Retro-Ene Reactions in Heterocyclic Synthesis. III. A New Route to 4,5-Dihydrooxazoles and 5,6-Dihydro-4*H*-1,3-oxazines

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Methyl (*E*)-4,4-dimethyl-5-oxo-2-pentenoate (**1**, X = O) reacted with 1,2- or 1,3-aminoalcohols **3** to yield oxazolidines **4a-c** or tetrahydro-1,3-oxazines **4d,e**. The corresponding imino ester **1** (X = NBu-*t*) also gave **4** on reaction with **3**. Compounds **4** on heating at 230° yielded 4,5-dihydrooxazoles **5a-c** or 5,6-dihydro-4*H*-1,3-oxazines **5d,e** along with methyl 4-methyl-3-pentenoate (**6**).

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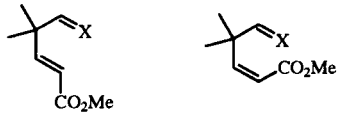
In previous papers we reported new synthetic methods for a variety of 2-amino and 2-hydroxypyridine derivatives through retro-ene reactions [1,2]. This paper deals with a further investigation on the retro-ene reaction, which leads to 4,5-dihydrooxazoles and 5,6-dihydro-4*H*-1,3-oxazines.

Previously we demonstrated that *N*-isobutylidene-*t*-butylamine reacts with methyl propiolate to form the Michael adducts, methyl (*E*)- (**1**, X = NBu-*t*) and methyl (*Z*)-5-(*t*-butylimino)-4,4-dimethyl-2-pentenoate (**2**, X = NBu-*t*), along with a minor isomeric product, methyl 2-(*t*-butylaminomethylene)-4-methyl-3-pentenoate [3]. The isomeric mixture was heated at 200° in the presence of 5% rhodium-carbon. Fractional distillation afforded (*E*)-Michael adduct **1** (X = NBu-*t*) (65%), which on hydrolysis yielded methyl (*E*)-4,4-dimethyl-5-oxo-2-pentenoate (**1**, X = O).

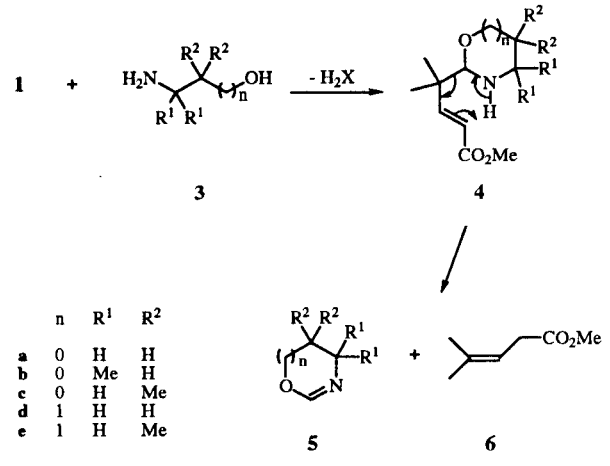


1 **2**

X: NBu-*t*, O

When a solution of 1,2- or 1,3-aminoalcohols **3** in monoglyme was gradually added to a stirred, ice-cold mixture of a solution of (*E*)-oxo ester **1** (X = O) in monoglyme and 4A molecular sieves and the mixture was stirred at room temperature, intramolecular addition of the hydroxy group to the initially formed carbon-nitrogen double bond took place and oxazolidines **4a-c** or tetrahydro-1,3-oxazines **4d,e** were obtained in high yields (Method A). Compounds **4** could also be obtained from (*E*)-imino ester **1** (X = NBu-*t*) and amino alcohols **3** *via* an exchange reaction of the amines when heated at 100°, although in the cases of **3a** and **3d** the reactions were accompanied by formation of considerable amounts of resinous materials (Method B). The structures of **4** were confirmed on the basis of their analytical and spectral data.

Scheme 1



	n	R^1	R^2
a	0	H	H
b	0	Me	H
c	0	H	Me
d	1	H	H
e	1	H	Me

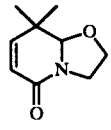
Compounds **4** when heated at 230° underwent a retro-ene reaction and yielded 4,5-dihydrooxazoles **5a-c** or 5,6-dihydro-4*H*-1,3-oxazines **5d,e** along with methyl 4-methyl-3-pentenoate (**6**). The results obtained are summarized in Table 1.

Table 1

Preparation of Compounds **4** and **5**

3	Method	Yield %		
		4	**5**	**6**
a	A	92	73	70
	B	47		
b	A	89	71	63
	B	81		
c	A	92	75	77
	B	91		
d	A	94	61	57
	B	65		
e	A	90	75	72
	B	94		

The reaction of (*Z*)-oxo ester **2** (X = O) [3] with 2-aminoethanol (**3a**) resulted in the formation of fused oxazole derivative **7**.



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The method described in this paper offers a new route to 4,5-dihydrooxazoles and 5,6-dihydro-4*H*-1,3-oxazines through a retro-ene reaction.

EXPERIMENTAL

The ir spectra were recorded on a JEOL JIR-7000 spectrometer. The ^{1}H nmr data were obtained with a JEOL JNM-EX400 (400 MHz) spectrometer using tetramethylsilane as an internal standard. Mass spectra were measured with a Shimadzu GCMS-QP1000 spectrometer at 70 eV of ionization energy. Elemental analyses were performed by using a Perkin-Elmer 2400 II CHN Analyzer.

Methyl (*E*)- (**1**, X = O) and methyl (*Z*)-4,4-dimethyl-5-oxo-2-pentenoate (**2**, X = O) were prepared from the corresponding imino esters as described previously [3]. Amino alcohols **3** were commercially available except for 1-amino-2-methyl-2-propanol (**3c**), which was obtained according to the procedure of Cairns and Fletcher [4].

Methyl (*E*)-5-(*t*-Butylimino)-4,4-dimethyl-2-pentenoate (**1**, X = NBu-*t*).

To a stirred solution of *N*-isobutylidene-*t*-butylamine (63.6 g, 500 mmoles) in tetrahydrofuran (60 ml) heated at a bath temperature of 80° was added a solution of methyl propiolate (46.2 g, 550 mmoles) in tetrahydrofuran (50 ml) over a period of 1 hour. Stirring and heating were continued for an additional 10 hours. After removal of the solvent *in vacuo*, the residue was heated with stirring at 200° for 3.5 hours with 5% rhodium-carbon (10.7 g). The catalyst was removed by filtration and washed with tetrahydrofuran. The combined filtrates were concentrated and distilled through a 50-cm spinning band column to give 68.4 g (65%) of **1** (X = NBu-*t*).

General Procedure for the Preparation of Methyl (*E*)-4-Methyl-4-(2-oxazolidinyl)-2-pentenoates **4a-c** and Methyl (*E*)-4-Methyl-4-[2-(tetrahydro-1,3-oxazinyl)]-2-pentenoates **4d,e**.

Method A.

To a stirred, ice-cold mixture of a solution of **1** (X = O) (80.0 mmoles) in monoglyme (60 ml) and 4A molecular sieves (60 g) was added a solution of **3** (88.0 mmoles) in monoglyme (30 ml) over a period of 1 hour. The mixture was stirred for an additional 2 hours at room temperature. The molecular sieves were removed by filtration and washed with monoglyme. The combined filtrates were concentrated and distilled to yield **4**.

Method B.

A mixture of **1** (X = NBu-*t*) (80.0 mmoles) and **3** (88.0 mmoles) was heated with stirring at 100° for 2 hours in a distilling flask. The *t*-butylamine formed was allowed to escape from a condenser. Distillation gave **4**.

Methyl (*E*)-4-Methyl-4-(2-oxazolidinyl)-2-pentenoate (**4a**).

This compound was obtained as a colorless liquid, bp 109-110°(0.7 mm Hg); ir (liquid film): 3336 (NH), 1724 (C=O), 1653 (C=C) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.14 and 1.15 (each 3H, s, CH_3), 1.85 (1H, br s, NH), 3.01 and 3.15 (each 1H, m, CH_2N), 3.62-3.73 (2H, m, CH_2O), 3.73 (3H, s, CO_2CH_3), 4.23 (1H, s, CH), 5.88 and 7.05 (each 1H, d, J = 16.1 Hz, CH=CH); ms: (CI), m/z 200 (MH^+).

Anal. Calcd. for $C_{10}H_{17}NO_3$: C, 60.28; H, 8.60; N, 7.03. Found: C, 59.99; H, 8.53; N, 7.18.

Methyl (*E*)-4-Methyl-4-[2-(4,4-dimethyloxazolidinyl)]-2-pentenoate (**4b**).

This compound was obtained as a colorless liquid, bp 98-99°(0.5 mm Hg); ir (liquid film): 3346 (NH), 1726 (C=O), 1655(C=C) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.13, 1.15, 1.18 and 1.23 (each 3H, s, CH_3), 1.61 (1H, br s, NH), 3.25 and 3.56 (each 1H, d, J = 7.3 Hz, CH_2O), 3.73 (3H, s, CO_2CH_3), 4.41 (1H, s, CH), 5.88 and 7.04 (each 1H, d, J = 16.1 Hz, CH=CH); ms: (CI), m/z 228 (MH^+).

Anal. Calcd. for $C_{12}H_{21}NO_3$: C, 63.41; H, 9.31; N, 6.16. Found: C, 63.60; H, 9.31; N, 6.16.

Methyl (*E*)-4-Methyl-4-[2-(5,5-dimethyloxazolidinyl)]-2-pentenoate (**4c**).

This compound was obtained as a colorless liquid, bp 105-107°(0.3 mm Hg); ir (liquid film): 3356 (NH), 1724 (C=O), 1655 (C=C) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.11, 1.12, 1.20 and 1.24 (each 3H, s, CH_3), 2.24 (1H, br s, NH), 2.76 and 2.81 (each 1H, d, J = 11.5 Hz, CH_2N), 3.73 (3H, s, CO_2CH_3), 4.34 (1H, s, CH), 5.86 and 7.08 (each 1H, d, J = 16.1 Hz, CH=CH); ms: (CI), m/z 228 (MH^+).

Anal. Calcd. for $C_{12}H_{21}NO_3$: C, 63.41; H, 9.31; N, 6.16. Found: C, 63.50; H, 9.51; N, 6.22.

Methyl (*E*)-4-Methyl-4-[2-(tetrahydro-1,3-oxazinyl)]-2-pentenoate (**4d**).

This compound was obtained as a colorless liquid, bp 118-120°(0.5 mm Hg); ir (liquid film): 3321 (NH), 1724 (C=O), 1653 (C=C) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.09 and 1.10 (each 3H, s, CH_3), 1.26 (1H, br s, NH), 1.34 and 1.67 (each 1H, m, $CH_2CH_2CH_2$), 2.88 and 3.15 (each 1H, m, CH_2N), 3.69 and 4.10 (each 1H, m, CH_2O), 3.73 (3H, s, CO_2CH_3), 3.84 (1H, s, CH), 5.82 and 7.07 (each 1H, d, J = 16.1 Hz, CH=CH); ms: (CI), m/z 214 (MH^+).

Anal. Calcd. for $C_{11}H_{19}NO_3$: C, 61.95; H, 8.98; N, 6.57. Found: C, 62.17; H, 8.91; N, 6.54.

Methyl (*E*)-4-Methyl-4-[2-(5,5-dimethyl-tetrahydro-1,3-oxazinyl)]-2-pentenoate (**4e**).

This compound was obtained as a colorless liquid, bp 115-117°(0.5 mm Hg); ir (liquid film): 3342 (NH), 1726 (C=O), 1657 (C=C) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 0.70, 1.02, 1.12 and 1.13 (each 3H, s, CH_3), 1.57 (1H, br s, NH), 2.64 and 2.66 (each 1H, d, J = 11.7 Hz, CH_2N), 3.34 and 3.57 (each 1H, d, J = 11.2 Hz, CH_2O), 3.72 (3H, s, CO_2CH_3), 3.73 (1H, s, CH), 5.84 and 7.11 (each 1H, d, J = 16.1 Hz, CH=CH); ms: (CI), m/z 242 (MH^+).

Anal. Calcd. for $C_{13}H_{23}NO_3$: C, 64.70; H, 9.61; N, 5.80. Found: C, 64.75; H, 9.62; N, 5.99.

General Procedure for the Preparation of 4,5-Dihydrooxazoles **5a-c** and 5,6-Dihydro-4*H*-1,3-oxazines **5d,e**.

In a distilling flask **4** (60.0 mmoles) was heated at 230° for 2 hours, during which the products **5** and **6** formed distilled. The distillate was redistilled through a 50-cm spinning band column to give **5** and **6** [bp 69-70°(30 mm Hg) (reference [5], bp 153-154°)].

4,5-Dihydrooxazole (**5a**).

This compound was obtained as a colorless liquid, bp 53-54°(160 mm Hg) [(reference [6], bp 40-45°(100 mm Hg)]; ir (liquid film): 1630 (C=N) cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.82 (2H, td, J = 9.8, 2.4 Hz, CH_2N), 4.21 (2H, t, J = 9.8 Hz, CH_2O), 6.85 (1H, t, J = 2.4 Hz, CH=N); ms: m/z 71 (M^+).

4,4-Dimethyl-4,5-dihydrooxazole (**5b**).

This compound was obtained as a colorless liquid, bp 55-56°(145 mm Hg) (reference [7], bp 99-100°); ir (liquid film): 1630 (C=N) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.29 (6H, s, $2CH_3$), 3.89 (2H, s, CH_2O), 6.72 (1H, s, CH=N); ms: m/z 99 (M^+).

5,5-Dimethyl-4,5-dihydrooxazole (**5c**).

This compound was obtained as a colorless liquid, bp 60-61°(125 mm Hg); ir (liquid film): 1630 (C=N) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.39 (6H, s, $2CH_3$), 3.53 (2H, d, J = 2.4 Hz, CH_2N), 6.74 (1H, t, J = 2.4 Hz, CH=N); ms: m/z 99 (M^+).

Anal. Calcd. for C_5H_9NO: C, 60.58; H, 9.15; N, 14.13. Found: C, 60.30; H, 9.28; N, 14.06.

5,6-Dihydro-4*H*-1,3-oxazine (**5d**).

This compound was obtained as a colorless liquid, bp 64-65°(95 mm Hg) [reference [8], bp 85°(70 mm Hg)]; ir (liquid film): 1651 (C=N) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.94 (2H, tt, J = 5.9, 5.4 Hz, $CH_2CH_2CH_2$), 3.33 (2H, td, J = 5.9, 1.5 Hz, CH_2N) 4.15 (2H, t, J = 5.4 Hz, CH_2O), 6.98 (1H, t, J = 1.5 Hz, CH=N); ms: m/z 85 (M^+).

5,5-Dimethyl-5,6-dihydro-4*H*-1,3-oxazine (**5e**).

This compound was obtained as a colorless liquid, bp 72-73°(85 mm Hg); ir (liquid film): 1659 (C=N) cm^{-1}; ^1H nmr (deuteriochloroform): δ 0.98 (6H, s, $2CH_3$), 3.05 (2H, d, J = 1.0 Hz, CH_2N), 3.70 (2H, s, CH_2O), 7.00 (1H, t, J = 1.0 Hz, CH=N); ms: m/z 113 (M^+).

Anal. Calcd. for $C_6H_{11}NO$: C, 63.69; H, 9.80; N, 12.38. Found: C, 63.63; H, 10.01; N, 12.40.

8,8-Dimethyl-5-oxo-2,3,8,8a-tetrahydro-5*H*-oxazolo[3,2-*a*]-pyridine (**7**).

To a stirred, ice-cold mixture of a solution of **2** (X = O) (6.25 g, 40.0 mmoles) in monoglyme (30 ml) and 4A molecular sieves (30 g) was added a solution of **3a** (2.69 g, 44.0 mmoles) in monoglyme (15 ml) over a period of 1 hour. The mixture was stirred for an additional 2 hours at room temperature. The molecular sieves were removed by filtration and washed with monoglyme. The combined filtrates were concentrated and distilled to yield 5.54 g (83%) of **7**, bp 86-87°(0.5 mm Hg); ir (liquid film): 1674 (C=O), 1605 (C=C) cm^{-1}; ^1H nmr (deuteriochloroform): δ 0.96 and 1.22 (each 3H, s, CH_3), 3.60-3.70 (2H, m, CH_2N), 3.97 and 4.25 (each 1H, m, CH_2O), 4.72 (1H, s, CH), 5.83 and 6.25 (each 1H, d, J = 9.7 Hz, CH=CH); ms: m/z 167 (M^+).

Anal. Calcd. for $C_9H_{13}NO_2$: C, 64.65; H, 7.84; N, 8.38. Found: C, 64.51; H, 8.02; N, 8.50.

REFERENCES AND NOTES

[1] K. Ito, S. Yokokura and S. Miyajima, *J. Heterocyclic Chem.*, **26**, 773 (1989).

[2] K. Ito and S. Miyajima, *J. Heterocyclic Chem.*, **29**, 1037 (1992).

[3] S. Miyajima and K. Ito, *Bull. Chem. Soc. Japan*, **58**, 2659 (1985).

[4] T. L. Cairns and J. H. Fletcher, *J. Am. Chem. Soc.*, **63**, 1034 (1941).

[5] E. Caspi and K. R. Varma, *J. Org. Chem.*, **33**, 2181 (1968).

[6] F. T. Smith and R. V. Atigadda, *J. Heterocyclic Chem.*, **28**, 1813 (1991).

[7] A. I. Meyers and E. W. Collington, *J. Am. Chem. Soc.*, **92**, 6676 (1970).

[8] Y. Ito, Y. Inubushi, M. Zenbayashi, S. Tomita and T. Saegusa, *J. Am. Chem. Soc.*, **95**, 4447 (1973).