SYNTHESIS OF PYRROLINE VIA CYCLIZATION OF 4-ISOCYANO-1-SILOXY-1-ALKENE INDUCED BY AN IMINIUM SALT [1]

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Abstract — 4-Isocyano-1-siloxy-1-alkenes, prepared by the fluoride-catalyzed 1,4-addition of α-isocyanocarboxylates to α,β-unsaturated ketones, underwent cyclization on treatment with an iminium salt to afford pyrroline derivatives.

α-Isocyanocarboxylates are convenient precursors for the synthesis of nitrogen-containing compounds like amino acids.[2] The α-position readily becomes nucleophilic under basic conditions to form a carbon–carbon bond with an electrophile. Besides, interesting reactivities are expected for the isocyano functionality on the grounds of the similarity of its electronic structure with that of carbon monoxide. Cyclization through intramolecular α-addition of a nucleophilic group to an isocyano carbon has been utilized in synthesis of various nitrogen-containing heterocycles.[2] We have reported that a fluoride anion catalyzes 1,4-addition of α-isocyanocarboxylate to α,β-unsaturated ketone in the presence of *N,O*-bis(trimethylsilyl)acetamide to give an adduct as the silyl enolate in high yield.[3] The zinc(II)-catalyzed cyclization of the produced silyl enolate and the subsequent hydrogenation afford pyrrolidinecarboxylic acid stereoselectively. The sequential procedure has been successfully applied to a total synthesis of α-allokainic acid.[4] As a continuation of our studies on the intramolecular cyclization procedure based on activation of an isocyano functionality, we describe herein the synthesis of an pyrroline derivative by the reaction of 4-isocyano-1-siloxy-1-alkene with an iminium salt.[5]

A siloxycyclopentene derivative (**1a**), prepared by the fluoride-catalyzed reaction of 2-isocyanopropionate with 2-methylcyclopent-2-enone,[3] was treated with *N,N*-dimethylmethyleneammonium iodide (Eschenmoser's salt) in CH_2Cl_2 at the temperature ranging from -30 °C to 0 °C for 1 h. Extractive workup followed by column chromatography (silica gel) afforded **2a** as a mixture of diastereomers in 88% yield. It is likely that the iminium salt couples with the isocyano carbon atom to facilitate the intramolecular nucleophilic attack of the silyl enolate moiety.[5]

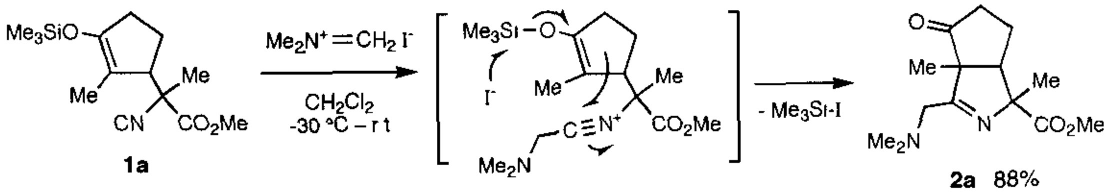
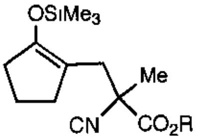
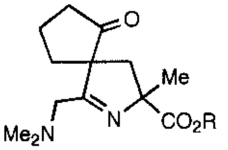
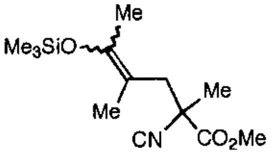
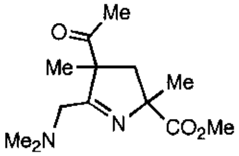
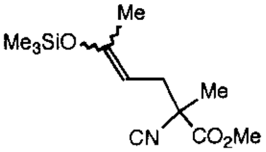
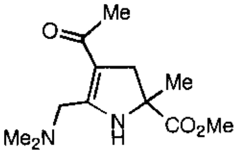


Table 1. Reactions of 4-Isocyano-1-siloxy-1-alkenes (**1**) with $CH_2=N^+Me_2 \cdot I^-$

1		product (**2**)		isolated yield, %
	**1b** R = Me **1c** R = Et		**2b** R = Me **2c** R = Et	82 [a] 94 [a]
	**1d**		**2d**	87 [a]
	**1e**		**2e**	— [b]

[a] A mixture of diastereomers [b] Not isolated

Other examples of the iminium salt-induced cyclization of 4-isocyano-1-siloxy-1-alkenes are listed in Table 1. 1-Pyrroline derivatives (**2b–d**) were obtained as a mixture of diastereomers in good yield from **1b–d**. In case of a silyl enolate having a hydrogen atom at the α-position (**1e**), cyclization was immediately followed by prototropic rearrangement. Although efficient transformation to a 2-pyrroline derivative (**2e**) was confirmed by ^1H NMR, **2e** was too unstable to be isolated by chromatography.

Danishefsky *et al.* have reported that a silyl enolate reacts with an iminium salt to produce a β-amino ketone.[6] It should be noted that, in the present reaction, appropriate placement of an isocyano group results in insertion of the isocyano carbon between a silyl enolate moiety and an iminium salt through formation of carbon–carbon bonds. The results described herein suggest the possibility to synthesize various nitrogen-containing heterocycles by use of a reaction of an analogous pattern.

Procedure for the synthesis of ***2a***: To a solution of *N,N*-dimethylmethyleneammonium iodide (37.0 mg, 0.200 mmol) in CH_2Cl_2 (2 mL) under a nitrogen atmosphere at -30 °C was added **1a** (49.4 mg, 0.176 mmol). The reaction mixture was stirred with the temperature being raised to 0 °C over 1 h. Methanol and an aqueous buffer solution (pH 7) were added to the mixture, which was extracted with CH_2Cl_2. Column chromatography (silica gel, CH_2Cl_2:MeOH = 1:8) afforded **2a** (40.9 mg, 88%) as an oil.

REFERENCES AND NOTES

1. Dedicated to Emeritus Professor Koji Nakanishi in celebration of his 75th birthday.

2. D. Hoppe, *Angew. Chem., Int. Ed. Engl.*, **1974**, *13*, 7893; U. Schollkopf, *Angew. Chem., Int. Ed. Engl.*, **1977**, *16*, 339 and the references cited therein.
3. M. Murakami, N. Hasegawa, I. Tomita, M. Inouye, and Y. Ito, *Tetrahedron Lett.*, **1989**, *30*, 1257.
4. M. Murakami, N. Hasegawa, M. Hayashi, and Y. Ito, *J. Org. Chem.*, **1991**, *56*, 7356.
5. I. Ugi, *Angew. Chem., Int. Ed. Engl.*, **1962**, *1*, 8.
6. S. Danishefsky, M. Prisbylla, and B. Lipisko, *Tetrahedron Lett.*, **1980**, *21*, 805.

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