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A New Synthesis of Substituted Butenolides via Cation-Initiated Ring Expansion/Elimination of β-Lactones

T. Howard Black* and Jianhua Huang

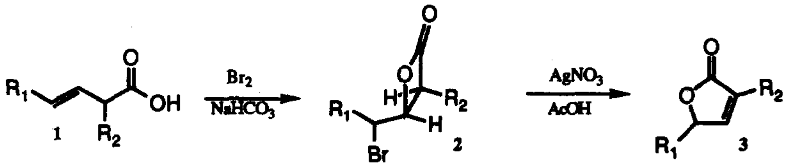
Department of Chemistry, Eastern Illinois University
Charleston, IL 61920

Abstract: When treated with silver ion, γ-bromo β-lactones, available via bromolactonization, undergo a ring expansion/elimination reaction to afford substituted butenolides.

Recently, we have been engaged in the development of new synthetic routes to butenolides, which form an important subunit of a host of naturally-occurring molecules[1] in addition to serving as versatile synthetic intermediates.[2] To date, our methods have centered on the Lewis acid-catalyzed ring expansion/elimination of α-chloro α-alkyl β-lactones, which, although convertible to the corresponding α-alkyl butenolides in high yield, must be acquired via a two-step sequence involving a rather sensitive low-temperature aldol reaction.[3] Also, in cases where migration in two directions is possible, mixtures of regioisomeric butenolides are obtained.

To address the above points and to enhance the utility of the method, we initiated a conceptually distinct approach, detailed in the Scheme, that would rely on the generation of a cation adjacent to the β-lactone ring oxygen atom, via departure of an appropriate nucleofuge, to initiate the ring expansion. Migration of the oxygen atom would result in a β-carbocation that we hoped would then enable double bond formation via loss of the α-proton. We herein report the successful realization of this plan utilizing γ-bromo β-lactones, secured via bromolactonization, as model compounds.

Scheme



The β,γ-unsaturated carboxylic acids employed as bromolactonization substrates were either obtained commercially or prepared via alkylation of the appropriate dianion (employing two equivalents of LDA in THF followed by reaction with the appropriate alkyl halide). Bromolactonization was carried out at 0 °C in the presence of sodium bicarbonate according to a literature procedure.[4] Treatment of the resulting lactones with silver nitrate in refluxing acetic acid effected transformation to the butenolides.

The specific substrates examined in this study are indicated in the Table. Consistent with the literature report,[4] several of the carboxylic acids **1** (specifically, **1f-1i**) provided mixtures of β- and γ-lactones upon bromolactonization. The yields of butenolides obtained indicate that both β-lactone **2** and the corresponding βbromo γ-lactone provide the butenolide when treated with silver ion; this was confirmed via separation of the products from **1f** and treatment of both with silver ion to obtain the same butenolide in both cases.

Table. Yield Data

compound	R_1	R_2	2	3	compound	R_1	R_2	2	3
a	H	H	32%	53%	f	Et	H	60%*	31%
b	H	Me	42%	59%	g	Et	Et	67%*	64%
c	H	*i*-Pr	24%	52%	h	Et	*i*-Pr	78%*	65%
d	H	Bzl	50%	52%	i	Et	Bzl	58%*	60%
e	H	*n*-Bu	66%	50%					

* β-lactone **2** and the corresponding γ-lactone; mixture used without purification

The synthesis of **3g** illustrates the method. 4-(1-Bromopropyl)-3-ethyl-2-oxetanone (**2g**, >90% trans by ^{1}H-NMR, 1.32 g, 6 mmol) was dissolved in acetic acid (30 mL). Silver nitrate (1.53g, 9 mmol) was added with stirring, whereupon the heterogeneous mixture was heated at reflux until TLC indicated the absence of remaining starting material (16 hrs). After removal of the solvent under reduced pressure, ether (40 mL) was added, and the solution was washed with 5% aqueous sodium bicarbonate and with water, and was then dried over anhydrous magnesium sulfate. Evaporation of the ether afforded 3,5-diethyl-2(5*H*)furanone (**4g**) as a yellow oil (542 mg, 64%). An analytical sample was secured via column chromatography over silica gel (15% (v/v) ethyl acetate/hexane eluent) followed by bulb-to-bulb distillation (80-90 °C, 1 mm), and displayed the following spectral parameters: IR (film) 1750, 1651 cm^{-1} (lit.[5] 1750 cm^{-1}); ^{1}H-NMR ($CDCl_3$) 6.98 (m, 1H); 4.82 (m, 1H), 2.20-2.35 (q, 2H), 1.55-1.85 (m, 2H), 1.15 (t, 3H), 0.96 (t, 3H) ppm; ^{13}C-NMR ($CDCl_3$) 9.015, 11.712, 18.572, 26.533, 82.185, 136.046, 146.831, 172.456 ppm.

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