Synthesis of Substituted Butenolides

An Undergraduate Organic Laboratory Experiment Utilizing Two 3-Step Preparatory Sequences

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Overview

Butenolides (structure a below) form an important class of natural products among which the one best known is vitamin C (structure b). Actually, many biologically active compounds contain butenolide structures (I).

![Butenolide structures](image)

The synthesis of substituted butenolides was readily achieved by the condensation of an α-hydroxyketone with an active methylene (ethyl cyanoacetate or diethyl malonate) in basic medium (2, 3). We prepared compound 2 (Scheme I) by a published procedure (3) and used it in two ways to synthesize three new compounds (3a, 3b, and 4).

![Scheme I](image)

The sequence in Scheme I, which is designed for undergraduate organic laboratory work, can be accomplished in three 4-hour sessions. Pedagogically, the interests of this sequence are multiple:

1. Illustrating a multistep synthesis
2. Demonstrating a domino reaction (step b)
3. Using different purification methods (distillation, chromatography, and crystallization)
4. Involving five basic organic reactions (alkyne hydration, Knoevenagel condensation, lactonization, aldolization-type reaction, hydration of nitrile).

Moreover, spectroscopic data for the products are useful in illustrating types of organic spectroscopy (NMR and IR), and the presence of a diastereotopic effect in compound 2 can easily be confirmed by molecular modeling.

Hydration of an Alkyne: Step a, Scheme I

The hydration of 3-methylpentyn-3-ol catalyzed by mercury salt leads to compound 1, 3-hydroxy-3-methylpentan-2-one. The procedure described in the literature (4) was modified by using smaller amounts of substrates, which led to a cheaper synthesis and avoided using a large amount of mercury salt. We chose 3-methylpentyn-3-ol as substrate instead of 2-methyl-3-butyln-2-ol as described by Rose (4) in order to synthesize a more interesting product, with the aim to initiate analysis and discussion of the 1H NMR spectrum of compound 2. It is worth noting that the two hydrogens of the methylene group of compound 1, which are diastereotopic, do not exhibit a diastereotopic effect (a fortuitous isochrony is observed). This first step is easily achieved to give high yield of 1 from commercial 3-methylpentyn-3-ol in a 4-hour session.

A Domino Reaction: Step b, Scheme I

This sequence leads to compound 2 by a domino reaction comprising a Knoevenagel reaction (condensation of hydroxyketone 1 with ethylcyanoacetate) and a lactonization. This tandem reaction is catalyzed by sodium ethoxide and takes place only with α,α-dialkyl-α-hydroxyketone—for example, compound 1. This may be explained by the Thorpe–Ingold effect (5), which states that alkyl substitution on a central methylene causes compression of the internal angle that leads to an easier cyclization. The infrared data for compound 2 illustrate some characteristic vibrations of functional groups:
2240 (vCN); 1770 (vC=O α,β-un saturated lactone); 1652 (conjugated vC=C. Interestingly, the 1H NMR spectrum reveals 2 doublets of quartets at 1.99 and 1.77 ppm that must be attributed to the CH₂ (Fig. 1a).

The nonequivalence of these two protons is due to a diastereotopic effect. Two protons in α-position of a chiral carbon are diastereotopic. They form an AB system producing two signals. In other words, an anisochrony of these protons is observed (an isochrony may be observed fortuitously, as it is for compound 1). Therefore, in this ABX₃ system, protons A and B appear as a doublet of quartet. A proton-proton homonuclear decoupling experiment confirms this multiplicity (Fig. 1b). Spectrum b, which was recorded with decoupling at 0.83 ppm, exhibits doublets at 1.75 ppm and 1.99 ppm, which correspond to each proton of the methylene group with a geminal coupling constant of ~14.5 Hz.

Although the diastereotopic effect is well known (6), further experiments were carried out to demonstrate that the nonequivalence of the 2 protons born by carbon 6 is not the result of a blocked conformation that might prevent rotation about the C₁₀-C₉ bond. The energies of compounds 1 and 2 were calculated using the AM1 method (7), with different locked dihedral angles defined by carbon atoms a, b, c, and d (Figs. 2 and 3). These diagrams exhibit 3 energetic minima corresponding to the 3 staggered conformations and 3 energetic maxima corresponding to the 3 eclipsed conformations. For compound 1 (Fig. 2), the difference in energy between an eclipsed and a staggered conformation varies from 1.36 to 2.34 kcal/mol; this difference varies from 1.22 to 2.05 kcal/mol for compound 2.

Further energy calculations, greater with accuracy for each minimum and maximum of the energy diagrams (Figs. 2 and 3) (8), were done using the ab initio 321G* method (9). Each difference in energy from a minimum to a maximum is sharply increased by using 321G*. For compound 1, the smallest energy gap is 3.77 kcal/mol by the 321G* method (vs 1.36 kcal/mol by the AM1 method); the highest energy gap is 7.32 kcal/mol by 321G*, vs 2.34 kcal/mol by AM1. Results for compound 2 were similar: the smallest energy gap is 3.24 kcal/mol with 321G* and 1.22 kcal/mol with AM1; the highest energy gap is 8.98 kcal/mol with 321G* method and 2.04 kcal/mol with AM1.

Note that the first minimum observed for a dihedral angle of 85° does not correspond to the expected angle (60°) (a positive dihedral angle corresponds to a rotation of the methyl group, designated d in Fig. 3, according to the trigonometric convention). This result (an angle >60°) may be explained by the presence of an sp² carbon (designated a in Fig. 3) that increases the steric hindrance on this side. The differences in energy obtained from AM1 or 321G* vary in a similar way and with almost the same intensity for compounds 1 and 2. In view of these results, the hypothesis that a blocked conformation exists only in compound 2 and not in compound 1 may be discarded. The observation of a diastereotopic effect only in compound 2 might be due to a different environment. Blocking two rotations about the C–O and C₇–C₈ bonds in compound 2 might contribute to increase the nonequivalence of the two methylene protons. For the molecular modeling calculations, the AM1 method,
which gives the energy curve quite rapidly, and the 3.21G* method, which increases the accuracy of the difference in energy between conformers from only a few calculations, are complementary.

**Aldol-Type Reaction: Step c, Scheme I**

The methyl group in position 3 of compound 2 is acidic owing to the stabilization of the conjugate base by resonance (10). This property contributes to the condensation of this activated methyl group with an aldehyde in an aldol-type reaction (11). The condensation of o-anisaldehyde or p-anisaldehyde with compound 2 in a sodium ethoxide solution leads to compounds 3a and 3b (eq 1) in 31 to 61% yield. The double bond formed has the E configuration according to 1H NMR spectra (\(J = 16.4 \text{ Hz or 16.6 Hz}\).

![Chemical Structure](image)

**Synthesis of 1 from 3-Methylpent-3-ol**

Mercury(II) oxide (0.77 g, 3.55 mmol) was added to an aqueous sulfuric acid solution (2.7 M, 7 mL) in a two-neck 250-mL round-bottom flask to form a solution. 3-Methylpent-3-ol (5.79 g, 59.0 mmol) was added dropwise through an addition funnel at room temperature over 5 min. The mixture was gradually warmed with an isomantle for 20 min. During heating an exothermic reaction took place, producing a black mixture. After cooling to room temperature, the precipitate (mercury salts) was filtered off on Büchner filter and washed on the filter with 20 mL of dichloromethane. The combined filtrate was extracted with dichloromethane (2 x 20 mL) in a separatory funnel. The aqueous phase (about 5 mL) was collected in a special bottle, as it may contain traces of mercury salts. The combined organic layers were dried over anhydrous MgSO\(_4\) filtered, and concentrated. The residue was purified by distillation to afford compound 1 (3-hydroxy-3-methylpentan-2-one) as a pale yellow oil in a 60 to 65% yield: \(R_f\) (CH\(_3\)Cl\(_2\)) = 0.31; mp 128–130 °C, 760 mm Hg (lit. [14] 58–59 °C, 24 mm Hg).

**Synthesis of 2 from 1**

To 8 mL of ethanol in a dry two-neck 100-mL round-bottom flask, 0.2 g (8.7 mmol) of sodium was added with stirring at room temperature until the sodium was completely consumed (about 10 min). A mixture of 2.0 g (17.2 mmol) of 3-hydroxy-3-methylpentan-2-one 1 and 1.94 g (17.1 mmol) of ethylglycine butyrate was added. The mixture was stirred at room temperature for 5 min and then heated at reflux for 15 min. After cooling to room temperature, the mixture was acidified by aqueous hydrochloric acid (16 mL of 2 M HCl [32 mmol] diluted with 30 mL of water) and extracted with dichloromethane (3 x 15 mL). The combined organic layers were dried over anhydrous MgSO\(_4\) and filtered, and the solvent was removed under reduced pressure. The red oily residue was purified on silica gel (40 g) and eluted with about 220 mL of dichloromethane to yield 2-cyano-3,4-dimethylhex-2-en-4-olide 2 (1.5 g to 1.8 g, yield 52 to 63%) as a light yellow oil.

**Synthesis of 3 from 2**

Sodium (0.03 g, 1.30 mmol) was added to ethanol (8 mL) in a dry two-neck 50-mL round-bottom flask, with stirring at room temperature until the sodium was completely consumed. A solution of 2-cyano-3,4-dimethylhex-2-en-4-olide 2 and anisaldehyde was added. The mixture was stirred at room temperature for 24 h, acidified with aqueous hydrochloric acid (5 mL of 2 M HCl [10 mmol] diluted with 20 mL of water), and extracted with dichloromethane (2 x 20 mL). The combined organic layers were dried over MgSO\(_4\), filtered, and concentrated under reduced pressure to afford the crude product.

For compound 3a, 1.41 g (8.57 mmol) of compound 2 and 1.17 g (8.59 mmol) of o-anisaldehyde were used. The crude product was crystallized in methanol–H\(_2\)O (14 mL:0.5 mL) to yield 2-cyano-4-methyl-3-((1E)-2-(2-methoxyphenyl)ethenyl)-hex-2-en-4-olide 3a as a yellow crystals after 18 h at room temperature: 750 mg, yield 31%; mp 95–97 °C; \(R_f\) (CH\(_3\)Cl\(_2\)) = 0.67.

For 3b, 1.00 g (6.10 mmol) of compound 2 and 0.84 g (6.14 mmol) of p-anisaldehyde were used. The crude product was purified by chromatography on silica gel (elucent CH\(_3\)Cl\(_2\))
to produce a red oil (1.11 g, yield 64.3%) having a low level of impurity according to NMR analysis. Crystallization from methanol-water (10 mL: 2 mL) at room temperature for 36 h yielded yield 2-cyano-4-methyl-3-((1E)-2-(4-methoxyphenyl)ethenyl)hex-2-en-4-olide 3b as yellow crystals: 0.9 g, yield 52.6% yield; mp 126 °C; Rf (CH₂Cl₂) = .65.

**Synthesis of Compound 4 from 2**

A mixture of 2-cyano-3,4-dimethylhex-2-en-4-olide 2 (0.87 g, 5.26 mmol) and sulfuric acid (96%, 4 mL) was heated at 100 °C for 5 min. This solution was cooled to 0 °C and carefully added dropwise to a cold water solution of ammonia (28%, 50 mL) and extracted with dichloromethane (3 x 20 mL). The combined organic layers were dried over MgSO₄, filtered, and concentrated under reduced pressure to yield 2-carboxamide-3,4-dimethylhex-2-en-4-olide 4 as a viscous oil (0.87 g, yield 90%), which crystallized spontaneously after 18 h at room temperature. Compound 4 was recrystallized in cyclohexane with a trace of ethyl acetate to yield white plate crystals, mp 70 °C.

**Hazards**

Like all mercury derivatives, mercuric oxide is highly toxic. All the reactions and workup should be carried out in an efficient hood. Laboratory coat and protective glasses should be worn. All aqueous and solid waste that may contain mercuric salt should be collected in a special bottle. Care should be taken when concentrated H₂SO₄ is handled. All contacts of water with metallic sodium must be avoided because of its pyrophoric property. Butenolides are potential biologically active compounds; therefore care should be taken when compounds 2, 3a, 3b, and 4 are synthesized or used.

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**Supplemental Material**

Supplemental material is available in this issue of *JCE Online*. It includes the data used to draw Figures 2 and 3, obtained by geometry optimization of each conformation of compounds 1 and 2 according to AM1 method; notes for the instructor; and NMR and IR assignments.

**Literature Cited**