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DIANIONS OF ß-HYDROXY SULFONES: NEW AND GENERAL APPROACH TO SELECTIVE SYNTHESIS OF 2(5*H*)-FURANONES

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Dianions derived from ß-hydroxy sulfones are highly reactive toward a variety of electrophiles including alkyl halides, carbonyl compounds, and sodium iodoacetate. A convenient synthetic method for 4-alkyl- and 5-alkyl-2(5*H*)-furanones has been developed by using these dianions. A new synthetic approach to trans-3,4-bis(3-hydroxybenzyl)dihydro-2(3*H*)-furanone, the first lignan found in humans, via a facile reduction of 2(5*H*)-furanone with Mg-methanol is also decribed.

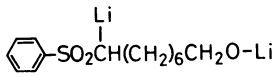
Furanones and their dihydro derivatives are frequently found in natural products such as lignans,[1] Mokupalide[2] isolated from a marine sponge, and sex pheromones[3] from the black-tailed deer, the Japanese beetle, or the rove beetle, and also are useful intermediates for the synthesis of cerulenin,[4] perillene, and dendrolasin.[5] For this reason, considerable effort has been devoted toward the discovery of useful synthetic methods for the construction of such a framework.[6] In this communication, we describe a general methodology for the preparation of 2(5*H*)-furanones and its application to the efficient synthesis of trans-3,4-bis(3-hydroxybenzyl)dihydro-2(3*H*)-furanone.

Our concern in this field lay in the development of the structural equivalents of ß-anion (1) and γ-anion (2) of 2(5*H*)-furanone. Toward this end, we investigated the reactivity of functionalized sulfones because of the readily availability as the starting materials.[7] Addition of 2.2 equiv. of butyllithium to a solution of 8-phenylsulfonyl-1-octanol in THF containing 2.2 equiv. of TMEDA at 0°C produced an orange suspension, which was treated with excess CH_3OD after 4 h. ^{1}H-NMR analysis of the product (98% yield) isolated after aqueous workup showed quantitative deuterium incorporation at the 8-position indicating the exclusive formation of the dianion (3). However,

1

2

attempts to introduce a carboxymethyl group at this position by the reaction of 3 with sodium iodoacetate even in the presence of 3.4 equiv. of HMPA were unsuccessful. In contrast, the dianion (4) of 2-phenylsulfonyl-1-octanol generated on treatment with 2.2 equiv. of butyllithium in THF-TMEDA at 0°C is a homogeneous, stable solution, and highly reactive toward sodium iodoacetate, in spite of tendency of ß-substituted organometallic derivatives to decompose into olefins by ß-elimination.[8]



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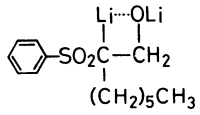

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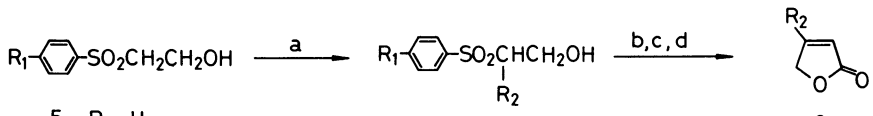
The enhanced reactivity of the dianion (4) may be caused by the proximity of two anionic parts due to the intramolecular complexation.[9]
Thus, treatment of 4 with sodium iodoacetate gave the corresponding hydroxy acid, which was directly transformed into 4-hexyl-4-(phenylsulfonyl)dihydro-2(3*H*)-furanone by refluxing in benzene for 3 h in the presence of a catalytic amount of *p*-TsOH.

Table 1. Preparation of 4-alkyl-2(5*H*)-furanones and 5-alkyl-2(5*H*)-furanones.

Sulfone	Electrophile (R_2X or R_3CHO)	Adduct 7,8 or 15	Furanone 9 or 16
5	1-Iodohexane	7a (96%)	9a (67%)
5	1-Iododecane	7b (73%)	9b (61%)
5	1-Iodododecane	7c (88%)	9c (64%)
5	Geranyl bromide	7d (73%)	9d (46%)
6	1-Bromooctane	8e (81%)	9e (53%)
6	1-Iododecane	8f (92%)	9b (57%)
14	Cyclohexanecarbaldehyde	15g (100%)	16g (50%)
14	Valeraldehyde	15h (100%)	16h (52%)
14	Isobutyraldehyde	15i (99%)	16i (52%)
14	Isovaleraldehyde	15j (99%)	16j (60%)
14	Heptanal	15k (98%)	16k (51%)
14	Nonanal	15l (99%)	16l (55%)



5, R_1 = H
6, R_1 = CH_3

7, R_1 = H
8, R_1 = CH_3

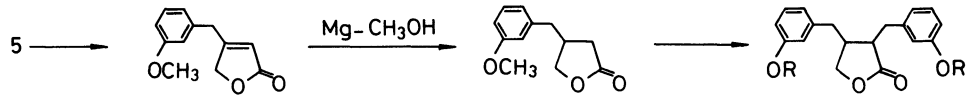
9

(a) 2.2 eq. n-BuLi, THF-TMEDA, electrophile (R_2X), -78°C-room temperature;
(b) 2.2 eq. n-BuLi, THF-TMEDA, 1.2 eq. ICH_2COONa;
(c) p-TsOH, benzene, reflux;
(d) 2.5 eq. Et_3N, benzene, room temperature.

The desired 4-alkyl-2(5*H*)-furanone (9) was readily obtained upon treatment of 4-alkyl-4-(phenylsulfonyl)dihydro-2(3*H*)-furanone with excess triethylamine in

benzene at room temperature for 17 h (Table 1).

The versatility of this methodology is apparent from the following convenient one-pot synthesis of trans-3,4-bis(3-hydroxybenzyl)dihydro-2(3*H*)-furanone (13), isolated from female urine as a non-steroidal constituent.[10] Thus, 4-(3-methoxybenzyl)-2(5*H*)-furanone (10) was prepared in 51% by sequential treatments (a, b, c, and d), starting with 2-(phenylsulfonyl)ethanol (5).



10 (51%) 11 (68%) 12, R=CH_3 (72%)

13, R=H

The most crucial step in this synthesis involves reduction of the carbon-carbon double bond in furanone unit of 10. The ordinary reduction procedures using 5% or 10% palladium on carbon were found to be fruitless, however the facile conversion of 10 into 11 could be achieved on treatment with Mg in methanol at room temperature for 3 h.[11] Treatment of 11 with LDA in THF containig a small amount of HMPA followed by the addition of 3-methoxybenzyl bromide produced 12 in 72%.[10c]

14 15 16

The synthesis of 5-alkyl-2(5*H*)-furanone (16) utilizes the ß-hydroxy sulfones derived from lithiomethyl phenyl sulfone and aldehydes.[7] The dianion of 15 was also found to be reactive toward sodium iodoacetate. The conversion into 16 was carried out by a similar procedure for the 4-alkyl-2(5*H*)-furanone synthsis. The results are summarized in Table 1.

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