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SYNTHESIS AND APPLICATION OF A HIGHLY EFFICIENT, HOMOCHIRAL DIENOPHILE

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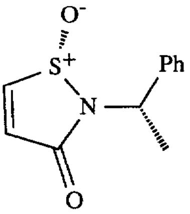
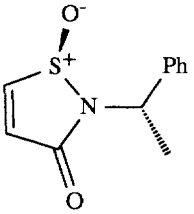
Summary: The synthesis and application of a highly efficient, homochiral dienophile is described. Cycloaddition of 2-((S)-1-phenylethyl)-1,2- thiazolin-3-on-(S)-1-oxide **1a** with a 1-azadiene and cyclopentadiene affords the corresponding cycloadducts in good yield and excellent diastereoselectivity.

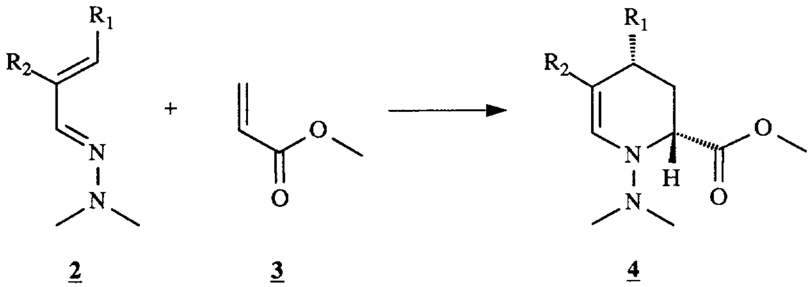
In the context with our ongoing work on [4+2]-cycloadditions with 1-dimethylamino-1-aza-butadienes [1][2] we wish to report the synthesis and application of the new homochiral dienophile **1**. The basic problem was the need for a diastereoselective [4+2]-cycloaddition of an acrylate-type dienophile **3** with the electron rich 1-azabutadienes **2** to give **4** (Scheme 1).



1a

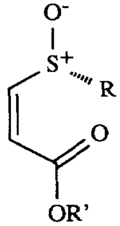


1b



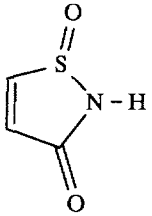
Scheme 1

Those dienophiles which need an additional *Lewis* acid for good diastereoselection (i.e. chelation controlled cycloaddition, see [3][4]) can not be used due to the sensitivity of compounds 2 towards acid [1]. We therefore concentrated our effords on reactive dienophiles containing a chiral auxiliary attached in α-position of the CC-double bond. Cycloadditions with homochiral 3-arylsulfinyl-propenoic acid esters 5 have been applied successfully in the enantio- and diastereoselective synthesis of biologically activ compounds [5][6]. But the synthesis of **cis-5a** and **cis-5b** described by



cis-5a **R=2-Py, R'=Menthyl**

cis-5b **R=p-Tolyl, R'=CH_3**



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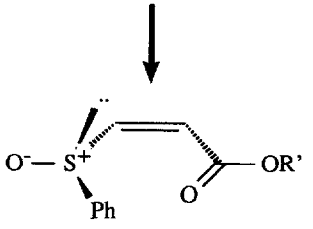
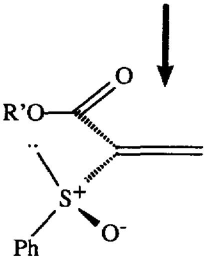
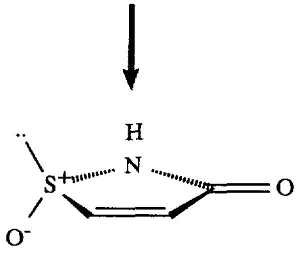
Koizumi [5] and Maignan [7] suffer from low yields. In addition Maignan [7] has shown that the major product in the synthesis, **trans-5b**, leads to poor diastereoselection in the reaction with cyclopentadiene. Nevertheless the proximity of the chiral inductor to the reaction center allows to accomplish cycloaddition reactions without *Lewis* acid catalysis. Thereafter the chiral auxiliary may be removed by reduction or elimination [8][6]. The steric course of the reaction is best explained by the attack of the diene from the less hindered face of the CC-double bond in either the **3-s-trans** or the **2-s-cis** vinyl-sulfoxide (i.e. syn to the sulfur lone pair). The discriminating effect in these cases is the steric difference between the aromatic ring and the sulfur lone pair.



3-s-trans



2-s-cis



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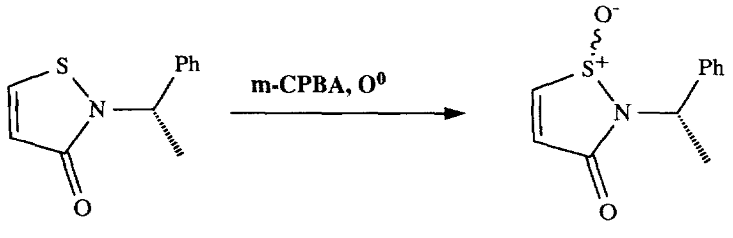
The requisite cis-configuration of the double bond may be affected by linking the sulfur- and the esterfunctionality; but by forming a cyclic compound like 6 the steric difference between the two sides of the CC-double bond is also changed. Steric differentiation occurs only between the sulfur lone pair and the sulfinyl oxygen. In 1978 Weiler and Brennan [9] have shown that racemic 4-isothiazolin-3-on-1-oxide 6 cycloadds cleanly to cyclopentadiene and 2,3-dimethyl- butadiene. The products obtained from 6 in very good yield must be diastereochemically pure according to their reported melting points and NMR spectra. This unnoticed finding of Weiler and Brennan [9] led us to the synthesis of the (S)-1-phenylethyl-substituted derivative 7 based on the procedure of Lewis and coworkers [10] (3 steps, overall yield 76%).



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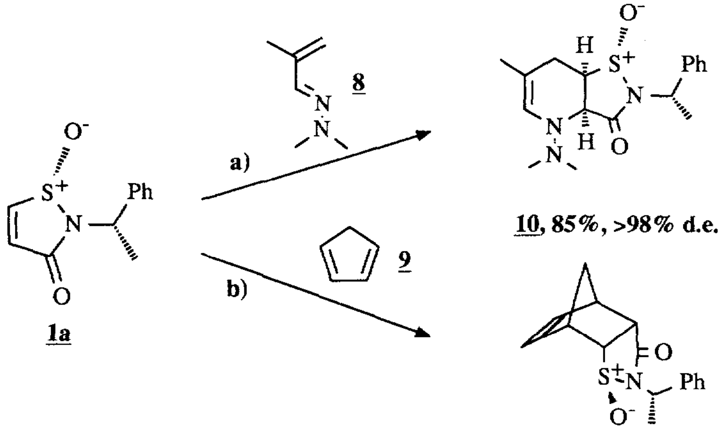
1a, 1b (2.2 : 1)

Oxidation of 7 in 82% yield afforded a 2.2:1-mixture of the easily separable diastereomers 1a, 1b [11]. The major isomer served as starting material for the following Diels-Alder reactions (Scheme 2)[12]:



1a

10, 85%, >98% d.e.

11, 94%, 96% d.e.

a) 1.1 equiv. 8, 70^0, 6 h b) 10 equiv. 9, -20^0, 15 min.

Scheme 2

The results obtained under the conditions indicated allow the following conclusions:

1. *The steric discrimination occurs between the oxygen and the lone pair on the sulfur atom and is sufficient for excellent diastereoselectivity with dienes like cyclopentadiene.* The reaction conditions indicated in scheme 2 (b)) demonstrate the great reactivity of 1. Furan and 2-methoxyfuran lead to comparable yields and selectivities (see also [5][8]), whereas the cycloaddition with 2,3-dimethylbutadiene occurs in 89% yield with a diastereoselectivity 74% at 80^0 [13].

2. *An additional electronic effect is observed in the reaction with electron-rich dienes like the 1-azadiene [14]. The electron rich C(4)-atom of the diene attacks the dienophile from the opposite side of the negative end of the S-O-dipole.* The result is preserved selectivity even at higher temperatures [15].

3. *The reaction with the azadienes is regiospecific. The acrylate-substructure is controlling the regiochemistry whereas the sulfinyl-function activates the CC-double by its inductive effect only.*

Structures **10** and **11** have been verified by X-ray analysis. In order to check whether the chiral auxiliary (the 1-phenylethyl moiety) has an influence on the induction in the cycloaddition we performed the cycloaddition with the doubly oxidized sulfur compound **7** and the maleic acid imide from 1-phenylethylamine with the 1-azadiene **8**. In both cases a 1:1 mixture of the possible diastereomers was isolated; the unoxidized compound **7** does not undergo cycloaddition reactions. This means that the chiral auxiliary is to far away from the reaction center to become effective. The sulfur-containing functionality is removed by treatment with PhMgBr in THF (formation of a phenylsulfoxide by S-N-bond cleavage) and subsequent reduction with Raney-nickel. The results reported here clearly demonstrate that the homochiral isothiazolinons **1a** and **1b** are readily available building blocks and that reactions of the CC-double bond are controlled solely by the steric and electronic influence of the sulfinyl-oxygen. Further transformations with **1a**, **1b** and similar systems are under current investigation.

Literature, remarks

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[11] Separated by column chromatography (silica gel, hexane/ethyl acetate 1:1, ΔRf= 0.075): **1a**: m.p. 68-70^0, $[\alpha]_D^{20}$= -275.2^0 (c= 1, MeOH), **5b**: m.p. 97-100^0, $[\alpha]_D^{20}$= -54.3^0 (c= 1, MeOH).

[12] **10**: m.p. 106-8^0, $[\alpha]_D^{20}$= -190.9^0 (c= 0.9, MeOH), **11**: m.p. 64-6^0, $[\alpha]_D^{20}$= +125.2^0 (c= 1, MeOH).

[13] A similar effect was recently described by Overman and coworker for a sulfoxide containing diene: M.J. Fisher and L. Overman, J. Org. Chem., **1988**, *53*, 2630.

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[15] Reaction of **8** with Koizumi's **2a** under the same conditions led mostly to decomposition of **2a**.

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