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A FACILE RING CLEAVAGE OF CYCLIC KETONES. SYNTHESIS OF 9-(ALKOXYCARBONYLALKYL)PYRIDO[1,2-a]PYRIMIDINES

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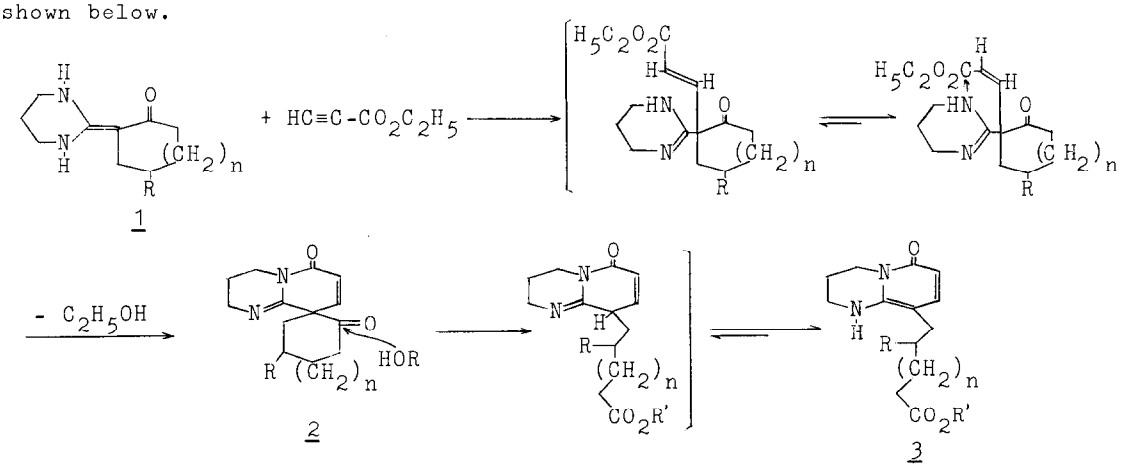
Abstract: 2-(Hexahydro-2-pyrimidinylidene)cycloalkanones 1 react with ethyl propiolate in alcoholic solution to give 9-(alkoxycarbonylalkyl)-pyrido[1,2-a]pyrimidines 3 via ring cleavage of cyclic ketones.

We have reported the reaction of heterocyclic ketene aminals with ester of α,β-unsaturated acids to give imidazo[1,2-a]pyridine and pyrido[1,2-a]pyrimidine derivatives via addition, cis-trans-isomerization and cyclocondensation sequence[1]. In cases of γ-lactone substituted ketene aminals, the spiro compounds may be obtained[2], but as it reacted with propiolate in alcoholic solution, ring cleavage of γ-lactone also occurred[3]. Here we wish to report the results of the reaction of cycloalkanone substituted ketene aminals 1 with ethyl propiolate.

2-(Hexahydro-2-pyrimidinylidene)cycloalkanones 1 readily reacted with ethyl propiolate in heated methanol, and instead of the spiro compounds 2, 9-(methoxycarbonylalkyl)pyrido[1,2-a]pyrimidines 3 were obtained in good yields. The constitutions of 3 ($R' = CH_3$) were determined by MS, elemental analyses and the IR, and ^1H and ^{13}C NMR spectra. When the reaction was conducted in ethanol, 3 obtained were ethyl ester ($R' = C_2H_5$).

The formation of 3 is obviously due to the ring cleavage of cyclic ketones 2 formed initially. Therefore, a reasonable reaction path of the formation of 3 from 1 and ethyl propiolate in alcoholic solution can be rationalized as shown below.



In the literature, ring cleavage of cyclic α-nitroketones under basic or acidic conditions have widely been investigated, and the results have been reviewed by Fischer and Weitz[4]. The ring cleavage of cyclic ketones[5,6] and

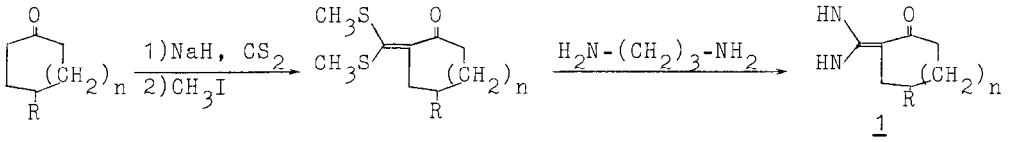
α-acyl cyclic ketones[7] were also reported, but the reaction conditions were always drastic or in strongly basic medium. The ring cleavage of spiro diketone in alkali solution was also once reported[8]. The formation of 3 by ring cleavage of cyclic ketone in neutral and mild conditions is a rather seldom example. The causes of easy cleavage of cyclic ketone of 2 are probably due to the α-vinylogous amide and α-imine groups, and also most possibly to this spiro structure.

The reaction conditions, m. p. and yields of products are listed in Table.

Entry	Substrate[a]		Conditions[b]	Product[a]		m.p.(°C)	Yield[c](%)
1	1a	n=0, R=H	methanol, 40° C, 25 h	3a	R'=CH_3	118-120	78
2	1b	n=1, R=H	methanol, 40° C, 20 h	3b	R'=CH_3	120.5-122.5	86
3	1c	n=2, R=H	methanol, reflux, 40 h	3c	R'=CH_3	97-98.5	90
4	1d	n=3, R=H	methanol, reflux, 40 h	3d	R'=CH_3	92-95	82
5	1e	n=1, R=CH_3	methanol, 40° C, 20 h	3e	R'=CH_3	120-123	83
6		1c	ethanol, 50° C, 30 h	3f	R'=C_2H_5	88-90	61
7		1e	ethanol, 50° C, 25 h	3g	R'=C_2H_5	126-128.5	71

[a]MS, IR, ^1H and ^{13}C NMR data and elemental analyses are consistent with all new compounds obtained. [b]Molar ratio of 1 : ethyl propiolate is 1 :1. [c]Isolated yields.

The starting compounds 1 were obtained by the reaction sequence shown below.



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