# REACTIONS OF CHIRAL 2-p-TOLYLSULFINYLCYCLOALKANONES WITH AlMes

## Ana B. Bueno,<sup>a</sup> M. Carmen Carreño,<sup>a\*</sup> Jean Fischer,<sup>b</sup> J. L. García Ruano,<sup>a\*</sup> Begoña Peña,<sup>a</sup> Lorenzo Peñas<sup>a</sup> and Almudena Rubio<sup>a</sup>

a Departamento de Química, Universidad Autónoma. Cantoblanco, 28049-Madrid, SPAIN.
b Laboratoire de Cristallochimie, UA 424, Université Louis Pasteur, 67070-Strasbourg, FRANCE

The reactions of  $(\mathfrak{D}_2, \mathfrak{R}_3)$  and  $(\mathfrak{R}_2, \mathfrak{R}_3)-2-p$ -tolylsulfinylcyclohexanones with AlMes/ZnCl<sub>2</sub> only yield the cyclohexylmethylcarbinols with  $\mathfrak{R}$  configuration at hydroxylic carbon. The  $(\mathfrak{R}_1, \mathfrak{S}_2, \mathfrak{R}_3)-1$ -methyl-2-p-tolylsulfinylcyclopentanol was the only compound obtained in the reaction of MesAl with both epimeric 2-p-tolylsulfinylcyclopentanones. The d.e. of both reactions are higher than 96%.

The high stereoselectivity observed in the DIBAL and DIBAL/ZnCl<sub>2</sub> reductions of 2-ptolylsulfinylcyclohexanones was explained by assuming an intramolecular hydride transfer from a species involving the association between the aluminium and the sulfinyl group.<sup>1,2</sup> The great interest of the chiral cyclic methylcarbinols and the similarity between DIBAL and AlMe<sub>3</sub>, prompted us to study the AlMe<sub>3</sub> and AlMe<sub>3</sub>/ZnCl<sub>2</sub> reactions with chiral 2-ptolylsulfinylcyclohexanones and cyclopentanones, in order to obtain these alcohols. In the present paper we report the good chemical yields and the high stereoselection obtained in these reactions, which contrast with the results shown in the only so far reported paper, concerning the diastereoselective addition of Me3Al to acyclic  $\beta$ -ketosulfoxides,<sup>3</sup> where long reaction times were required to obtain moderated yields and low diastereomeric excesses.

The addition of a toluene<sup>4</sup> solution of  $(S_2,R_5)-2-p$ -tolylsulfinylcyclohexanone<sup>1,5</sup> 1 to a 2M hexane solution of AlMes (4 eq.) at room temperature (the order in the reagent addition is critical to get high yields6, afforded in 15 minutes a 80:20 mixture (95% yield) of two methylcarbinols, 3 and 4,<sup>7</sup> that were easily separated by column chromatography (eluent ethyl acetate-hexane 2:1). The same 3:4 ratio was obtained starting from a 75:25 mixture of epimeric ketosulfoxides 1 and 2 ( $R_2, R_5$ ).<sup>1,5</sup> In the presence of ZnCl<sub>2</sub>, compound 1 gave only alcohol 3 (94% yield in 15 minutes, r.t.), whereas the 75:25 mixture of 1 and 2 afforded 3 and 5<sup>7</sup> in the same 75:25 ratio (95% yield), which were also separated by chromatography. This high reactivity contrasted with that reported for acyclic ketosulfoxides,<sup>3</sup> and could be attributed to the differences in the experimental conditions used in both cases. All these results are collected in Scheme 1. The enantiomeric purity of 3, 4 and 5 (>97%) was established by <sup>1</sup>H-nmr (200 MHz) using Eu(tfc)<sub>3</sub>, which required the study of the racemic substrates.

Assuming that sulfur configuration was not affected by experimental conditions and taking into account that the reactions of 1 and 2 are stereospecific in the presence of  $ZnCl_2$  (entries 3 and 4 in Scheme 1), the absolute configurations of 3, 4 and 5 could be established by chemical correlations (the sulfones obtained by MCPBA oxidation of sulfoxides 3 and 5

#### ACKNOWLEDGEMENTS

We thank DGICYT (Grants PB86-0120 and PB88-0176) and Asociación Hispano-Francesa (Acción Integrada no. 202) for financial support.

#### REFERENCES AND NOTES

1.- M.C. Carreño, J.L. García Ruano and A.Rubio, Tetrahedron Lett., 1987, 28, 4861.

2.- M.C. Carreño, J.L. García Ruano, A.M. Martín, C. Pedregal, J.H. Rodriguez, A.Rubio, J. Sanchez and G. Solladié, *J. Org. Chem.*, 1990, 55, 2120.

3.- T. Fujisawa, A. Fujimura and Y.Ukaji, Chem. Lett. 1988, 1541.

4.- Benzene and CH2Cl2 gave the same results. The reaction did not work in THF or Et2O.

5.- M.C. Carreño, J.L. García Ruano, C. Pedregal and A.Rubio; J. Chem. Soc. Perkin Trans. 1, 1989, 1335.

6.- We have carried out several trials by adding the AlMes solution on the ketosulfoxide 1. In these conditions, compound 1 was recovered almost unaltered after 15 minutes.

7.- In strict sense, the 3:4 ratio ranged from 76:24 to 92:8 in different trials. Compound 3: m.p. 136-138°C, [a]p=+255° (c 1.0, CHCl3), <sup>1</sup>H-nmr (CDCl3) δ 7.35 (4H, aromatics), 3.50 (br s, 1H, OH), 2.42 (s, 3H, CH3-Ar), 2.27 (dd, 1H, J=12.6 and 3.4 Hz, CH-SO), 2.10-1.60 (m, 5H), 1.72 (s, 3H, CH3-COH), 1.53-1.09 (m, 3H). <sup>1</sup>H-nmr (dry C6D6) δon 4.65 ppm (remains unaltered with dilution) <sup>4</sup>JOH,H(6xx)=2.3 Hz. <sup>13</sup>C-nmr (CDCl3); 141.0, 136.8, 129.8 (2C), 124.2 (2C), 71.3, 67.5, 40.3, 29.6, 24.7, 21.4, 20.3, 16.6/

Compound 4: m.p. 222-224°C, [a]n=+195° (c 1.0, CHCl3), <sup>1</sup>H-nmr (CeDe) & 7.60 and 6.90 (4H, aromatics), 2.49 (dd, 1H, J=12.2 and 4.0 Hz, CH-SO), 1.94 (s, 3H, CH3-Ar), 1.90-1.60 (m, 2H), 1.59 (s, 3H, CH3-COH), 1.40-0.60 (m, 7H). <sup>13</sup>C-nmr (CDCl3): 140.5, 139.8, 129.6 (2C), 124.1 (2C), 74.2, 72.5, 42.4,24.7, 23.4. 23.2, 21.3, 18.5

Compound 5: m.p. 130-132<sup>Q</sup>C, [a]b=+217<sup>2</sup> (c 1.0, CHCls), <sup>1</sup>H-nmr (CDCls) δ 7.65 and 7.35 (4H, aromatics), 5.60 (s, 1H, OH), 2.86 (dd, 1H, J=12.0 and 4.6 Hz, CH-SO), 2.44 (s, 3H, CH<sub>3</sub>-Ar), 2.00-1.00 (m, 8H), 1.66 (s, 3H, CH<sub>3</sub>-COH). <sup>1</sup>H-nmr (dry CeDe) δон 6.13 ppm (remains unaltered with dilution. No long range coupling constant was observed). <sup>13</sup>C-nmr (CDCls): 142.7, 138.7, 129.8 (2C), 125.8 (**20**), 73.3, 71.4, 41.1, 25.1, 23.0, 22.5, 21.9, 21.4.

142.7, 138.7, 129.8 (2C), 125.8 (2O), 73.3, 71.4, 41.1, 25.1, 23.0, 22.5, 21.9, 21.4. 8.- Compound 8: m.p. 103-106<sup>9</sup>Cr. [a]p=+300<sup>°</sup>(c 1.0, CHCl3), <sup>1</sup>H-nmr (CDCl3) δ 7.44 and 7.31 (4H, aromatics), 3.70 (s, 1H, OH), 2.65 (t, 1H, J=9.0 Hz, CH-SO), 2.50-1.20 (m, 5H), 2.41 (s, 3H, CH3-Ar), 1.58 (s, 3H, CH3-COH). <sup>13</sup>C-nmr (CDCl3) 140.8, 138.8, 129.6, 123.9, 80.1, 70.5, 41.9, 26.9, 21.2, 21.0, 19.9.

Compound 9: (From a 8+9 mixture) <sup>1</sup>H-nmr (CDCl<sub>3</sub>) δ 7.44 and 7.31 (4H, aromatics), 2.82 (t, 1H, J=8.7 Hz, CH-SO), 2.50-1.20 (m, 5H), 2.41 (s, 3H, CH<sub>3</sub>-Ar), 1.58 (s, 3H, CH<sub>3</sub>-COH).

Compound 10: yellow oil, <sup>1</sup>H-nmr & 7.59 and 7.33 (4H, aromatics), 3.07 (t, 1H, J=9.0 Hz, CH-SO), 2.42 (s, 3H, CH3-Ar), 2.50-0.80 (m, 6H), 1.67 (s, 3H, CH3-COH). These data were obtained from the mixture 8+10 resulting from the epimerization of 8 in basic medium.

Compound 11: m.p. 137-139°C, [a]p=+215° (c 0.96, CHCls), <sup>1</sup>H-nmr & 7.62 and 7.32 (4H, aromatics), 2.90 (t, 1H, J=9.0 Hz, CH-SO), 2.42 (s, 3H, CH3-Ar), 2.0-1.40 (m, 5H), 1.54 (s, 3H, CH3-COH); <sup>13</sup>C-nmr (CDCls) 141.9, 140.2, 129.8, 125.3, 81.2, 72.4, 42.5, 29.7, 26.7, 22.4, 21.4.

9.- Crystals of 8 belong to the orthorhombic space group P212121, and accurate lattice constants of a=24.947(6), b=8.078(3) and c=6.297(3) A. All unique diffraction maxima [theta limits (deg) = 3/51] were collected using 20:0 scans and Cu Ka radiation. Of the 860 reflections measured in this fashion, 836 (97%) were judged observed [D3 $\sigma$ (I)] and used in subsequent calculations. The structure, solved by the heavy atom method using Enraf-Nonius SDP/VAX package (B.A. Frenz, "The Enraf-Nonius CAD4-SDP" in Computing in Crystallography, Ed., H. Schenk, R. Olthof-Hazekamp, H. Van Koningveld, G.C. Bassi, pp. 64-71, Delft University Press, 1978), was refined to R=0.035. The absolute structure was determined by comparing xyz and -x-y-z refinements. Tables of atomic coordinates, bond lengths and angles, and thermal parameters (supplementary material) are available on request from the Cambridge Crystallographic Data Centre.

10.- The stereoselective formation of the methylcarbinols 8 and 11 and their subsequent epimerization at C-1 in the presence of AlMes/ZnCl2, could be disregarded when a sample of pure carbinol 8 remained unaltered after treating with AlMes/ZnCl2 in CH2Cl2 in the same conditions used for the methylation reaction.



Figure 1. ORTEP plot of one molecule of 8 in the solid state. Ellipsoids are scaled to enclose 50% of the electronic density. Hydrogen atoms have arbitrary radies.

Once established the configuration of all hydroxysulfoxides, we can state that the chirality induced at C-1 in the AlMe3/ZnCl2 additions to 2-sulfinylcyclohexanones only depends on the sulfur configuration [in the case of our  $(R_0)$ -sulfoxides,  $(R_1)$ -carbinols were is independent of that on C-2. The results obtained for 2obtained], and sulfinylcyclopentanones suggested that the equilibration of epimers 6 and 7 was taking place stage of the methylation. In addition, the methylation a previous less as was stereoselective<sup>10</sup> than in the case of cyclohexanone derivatives (yielding a mixture of the four possible carbinols, see entries 7-10). The different behaviour of cyclopentanone with respect to the cyclohexanone derivatives must be due to differences in steric hindrance and torsional strain for the axial and equatorial approaches respectively, imposed by the size of the ring in both cases.

The results obtained in the absence of ZnCl<sub>2</sub> indicate that C-2 epimerization of  $\beta$ ketosulfoxides [1 and 2, 6 and 7 (entries 1, 2, 5 and 6)] is also occurring. The only products obtained from these epimerized mixtures result from the reaction of ( $S_2$ ,  $R_3$ ) diastereomers 1 and 6 respectively. The high stereoselectivity observed (specially in cyclopentanone derivatives) suggests an intramolecular transfer of the methyl group, like that of the hydride in DIBAL reductions, but the fact that the reagent approach takes place from a different face of the carbonyl group in both processes, inducing the opposite configuration at C(1), indicates that the stereochemical course is not identical for both reactions.

In conclusion, the high chemical yields and diastereomeric excesses obtained in reactions of AlMe3/ZnCl2 with chiral 2-p-tolylsulfinylcyclohexanones, and those of AlMe3 with cyclopentanone derivatives, suggest that these reactions might became a useful way to obtain chiral tertiary methylcarbinols with R configuration, starting from cyclic (Rs)- $\beta$ -ketosulfoxides, (the *S* configuration of the carbinols would require to start from the (Ss)- $\beta$ -ketosulfoxides) similarly to their DIBAL and DIBAL/ZnCl2 reductions allowing the synthesis of the corresponding secondary alcohols. We are now studying the application of these reactions to other cyclic and acyclic substrates in order to extend their synthetic scope and to understand their stereochemical course.

#### ACKNOWLEDGEMENTS

We thank DGICYT (Grants PB86-0120 and PB88-0176) and Asociación Hispano-Francesa (Acción Integrada no. 202) for financial support.

### REFERENCES AND NOTES

1.- M.C. Carreño, J.L. García Ruano and A.Rubio, Tetrahedron Lett., 1987, 28, 4861.

2.- M.C. Carreño, J.L. García Ruano, A.M. Martín, C. Pedregal, J.H. Rodriguez, A.Rubio, J. Sanchez and G. Solladié, J. Org. Chem., 1990, 55, 2120.

3.- T. Fujisawa, A. Fujimura and Y.Ukaji, Chem. Lett. 1988, 1541.

4.- Benzene and CH2Cl2 gave the same results. The reaction did not work in THF or Et2O.

5.- M.C. Carreño, J.L. García Ruano, C. Pedregal and A.Rubio; J. Chem. Soc. Perkin Trans. 1, 1989, 1335.

6.- We have carried out several trials by adding the AlMes solution on the ketosulfoxide 1. In these conditions, compound 1 was recovered almost unaltered after 15 minutes.

7.- In strict sense, the 3:4 ratio ranged from 76:24 to 92:8 in different trials. Compound 3: m.p. 136-1382d, [a]p=+255° (c 1.0, CHCl3), 4H-nmr (CDCl3) & 7.35 (4H, aromatics), 3.50 (br s, 1H, OH), 2.42 (s, 3H, CH<sub>3</sub>-Ar), 2.27 (dd, 1H, J=12.6 and 3.4 Hz, CH-SO), 2.10-1.60 (m, 5H), 1.72 (s, 3H, CH<sub>3</sub>-COH), 1.53-1.09 (m, 3H). <sup>1</sup>H-nmr (dry C<sub>6</sub>D<sub>6</sub>) δ<sub>0H</sub> 4.65 ppm (remains unaltered with dilution) <sup>4</sup>J<sub>0H,H(6gx)</sub>=2.3 Hz. <sup>13</sup>C-nmr (CDCl<sub>3</sub>); 141.0, 136.8, 129.8 (2C), 124.2 (2C), 71.3, 67.5, 40.3, 29.6, 24.7, 21.4, 20.3, 16.6.

Compound 4: m.p. 222-224°C, [a]=+195° (c 1.0, CHCl3), <sup>1</sup>H-nmr (C6D6) & 7.60 and 6.90 (4H, aromatics), 2.49 (dd, 1H, J=12.2 and 4.0 Hz, CH-SO), 1.94 (s, 3H, CH3-Ar), 1.90-1.60 (m,

(41, aromatics), 2.49 (dd, 14, 5-12.2 and 4.0 Hz, CH-SO), 1.94 (s, 5H, CH3-AF), 1.90-1.80 (df, 2H), 1.59 (s, 3H, CH3-AF), 1.90-1.80 (df, 2H), 1.50 (s, 3H, CH3-AF), 1.90-1.80 (df, 2H), 1.50 (s, 5H, CH3-AF), 1.90-1.80 (df, 2H), 1.90 (c), 1.91 (c), unaltered with dilution. No long range coupling constant was observed). <sup>13</sup>C-nmr (CDCl<sub>3</sub>):

142.7, 138.7, 129.8 (2C), 125.8 (2C), 73.3, 71.4, 41.1, 25.1, 23.0, 22.5, 21.9, 21.4. 8.- Compound 8: m.p. 103-105<sup>o</sup>C, [a]p=+300°(c 1.0, CHCl<sub>3</sub>), <sup>1</sup>H-nmr (CDCl<sub>3</sub>) δ 7.44 and 7.31 (4H, aromatics), 3.70 (s, 1H, OH), 2.65 (t, 1H, J=9.0 Hz, CH-SO), 2.50-1.20 (m, 5H), 2.41 (s, 3H, CH<sub>3</sub>-Ar), 1.58 (s, 3H, CH<sub>3</sub>-COH). <sup>13</sup>C-nmr (CDCl<sub>3</sub>) 140.8, 138.8, 129.6, 123.9, 80.1, 70.5, 41.9, 26.9, 21.2, 21.0, 19.9.

Compound 9: (From a 8+9 mixture) <sup>1</sup>H-nmr (CDCl<sub>3</sub>) δ 7.44 and 7.31 (4H, aromatics), 2.82 (t, 1H, J=8.7 Hz, CH-SO), 2.50-1.20 (m, 5H), 2.41 (s, 3H, CH3-Ar), 1.58 (s, 3H, CH3-COH).

Compound 10: yellow oil, <sup>1</sup>H-nmr  $\delta$  7.59 and 7.33 (4H, aromatics), 3.07 (t, 1H, J=9.0 Hz, CH-SO), 2.42 (s, 3H, CH<sub>3</sub>-Ar), 2.50-0.80 (m, 6H), 1.67 (s, 3H, CH<sub>3</sub>-COH). These data were obtained from the mixture 8+10 resulting from the epimerization of 8 in basic medium.

Compound 11: m.p. 137-139°C, [a]p=+215° (c 0.96, CHCl3), <sup>1</sup>H-nmr & 7.62 and 7.32 (4H, aromatics), 2.90 (t, 1H, J=9.0 Hz, CH-SO), 2.42 (s, 3H, CH3-Ar), 2.0-1.40 (m, 5H), 1.54 (s, 3H, CH3-COH); <sup>13</sup>C-nmr (CDCl<sub>3</sub>) 141.9, 140.2, 129.8, 125.3, 81.2, 72.4, 42.5, 29.7, 26.7, 22.4, 21.4.

9.- Crystals of 8 belong to the orthorhombic space group P212121, and accurate lattice constants of a=24.947(6), b=8.078(3) and c=6.297(3) A. All unique diffraction maxima [theta limits (deg) = 3/51] were collected using 20:0 scans and Cu Ka radiation. Of the 860 reflections measured in this fashion, 836 (97%) were judged observed [I>3 $\sigma$ (I)] and used in subsequent calculations. The structure, solved by the heavy atom method using Enraf-Nonius "The Frenz, SDP/VAX package (B.A. Enraf-Nonius CAD4-SDP" in Computing in Crystallography, Ed., H. Schenk, R. Olthof-Hazekamp, H. Van Koningveld, G.C. Bassi, pp. 64-71, Delft University Press, 1978), was refined to R=0.035. The absolute structure was determined by comparing xyz and -x-y-z refinements. Tables of atomic coordinates, bond lengths and angles, and thermal parameters (supplementary material) are available on request from the Cambridge Crystallographic Data Centre.

10.- The stereoselective formation of the methylcarbinols 8 and 11 and their subsequent epimerization at C-1 in the presence of AlMe<sub>3</sub>/ZnCl<sub>2</sub>, could be disregarded when a sample of pure carbinol 8 remained unaltered after treating with AlMes/ZnClz in CHzClz in the same conditions used for the methylation reaction.

(Received in UK 8 April 1991)