Synthesis of Dihydropyrroles and Tetrahydropyridines by the Intramolecular Cyclization of *O*-Methylsulfonyloximes Having an Active Methine Group

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3,4-Dihydro-2*H*-pyrroles and 2,3,4,5-tetrahydropyridines are prepared from (*E*)-*O*-methylsulfonyloximes having an active methine group at γ- and δ-positions, respectively, by the treatment with DBU.

Though many amination methods have been developed, electrophilic amination of carbon nucleophiles has not been generally employed for the synthesis of nitrogen containing compounds.[1] Oxime derivatives seem to be good candidates for electrophilic aminating reagents, if carbon nucleophiles could attack the nitrogen atom of oximes.[2] There have been, however, a few examples of this type of reaction, because oximes and their derivatives readily suffer from Beckmann rearrangement[3] and Neber reaction.[3c] We have been investigating electrophilic amination by the use of oxime derivatives,[4] and recently found that the intramolecular cyclization of phenethyl ketone oximes proceeds on the nitrogen atom of the oximes by the use of $(n\text{-}Bu)_4NReO_4$ and CF_3SO_3H.[4a,b,c] As disclosed by *ab initio* calculation, the reaction proceeds by SN2 mechanism on the sp^2 nitrogen atom of oximes by the attack of the aromatic moiety.[4d] It was expected that various carbon nucleophiles would also attack on the nitrogen atom of oxime derivatives, when oxime hydroxyl group is converted to a suitable leaving group.

We chose methyl (*E*)-2-methoxycarbonyl-5-(methylsulfonyloxyimino)-3-phenylhexanoate ((*E*)-**1a**)[5] as a model compound, expecting that the cyclization between the active methine group and the nitrogen atom would proceed to provide a dihydropyrrole derivative **2a**. After screening of the reaction conditions as listed in Table 1, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was found to be a suitable amine. That is, treatment of (*E*)-**1a** with DBU at 0 °C in dichloromethane gave **2a** quantitatively, while the use of NaH or triethylamine gave poor results. The reaction also proceeded smoothly in various solvents, such as dichloromethane, dichloroethane, acetonitrile, toluene, and THF. Though the *O*-methylsulfonyloxime (*E*)-**1a** was thus smoothly cyclized to **2a** by the treatment with DBU, an *O*-acetyloxime could not be converted to the cyclized product. Cyclization of an *O*-trifluoroacetyloxime proceeded much slower than **1a** and did not complete within 1.5 h at 0 °C, giving the cyclized adduct **2a** in 57% yield with the 41% recovery of the *O*-trifluoroacetyloxime.

The cyclization of (*E*)-**1a** proceeded smoothly, while the reaction of the corresponding (*Z*)-isomer (*Z*)-**1a** did not afford the cyclized product **2a**: The starting material was recovered under the same reaction conditions, and the prolonged reaction (3 h) at room temperature afforded several products, one of which was the Neber reaction product. This stereospecificity of the intramolecular cyclization is an evidence that SN2 substitution occurs on the nitrogen atom of the oxime **2a**.

Various substituted dihydropyrrole derivatives **2** were prepared from (*E*)-*O*-methylsulfonyloximes (*E*)-**1**[6] and the results are listed in Table 2. In all cases, the reaction was completed within 30 min to provide 2*H*-pyrrole derivatives **2** in high yield (85-99%) and

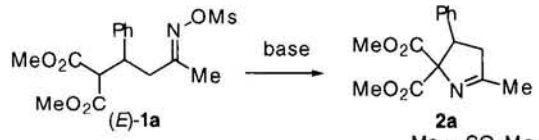


Table 1. The effect of base

Entry	Base	Solvent	Temp / °C	Time / h	Yield / %
1	NaH	THF	50	5	complex mixture
2	Et_3N	$ClCH_2CH_2Cl$	reflux	4	38
3	DMAP[a]	$ClCH_2CH_2Cl$	50	13	69
4	DABCO[b]	$ClCH_2CH_2Cl$	50	2.5	42
5	DBU	CH_2Cl_2	0	0.25	99

[a] DMAP = 4,4-dimethylaminopyridine.
[b] DABCO = 1,4-diazabicyclo[2.2.2]octane.

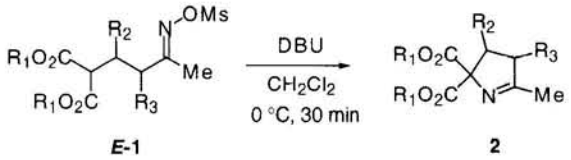
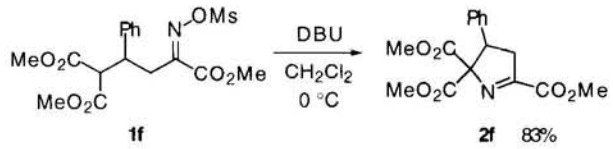


Table 2. Intramolecular cyclization of (*E*)-**1**

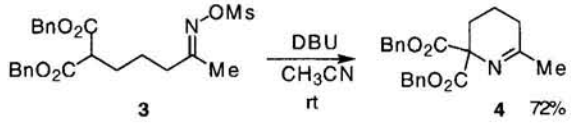
Entry	R^1	R^2	R^3		Yield / %	
1	Me	Ph	H	(**1a**)	99	(**2a**)
2	Me	*i*-Pr	H	(**1b**)	87	(**2b**)
3	Me	$n\text{-}C_5H_{11}$	H	(**1c**)	86	(**2c**)
4	Bn	H	Me	(**1d**)	85	(**2d**)
5	Bn	H	H	(**1e**)	87	(**2e**)

neither Beckmann rearrangement nor Neber reaction product was obtained. Oximes having not only phenyl substituent but also isopropyl and *n*-pentyl substituents at the β-position of oximes cyclized to provide 3,4-dihydro-3-substituted-2*H*-pyrroles in good yield (Entries 2, 3). 4-Substituted 2*H*-pyrrole derivative **2d** was synthesized from the α-substituted oxime **1d** (Entry 4). The oxime **1e** having no substituent at α and β positions ($R^2 = R^3 = H$) was similarly converted to **2e** in 87% yield (Entry 5).

A 5-methoxycarbonyl-2*H*-pyrrole derivative **2f** was also synthesized from *O*-methylsulfonyloxime (*E*)-**1f** derived from an α-keto ester.[6]

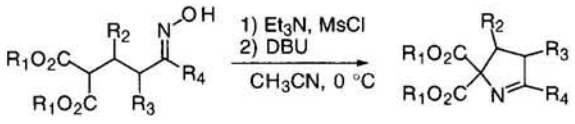


In addition to 2*H*-pyrrole derivatives **2**, synthesis of tetrahydropyridine derivative from the oxime of 6-oxoheptanoate (**3**) was examined by applying the present method. Although the cyclization of **1** proceeded in various solvents, marked solvent effect was observed in the reaction of **3**. That is, when **3** was treated with DBU for 9 h in refluxing dichloromethane, 2,2-di(benzyloxycarbonyl)-6-methyl-2,3,4,5-tetrahydropyridine (**4**) was obtained only in 31% yield. By employing acetonitrile as a solvent, the cyclization proceeded at room temperature to give the tetrahydropyridine **4** in 72 % yield.



3 **4** 72%

Though the *O*-methylsulfonyloximes **1** are prepared from the corresponding oximes in 80-90% yields, they are generally labile and decompose gradually. Therefore, the one-pot synthesis of dihydropyrroles from the corresponding (*E*)-oximes was examined without the isolation of the *O*-methylsulfonyloximes. Thus, (*E*)-oximes **5** were treated with triethylamine and methanesulfonyl chloride in acetonitrile and then with 2.2-3.0 molar amounts of DBU, giving the dihydro-2*H*-pyrroles **2** in good yield as shown in Table 3.



***E*-5** **2**

Table 3. One pot synthesis of **2**

R^1	R^2	R^3	R^4	Yield / %
Bn	H	H	Me	97 (**2d**)
Bn	H	Me	Me	79 (**2e**)
Me	Ph	H	CO_2Me	80 (**2f**)
Me	*i*-Pr	H	Me	71 (**2g**)

General experimental procedure is as follows (one pot synthesis of **2d**): To an acetonitrile (2 ml) solution of (*E*)-**5d** (176.9 mg, 0.48 mmol) was added triethylamine (58.1 mg, 0.57 mmol) and an acetonitrile (1.5 ml) solution of methanesulfonyl chloride (60.3 mg, 0.53 mmol) at 0 °C. After the mixture was stirred for 30 min at 0 °C, an acetonitrile (1.5 ml) solution of DBU (160.4 mg, 1.05 mmol) was added. After the mixture was stirred for 30 min at 0 °C, acetonitrile was removed *in vacuo*. The crude products were purified by thin-layer chromatography (Silica gel, ethyl acetate) to afford 3,4-dihydro-2*H*-pyrrole **2d** (161.9 mg, 0.46 mmol, 97%).

References and Notes

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5 (*E*)-**1a** was prepared as follows: The Michael reaction of dimethyl malonate and (*E*)-4-phenyl-3-butene-2-one in the presence of NaH (1.2 molar amounts) in MeOH provided methyl 2-methoxycarbonyl-5-oxo-3-phenylhexanoate, treatment of which with NH_2OH•HCl and $NaHCO_3$ in aq. MeOH (pH 5) gave the corresponding oxime (*E*:*Z* = 2:1). The pure (*E*)-oxime was obtained after recrystallization from hexane-CH_2Cl_2. (*E*)-**1a** was prepared from (*E*)-oxime by the reaction with methanesulfonyl chloride (1.5 molar amounts) and NEt_3 (2.0 molar amounts) in CH_2Cl_2.

6 (*E*)-*O*-Methylsulfonyloximes (*E*)-**1b-f** were prepared from the corresponding (*E*)-oximes (*E*)-**5** which were separated from the (*Z*)-isomers by Silica gel column chromatography.