A Useful Method for α-Methylation of γ-Butyrolactones

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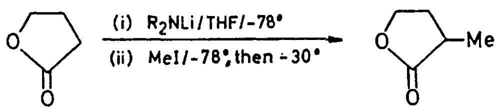
Summary γ-Butyrolactone in tetrahydrofuran at −78° reacts with lithium di-isopropylamide or lithium isopropylcyclohexylamide and then with an excess of deuterium oxide, methyl iodide, or allyl bromide to form α-deuterio-, α-methyl-, or α-allyl-γ-butyrolactone in good yield.

In connection with our work on total synthesis of sesquiterpene lactones we required a convenient procedure for α-methylation of γ-butyrolactones.† γ-Butyrolactones have been α-alkylated indirectly by hydrogenation of the corresponding α-alkylidene-lactones;[1] γ-butyrolactams have been α-alkylated in modest yields,[2] and one $\Delta_{\alpha\beta}$-butenolide has been α-methylated in unspecified yield.[3] We report now the first direct conversion of γ-butyrolactone into α-methyl-γ-butyrolactone, using a lithium dialkylamide as a non-nucleophilic base to form the lactone enolate[4] which reacts under mild conditions with methyl iodide:



The lithium dialkylamides were generated by reaction of the corresponding amines with n-butyl-lithium at − 78° in tetrahydrofuran as previously described.[4] To prevent self-condensation,[1b,5] a tetrahydrofuran solution of the lactone was added slowly to the solution of lithium amide (1 equiv.). Portions were removed *via* a pre-cooled syringe at −78°, −30°, and 0° and were added to a cold solution of tetrahydrofuran containing an excess of deuterium oxide. Only from the −78° portion could lactone be recovered (91% yield); the higher-temperature portions gave largely intractable material. Mass spectral and n.m.r. analysis of recovered lactone indicated 62% deuterium incorporation in the α-position only.‡

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† The α-methyl-γ-butyrolactone structural unit is found in many naturally occurring eudesmanolides, guaianolides, germacranolides, and pseudoguaianolides.

‡ Deuterium oxide quenching of ester enolates[4] has been reported to yield esters with 45—75% deuterium incorporation.

Reaction of lithium isopropylcyclohexylamide with γ-butyrolactone in tetrahydrofuran at −78°, followed by addition of methyl iodide

	% Yield[a]		
Equiv. of amide	α- Methyl-γ-butyrolactone	αα-Dimethyl-γ-butyrolactone	γ-Butyrolactone
1·0	36	0	trace
1·2	56	trace	0
1·5	70	5	0
2·0[b]	80	13	0

[a] Yields were determined by analytical g.l.c. using internal standards and are based on γ-butyrolactone.

[b] The reason why an excess of amide is required for good mass balance is unclear; solvents and reactants were dried rigorously before use.

α-Methyl-γ-butyrolactone is formed by adding an excess of methyl iodide to a solution of the γ-butyrolactone enolate at −78°, and then allowing the reaction mixture to reach −30° (*ca.* 1 h) at which temperature it is kept for 2—3 h. Anhydrous hydrogen chloride is then added, the solvent is removed under reduced pressure, and the residue extracted with benzene. The yield of α-methylated lactone increases as the amount of lithium dialkylamide is increased from 1 to 2 equiv; with more than 1 equiv. of amide, however, αα-dimethylation begins to occur (Table).[§]

α Allyl-γ-butyrolactone[¶] is prepared in 74% yield (with essentially no diallylation occurring) by adding an excess of allyl bromide to the lactone enolate (generated using 2 equiv. of lithium di-isopropylamide). Addition of n-butyl iodide to the enolate produces α-n-butyl-γ-butyrolactone in very low yield.[**] Apparently, effective alkylation of the γ-butyrolactone enolate is limited to those electrophiles which readily undergo S_N2 displacement reactions.[6]

The stereochemistry of this lactone methylation remains to be established using suitable substituted butyrolactones and various methylating agents.

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[§] Conversion of an α-methyl-γ-butyrolactone into the corresponding αα-dimethyl-lactone has been reported using trityl-lithium and methyl iodide (A. E. Greene, J.-C. Muller, and G. Ourisson, *Tetrahedron Letters*, 1971, 4147).

[¶] Satisfactory microanalyses were obtained for new compounds.

[**] No *O*-alkylated lactone enolate was detected in any of our alkylation reactions.

[1] (a) H. Zimmer and J. Rothe, *J. Org. Chem.*, 1959, **24**, 28, and refs cited therein; (b) W Reppe, *et al.*, *Annalen*, 1955, **596**, 158.

[2] P. G. Gassman and B. L. Fox, *J. Org. Chem.*, 1966, **31**, 982.

[3] E. Piers, M. B. Geraghty, and R. D. Smillie, *Chem. Comm.*, 1971, 614.

[4] M. W. Rathke and A. Lindert, *J. Amer. Chem. Soc.*, 1971, **93**, 2318.

[5] O. C. Curtis, jun., J. M. Sandri, R. E. Crocker, and H. Hart, *Org. Syntheses*, Coll. Vol. IV, 1963, 278.

[6] A. Streitwieser, jun., 'Solvolytic Displacement Reactions', McGraw-Hill, New York, 1962, p. 13.