Method for Alkylating Lactones

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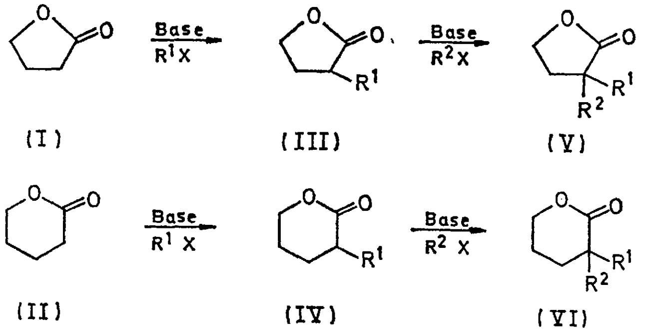
Summary A high yield, experimentally convenient method for the controlled alkylation of lactone enolates is described.

RECENTLY, we have had to alkylate lactone systems. A few examples of this process are known but the reported results suggest these reactions proceed in low yield under conditions of non-ideal stoicheiometry.[1] We describe a convenient method for alkylating lactones which proceeds in uniformly high yield with several alkylating agents under conditions of almost ideal stoicheiometry.

The lithium enolates of the lactones (I) and (II) are formed at −78° by slowly adding a solution of the lactone (1 equiv., 1 M in THF) to a solution of lithium di-isopropylamide (1 equiv., 1 M in THF). After stirring for 20 min, the alkylating agent (1·1 equiv.) dissolved in hexamethylphosphoramide (1·2 equiv.) is added and the temperature of



the reaction mixture adjusted to −40°.† Under these conditions the lactones (I) and (II) alkylate with ethyl iodide, allyl bromide, and prop-2-ynyl bromide‡ in $>90\%$ yield.§ Difunctional alkylating agents such as trimethylene dibromide also undergo alkylation with (I) and (II) in yields of 80 and 60%, respectively.†

A second alkylation step leading to lactones with a quaternary α carbon atom is also possible. These reactions have been carried out in the same way with compounds (III); ($R^1 = Et$) and (IV; $R^1 = Et$). Alkylation yields of 95% for (III) and (IV) are obtained with ethyl iodide, allyl bromide, prop-2-ynyl bromide,‡ and trimethylene dibromide.†

The simple alkylation procedures described above are convenient to use on both small and large scale.

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† Dialkylation was not observed to occur under these conditions of stoicheiometry and temperature; *cf.* the results of Posner and Loomis (ref. 1).

‡ For optimum results these reactions are best carried out at −78°.

§ It is essential that the reactions described here be worked-up using saturated ammonium chloride. The yields reported are for isolated products and are based on the amount of lactone used. All compounds exhibited satisfactory spectral and physical properties.

[1] For a report on the methylation and allylation of γ-butyrolactone, see G. H. Posner and G. L. Loomis ,*J.C.S. Chem. Comm.*, 1972, 892. Dimethylation of a substituted γ-butyrolactone has been reported by A. E. Green, J. C. Muller, and G. Ourisson, *Tetrahedron Letters*, 1971, 4147.