A Convenient Synthesis of β-Acetyl-γ-substituted-γ-butyrolactones and γ-Acetyl-δ-substituted-δ-valerolactones

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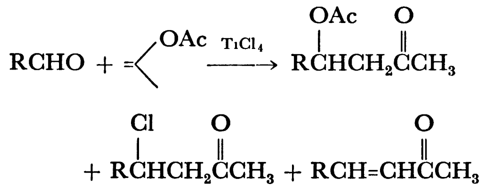
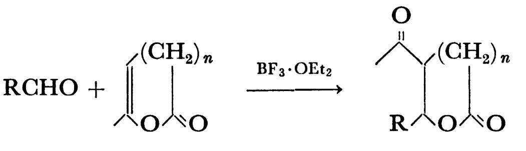
A convenient method for the preparation of β-acetyl-γ-substituted-γ-butyrolactones (III) and γ-acetyl-δ-substituted-δ-valerolactones (IV) is described. It was established that α-angelicalactone (I) and 3,4-dihydro-6-methyl-2*H*-pyran-2-one(II) react with various aldehydes in the presence of boron trifluoride etherate ($BF_3 \cdot OEt_2$) to afford the corresponding γ and δ-lactones, respectively, in good yields.

In the course of our continuing studies of useful synthetic reactions promoted by $TiCl_4$, it was found recently that trimethylsilyl enol ethers or isopropenyl acetate react with various aldehydes, ketones, or acetals to give the aldol type addition products in good yields.[1] For example, isopropenyl acetate reacts with aldehydes to afford β-acetoxy methylketones along with β-chloroketones and α,β-unsaturated ketones. The latter two products are formed by the subsequent displacement or elimination reaction



of the β-acetoxy methylketones initially formed.

In the present experiment, it was found that β-acetyl-γ-substituted-γ-butyrolactones (III)[2] and γ-acetyl-δ-substituted-δ-valerolactones (IV) are synthesized in good yields by the reactions of α-angelicalactone (I) or 3,4-dihydro-6-methyl-2*H*-pyran-2-one (II), chosen as cyclic enol esters in place of isopropenyl acetate in the above experiment, with various aldehydes activated by $BF_3 \cdot OEt_2$.



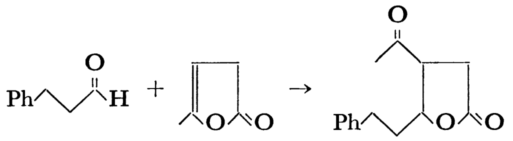
I, II   I, III (n=1)   III, IV
II, IV (n=2)

Rothe *et al.*[3] reported that β-acetyl-γ-butyrolactones are produced by treating levulinic acid and aldehydes with potassium carbonate; however, this is not suited to the preparative method since the reaction was carried out under rather severe conditions and the yields were very low.

Results and Discussion

In the present experiment, it was found that, when the mixture of α-angelicalactone (I) and 3-phenylpropanal in methylene chloride was stirred in the presence of $TiCl_4$ or $SnCl_4$ at room temperature over night, β-acetyl-γ-phenethyl-γ-butyrolactone (IIIa) was obtained in 54% or 44% yield, respectively, along with a considerable amount of levulinic acid produced by hydrolysis of α-angelicalactone. In the above experiment, the reaction was carried out in a heterogeneous system, since $TiCl_4$ or $SnCl_4$ formed solid complexes between the aldehydes, α-angelicalactone, and the products in methylene chloride. On the other hand, when $BF_3 \cdot OEt_2$ is used in place of $TiCl_4$ or $SnCl_4$ in the above experiment, the reaction was carried out in a homogeneous system and the corresponding lactone was obtained in 94% yield after 8 h at 0 °C. This result showed that $BF_3 \cdot OEt_2$ was more suitable for this reaction than $TiCl_4$ and $SnCl_4$. It was also found that the lactone was produced in 94 or 87% yield, respectively, when a half molar or a catalytic amount of $BF_3 \cdot OEt_2$ was used.

Table 1. The effect of solvent on the yield of the γ-butyrolactone (IIIa)



Solvent	Temp	Time (h)	Yield of IIIa (%)
CH_2Cl_2	0 °C	1	85
C_6H_5	r. t.	1	84
CCl_4	0 °C	6	71
Et_2O	0 °C r. t.	12 20	83

Concerning the effect of solvents, it was shown that benzene and methylene chloride are more suitable solvents than diethyl ether and carbon tetrachloride with respect to yield and reaction velocity, as shown in Table 1.

In a similar manner, the reaction of α-angelicalactone with various aldehydes, such as benzaldehyde, cinnamaldehyde, chloroacetaldehyde, dichloroacetaldehyde, and formaldehyde, were carried out in the presence of an equimolar amount of $BF_3 \cdot OEt_2$ in methylene chloride, and the corresponding β-acetyl-γ-butyrolactones were obtained in good yields, as shown in Table 2.

Next, it was established that γ-acetyl-δ-phenethyl-δ-valerolactone (IVa) was obtained in 69% yield by treating 3,4-dihydro-6-methyl-2*H*-pyran-2-one (II) with 3-phenylpropanal in the presence of $BF_3 \cdot OEt_2$ in methylene chloride at 0 °C over night. The yield of the lactone was increased to 84% by employing two molar amounts of II against one molar amount

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TABLE 2. SYNTHESIS OF β-ACETYL-γ-BUTYROLACTONES (III) AND γ-ACETYL-δ-VALEROLACTONES (IV)

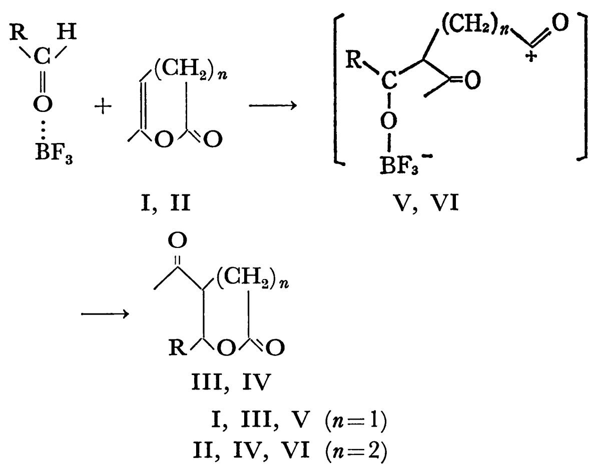
Compound	Reaction condition		Bp °C/Torr Mp °C	Analysis (%)			
	Temp (h)	Yield (%)		Calcd C	Calcd H	Found C	Found H
IIIa ($R=PhCH_2CH_2$)	0 °C (8)	94	157—158/0.03	72.39	6.24	72.36	7.11
IIIb ($R=Ph$)	r. t. (24)	62	165—170/0.35	70.57	5.92	70.59	6.02
IIIc ($R=PhCH{=}CH$)	0 °C (12)	79[a]	(91.5—92.0)[a] (53—63)[a]	73.02 73.02	6.13 6.13	72.81 73.22	6.16 6.23
IIId ($R=ClCH_2$)	0 °C (1)	90	122—123/0.09	47.60	5.13	47.62	5.12
IIIe ($R=Cl_2CH$)	0 °C (12)	60	116—117/0.062	39.85	3.79	40.01	3.83
IIIf ($R=H$)	0 °C (1)	93	120—121/4[b]	56.24	6.29	56.19	6.28
IVa ($R=PhCH_2CH_2$)	0 °C (14—15)	84	174—176/0.4	73.14	7.37	72.88	7.26
IVb ($R=CH_3CH_2$)	0 °C (14—15)	78	107—108/0.01	63.51	8.29	63.22	8.57
IVc ($R=ClCH_2$)	0 °C (14—15)	65	oil[c]	50.40	5.81	50.62	5.88
IVd ($R=PhCH_2$)	0 °C (14—15)	61	152—154/0.05	72.39	6.94	72.21	7.10
IVe ($R=Ph$)	0 °C (14—15)	75	(106—109)	71.54	6.47	71.78	6.57
IVf ($R=H$)	0 °C (0.33)	90	111—113/0.16	59.14	7.09	58.92	7.38

a) Two isomers (*trans* (higher melting point) : *cis*(lower melting point) = 8 : 1) were isolated by silica gel chromatography (solvent: benzene-ethyl acetate). These were isomerized by $BF_3 \cdot OEt_2$ in methylene chloride and the ratio of *trans* and *cis* was 8 : 1 at equilibrium. b) Lit, 118—125/5.[3] c) Decomposed during the course of vacuum distillation.

of 3-phenylpropanal, based on the observation that II reacted with aldehydes more slowly than α-angelicalactone and that II was gradually decomposed by $BF_3 \cdot OEt_2$.

Similarly, various γ-acetyl-δ-valerolactones were obtained by the reaction of II with various aldehydes, such as propionaldehyde, chloroacetaldehyde, phenylacetaldehyde, benzaldehyde, and formaldehyde, as shown in Table 2.

This reaction may be explained by assuming an initial formation of aldehyde–$BF_3 \cdot OEt_2$ complex, which in turn reacts with α-angelicalactone (I) or 3,4-dihydro-6-methyl-2*H*-pyran-2-one (II) to give an addition product of V or VI. The intermediate adduct (V or VI) immediately cyclizes to form γ or δ-lactone (III or IV).



I, II V, VI

III, IV

I, III, V ($n=1$)
II, IV, VI ($n=2$)

It is expected that the present reaction provides a simple and useful method for the syntheses of naturally occurring γ or δ-lactone derivatives. Actually, we recently reported the stereospecific synthesis of antibiotic botriodiplodin from β-acetyl-α-methyl-γ-butyrolactone produced by the reaction of α-methyl-α-angelicalactone with formaldehyde.[4]

Experimental

All boiling points and melting points were uncorrected. The IR spectra were recorded with a Hitachi Model EPI G3 spectrometer. The proton NMR spectra were obtained in carbon tetrachloride or deuterio chloroform solutions on a Varian T-60 spectrometer with TMS as an internal standard.

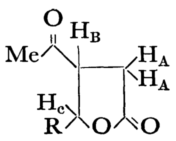
α-Angelicalactone (I) was prepared from levulinic acid. Bp 56—58 °C/12 Torr.[5] 3,4-Dihydro-6-methyl-2*H*-pyran-2-one (II) was prepared according to Shiroyan *et al.*[6] Bp 82—83 °C/23 Torr.

Reaction of α-Angelicalactone with 3-Phenylpropanal. $BF_3 \cdot OEt_2$ (0.142 g, 1 mmol) in 4 ml of methylene chloride was added slowly at 0 °C into a mixture of α-angelicalactone (0.098 g, 1 mmol) and 3-phenylpropanal (0.134 g, 1 mmol) in 6 ml of methylene chloride. The reaction mixture was stirred for 8 h at 0 °C. After being quenched with saturated NaCl solution, it was extracted with benzene. The extract was dried over anhydrous sodium sulfate. After removal of the solvent, 0.201 g (94%) of β-acetyl-γ-phenetyl-γ-butyrolactone (IIIa) was isolated by silica gel chromatography (solvent: benzene–ethyl acetate).

Similarly, IIIb—d were obtained under the reaction conditions shown in Table 2. The NMR and IR spectra of IIIa—f are shown in Table 3.

Reaction of α-Angelicalactone with Formaldehyde. Formaldehyde gas, prepared by thermal cracking of paraformaldehyde (0.604 g, 20 mmol) at 200 °C, was introduced into α-angelicalactone (0.982 g, 10 mmol) in 25 ml of methylene chloride at 0 °C. After stirring for 15 min, $BF_3 \cdot OEt_2$ (1.42 g, 10 mmol) in 5 ml of methylene chloride was added slowly into the reaction mixture at 0 °C and the reaction mixture was stirred for 1 h. After being quenched with saturated sodium hydrogen carbonate solution, it was extracted with methylene chloride. The extract was dried over anhydrous sodium sulfate, concentrated, and the residue was chromatographed on silica gel (solvent: benzene–ethyl acetate) to

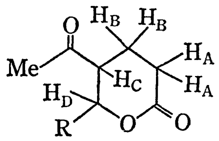
Table 3. NMR and IR spectra of γ-butyrolactones[a] (IIIa—f)



Butyrolactones	R	NMR (in CDCl$_3$)		H$_C$(1H)	Me(3H)	IR (cm^{-1})[b]
		H$_A$(2H)	H$_B$(1H)			
IIIa	7.16(s, 5H), 1.83—2.13 (m, 5H), 2.66—3.53(m, 5H)	c)	c)	5.52 (q)	2.17 (s)	1780 1715
IIIb	7.29 (s, 5H)	2.76—2.92 (m)	3.30—3.72 (m)	5.52 (d, J=7 Hz)	2.10 (s)	1780 1715
IIIc(*trans*)	7.30(s, 5H), 5.83—6.40 (m, 1H), 6.45—6.88(m, 1H)	2.50—2.93 (m)	3.33 (q)	5.01 (t)	2.17 (s)	1785 1715
IIIc(*cis*)	7.29(s, 5H), 5.73—6.23 (m, 1H), 6.50—6.90(m, 1H)	2.53—2.97 (m)	3.78 (q)	5.39 (t)	2.10 (s)	1785 1715
IIId	3.82 (d, 2H, J=4 Hz)	2.70—2.95 (m)	3.20—3.82 (m)	4.80—5.20 (m)	2.21 (s)	1800 1680
IIIe[d]	6.00 (d, 1H, J=4 Hz)	2.40—3.02 (m)	3.20—3.82 (m)	5.00 (t)	2.21 (s)	1800 1725
IIIf	4.40(s, 1H), 4.53(d, 1H, J=3 Hz)	2.66(s, 1H) 2.80(s, 1H)	3.64 (quin)	c)	2.26 (s)	1780 1715

a) These lactones were probably composed of *cis* and *trans* isomers. b) Spectra of lactone (higher wave number) and acetyl (lower wave number) carbonyl. c) These protones were overlapped with R. d) The ratio of *cis* and *trans* isomer was *ca.* 1 : 11 by NMR spectra (the chemical shift of the methyl of *cis* isomer was 2.11). However, the other butyrolactones, except IIIc and IIIe, showed only one peak as the signal of the methyl (CH_3C=O).

Table 4. NMR spectra of δ-valerolactones[a] (IVa—f)



Valerolactones		H$_A$(2H)	H$_B$(2H)	H$_C$(1H)	H$_D$(1H)	Me(3H)
IVa	7.15(s, 5H), 1.53—2.27 (m, 4H), 2.77—3.10(m, 5H)	b)	b)	b)	4.33—4.75 (m)	2.18 (s)
IVb	0.97—1.15(m, 3H) 1.42—1.60(m, 2H)	2.35—2.71 (m)	1.88—2.71 (m)	2.73—3.09 (m)	4.38—4.77 (m)	2.21 (s)
IVc	3.7—3.9 (m, 2H)	2.4—2.7 (m)	1.7—2.3 (m)	2.97—3.47 (m)	4.77—5.16 (m)	2.33 (s)
IVd	7.17(s, 5H) 2.9—3.1(m, 2H)	2.33—2.67 (m)	1.9—2.3 (m)	2.6—2.9 (m)	4.7—5.1 (m)	2.10 (s)
IVe	7.33(s, 5H)	2.50—2.83 (m)	2.15 (t)	3.0—3.4 (m)	5.4 (d, J=10 Hz)	1.87 (s)
IVf	4.50(d, J=6 Hz, 2H)	2.3—2.7 (m)	2.0—2.3 (m)	3.0 (q)	b)	2.35 (s)

a) These lactones were probably composed of *cis* and *trans* isomers. b) These protones were overlapped with R.

give 1.196 g (93%) of β-acetyl-γ-butyrolactone (IIIf).

Reaction of 3,4-Dihydro-6-methyl-2H-pyran-2-one with 3-Phenylpropanal. BF$_3$·OEt$_2$ (0.142 g, 1 mmol) in 1 ml of methylene chloride was added into a mixture of 3,4-dihydro-6-methyl-2*H*-pyran-2-one (0.244 g, 2 mmol) and 3-phenylpropanal (0.134 g, 1 mmol) in 2 ml of methylene chloride at 0 °C. After the reaction mixture was stirred for 15 h at 0 °C, it was worked up as in the preparation of IIIf, to give 0.206 g (84%) of γ-acetyl-δ-phenethyl-δ-valerolactone (IVa).

IVb—e were obtained by the same procedure. The physical properties and analytical data of IVa—f are shown in Table 2. IR spectra of IVa—f indicated the carbonyl of lactone (1735 cm^{-1}) and acetyl (1710 cm^{-1}). NMR spectra of IVa—f are listed in Table 4.

Reaction of 3,4-Dihydro-6-methyl-2H-pyran-2-one with Formaldehyde. Formaldehyde gas, produced from paraformaldehyde (0.121 g, 4 mmol), was bubbled into a mixture of 3,4-dihydro-6-methyl-2*H*-pyran-2-one (0.224 g, 2 mmol) and BF$_3$·OEt$_2$ (0.284 g, 2 mmol) at 0 °C. After the reaction mixture was stirred for 30 min at 0 °C, it was worked up as in the preparation of IIIf, to afford 0.255 g, (90%) of γ-acetyl-δ-valerolactone (IVf).

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