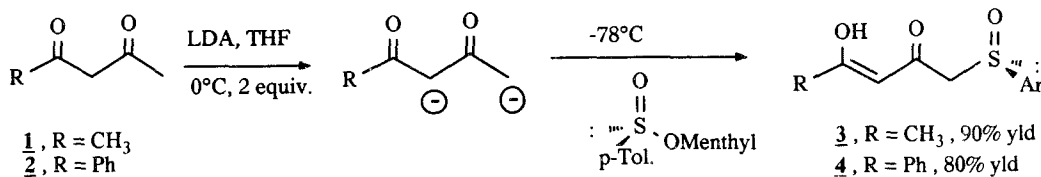


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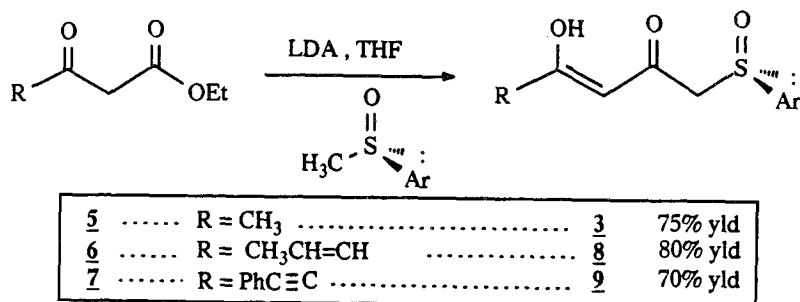
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The first approach is related to the Andersen's synthesis² of sulfoxides from menthyl (-)(S) p-tolylsulfinate³ and Grignard reagents. We have shown that dianions of 1,3-diketones prepared with LDA, reacted cleanly with menthyl (-)(S) p-tolylsulfinate at -78°C to give in high yield (80 to 90%) the corresponding (R) β,γ -diketosulfoxide (3 and 4, scheme 1). The chromatographic purification of β,γ -diketosulfoxides must be carried out on silicagel free of metallic impurities⁴. The NMR spectra of compounds 3 and 4 showed clearly that the γ -carbonyl was totally enolized (one singlet corresponding to one vinylic proton) and that the β -carbonyl was not enolized (one AB pattern corresponding to the 2 methylenic protons α to the sulfoxide group).



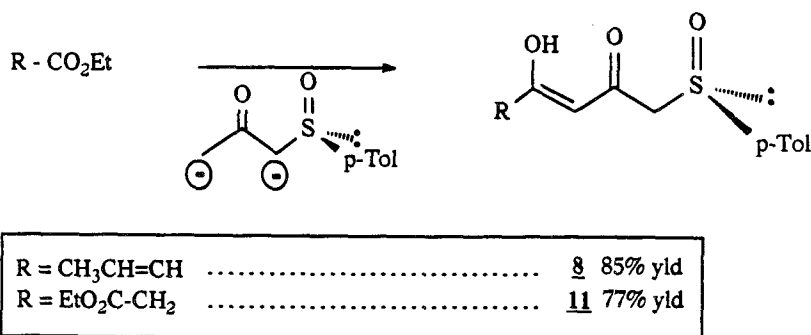
Scheme 1

The second approach we developed, is related to the synthesis of β -ketosulfoxides from carboxylic esters and methyl (+) (R) p-tolylsulfoxide anion. In that case the reaction was carried out by adding a THF solution of methyl p-tolylsulfoxide anion, prepared with LDA, at 0°C, to a solution of β -ketoester and then heating the reaction mixture under reflux for 15 min. (Scheme 2). Yields are between 70 and 80% even in the case of unsaturated β -ketoesters or propargylic β -ketoesters.



Scheme 2

The third approach is the direct condensation of the dianion of (+) (R) 1-(p-tolylsulfinyl) 2-propanone **10** to a carboxylic ester solution at 0°C followed by a 45 min. reflux (Scheme 3). Yields are in the range of 77 to 85%.



Scheme 3

In conclusion, our results showed indeed that chiral β,γ -diketo p-tolylsulfoxides are readily prepared by any of these three methods. Results concerning the asymmetric induction observed during reactions of these molecules with different reagents will be shortly reported.

Experimental part.

Synthesis of β,γ -diketosulfoxides from menthyl (-)(S) *p*-tolylsulfinat and 1,3-diketone dianions, general procedure.

The 1,3-diketone dianion was prepared by adding at 0°C the 1,3-diketone (34 mmol., 2 equiv.) in THF (30 mL) to a LDA solution [prepared at -15°C from diisopropylamide (68 mmol., 4 equiv.) and *n*-BuLi (68 mmol., 4 equiv.) in THF (150 mL)]. After stirring for 2 h., the reaction mixture was cooled at -78°C and menthyl (-)(S) *p*-tolylsulfinat (17 mmol., 1 equiv.) in THF (40 mL) was added. After stirring for 1.5 h. to 2.5 h., the reaction mixture was hydrolyzed with saturated ammonium chloride solution (100 mL) and a 5% sulfuric acid solution till pH = 2. After extraction with ethyl acetate (3 x 150 mL), the organic phase was dried (SO₄Na₂) and the solvent evaporated. Finally the product was purified by chromatography on metal free silicagel⁴, eluent: hexane - ethyl acetate gradient.

(+)(R) 1-(*p*-tolylsulfinyl)-2,4-pentanedione, 3:

Reaction time: 2.5 h.; m.p. 74-8°C; 85% yield; R_f = 0.35 (ethyl acetate); [α]_D = +340 (c=2, acetone).

IR (CCl₄): 1600, 1051 cm⁻¹.

¹H NMR (200 MHz, CDCl₃): δ : 2.09 (s, 3H, CH₃CO), 2.43 (s, 3H, CH₃C₆H₄), 3.62 (AB, 2H, J_{AB} = 12.6 Hz, $\Delta\nu$ = 23 Hz, CH₂S(O)), 5.59 (s, 1H, vinylic H), 7.44 [(AB)₂, 4H, J_{AB} = 8.3 Hz, $\Delta\nu$ = 40 Hz, arom.H].

Anal. calcd. for C₁₂H₁₄O₃S : C, 60.56; H, 5.93. Found : C, 61.00; H, 6.13.

(+)(R) 1-(*p*-tolylsulfinyl) 4-phenyl 2,4-butanedione, 4:

Reaction time: 1.5 h.; m.p. 46-49°C; 91% yield; R_f = 0.73 (ethyl acetate / ether: 4/1); [α]_D = +331 (c = 2.04, acetone).

IR (CCl₄): 1600, 1050, 750 cm⁻¹.

¹H NMR (200 MHz, CDCl₃): δ : 2.40 (s, 3H, CH₃-C₆H₄), 3.79 (AB, 2H, J_{AB} = 12.58 Hz, $\Delta\nu$ = 26.5 Hz, CH₂S(O)), 6.17 (s, 1H, vinylic H), 7.42 (m, 5H, arom.H), 7.77 [(AB), 4H, J_{AB} = 7 Hz, $\Delta\nu$ = 52.5 Hz, arom.H].

Anal. calcd. for C₁₇H₁₆O₃S : C, 68.06; H, 5.38. Found: C, 68.07; H, 5.61.

Synthesis of β,γ -diketosulfoxides from methyl (+)(R) *p*-tolylsulfoxide and β -ketoesters, general procedure.

The methyl *p*-tolylsulfoxide anion was prepared by adding at -78°C methyl (+)(R) *p*-tolylsulfoxide (6.34 mmol., 1.1 equiv.) in THF (15 mL) to a LDA solution [prepared at -15°C from

diisopropylamide (15 mmol., 2.6 equiv.) and *n*-BuLi (13.8 mmol., 2.4 equiv.) in THF (30 mL)]. After stirring for 0.5 h., the anion solution was allowed to reach 0°C and added at 0°C to a solution of the β - ketoester (5.76 mmol., 1 equiv.). Then the solution was allowed to reach room temperature and heated under reflux for 15 min.. The reaction mixture was hydrolyzed with saturated ammonium chloride solution (100 mL) and a 5% sulfuric acid solution till pH = 2. After extraction with ethyl acetate (3 x 100 mL), the organic phase was dried (SO_4Na_2) and the solvent evaporated. Finally the product was purified by chromatography on metal free silicagel⁴, eluent: hexane - ethyl acetate gradient.

(+)(R) 1-(*p*-tolylsulfinyl) 2,4-pentanedione, 3:

75% yield, product having the same characteristics as before.

(+)(R) 1-(*p*-tolylsulfinyl) 5-heptene 2,4-dione, 8:

m.p. 75-5°C; 80% yield; Rf = 0.5 (EtOAc/ether:2/8); $[\alpha]_D = +312$ (c=1.73, acetone).

IR (CCl_4): 1600, 1050, 750 cm^{-1} .

^1H NMR (200 MHz, CDCl_3): δ : 1.92 (dd, 3H, $J_{12} = 7$ Hz, $J_{13} = 1.5$ Hz, CH_3), 2.42 (s, 3H, $\text{CH}_3\text{C}_6\text{H}_4$), 3.71 (AB, 2H, $J_{AB} = 12.8$ Hz, $\Delta\nu = 29$ Hz, $\text{CH}_2\text{S(O)}$), 5.55 (s, 1H, H_3), 5.88 (dq, 1H, $J_{32} = 15.5$ Hz, $J_{31} = 1.4$ Hz, H_5) 6.92 (dq, 1H, $J_{21} = 7$ Hz, $J_{23} = 15.5$ Hz, H_6) 7.46 [(AB), 4H, $J_{AB} = 8.22$ Hz, $\Delta\nu = 42$ Hz, arom.H].

Anal. calcd. for $\text{C}_{14}\text{H}_{16}\text{O}_3\text{S}$: C, 63.69; H, 6.11. Found : C, 63.53; H, 6.32.

(+)(R) 1-(*p*-tolylsulfinyl) 6-phenyl 5-hexyne 2,4-dione, 2:

m.p. 126-128°C; 70% yield; Rf = 0.42 (EtOAc/ether: 2/8); $[\alpha]_D = +82$ (c=2.02, acetone).

IR (CCl_4): 2360, 1630, 1030, 750 cm^{-1} .

^1H NMR (200 MHz, CDCl_3): δ : 2.42 (s, 3H, $\text{CH}_3\text{C}_6\text{H}_4$), 3.73 (AB, 2H, $J_{AB} = 12.6$ Hz, $\Delta\nu = 22$ Hz, $\text{CH}_2\text{S(O)}$), 5.9 (s, 1H, vinylic H), 7.46 (m, 9H, arom.H).

Anal. calcd. for $\text{C}_{19}\text{H}_{16}\text{O}_3\text{S}$: C, 70.43; H, 4.98. Found : C, 70.58; H, 5.23.

β -ketoester synthesis, general procedure:

The lithium enolate of ethyl acetate was prepared by adding ethyl acetate (8 mmol., 2.4 equiv.) to a LDA solution (8.66 mmol., 2.6 equiv.) in THF (15 mL) at -78°C. The reaction mixture was then stirred at -25°C for 30 min. and added at 0°C to the ester (3.33 mmol., 1 equiv.) in THF (20 mL). Stirring was maintained at 0°C till complete reaction of the ester (TLC, usually 1 or 2h). After hydrolysis with saturated ammonium chloride (50 mL) and diluted sulfuric acid (5%) till pH = 2, the product was extracted with ethyl acetate (3 x 100 mL), dried (Na_2SO_4), and the solvent evaporated.

Ethyl 3-oxo 4-heptenoate, 6:

liquid purified by chromatography on silicagel (hexane/Ethyl acetate: 8/2); 45% yield; $R_f = 0.44$ (Hexane/ethyl acetate: 9/1).

IR (CCl₄): 1730, 1660, 1230, 950 cm⁻¹.

¹H NMR (200 MHz, CDCl₃): δ : 1.19 (t, 3H, $J = 6.4$ Hz, $\underline{\text{CH}_3\text{CH}_2\text{O}}$), 1.86 (dd, 3H, $J_{12} = 6.95$ Hz, $J_{13} = 1.6$ Hz, CH₃), 3.5 (s, 2H, CH₂), 4.15 (q, 2H, $J = 6.4$ Hz, $\text{CH}_3\underline{\text{CH}_2\text{O}}$), 6.11 (dq, 1H, $J_{32} = 14.1$ Hz, $J_{31} = 1.7$ Hz, H₄), 6.84 (dq, 1H, $J_{21} = 6.86$ Hz, $J_{23} = 15.8$ Hz, H₅). A small amount (30%) of enolized 6 was identified on the NMR spectrum by a signal at 4.88 ppm (s, 1H, H₂).

Ethyl 3-oxo-5-phenyl 4-pentynoate, 7:

Liquid purified by chromatography on silicagel (hexane/CH₂Cl₂: 3/7); 95% yield; $R_f = 0.46$ (Hexane/CH₂Cl₂: 3/7).

IR (CCl₄): 2200, 1730, 1660, 1240, 750 cm⁻¹.

¹H NMR (200 MHz, CDCl₃): δ : 1.31 (t, 3H, $J = 7.2$ Hz, $\underline{\text{CH}_3\text{CH}_2\text{O}}$), 3.7 (s, 2H, CH₂), 4.25 (q, 2H, $J = 7.2$ Hz, $\text{CH}_3\underline{\text{CH}_2\text{O}}$), 7.47 (m, 5H, arom.H). A small amount (40%) of enolized 7 was identified on the NMR spectrum by a signal at 5.46 ppm (s, 1H, H₂).

(+)(R) 1-(*p*-tolylsulfinyl) 2-propanone, 10:

A solution of methyl (+) (R) *p*-tolylsulfoxide (13.3 mmol., 2 equiv.) in THF (16 mL) was added at -40°C to a LDA solution (16 mmol., 2.4 equiv.) in THF (16 mL). After 45 min., ethyl acetate (15.3 mmol., 2.3 equiv.) was added and the reaction mixture stirred for 30 min., hydrolyzed with saturated ammonium chloride (100 mL), then with diluted sulfuric acid (5%) till pH = 2, extracted with ethyl acetate (3x100 mL), dried (Na₂SO₄) and the solvent evaporated.

White solid; m.p. 38°C; 95% yield; $R_f = 0.5$ (EtOAc/ether: 3.5/1); $[\alpha]_D = +260$ ($c = 1.97$, acetone).

IR (CCl₄): 1720, 1060 cm⁻¹

¹H RMN (200 MHz, CDCl₃): δ : 2.24 (s, 3H, CH₃), 2.43 (s, 3H, $\underline{\text{CH}_3\text{C}_6\text{H}_4}$), 3.83 (AB, $J_{AB} = 13.5$ Hz, $\Delta\nu = 14$ Hz, $\underline{\text{CH}_2\text{S(O)}}$), 7.45 (AB, $J_{AB} = 8.2$ Hz, $\Delta\nu = 40$ Hz, arom.H).

Anal. calcd. for C₁₀H₁₂O₂S: C, 61.2; H, 6.16. Found: C, 61.23; H, 6.24.

Synthesis of β,γ -diketosulfoxides from (+)(R) 1-(*p*-tolylsulfinyl) 2-propanone, 10, and esters, general procedure.

A solution of (+)(R) 1-(*p*-tolylsulfinyl) propanone-2, 10, (3.09 mmol., 1.1 equiv.) in THF (10 mL) was added at 0°C to a solution of LDA (6.72 mmol., 2.3 equiv.) in THF (15 mL) and stirred for 45 min.. The resulting solution was added to a solution of ester (2.8 mmol., 1.1 equiv.) in THF (10 mL)

at 0°C. The reaction mixture was allowed to reach room temperature and then refluxed for 45 min. The solution was finally hydrolyzed at room temperature with saturated ammonium chloride (50 mL), diluted sulfuric acid (5%) till pH = 2, extracted with ethyl acetate (3x50 mL), dried (Na₂SO₄) and evaporated. The crude product was purified by chromatography on metal free silicagel.

(+)(R) 1-(p-tolylsulfinyl) 5-heptene 2,4-dione, 8:

85% yield, product having the same characteristics as before.

Ethyl (+)(R) 1-(p-tolylsulfinyl) 2,4-dioxo hexanoate, 11:

Liquid; 77% yield; R_f = 0.22 (EtOAc/ether: 2/8); [α]_D = +109 (c = 2, acetone).

IR (CHCl₃): 1710, 1690, 1200, 1020 cm⁻¹.

¹H NMR (200 MHz, CDCl₃): δ : 1.28 (t, 3H, J = 7.1 Hz, CH₃CH₂O), 2.42 (s, 3H, CH₃C₆H₄), 3.36 (s, 2H, CH₂CO₂Et), 3.6 (AB, 2H, J_{AB} = 11.5 Hz, Δν = 21 Hz, CH₂S(O)), 4.2 (q, 2H, J = 7.1 Hz, CH₃CH₂O), 5.68 (s, 1H, vinylic H), 7.44, [(AB), 4H, J_{AB} = 8.3 Hz, Δν = 38 Hz, arom. H].

Anal. calcd. for C₁₅H₁₈O₅S: C, 58.11; H, 5.85. Found: C, 58.2; H, 6.00.

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