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THE OXIDATIVE CYCLIZATION OF α,β-UNSATURATED KETOXIMES[1]

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The autoxidation of dibenzalacetone oxime in the presence of several kinds of transition metal salts gave 4-hydroxy-5-phenyl-3-styryl-4,5-dihydroisoxazole, accompanied with cinnamonitrile and benzaldehyde. Similar treatment of benzalacetophenone oxime, benzalacetone oxime and their p-substituted derivatives also afforded 4-hydroxy-4,5-dihydroisoxazole derivatives.

Recently palladium(II)-induced cyclization of unsaturated ketoximes under an atmosphere of argon to give isoxazoles or pyridines has been reported.[2,3] In this paper we wish to report the oxidative cyclization of α,β-unsaturated ketoximes to 4-hydroxy-4,5-dihydroisoxazoles under the catalytic effect of copper(II), cobalt(II), and manganese(II) salts.

When a solution of dibenzalacetone oxime (**1a**, 3 mmol) and cobalt(II) acetate (0.3 mmol) in methanol (20 ml) was stirred under an atmosphere of oxygen at 30 ± 0.5°C, rapid uptake of oxygen took place. Separation of the reaction mixture gave 4-hydroxy-5-phenyl-3-styryl-4,5-dihydroisoxazole (**2a**), mp 194-195°C; ν_{max}^{KBr} 3235 cm^{-1}; λ_{max}^{MeOH} 293 nm (logε 4.97). O-acetate, mp 128-130°C; ν_{max}^{KBr} 1740 cm^{-1}; $\delta_{ppm}^{CDCl_3}$ 5.68 (C_4-H, d, J=2 Hz), 6.34 (C_5-H, d, J=2 Hz). Heating of **2a** with sulfuric acid-acetic acid gave 5-phenyl-3-

Table 1. The Oxidative Cyclization and the Oxidative Fission of 1a.[a)]

Reaction time (hr)	Solvent	Metal salt	O_2 absorbed (ml)	Yield (%)[b)]		
				2a	3	4
2	Methanol	$Cu(OAc)_2$	53	18 (13)	7	34
"	"	$Co(OAc)_2$	57	42 (40)	7	10
"	"	$Mn(OAc)_2$	53	39 (37)	5	15
5	"	$Ni(OAc)_2$	31	23 (20)	4	22
"	"	$Zn(OAc)_2$	5	7 (5)	1	4
2	Acetone	$Cu(OAc)_2$	49	19 (16)	3	17
"	Benzene	"	56	18 (14)	7	17
"	Methanol	$Cu(acac)_2$	19	15 (10)	7	22
"	"	$Co(acac)_2$	68	52 (50)	4	11
"	"	$Mn(acac)_2$	73	38 (36)	5	25

a) The oxime (3 mmol), metal salt (0.3 mmol), and the solvent (20 ml) were used, and the reaction temperature was 30 ± 0.5°C. b) The yield of 2a was obtained by the TLC separation of the product followed by UV analysis (isolated yields were listed in parentheses), and the yields of 3 and 4 were estimated by TLC separation followed by NMR analysis using peak areas at 10.05 ppm (for 3) and at 5.80 ppm (for 4), relative to the area of CH_3 protons of known amount of toluene added as an internal standard.

styrylisoxazole[4] in 63% yield. Benzaldehyde (3) and cinnamonitrile (4) were the by-products. The effect of several kinds of metal salts on the yields of 2a, 3, and 4 was shown in Table 1. It is apparent that Co(II) and Mn(II) salts are very effective, while Zn(II) salt is almost ineffective. When Cu(II) salt was used the yield of 2a was low.

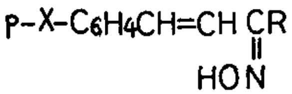
Similar reaction was carried out with benzalacetophenone oxime (1b), its 4-methoxy (1c), 4'-methoxy (1d), and 4'-chloro (1e) derivatives, as well as benzalacetone oxime (1f), its 4-methyl (1g), 4-methoxy (1h), and 4-chloro (1i) derivatives. The melting points, the yields, and the spectral data of the resulting 4-hydroxy-4,5-dihydroisoxazoles (**2b**~**2i**) are listed in Table 2.

In these oxidative cyclization reactions it was observed that 1) the reaction of benzalacetone oxime derivatives was very slow compared with

Table 2. The Melting Points, the Yields, and the Spectral Data of **2b**~**2i**.[a)]

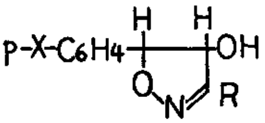
Compound	Mp (°C)	Yield[b)] (%)	ν_{max}^{KBr} (cm^{-1})	λ_{max}^{MeOH} nm (log ε)		
2b[c)]	168-169	49	3315	264 (4.15)		
2c	131-133	46	3280	266 (4.21)		
2d	151-152	47	3275	277 (4.29)		
2e	141-142	50	3250	269 (4.29)		
2f	101-103	36	3250	254 (2.20)	260 (2.31)	266 (2.21)
2g	68-69	38	3270	261 (2.47)	266 (2.55)	274 (2.47)
2h	116-117	40	3255	277 (3.19)	284 (3.12)	
2i	102-103	37	3275	263 (2.43)	269 (2.49)	276 (2.36)

a) The oxime (3 mmol), cobalt(II) acetate (0.3 mmol), and methanol (20 ml) were used. The reaction temperature and the reaction time for **1b**~**1e** were 30°C and 2 hr, while those for **1f**~**1i** were 50°C and 5 hr. b) The yields were estimated by UV and NMR analyses. c) O-acetate, mp 177-179°C. [$\delta_{ppm}^{CDCl_3}$ 5.61 (C_4-H, d, J=2 Hz), 6.31 (C_5-H, d, J=2 Hz)]. Reported mp of **2b** is 193-194°C,[5] and that of the acetate is 198-199°C[5] and 171-174°C.[6] The dehydration of **2b** that we have obtained gave also 3,5-diphenylisoxazole in 72% yield, and therefore it must be a stereoisomer of that described in the literature.



$p\text{-}X\text{-}C_6H_4CH{=}CH\underset{\underset{HON}{\|}}{C}R$

1a~**1i**



2a~**2i**

a:	X=H	R=CH=CHC$_6$H$_5$	d:	X=H	R=C$_6$H$_4$OCH$_3$-p	g:	X=CH$_3$	R=CH$_3$
b:	X=H	R=C$_6$H$_5$	e:	X=H	R=C$_6$H$_4$Cl-p	h:	X=OCH$_3$	R=CH$_3$
c:	X=OCH$_3$	R=C$_6$H$_5$	f:	X=H	R=CH$_3$	i:	X=Cl	R=CH$_3$

those of benzalacetophenone oximes and dibenzalacetone oxime, and it was necessary to raise the reaction temperature to 50°C for obtaining the comparable oxygen absorption rate; 2) introduction of chlorine on 4- or 4'-position slowed down the reaction rate, while the introduction of methyl or methoxyl group accelerated the reaction rate; 3) the yields of 4-hydroxy-4,5-dihydroisoxazoles were high when Co(II) or Mn(II) salt was used compared to that with Cu(II) salt.

In order to examine the behavior of a pair of stereoisomers of the oximes both E- and Z-forms of **1h**[7] were subjected to oxidative cyclization under the same conditions, giving **2h** in 37% and 40% yields respectively. Similar treatment of E- and Z-forms of **1i**[7] gave **2i** in 37% and 36% yields respectively. These results indicate that rapid isomerization must has occurred between the two isomers under the effect of these metal salts.

References

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