Synthesis of 3,4-Dihydro-2*H*-pyrroles from γ,δ-Unsaturated Ketone *O*-Acetyloximes

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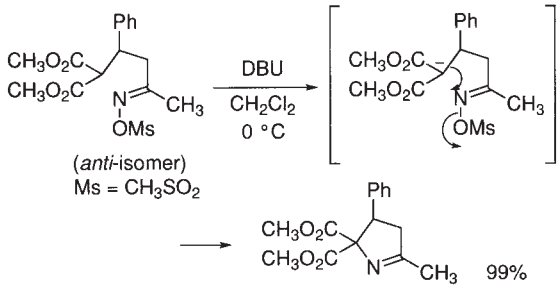
3,4-Dihydro-2*H*-pyrroles were synthesized from γ,δ-unsaturated ketone *O*-acetyloximes by treatment with acetic acid and 1,4-cyclohexadiene in the presence of a catalytic amount of 1,5-naphthalenediol. During the cyclization, *syn-anti* isomerization of the *O*-acetyloximes easily occured and so, both stereoisomers of oximes could be employed.

Recently, we reported unusual intramolecular SN2-type substitution on sp^2 nitrogen atom of oximes.[1] For example, *O*-methylsulfonyloximes having an active methine group are converted to cyclic imines by treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).[1e,f] Due to a characteristic nature of SN2 reaction, only *anti*-isomers[2] of oximes are converted to cyclic imines. This stereospecificity seems to be a serious drawback in applying this reaction for organic synthesis.

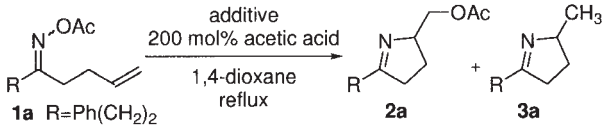


It was expected that both of the stereoisomers of oxime derivatives could be employed in the cyclization if *syn-anti* isomerization occurs under the reaction conditions. Although oximes themselves easily isomerize under acidic conditions, isomerization of *O*-substituted oximes hardly occurs under mild conditions.[3] We investigated oxime derivatives that isomerize under mild conditions, and *O*-acetyloximes were found to be isomerized by treatment with acetic acid. The isomerization proceeded slowly, but it was accelerated in the presence of a catalytic amount of 1,4-hydroquinone or 1,5-naphthalenediol. That is, isomerization of (*E*)-4-phenyl-2-butanone *O*-acetyloxime attained an equilibrium ($E : Z = 3 : 1$) by treatment with 5 molar amounts of acetic acid in toluene-d_8 at 80 °C after 3 h, while it took only 1.5 h in the presence of a 5% molar amount of 1,4-hydroquinone.

Based on these findings, we examined the intramolecular cyclization of γ,δ-unsaturated ketone *O*-acetyloxime **1a** (*syn* : *anti* = 1 : 1), expecting the formation of 2-acetoxymethyl-5-phenethyl-3,4-dihydro-2*H*-pyrrole (**2a**) by intramolecular nucleophilic attack of the olefinic moiety on sp^2 nitrogen of the *O*-acetyloxime (Table 1).

By treating **1a** with 2 molar amounts of acetic acid and a catalytic amount of 1,4-hydroquinone or 1,5-naphthalenediol in refluxing 1,4-dioxane, the expected cyclization product **2a** was obtained in about 20% yield with 45% yield of 2-methyl-5-phenethyl-3,4-dihydro-2*H*-pyrrole (**3a**) (Table 1, Entries 1 and 2). It is noteworthy that the addition of 1,4-cyclohexadiene increased the total yield of **2a** and **3a** to 85-86% as shown in Entries 4 and 5. Without the phenol derivatives, the reaction proceeded very slowly and the products yield was low (Entries 3 and 6). Thus, 1,4-hydroquinone and 1,5-naphthalenediol have not only a significant effect on the isomerization of **1a** but also on the acceleration of the cyclization reaction.

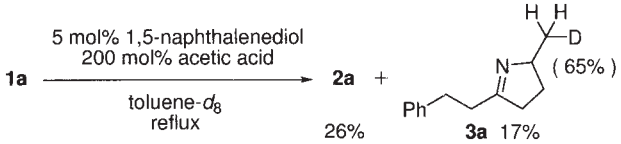
Table 1. Cyclization reaction of *O*-acetyloxime **1a**



1a R=Ph(CH$_2$)$_2$ **2a** **3a**

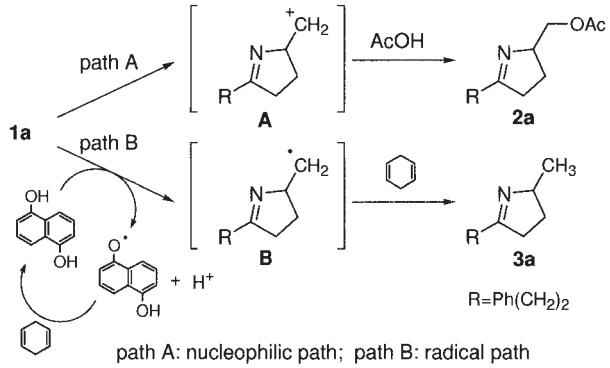
Entry	Additive 1 (5 mol%)	Additive 2 (1000 mol%)	Time / h	Yield / % 2a	3a
1	1,4-hydroquinone	none	6	22	44
2	1,5-naphthalenediol	none	6	23	43
3	none	none	24	19	20
4	1,4-hydroquinone	1,4-cyclohexadiene	6	32	53
5	1,5-naphthalenediol	1,4-cyclohexadiene	6	34	52
6	none	1,4-cyclohexadiene	24	12	29

The formation of the unexpected product **3a** could not be explained by the SN2-type mechanism, but was considered to be generated from radical intermediate.[4,5] In fact, by the reaction in toluene-d_8 without 1,4-cyclohexadiene, the cyclic imine **3a** was obtained in 17% yield containing 65% deuterium in the methyl group along with 26% yield of **2a**.



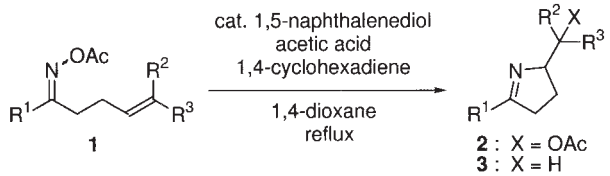
A plausible mechanism of the formation of **2a** and **3a** is depicted in Scheme 1. Imine **2a** is caused by the nucleophilic substitution reaction. The olefinic moiety of **1a** intramolecularly attacks on the nitrogen of *O*-acetyloxime **1a**, and imine **2a** is generated by trapping the cationic intermediate **A** with acetic acid. For the formation of **3a**, one-electron transfer occurs from 1,5-naphthalenediol to **1a**.[5c,f,g,7] The resulting anion radical then cyclizes to generate alkyl radical **B**,[5g] which captures hydrogen from 1,4-cyclohexadiene. The catalyst, 1,5-naphthalenediol, is regenerated from hydroxynaphthalenoxyl radical by hydrogen abstraction from 1,4-cyclohexadiene.

The reaction of various *O*-acetyloximes was examined and the results are shown in Table 2. By the reaction of *O*-



Scheme 1.

Table 2. Preparation of imines **2**, **3** from *O*-acetyloxime **1**[a]

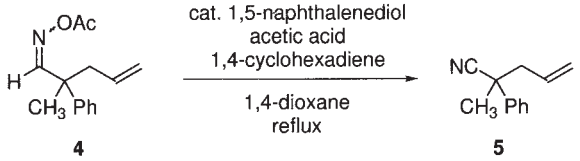


Entry	R^1	R^2	R^3	Time / h	Yield / %			
1	$PhCH_2CH_2$[b]	H	H	6	**2a**	34	**3a**	52
2	$PhCH_2CH_2$[b]	Me	Me	6	**2b**	72	**3b**	5
3	$PhCH_2CH_2$[c]	H	CN	12	**2c**	0	**3c**	69
4	$PhCH_2CH_2$[b]	H	CO_2Et	12	**2d**	0	**3d**	72
5	Ph[d]	H	H	8	**2e**	0	**3e**	75
6	$Ph(CH_2)_3O_2C$[d,e]	H	H	6	**2f**	0	**3f**	61

[a]Cyclization was carried out under the following conditions; 1,5-naphthalenediol (5 mol%), acetic acid (2 molar amounts), 1,4-cyclohexadiene (10 molar amounts). [b]*syn* : *anti* = 1 : 1. [c]*syn* : *anti* = 1 : 2. [d]Only syn isomers were used. [e]*O*-Pivaloyloxime was used instead of *O*-acetyloxime.

acetyloxime having an electron-rich olefinic moiety, acetoxy imine **2b** was yielded as a major product (Entry 2). In contrast, only radical cyclization products **3c** and **3d** were obtained from oximes having electron deficient olefinic moieties (Entries 3 and 4). Radical cyclization product **3e** was obtained exclusively from *O*-acetyloxime of phenyl ketone (Entry 5). Presumably, the steric repulsion between phenyl and acetoxy group give rise to preferential formation of the *syn*-isomer, which prevents the nucleophilic substitution with the alkenyl group. *O*-Pivaloyloxime[6] of α-keto ester also cyclized to imino ester **3f** in 61% yield (Entry 6).

Thus the cyclization of *O*-acetyl ketoximes proceeded successfully, whereas *O*-acetyl aldoxime **4** did not cyclize but gave nitrile **5** by the Beckmann fragmentation.



In conclusion, a synthetic method of 3,4-dihydro-2*H*-pyrroles from γ,δ-unsaturated ketone *O*-acetyloximes was developed with the use of acetic acid and 1,4-cyclohexadiene in the presence of a catalytic amount of 1,5-naphthalenediol. In this reaction, both stereoisomers of oximes can be employed, because *O*-acetyloximes are readily isomerized under the reaction conditions.

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We dedicate this article to Professor Teruaki Mukaiyama for his 75th birthday.

References and Notes

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2 In this manuscript, *syn* isomers mean the oximes having leaving group on oxime nitrogen and nucleophile or olefin in the same side of oxime carbon-nitrogen double bond and *anti* isomers mean the other.

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6 Because 3-phenylpropyl 2-oxo-hexenoic acid *O*-acetyloxime was easily hydrolyzed, *O*-pivaloyloxime **1f** was used in stead of the *O*-acetyloxime.

7 M. Horspool, G. Hynd, and U. Ixkes, *Tetrahedron Lett.*, **40**, 8295 (1999).

8 *O*-acetyloxime was prepared in 70–80% yield from ketones[5f] by treatment with hydroxylamine hydrochloride and pyridine in ethanol, and then triethylamine and acetic anhydride in dichloromethane.