An Efficient One-Pot Synthesis of Bis Butenolides

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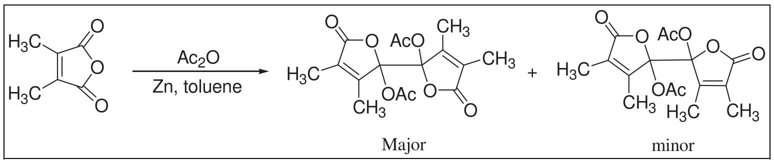

3,3′,4,4′-Tetramethyl-5,5′-dioxo-2,2′-bifuran-2,2′(5*H*,5′*H*) diyl diacetate was obtained from the reaction between 2,3-dimethyl maleic anhydride and acetic anhydride in the presence of zinc in toluene. This easy synthetic route gave bis butenolide in excellent yield.

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INTRODUCTION

Butenolides or γ-butyrolactones are important structural units in natural products and are intermediates in organic synthesis [1,2]. Compounds with butenolide substructures have received much interest for their utility in synthesis [3] and their prevalence in biologically active molecules and natural products [4]. There has been considerable work on the synthesis of these compounds [5,6] because of the discovery of many naturally occurring cytotoxic or antitumour agents containing this structural unit. Although this ring system has been the objective of synthetic projects in several laboratories [1–3], the number of different approaches is not large. A number of methods for preparing butenolides involve the reaction of furan derivatives, including asymmetric variants based on the Michael [7], Mukaiyama Michael [8], vinylogous Mannich [9], and aldol reactions [10].

Herein, we report an efficient synthetic route to 3,3′,4,4′-tetramethyl-5,5′-dioxo-2,2′-bifuran-2,2′(5*H*,5′*H*) diyl diacetate using 2,3-dimethylmaleic anhydride in the presence of zinc and acetic anhydride. The one-pot reaction of 2,3-dimethylmaleic anhydride **1** proceeded at 86°C in toluene and completed after 2 days to afford bis butenolide **2** in excellent yield (Scheme 1).

Compound **2** has two stereogenic centers, and therefore, two diastereomers are expected (Scheme 1). This result is not in accord with the similar pathway that is known to operate in the reduction of π-bond of unsaturated anhydrides. It seems that electron-donating groups like methyl (increase Lowest Unoccupied Molecular Orbital (LUMO)) cause π-bonds to not be reduced by the Zn/Ac_2O reagent. The structures of bis butenolide **2** were deduced from their IR, ^1H NMR, and ^{13}C NMR spectra, and by single-crystal X-ray analysis. Unambiguous evidence for the structure and stereochemistry of **2** was obtained from a single-crystal X-ray analysis. An Oak Ridge Thermal Ellipsoid Plot (ORTEP) diagram of **2** is shown in Figure 1.

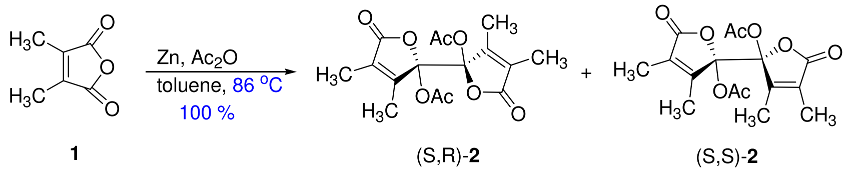
The ^1H NMR spectrum of crude product clearly showed both bis butenolide stereoisomers in a nearly 9 : 1 ratio. The ^1H NMR spectrum of bis butenolide **(S,R)-2** consisted of a singlet for the acetyl group at 1.98 ppm and two methyl proton signals at 1.95 and 2.05 ppm (doublets, $J = 2.05$ Hz). The corresponding signals for the minor diastereomer **(S,S)-2** were observed at 2.28 for the acetyl group and two methyl proton signals at 2.45 and 2.58 ppm (doublets, $J = 1.94$ Hz). The ^1H decoupled ^{13}C NMR spectrum of bis butenolide **(S,R)-2** showed eight sharp signals in agreement with the proposed structure.

The ^1H NMR spectrum of the crude reaction mixtures obtained from 2-methylmaleic anhydride and acetic anhydride was consistent with 2-methyl succinic anhydride **4** with the presence of only one diastereomer **5** (Scheme 2). When the reaction was carried out with 2-methylmaleic anhydride, both **4** and **5** were produced in 65 and 30% yields, respectively.

We then switched our attention to maleic anhydride (MA), In this case, we did not observe the expected bis butenolide product as a major product; instead, the reaction afforded the succinic anhydride (SA). We found that the reaction of maleic anhydride is to be highly chemoselective, and the reaction led to complete chemoselective reduction of the C=C bond and gave the SA in quantitative yield (Scheme 3). The ^1H NMR spectrum of SA consisted of a singlet at 3.12 ppm. The ^{13}C NMR spectrum of SA showed two sharp signals at 28.4 and 170.6 ppm in agreement with the structure.

We studied the chemoselective reduction of MA (Table 1). We examined the effect of MA, Zn, and Ac_2O concentrations on the conversion of MA to SA. It was found that conversion became higher with the increasing of Zn amount. In terms of the amount of Zn required

Scheme 1. Synthesis of bis butenolide. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]



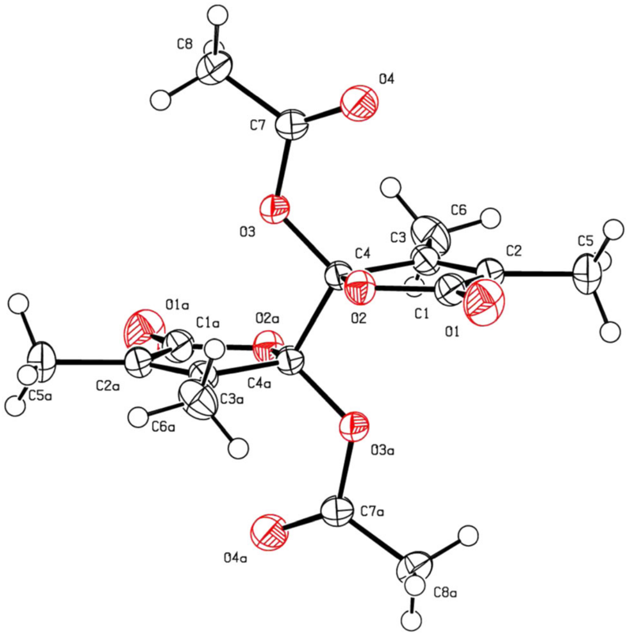
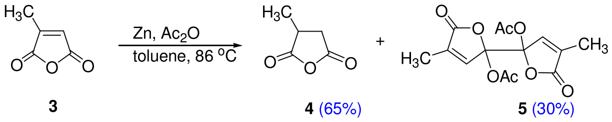


Figure 1. X-ray crystal structure (ORTEP) of **2**. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

for the reaction of MA to afford SA, the best results were obtained in the presence of 13 m*M* of Zn and 7 m*M* of acetic anhydride. In the absence of Zn, no products formed whilst in the presence of 10–30 mol% of Zn; the products were obtained in low yields (gave SA in only 5–10% yield).

We examined the chemoselective reduction of MA using Zn $(OAc)_2$ or only Zn in toluene (Table 2); in the same conditions, no products formed. Neither Fe nor Cu dust promoted the reaction under similar conditions (entries 3 and 4).

Scheme 2. Synthesis of γ-butyrolactone. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]



Scheme 3

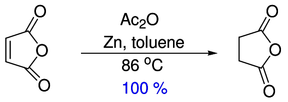


Table 1

Effect of amount of Zn and $\mathrm{Ac_2O}$ on the synthesis of **2**.

Entry	MA (m*M*)	Zn (m*M*)	$\mathrm{Ac_2O}$ (m*M*)	Yield (%)
1	1	0.1	0.1	trace
2	1	0.2	0.2	trace
3	1	0.3	0.3	trace
4	1	0.1	3	trace
5	1	3	0.1	trace
6	1	1	1	35
7	1	13	7	100

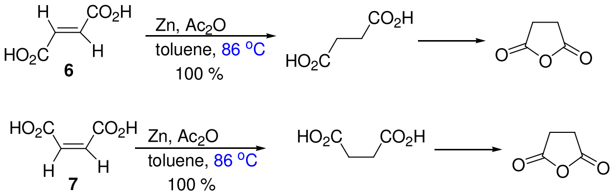
Table 2

Metal effect on the synthesis of **2**.

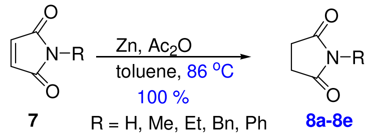
Entry	MA (m*M*)	Metal (m*M*)	$\mathrm{Ac_2O}$ (m*M*)	Yield (%)
1	1	$\mathrm{Zn(OAc)_2}$ (13)	—	0
2	1	Zn (13)	—	0
3	1	Fe (13)	7	0
4	1	Cu (13)	7	0

We investigated suitable α,β unsaturated carbonyl compounds for the chemoselective reduction as alternatives to this reduction. We were pleased to find that with a variety of compounds, the expected chemoselective reduction takes place, again in quantitative yields. The reactions of fumaric acid **6** or maleic acid **7** in toluene gave SA in quantitative yield in the same way (Scheme 4). SA is used as an intermediate in chemical, pharmaceutical, and food industries. The analysis of literatures on hydrogenation of MA shows that the most papers refer to catalytic studies at temperature over 200°C by batch process [11].

Scheme 4. Synthesis of succinic anhydride by using fumaric acid and maleic acid. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]



Scheme 5. Synthesis of *N*-substitutedsuccinimide. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]



The broad potential scope for this chemoselective reduction is further examined by using maleimide derivatives. The reaction of maleimide or *N*-substitutedmaleimide **7** in the same condition proceeds smoothly to produce the succinimide or *N*-substitutedsuccinimide **8** compounds in fairly good yields (Scheme 5). Although numerous examples of metal reductions methods appear in the literature [12], no broad study of the scope of this method for the preparation of *N*-alkyl succinimides has been reported.

In conclusion, the reaction of 2,3-dimethyl maleic anhydride with Zn in the presence of acetic anhydride provides a simple one-pot entry into the synthesis of stable bis butenolide compounds of potential interest. The simplicity of the present procedure makes it an interesting alternative to other approaches. SA generated by using maleic anhydride, maleic acid, or fumaric acid in highly efficient chemoselective reduction. We envisage broad potential applications for it that can be utilized for suitable substrates such as α,β unsaturated carbonyl compounds to afford the corresponding compounds. We hope that this methodology will be useful for production of SA in industrial scales.

EXPERIMENTAL

Maleic anhydride, 2,3-dimethylmaleic anhydride and other reagents and solvents used in this work were obtained from Aldrich chemical Co. and used without further purification. NMR spectra were recorded with a Bruker DRX-300 AVANCE instrument (400 MHz for ^{1}H and 100 MHz. for ^{13}C) with $CDCl_3$ as solvent. Chemical shifts are given in ppm (δ) relative to internal TMS, and coupling constant (J) are reported in hertz (Hz). Melting points were measured with an electrotherma1 9100 apparatus. IR spectra were measured with Bruker Tensor 27 spectrometer.

Typical procedure for preparation of bis butenolide 2. A solution of 2,3-dimethylmaleic anhydride (0.126 g, 1 m*M*) in toluene (6 mL) and Ac_2O (0.7 mL, 7 m*M*) was warmed to 40°C, and heating was pursued until complete dissolution of the solid. Activated Zn dust (0.8 g, 13 m*M*) was then added in one portion. The mixture was mechanically stirred at 86°C for 48 h; under N_2; vigorous stirring is recommended in order to maintain the zinc in suspension. It was then allowed to cool to r.t. and filtered through a Celite pad. The solid was washed several times with toluene, and the combined filtrate and washings were evaporated under reduced pressure to afford the product.

***3,3′,4,4′-tetramethyl-5,5′-dioxo-2,2′-bifuran-2,2′(5H,5′H) diyl diacetate* (S,R)-2.** Yield: 0.159 g (90%), Colorless crystal, m.p. 258–260°C (dec.). ^{1}H NMR ($CDCl_3$): $\delta = 1.91$ (6H, *d*, $J = 2$ Hz, 2 CH_3), 1.98 (6H, *s*, 2 OAc), 2.05 (6H, *d*, $J = 2$ Hz, 2 CH_3). ^{13}C NMR ($CDCl_3$): $\delta = 8.9$ (CH_3), 12.2 (CH_3CO), 21.3 (CH_3), 103.6 (C), 129.5 and 153.6 (C=C), 166.8 and 170.2 (C=O).

***3,3′,4,4′-tetramethyl-5,5′-dioxo-2,2′-bifuran-2,2′(5H,5′H) diyl diacetate* (S,S)-2.** Yield: 0.017 g (10%),White powder, m.p. 248–250°C (dec.). ^{1}H NMR ($CDCl_3$): $\delta = 2.28$ (6H, *s*, 2 OAc), 2.45 (6H, *d*, $J = 1.94$ Hz, 2 CH_3), 2.58 (6H, *d*, $J = 1.94$ Hz, 2 CH_3). ^{13}C NMR ($CDCl_3$): $\delta = 9.2$ (CH_3), 12.1 (CH_3CO), 20.0 (CH_3), 104.3 (C), 129.1 and 153.5 (C=C), 167.4 and 170.0 (C=O).

***2-methylsuccinic anhydride* (4).** Yield: 0.074 g (65%),^{1}H NMR ($CDCl_3$): $\delta = 1.45$ (3H, *d*, $J = 6.5$ Hz, CH_3), 3.15 (2H, *m*, CH_2), 3.21 (1H, *m*, CH). ^{13}C NMR ($CDCl_3$): $\delta = 16.1$ (CH_3), 35.4 (CH_2), 35.8 (CH), 170.1 and 170.5 (2C=O).

***3′,4,4′-tetramethyl-5,5′-dioxo-2,2′-bifuran-2(5H)yl acetate* (5).** Yield: 0.046 g (30%), White solid, ^{1}H NMR ($CDCl_3$): $\delta = 1.25$ (6H, *d*, 2 CH_3), 2.12 (6H, *s*, 2 OAc), 7.31 (2H, *br s*, =CH). ^{13}C NMR ($CDCl_3$): $\delta = 16.8$ (CH_3), 38.3 and 66.3, 128.2 and 128.6 (C=C), 177.4 and 180.9 (2C=O).

***Sccinic anhydride* (SA).** Yield: 0.100 g (100%),White solid, m.p. 128–130°C. ^{1}H NMR (400 MHz, Acetone-d_6): $\delta = 3.12$ (4H, *s*, CH). ^{13}C NMR (151 MHz, $CDCl_3$): $\delta = 28.4$ (CH) and 170.6 (C=O).

***Succinimide* (8a).** Yield: 0.099 g (100%),White solid, m.p. 123–125°C. ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 2.89$ (4H, *s*, CH_2), 8.95 (1H, *br s*, NH). ^{13}C NMR (151 MHz, $CDCl_3$): $\delta = 29.9$ (CH_2), 177.9 (C=O).

***N-methyl succinimide* (8b).** Yield: 0.113 g (100%), White solid, m.p. 70–72°C. ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 2.71$ (4H, *s*, CH_2), 2.99 (3H, *s*, CH_2). ^{13}C NMR (151 MHz, $CDCl_3$): $\delta = 24.6$ (CH_2), 28.2 (NCH_3), 177.3 (C=O).

***N-phenyl succinimide* (8f).** Yield: 0.175 g (100%), White solid, m.p. 154–156°C. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.86$ (4H, *s*, CH_2), 7.15–7.49 (5H, *m*, arom.).

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