

PALLADIUM-INDUCED PYRIDINE SYNTHESIS FROM UNSATURATED KETOXIMES

Takahiro Hosokawa, Nobuo Shimo, Kazuyuki Maeda, Akio Sonoda, and Shun-Ichi Murahashi

Department of Chemistry, Faculty of Engineering Science, Osaka University,  
Osaka, Toyonaka, Japan, 560

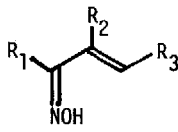
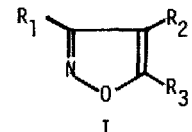
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Recently we reported that  $\alpha,\beta$ -unsaturated ketoximes can be converted into isoxazoles by using dichlorobis(triphenylphosphine)palladium.<sup>1)</sup> During the course of the study on this oxidative cyclization we came across an interesting pyridine formation reaction. We now wish to report a novel palladium-induced pyridine synthesis from  $\beta,\gamma$ - and  $\gamma,\delta$ -unsaturated ketoximes and 1,3-hexadiene-5-one oximes. There have been few reports<sup>2)</sup> on the pyridine formation by utilizing transition metal complexes, among which cobalt-catalyzed pyridine synthesis from acetylenes and nitriles developed by Yamazaki<sup>3)</sup> and Bönnerman<sup>4)</sup> are noteworthy.

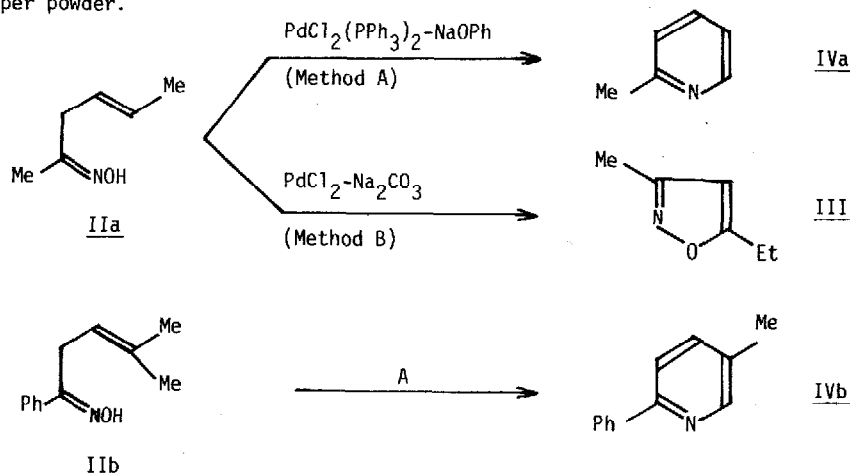
$\alpha,\beta$ -Unsaturated ketoximes are transformed into isoxazoles by the treatment with an equimolar amount of  $\text{PdCl}_2(\text{PPh}_3)_2$  in the presence of 5-fold excess of NaOPh in benzene at reflux (Method A) as reported previously.<sup>1)</sup> When the yield of this reaction is not satisfactory, an alternative method using  $\text{PdCl}_2\text{-Na}_2\text{CO}_3$  (1 : 1.2) in methylene chloride at room temperature (Method B) is efficient. Thus, isoxazoles Ia-d were conveniently obtained in moderate yields as summarized in Table I (see next page).

Next, we extended the reaction system to  $\beta,\gamma$ -unsaturated ketoximes and found a marked discrepancy between Method A and B. Thus, the reaction of 2-hexen-5-one oxime (IIa) by Method B afforded 3-methyl-5-ethylisoxazole (III) in 45 % yield, while when the oxime Ia

Table I. Isoxazole Synthesis From  $\alpha,\beta$ -Unsaturated Ketoximes

		 I			
$R_1$	$R_2$	$R_3$	Method	Yield of I (%)	
a	t-Bu	H	Ph	B	69
b	i-Pr	H	Ph	B	47
c	Me	H	Ph	B	39
d	Ph	H	Et	B	51
e	Ph	H	Ph	A	92

was allowed to react by Method A,  $\alpha$ -picoline (IVa) was interestingly obtained in 21 % yield. Similarly, with Method A, 2-methyl-5-phenyl-2-penten-5-one oxime (I**ib**) was converted into 2-phenyl-5-methylpyridine (IVb) in 43 % yield. The structures of these products were determined by analytical and spectroscopic data<sup>5</sup>; that of IVb was confirmed by comparison of the authentic sample independently synthesized by condensation of  $\beta$ -amino- $\alpha$ -methylacrolein and ethylbenzoylacetate followed by hydrolysis and decarboxylation at 200° in the presence of copper powder.

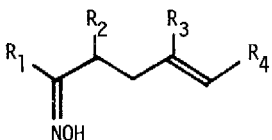
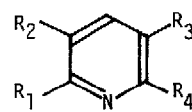
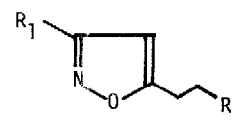


Pyridines IVa, IVb are formally derived from the coupling between the nitrogen atom and the methyl carbon of the oximes. This unique cyclization is the first case of pyridine formation from  $\beta,\gamma$ -unsaturated ketoxime,<sup>6</sup> although the precise process of the

reaction is quite obscure.

Analogously, under the condition of A,  $\gamma,\delta$ -unsaturated ketoximes Va-e gave the corresponding pyridines VIa-e quite generally as summarized in Table II, while isoxazoles VIIa (76 %) and VII d (12 %) were obtained from the oximes Va and Vd by Method B.

Table II. Pyridine Formation From  $\gamma,\delta$ -Unsaturated Ketoximes.

	 $\text{R}_1$ $\text{R}_2$ $\text{R}_3$ $\text{R}_4$					 $\text{R}_1$ $\text{R}_2$ $\text{R}_3$ $\text{R}_4$	 $\text{R}_1$ $\text{R}_4$
	$\text{R}_1$	$\text{R}_2$	$\text{R}_3$	$\text{R}_4$	Method	<u>VI</u> (%)	<u>VII</u> (%)
a	Ph	H	H	H	A	33	—
					B	—	76
b	Me	H	Me	H	A	21	—
c	Me	H	H	H	A	19	—
d	Ph	H	H	Me	A	9 <sup>a)</sup>	—
					B	—	12
e	$-(\text{CH}_2)_4-$	H	H	H	A	8 <sup>b)</sup>	—

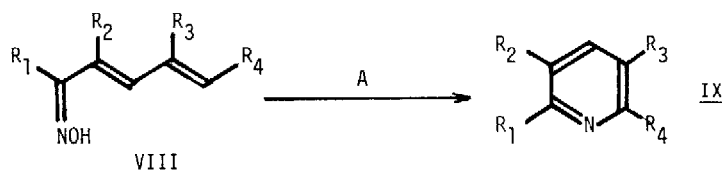
a) 1-Phenyl-4-hexen-1-one (17 %) and 2-phenyl-5-ethyl-3H-4,5-dihydropyrrole (16 %) were also obtained along with an unidentified product (~5 %).

b) Other products were 2-allylcyclohexanone (8 %) and 2-(3-phenylallyl)cyclohexanone (13 %).

The formation of isoxazoles from Va,d and IIa ( $\beta,\gamma$ -unsaturated ketoxime) can be explained by initial isomerization of the double bond toward conjugated position with the oxime group followed by intramolecular oxypalladation.<sup>1),7)</sup>

The pyridine formation from  $\gamma,\delta$ -unsaturated ketoximes Va-e apparently involves the dehydrogenation process from  $\alpha,\beta$ -positions in addition to the coupling between the nitrogen and  $\delta$ -carbon atom of the oximes. Then, with anticipating that conjugated ketoximes would give pyridines more smoothly, we investigated the cyclization with Method A upon 1,3-hexadiene-5-one oximes which are readily available by aldol condensation of unsaturated aldehydes and ketones bearing two hydrogen atoms on  $\alpha$ -position.<sup>8)</sup> Expectedly, the oximes VIIIa-e can be converted into pyridines IXa-e in moderate yields. The results are summarized in Table III.

Table III. Synthesis of Substituted Pyridines From Conjugated Ketoximes.



	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	R <sub>4</sub>	Yield of IX (%)
a	Me	H	H	Me	50
b	Me	H	Me	Ph	45
c	Me	H	H	Ph	40
d	Me	Me	H	Ph	35
e	Et	H	H	Ph	19

Although these ketoximes are known to be transformed into pyridines on heating at extremely high temperature around 300°,<sup>9)</sup> the palladium-induced cyclization can proceed under milder conditions, and therefore the reaction would provide a potentially useful method for the synthesis of substituted pyridines.

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