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Cycloisomerization of Bifunctionalized Allenes: Synthesis of 3(2*H*)-Furanones in Water

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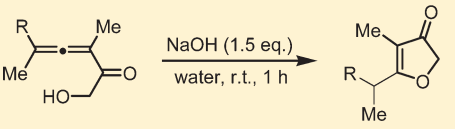
Supporting Information

ABSTRACT: A simple protocol for the efficient synthesis of 3(2*H*)-furanones by cycloisomerization of allenic hydroxyketones is described. This transformation is achieved in water and in the absence of any expensive metal catalysts.



The 3(2*H*)-furanone moiety is a central structural unit in a number of natural products such as bullatenone,[1] jatrophone,[2] eremantholide,[3] geiparvarin,[4] pseurotin,[5] and the recently reported metabolite longianone,[6] some of which were considered as promising pharmaceutical candidates (Figure 1). Therefore, many strategies have been developed for the construction of this five-membered ring system, among which the acid-catalyzed cyclization−dehydration of appropriately substituted α′-hydroxy-1,3-diketones[2c,4c] is the most general method. Other approaches include the hydrogenolysis and subsequent acidic hydrolysis of isoxazoles,[7] the aldol reaction of 3-silyloxyfuranes,[8] the cyclization of 1-halo-2,4-diketones with bases,[9] and the Knoevenagel-type condensation of γ-acetoxy-β-ketoesters.[10] Recent developments in the synthesis of 3(2*H*)-furanones involve the use of transition metal catalysts, for example, in the Au-, Pd-, or Hg-catalyzed cyclization of hydroxyalkynones,[11] the Pt- or Au-catalyzed cyclization/rearrangement of propargyl alcohols,[12] or the gold-catalyzed cyclization of 2-oxo-3-butynoates.[13] In this paper, we report that allenic hydroxyketones can be cyclized to 3(2*H*)-furanone derivatives by using simple aqueous NaOH.

In the past decade, allene chemistry[14] has been a rapidly growing research area in organic synthesis, providing various reactivity modes to construct complex chemical architectures in a stereoselective manner. As a part of our studies directed toward the development of efficient cycloisomerization reactions of functionalized allenes,[15] we became interested in bifunctionalized allenes comprising a carbonyl and hydroxyl group such as **A**. This molecule can be considered as a combination of an α-allenone and a β-allenol and might have different reactivity profiles under Brønsted or Lewis acid catalysis (Scheme 1). Besides 5-*endo*-trig cycloisomerization to furans **B**[16] or 6-*endo*-trig cyclization to pyranones **D**,[17] intramolecular oxa-Michael addition might afford 3(2*H*)-furanones **C**.

An attempt to synthesize an allenic hydroxyketone by selective oxidation of a 3,4-dien-1,2-diol with activated manganese dioxide resulted in the formation of the corresponding allenic aldehyde by glycol cleavage.[18] In contrast to this, monoprotected allenic diols **2** (which are readily accessible from propargyl oxiranes **1** by copper-promoted S_N2'-substitution[19]) were smoothly oxidized to allenones **3** with activated manganese dioxide in dichloromethane at 0 °C (Scheme 2). When phenyl-substituted allenone

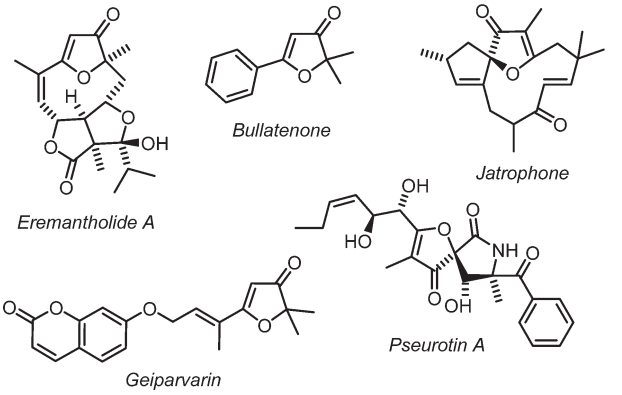
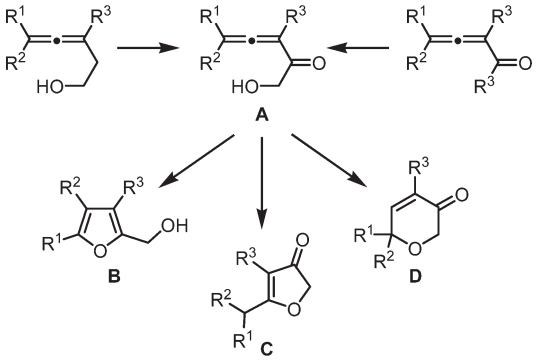


Figure 1. Natural products containing a 3(2*H*)-furanone subunit.

Scheme 1. Possible Reactions of Allenic Hydroxyketones A



3a was subjected to TBS deprotection by using TBAF·3H_2O at 0 °C, 3(2*H*)-furanone **5a** was formed directly after just 20 min (Scheme 3). In an analogous manner, the benzyl-substituted allenone **3b** afforded heterocycle **5b** with 57% yield; in this case, 2.5 h of reaction time was required for a complete conversion.

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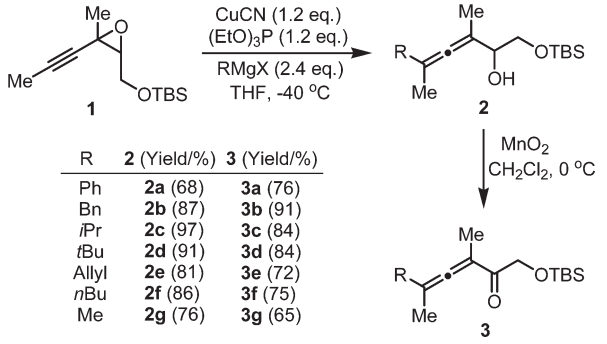
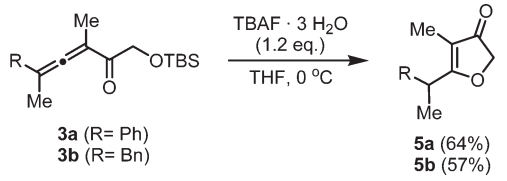
Scheme 2. Synthesis of Allenones 3.



R	2 (Yield/%)	3 (Yield/%)
Ph	**2a** (68)	**3a** (76)
Bn	**2b** (87)	**3b** (91)
*i*Pr	**2c** (97)	**3c** (84)
*t*Bu	**2d** (91)	**3d** (84)
Allyl	**2e** (81)	**3e** (72)
*n*Bu	**2f** (86)	**3f** (75)
Me	**2g** (76)	**3g** (65)

Scheme 3. Deprotection and Spontaneous Cyclization of Allenones 3a/b



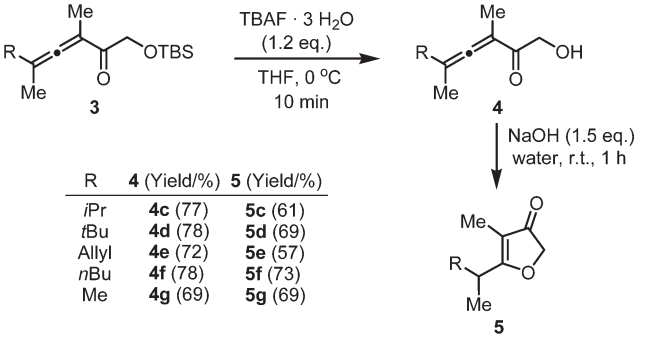
3a (R= Ph)
3b (R= Bn)

5a (64%)
5b (57%)

With alkyl-substituted allenones **3c**−**g**, TBS deprotection gave the bifunctionalized allenes **4** as the exclusive product within 10 min (Scheme 4). Prolonged reaction times (2.5 h) afforded a trace amount of the furanone product, whereas stirring of **3e** with TBAF·$3H_2O$ for 18 h resulted in polymerization. Surprisingly, the allenic hydroxyketones failed to give any cycloisomerization product in the presence of various gold or silver catalysts which were used previously for the cyclization of allenic ketones[16] and alcohols.[15,17] Thus, treatment of **4c** with $AuCl_3$, AuCl, Ph_3PAuCl, IPrAuCl, $HAuCl_4 \cdot 3H_2O$, $AgNO_3$, or AgOTf resulted in reisolation of the starting material. However, treating allene **4c** with a stoichiometric amount of K_2CO_3 in methanol at room temperature furnished 3(2*H*)-furanone **5c** with moderate yield (41%). Use of other bases (NaHMDS in THF, KO*t*Bu in *t*BuOH, DBU or DABCO in dichloromethane), as well as treatment with nBu_3P or Ph_3P in dichloromethane gave no satisfactory results. A trace of the furanone product **5c** was formed when **4c** was stirred with 25 mol % of *p*-TsOH in methanol for 16 h. These results seem to indicate that the furanone is formed only when a protic solvent is used. Accordingly, treatment of **4c** with aqueous NaOH for 1 h induced a clean conversion of the starting material to the 3(2*H*)-furanone **5c**, which was isolated with 61% yield (Scheme 4). Likewise, allenones **4d**−**g** afforded the corresponding furanones **5** with 57−73% yield under these conditions. Mechanistically, the transformation may proceed via a 5-*endo*-dig (oxa-Michael) pathway, followed by base-catalyzed isomerization of the exocyclic double bond.

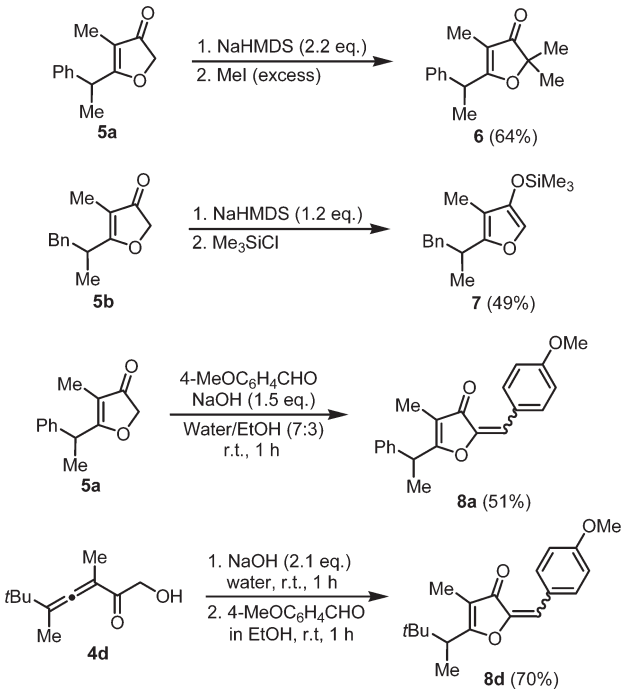
The synthetic utility of the 3(2*H*)-furanones **5** formed by this method was demonstrated by the smooth dialkylation of **5a** to product **6**, as well as by the formation of siloxyfuran **7** from furanone **5b** (Scheme 5). Moreover, the heterocycles participate in aldol reactions. Thus, adduct **8a**[20] was obtained with 51% yield from **5a** and anisaldehyde with NaOH in water/ethanol. These conditions are similar to those used for the formation of the furanones; accordingly, it is possible to conduct the cyclization/

Scheme 4. Deprotection and Basic Cyclization of Allenones 3c−g



R	4 (Yield/%)	5 (Yield/%)
*i*Pr	**4c** (77)	**5c** (61)
*t*Bu	**4d** (78)	**5d** (69)
Allyl	**4e** (72)	**5e** (57)
*n*Bu	**4f** (78)	**5f** (73)
Me	**4g** (69)	**5g** (69)

Scheme 5. Transformations of/via 3(2*H*)-Furanones 5



aldol addition in one pot, as demonstrated by the efficient formation of product **8d**[20] from allenic hydroxyketone **4d** and anisaldehyde. This procedure may be particularly useful for the combinatorial synthesis of compound libraries.

In summary, we present a novel method for the synthesis of 3(2*H*)-furanones by cycloisomerization of allenic hydroxyketones with aqueous NaOH. With respect to operational convenience, it is important to note that this cyclization protocol does not require any heating or cooling, or any expensive or toxic metal catalysts. In addition to their importance as the core structure of a variety of natural products, the 3(2*H*)-furanones can be subjected to various synthetic manipulations. We anticipate that further investigation of bifunctionalized allenes will lead to novel pathways to other interesting heterocyclic systems.

EXPERIMENTAL SECTION

Representative Procedure. Allenic hydroxyketone **4c** (31 mg, 0.18 mmol) was added to a solution of NaOH (12 mg, (0.28 mmol)

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in 1.5 mL water, and the mixture was stirred at room temperature until the TLC control showed complete consumption of the starting material (1 h). The reaction mixture was then extracted with 3 × 4 mL of diethyl ether. The combined organic phases were dried with Na_2SO_4 and the solvent was removed in the rotary evaporator (pressure not lower than 250 mbar) to furnish 19 mg (0.11 mmol, 61%) of **5c** as a faint yellow liquid.

4-Methyl-5-(3-methylbutan-2-yl)furan-3(2*H*)-one (5c): IR (neat) 2967, 2929, 2873, 1688, 1618, 1462, 1403, 1170, 1054, 909, 735, 650 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.42 (s, 2 H), 2.58−2.51 (m, 1 H), 1.87 (m, 1 H), 1.66 (s, 3 H), 1.19 (d, J = 7.0 Hz, 3 H), 0.99 (d, J = 6.7 Hz, 3 H), 0.88 (d, J = 6.7 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.0, 193.0, 111.3, 73.8, 41.0, 31.9, 21.1, 20.6, 15.1, 5.8; HRMS (ESI) calcd for $C_{10}H_{16}O_2$ (M^+) 168.1150, found 168.1138.

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures, spectral data, and copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ ACKNOWLEDGMENT

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(20) Aldol adducts **8a**/**d** were obtained as a single isomer, but the configuration could not be determined spectroscopically.