Tetrahedron Letters No. 1, pp 51 - 54, 1975. Pergamon Press. Printed in Great Britain.

CATALYTIC SYNTHESIS OF α-METHYLENE LACTONES BY CARBONYLATION OF ACETYLENIC ALCOHOLS

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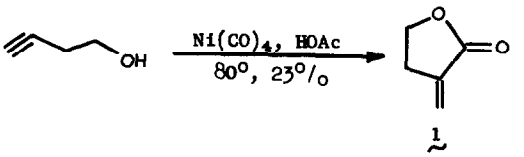
(Received in USA 7 October 1974; received in UK for publication 26 November 1974)

Because of the biological activity of many compounds containing α-methylene-γ-butyrolactones,[1] current interest in the synthesis of this structural unit is intense.[2] Most routes thus far reported entail modification of a preformed lactone ring. A recently reported synthesis[2a] of bicyclic α-methylene-γ-butyrolactones involves the rearrangement of a substituted cyclopropane; however, it gives, preferentially, cis stereochemistry at the ring juncture whereas almost all natural products of interest have trans ring fusion. Clearly, the ability to construct an α-methylene-γ-butyrolactone unit easily, under mild conditions, from readily accessible precursors would find immediate application in the synthesis of pharmacologically exciting molecules. We wish to report a route which meets these requirements.

The low yield synthesis of unsubstituted α-methylene-γ-butyrolactone (1) from 3-butyn-1-ol, $Ni(CO)_4$, water and acetic acid was reported many years ago (Reaction 1).[3] Although this hydrocarboxylation reaction involves toxic, volatile $Ni(CO)_4$ and an acidic solvent, the general process is attractive, as the starting material for the lactone ring can be any



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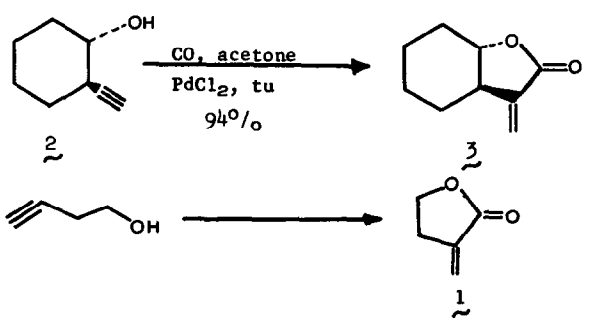
3-butyn-1-ol which, itself, can be prepared from an epoxide. Moreover, the epoxide of a cyclic olefin would readily serve as the precursor for trans acetylenic alcohols and hence for trans-fused bicyclic α-methylene lactones.

We now report that $PdCl_2$/thiourea mixtures[4] catalyze, in high yield and under mild conditions, the carbonylation of appropriate acetylenic alcohols to α-methylene lactones. In a typical reaction, acetylenic alcohol 2[5] (1.2 g,10 mmole) in 5 ml acetone was stirred overnight at 50° under 50 psi CO with 230 mg $PdCl_2$ (.13 equiv) and 100 mg thiourea (tu, .13 equiv). During this time, the orange reaction mixture darkened and Pd metal was deposited. The product, 3, was obtained in 94% yield based on 2.[6] It had nmr and ir spectra identical with those previously reported.[7,8] No other products (< 1%) were detectable.



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We believe the $PdCl_2$/tu system will prove to be the method of choice for the facile synthesis of α-methylene bicyclic lactones. The mechanism of the reaction is unclear, although the thiourea is known to be essential: an identical reaction in its absence yielded only traces of product. We are now exploring the use of this system to catalyze the synthesis of α-methylene lactones of varying ring size from other acetylenic alcohols and are examining the tolerance of the catalytic system for various other types of functionality.

Acknowledgment is made to the Research Corporation and to the Petroleum Research Fund, administered by the American Chemical Society (to J.R.N.), and to the National Institutes of Health (GM-19658-02, to J.S.) for financial support of this work. The authors also thank Hoffman-La Roche, Inc., for providing them with elemental analyses and Prof. Kathlyn A. Parker for her helpful comments and suggestions.

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8. A sample of 3 purified by preparative gc gave the correct elemental analysis.