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A SIMPLE, STEREOCONTROLLED SYNTHESIS OF α-ALKYLIDENE-γ-BUTYROLACTONES

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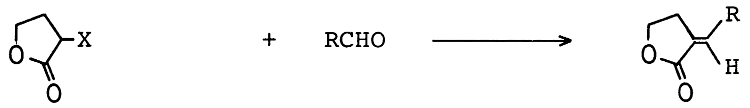
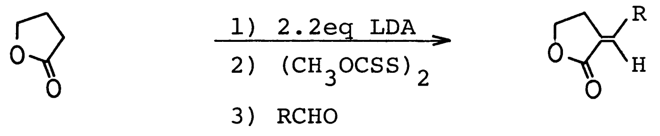
Treatment of γ-butyrolactone with bis[methoxy(thiocarbonyl)] disulfide in the presence of 2.2 equivalents of lithium diisopropylamide followed by the addition of aldehydes gave predominantly (*E*)-α-alkylidene-γ-butyrolactones. In contrast, when the reaction was carried out in the presence of metal salt such as cuprous iodide or zinc chloride, (*Z*)-α-alkylidene-γ-butyrolactone was obtained as the major product.

We have recently reported the stereoselective synthesis of (*E*)-α-alkylidene-γ-butyrolactones using the monoanion of *O*-ethyl *S*-(tetrahydro-2-oxo-3-furanyl) thiocarbonate (Ia), or the dianion of α-mercapto-γ-butyrolactone (Ib).(1,2)



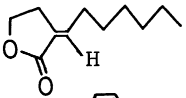
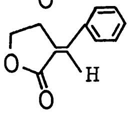
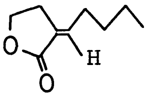
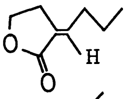
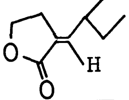
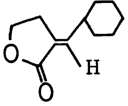
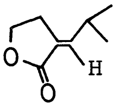
Ia: X = SCOOEt
Ib: X = SH

We now wish to report a simple and efficient procedure for the stereoselective synthesis of α-alkylidene-γ-butyrolactones, starting with γ-butyrolactone and easily available bis[methoxy(thiocarbonyl)] disulfide.(3,4) The present method precludes the preparation of the reagent such as Ia, or Ib.



The preparation of α-heptylidene-γ-butyrolactone is given here as a typical experiment. To a solution of lithium diisopropylamide (44 mmol) in 60 ml of THF was added dropwise 1.72 g (20 mmol) of γ-butyrolactone in 10 ml of THF at -78°C under N_2. After stirring for 30 min, 4.72 g (22 mmol) of bis[methoxy(thiocarbonyl)] disulfide in 6 ml of THF was added and the reaction mixture was stirred at -78°C for 2h. Heptanal (2.51 g, 22 mmol) in 6 ml of THF was then added portionwise to the above solution and the reaction mixture was stirred at -78°C for 2h and at room temperature for 1.5h. Usual workup and distillation of the product after column chromatography gave a 88:12 ratio of (*E*)- and (*Z*)-α-heptylidene-γ-butyrolactone in 54% yield, bp 108-112°C/0.4 mmHg: IR(neat) 1755 (COO), 1683 (C=C) cm^{-1}; ^1H NMR(CCl_4) δ 6.52, 6.06 (m, 1H, CH=C), 4.26 (t, J=7Hz, 2H, OCH_2), 2.83 (m, 2H, CH_2), 2.18 (m, 2H, CH_2), 1.35 (m, 8H, CH_2), 0.90 (m, 3H, CH_3). Anal. Found: C, 72.31; H, 9.65%. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95%. Other examples of this new process are listed in Table 1.

Table 1. Stereoselective synthesis of (*E*)-α-alkylidene-γ-butyrolactones

Aldehyde	Product[a)	Yield[b) %	*E*:*Z*[c) ratio
Heptanal		54	88:12
Benzaldehyde		52	100:0[d)
Pentanal		58	96:4
Butyraldehyde		57	96:4
2-Methylbutyraldehyde		42	95:5
Cyclohexanecarboxaldehyde		51	95:5
Isobutyraldehyde		49	97:3

a) All compounds provided satisfactory elemental analytical and spectral data. b) Yields of the isolated product. c) Determined by ^1H NMR and GLPC analyses of the isolated product. d) (*E*)-isomer: mp 117.5-118.5°C (lit.[2) mp 117.5-118.5°C).

We have found that the presence of metal salt such as cuprous iodide[5), or zinc chloride[6) causes a dramatic alteration in the stereoselectivity of this reaction.

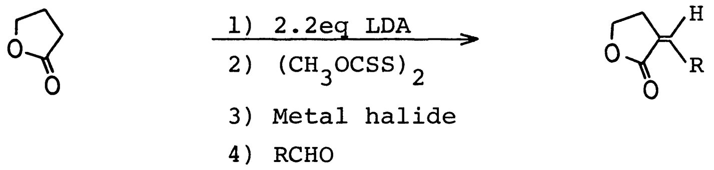
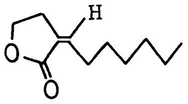
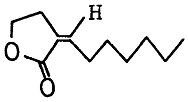
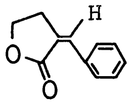
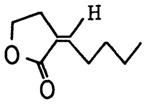
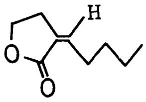
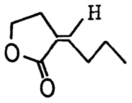
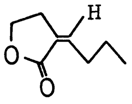
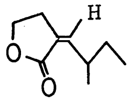
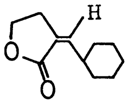
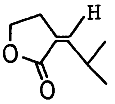


Table 2. Stereoselective synthesis of (*Z*)-α-alkylidene-γ-butyrolactones

Aldehyde	Metal halide	Product[a]	Yield[b] %	*E*:*Z*[c] ratio
Heptanal	CuI (1.5eq)		69	16:84
Heptanal	$ZnCl_2$ (1.5eq)[d]		63	15:85
Benzaldehyde	CuI (1.5eq)		51	17:83[e]
Pentanal	CuI (1.5eq)		53	7:93
Pentanal	$ZnCl_2$ (1.5eq)[d]		65	11:89
Butyraldehyde	CuI (1.5eq)		56	7:93
Butyraldehyde	$ZnCl_2$ (1.5eq)[d]		58	9:91
2-Methylbutyraldehyde	$ZnCl_2$ (1.5eq)[d]		54	7:93
Cyclohexanecarboxaldehyde	$ZnCl_2$ (1.5eq)[d]		59	8:92
Isobutyraldehyde	$ZnCl_2$ (1.5eq)[d]		49	4:96

a) All products gave satisfactory analytical results and spectral data.

b) Isolated yield. c) Determined by ^{1}H NMR and GLPC analyses of the isolated product. d) A solution of zinc chloride (30 mmol) in 35 ml of THF was added portionwise. e) (*Z*)-isomer: mp 91-92°C.

Thus, to a solution of lithium diisopropylamide (44 mmol) in 60 ml of THF was added dropwise 1.72 g (20 mmol) of γ-butyrolactone in 10 ml of THF at -78°C under N_2. After stirring for 30 min, 4.72 g (22 mmol) of bis[methoxy(thiocarbonyl)] disulfide in 6 ml of THF was added. Stirring was continued for 2h at -78°C. Cuprous iodide (30 mmol) was then added and the resulting orange suspension was stirred at -78°C for 30 min. A solution of 1.89 g (22 mmol) of pentanal in 6 ml of THF was added portionwise. The reaction mixture was stirred at -78°C for 2h and at room temperature for 1.5h, then worked up as usual. Isolation by column chromatography and distillation gave a 53% yield of (*E*)- and (*Z*)-α-pentylidene-γ-butyrolactone in the ratio of 7:93, bp 105-109°C/0.8 mmHg: IR(neat) 1750 (COO), 1670 (C=C) cm^{-1}; ^1H NMR(CCl_4) δ 6.12 (m, 1H, CH=C), 4.22 (t, J=7Hz, 2H, CH_2O), 2.90 (m, 2H, CH_2), 2.70 (m, 2H, CH_2), 1.42 (m, 4H, CH_2), 0.95 (m, 3H, CH_3). Anal. Found: C, 70.31; H, 9.18%. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15%.

This is the first example of a general and stereoselective synthesis of (*Z*)-α-alkylidene-γ-butyrolactones.7) By this procedure, a variety of aldehydes were converted into α-alkylidene-γ-butyrolactones. In all cases (*Z*)-isomers8) were obtained predominantly (Table 2).

In summary, a convenient method is now available for the synthesis of either (*E*)- or (*Z*)-α-alkylidene-γ-butyrolactones in a highly stereoselective manner from γ-butyrolactone. The effect of metal salt is remarkable. We are presently engaged in studying the mechanistic aspects of these reactions.

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References and Notes

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7) Base-catalyzed condensation of γ-butyrolactone with benzaldehyde gave (*E*)-α-benzylidene-γ-butyrolactone in 17% yield: A. R. Pinder, J. Chem. Soc., 1952, 2236.

8) The *Z*-configuration of the double bond was assigned on the basis of the higher field ^1H NMR resonance at δ 5.7-6.3 for the vinyl proton β to the carbonyl.

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