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

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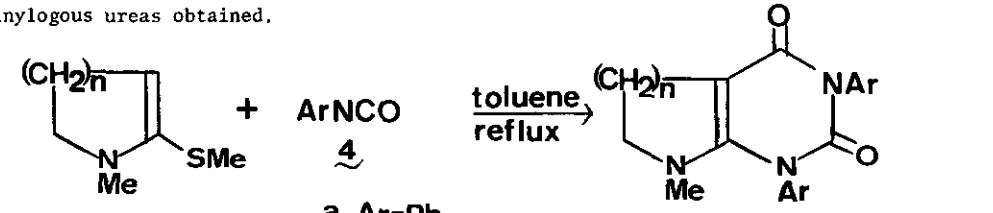
Abstract — Reaction of ketene-S,N-acetals (1, 2, and 3) as activated lactams with aryl isocyanates (4a-d) has been described. The vinylogous ureas (6a-d and 7a-d) obtained by this reaction have been utilized as intermediates for the synthesis of some uracil derivatives.

We have been interested in developing a new synthesis of heterocycles using ketene-S,N-acetals[1] (1, 2, and 3) as activated lactams.[2] In the previous paper,[3] 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 vinylogius ureas and a two-step synthesis of azacycloalkano[2,3-d]pyrimidines via the vinylogous ureas obtained.



1 n=1
2 n=2
3 n=3

a Ar=Ph
b Ar= p-Me-C6H4
c Ar= p-Cl-C6H4
d Ar= p-Br-C6H4

azacycloalkano[2,3-d]pyrimidines (uracil derivatives)

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.

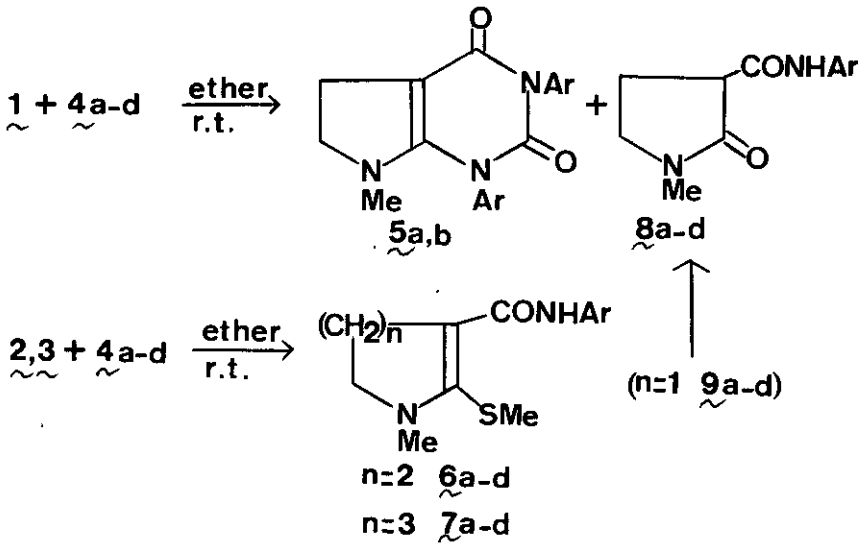


Table I. Reaction of ketene-S,N-acetals (1-3) with aryl isocyanates (4a-d)[a]

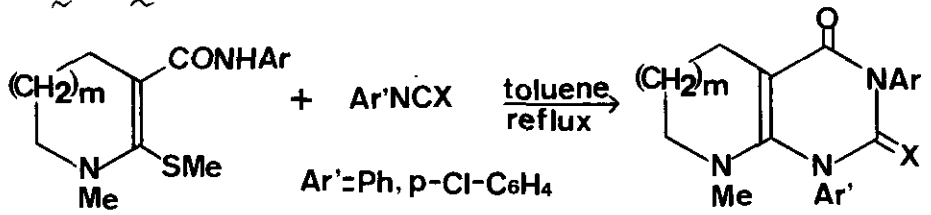
Product[b]	Yield (%)	mp[c] (°C)	nmr ($CDCl_3$) δ[ppm] SMe	NMe	NH	ir (Nujol) ν[cm^{-1}] NH	C=O	MS m/e (M^+)
5a	31	234-235		2.17			1690, 1650, 1590	319
5b	26	218-220		2.13			1700, 1660, 1600	347
6a	100	135-137	2.33	3.00	9.05	3300, 1640		262
6b	95	134-136	2.25	3.00	9.05	3350, 1620		276
6c	92	140-142	2.30	3.03	9.20	3360, 1630		298, 296
6d	93	146-147	2.30	3.03	9.20	3360, 1630		342, 340
7a	60	147-149	2.20	3.03	8.43	3360, 1630		276
7b	66	144-146	2.27	2.93	8.33	3340, 1635		290
7c	57	152-154	2.30	3.03	8.47	3300, 1640		312, 310
7d	53	157-159	2.30	3.05	8.47	3300, 1640		356, 354
8a	32	168-170		2.90	9.87	3280, 1660, 1600		218
8b	33	189-195		2.90	9.67	3280, 1660, 1610		232
8c	46	197-201		2.97	9.95	3280, 1660, 1610		254, 252
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_2Cl_2-$^iPr_2O$ 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.[3] 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.



10a, m=1, Ar=Ar'=Ph, X=O
11a, m=2, 〃
10c, m=1, Ar=Ar'=p-Cl-C_6H_4, X=O
11c, m=2, 〃
12, m=1, Ar=Ph, Ar'=p-Cl-C_6H_4, X=O
13, m=2, 〃
14, m=1, Ar=p-Cl-C_6H_4, Ar'=Ph, X=O
15, m=2, 〃
16, m=1, Ar=Ar'=Ph, X=S
17, m=2, 〃

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.[a]

Product[b]	Yield (%)	mp[c] (°C)	nmr[d] ($CDCl_3$) δ[ppm] NMe	ir (Nujol) ν(cm^{-1})	MS m/e (M^+)
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

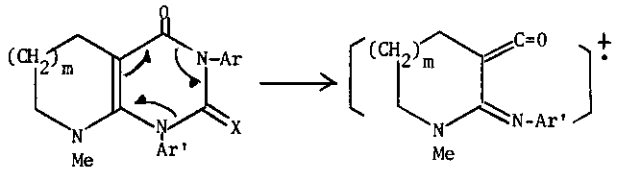
a) Reaction time was overnight.

b) All compounds afforded satisfactory analyses.

c) CH_2Cl_2-$^iPr_2O$ was used as the solvent for recrystallization.

d) The signals of NCH_3 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 $[M\text{-}ArNCX]^{+\cdot}$.



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