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Lewis Acid-Mediated Carbon-Carbon Bond Forming Reaction Using the Pummerer Rearrangement Products from Chiral β-Hydroxy Sulfoxides

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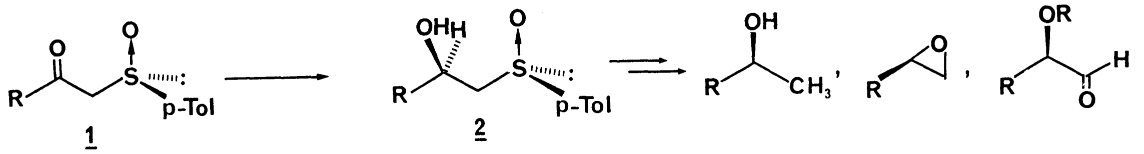
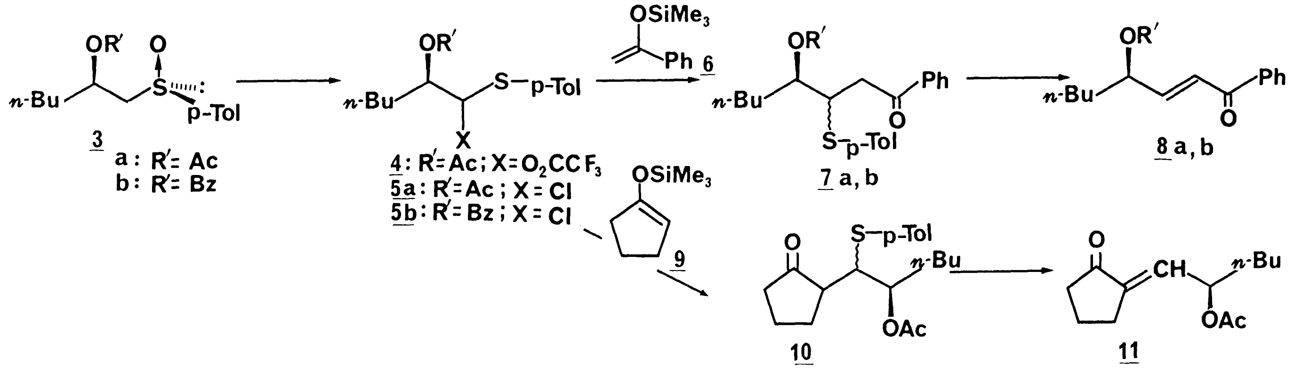
The Pummerer rearrangement products, obtained from (R_C,R_S)-β-hydroxy sulfoxide derivatives, react with silyl enol ethers or a ketene silyl acetal in the presence of $ZnBr_2$ to give the γ-hydroxy-β-tolylthio carbonyl derivatives, which, in turn, are converted to optically pure (E)-γ-hydroxy-α,β-unsaturated carbonyl compounds and 5-substituted 2(5H)-furanones, respectively.

Recently, we and Solladié have independently reported that the carbonyl moiety of chiral β-keto sulfoxides 1 are diastereoselectively reduced with diisobutylaluminum hydride in the presence of $ZnCl_2$ to give the chelation controlled products, β-hydroxy sulfoxides 2 (Eq. 1).[1] Since the sulfur functionality of 2 can be easily removed either reductively or oxidatively, they are synthetically useful intermediates for the preparation of chiral secondary alcohols, epoxides, and α-hydroxy aldehydes.[1,2] Moreover, it has been reported that the dianion of the hydroxy sulfones, derived from 2, can be employed for the alkylation at the carbon bearing the sulfonyl group.[3] For further extension of the synthetic utility of such readily available β-hydroxy sulfoxides, we have examined the reactivity of chiral β-oxy-α-thiocarbocations generated from the Pummerer rearrangement products of 2.



(1)

The reaction of α-chloro sulfides with the silyl enol ethers of carbonyl compounds in the presence of a Lewis acid is a useful method for the introduction of a thioalkyl group to the α-position of carbonyl compounds.[4] Such α-chloro sulfides are usually prepared by chlorination of sulfides.[4] However, the Pummerer rearrangement reaction of sulfoxides would provide an alternative method for preparation of α-chloro sulfides or their equivalents. Thus, we anticipated that such Pummerer rearrangement products from the sulfoxides bearing a β-hydroxy functionality would be also employed for thioalkylation.



Scheme 1.

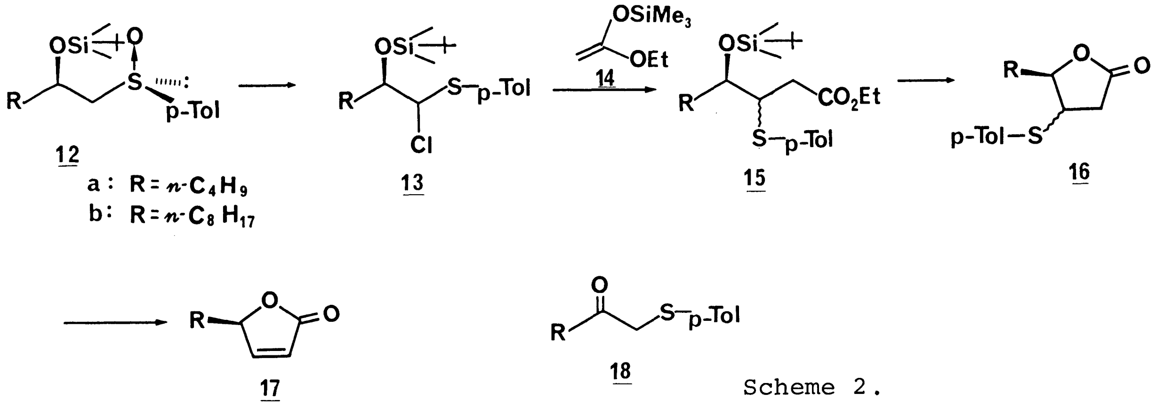
Our initial experiments were carried out with α-trifluoroacetoxy sulfides 4. The compound 4 can be prepared from (R_C,R_S)-2-acetoxy-1-p-tolylsulfinylhexane (3a)[5] by treatment with 3 equiv. of trifluoroacetic anhydride in CH_2Cl_2 at 0 °C for 0.5 h, followed by evaporation of the excess reagent and solvent. The reaction of 4 with 1-phenyl-1-(trimethylsilyloxy)ethene (6) proceeded in the presence of 2.7 mol. equiv. of diethylaluminum chloride in CH_2Cl_2 at -20 °C, affording the thioalkylation products 7a in 59% yield. Furthermore, it was found that the chloro sulfide 5a was superior to 4 as a substrate. The requisite α-chloro sulfide 5a was prepared from 3a by treatment with 3.8 equiv. of thionyl chloride in CH_2Cl_2 followed by evaporation of the excess reagent and solvent. Reaction of 5a with 6 was carried out in CH_2Cl_2 in the presence of a catalytic amount (4 mol%) of $ZnBr_2$ at r.t. for 0.5 h, yielding almost quantitatively the acetoxy sulfide 7a. Oxidation of 7a with m-chloroperoxybenzoic acid followed by thermolysis of the resulting sulfoxide afforded exclusively (R,E)-4-acetoxy-1-phenyl-2-octen-1-one (8a), $[\alpha]_D^{23}$ +27.8°(c 0.471, $CHCl_3$) in 82% yield. Similarly, the reaction of 5a with 1-(trimethylsilyloxy)cyclopentene (9) gave the alkylated product 10. Oxidation of 10 to the sulfoxide followed by thermolysis resulted in the formation of a 1:1 mixture of E and Z isomers 11. On the other hand, elimination of the sulfinic acid from the corresponding sulfone with 1,8-diazabicyclo[5,4,0]-undec-7-ene proceeded smoothly, yielding exclusively the E-isomer 11, $[\alpha]_D^{23}$ +9.0°(c 0.59, $CHCl_3$) in 86% overall yield from 3a. Application of the above reaction sequence to benzoate 5b led to the formation of (E)-enone 8b, the optical purity of which was confirmed to be 100% by HPLC analysis.[6] Accordingly, no epimerization occurred at the β-position of 4 or 5 during the reaction.

Next, we examined the reaction of chloro sulfides for the synthesis of optically active 5-substituted 2(5H)-furanones 17, which are synthetically important intermediates for the asymmetric synthesis of some biologically active natural compounds.[7] For this purpose, we chose the t-butyldimethylsilyl protected derivatives 12 of 2 as the starting material.[5] The Pummerer rearrangement of 12a with thionyl chloride (1.7 equiv.) in CH_2Cl_2 at 0 °C proceeded as well to give the α-chlorinated product 13a. Treatment of 13a with 1-ethoxy-1-(trimethylsilyloxy)-

ethene (14)8) in CH_2Cl_2 containing a catalytic amount of $ZnBr_2$ at 0 °C for 2 h afforded, after usual workup, the γ-silyloxy-β-tolylthioester 15a in 97% yield. Acidic hydrolysis of 15a with aq. HF in acetonitrile and concomitant lactonization furnished the β-tolylthio-butyrolactone derivatives 16a as a 4:1 diastereomeric mixture9) in 92% yield. Oxidation with m-chloroperoxybenzoic acid followed by thermal elimination afforded optically pure (R)-5-butyl-2(5H)-furanone (17a) in 78% yield: $[\alpha]_D^{23}$ -108°(c 0.862, $CHCl_3$), lit.7g) $[\alpha]_D^{23}$ -101.0°($CHCl_3$). In a similar fashion, (R)-5-octyl-2(5H)-furanone (17b) could be prepared from 12b in 88% overall yield: $[\alpha]_D^{23}$ -71.4°(c 0.570 dioxane), lit.7a) $[\alpha]_D^{23}$ -69.2°(dioxane).

It should be noted that the use of less reactive 1-t-butoxy-1-(t-butyldimethylsilyloxy)ethene was unsuccessful under the identical conditions, resulting in the formation of the α-tolylthio ketone 18.

Thus, the Pummerer rearrangement products from chiral β-hydroxy sulfoxides are shown to serve as thioalkylating reagents. Since both enantiomers of β-keto sulfoxides are readily available,1a) the present method offers an easy access to the synthesis of a variety of γ-hydroxy-α,β-enones and 5-substituted 2(5H)-furanones in a desired enantiomeric form with high optical purity.



Scheme 2.

A typical procedure is described for (R)-5-butyl-2(5H)-furanone (17a) as follows: To a solution of (R_C,R_S)-2-(t-butyldimethylsilyloxy)-1-(p-tolylsulfinyl)-hexane (512 mg, 1.45 mmol)5) in CH_2Cl_2 (5 mL) was added dropwise at 0 °C under nitrogen a solution of thionyl chloride (2.5 mmol, 1.7 equiv.) in 5 mL of CH_2Cl_2. After 10 min, the excess thionyl chloride and the solvent were evaporated in vacuo, and then a solution of 1-ethoxy-1-(trimethylsilyloxy)ethene (1.07 g, 2.8 equiv.)8) in CH_2Cl_2 (5 mL) and $ZnBr_2$ (15 mg, 0.067 mmol) were added successively. The mixture was stirred at r.t. for 2 h. Usual aqueous workup and chromatography on silica gel gave 581 mg (97% yield) of 15a. Lactonization: 15a (436 mg, 1.06 mmol) was dissolved in acetonitrile (5 mL) containing 0.25 mL of 46% aq. HF solution and the solution was stirred for 3 h at r.t. Usual aqueous workup gave a mixture of cis-16a and trans-16a which, without purification, was treated with m-chloroperoxybenzoic acid (1.1 equiv.) in CH_2Cl_2 at 0 °C for 5 min. The organic phase was washed with sat. $NaHCO_3$ and then with brine. After the evaporation of the solvent, the crude sulfoxide was dissolved in toluene (5 mL) and heated under reflux for 1.5 h. Concentration of the mixture and chromatography of the oily residue on silica gel afforded 115 mg (78%) of 17a.

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5) (R_C,R_S)-β-Hydroxy sulfoxides used here are diastereomerically pure(>99:1). The protected hydroxy sulfoxides are prepared from 2 as follows: Acetate: Ac_2O/DMAP/CH_2Cl_2, t-Butyldimethylsilylether: t-$BuMe_2SiCl$/DMAP/CH_2Cl_2, Benzoate: benzoic acid/DCC/DMAP/CH_2Cl_2.

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8) A 60:40 mixture of O-silylated and C-silylated products, prepared from ethyl acetate according to the Rathke's method, was directly used. M. W. Rathke and D. F. Sullivan, Synth. Commun., 3, 67 (1973).

9) The stereochemistry of the major stereoisomer has been determined to be cis by observation of the NOE interaction between H_4 and H_5 of the corresponding sulfone. Further investigations concerning diastereoselectivity in the condensation reaction are now in progress.

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