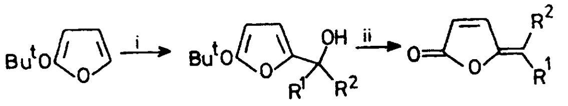
General Route to γ-Alkylidene Butenolides

By GEORGE A. KRAUS* and HIROHIKO SUGIMOTO
(*Department of Chemistry, Iowa State University, Ames, Iowa* 50011)

Summary A two-step route to γ-alkylidene butenolides from t-butoxyfuran is described.

PROTONANEMONIN (**1**; $R^1 = R^2 = H$) and its analogues possess antiviral and antibiotic activity which has been intensely investigated.[1] Marine metabolites such as the recently isolated fibrolides[2] and Matricarialactone,[3] acetongenin, also have the γ-alkylidene butenolide skeleton. A recent review of Rao[4] summarizes present methodology and illustrates the absence of a general synthetic route to this class of compounds. We have developed a short, convenient, and extremely versatile method using readily available t-butoxyfuran.[5]



(**1**)

SCHEME. i, (a) Bu^{t}Li, (b) R^1R^2CO; ii, MeC_6H_4-*p*-SO_3H, aq. THF.

Metallation of t-butoxyfuran† in anhydrous ether at −40 °C, 1 h, and reaction with a carbonyl compound at −40 °C followed by warming to 0 °C and ammonium chloride work-up provides a furyl alcohol which can be smoothly transformed into (**1**)‡ by treatment with a catalytic amount of toluene-*p*-sulphonic acid in aqueous THF at 25 °C. This method is compatible with the presence of protected allylic alcohols and polyenes (see Table).

TABLE. Yield of (**1**).

R^1	R^2	Yield/%
Ph	H	61[a]
Pr	H	45[a]
Me·CH:CH·CH:CH	H	44[b]
$Me_2C:CH·CH_2·CH_2$	Me	70[b]
1-Methyl-2-triethylsiloxycyclohex-3-enyl	Me	81[b]

[a] Isolated pure. [b] Mixture of isomers (*ca.* 4:1).

A recent report[6] describes the use of alkylidene butenolides as annelating agents. The general availability of this class of compounds is certain to provoke increased activity in this area.

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† The use of n-butyl-lithium resulted in polymer formation at 0 °C and incomplete metallation at lower temperatures.

‡ All compounds possess spectral properties (n.m.r., i.r., mass) consistent with their assigned structures. Compound (**1**; $R^1 = H$, $R^2 = Ph$) was identical with that prepared by another route (H. Gilman, *J. Amer. Chem. Soc.*, 1950, **72**, 3).

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