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Synthesis of menthyl sulfinate and sulfoxides on solid phase

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Abstract—*p*-Hydroxyphenyl menthyl sulfinate was readily linked to Wang resin. The resulting sulfinate reacted with Grignard reagents and potassium or lithium enolates to give the corresponding sulfoxides or β-ketosulfoxides allowing a study of the chemistry of sulfoxides for solid phase synthesis. © 2001 Elsevier Science Ltd. All rights reserved.

In the last decade solid phase methodology has been considerably developed due to the increasing interest in combinatorial and parallel synthesis.[1] In order to access new target molecules, chemists must adapt reactions to the solid phase and, therefore, define new linkers which should be chemically stable to many experimental conditions. The next challenge will be the adaptation to asymmetric synthesis.

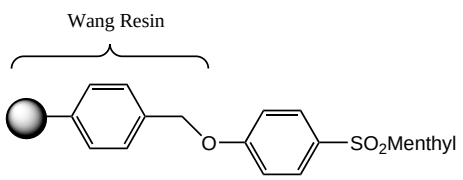
The sulfinyl group is an important and useful tool in numerous asymmetric transformations. Besides the high configurational stability of the sulfinyl group,[2] the existence of several efficient methods to obtain chiral sulfoxides[3] as well as their synthetic versatility has led to numerous applications of chiral sulfinyl derivatives to the synthesis of enantiomerically enriched molecules over the last three decades.[3,4]

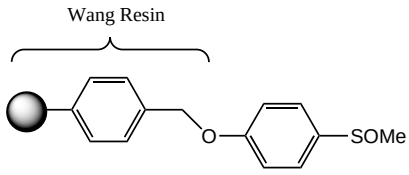
Moreover, the facility of cleaving the sulfoxide moiety from the molecule (desulphurisation, Pummerer reaction or *syn*-elimination),[5] in conditions compatible with many chemical reactions, allowed us to consider this functionality as a very promising new linker.

We have recently reported the synthesis of racemic β-keto-*p*-alkoxyphenylsulfoxide on a Wang resin by oxidation of the corresponding β-ketosulfide.[6] We report in this paper the synthesis of menthyl *p*-tolylsulfinate on a Wang resin and its application for the formation of β-ketosulfoxides on solid support.

Among the different ways of obtaining sulfoxides, the most widely used approaches are based on nucleophilic substitution on chiral sulphur derivatives[7] such as menthyl *p*-toluenesulfinate. The literature also describes *p*-tolyl-methyl sulfoxide as an important synthon for numerous asymmetric transformations. In order to develop sulfoxide chemistry on solid support, we chose to prepare a Wang resin bearing a menthyl *p*-substituted-benzenesulfinate or a methyl sulfoxide.[8] The link between the sulfinate or the sulfoxide moiety and the solid support can be a benzyl ether group, easily cleaved in acidic conditions[9] to permit monitoring of each step of the synthesis. Therefore, the menthyl *p*-hydroxyphenylsulfinate **4** and the *p*-hydroxyphenyl-methyl sulfoxide **6** were selected to prepare the supported reagents **A** and **B** (Scheme 1).

The synthesis of these two compounds started from sulfinyl chloride **2** obtained by chlorination of the corresponding sodium sulfonate **1** (Scheme 2). The reduc-





B

Scheme 1.

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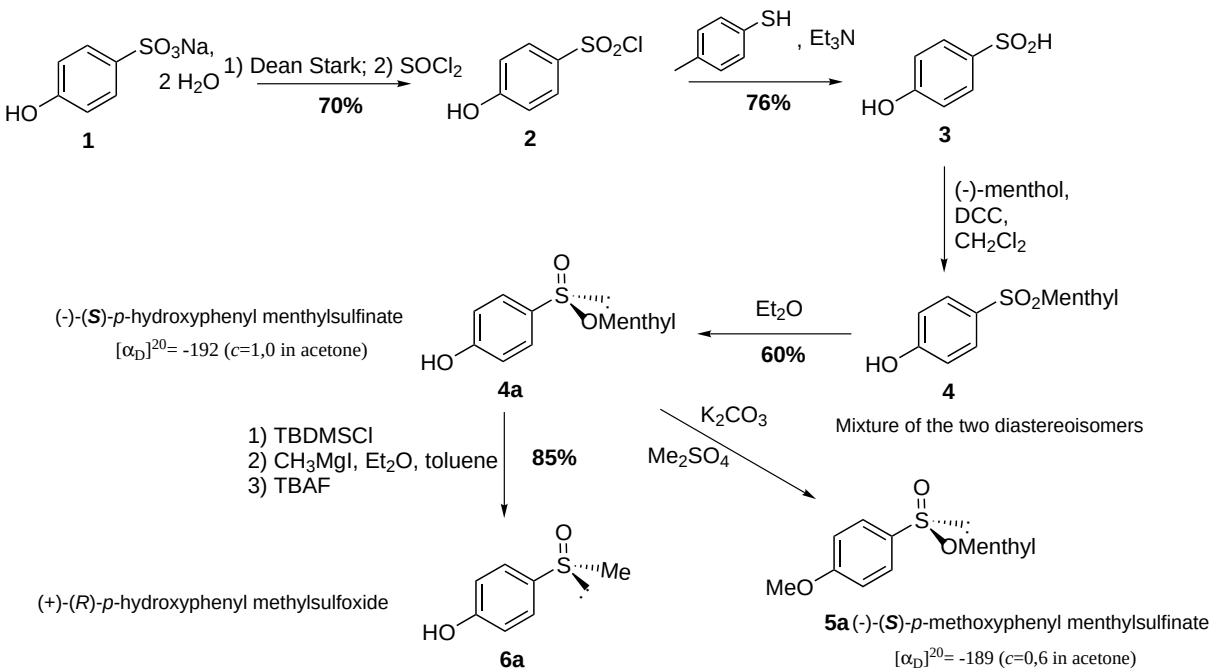
tion of **2** gave the sulfinic acid **3**, which was esterified with (−)-menthol to a mixture of the two diastereoisomers of the menthyl *p*-hydroxyphenylsulfinate **4**. Only one of the two diastereoisomers **4** was isolated by crystallisation in ether in 60% yield. The absolute configuration of this compound **4a** was determined by chemical correlation with the *p*-methoxy derivative **5a** described in the literature.[10] The corresponding (*p*-hydroxyphenyl)methylsulfoxide **6a** was obtained from the *p*-*t*-butyldimethylsilyloxy derivative with Grignard reagents[11,3d] with complete inversion of configuration at sulphur.

The menthylsulfinate **4** (diastereoisomeric mixture) was attached to the resin via a Mitsunobu reaction[12] (see Scheme 3) as well as the racemic sulfoxide **6**. We then tried to adapt the sulfoxide chemistry to the solid support. We focused our attention on the two main reactions usually used in our laboratory to get a wide variety of sulfoxides: the action of the methylsulfoxide anion on electrophiles and the nucleophilic substitution of menthylsulfinate with enolates or Grignard reagents (Scheme 4).

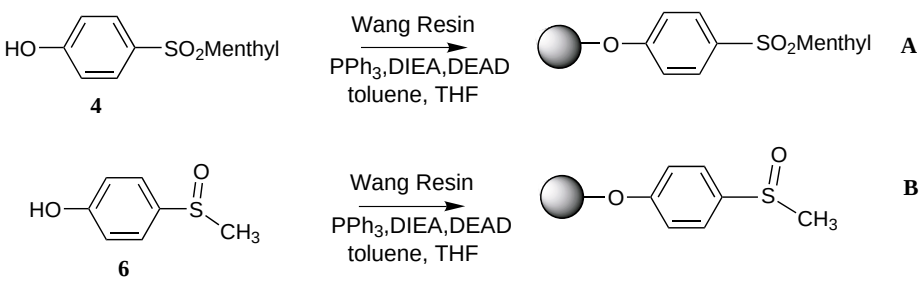
The first reaction includes the methodology described by Corey,[13] the reaction of α-sulfinyl anions with esters to form β-ketosulfoxides. This method has been widely used and developed, and remains an efficient way to prepare this compound in enantiomerically pure form.

After a large number of experiments it appeared to us that the formation and the reactivity of the anion of the methyl sulfoxide **B**, even versus the most reactive electrophiles,[14] cannot be observed on solid support. The *p*-hydroxyphenylmethyl sulfoxide **6** is quantitatively recovered after treatment of the resin with TFA.[15]

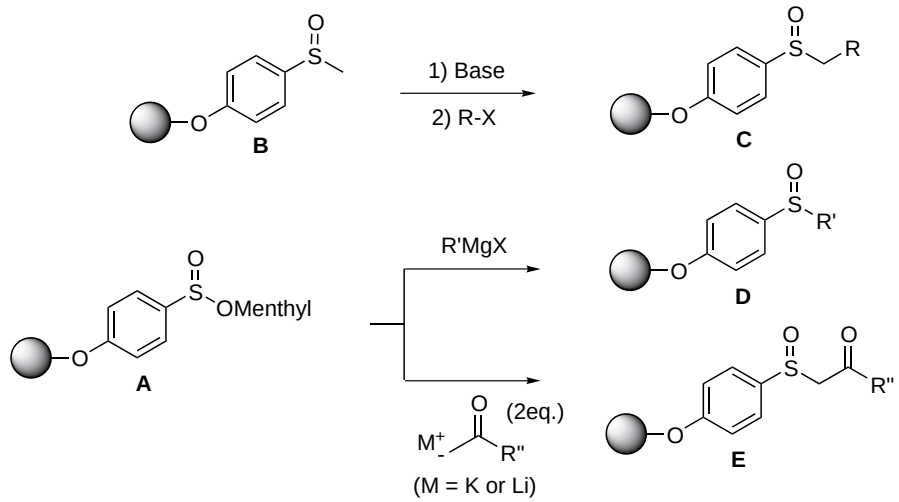
Having explored a wide range of variations around this reaction (by changing the base, the support, the reaction conditions, and the electrophilic species for instance), we finally concluded that these difficulties were probably due to a lack of stability of the anion on the solid support. This hypothesis was confirmed later by the experiment described in Scheme 5, which shows that a stabilised sulfinyl anion reacts smoothly with iodomethane.



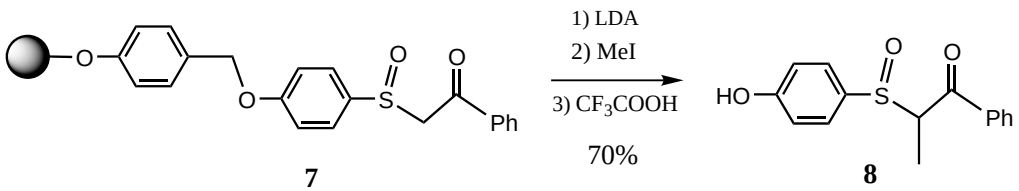
Scheme 2.



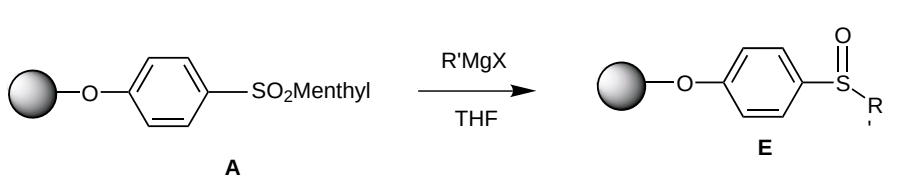
Scheme 3.



Scheme 4.



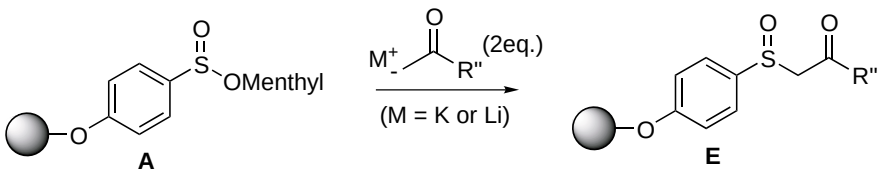
Scheme 5.



R'	Yield
Me	q.
Et	q.
Ph	q.
Bz	75%

q. : quantitative

Scheme 6.



R"	Yield
Ph	67%
-(CH2)2Ph	52%
-CH2C(O)O(CH3)3	40%

Scheme 7.

In sharp contrast, the results concerning the reaction of the menthyl sulfinate linked to the resin **A** with a Grignard reagent were much more encouraging. We have been able to generalise this reaction and to use it in a small-scale parallel synthesis. The first step was to adapt the reaction to the quantitative formation of methyl sulfoxide on solid support and to determine the most promising reaction conditions for a generalisation to a wide variety of reactive species. This was achieved using the conditions described in Scheme 6. We obtained quantitative yields for the most common species.

In order to obtain β-ketosulfoxide from menthyl sulfinate, we studied the action of enolates on the menthyl sulfinate linker. The promising first results concerning this reaction are presented in Scheme 7. All these results were established by cleavage of the resulting sulfoxide with TFA.[15]

In conclusion, these results describe a new type of linker, the alkoxy-phenyl-sulfinyl group and are complementary to those of our previous report.[6] We have shown that sulfoxides and β-ketosulfoxides can be obtained from menthyl sulfinate linked to a Wang resin. This opens the route to the rich chemistry of sulfoxides to combinatorial synthesis on solid support including the Pummerer rearrangement[6] to release the final product. In addition, these data also open the route to optically active sulfoxides on solid support.

Acknowledgements

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