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Regioselective Synthesis of Trisubstituted 2,3-Dihydrofurans from Donor–Acceptor Cyclopropanes or from Reaction of the Corey Ylide with α-Sulfenyl-, α-Sulfinyl-, or α-Sulfonylenones

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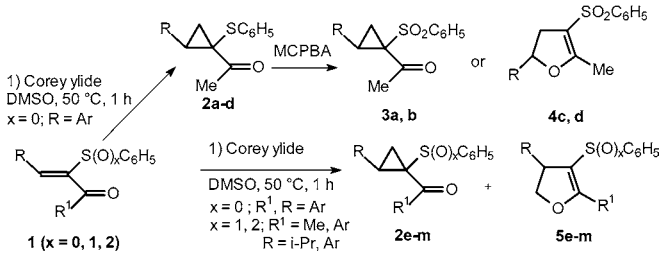
ABSTRACT



Regioselective synthesis of 2,4,5- or 3,4,5-trisubstituted 2,3-dihydrofurans has been realized by using donor–acceptor cyclopropanes or by a Corey ylide reaction with α-sulfenyl-, α-sulfinyl-, or α-sulfonylenones. The method allowed a straightforward synthesis of the natural product calyxolane B.

The dihydrofuran ring system is commonly found in the molecular skeleton of naturally occurring and biologically active derivatives.[1] Its importance has stimulated several synthetic approaches, among which the methods that entail ionic[2] or radical[3] reactions of 1,3-dicarbonyl compounds with appropriate olefins are particularly important. Very recently, methods have been reported on the basis of the ring enlargement of suitably substituted cyclopropanes[4,5] and by reaction of β-ketosulfides of benzothiazole[6] or β-keto polyfluoroalkanesulfones[7] with aldehydes. Moreover, dihydrofurans have been obtained by the reaction of ethyl (dimethylsulfuranylidene)acetate (EDSA) with enones containing two activating groups[8] and by treatment of cyclic or

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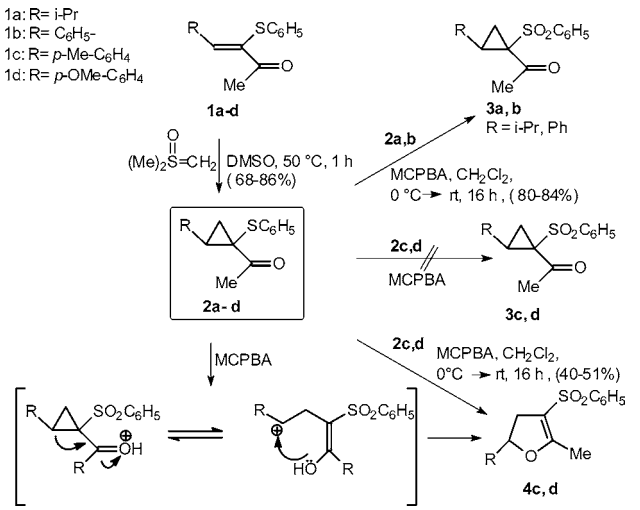
acyclic α-haloenones with carbon nucleophiles involving active methylene functions.[9] Following on from our involvement in the field of cyclopropanes, expecially their use in the synthesis of new heterocycles and of naturally occurring biologically active compounds,[10] we now report the synthesis of new 2,4,5-trisubstituted or 3,4,5-trisubstituted 2,3-dihydrofurans **4** and **5**, the regiochemistry of which depends on the nature of the groups R and R^1 or the oxidation state of the sulfur atom. (Schemes 1−3).

The present research started when we tried to prepare the cyclopropyl sulfones **3a**−**d** (Scheme 1) to be used as a

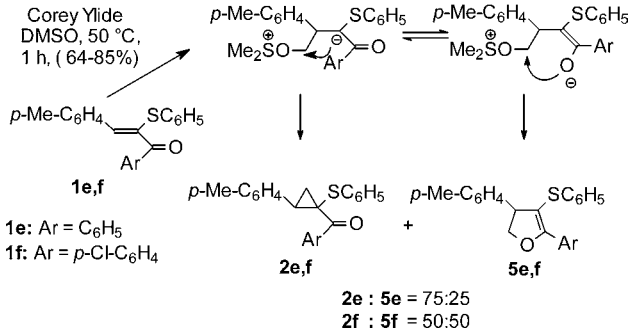
Scheme 1



starting material for the synthesis of alkylidenecyclopropanes according to our recently published approach.[11] We first prepared selectively (*cis* stereochemistry based on NOE experiments) the cyclopropylsulfides **2a**−**d** from the stereochemically defined Z alkenes **1a**−**d**. When we treated **2a**−**d** with *m*-CPBA in dichloromethane, the expected cyclopropyl sulfones **3a**,**b** were obtained from **2a**,**b**. The oxidation of the other two cyclopropylsulfides **2c**,**d** unexpectedly gave, probably through the proposed mechanism, the 2-aryl-4-phenylsulfonyl-5-methyl-2,3-dihydrofurans **4c**,**d** instead of the cyclopropyl sulfones **3c**,**d**. To our knowledge, apart from another reported case,[5a] derivatives **2c**,**d** represent the first example of donor−acceptor cyclopropanes[12] where the donor substituent is a substituted aromatic ring. It is clear that subtle electronic effects were at work in the syntheses of the dihydrofurans **4c**,**d**, as it appears that only aromatic rings (sufficiently electron-donating due to the presence of the groups Me, OMe) can assist successfully in the acid-induced cyclopropane ring fission.[13] Even though it is known that, during the synthesis of cyclopropanes, sometimes it is possible to isolate dihydrofuran derivatives,[5] as far as we know, the latter compounds have never been prepared from cyclopropanes under such mild conditions.

We next planned to extend the above reaction to the cyclopropylsulfides **2e** and **2f**. These, in principle would be obtainable from the cyclopropanation of alkenes **1e** and **1f**. The latter can easily be prepared as a 85:15 mixture of *Z*/*E* isomers by Knoevenagel condensation of phenylthioaryl ketones with aryl aldehydes. The expected cyclopropanes **2e** and **2f** were obtained together with the 3-substituted dihydrofurans **5e** and **5f**, very likely through the intermediate enolate, which can react either through the carbon or the oxygen atom (Scheme 2, Table 1).

Scheme 2



Probably the dihydrofurans **5e** and **5f** arise from ring closure through the oxygen atom, as a consequence of the

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increased enolate stability arising from the presence of an aromatic ketone. Support for this hypothesis comes from the increased dihydrofuran/cyclopropane ratio in the case of **1f** when a chlorine atom is present in the ketone aromatic ring.[15]

Additional support is furnished by the results (Table 1)

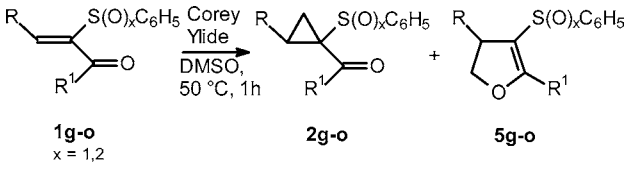
Table 1. Corey Ylide Reaction with the Enones **1e**−**o**

entry	**1e**−**o**[a]	R	R^1	*x*	**2 (2:5)**[14]	yield[b](%)
1	**1e**	*p*-Me-C_6H_4	C_6H_5	0	**2e** (75:25)	85
2	**1f**	*p*-Me-C_6H_4	*p*-Cl-C_6H_4	0	**2f** (50:50)	64
3	**1g**	C_6H_5	Me	1	**2g** (50:50)	95
4	**1h**	C_6H_5	Me	2	**2h**[c] (14:86)	75
5	**1i**	*i*-Pr	Me	2	**2i**[d] (30:70)	90
6	**1l**	*p*-Me-C_6H_4	C_6H_5	2	**2l** (0:100)	90
7	**1m**	C_6H_5	C_6H_5	1	**2m** (0:100)	71
8	**1n**	*p*-Me-C_6H_4	OMe	1	**2n** (100:0)	85
9	**1o**	*p*-Me-C_6H_4	OMe	2	**2o** (100:0)	63

[a] Alkenes **1g**,**h**,**n**,**o** were obtained, as a single geometric *E*- isomer, by reacting the appropriate α-phenylsulfoxide- or α-phenyl sulfone-carbonyl compound with the corresponding aldehyde. Alkenes **1i**,**l**,**m** were obtained by oxidation of the corresponding sulfides: **1i**, *Z*; **1l**, *Z*/*E* = 85:15; **1m**, *Z*/*E* = 75:25. [b] Isolated products. [c] Geometric isomer of **3b**. [d] Geometric isomer of **3a**.

obtained from the reaction of the Corey ylide with the derivatives **1g**−**m** (Scheme 3) where the stability of the intermediate enolate was increased by varying the R^1 group and the oxidation state of the sulfur atom. We found that the sulfoxide **1g** (entry 3) gave a 1:1 mixture of the dihydrofuran **5g** and the corresponding cyclopropane **2g**, present as a diastereoisomeric mixture of the two geometric isomers.

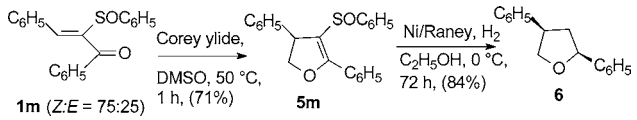
Scheme 3



As expected, increased quantities of the dihydrofuran **5h** were obtained in the case of the sulfone **1h** (entry 4), while **1i** gave only 30% of the dihydrofuran **5i** (entry 5). As a consequence of this result and the fact that the presence of an arylketo group, like in **1e** and **1f** (entries 1,2), led to the formation of moderate amounts of the dihydrofurans **5e** and **5f**, we expected that the contemporaneous presence of a sulfoxide or a sulfone group and an aromatic ketone could be ideal for obtaining high yields of dihydrofuran. This was confirmed using the derivatives **1l** and **1m** which led exclusively to **5l** and **5m** (entries 6 ,and7) with no detectable traces of the corresponding cyclopropanes **2l** and **2m**.

As an application of our synthetic approach, **5m** was treated with Ni/Raney to give, in a remarkably short and straightforward way, the natural product **6** calyxolane B (Scheme 4) recently isolated from a marine sponge,[16] whose

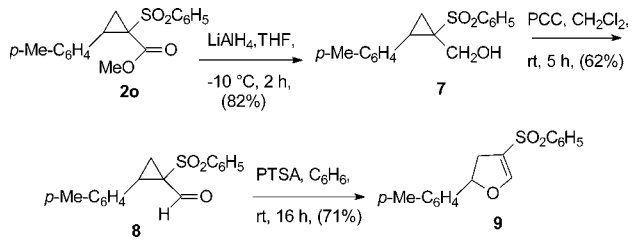
Scheme 4



chiral nonracemic synthesis has been previously reported.[17]

We have also investigated the behavior of the sulfoxide and sulfone ester derivatives **1n** and **1o** (Table 1, entries 8 and 9). When submitted to the action of the Corey ylide, no detectable amounts of dihydrofuran were found, and the sulfoxide ester **1n** led stereoselectively to the cyclopropane **2n** as a single geometric isomer, while the sulfone ester **1o** gave a 1:1 mixture of the two corresponding geometric isomers **2o**. While the sulfoxide and the sulfone esters **1n**,**o** were not suitable substituents for formation of the corresponding dihydrofurans, they could be used for the preparation of 2-substituted dihydrofurans of type **9** after executing the following reaction sequence of Scheme 5 for the

Scheme 5



cyclopropyl sulfone ester **2o**.[18] These types of dihydrofuran are particularly important as they have been previously

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(13) Carrying out the oxidation with hydrogen peroxide in refluxing methanol, in the presence of ammonium molybdate, **2c** gave the expected corresponding sulfone **3c** as a mixture of the two geometric isomers.

(14) A possible conversion of **2** into **5** was ruled out by re-subjecting the pure isolated **2c**,**e** to the same reaction conditions. The only isolated products were the 6-methyl-4-(4methylphenyl)-5-(phenylsulfanyl)-3,4-dihydro-2*H*-pyran and the 4-(4methylphenyl)-6-phenyl-5-(phenylsulfanyl)-3,4-dihydro-2*H*-pyran, probably through the cylization of the intermediate coming from nucleophilic ring opening of the cyclopropane ring by the Corey ylide.

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(18) The ester **2o** used for this reaction was a single *trans* geometric isomer obtained by oxidation of the corresponding sulfoxide **2n**.

reported[19] to be precursors of spiroketals by reaction with the γ-lactone.

In summary, we have found that the synthesis of 2,4,5-trisubstituted or 3,4,5-trisubstituted 2,3-dihydrofurans can be easily addressed and controlled by a careful choice of the substituents and by modulation of the oxidation state of sulfur in alkenes obtained by Knoevenagel condensation of alkyl- or arylthio ketones with aldehydes. The method has allowed an easy entry to the family of spiroketals and a very short synthesis of the natural derivative calyxolane B to be achieved. Studies on the chiral nonracemic version of these reactions are now in progress in our laboratory that will take advantage of the stereoselective cyclopropanation of phenylthioketones **1a**−**f** and of the sulfoxide **1n**.

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Supporting Information Available: Detailed descriptions of experimental procedures and characterization of compounds **2a**−**i**,**n**,**o**, **3a**,**b**, **4c**,**d**, **5e**−**m**, and **6**−**9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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