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# A NEW APPROACH TO THE SYNTHESIS OF α-ALKYLIDENE-γ-BUTYROLACTONES AND $\Delta^{\alpha,\beta}$-BUTENOLIDES

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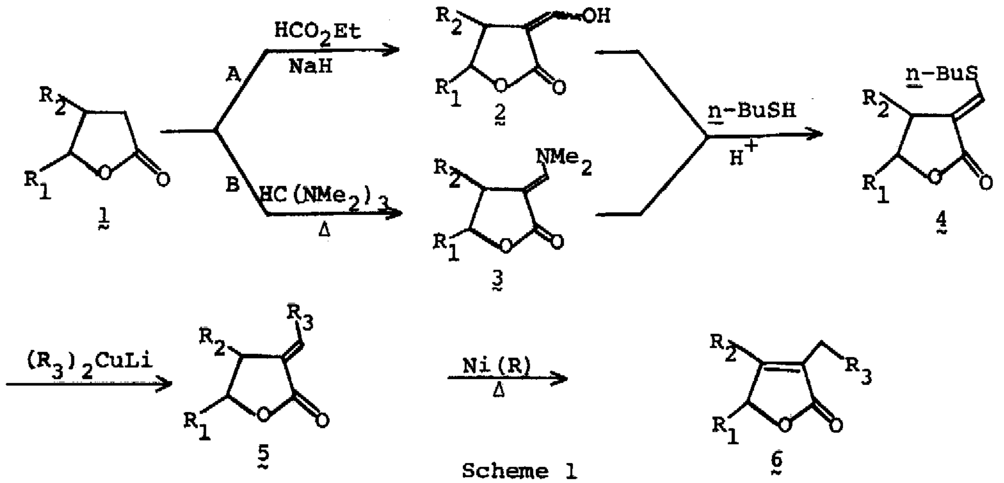
The widespread occurrence of the α-alkylidene-γ-butyrolactone and the $\Delta^{\alpha,\beta}$-butenolide structural units in a variety of biologically active natural products has stimulated considerable interest in the development of new synthetic methods for their construction.[1-4] We now wish to report a facile, new procedure for the efficient preparation of a number of α-alkylidene-γ-butyrolactones and $\Delta^{\alpha,\beta}$-butenolides from readily available γ-butyrolactones (Scheme 1). Because the $\Delta^{\alpha,\beta}$-butenolides may be easily converted to furans,[5] this new synthetic method promises to be a convenient entry to a variety of furanoid natural products.



Scheme 1

Since lithium dialkycuprates were known to react readily with β-n-butylthio-α,β-unsaturated carbonyl compounds to give the corresponding β-alkyl-α,β-unsaturated derivatives,[6] we envisioned that the α-n-butylthiomethylene-γ-lactones **4** would be the key intermediates in the reaction sequence depicted in Scheme 1. The synthesis of the vinylogous thiocarbonates **4** by the one carbon homologation of the γ-lactones **1** could be achieved by several methods. Formylation of the lactones **1b**-d with ethyl formate and sodium hydride in anhydrous ether[7] gave the α-hydroxymethylene compounds **2**b-d which were treated immediately with n-butanethiol in the presence of p-toluenesulfonic acid to give the requisite α-n-butylthiomethylene lactones **4**b-d, albeit in only moderate overall yields (Method A). However, when the γ-lactones **1**a-c were heated with tris(dimethylamino)methane,[8] the vinylogous urethanes **3**a-c[9] were obtained in nearly quantitative yield. Subsequent treatment of **3**a-c with n-butanethiol and p-toluenesulfonic acid afforded the desired α-n-butylthiomethylene lactones **4**a-c[9] in high overall yields (Method B) (see Table 1).[10] The γ-lactones **4**a-d reacted smoothly with either lithium dimethylcuprate or lithium di-n-butylcuprate to give the corresponding α-alkylidene-γ-lactones **5**[9] in 85-95% yield. Isomerization of the exocylic double bond to the more stable endocyclic position[11] by heating with deactivated Raney Nickel afforded the $\Delta^{\alpha,\beta}$-butenolides **6** in 70-98% yield (see Table 2).

Table 1. Preparation of α-n-Butylthiomethylene-γ-Butyrolactones **4**.

| γ-Butyrolactone **1** | % yield[a] of **3** | % yield[a] of **4** |
|---|---|---|
| a; $R_1=R_2=H$ | 96 | 92[b] |
| b; $R_1=CH_3$, $R_2=H$ | 96 | 96[b] (45[c]) |
| c; $R_1=\underline{n}\text{-}C_6H_{13}$, $R_2=H$ | 98 | 92[b] (50[c]) |
| d; $R_1$, $R_2$=$-(CH_2)_4-$[d] | | (56[c]) |

[a]Yields of pure product but not optimized. [b]Method B. [c]Method A. [d]M. S. Newman and C. A. VanderWerf, J. Am. Chem. Soc., **67**, 233 (1945).

Table 2. Preparation of α-Alkylidene-γ-Butyrolactones **5** and $\Delta^{\alpha,\beta}$-Butenolides **6**

| Starting Compound | % yield[a] of **5** | | % yield[a] of **6** | |
|---|---|---|---|---|
| | $R_3=CH_3$ | $R_3=\underline{n}\text{-}C_4H_9$ | $R_3=CH_3$ | $R_3=\underline{n}\text{-}C_4H_9$ |
| **4**a | 92 | 85 | 81 | 92 |
| **4**b | 91 | 85 | 85 | 96 |
| **4**c | 87 | 95 | 76 | 98 |
| **4**d | 90 | 88 | 70 | 80 |

[a]Yields of pure product but not optimized.

A typical $\Delta^{\alpha,\beta}$-butenolide synthesis is illustrated below for the conversion of γ-valerolactone (1b) to α-*n*-pentyl-γ-methyl-$\Delta^{\alpha,\beta}$-butenolide (6) ($R_1$=$CH_3$, $R_2$=H, $R_3$=*n*-$C_4H_9$). A mixture of γ-valerolactone (1b) (1 equiv.) and tris(dimethylamino)methane (1.5 equiv.) was stirred under dry nitrogen at 75° for 2 days to give 3b (96%) [$bp_{.75}$=161°; ir ($CHCl_3$) 5.82 and 6.13μ; nmr ($CDCl_3$) δ 7.07 (t, 1H, J=2Hz), 4.47 (m, 1H), 3.07 (s, 6H), 1.35 (d, 3H, J=6Hz)]. A solution containing the α-dimethylaminomethylene-γ-lactone 3b (1 equiv.), *n*-butanethiol (1.1 equiv.), and *p*-toluenesulfonic acid (1 equiv.) in benzene was heated at reflux overnight to give, upon an aqueous work-up, the α-*n*-butylthiomethylene-γ-lactone 4b (96%) [$bp_{.05}$=120°; ir ($CHCl_3$) 5.78 and 6.17μ; nmr ($CDCl_3$) δ 7.58 (t, 1H, J=3Hz), 4.71 (m, 1H), 1.43 (d, 3H, J=6Hz)]. After a solution of 4b (1 equiv.) in anhydrous ether was added to a solution of lithium di-*n*-butylcuprate (1.1 equiv.) in ether at -78°, the resulting mixture was stirred at -78° for an additional 1/2 hr and then quenched with methanol. Work-up afforded the α-alkylidene-γ-valerolactone 5 ($R_1$=$CH_3$, $R_2$=H, $R_3$=*n*-$C_4H_9$) (85%) [$bp_{.025}$=85°; ir ($CHCl_3$) 5.71μ; nmr ($CDCl_3$) δ 6.75 (m, 1H), 4.68 (m, 1H), 1.43 (d, 3H, J=6Hz)]. Freshly prepared W-2 Raney Nickel (*ca*. 3 parts) was deactivated by refluxing in benzene for 1 hr whereupon 5 ($R_1$=$CH_3$, $R_2$=H, $R_3$=*n*-$C_4H_9$) (*ca*. 1 part) was added, and the mixture was heated at reflux under nitrogen for 24-48 hr, the reaction being monitored by glc. After complete washing of the Raney Nickel with hot benzene, the product α-*n*-pentyl-γ-methyl-$\Delta^{\alpha,\beta}$-butenolide 6 ($R_1$=$CH_3$, $R_2$=H, $R_3$=*n*-$C_4H_9$) was obtained (96%) [$bp_{.05}$ =81°; ir ($CHCl_3$) 5.67μ; nmr ($CDCl_3$) δ 7.13 (m, 1H) 4.98 (m, 1H), 1.42 (d, 3H, J=6Hz)].

Further extensions of these reactions are currently under active investigation.

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9) It is apparent from the nmr spectra of the α,β-unsaturated-γ-lactones **3**, **4** and **5** that there is primarily (>98%) one geometric isomer present. Studies using Siever's reagent, Eu(fod)$_3$, indicate that this is the E-isomer.

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