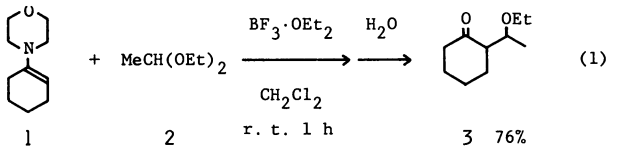
Reaction of Enamines with Acetals or Trialkyl Orthoformates Activated by Lewis Acids

Osamu TAKAZAWA,* Kunio KOGAMI, and Kazuo HAYASHI
Kawasaki Research Laboratories, T. Hasegawa Co., Ltd., 335 Kariyado, Nakahara-ku, Kawasaki 211
(Received October 13, 1983)

Enamines, prepared readily from various carbonyl compounds, react with acetals or trialkyl orthoformates in the presence of Lewis acids such as $BF_3 \cdot OEt_2$ to give corresponding β-alkoxy carbonyl compounds or α-dialkoxymethyl carbonyl compounds in good yields. The reaction of dienamines with acetals or trialkyl orthoformates also selectively gives corresponding β,γ-unsaturated α-(α-alkoxyalkyl) carbonyl compounds or β,γ-unsaturated α-diakoxymethyl carbonyl compounds in good yields.

The reaction of enamines with trialkyl orthoformates was briefly reported in our previous paper.[1] In this report, the above reaction is investigated in detail.

In the preceding paper,[2] it was shown that the β-alkoxy carbonyl compounds or α-dimethoxymethyl carbonyl compounds are obtained by the reaction of enol silyl ethers with acetals or trimethyl orthoformate in the presence of $TiCl_4$. In the present investigation, it has been found that enamines react with acetals or trialkyl orthoformates in the presence of Lewis acids similarly to enol silyl ethers. For example, to a dichloromethane solution of a 1.2 molar amount of acetaldehyde diethyl acetal (**2**) was added a 1.3 molar amount of $BF_3 \cdot OEt_2$ at −40 °C in argon atmosphere. Then 1-morpholino-1-cyclohexene (**1**) was added and the reaction mixture was stirred for 1 h at room temperature. After hydrolysis, the resulting organic layer was concentrated. The reaction product, 2-(1-ethoxyethyl)-1-cyclohexanone (**3**), was obtained in 76% yield after distillation under reduced pressure, the reaction concerned being summarized as:



In order to investigate the effect of Lewis acids, reactions of **1** with **2** in the presence of various Lewis acids were tried according to the procedure mentioned above (Table 1). The results described in Table 1 demonstrate that, of the Lewis acids examined, $BF_3 \cdot OEt_2$ exhibits a remarkable effect as compared with the others. In case $TiCl_4$ was employed, 2-ethylidenecyclohexanone was obtained as a major product along with **3**.

The effect of the amount of $BF_3 \cdot OEt_2$ upon the yield of **3** was then investigated by using the reaction between **1** and a 1.2 molar amount of **2** at room temperature for 1 h as a reference reaction. It was found that the product **3** was obtained in the highest yield when a 1.3 or 1.5 molar amount of $BF_3 \cdot OEt_2$ was applied (Table 2).

Furthermore, the effect of amines used in enamine synthesis was studied by treating enamines derived from various amines and cyclohexanone with a 1.2 and 1.3 molar amount of **2** and $BF_3 \cdot OEt_2$, respectively, under similar conditions as described above. The results shown herein indicate that morpholine enamine (**1**) is significantly favored in this reaction to afford the best yield (Table 3).

Reactions of **1**, 3,7-dimethyl-1-morpholino-1,6-octadiene (**11**), or 1-piperidino-1-hexene (**14**) with a variety of acetals were tried in the presence of $BF_3 \cdot OEt_2$ according to the typical procedure, and the corresponding β-alkoxy carbonyl compounds were obtained in good yields as shown in Table 4.

The reaction of crotonaldehyde dimethyl acetal with **1** gave a Michael type adduct (**18**) in 13% yield

TABLE 1. REACTION OF THE ENAMINE **1** WITH THE ACETAL **2** IN THE PRESENCE OF VARIOUS LEWIS ACIDS

Lewis acid	Reaction conditions		Yield[a] of **3**[b]
	Temp./°C	Time/h	%
$BF_3 \cdot OEt_2$	0	3	68
$BF_3 \cdot OEt_2$	r. t.	1	76
$TiCl_4$	r. t.	1	21 (52)[c]
$SnCl_4$	r. t.	2	trace
$AlCl_3$	r. t.	24	15 (6)[c]
$ZnCl_2$	r. t.	24	trace
$ZnBr_2$	r. t.	24	trace
$FeCl_3$	r. t.	24	trace
$MgCl_2$	r. t.	24	0

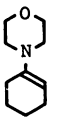
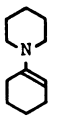
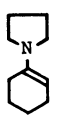
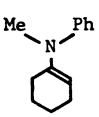
a) Isolated yield. b) An erythro and threo mixture. c) Yield of 2-ethylidenecyclohexanone.

TABLE 2. EFFECT OF THE AMOUNT OF $BF_3 \cdot OEt_2$ ON THE YIELD

Molar ratio of $BF_3 \cdot OEt_2$	0.1	0.5	1.0	1.2	1.3	1.5	2.0
Yield[a] of **3**[b]/%	Trace	16	48	72	76	76	55

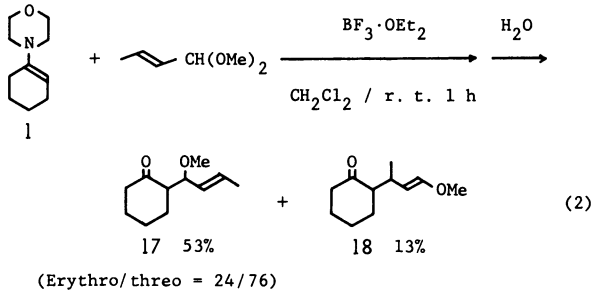
a) Isolated yield. b) An erythro and threo mixture.

TABLE 3. EFFECT OF AMINES USED IN ENAMINE SYNTHESIS

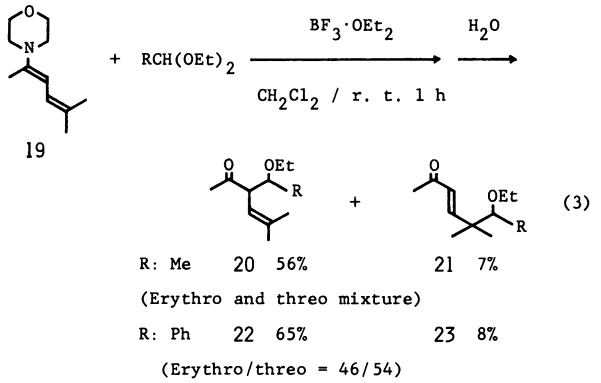
Enamine				
	1	4	5	6
Yield[a] of **3**[b]/%	76	32	Trace	44

a) Isolated yield. b) An erythro and threo mixture.

together with β-methoxy ketone (**17**) in 53% yield:[3]

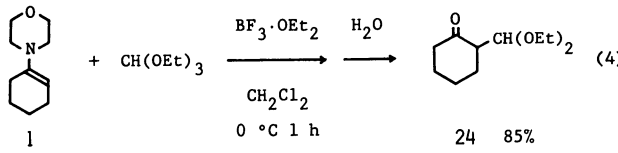


In contrast to the result[4] that the reaction of dienyloxysilanes with acetals gave α,β-unsaturated γ-(α-alkoxyalkyl) carbonyl compounds, the present reaction of a dienamine, 2-methyl-5-morpholino-2,4-hexadiene (**19**), with acetals selectively afforded β,γ-unsaturated α-(α-alkoxyalkyl) carbonyl compounds, **20**, or **22**, as shown by the following equation:



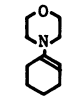
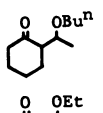
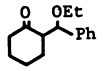
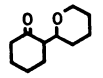
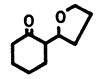
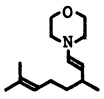
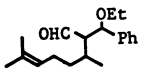
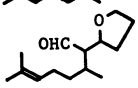
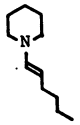
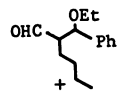
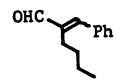
It is known that the reaction of enamines with alkyl halomethyl ethers affords α-alkoxymethyl carbonyl compounds.[5] In contrast to this finding, the present reaction gives α-(1-alkoxyalkyl) carbonyl compounds in good yields.

On the other hand, α-dialkoxymethyl carbonyl compounds are obtained by the reaction of enamines with trialkyl orthoformates. For example, to a dichloromethane solution of **1** and a 1.3 molar amount of triethyl orthoformate was added a 1.3 molar amount of $BF_3 \cdot OEt_2$ at −40 °C in argon atmosphere. Then the reaction mixture was stirred for 1 h at 0 °C. After hydrolysis, the resulting organic layer was concentrated. The reaction product, 2-diethoxymethyl-1-cyclohexanone (**24**), was obtained in 85% yield after distillation under reduced pressure, the reaction concerned being summarized as:



In a similar manner, the reaction of enamines derived from various carbonyl compounds with trialkyl orthoformates afforded the corresponding α-dialkoxymethyl carbonyl compounds as listed in Table 5.

Table 4. Synthesis of β-alkoxy carbonyl compounds from enamines and acetals in the presence of $BF_3 \cdot OEt_2$

Enamine	Acetal		Product	Isolated yield/%	Isomer ratio[a] a/b
 1	$MeCH(OBu^n)_2$	7		81	-
	$PhCH(OEt)_2$	8		89	38/62[b]
		9		57	59/41[c]
		10		70	55/45[c]
 11	$PhCH(OEt)_2$	12		81	48/52[b]
		13		79	54/46[c]
 14	$PhCH(OEt)_2$	15		56	30/70[b,d]
		16		12	-

a) Erythro and threo isomers. Determined by GLC analysis. b) a/b = erythro/threo. c) The stereochemistries of a and b are not determined. d) Determined by NMR analysis.

Since the reactivity of trialkyl orthoformates toward enamines is higher than that of acetals, α-dialkoxymethyl carbonyl compounds were obtained in good yields in the presence of $TiCl_4$, $SnCl_4$, or $ZnCl_2$.

In contrast to the result that the reaction of dienoxysilanes with trialkyl orthoformates gave α,β-unsaturated γ-dialkoxymethyl carbonyl compounds,[4] the present reaction of dienamine **19** with trimethyl orthoformate afforded β,γ-unsaturated α-dimethoxymethyl ketone (**28**).

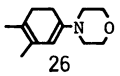
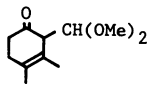
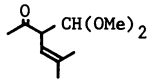
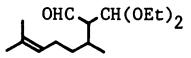
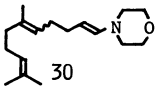
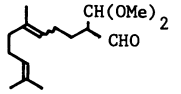
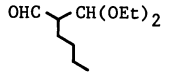
It is known that the reaction of enamines with a mixed anhydride of formic acid and acetic acid[5c] or the Vilsmeier reagent ($POCl_3$–DMF)[6] affords 2-formyl ketones. In comparison with the above reaction, the present reaction has an advantage in that α-dialkoxymethyl carbonyl compounds, having the protected formyl and carbonyl groups in the same molecule, is exclusively formed by a one-step procedure.

Experimental

Spectra. ^1H NMR spectra were recorded on a Hitachi R-24A spectrometer. Chemical shifts are reported on the δ scale relative to tetramethylsilane as an internal standard. IR spectra were taken with a JASCO IRA-2 spectrometer. Products were identified by NMR and IR spectra and elemental analyses.

Materials. Commercially available $BF_3 \cdot OEt_2$, $TiCl_4$,

Table 5. Reaction of enamines with methyl or ethyl orthoformate

Enamine	Methyl or ethyl orthoformate	Lewis acid	Reaction conditions		Product	Isolated yield
			Temp/°C	Time/h		%
1	$CH(OEt)_3$	$BF_3 \cdot OEt_2$	0	1	24	85
		$SnCl_4$	0	1		90
		$ZnCl_2$	r.t.	14		54
1	$CH(OMe)_3$	$BF_3 \cdot OEt_2$	0	1	25	74
		$TiCl_4$	-40	1		64
 26	$CH(OMe)_3$	$TiCl_4$	-78	0.5	 27	70
19	$CH(OMe)_3$	$BF_3 \cdot OEt_2$	0	1	 28	75
		$SnCl_4$	0	1		68
		$TiCl_4$	0	1		63
11	$CH(OEt)_3$	$BF_3 \cdot OEt_2$	-40	1	 29	78
		$ZnCl_2$	r.t.	3		43
 30	$CH(OMe)_3$	$BF_3 \cdot OEt_2$	-40	1	 31	61
14	$CH(OEt)_3$	$BF_3 \cdot OEt_2$	-40	1	 32	71
		$SnCl_4$	-40	1		70

and $SnCl_4$ were distilled in argon atmosphere before use. Anhydrous $AlCl_3$, $ZnCl_2$, $ZnBr_2$, $FeCl_3$, and $MgCl_2$ were used without purification. Enamines of carbonyl compounds, 1-morpholino-1-cyclohexene (**1**), 1-pyrrolidino-1-cyclohexene (**5**), and *N*-(1-cyclohexenyl)-*N*-methylaniline (**6**), were prepared according to literature procedures[5c,7] and purified by distillation. **1**: bp 116—117 °C/10 mmHg (1 mmHg≈133.322 Pa) (lit,[7] 118—120 °C/10 mmHg); **5**: bp 103—104 °C/10 mmHg (lit,[5c] 105—107 °C/13 mmHg); **6**: bp 95—97 °C/1 mmHg (lit,[5c] 148—153 °C/12 mmHg). In a similar manner, 1-piperidino-1-cyclohexene (**4**), 3,7-dimethyl-1-morpholino-1,6-octadiene (**11**), 1-piperidino-1-hexene (**14**), 5-methyl-2-morpholino-2,4-hexadiene (**19**), 3,4-dimethyl-1-morpholino-1,3-cyclohexadiene (**26**), and 6,10-dimethyl-1-morpholino-1,5,9-undecatriene (5*E*:5*Z*=1:1) (**30**) were prepared from the corresponding carbonyl compounds and amines, and the physical data are as follows. **4**: bp 109—110 °C/10 mmHg; NMR ($CDCl_3$) δ=1.52 (10H, m), 2.04 (4H, m), 2.74 (4H, m), and 4.66 (1H, t, J=3.0 Hz). **11**: bp 113 °C/2 mmg; NMR ($CDCl_3$) δ=1.00 (3H, d, J=6.0 Hz), 1.2—2.3 (5H, m), 1.61 (3H, s), 1.70 (3H, s), 2.75 (4H, m), 4.30 (1H, dd, J=14.5 and 8.5 Hz), 5.10 (1H, t, J=7.0 Hz), and 5.75 (1H, d, J=14.5 Hz). **14**: bp 103 °C/13 mmHg; NMR ($CDCl_3$) δ=0.90 (3H, t, J=5.5 Hz), 1.1—1.8 (10H, m), 1.97 (2H, q, J=7.0 Hz), 2.75 (4H, m), 4.38 (1H, dt, J=14.0 and 7.0 Hz), and 5.80 (1H, d, J=14.0 Hz). **19**: bp 125—127 °C/9 mmHg; NMR ($CDCl_3$) δ=1.72 (3H, s), 1.80 (3H, s), 1.88 (3H, s), 2.88 (4H, m), 3.75 (4H, m), 5.30 (1H, d, J=11.5 Hz), and 5.96 (1H, d, J=11.5 Hz). **26**: bp 97—98 °C/0.6 mmHg; NMR ($CDCl_3$) δ=1.70 (6H, s), 2.15 (4H, s), 2.82 (4H, m), 3.69 (4H, m), and 4.76 (1H, s). **30**: NMR ($CDCl_3$) δ=1.60 and 1.68 (9H, s), 1.8—2.2 (8H, m), 2.70 (4H, m), 3.65 (4H, m), 4.45 (1H, m), 5.10 (2H, m), and 5.80 (1H, d, J=14.0 Hz).

Reaction of 1-Morpholino-1-cyclohexene (1) with Acetaldehyde Diethyl Acetal (2) in the Presence of $BF_3 \cdot OEt_2$. To a dichloromethane (50 ml) solution of 7.08 g (60 mmol) of acetaldehyde diethyl acetal (**2**) was added 9.23 g (65 mmol) of $BF_3 \cdot OEt_2$ at −40 °C in argon atmosphere. Then 8.35 g (50 mmol) of 1-morpholino-1-cyclohexene (**1**) was added immediately and the reaction mixture was stirred for 1 h at room temperture. The mixture was quenched with water and stirred for 1 h at room temperature. After hydrolysis, the organic layer was washed with a saturated solution of $NaHCO_3$ and dried over $MgSO_4$. After removal of the solvent, the residue was distilled under reduced pressure to give a mixture of diastereomers (**3a** and **3b**) of 2-(1-ethoxyethyl)cyclohexanone (**3**) (6.50 g, 93—94 °C/10 mmHg, 76%). **3a** and **3b** were in the ratio 46:54 as found by means of gas chromatography (PEG-20 M). Analytically pure samples of **3a** and **3b** were prepared by preparative gas chromatography (20% PEG-20 M).

Reactions of enamines, such as 1-morpholino-1-cyclohexene (**1**), 1-piperidino-1-cyclohexene (*4*), 1-pyrrolidino-1-cyclohexene (**5**), *N*-(1-cyclohexenyl)-*N*-methylaniline (**6**), 3,7-dimethyl-1-morpholino-1,6-octadiene (**11**), and 1-piperidino-1-hexene (**14**), with various acetals were carrid out according to the same procedure, and the yields of the corresponding β-alkoxy carbonyl compounds are listed in Tables 3 and 4. The physical properties and analytical data of the products are shown in Table 6.

Reaction of 1-Morpholino-1-cyclohexene (1) with Acetaldehyde Diethyl Acetel (2) in the Presence of Various Lewis Acids. To a dichloromethane (50 ml) solution of 7.08 g (60 mmol) of acetaldehyde diethyl acetal (**2**) was added a Lewis acid (65 mmol) at −40 °C in argon atmosphere. Then 8.35 g (50 mmol) of 1-morpholino-1-cyclohexene (1) was added immediately. The reaction mixture was worked up as described above and purified by distillation. The reaction conditions and the yields of **3** are listed in Table 1.

Reaction of 1-Morpholino-1-cyclohexene (1) with Crotonaldehyde Dimethyl Acetal. Into a mixture of 8.35 g (50 mmol) of **1** and 6.96 g (60 mmol) of crotonaldehyde dimethyl acetal in dichloromethane (50 ml) was added 8.52 g (60 mmol) of $BF_3 \cdot OEt_2$ at −40°C in argon atmosphere and the reaction mixture was stirred for 1 h at room temperature. The reaction mixture was worked up as described above and the resulting residue was distilled under reduced pressure to give a mixture of diastereomers (**17a** and **17b**) of 2-(*trans*-1-methoxy-2-butenyl)-1-cyclohexanone (**17**) and 2-(*trans*-3-

Table 6. Physical properties and analytical data of products

Product	Bp θ_b/°C(mmHg)	Isomer[a]	IR cm^{-1}	NMR (δ, $CDCl_3$, J/Hz)	Found(Calcd)/% C	H
3	93—94(10)[b]	a	1710 1105	1.14(3H, t, J=7.0), 1.14(3H, d, J=6.0), 1.4—2.1(6H, m), 2.1—2.5(3H, m), 3.47(2H, m), 3.76 (1H, quint, J=6.0).	70.40 (70.55)	10.69 (10.66)
		b	1710 1105	1.10(3H, d, J=6.0), 1.16(3H, t, J=7.0), 1.4—2.2(6H, m), 2.2—2.7(3H, m), 3.48(2H, m), 3.90 (1H, quint, J=6.0).	70.40 (70.55)	10.58 (10.66)
7	82—83(1.0)[b]	Mixture	1710 1105	0.88(3H, t, J=7.0), 1.06 and 1.08(3H, d, J=6.0), 1.2—2.1(10H, m), 2.1—2.5(3H, m), 3.37(2H, m), 3.82(1H, quint, J=6.0).	72.62 (72.68)	11.14 (11.18)
8	117—118 (1.0)[b]	a (erythro)	1710 1100 700	1.13(3H, t, J=7.0), 1.4—2.1(6H, m), 2.1—2.6 (3H, m), 3.37(2H, q, J=7.0), 4.84(1H, d, J=4.4), 7.26(5H, s).	77.56 (77.55)	8.68 (8.68)
		b (threo)	1713 1095 700	1.10(3H, t, J=7.0), 1.3—2.1(6H, m), 2.2—2.9 (3H, m), 3.35(2H, q, J=7.0), 4.67(1H, d, J=8.0), 7.26(5H, s).	77.59 (77.55)	8.68 (8.68)
9	87—88(1.2)[b]	a	1710 1090	1.2—2.1(12H, m), 2.1—2.5(3H, m), 3.2—4.2(3H, m).	72.22 (72.49)	9.90 (9.95)
		b	1710 1090	1.2—2.2(12H, m), 2.2—2.7(3H, m), 3.2—4.1(3H, m).	72.46 (72.49)	9.96 (9.95)
10	80—81(1.2)[b]	a	1710 1053	1.2—2.2(10H, m), 2.2—2.6(3H, m), 3.72(2H, m), 3.98(1H, q, J=7.0).	71.21 (71.39)	9.72 (9.59)
		b	1710	1.3—2.2(10H, m), 2.2—2.8(3H, m), 3.78(2H, m), 4.17(1H, q, J=7.0).	71.25 (71.39)	9.61 (9.59)
12	144—145 (1.0)[b]	a (erythro)	1722 1100 698	1.06(3H, d, J=6.0), 1.12(3H, t, J=7.0), 1.60(3H, s), 1.67(3H, s), 1.3—2.4(5H, m), 2.75(1H, m), 3.32(2H, q, J=7.0), 4.66(1H, d, J=8.0), 5.08 (1H, m), 7.28(5H, s), 9.52 and 9.57(1H, d, J=3.2).	78.92 (79.12)	9.72 (9.78)
		b (threo)	1723 1090 698	0.95(3H, d, J=6.0), 1.10(3H, t, J=7.0), 1.53 (3H, s), 1.57(3H, s),1.3—2.1(5H, m), 2.52(1H, m), 3.32(2H, q, J=7.0), 4.72(1H, d, J=9.2), 4.80(1H, m), 7.31(5H, s), 9.83 and 9.86(1H, d, J=4.5).	78.85 (79.12)	9.70 (9.78)
13	109—111 (1.0)[b]	a	1720 1068	1.02(3H, d, J=6.0), 1.60(3H, s), 1.67(3H, s), 1.2—2.3(9H, m), 2.47(1H, m), 3.72(2H, m), 4.12 (1H, q, J=7.0), 5.10(1H, t, J=6.0), 9.72 and 9.76(1H, d, J=2.4).	74.81 (74.95)	10.93 (10.78)
		b	1725 1060	1.00 and 1.03(3H, d, J=6.0), 1.60(3H, s), 1.67 (3H, s), 1.2—2.3(10H, m), 3.75(2H, m), 4.20(1H, m), 5.50(1H, t, J=6.0), 9.70 and 9.75 (1H, d, J=4.4).	74.78 (74.95)	10.71 (10.78)
15		Mixture (e/t=30/70)[c]	1727 1095 700	0.7—1.6(12H, m), 2.50(1H, m), 3.28(2H, m), 4.42 (1H, d, J=9.0, CH-O threo), 4.58(1H, d, J=5.7, CH-O erythro), 7.25 and 7.28(5H, s), 9.63 (1H, d, J=2.7, CHO erythro), 9.70(1H, d, J=4.0, CHO threo).	76.72 (76.88)	9.53 (9.46)
16			1680 1620	0.92(3H, m), 1.2—1.7(4H, m), 2.50(2H, m), 7.11 (1H, s), 7.37(5H, s), 9.45(1H, s).		
17		a (erythro)	1710 1090 970	1.72(3H, d, J=5.5), 1.5—2.1(6H, m), 2.2—2.6(3H, m), 3.25(3H, s), 3.99(1H, dd, J=7.0, 4.4), 5.42 (1H, dd, J=15.5, 7.0), 5.68(1H, dq, J=15.5, 5.5).	72.54 (72.49)	10.02 (9.95)
		b (threo)	1713 1090 970	1.75(3H, d, J=6.0), 1.4—2.2(6H, m), 2.2—2.7 (3H, m), 3.24(3H, s), 3.92(1H, t, J=8.0), 5.27 (1H, dd, J=16.0, 8.0), 5.68(1H, dq, J=16.0, 6.0).	72.43 (72.49)	10.06 (9.95)
18			1710 1650	1.03(3H, dd, J=6.4, 1.0), 1.4—2.8(10H, m), 3.48 (3H, s), 4.75(1H, dd, J=12.6, 8.4), 6.30(1H, d,	72.55 (72.49)	10.03 (9.95)

Table 6. Continued

Product	Bp θ_b/°C(mmHg)	Isomer[a]	IR cm^{-1}	NMR (δ, $CDCl_3$, J/Hz)	Found(Calcd)/% C	H
			1205	J=12.6).		
			935			
20		Mixture	1713	1.08(3H, d, J=6.0), 1.11 and 1.13(3H, t, J=	71.66	10.86
			1100	7.0), 1.64—1.78(6H, m), 3.16—3.95(4H, m), 4.95 and 5.23(1H, d, J=9.0).	(71.70)	(10.94)
21			1700	1.02(3H, d, J=6.0), 1.05(6H, s), 1.15(3H, t, J=	71.75	10.88
			1680	7.0), 2.23(3H, s), 3.15(1H, q, J=6.0), 3.47(2H,	(71.70)	(10.94)
			1620	m), 6.03(1H, d, J=16.0), 6.88(1H, d, J=16.0).		
			1100			
22		Mixture	1715	1.08 and 1.13(3H, t, J=7.0), 1.22 and 1.39(3H,	77.98	9.14
		(e/t=46/54)[c]	1095	d, J=1.5), 1.53 and 1.74(3H, d, J=1.5), 2.02	(78.01)	(9.00)
			698	(3H, s, $COCH_3$ erythro), 2.22(3H, s, $COCH_3$ threo), 3.10—3.83(3H, m), 4.46(1H, d, J=10.0, CH-O threo), 4.67(1H, d, J=5.6, CH-O erythro), 4.93 and 5.48(1H, d, J=10.0), 7.24(5H, s).		
23			1700	1.01(3H, s), 1.09(3H, s), 1.14(3H, t, J=7.0), 2.23	78.10	9.07
			1677	(3H, s), 3.32(2H, m), 4.02(1H, s), 5.92(1H, d,	(78.01)	(9.00)
			1623	J=16.0), 6.93(1H, d, J=16.0), 7.23(5H, s).		
			1100			
			1070			
24	76(0.9)		1713	1.17(6H, t, J=7.0), 1.4—2.5(8H, m), 2.60(1H,	65.88	10.05
			1105	m), 3.62(4H, m), 4.82(1H, d, J=6.0).	(65.97)	(10.07)
			1060			
25	67(1.0)		1713	1.4—2.5(8H, m), 2.60(1H, m), 3.37(6H, s), 4.65	62.57	9.25
			1105	(1H, d, J=6.0).	(62.77)	(9.36)
			1070			
27	77/0.7		1720	1.75(6H, s), 2.1—2.8(4H, m), 2.92(1H, d, J=6.0),	66.58	9.08
			1100	3.40(6H, s), 4.63(1H, d, J=6.0).	(66.64)	(9.15)
			1070			
28	62/1.2		1710	1.75(6H, m), 2.12(3H, s), 3.28(3H, s), 3.35(3H,	64.52	9.69
			1120	s), 3.66(1H, dd, J=10.0, 8.4), 4.60(1H, d, J=	(64.49)	(9.74)
			1080	8.4), 5.14(1H, d, J=10.0).		
			1060			
29	111—112		1725	1.05(3H, t, J=7.0), 1.17(3H, t, J=7.0), 1.19(3H,	70.21	10.95
	(1.0)		1120	t, J=7.0), 1.60(3H, s), 1.68(3H, s), 1.3—2.3(5H,	(70.27)	(11.01)
			1060	m), 2.50(1H, m), 3.57(4H, m), 4.87(1H, m), 5.08 (1H, t, J=6.0), 9.71(1H, d, J=4.0).		
31			1725	1.60 and 1.68(9H, s), 1.6—2.2(8H, m), 2.65(1H,		
			1120	m), 3.38(6H, s), 4.50(1H, d, J=6.0), 5.10(2H,		
			1070	m), 9.67(1H, d, J=3.0).		
32	70/1.2		1727	0.88(3H, t, J=6.0), 1.18(3H, t, J=7.0), 1.20(3H,	65.20	10.87
			1120	t, J=7.0), 1.0—1.8(6H, m), 2.55(1H, m), 3.60	(65.31)	(10.96)
			1060	(4H, m), 4.64(1H, d, J=6.0), 9.68(1H, d, J= 3.0).		

a) Erythro and threo isomers. b) An erythro and threo mixture. c) e stands for erythro and t for threo.

methoxy-1-methyl-2-propenyl)-1-cyclohexanone (**18**) (6.00 g, 77—84 °C/2.0 mmHg, 66%). **17a** (erythro), **17b** (threo), and **18** were found to be in the ratio 13:40:13 by means of gas chromatography (PEG 20 M). Analytically pure samples of products were prepared by silica-gel column chromatography (hexane–ether) and preparative gas chromatography (20% PEG-20 M).

Reaction of 5-Methyl-2-morpholino-2,4-hexadiene (19) with Acetals. To a dichloromethane (50 ml) solution of 10.8 g (60 mmol) of benzaldehyde diethyl acetal was added 9.23 g (65 mmol) of $BF_3 \cdot OEt_2$ at −40 °C in argon atmosphere. Then 9.05 g (50 mmol) of 5-methyl-2-morpholino-2,4-hexadiene (**19**) was added immediately and the reaction mixture was stirred for 1 h at room temperature. The reaction mixture was worked up as described above and purified by silica-gel column chromatography. Elution with hexane and ether afforded 8.01 g (65%) of a mixture of diastereomers (**22a** and **22b**) of 3-(α-ethoxybenzyl)-5-methyl-4-hexen-2-one (**22**) and 0.98 g (8%) of 5-(α-ethoxybenzyl)-5-methyl-3-hexen-2-one (**23**). **22a** (erythro) and **22b** (threo) were in the ratio 46:54 as

Table 7. NMR signals of methylene protons in β-alkoxy carbonyl compounds

Product			Ha/δ	Jab/Hz	Solvent
8	a	(erythro)	4.84	4.4 (2.5)[a]	$CDCl_3$
	b	(threo)	4.67	8.0 (9.0)[a]	$CDCl_3$
12	a	(erythro)	4.66	8.0	$CDCl_3$
	b	(threo)	4.72	9.3	$CDCl_3$
15	a	(erythro)	4.58	5.7	$CDCl_3$
	b	(threo)	4.42	9.0	$CDCl_3$
17	a	(erythro)	3.99	4.4 (3.7)[a]	$CDCl_3$
	b	(threo)	3.92	8.0 (7.0)[a]	$CDCl_3$
22	a	(erythro)	4.67	5.6	$CDCl_3$
	b	(threo)	4.46	10.0	$CDCl_3$

a) The value of the corresponding aldol.

found by means of NMR.

Similarly, the reaction of **19** (9.05 g, 50 mmol) and acetaldehyde diethyl acetal (7.08 g, 60 mmol) in the presence of $BF_3 \cdot OEt_2$ (9.23 g, 65 mmol) gave 5.15 g (56%) of a mixture of diastereomers of 3-(1-ethoxyethyl)-5-methyl-4-hexen-2-one (**20**) and 0.65 g (7%) of *trans*-5-(1-ethoxyethyl)-5-methyl-3-hexen-2-one (**21**).

Stereochemistry of β-Alkoxy Carbonyl Compounds. The diastereomers **8a** and **8b** were stereospecifically converted into the corresponding *O*-methyloximes **33a** and **33b** by treatment with *O*-methylhydroxylamine (1.5 equiv., H_2O–MeOH, r. t, quant.). Then, it was found that **33a** and **33b** were erythro and threo isomers, respectively, by comparison with authentic samples prepared stereospecifically from the corresponding aldols[8] by treatment with *O*-methylhydroxylamine (1.5 equiv., H_2O–MeOH, r. t.) and NaH–EtI (THF, reflux, 30—50% yields). Therefore, it was determined that **8a** and **8b** were erythro and threo isomers, respectively. The stereochemistry of the diastereomers **17a** and **17b** was determined in a similar manner as above.

The stereochemistry of the diastereomers of **12**, **15**, and **22** was assigned on the basis of NMR spectra (shown in Table 7). Each of the diastereomers of **12**, **15**, and **22** has an absorption due to the proton (Ha) of the O–CH group or the other tertiary hydrogen (Hb), and a comparison of the coupling constant (Jab) of the isomers suggests the assigned stereochemistry.

Reaction of 1-Morpholino-1-cyclohexene (1) with Triethyl Orthoformate in the Presence of $SnCl_4$. To a mixture of 8.35 g (50 mmol) of 1-morpholino-1-cyclohexene (**1**) and 9.62 g (65 mmol) of triethyl orthoformate in dichloromethane (50 ml) was added 16.9 g (65 mmol) of $SnCl_4$ at −40 °C in argon atmosphere. Then the reaction mixture was stirred for 1 h at 0 °C. The mixture was quenched with water and stirred for 1 h at room temperature. After hydrolysis, the resulting organic layer was washed with a saturated solution of $NaHCO_3$ and dried over $MgSO_4$. After removal of the solvent, the residue was distilled to afford 9.00 g (90%) of 2-diethoxymethyl-1-cyclohexanone (**24**) (76 °C/0.9 mmHg).

The reaction of enamines, such as **1**, **11**, **14**, **19**, 3,4-dimethyl-1-morpholino-1,3-cyclohexadiene (**26**), and 1-morpholino-6,10-dimethyl-1,5,9-undecatriene (5*E*:5*Z*=1:1) (**30**), with triethyl or trimethyl orthoformate in the presence of various Lewis acids were carried out according to the same procedure, and the yields of the corresponding α-dialkoxymethyl carbonyl compounds are listed in Table 5. The physical properties and analytical data of the products are shown in Table 6.

The authors wish to express their thanks to Professor Teruaki Mukaiyama, the University of Tokyo for his helpful discussions.

Reference

1) O. Takazawa and T. Mukaiyama, *Chem. Lett.*, **1982**, 1307.
2) T. Mukaiyama and M. Hayashi, *Chem. Lett.*, **1974**, 15.
3) K. Narasaka, K. Soai, Y. Aikawa, and T. Mukaiyama, *Bull. Chem. Soc. Jpn.*, **49**, 779 (1976).
4) a) T. Mukaiyama and A. Ishida, *Chem. Lett.*, **1975**, 319; b) M. Asaoka, N. Sugimura, and H. Takei, *Bull. Chem. Soc. Jpn.*, **52**, 1953 (1979); c) I. Fleming, J. Goldhill, and I. Paterson, *Tetrahedron Lett.*, **1979**, 3209; d) O. Takazawa, H. Tamura, K. Kogami, and K. Hayashi, *Bull. Chem. Soc. Jpn.*, **55**, 1907 (1982).
5) a) A. T. Blomquist and E. Moriconi, *J. Org. Chem.*, **26**, 3761 (1961); b) G. Opitz, H. Hellmann, H. Mildenberger, and H. Suhr, *Justus Liebigs Ann. Chem.*, **649**, 39 (1961); c) G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *J. Am. Chem. Soc.*, **85**, 207 (1963).
6) W. Ziegenbein, *Angew. Chem.*, **77**, 380 (1965).
7) S. Hünig, E. Lücke, and W. Brenniger, *Org. Synth.*, Coll. Vol. V, 808 (1973).
8) T. Mukaiyama, K. Banno, and K. Narasaka, *J. Am. Chem. Soc.*, **96**, 7503 (1974).