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THE CONVERSION OF FURANS TO 2(3H)-BUTENOLIDES

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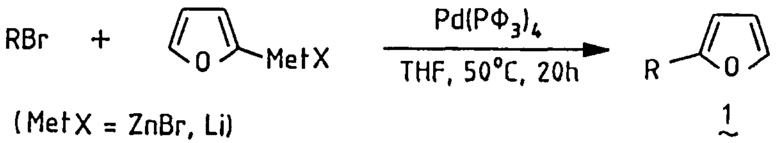
2-Aryl- and 2-alkylfurans are converted into the corresponding 5-organyl-2(3H)-butenolides by the oxidation of boron derivatives with m-chloroperbenzoic acid.

Due to our interest in butenolides,[1] particularly those related to the fadyenolides[2] and piperolides[3] and because of our need for synthons for lignan synthesis[4] we required a general preparation of 5-organylbutenolides for further elaboration. In particular a synthesis based on 2-organylfurans, 1 seemed desirable, as compounds 1 should be stable enough to be safely carried through a variety of procedures prior to a mild controlled oxidation to the required butenolides.

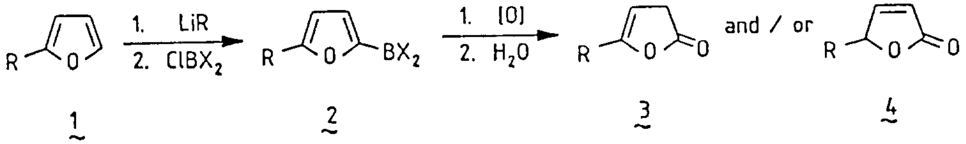
We first accomplished the synthesis of a wide variety of furans 1 by the process shown in equation (1).



(1)

We could find no example of the direct conversion of 1 to 5-organylbutenolides. This paper describes such a process which can give rise to a large number of substituted butenolides.[6] Of relevance to our work is the conversion by oxygen of 2-trimethylsilylfurans to the corresponding 5-hydroxy-2(5H)-butenolides[7] and the oxidation of 2-methyl- and 2-ethyl-5-(dimethoxyboryl)thiophenes by alkaline hydrogen peroxide to the 5-alkyl-1-thio-2(3H)-butenolides.[8]

We felt that the sequence shown in equation (2) held promise of being a general route, though we were unable to predict in any specific case whether 2(3H)-butenolides, 3 or 2(5H)-butenolides, 4 or mixtures, would result.



(2)

(a) R = Ph
(b) R = 4-MeC$_6$H$_4$
(c) R = 3-MeC$_6$H$_4$
(d) R = 3-MeOC$_6$H$_4$
(e) R = 4-MeOC$_6$H$_4$
(f) R = 3,4-diMeOC$_6$H$_3$
(g) R = 4-NO$_2$C$_6$H$_4$
(h) R = PhCH:CH.CH$_2$
(i) R = PhCH$_2$
(j) R = Octyl

We first tried the sequence in which X = mesityl, on the premise that the intermediates **2** would be stable and crystalline.[9] Reaction of furylmagnesium bromide with dimesitylfluoroborane gave **2** (R = H, X = mesityl) as a crystalline solid, but only in 30% isolated yield. Oxidation of this compound with alkaline hydrogen peroxide gave 2(5H)-butenolide in 35% yield. 2-Octylfuran did not give any of the desired product and this approach was abandoned.

We then examined the sequence in which X = OMe. However, yields of **2** (R = H, X = OMe) were poor when trimethoxyborane was used as boronating reagent. However, one equivalent of chlorodimethoxyborane[10] in trimethoxyborane proved a highly effective reagent to yield **2** (X = OMe). In practice these furyldimethoxyboranes are prone to unexpectedly rapid hydrolysis and were generally oxidised in situ.

The results of the study of the oxidation of **2** (X = OMe) are given in the Table.

TABLE

Oxidation of 2-organyl-5-(dimethoxyboryl)furans to 5-organyl-2(3H)-butenolides

Exp. No.	Organylfuran	Temp.(°C)	Oxidising agent	Product^a	Yield of **3** (%)^b
1	**1a**	20	NaOH/H$_2$O$_2$	**1a** (95%)	0
2	"	"	PCC^c	" (20%)	0
3	"	"	PDC^c	" (30%)	0
4	**1e**	"	O$_2$^{d}	**1e** (100%)	0
5	**1b**	0	MCPBA,THF	**3b**	0^e
6	"	"	MCPBA,Et$_2$O	"	32^e
7	"	"	MCPBA/Et$_2$O/Na$_2$CO$_3$	"	59^f
8	"	-78	"	"	94^e
9	**1c**	0	"	**3c**	72^f
10	**1d**	"	"	**3d**	67^e
11	**1a**	-78	"	**3a**	90^f
12	**1e**	"	"	**3e**	91^f
13	**1f**	"	"	**3f**	89^e
14	**1i**	"	"	**3i**	88^e
15	**1j**	0	"	**3j**	86^f

a) All products fully characterised. b) Yields are of isolated, purified product.
c) Reaction time of 4h. d) Reaction time of 12h. e) 85% MCPBA. f) 100% MCPBA.

Oxidation with oxygen in a Brown hydrogenator[11] was ineffective (exp.4) due to lack of reaction. Oxidation with alkaline hydrogen peroxide (exp.1) was also unsuccessful due to preferential hydrolysis. Anhydrous oxidation with chromium reagents (exp.2,3)[12] proved difficult to control and gave low yields of recovered furan. Lithiation of **1b** in THF followed by oxidation with meta-chloroperbenzoic acid (MCPBA) was also ineffective, but some product was obtained in ether (exp.5,6). Sodium carbonate was added to the ether prior to oxidation at 0°C, in order to neutralise the meta-chlorobenzoic acid as it formed and this increased the yield (exp.7). Finally, lowering the temperature to -78°C inhibited hydrolysis and ring opening[13] to give 94% of isolated butenolide **3c** based on starting furan **1c**, and this became our favoured procedure. Although we generally used 100% MCPBA[14] this was not necessary when anhydrous sodium carbonate was previously added (exp.8,10,13,14). Again, although lowering the temperature of the oxidation to -78°C was generally advantageous, an excellent yield of 5-octyl-2(3H)-butenolide was obtained at 0°C (exp.15).

Of particular note is that in every case, even when R = alkyl (exp.14 and 15) the product was always the 2(3H)-butenolide, **3**, and no trace was found of the readily distinguishable 2(5H)-butenolide, **4**. Thus, when water is added to the reaction mixture in the presence of sodium carbonate, protonation occurs at C-3 only without any equilibration, even for the 5-alkyl products.

The sequence failed with furans **1g** and **1h**, in each case because lithiation was complex or difficult in the conditions tried. With these exceptions the process described is a mild, high yield, one-pot sequence for the conversion of 2-organylfurans into 5-organyl-2(3H)-butenolides, and as such should find wide application.

Preparation of 5-phenyl-2(3H)-butenolide, **3a** from 2-phenylfuran **1a**.

n-Butyl lithium in hexane (6.4 ml of 1.57M, 10 mmol) was slowly added by syringe to a stirred solution of 2-phenylfuran (1.44g, 10 mmol) in dry ether (50 ml) at 0°C under argon. Boron trichloride in hexane (3.33 ml, 1M, 3.33 mmol) was added with stirring to trimethoxyborane (25 ml) in dry ether (50 ml) at 0°C under argon. Both mixtures were allowed to stir for 3h at room temperature and then the chlorodimethoxyborane solution was added by double-ended needle to the stirred solution of 2-phenyl-5-lithiofuran at 0°C. Lithium chloride precipitated and the mixture was allowed to stir for a further hour at room temperature.

MCPBA (3.45 g of 100%, 20 mmol) was added to a 250 ml round bottomed flask containing anhydrous sodium carbonate (10.5g, 100 mmol) under argon. Dry ether (75 ml) was added and the mixture cooled to -78°C and maintained at this temperature whilst the solution of **2a** was rapidly added by double-ended needle. After 5 min., the solution was allowed to warm to 0°C and then water (50 ml) added.

The organic layer was removed and the aqueous layer washed with ether (2 x 25 ml). The combined organic phases were washed with saturated sodium sulphite (50 ml), saturated sodium bicarbonate (50 ml) 1M sodium bicarbonate (50 ml), water (3 x 50 ml) and dried ($MgSO_4$). Filtration and evaporation of solvent was followed by sublimation at 75°C/0.005 mm Hg to give 5-phenyl-2(3H)-butenolide m.p. 91-92°C, (1.45 g, 90.6%).

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