | 9.87 | 3280, 1660, 1600                     |                  | 218                      |
| $\sim 8b$            | 33        | 189-195              |                                         | 2.90 | 9.67 | 3280, 1660, 1610                     |                  | 232                      |
| $\sim 8c$            | 46        | 197-201              |                                         | 2.97 | 9.95 | 3280, 1660, 1610                     |                  | 254, 252                 |
| $\sim 8d$            | 53        | 207-213              |                                         | 2.90 | 9.87 | 3260, 1660, 1610                     |                  | 298, 296                 |

a) Reaction time was overnight.

b) All compounds gave satisfactory analyses.

c) CH<sub>2</sub>Cl<sub>2</sub>-<sup>i</sup>Pr<sub>2</sub>O was used as the solvent for recrystallization.

The products formed were dependent on the ring size of ketene-S,N-acetals. The five-membered ketene-S,N-acetal (1) behaved more reactive toward aryl isocyanates compared with the six- and seven-membered ketene-S,N-acetals (2 and 3). The lactams (8a-d) would be probably yielded by hydrolysis of 9 through alumina column chromatography. However, 9 could not be isolated. The fused pyrimidinedione derivatives would be formed by the reaction of a second molecule of ArNCO with vinylogous ureas (1:1 adducts) as intermediates. This supposition was confirmed by the following experiments. Reaction of 6a and 7a with 4a in boiling toluene afforded the corresponding ring closure products (10a and 11a), respectively, which were identical with products prepared by the one-step synthesis.<sup>3</sup> Compounds 10c and 11c were also generated by the similar procedure. Next, we attempted the reaction of 1:1 adducts with another aryl isocyanates (Ar'NCO). The cyclization reaction of 6a with 4c in boiling toluene gave the fused pyrimidine derivative (12). In a similar manner, the fused uracil derivatives (13, 14, and 15) were synthesized. Further, the reaction of 6a and 7a with phenyl isothiocyanate was carried out to give the monothiones (16 and 17), respectively. These results are summarized in Table II.



From these results, it was proved that the vinylogous ureas were the intermediates for one-step synthesis of the fused pyrimidines. In conclusion, reaction of ketene-S,N-acetals with aryl isocyanates was dependent on the reaction condition (solvents and temperature) and the ring-size using ketene-S,N-acetals. The vinylogous ureas having the bifunctional character were converted to some uracil derivatives, reacting to aryl isocyanates or isothiocyanate, which are of biological interest. In addition, the extensive application to a new heterocyclic synthesis is expected by the reaction of the vinylogous ureas based on the bifunctional property with other heterocumulenes and is now under investigation.

Table II. Reaction of the vinylogous ureas (1:1 adducts) with aryl isocyanates and isothiocyanate.<sup>a</sup>

| Prod-<br>uct <sup>b</sup> | Yield<br>(%) | mp <sup>c</sup><br>(°C) | nmr <sup>d</sup> (CDCl <sub>3</sub> ) δ[ppm]<br>NMe | ir (Nujol) ν(cm <sup>-1</sup> ) | MS m/e (M <sup>+</sup> ) |
|---------------------------|--------------|-------------------------|-----------------------------------------------------|---------------------------------|--------------------------|
| 10a                       | 55           | 215-218                 | 2.32                                                | 1700, 1640, 1605                | 333                      |
| 11a                       | 74           | 273-276                 | 2.27                                                | 1700, 1650, 1610                | 347                      |
| 10c                       | 36           | 200-203                 | 2.33                                                | 1705, 1640, 1605                | 405, 403, 401            |
| 11c                       | 42           | 227-229                 | 2.30                                                | 1700, 1650, 1610                | 419, 417, 415            |
| 12                        | 32           | 214-216                 | 2.20                                                | 1710, 1640, 1610                | 370, 368                 |
| 13                        | 38           | 199-202                 | 2.33                                                | 1710, 1660, 1620                | 384, 382                 |
| 14                        | 22           | 213-215                 | 2.20                                                | 1715, 1640, 1615                | 370, 368                 |
| 15                        | 27           | 269-272                 | 2.30                                                | 1700, 1650, 1625                | 384, 382                 |
| 16                        | 19           | 238-240                 | 2.15                                                | 1690, 1640, 1620                | 365                      |
| 17                        | 45           | 273-276                 | 2.20                                                | 1690, 1640, 1610                | 379                      |

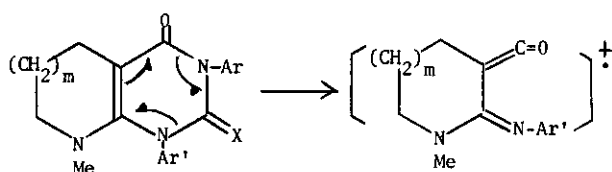
a) Reaction time was overnight.

b) All compounds afforded satisfactory analyses.

c) CH<sub>2</sub>Cl<sub>2</sub>-<sup>i</sup>Pr<sub>2</sub>O was used as the solvent for recrystallization.

d) The signals of NCH<sub>3</sub> were considerably shielded by the orthogonal aryl group, which could be attributed to the plane of the fused pyrimidines.

e) In the fragmentation of the fused pyrimidines, retro-Diels-Alder decomposition with the expulsion of ArNCX proceeded to produce the ion radical peak [M-ArNCX]<sup>+</sup>.



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#### References

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- 2) H. Takahata, A. Tomiguchi, and T. Yamazaki, *Heterocycles*, 1981, 16, 1569.
- 3) H. Takahata, A. Tomiguchi, M. Nakano, and T. Yamazaki, *Synthesis*, in press.

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