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Stereoselective Synthesis of 1,4-Dienes by Chelation-controlled Reduction of Benzothiazole β-Oxosulfides

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Abstract: Allylated β-oxosulfides of benzothiazole can replace β-oxophosphane oxides to provide a stereospecific alkene synthesis. These sulfides, by reduction with sodium borohydride afford predominantly *syn* β-hydroxy sulfides. DIBAL reduction in the presence of magnesium bromide improves the *syn* stereomer formation. Base treatment of these β-hydroxy sulfides affords (Z)-allyl thiiranes which are converted into (E, Z)-dienes. © 1998 Elsevier Science Ltd. All rights reserved.

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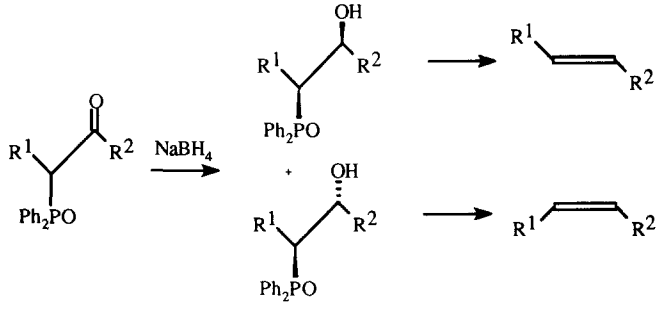
Reduction of β-oxophosphane oxides affords a mixture of *syn* and *anti* β-hydroxy phosphane oxides whose reaction with bases, called the Horner-Wittig elimination, allows the synthesis of E- and Z-alkenes respectively[1] (scheme1). The simplicity of this alkene synthesis has gained popularity and numerous synthetic variants were introduced to control the stereochemistry of the reduction process. It was found[2-4] that chelation assisted reduction was *anti*-selective whereas the non chelated one gave a predominance of the *syn* product.[5] In most cases, however, to obtain pure E- or Z-alkenes it was necessary to carry out a preliminary separation of stereoisomeric alcohols.

Scheme 1



During a study on the palladium catalysed synthesis of α,α-diallylated ketones we have found[6] that allylated β-ketosulfides of benzothiazole, upon reduction to β-hydroxy sulfides, may be transformed into episulfides and 2-hydroxybenzothiazole (scheme 2) thus allowing the exchange, on the heterocyclic nucleus of a S- with an O-functionality. Since it is known[7,8] that episulfides can be converted stereospecifically into alkenes, this

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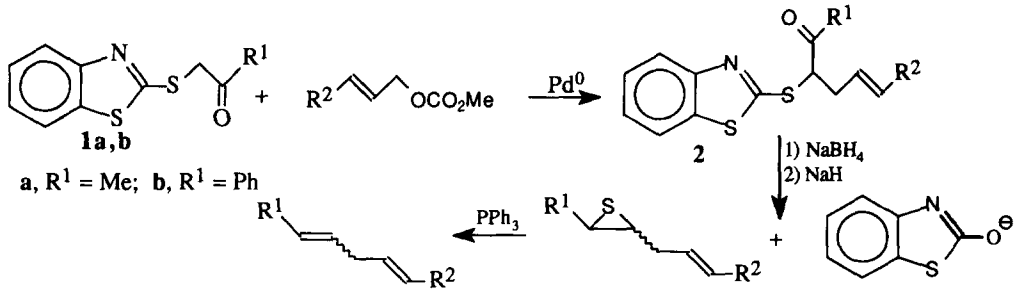
methodology would compare favourably, in some cases, with the Horner-Wittig alkene synthesis.

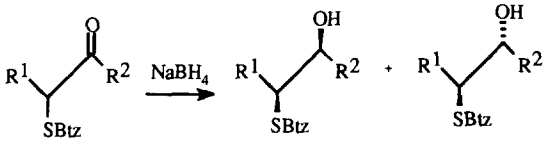
Scheme 2



Monoallylation with allylic carbonates affords stereoselectively allylated ketones whose reduction with an excess of sodium borohydride in isopropanol yields episulfides which were desulfurated into 1,4-dienes.[9] It was therefore of interest to study the stereochemistry of carbonyl reduction in compounds of type **2** as a chance of making any given 1,4-diene in good yield and stereochemical purity.

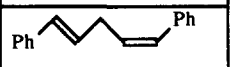
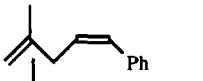
In a striking resemblance with the $NaBH_4$ reduction of β-oxophosphane oxides, **2** react with stoichiometric quantities of $NaBH_4$ in isopropanol to give a predominance of *syn* β–hydroxy sulfides (scheme 3).

Scheme 3



Since it is known[2-4] that reduction of β-oxophosphane oxides in the presence of chelating metals shifts the stereoselectivity towards the *anti* diastereomer, we tried other reducing agents to obtain an inversion of stereoselectivity. Whereas reaction of **2** with $NaBH_4$ in isopropanol in the presence of $MgBr_2$ does not show any change, surprisingly, diisobutyl aluminium hydride (DIBAL) reduction at -78 °C in THF in the presence of stoichiometric quantities of $MgBr_2$ does not give a predominance of the *anti* isomer, as found in the reduction of β-oxophosphane oxides in the presence of $CeCl_3$ or $TiCl_4$, but improves the *syn* stereoselectivity to afford an almost pure *syn* stereomer (table 1). The *syn: anti* ratio appears to be temperature dependent (entry 5) and that in the absence of magnesium bromide, DIBAL reduction is devoid of stereoselectivity (entry 6). These results show that the hydride delivery by DIBAL occurs on a magnesium-chelated β-oxosulfide. Moreover, contrary to that observed in the case of β-phosphane oxides,[1] the stereoselectivity observed in the reduction of these β-oxosulfides appears to be quite independent on the steric effects exerted by the substituents R^1 and R^2. Another difference between *syn* β-hydroxy sulfides and *syn* β-hydroxy phosphane oxides lies in the alkene which are produced by base treatment. Whereas *syn* β-hydroxy phosphane oxides afford (E)-alkenes directly, *syn* β-hydroxy sulfides give (Z)-thiiranes which are converted into (Z)-alkenes. For example reaction of these *syn* β-hydroxy sulfides with NaH in isopropanol or methanol affords allylated (Z)-episulfides which can be desulfurated stereospecifically into (E,Z)-dienes by triphenyl phosphane[7] or 2-selenoxo benzothiazole.[8]

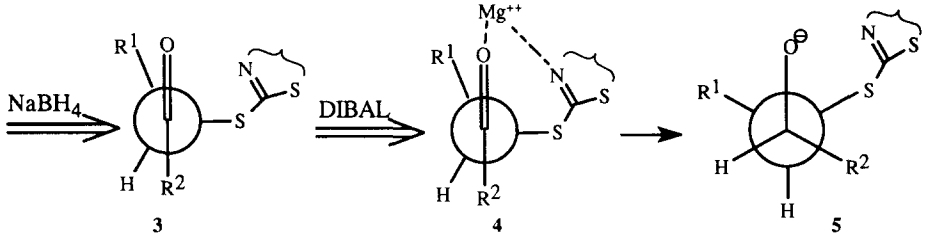
Table 1. Stereoselective Reduction of Benzothiazole β-Oxosulfides.

Entry	Ketone[a] R^1	R^2	$NaBH_4$[b] *Syn: Anti*[d]	$DIBAL/MgBr_2$[c] *Syn: Anti*	Isolated *syn* (%)[g]	Diene[h]
1	(E)-PhCH=CHCH$_2$	Ph	90: 10	96: 4	88	
2	(E)-EtCH=CHCH$_2$	"	92: 8	>98: 2	91	
3	(E)-EtCH=CHCH$_2$	Me	60: 40	90: 10	90	
4	CH$_2$=CHCH$_2$	Ph	70: 30	>98: 2	83	
5	CH$_2$=CHCH$_2$	"	-	78: 22[e]	-	
6	CH$_2$=CHCH$_2$	"	-	50:50[f]	-	
7	CH$_2$=C(CH$_3$)CH$_2$	"	89: 11	>98: 2	85	
8	CH$_2$=C(CH$_3$)CH$_2$	Me	85: 15	96: 4	90	

[a]The yields of hydroxy sulfides are almost quantitative. [b]$NaBH_4$ added at r.t. to equiv. quantitity of ketone dissolved in isopropanol. [c]DIBAL in toluene added to stoichiometric quantities of ketone and magnesium salt dissolved in THF at -78 °C. [d]The *syn:anti* ratio was evaluated by ^1H NMR, HPLC and by transforming the separated stereoisomers into the corresponding episulfides and thence into (Z,E)-dienes (see text). [e]Reaction performed at -30 °C. [f]Reaction with DIBAL but without added magnesium salt. [g]Isolated by flash chromatography. [h]The conversion of the hydroxy sulfides into episulfides followed by their desulfurization into dienes occurs with an overall yield of 70-85%.

The *syn* selectivity of the borohydride reduction is easily explained by a Felkin-Anh[10,11] transition state structure **3**[12] in which the large S-benzothiazolyl group occupies a position perpendicular to the carbonyl group and the allyl group R^1 adopts the position furthest from R^2. Chelation effect in the reduction with DIBAL in the presence of $MgBr_2$ appears to be responsible for the *syn* improvement. Probably, by chelating the heterocyclic nitrogen and/ or the exocyclic sulfur, the magnesium ion can now pull R^1 away from its blocking position on the left -hand side of the carbonyl group and allows attack *anti* to the S-benzothiazolyl group, as shown in **4**, giving a product with a *syn* hydroxyl group **5**.[13]

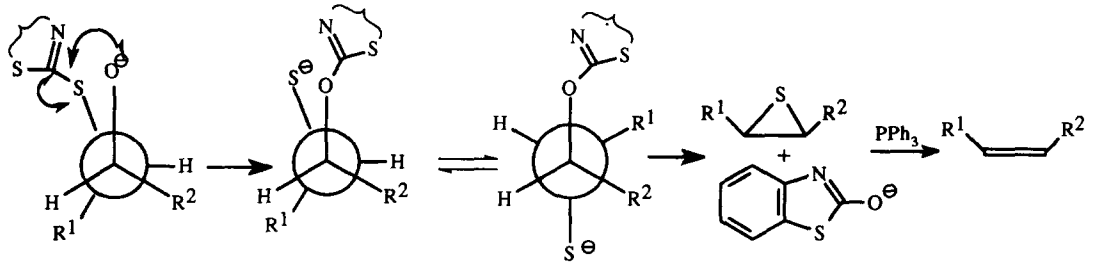
Scheme 4



The *syn* hydroxy sulphide **5**, by sodium hydride treatment in THF, gives a (Z)-episulfide and 2-hydroxybenzothiazole (scheme 5) thus allowing the exchange, on the heterocyclic nucleus of an S- with an O-

functionality through a five-membered transition state as proposed some years ago by Meyer,[14] Johnson[15] and us[16] for correlated β-hydroxy sulfides.

Scheme 5



In summary, we have demonstrate that the reduction of allylated β-oxosulfides of benzothiazole is a synthetically viable method for a stereoselective preparation of 1,4-dienes which compares favourably with the synthesis of (Z)- alkenes by using the β-oxophosphane oxide methodology.

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