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ASYMMETRIC SYNTHESIS OF PROTECTED α-HYDROXYALDEHYDES FROM ACYL CHLORIDES USING *p*-TOLYL *p*-TOLYLTHIOMETHYL SULFOXIDE AS CHIRAL CARBONYL SYNTHON

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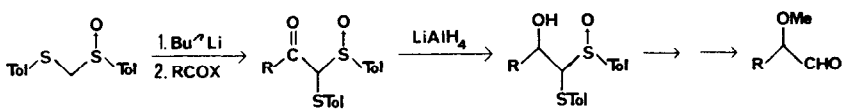
Abstract. *Carbonyl protected α-hydroxyaldehydes* ***3*** *were obtained in high diastereomeric purity through* $LiAlH_4$ *reduction of corresponding β-oxosulfoxides* ***2*** *prepared via acylation of p-tolyl p-tolylthiomethyl sulfoxide* ***1****.*

In connection with previous researches on the use of chiral synthons of carbonyl function in organic synthesis,[1] we wish to report here the results of a stereochemical study on the synthesis of chiral protected α-hydroxyaldehydes through a two-step procedure involving acylation[2] of the lithium salt of *p*-tolyl *p*-tolylthiomethyl sulfoxide **1** and successive reduction with $LiAlH_4$[3] of α-tolylthio-β-oxosulfoxide **2** to α-tolylthio-β-hydroxysulfoxide **3**, namely carbonyl protected α-hydroxyaldehyde.



1 **2a,b** **3a,b** **4**

Two successive asymmetric inductions are involved in this procedure and in principle four diastereomeric alcohols **3** would be expected to be found at the end of the synthesis as three chiral centres are present in **3**. Actually, only two α-tolylthio-β-hydroxysulfoxides (**3a,b**) were found in final reduction mixture when the acylation product obtained in the first step was reduced with $LiAlH_4$ in Et_2O-THF at -78°C, thus suggesting that one of the two steps is most likely highly stereospecific. A detailed examination of the stereochemical course of both reactions revealed that the key step is the $LiAlH_4$ reduction in which each of the two diastereomeric β-oxosulfoxides obtained in the acylation furnishes only one of the two possible diastereomeric alcohols, so that only two of the four expected diastereomers (**3a,b**) were found at the end of the synthesis.

Full data are shown in Table. **2a:2b** Ratios of entries 3, 6, and 8 refer to asymmetric induction in the acylation step; **3a:3b** ratios obtained reducing diastereomerically pure **2** or different diastereomeric mixtures **2a:2b** are listed in the last column but one.

The exploitation of the observed stereoselectivity was then evaluated for synthetic purposes. An important feature of the described procedure is that the diastereomeric mixtures **2a-2b** and/or **3a-3b** can be readily separated by crystallisation and/or chromatography in order to obtain **3a** and **3b** as pure diastereomers, which in turn can independently be transformed into corresponding carbonyl compounds **4** through a previously reported method.[1] This fact suggests that the herein described synthesis could be exploited to achieve enantiomeric *O*-protected-α-hydroxyaldehydes if optically active **1** is used as formyl anion synthon. Actually, starting from benzoyl chloride and optically pure **1** with *S*-configuration $(\alpha)_D$ +76°, *c* 1 in acetone),[1] both (-)-(*R*)- and (+)-(*S*)-α-methoxyphenylacetaldehyde in 100% optical purity[4] were easily obtained from **3a** and **3b** respectively.

Studies on the absolute configuration of **2a,b** and **3a,b**, as well as on the role played by the two chiral centres α and β to carbonyl group during asymmetric reduction are in progress in our laboratory.

Table. $LiAlH_4$ Reduction of α-tolylthio-β-oxosulfoxides **2** in Et_2O-THF at -78°C

Entry	R	**2a**:**2b** Ratio[a]	**3a**:**3b** Ratio[b]	% Yield[c]
1	Ph	>99: 1[d]	>99: 1[d]	76
2	Ph	82:18	92: 8	67
3	Ph	68:32[e]	83:17	64
4	*n*-C_6H_{13}	>99: 1[d]	>99: 1[d]	76
5	*n*-C_6H_{13}	86:14	93: 7	71
6	*n*-C_6H_{13}	59:41[e]	74:26	60
7	*t*-Bu	< 1:99[d]	< 1:99[d]	76
8	*t*-Bu	36:64[e]	36:64	75
9	*t*-Bu	68:32	68:32	77

[a]Determined by nmr: δ[CH] ($CDCl_3$) 5.47 and 5.39 (R=Ph), 4.67 and 4.48 (R=*n*-C_6H_{13}), 4.87 and 4.70 (R=*t*-Bu) for **2a** (diastereomer with the higher δ) and **2b** respectively. [b]Determined by nmr: δ[*CH*CHOH] ($CDCl_3$) 3.98 and 3.81 (R=Ph), 3.93 and 3.76 (R=*n*-C_6H_{13}), 3.97 and 4.35 (R=*t*-Bu) for **3a** and **3b** respectively. The stability of each diastereomer **3a-d** under reaction conditions was tested. [c]Isolated products (**3a+3b**), based on (**2a+2b**). [d]Only one diastereomer could be detected by nmr. [e]**2a**:**2b** Ratios directly obtained by quenching (aqueous NH_4Cl) the final acylation mixtures at -78°C, while the other ratios refer to different mixtures of **2a** and **2b** obtained by successive crystallisations from Et_2O. Pure **2a** (R=Ph, *n*-C_6H_{13}) and **2b** (R=*t*-Bu) could be obtained by just two crystallisations.

References and Notes

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[4]The optical purity was determined by converting enantiomeric methoxyaldehydes (**4**, R=Ph) to corresponding methoxyalcohols $(\alpha)_D$ -131° and +132° respectively).[1]

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