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Phenylsulfonyl-substituted 5-Alkoxy-2(5H)-furanones; a New Class of Highly Reactive Chiral Dienophiles.

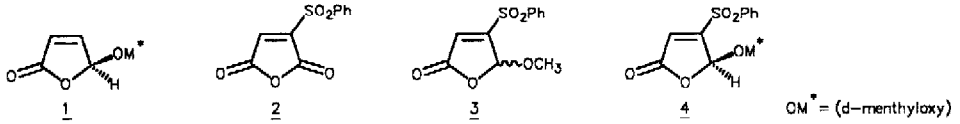
Johannes C. de Jong, Keimpe J. van den Berg, Albert M. van Leusen and Ben L. Feringa*

Department of Organic Chemistry, University of Groningen,
Nijenborgh 16, 9747 AG Groningen, The Netherlands.

Abstract: **The synthesis of enantiomerically pure (5S)-5-(*d*-menthyloxy)-4-(phenylsulfonyl)-2(5H)-furanone (4) and the application of 4 as efficient dienophile in Diels-Alder reactions under mild conditions with enantioselectivities >98% e.e. are described.**

The chiral butenolide 5-(d-menthyloxy)-2(5H)-furanone[1] (1) is a versatile dienophile in enantioselective Diels-Alder reactions[2] and other (cyclo)additions.[3,4] Due to π-face shielding exerted by the γ-alkoxy substituent in 1 excellent stereocontrol is found in thermal (non-catalyzed) cycloadditions as has been demonstrated in the synthesis of enantiomerically pure cyclohexane-, decaline- and indane-derivatives.[2,3] Furthermore, the use of d- or l-menthol as chiral auxiliaries allows ready access to both enantiomers of the addition products of 1. Unfortunately, Diels-Alder reactions of 1 with less reactive dienes require rather long reaction times or high temperatures, whereas trapping reactions of extremely reactive dienes, such as o-xylylene, are to slow to be synthetically useful. Inspired by a recent report of Hall and coworkers[5] on α-(phenylsulfonyl)maleic anhydride (2) as a "super-electrophile", we designed 5-alkoxy-4-(phenylsulfonyl)-2(5H)-furanones 3 and 4 as new highly reactive chiral dienophiles.

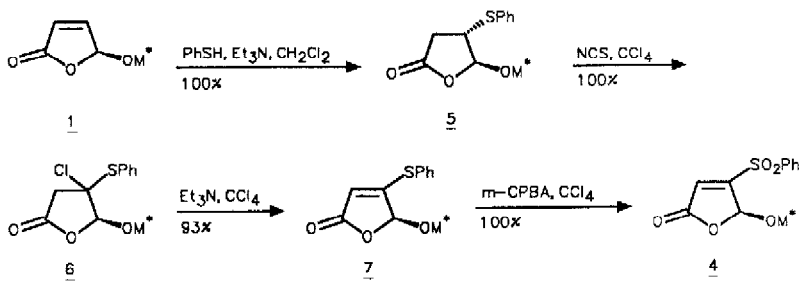
For the synthesis of racemic 3 a four step sequence (i. C_6H_5SH, Et_3N, CH_2Cl_2; ii. NCS, CCl_4; iii. 135 °C, 12 mm Hg; iv. m-CPBA, CCl_4, overall yield 78%), corresponding to the route described for 2, was followed starting with 5-methoxy-2(5H)-furanone.[6]



1 2 3 4

For the preparation of (5S)-5-(d-menthyloxy)-4-(phenylsulfonyl)-2(5H)-furanone (4 93% overall yield), using enantiomerically pure (5S)-5-(d-menthyloxy)-2(5H)-furanone (1) as starting material, a modified sequence was followed in order to prevent epimerization (Scheme 1).

Scheme 1



1 5 6 7 4

Thiophenol addition to 1, which is catalyzed by triethylamine,[7] afforded sulfide 5 as a single diastereoisomer in quantitative yield. The small coupling constant for the acetal hydrogen (J = 1.1 Hz) indicates that the menthyloxy group and the phenylthio group are trans oriented, which is in accordance with the expected addition of thiophenol to the less hindered side of furanone 1.[7] Reaction of sulfide 5 with N-chlorosuccinimide in refluxing carbon tetrachloride afforded, according to ^{1}H NMR, compound 6 in quantitative yield. Attempts to isolate 6 were frustrated by partial elimination of HCl. The elimination of HCl was achieved by prolonged refluxing of 6 in carbon tetrachloride to provide 7 in 85% yield, after crystallization from *n*-hexane. The time needed for complete elimination of HCl appeared to be highly variable, i.e. from several hours to 6 days. Elimination at more elevated temperatures or *via* distillation under high vacuum, as was used for the racemic 5-methoxy analog 3, is less useful since under these conditions considerable epimerization occurs at the acetal stereogenic center in 7. Epimerization is suppressed by continuously bubbling air through the refluxing solution, which results in fast removal of HCl. Although in most cases the epimerization cannot be suppressed completely, it can be reduced to 10% or less. The undesired epimer of 7 can readily be removed by a single crystallization from *n*-hexane or petroleum-ether (bp 40-60 °C).

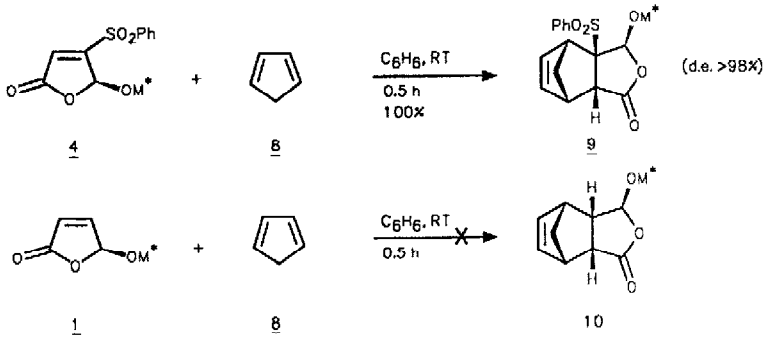
Partial epimerization of 7 under above conditions, and the variable reaction times, led us to search for a more efficient approach. Base induced elimination of HCl is an obvious choice and triethyl-amine appeared to be very suitable for this purpose. When chlorination of 5 with N-chloro-succinimide (NCS) was followed immediately by treatment of adduct 6 with Et_3N, the unsaturated sulfide 7 was isolated in 93% yield without epimerization.

In the final step sulfide 7 was oxidized quantitatively using 2 eq of *m*-chloroperbenzoic acid (*m*-CPBA) in CCl_4. To prevent epimerization during the oxidation of 7 the reaction was performed at 0 °C, using reaction times as short as possible. Progresss of the reaction was monitored by ^{1}H NMR on the basis of the shift of the acetal hydrogen from δ 5.34 in 7 to δ 6.28 in 4. At higher reaction temperatures (>20 °C) and extended reaction times (18 h) substantial epimerization of 4 is observed (ultimate ratio of the epimers is 60:40). Epimer formation is readily deduced from ^{1}H NMR spectra as the acetal hydrogen of the epimer of sulfone 4 has an absorption at 6.19 ppm.[8]

Enantiomerically pure 4 ($[\alpha]^{20}_D$ +123.4° (c 1, CH_2Cl_2)) is a highly viscous oil which is stable towards epimerization at ambient temperatures in the absence of acids.[9]

Next, the reactivity of 4-phenylsulfonyl substituted furanones 4 was studied. Both (5S)-5-(*d*-menthyloxy)-2(5H)-furanone (1) and (5S)-5-(*d*-menthyloxy)-4-(phenylsulfonyl)-2(5H)-furanone (4) were reacted with cyclopentadiene (8) for 0.5 h at RT in benzene (Scheme 2).

Scheme 2

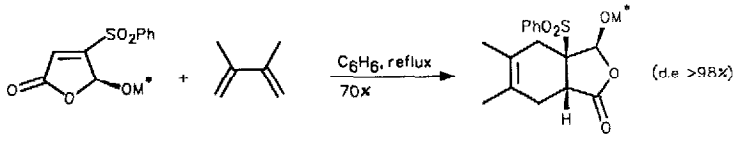


With the sulfone-substituted dienophile 4 complete conversion was observed, whereas in the case of 1 the starting materials were recovered. The cycloaddition product 9 was obtained in 92% yield after column chromatography as a single enantiomer.[9,10] Compound 9 most likely is the *endo*-adduct in accordance with the results obtained by Hall *et al.*[5] with cyclopentadiene and 2. Our experiments clearly demonstrate that the introduction of a sulfonyl substituent enhances the furanone reactivity in

Diels-Alder reactions considerably. Unfavorable steric effects of the phenylsulfonyl substituent in furanone 4 are clearly overruled by C,C double bond activation caused by its electron withdrawing properties.

The cycloaddition reaction of 4 with 2,3-dimethyl-1,3-butadiene (11) was performed in refluxing benzene for 20 h, although a shorter reaction time might be sufficient for a complete conversion (Scheme 3). After purification by flash column chromatography adduct 12 was obtained as a single diastereoisomer in 70% yield.[9,10] On the basis of NMR data[9] and in analogy to the addition of 2,3-dimethyl-1,3-butadiene to 1,[2] it is deduced that also in the case of furanone 4, the addition of the diene is taking place from the less hindered side of the furanone ring, i.e. *trans* relative to the menthyloxy substituent.

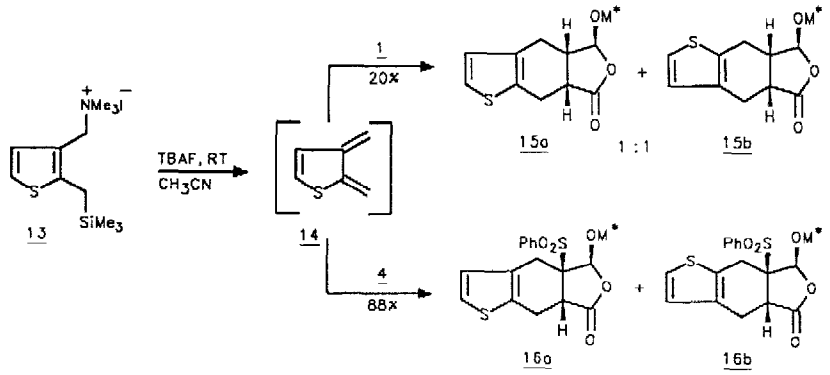
Scheme 3



4 11 12

Further support for the strongly increased reactivity of 4 compared to 1 is found in trapping experiments of the highly reactive *in situ* prepared diene 2,3-dimethylene-2,3-dihydrothiophene (14, Scheme 4). Formation of this heterocyclic analog of *o*-xylylene was recently developed by some of us and by others.[11] The cycloaddition of 14, in situ prepared from precursor 13, to furanones 1 and 4 was examined.

Scheme 4



13 14 15a 15b 16a 16b

Both reactions were performed at room temperature by slow addition of tetrabutylammonium fluoride (TBAF), dissolved in acetonitrile, to a mixture of precursor 13 and furanone 1 or 4. Like above, a dramatic difference was observed between sulfone substituted furanones 4 and 1 in the cycloaddition reaction with 2,3-dimethylene-2,3-dihydrothiophene. Reaction of diene 14 with furanone 1 (1.0 equivalent) predominantly gave dimeric products of 14,[11] in addition to unreacted furanone 1 and about 20% (NMR yield) of the cycloadducts 15a and 15b. However, formation of diene 14 in the presence of 1.0 equivalent of 4 resulted in the cycloadducts 16a and 16b in 88% isolated yield as a mixture of regioisomers in a 1:1 ratio.[9,10]

It is evident from these experiments that 14 is more efficient trapped by 4 and as a consequence dimerization of 14 can be suppressed successfully.

In conclusion a new highly reactive chiral dienophile has been developed for diastereoselective Diels-Alder reactions under mild conditions. Furthermore, the reagent is effective in trapping reactions of reactive dienes that tend to dimerize. It should be noted that the absolute stereocontrol in the cycloadditions is not affected by the introduction of the phenylsulfonyl substituent.

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8. The C_5-epimer of 4 was obtained as a white crystalline compound: mp 84.4-85.0 °C; $[\alpha]^{20}_D$ +36.7° (c 1.0, CH_2Cl_2).
9. All compounds showed IR, ^1H NMR, ^{13}C NMR and HRMS data in accordance with their structure. Satisfactory elemental analysis were obtained for 1, 4, 5, 7, 9, 12 and 16. The assignment of the bi- and tricyclic structures 9, 12, and 16 is based on 2D-^1H NMR COSY and NOESY spectroscopy using standard pulse sequences.
   The spectroscopic data for 4 are as follows: ^1H NMR ($CDCl_3$, 300 MHz): δ 0.55-0.96 (m, 13H), 1.28 (m, 1H), 1.56 (m, 3H), 2.13 (m, 1H), 3.48 (dt, J = 4.2, 10.1 Hz, 1H), 6.22 (d, J = 0.9 Hz, 1H), 6.72 (d, J = 0.9 Hz, 1H), 7.51 (m, 2H), 7.64 (m, 1H), 7.97 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 15.48 (q), 20.34 (q), 21.99 (q), 22.94 (t), 24.92 (d), 31.13 (d), 33.91 (t), 38.92 (t), 47.46 (d), 79.19 (d), 97.65 (d), 128.76 (d), 128.89 (d), 128.98 (d), 134.58 (d), 137.69 (s), 161.92 (s), 166.10 (s).
10. All diastereomeric ratios were defined by 300 MHz ^1H NMR spectroscopy. The absolute configuration of the products as shown in Scheme 1 is based on the 5S-configuration of 1, see ref 4.
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