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Synthesis of 3-Methyl-4-substituted Butenolides Using Regioselective Reaction of Phenylsulfonylbutenolide

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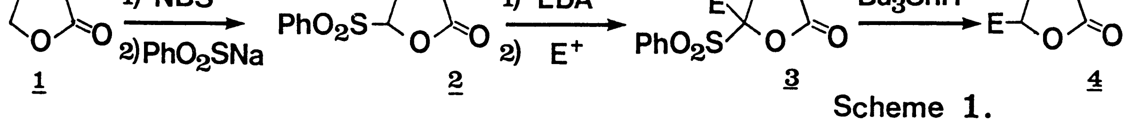
The anion of 4-phenylsulfonylbutenolide generated by deprotonation with lithium diisopropylamide reacted with a variety of electrophilic reagents regioselectively to afford 4-alkylated compounds, which were desulfurized in good yields to 4-substituted butenolides upon treatment with tri-n-butyltin hydride.

In recent years there has been considerable interest in the development of new processes for the synthesis of substituted butenolides because of their diverse biological activities[1)] and versatile utilization in the synthesis of natural products.[2)] Although various routes to substituted butenolides have been established until now,[3)] little attention has been given to the direct regioselective alkylations of this class of compounds.[4)]

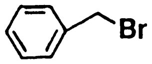
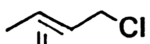
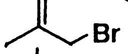
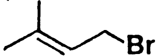
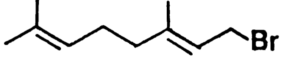
As part of a program designed to explore the use of butenolide (1), we have recently reported chemoselective alkylations of 4-hydroxybutenolides employing Grignard reagents.[5)] The purpose of this communication is to describe that by placing phenylsulfonyl group at the 4-position of 1 extremely high regioselective alkylation and normal allylation reactions could be accomplished.

Thus, 4-phenylsulfonyl-2-buten-4-olide (2) was easily prepared by bromination of butenolide (1) in CCl_4 followed by treatment with sodium benzenesulfinate in DMF in 60% yield. The anion of butenolide (2) deprotonated with LDA in THF containing 2-5 equiv. of HMPA was treated with a variety of electrophiles and proved to react at the 4-position of 2 exclusively in moderate to high yields.[6)] Furthermore it should be noted that when the alkylated substances (3) were refluxed in toluene for 2 h with 3 equiv. of Bu_3SnH in the presence of AIBN, the desulfonyiation reaction took place to afford cleanly 4-substituted butenolides (4) in good yields. The results are listed in Table 1.[7)] Especially in the case of the reactions with allylic halides these results offer the concise preparative opportunities for the synthesis of 4-allylated butenolides which could not be accomplished in the preceding report.[5)]



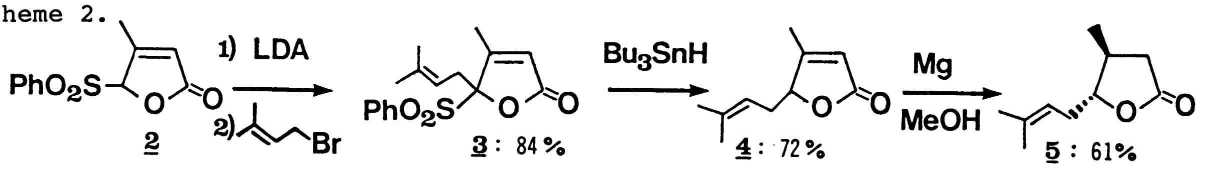
Scheme 1.

Table 1. Synthesis of 4-Substituted Butenolides

Entry	Electrophile[a)]	Temp °C	Yield of 3[b)] %	Yield of 4[b,c)] %
1		-78-r.t.	37	80
2		-78-r.t.	46	75
3		-78-0	59	80
4		-78-r.t.	42	69
5		-78-0	70	88
6		-78-r.t.	84	72
7		-78-r.t.	74	77

a) In the presence of 2-5 equiv. of HMPA. b) Isolated yield. c) Refluxed for 2 h with Bu_3SnH in toluene catalyzed by AIBN.

Application of this method leads to an efficient preparation of eldanolide (5)[2c,8)] by reduction of 4 with magnesium in methanol[9)] in 61% yield as shown in Scheme 2.



Scheme 2.

The present study develops a mild and convenient method for the regioselective formation of 3-methyl-4-substituted butenolides and has a wide potential utility in the synthesis of natural products.

References

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6) Although 4-phenylsulfenylbutenolide was also prepared and effected with prenyl bromide, the reaction afforded a mixture of 2-, 4-, 2,2-, and 2,4-prenylated butenolides in 34, 11, 15, and 11% isolated yields, respectively.
7) The structures of all the products were characterized by spectral data.
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