Tetrahedron Letters No. 51, pp 4661-4664, 1976. Pergamon Press. Printed in Great Britain.

MERCURY IN ORGANIC CHEMISTRY X.[1]
A NOVEL SYNTHESIS OF $\Delta^{\alpha,\beta}$-BUTENOLIDES

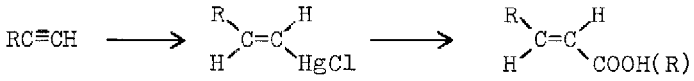
Richard C. Larock*[2] and Bernhard Riefling

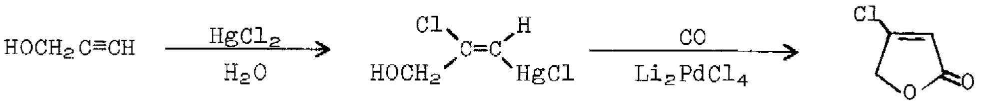
Department of Chemistry
Iowa State University
Ames, Iowa 50011

(Received in USA 2 August 1976; received in UK for publication 28 October 1976)

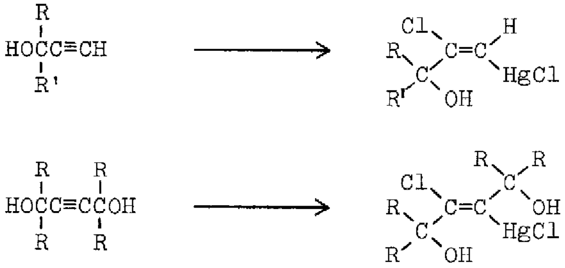
Unsaturated five member ring lactones, butenolides, occur widely in nature[3] and possess an unusual range of biological activity.[4] They appear throughout the plant and animal kingdoms and hold promise as insecticides, herbicides and plant growth regulators. Of considerable importance is their widespread allergenic, antibacterial and antifungal activity. An increasing number of butenolides exhibit cytotoxic and/or tumor inhibitory properties towards a variety of cancers. This unusual range of biological activity has stimulated considerable research on the synthesis of these valuable compounds.[5]

Our research into possible synthetic applications of vinylmercurials recently provided a convenient new route from acetylenes to α,β-unsaturated carboxylic acids and esters by the palladium promoted carbonylation of vinylmercurials.[6] During that work we observed that β-chloro-$\Delta^{\alpha,\beta}$-butenolide can be readily obtained from propargyl alcohol by a two step sequence involving mercuric chloride addition to the acetylenic alcohol, followed by carbonylation of the resulting vinylmercurial. This novel new approach to butenolides prompted us to examine the generality of this reaction sequence and we wish to report our initial findings at this time.





Several acetylenic alcohols and diols have previously been reported to react with a saturated solution of sodium chloride and mercuric chloride to give the corresponding trans-β-chlorovinylmercurials generally in good yield.[7] Using an essentially identical procedure we have been able to extend this reaction to a number of additional acetylenic alcohols to



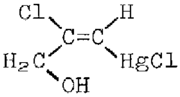
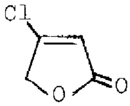
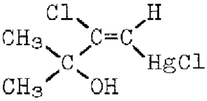
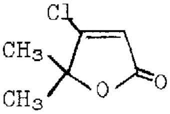
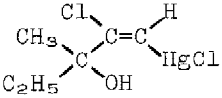
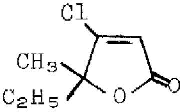
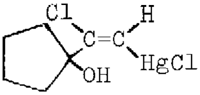
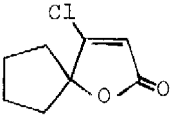
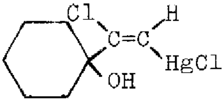
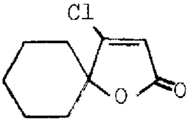
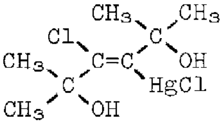
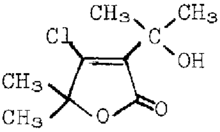
obtain the trans-β-chlorovinylmercurials indicated in the Table. Unfortunately, the yields are generally low (~30%) and the reaction appears limited to primary and tertiary acetylenic alcohols. We have been unable to obtain any solid vinylmercurials from secondary alcohols although spectroscopic evidence suggests that the reaction does occur to some extent. Nevertheless, the ease with which the vinylmercurials are prepared encouraged us to examine their carbonylation.

In attempting to carbonylate these vinylmercurials using our earlier reported procedure (Li_2PdCl_4, CO, Et_2O, -78° to 25°C, overnight), rather disappointing results were obtained. It was eventually found desirable to change to tetrahydrofuran (THF) as a solvent, to run the reaction at 0° for 16-24 hrs, and to add one equivalent of an inorganic salt (preferably MgO or K_2CO_3). Under these conditions we are able to obtain near quantitative yields of the corresponding β-chloro-$\Delta^{\alpha,\beta}$-butenolides as indicated in the Table.

The following general procedure is representative. Lithium chloride (10 mmol), palladium chloride (5 mmol), magnesium oxide (5 mmol) and 50 ml THF were placed in a round bottom flask with a septum inlet. After flushing with carbon monoxide and cooling to -78°C, the vinylmercurial (5 mmol) was added. A balloon filled with carbon monoxide was connected to the top of the flask and the reaction mixture was allowed to warm to 0°C and stirred 24 hrs at that temperature. Five ml saturated ammonium chloride solution, 50 ml ether and charcoal were added. The mixture was stirred an additional 30 minutes and then filtered. The filtrate was washed with saturated potassium carbonate solution and dried over anhydrous sodium sulfate. Filtration, evaporation and recrystallization (pentane) provided the isolated yields indicated in the Table. These reactions can be made catalytic in palladium chloride using cupric chloride (2 equiv) and benzene as solvent. Details of this procedure will be reported in the full paper.

In attempting to still further improve upon this procedure, we have studied the possibility of carrying out the above overall synthetic transformation from acetylenic alcohol to butenolide without the necessity of isolating and purifying the intermediate vinylmercurial. We have observed that the butenolide derived from 2,5-dimethylhex-3-yn-2,5-diol can be obtained

TABLE. Synthesis of β-Chloro-$\Delta^{\alpha,\beta}$-butenolides

VINYLMERCURIAL	MP(°C)[a]	BUTENOLIDE	MP(°C)[a]	% YIELD[b]
	105(105)[c]		(52.5-53)[d]	(96)[d]
	78(70)[c]		66-66.5	100(88)
	85-86		~ -5	91
	99-100		36-36.5	99
	137-138		55-55.5	100(92)
	(103)[c]		102	94

---

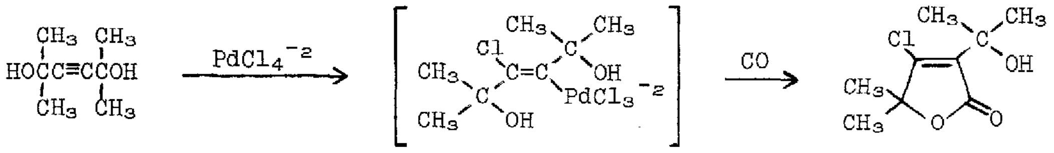
[a] Observed melting point (literature melting point).

[b] Yield determined by GLC (isolated yield).

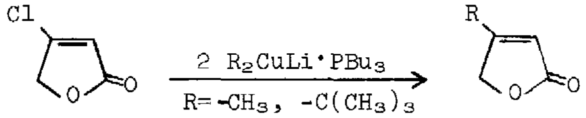
[c] See reference 7.

[d] See reference 6.

in 92% yield simply by adding mercuric chloride, lithium chloride (2 equiv) and palladium chloride directly to the acetylenic alcohol and refluxing in THF for 4 hrs under one atmosphere of carbon monoxide. Furthermore, even the addition of mercuric chloride can be avoided as indicated by a 70% yield of butenolide after refluxing 24 hrs in its absence. We are presently examining the generality of this direct approach to β-chlorobutenolides.



Although β-chloro-$\Delta^{\alpha,\beta}$-butenolides are not naturally occurring, they appear valuable as intermediates in the preparation of other β-substituted butenolides such as tetronic acids (β-hydroxy-$\Delta^{\alpha,\beta}$-butenolides). In fact, we have found that β-chloro-$\Delta^{\alpha,\beta}$-butenolide can be alkylated in good yield using Gilman reagents (2 mins, -78°, THF). We are presently studying this and further substitution reactions of the β-chloro-$\Delta^{\alpha,\beta}$-butenolides.



ACKNOWLEDGEMENTS

We gratefully acknowledge E. I. DuPont DeNemours and Company for a DuPont Young Faculty Grant and Matthey Bishop Inc. for a generous loan of palladium chloride. The partial financial support of the Research Corporation and the Petroleum Research Fund, administered by the American Chemical Society, is also greatly appreciated.

REFERENCES AND NOTES

1. Part IX., J. Am. Chem. Soc., in press.
2. DuPont Young Faculty Scholar, 1975-1976.
3. F. M. Dean, "Naturally Occurring Oxygen Ring Compounds," Butterworths, London (1963).
4. L. J. Haynes, Quart. Rev., 2, 46 (1948).
5. Y. S. Rao, Chem. Rev., 64, 353 (1964).
6. R. C. Larock, J. Org. Chem., 40, 3237 (1975).
7. A. N. Nesmeyanov and N. K. Kochetkov, Izv. Akad. Nauk SSSR, Otdel. Khim. Nauk, 76 (1949).