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# A CONVENIENT SYNTHESIS OF 2,2-DISUBSTITUTED 3(2H)-FURANONES[1]

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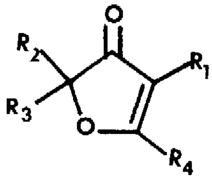
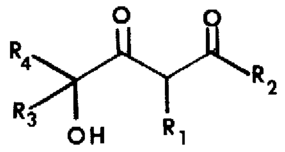
Summary: 2,2-Disubstituted 3(2H)-furanones can be prepared readily by 1,2-addition of organometallic compounds to γ,γ-disubstituted β-bromo-α,β-butenolides followed by treatment of the adducts with acid.

3(2H)-Furanones, which are valued for their aromas,[2] are useful synthetically as building blocks for muscarins[3] and tetronic acids[4] and as formyl ketone equivalents in photoannelation reactions.[5] Moreover, the findings that certain natural products such as jatrophone,[6] the eremantholides,[7] and geiparvarin[8] which exhibit anticancer activity contain a 3(2H)-furanone moiety have led to an increased interest in both the synthesis[9] and reactions[10] of these compounds.

Synthetic approaches to the 3(2H)-furanone system which vary in their degree of flexibility have appeared in the literature.[3,11] One of the general approaches to the synthesis of these compounds involves formation and acid-catalyzed cyclization of appropriate γ-hydroxy-β-dicarbonyl systems (2).[9,11c,d,g-j] It occurred to us that α,β-butenolides such as 4, having appropriate substituents at the β-carbon, should undergo 1,2-addition of organometallic reagents to yield masked γ-hydroxy-β-dicarbonyl compounds (3) which should be capable of undergoing hydrolysis and acid-catalyzed cyclization to the corresponding 3(2H)-furanones (1) possibly via intermediates such as 2.

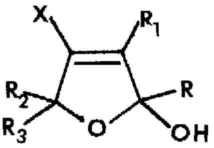


1

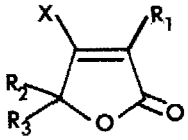


2

a. $R_1=R_2=R_3=R_4=CH_3$
b. $R_1=R_4=CH_3, R_3R_2=\leftarrow CH_2 \rightarrow_5$
c. $R_1=H, R_2=R_3=CH_3, R_4=Ph$
d. $R_1=H, R_2=R_3=R_4=CH_3$
e. $R_1=H, R_2R_3=\leftarrow CH_2 \rightarrow_5, R_4=CH_3$



3



4

a. $R_1=R_2=R_3=CH_3$, X=Br
b. $R_1=CH_3, R_2R_3={\leftarrow}CH_2{\rightarrow}_5$, X=Br
c. $R_1=H, R_2=R_3=CH_3$, X=Br
d. $R_1=H, R_2R_3={\leftarrow}CH_2{\rightarrow}_5$, X=Br
e. $R_1=CH_3, R_3=H, R_2=$i-Pr, X=Br

Various α,β-butenolides containing dialkylamino,[12] phenylthio,[13] or chloro[14] substituents at the β-position have been recently reported in the literature and appeared to be potentially useful candidates for the sesquence described above. However, we have found that lithium E-3-bromo-3-lithiopropenoate and its 2-methyl derivative, which can be obtained by treatment of the corresponding E-bromoacids with 2 equiv of n-butyllithium in ether or tetrahydrofuran at -70°C,[15] undergo facile addition to both aliphatic aldehydes and ketones[16] to give the corresponding γ-substituted β-bromobutenolides. Compounds 4a-e were prepared in yields in the 50-80% range by this method and their readily availability made them attractive precursors for the desired 3(2H)-furanones.

Benetti and coworkers have reported that β-alkyl substituted butenolides undergo 1,2-addition of 2 equiv. of Grignard or organolithium reagents to yield unsaturated 1,4-diols.[17] However, by carrying out inverse addition of phenyl- or methyllithium or methylmagnesium bromide to solutions of bromobutenolides 4a-e in ether at -25° it was possible to limit 1,2-addition to only 1 equiv. of the organometallic reagent and obtain, after acidification, adducts of the type 3. These adducts were not purified but were converted directly into 2,2-disubstituted furanones 1 by treatment with 20% aqueous sulfuric acid containing methanol as a cosolvent at room temperature for 14 h. The results of these runs are shown in the Table. The yields of products ranged from 47-76%. In the cases where relatively low yields were obtained, no improvement was observed when milder conditions applicable to the hydrolysis of vinyl halides[18] were employed.

The exact pathway for the conversions of the butenolide adducts 3 into the 3(2H)-furanones 1 is not known. An open chain γ-hydroxy-β-bromo-α,β-unsaturated ketone which may be in equilibrium with 3, may undergo hydrolysis of the vinyl halide to give a γ-hydroxy-β-dicarbonyl compound (2) which cyclizes to 1, or the hydroxyl group in 3 may undergo acid-catalyzed allylic rearrangement to the carbon atom bearing bromine followed by loss of hydrogen bromide.

When the γ-isopropyl butenolide 4e was reacted with 1 equiv. of methyllithium and the product subjected to hydrolysis as described above, 3-bromo-2-isopropyl-5-methylfuran was the only product obtained.[19] Thus the above sequence appears to be applicable to the synthesis 2,2-disubstituted 3(2H)-furanones only. However, it does offer remarkable flexibility particularly with regard to the substituents which may be introduced at the 2 and 5 positions.

Table. Preparation of 2,2-Disubstituted 3(2H)-Furanones (1) by Addition of Organometallic Reagents to β-Bromobutenolides Followed by Acid Hydrolysis.

| Butenolide | Organometallic Reagent | 3(2H)-Furanone$^a$ | Yield (%) | Ref. |
|---|---|---|---|---|
| 4a | $CH_3Li$ | 1a | 56 | - |
| 4b | $CH_3Li$ | 1b | 76 | - |
| | $CH_3MgI$ | 1b | 67 | - |
| 4c | PhLi | 1c | 71 | 4,20 |
| | $CH_3Li$ | 1d | 47 | 11i |
| 4d | $CH_3Li$ | 1e | 70 | 11j |

a. All of the 3(2H)-furanones exhibited the expected UV, IR, NMR ($^1$H and $^{13}$C), and mass spectral properties. All new compounds gave elemental analyses which were correct to within ±0.3%.

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