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Wang *p*-alkoxyphenylsulfoxide as a new linker and Pummerer cleavage strategy in solid-phase preparation of 1,2-diols

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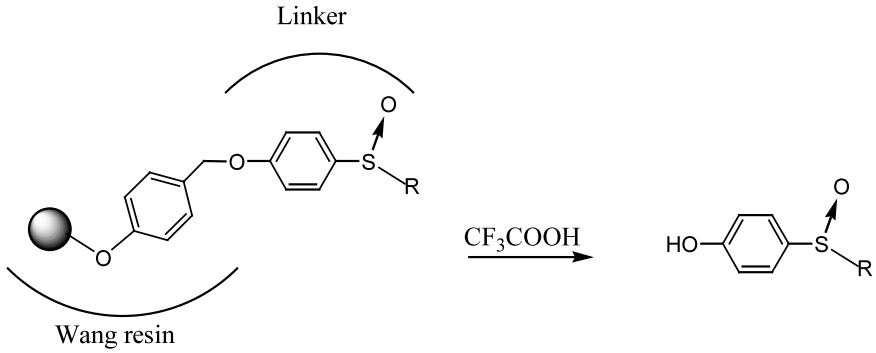
Abstract—*para*-Hydroxyphenyl-β-ketosulfide was attached to a Wang resin and oxidised to the corresponding sulfoxide with a *N*-protonated oxaziridinium trifluoroacetate. Reduction of the β-ketosulfoxides to the corresponding β-hydroxysulfoxides with Dibal-H was shown to be as stereoselective as in solution. Finally it was shown that the Pummerer reaction could be carried out on solid-phase and was a very efficient way to obtain diols that validates the sulfoxide group as a versatile linker for solid-phase chemistry.

There has been enormous interest in combinatorial and parallel synthesis in the last decade using solid-phase methodology.[1] A crucial key fragment in planning a solid-phase synthetic strategy is the linker group which connects the target molecule to the resin matrix.[2] It must be stable to the diverse reaction conditions on solid-phase and allow facile attachment, functionalisation and release of the target. We have focused our attention on sulfoxide functionality because, surprisingly, it has not been used as a linker so far. It presents several advantages, including a variety of possible cleavages and its use in an enantiomerically pure form allowing asymmetric parallel synthesis. Sulfoxide linker should allow the preparation of different products depending on the cleavage conditions (desulfurization, Pummerer reaction or *syn*-elimination).[3]

We decided to adapt the well-known β-ketosulfoxide chemistry[4] to the solid support in order to develop an efficient synthetic route to hydroxy-derivatives involving a new linker with sulfoxide moiety and Pummerer type cleavage of the target.

In this letter, we present the preliminary results of this strategy exemplified by racemic compounds.

In order to easily monitor the different reactions, we selected a Wang resin[5] and a sulfoxide linker which contains an alkoxy-phenyl group attached to the poly-



Scheme 1.

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mer which allows a facile cleavage under acidic conditions[6] (Scheme 1).

We planned to prepare the supported β-ketosulfoxides **1** by oxidation of the corresponding β-ketosulfide Wang derivatives **2** obtained from the corresponding *para*-hydroxyphenyl-β-ketosulfides **3** and a modified Wang resin.

The *para*-hydroxyphenyl-β-ketosulfide derivatives **3** were easily prepared from commercially available 4-mercaptophenol **4** and the corresponding α-bromo-ketones **5**. They were quantitatively attached to the polymer using trichloroacetimidate-activated Wang resin (Scheme 2).[7] The reaction was monitored by IR-analysis of a bead.[14]

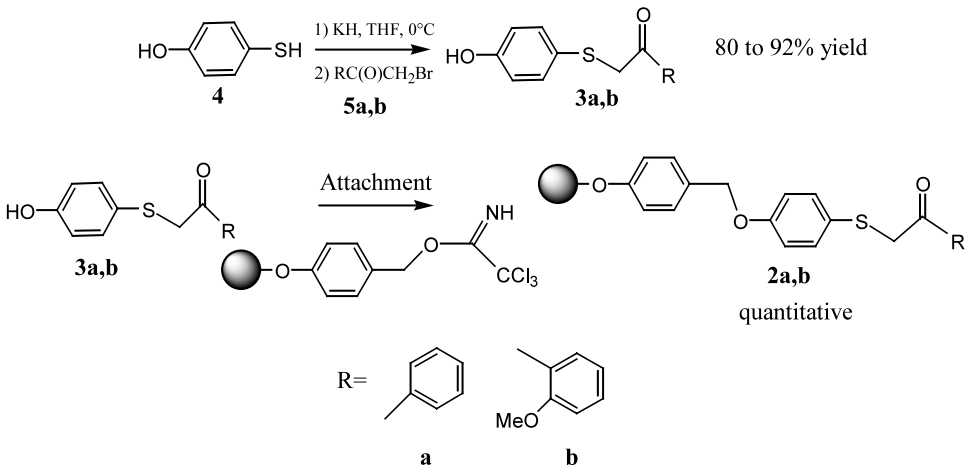
Next, we studied the selective oxidation of the sulfides **2** to the corresponding sulfoxides **1** and found that classical oxygen transfer reagents (*m*CPBA,[8] ozone[9]) were inefficient or non-selective. Finally, we carried out this oxidation using the very chemoselective acid-catalysed oxaziridine oxygen transfer methodology.[10]

Using 5 equiv. of oxaziridine **6**, easily prepared in 2 steps from 1,2,3,4-tetrahydroisoquinoline, and 5.5 equiv. of trifluoroacetic acid in dichloromethane, all sulphide derivatives **2** were quantitatively transformed into the corresponding sulfoxides **1** (Scheme 3). The efficiency of this reaction was determined by monitoring the ratio imine/oxaziridine+nitrone in the reaction mixture (see Ref. 11).

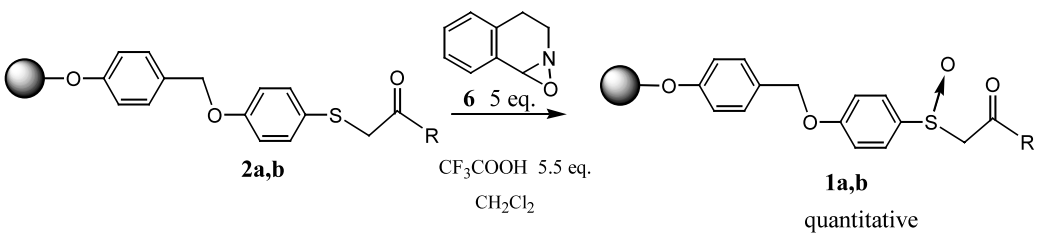
With polymer-bound β-ketosulfoxides **1** in hand, we studied the reduction of the carbonyl functionality to the corresponding alcohols using two methodologies. The first one using an excess of $NaBH_4$ in THF, which is not stereoselective in solution,[12] gives after acetic acid treatment and cleavage with CH_2Cl_2/TFA the four diastereomers **7** in an equimolar ratio. The second one, using 5 equiv. of Dibal-H in THF at −78°C, which is highly diastereoselective in solution,[13] gives as expected, after acetic acid treatment and cleavage, quantitatively only two diastereomers with a de up to 95% (Scheme 4). Attempts to obtain the two other diastereomers by addition of a chelating Lewis acid (ZnX_2)[13] failed and gave a mixture of the four diastereomers. The very low solubility of ZnX_2 in THF and the fact that the substrate was on a polymeric matrix probably explains this last result.

The reduction was monitored by ATR (attenuated transmitted reflectance) IR spectroscopy of a bead[14] extracted from the reaction mixture; this showed without any ambiguity the decrease of the intensity of the CO-stretch at 1690 cm^{-1} and the concomitant appearance of the OH-stretch at 3600 cm^{-1}. The diastereoselectivity was assigned from the ^1H NMR spectra of the alcohols **7** and their correlation with the data of the corresponding well-known β-hydroxy-*p*-tolyl-sulfoxides[13] based on the non-equivalence between the methylene protons α to the sulfoxide.

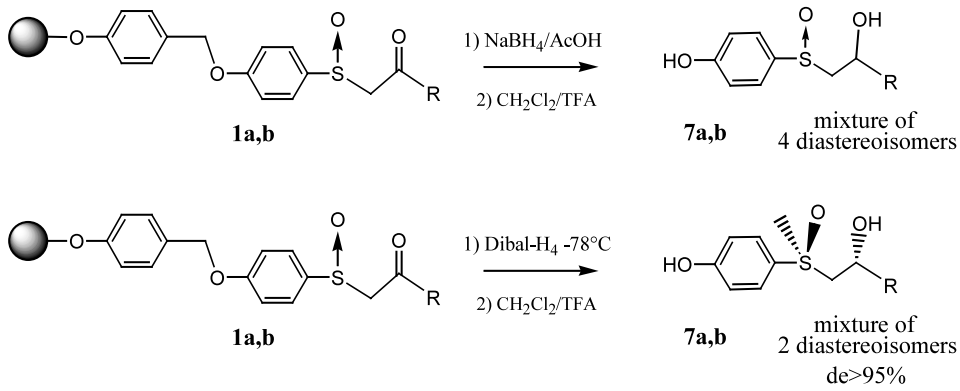
Finally, after protection of the alcohol by a *tert*-butyldimethylsilyl group under standard conditions,[15] we examined conditions for releasing the target from



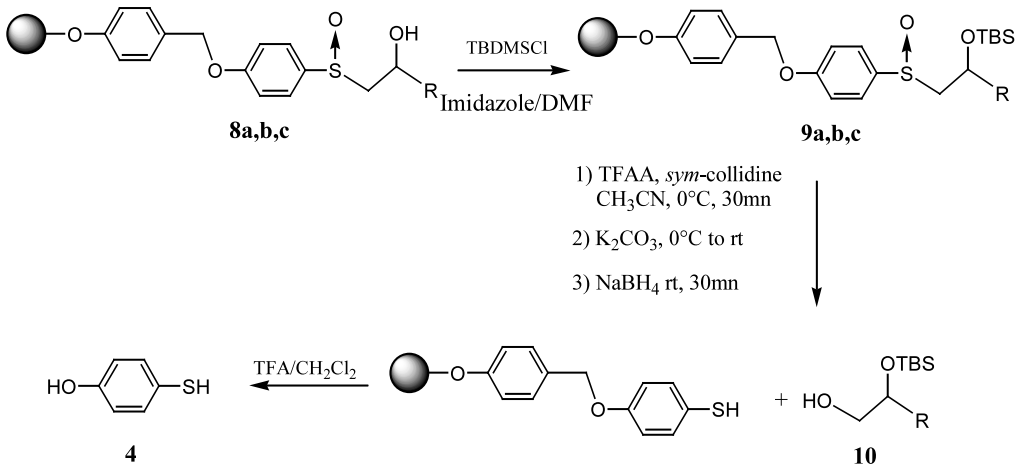
Scheme 2.



Scheme 3.



Scheme 4.



Scheme 5.

the linker and found that Pummerer rearrangement using the mild conditions described by Bravo[16] gave the corresponding monoprotected diols **10** almost quantitatively (Scheme 5). The treatment of the resulting product with TFA/CH_2Cl_2 provided the 4-mercaptophenol **4** as a single product.

In conclusion we have demonstrated that an alkoxyphenyl-sulfinyl type linker is suitable for solid-phase chemistry and that this system is efficient for the diastereoselective preparation of hydroxy derivatives involving reactions easily followed by ATR-IR spectroscopy of a bead.

Acknowledgements

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