

Synthesis of Dihydropyrrole Derivatives by Copper-Catalyzed Cyclization of γ, δ -Unsaturated Ketone *O*-Methoxycarbonyloximes

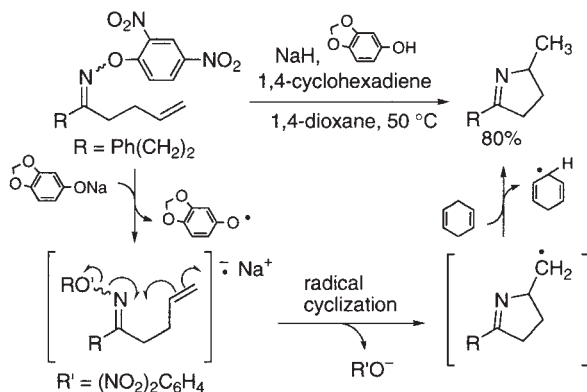
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2-Bromomethyl-3,4-dihydro-2*H*-pyrroles are prepared from γ, δ -unsaturated ketone *O*-methoxycarbonyloximes by treatment with a catalytic amount of $\text{CuBr} \cdot \text{SMe}_2$ and LiBr.

Recently, we reported the radical cyclization of γ, δ -unsaturated ketone *O*-2,4-dinitrophenyloximes to 3,4-dihydro-2*H*-pyrroles.¹ The reaction is initiated by one electron reduction of oximes with sodium hydride and 3,4-methylenedioxyphenol, followed by radical cyclization with eliminating 2,4-dinitrophenoxide (Scheme 1). This procedure has drawbacks as a synthetic method; the use of large excess amounts of NaH and a bulky leaving group such as 2,4-dinitrophenoxy group.



Scheme 1. Cyclization of *O*-2,4-dinitrophenyloxime.

It was expected that one electron reduction of oxime derivatives would proceed by treatment with low valent transition metal compounds. Such an example was reported by Zard. That is, the treatment of γ, δ -unsaturated *O*-acetyloximes with nickel powder and acetic acid in 2-propanol leads to the cyclization to dihydropyrroles.² The reaction, however, requires large excess amounts of nickel powder. It is desirable to conduct such a transformation in a catalytic manner. We would like to report herein a copper-catalyzed transformation of γ, δ -unsaturated ketone *O*-methoxycarbonyloximes to dihydropyrrole derivatives.

By using copper compounds³ as metal catalysts, we examined the cyclization of various γ, δ -unsaturated oximes. After screening the substituents on the oxime nitrogen atom (vide infra), *O*-methoxycarbonyloximes were found to be suitable for the transformation of γ, δ -unsaturated oximes to dihydropyrroles. When a *syn/anti* (1 : 1) mixture⁴ of *O*-methoxycarbonyloxime **1**⁵ and 5 mol% of $\text{CuBr} \cdot \text{SMe}_2$ ⁶ in 1,4-dioxane was heated to 80 °C, cyclic imine **2a** was obtained in 39% yield (Table 1, Run 1). Thus the reaction proceeded catalytically. Addition of radical trapping reagents such as tris(trimethylsilyl)silane did not improve the yield of cyclization products (Run 2). When the reaction carried

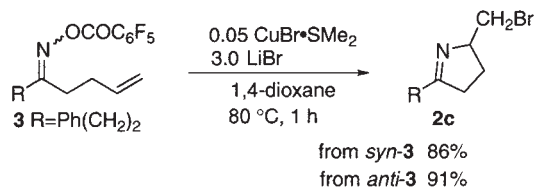
out in the presence of diphenyl disulfide, cyclized products **2b** and **2a** was obtained in 41% and 14% yield, respectively (Run 3). In the presence of LiBr, the cyclization product, 2-bromomethyl-dihydropyrrole **2c**, was obtained in high yield (86%, Run 4). 2-Chloromethyl-dihydropyrrole **2d** was prepared in 57% yield by using CuCl instead of $\text{CuBr} \cdot \text{SMe}_2$ in the presence of lithium chloride (Run 5).

Table 1. Copper-catalyzed cyclization of *O*-methoxycarbonyloxime **1**^a

Run	Additive	Time/h	X	Yield/%
1	none	1	H	2a 39
2	(Me ₃ Si) ₃ SiH	1	H	2a 49
3	PhSSPh	3	SPh	2b 41 ^b
4	LiBr	1	Br	2c 86
5	LiCl ^c	1	Cl	2d 57 ^d

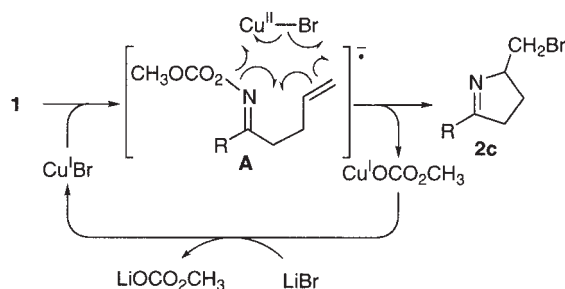
^aOxime **1** : Cu cat. : additive = 1.0 : 0.05 : 3.0. ^b**2a** was obtained in 14% yield. ^c CuCl was used instead of $\text{CuBr} \cdot \text{SMe}_2$. ^d**2a** was obtained in 18% yield.

In addition to *O*-methoxycarbonyloxime **1**, *O*-pentafluorobenzoyloxime **3** was transformed into **2c** in high yield, but the corresponding *O*-2,4-dinitrophenyl and *O*-acetyloxime were not appropriate for the $\text{CuBr} \cdot \text{SMe}_2$ -LiBr-catalyzed cyclization. The *syn* and *anti*-isomers of **1** were hard to separate, whereas *syn* and *anti*-**3** were separable by recrystallization.⁷ The influence of the stereochemistry of oximes was hence examined by the reaction of each isomer of **3**, which gave the cyclization product **2c** in 86% and 91% yield from the *syn* and *anti* isomers, respectively. Thus the cyclization proceeds irrespective of the stereochemistry of oximes.



The reaction probably proceeds as shown in Scheme 2. Electron transfer from copper(I) salt to the oxime **1** generates anion radical **A**. Successively, the N–O bond of **A** cleaves with elimination of methyl carbonate anion and the cyclization occurs simultaneously to give **2c**.⁸ Lithium bromide plays a role for

regeneration of CuBr from copper(I) carbonate.



Scheme 2. Mechanism of Cu(I)-catalyzed cyclization of **1**.

As listed in Table 2, the catalytic system with CuBr·SMe₂·LiBr could be applied to the cyclization of various γ,δ -unsaturated ketone *O*-methoxycarbonyloximes. Cyclization of **4a** and **4b** having disubstituted olefin moiety proceeded to give cyclic imines **5a** and **5b** in 85% and 74% yield, respectively (Runs 1, 2). 5,5-Disubstituted dihydropyrrole **5c** was obtained in 53% yield from γ -methyl substituted oxime **4c** along with 16% yield of disubstituted pyridine **6** (Run 3).⁹ Oxime derivatives of phenyl ketone **4d** and keto ester **4e** were smoothly transformed into 2-phenyl and 2-ethoxycarbonyl dihydropyrroles **5d** and **5e**, respectively (Runs 4, 5).

Table 2. Cyclization of several *O*-methoxycarbonyloxime^a

Oxime 4		cat. CuBr·SMe ₂ LiBr	Product(s)
		1,4-dioxane 80 °C, 1-3 h	
Run	Oxime 4		Product(s)
1	4a (R = CH ₃ ^b ; <i>syn</i> : <i>anti</i> = 1 : 1)		5a 85% (4 : 1) ^c
2	4b (R = Ph ^d ; <i>syn</i> : <i>anti</i> = 1 : 1)		5b 74% (20 : 1) ^c
3	4c (<i>syn</i> : <i>anti</i> = 1 : 1)		5c 53%
			6 16%
4	4d (R = Ph)		5d 83%
5	4e (R = CO ₂ Et)		5e 53%

^aOxime **4** : Cu cat. : LiBr = 1.0 : 0.05 : 3.0. ^bThe stereochemistry of olefin moiety was *E* : *Z* = 3 : 1. ^cDiastereomer ratio. ^dThe stereochemistry of olefin moiety was *E*.

γ,δ -Unsaturated ketone *O*-methoxycarbonyloximes were converted into dihydropyrrole derivatives by using CuBr·SMe₂-catalyst in the presence of LiBr. 5-Membered cyclic imines are thus prepared catalytically, whereas the formation of 6-membered imines is hard to proceed from δ,ϵ -unsaturated ketone oximes.

Very recently was reported a copper-catalyzed radical cyclization of unsaturated *N*-benzoyloxyamines to pyrrolidines.¹⁰ Totally, various dihydropyrroles and pyrrolidines can be prepared by copper-catalyzed radical cyclization processes.

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References and Notes

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- In this paper, *syn* isomer means the oxime having a leaving group on the oxime nitrogen and the olefin moiety in the same side of the oxime C=N bond; *anti* isomer means the other.
- O*-Methoxycarbonyloximes were prepared by treatment of the corresponding oximes with methyl chloroformate and NaH in THF.
- Some other copper compounds such as Cu powder, CuBr, CuCN, CuI and their amine complexes were employed in the cyclization of **1**. Among them, CuBr·SMe₂ was most suitable for this reaction.
- O*-Pentafluorobenzoyloxime **3** could be separated into the *syn*- and *anti*-isomers by recrystallization (EtOH). *syn*-**3** crystallized first, and then *anti*-**3** was purified by repeating recrystallization (EtOH).
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