RING TRANSFORMATION OF 1,3-OXAZIN-4-ONES INTO TRIAZOLES, PYRAZOLES, AND PYRIMIDINES

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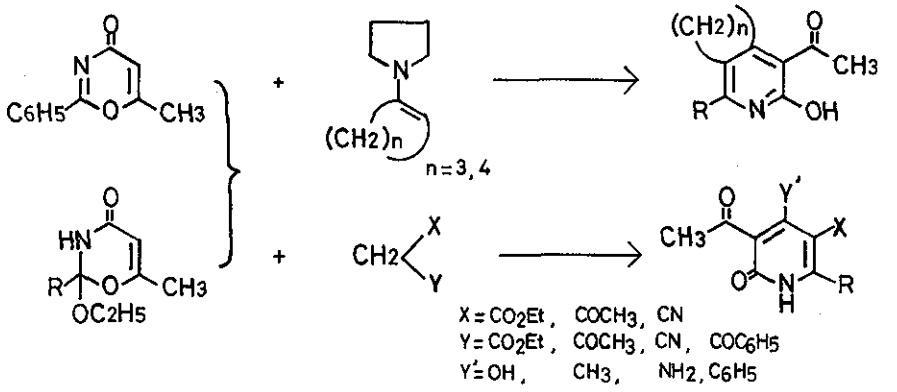
In the course of our continuing synthetic investigation of heterocycles using diketene,[1] 1,3-oxazin-4-one derivatives[2] were found to be potentially useful for the synthesis of N-heterocycles. Recently, we reported that the reactions of 1,3-oxazin-4-one derivatives with enamines[3] and with compounds having active methylene group[4] lead to the transformation into tetrahydroisoquinolines, pyrindines and 4,5,6-substituted 3-acetyl-2-pyridones, respectively (shown in Scheme 1).

Our interest has been in further development of these ring transformation of the 1,3-oxazine ring into a variety of heterocycles, and here the transformation of 1,3-oxazin-4-one derivatives into triazoles, pyrazoles, and pyrimidines are described.



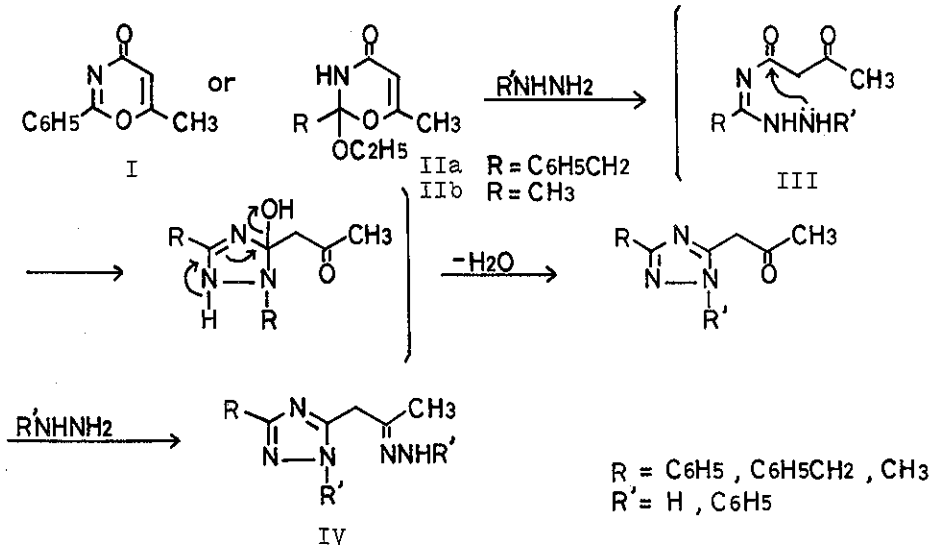
Scheme 1 R = CH_3, C_6H_5

Ring Contraction into Triazoles and Pyrazoles[6)]

The ring contraction of 1,3-oxazin-4-one derivatives into the 1,2,4-triazole ring and the pyrazole ring was carried out by treatment with appropriate hydrazines. Reaction of 6-methyl-2-phenyl-4H-1,3-oxazin-4-one (I) with two equimolar amounts of phenylhydrazine and hydrazine hydrate in ethanol under reflux gave the corresponding phenylhydrazone (IVa) and hydrazone (IVb) of the 3-acetonyl-1,2,4-triazole in nearly quantitative yield, respectively. Analogously, the dihydro-1,3-oxazin-4-one derivatives (II) were converted into the corresponding triazoles (shown in Table 1). In contrast to hydrazine base, hydrazine salts were allowed to react with the 1,3-oxazine I to lead the formation of the pyrazole instead of the triazole. Heating a solution of I with hydrazine sulfates in 80% ethanol under reflux afforded the corresponding pyrazole derivatives (VII) in good yield.

These results evidently propose the mechanism that the contraction reaction proceeds in two steps: the first involves ring

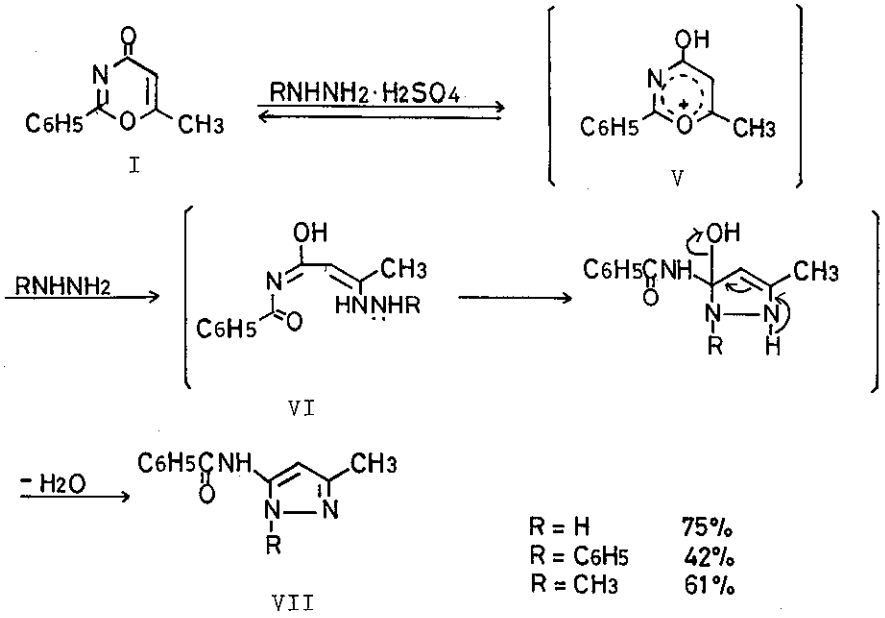
opening by alternative cleavage of carbon-oxygen bond (either C_2-O or C_6-O bond) of the 1,3-oxazine ring into open-chain intermediate, and the second is the ring closure of the intermediate. The cleavage is initiated by nucleophilic attack of the hydrazine. In the reaction with hydrazine base the initial attack on position 2 of the 1,3-oxazine ring seems to be much preferred rather than on position 6, and subsequently causes the cleavage of C_2-O bond leading to open-chain intermediate (III), whereas use of hydrazine sulfate brings about the predominant attack on posion 6 of the 1,3-oxazinium salt (V) resulted from interaction between the 1,3-oxazin-4-one and the hydrazine sulfate. Consequently, the pathway of the ring contraction into the triazole and the pyrazole which involves the formation of key intermediate (III) and (VI) can be depicted as shown in Schemes 2 and 3.



Scheme 2

Table 1. Ring Contraction into 1,2,4-Triazoles

Oxazine	Hydrazine	1,2,4-Triazole IV No.	R	R'	mp	Yield(%)
I	$C_6H_5NHNH_2$	IVa	C_6H_5	C_6H_5	177(dec)	78
I	$NH_2NH_2 \cdot H_2O$	IVb	C_6H_5	H	115(dec)	91
IIa	$C_6H_5NHNH_2$	IVc	$C_6H_5CH_2$	C_6H_5	207(dec)	78
IIb	$C_6H_5NHNH_2$	IVd	CH_3	C_6H_5	154	35

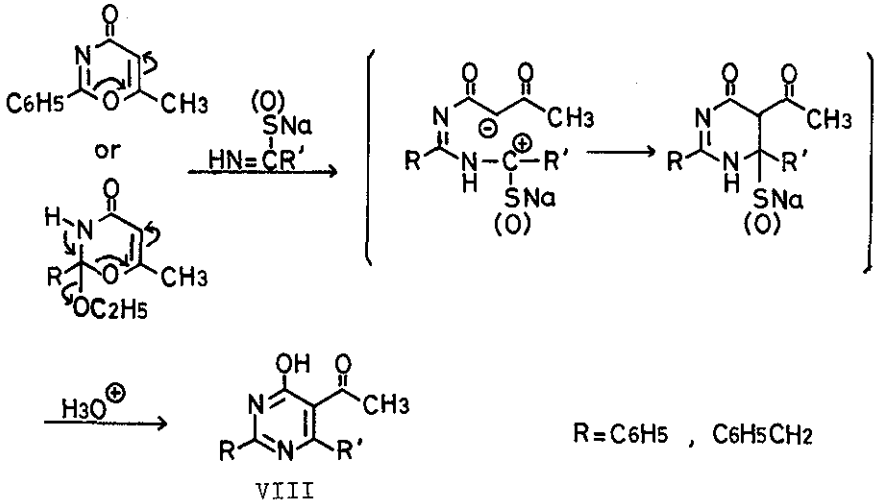


I V VI VII

Scheme 3

Transformation into Pyrimidines[7]

We previously reported [2,5] that the 1,3-oxazin-4-one was converted into the pyrimidine by treatment with ammonia, and that self-condensation of the 2,3-dihydro-1,3-oxazin-4-one (II) took place by heating or by treatment with acid to afford the pyrimidine. In addition, we have developed a route for facile synthesis of pyrimidines by the reaction of the 1,3-oxazine with appropriate carboxylic acid amides and thioamides which are readily available. When the 1,3-oxazine (I and II) was allowed to react with the amide in dimethylformamide in the presence of sodium hydride, followed by neutralization with acid, the corresponding 3-acetylpyrimidines (VIII) were obtained in low yield. Extension of this reaction with the thioamide instead of the amide resulted in satisfactory yields of the desired pyrimidines (VIIIa-f) as shown in Table 2. A probable pathway of the transformation into the pyrimidine can be elucidated as follows.



VIII

Scheme 4

Table 2. Transformation into Pyrimidines

Oxazine	Thioamide	Pyrimidine VIII No.	R	R'	mp	Yield(%)
I	$C_6H_5CSNH_2$	VIIIa	C_6H_5	C_6H_5	297(dec)	53(12)*
I	CH_3CSNH_2	VIIIb	C_6H_5	CH_3	267(dec)	85(8)
I	$C_2H_5CSNH_2$	VIIIc	C_6H_5	C_2H_5	215	52(10)
I	$C_6H_5CH_2CSNH_2$	VIIId	C_6H_5	$C_6H_5CH_2$	215	85(2)
IIa	$p\text{-}CH_3OC_6H_4CSNH_2$	VIIIe	$C_6H_5CH_2$	$p\text{-}CH_3OC_6H_4$	197(dec)	32
IIa	CH_3CSNH_2	VIIIf	$C_6H_5CH_2$	CH_3	188	12

* Numbers in parentheses show yields from the acid amide.

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