STUDIES ON KETENE AND ITS DERIVATIVES 114.[1]

1,4-CYCLOADDITION OF KETENE TO ETHYL *N*-(2-PYRIDYL)FORMIMIDATES

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Abstract —— Reaction of ketene with ethyl *N*-(2-pyridyl)formimidate (1a) in acetone at room temperature gave 3-acetylpyrido[1,2-*a*]pyrimidin-4(4*H*)-one (2) whereas excess ketene gas was passed over the imidate 1a without solvent at 75 °C to give pyrido[1,2-a]pyrimidin-4(4*H*)-one (3a) and 2-formamidopyridine (4a), both of which would be formed by 1,4-cycloaddition of ketene. Similarly, reactions of ketene with the methyl analogs 1b-e were also carried out to give pyridopyrimidines (3b-e) and 2-formamidopyridines (4b,c,e).

It had been recognized that, compared to substituted ketenes, ketene itself hardly reacted with imines because of its low reactivity.[2-5] However, we have found that α-unsubstituted β-lactams are obtained by passing ketene gas over Schiff bases without solvent under heating.[6] Under the same conditions ketene also reacts with compounds having conjugated C=N double bond such as *N*-cinnamylidene aniline to give β-lactams.[6] On the other hand, it has been reported that ketene undergoes 1,4-cycloaddition with ethyl α-(dimethylaminomethylene)-2-pyridineacetate to give a quinazoline derivative.[7]

In this communication we wish to report the 1,4-cycloaddition of ketene to ethyl *N*-(2-pyridyl)formimidates, which possess C=N double bond conjugated with pyridine ring C=N. When ethyl *N*-(2-pyridyl)formimidate (1a)[8] was allowed to react with excess ketene in acetone for 2 days at room temperature, 3-acetylpyrido-[1,2-a]pyrimidin-4(4*H*)-one (2) [mp 152 - 153 °C (lit.[9] mp 150 °C)] was obtained in 12% yield. Since diketene reacts with 1a to give 2,[10] compound 2 would be formed by the reaction of 1a with diketene derived from ketene.

Next, excess ketene gas was passed over 1a at 75 °C without solvent to give pyrido[1,2-*a*]pyrimidin-4(4*H*)-one (3a) [mp 131 - 132 °C (lit.[11] mp 127 °C)] and 2-formamidopyridine (4a) [mp 75 - 77 °C (lit.[12] mp 71 °C)] in 58 and 34% yields, respectively. Similarly, reaction of ketene with methyl analogs (1b,c,e) gave pyrido[1,2-*a*]pyrimidin-4(4*H*)-ones (3b,c,e) and 2-formamides (4b,c,e). However, reaction with ethyl *N*-(5-methyl-2-pyridyl)formimidate (1a) did not give the 2-formamide 4d, but gave a 68% yield of the pyrido-[1,2-*a*]pyrimidine 3d as a sole product.

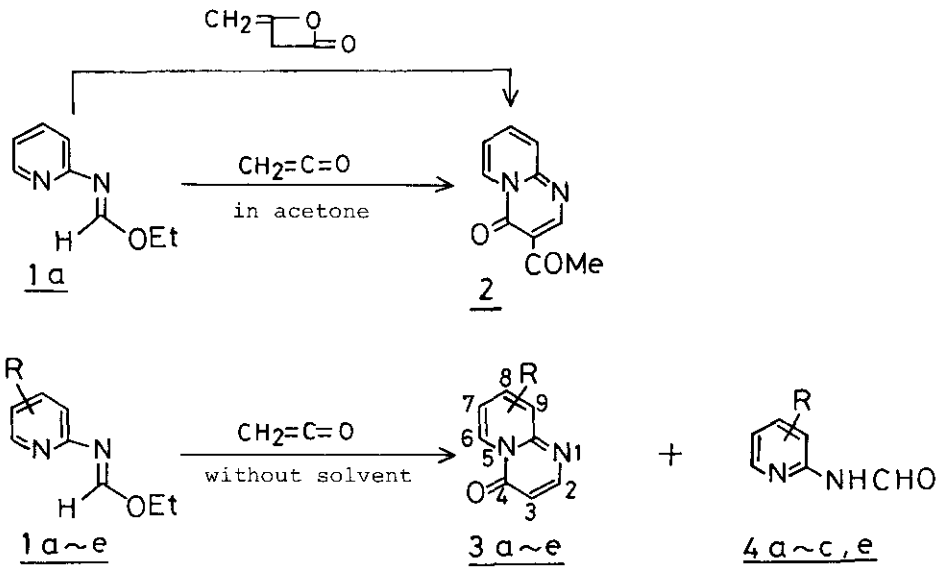


Table 1. Reaction of Ketene with Ethyl *N*-(2-Pyridyl)formimidates (1a-e)[a)]

Formimidate		Reaction	Product, Yield (%)	
Compd. No.	R	time (h)	3	4 (mp, °C)
1a	H	1.5	58	34 (75 - 77) (lit.[12] mp 71)
1b	3-Me	0.5	85	6 (122 - 124) (lit.[13] mp 138 - 139)
1c	4-Me	0.5	44	45 (87 - 88)
1d	5-Me	1.5	68	——
1e	6-Me	1.5	25	31 (78 - 79)

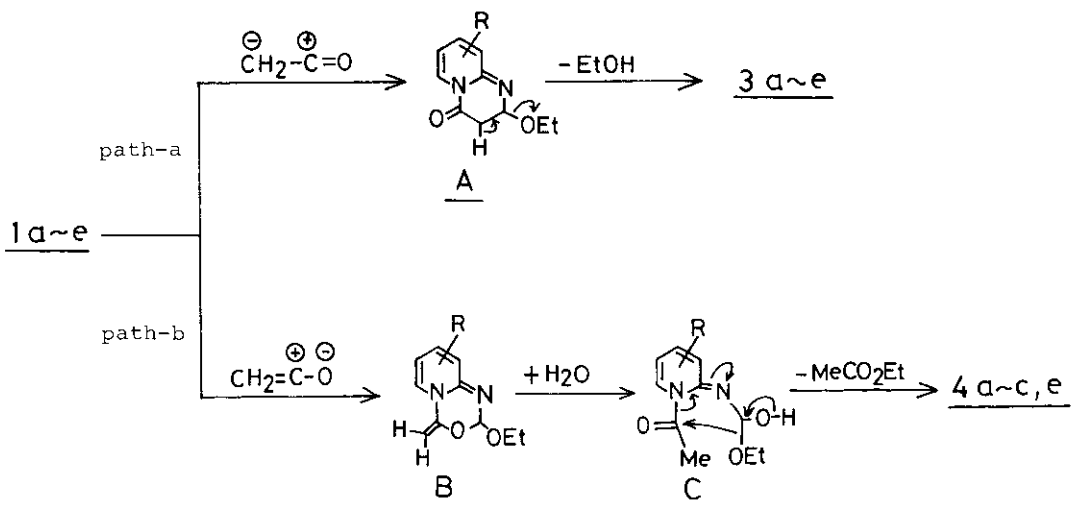
a) The reaction was carried out at 75 °C.

Table 2. Melting Points and Spectral Data for Pyrido[1,2-*a*]pyrimidin-4(4*H*)-ones (3a-e)[a)]

Compd. No.	mp (°C) [lit. mp (°C)]	^{1}H-nmr δ ($CDCl_3$) 2-H	3-H	6-H	$\nu_{max.}$ ($CHCl_3$) cm^{-1}	
3a	131 - 132 (127)[11]	8.33 (d)	6.50 (d)	9.13 (d)	1690	1640
3b	113 - 115 (113.8 - 114.8)[14]	8.21 (d)	6.45 (d)	9.00 (d)	1685	1635
3c	146 - 147	8.28 (d)	6.43 (d)	9.00 (d)	1685	1645
3d	98 - 99 (78.8 - 82.8)[14]	8.25 (d)	6.40 (d)	8.87 (s)	1680	1640
3e	109 - 111 (118 - 119)[14]	8.05 (d)	6.25 (d)	——	1690	1640

a) Satisfactory elemental analyses were obtained from all compounds.

The mechanisms of formation of the pyrido[1,2-*a*]pyrimidine 3 and the formamide 4 can be elucidated as follows; 1,4-cycloaddition of the C=C bond of ketene to the imidate 1 would give an intermediate A, which eliminates ethanol to be transformed into 3 (path-a). On the other hand, the C=O bond of ketene undergoes 1,4-cycloaddition with 1 to give an intermediate B, hydrolysis[15] of which gives 4 *via* an intermediate C (path-b).



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14. These compounds are synthesized from cyclic malonates, prepared by the somewhat troublesome method; Sterling Drug Inc. Brit. 1,147,760 (*Chem. Abstr.* 1969, 71, 49967a).
15. Hydrolysis would take place during the purification by column chromatography.

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