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A SIMPLE, STEREOCONTROLLED SYNTHESIS OF
\alpha-ALKYLIDENE-\gamma-BUTYROLACTONES
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Treatment of  $\gamma$ -butyrolactone with bis[methoxy(thiocarbonyl)] disulfide in the presence of 2.2 equivalents of lithium diisopropylamide followed by the addition of aldehydes gave predominantly  $(E) - \alpha - alkylidene - \gamma - butyrolactones.$  In contrast, when the reaction was carried out in the presence of metal salt such as cuprous iodide or zinc chloride, (Z)- $\alpha$ -alkylidene- $\gamma$ butyrolactone was obtained as the major product.

We have recently reported the stereoselective synthesis of  $(E) - \alpha$ -alkylidene- $\gamma$ -butyrolactones using the monoanion of O-ethyl S-(tetrahydro-2-oxo-3-furanyl) thiocarbonate (Ia), or the dianion of  $\alpha$ -mercapto- $\gamma$ -butyrolactone (Ib).<sup>1,2)</sup>



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



The preparation of  $\alpha$ -heptylidene- $\gamma$ -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 Y-butyrolactone in 10 ml of THF at -78°C under N2. 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*)- $\alpha$ -heptylidene- $\gamma$ -butyrolactone in 54% yield, bp 108-112°C/0.4 mmHg: IR(neat) 1755 (COO), 1683 (C=C) cm<sup>-1</sup>; <sup>1</sup>H NMR(CCl<sub>4</sub>) & 6.52, 6.06 (m, 1H, CH=C), 4.26 (t, J=7Hz, 2H, OCH<sub>2</sub>), 2.83 (m, 2H, CH<sub>2</sub>), 2.18 (m, 2H, CH<sub>2</sub>), 1.35 (m, 8H, CH<sub>2</sub>), 0.90 (m, 3H, CH<sub>3</sub>). Anal. Found: C, 72.31; H, 9.65%. Calcd for C<sub>11</sub>H<sub>18</sub>O<sub>2</sub>: C, 72.49; H, 9.95%. Other examples of this new process are listed in Table 1.

Aldehyde	Product <sup>a)</sup>	$\frac{\text{Yield}^{b}}{\$}$	E:Z <sup>C)</sup> ratio	
Heptanal	O H	54	88:12	
Benzaldehyde		52	100:0 <sup>d)</sup>	
Pentanal	€ ↓ H	58	96:4	
Butyraldehyde	€ KH	57	96:4	
2-Methylbutyraldehyde	€ KH	42	95 <b>:</b> 5	
Cyclohexanecarboxaldehyde	€ K H	51	95 <b>:</b> 5	
Isobutyraldehyde	€	49	97:3	

Table 1. Stereoselective synthesis of  $(E) - \alpha - alkylidene - \gamma - butyrolactones$ 

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

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Table 2. Stereoselective synthesis of  $(Z)-\alpha$ -alkylidene- $\gamma$ -butyrolactones

Aldehyde	Metal halide	Product <sup>a)</sup>	Yield <sup>b)</sup>	$E:Z^{C}$
			R	ratio
Heptanal	CuI (1.5eq)		, 69	16:84
Heptanal	$ZnCl_2$ (1.5eq) <sup>d)</sup>		63	15 <b>:</b> 85
Benzaldehyde	CuI (1.5eq)		51	17:83 <sup>e)</sup>
Pentanal	CuI (1.5eq)		53	7:93
Pentanal	$ZnCl_2$ (1.5eq) <sup>d)</sup>	€	65	11:89
Butyraldehyde	CuI (1.5eq)		56	7:93
Butyraldehyde	$ZnCl_2$ (1.5eq) <sup>d)</sup>		58	9:91
2-Methylbutyraldehyde	$ZnCl_2$ (1.5eq) <sup>d)</sup>		54	7:93
Cyclohexanecarboxaldehyde	$ZnCl_2$ (1.5eq) <sup>d)</sup>		59	8:92
Isobutyraldehyde	$\text{ZnCl}_2$ (1.5eq) <sup>d)</sup>		49	4:96

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

b) Isolated yield. c) Determined by <sup>1</sup>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  $\gamma$ -butyrolactone in 10 ml of THF at -78°C under N<sub>2</sub>. After stirring for 30 min, 4.72 g (22 mmol) of bis[methoxy(thio-carbonyl)] 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*)- $\alpha$ -pentylidene- $\gamma$ -butyrolactone in the ratio of 7:93, bp 105-109°C/0.8 mmHg: IR(neat) 1750 (COO), 1670 (C=C) cm<sup>-1</sup>; <sup>1</sup>H NMR(CCl<sub>4</sub>) & 6.12 (m, 1H, CH=C), 4.22 (t, J=7Hz, 2H, CH<sub>2</sub>O), 2.90 (m, 2H, CH<sub>2</sub>), 2.70 (m, 2H, CH<sub>2</sub>), 1.42 (m, 4H, CH<sub>2</sub>), 0.95 (m, 3H, CH<sub>3</sub>). Anal. Found: C, 70.31; H, 9.18%. Calcd for C<sub>9</sub>H<sub>14</sub>O<sub>2</sub>: C, 70.10; H, 9.15%.

This is the first example of a general and stereoselective synthesis of  $(Z)-\alpha-alkylidene-\gamma-butyrolactones.$ <sup>7)</sup> By this procedure, a variety of aldehydes were converted into  $\alpha-alkylidene-\gamma-butyrolactones$ . In all cases (Z)-isomers<sup>8)</sup> were obtained predominantly (Table 2).

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

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