Tetrahedron: Asymmetry Vol. 3, No. 2, pp. 251-254, 1992
Printed in Great Britain

0957-4166/92 $3.00+.00
Pergamon Press plc

BEHAVIOUR OF 2-*p*-TOLYLSULFINYL CYCLOHEXANOLS UNDER THE PUMMERER REACTION CONDITIONS

Ana B. Bueno, M. Carmen Carreño,* José L. García Ruano* and Almudena Rubio.

Departamento de Química (C-I), Universidad Autonoma,
Cantoblanco 28049-Madrid, SPAIN

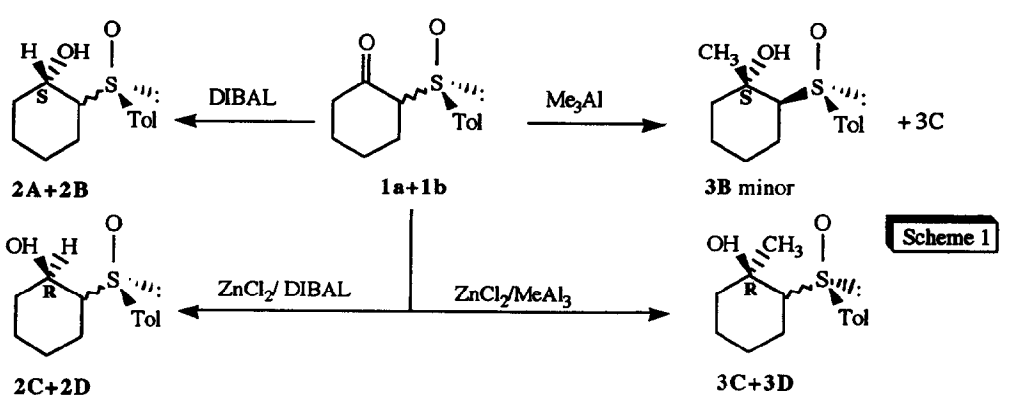
(*Received* 7 *January* 1992)

Key words: *2-p-tolylsulfinylcyclohexanol, Pummerer reaction, Hetero-Claisen rearrangement*

Abstract: The reactions of the chiral 2-*p*-tolylsulfinyl cyclohexanols with Ac_2O/NaOAc (or $(CF_3CO)_2O$/Py) at r.t. yielded the 2-*p*-tolylsulfenyl-2-cyclohexenyl acetates, which cannot be hydrolyzed into the α-hydroxyketones. The 1-methyl-2-*p*-tolylsulfinylcyclohexanols evolved with $(CF_3CO)_2O$/Py into the 3-methyl-2-*p*-tolylsulfenyl-2-cyclohexenyl trifluoroacetates, the latter resulting from a very highly stereoselective hetero-Claisen rearrangement (e.e.>97%) of the initially formed 1-methyl-2-*p*-tolylsulfenyl-2-cyclohexenyl trifluoroacetates.

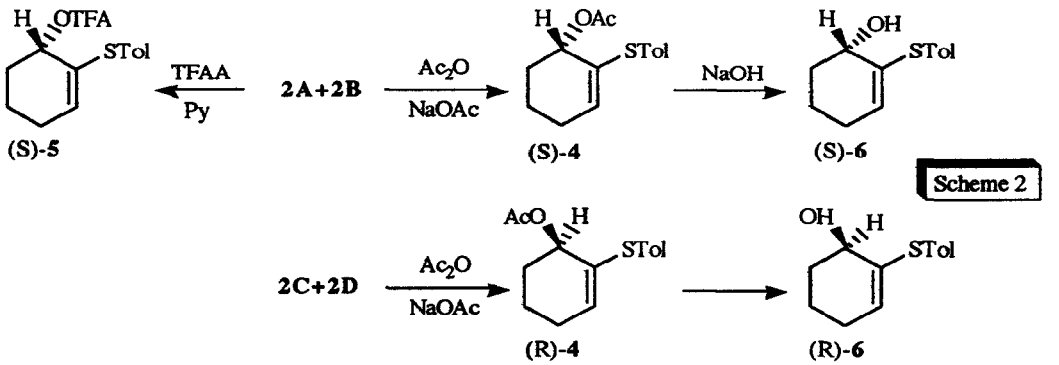
The stereoselectivities of the 2-*p*-tolylsulfinylcyclohexanone reductions with DIBAL and DIBAL/$ZnCl_2$,[1] as well as their methylation with $AlMe_3$/$ZnCl_2$,[2] are mainly controlled by the configuration at the sulfur atom, in such a way that the same configuration is induced at the hydroxylic carbon when starting from epimeric at C-2 ß-ketosulfoxides. This suggested that the reduction and methylation reactions could be carried out on the mixture of 2-*p*-tolylsulfinyl cyclohexanones obtained by sulfinylation of the cyclohexanone,[1] without previous separation, in those cases when the subsequent transformation of the obtained hydroxysulfoxides involved the loss of chirality at C-2. In this sense, the Pummerer reaction could be the chosen method to synthesize optically pure α-hydroxycyclohexanones.[3] In order to check this assumption, we have studied the evolution of the 2-*p*-tolylsulfinyl alcohols **2** and **3** (Scheme 1) under the Pummerer reaction conditions, the results of which we report here.

The reaction of cyclohexanone with (*R*)-menthyl *p*-toluenesulfinate in the presence of $(i\text{-}Pr_2N)MgBr$ yielded a 75:25 mixture of (S_S,R_S) and (R_S,R_S)-2-*p*-tolylsulfinyl cyclohexanones, **1a+1b**;[1] this reacted with DIBAL yielding only **2A** and **2B** (both exhibiting the same (*S*) configuration at C-1) and with DIBAL/$ZnCl_2$ and Me_3Al/$ZnCl_2$ affording the mixtures **2C+2D**[1] and **3C+3D**[2] respectively (all of them with (*R*) configuration at C-1, Scheme 1).



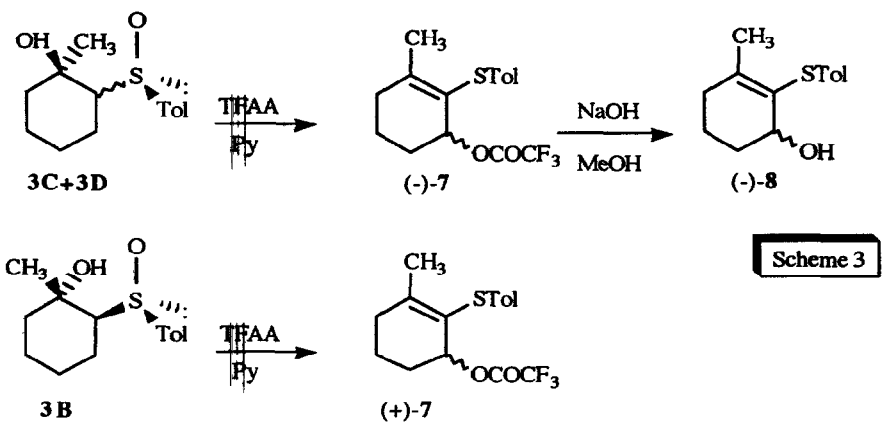
Scheme 1

The reactions of the mixtures **2A+2B** and **2C+2D** with Ac_2O/NaOAc yielded the 2-*p*-tolylsulfenyl-2-cyclohexenyl acetates, (*R*)-**4** ($[\alpha]_D$=+98.7, c=1.0, $CHCl_3$) and (*S*)-**4** ($[\alpha]_D$=-99.1, c=0.5, $CHCl_3$) respectively, instead of the expected hemisulfenylacetal derivatives.[4] In a similar way, the treatment of **2A+2B** with trifluoroacetic anhydride and pyridine in CH_2Cl_2 afforded the trifluoroacetate (*S*)-**5** (Scheme 2). The addition of different chiral lanthanide shift reagents did not split the signals on the samples of the racemic esters **4** and **5**, precluding the determination of their optical purity. Therefore, we hydrolyzed them into the alcohols (*R*)-**6** and (*S*)-**6**,[5] on which we could evaluate an e.e. higher than 97% (only one enantiomer was detected in each case) by nmr (Eu(tfc)$_3$). This confirms that the stereoselectivity of both DIBAL and DIBAL/$ZnCl_2$ reductions is only controlled by the configuration of the sulfur atom. All the trials to obtain the α-hydroxycyclohexanone from the hydrolysis of the vinylsulfides (**4-6**) were unsuccesful.[6]



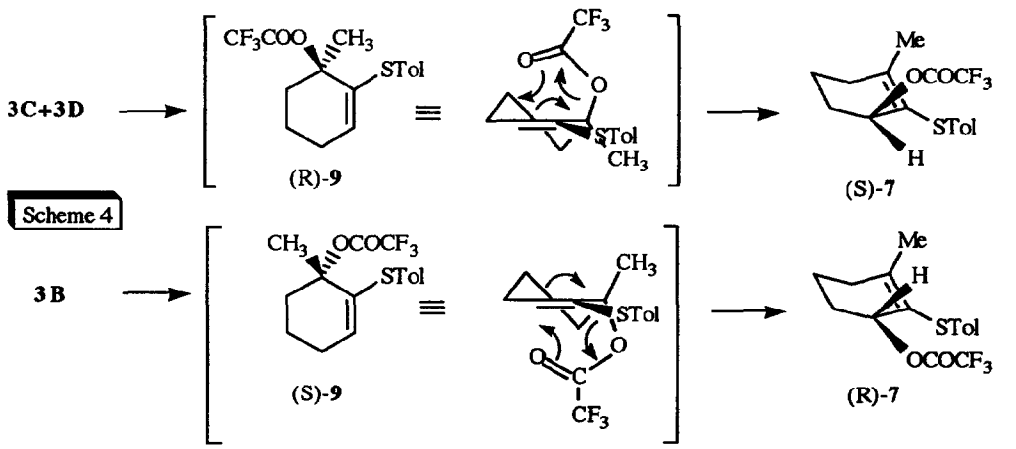
Scheme 2

More interesting were the results obtained when the mixture of methylcarbinols, **3C+3D**, was treated to Pummerer reaction conditions (Scheme 3).[7] The treatment of this mixture with $(CF_3CO)_2O$/Py in CH_2Cl_2 during 6 hours at room temperature yielded the trifluoroacetate (-)-**7**[8] (85% yield, $[\alpha]_D$=-200, c=1.0, $CHCl_3$). When the (S_1,S_2,R_S)-1-methyl-2-*p*-tolylsulfinyl cyclohexanol **3B** (Scheme 1) was treated with $(CF_3CO)_2O$/Py, the enantiomer (+)-**7** ($[\alpha]_D$=+207 c=1.0, $CHCl_3$) was isolated in 76% yield. Since the optical purity of these compounds could not be determined by the use of nmr Eu(tfc)$_3$, as had previously happened with **4** and **5**, the hydrolysis of (-)-**7** into the alcohol (-)-**8**[9] (84% yield, $[\alpha]_D$=-233, c=0.9, $CHCl_3$) with NaOH(2N)/MeOH (r.t., 4 h.) was again necessary. The enantiomeric excess of compound (-)-**8** is higher than 97% (determined by 200 MHz ^{1}H-nmr).



Scheme 3

Taking into account the behaviour of the secondary ß-hydroxysulfoxides (**2**) under these conditions (Scheme 2), the formation of the compounds **7** from the tertiary carbinols **3** could be rationalized by assuming the initial formation of (*R*) or (*S*)-**9**[9] (1-methyl-2-*p*-tolylsulfenyl-2-cyclohexenyl trifluoroacetate) which later evolved into the optically pure **7**. This last transformation must be highly stereoselective and has to involve a [3,3]-sigmatropic rearrangement (Scheme 4), such as the hetero-Claisen reaction. Nevertheless, the usual conditions of this kind of rearrangement (metallic salts as catalysts,[10,11] or very high temperatures[12]) strongly contrast with the mild conditions in which the transformation **9** to **7** takes place (room temperature and absence of catalyst). The study of the molecular model of the intermediates **9** evidenced strong steric interactions between the STol group at C-2 and both groups (Me and $OCOCF_3$) at C-1, which could be invoked to explain the large tendency of **9** to evolve into **7**.



As we can deduce from the proposed stereochemical course of the reaction (Scheme 4) the absolute configuration of the rearranged allylic ester **7** is the opposite to that of the starting one. Thus, the configuration of the trifluoroacetate (-)-**7**, obtained from the ester (*R*)-**9**, derived from the mixture **3C+3D**) must be (*S*), just like the ester (+)-**7** (resulting from (*S*)-**9**, derived from **3B**) has to be (*R*).

We are now studying the behaviour of other cyclic ketosulfoxides in order to know the scope of these reactions that allow us to obtain optically pure cyclic allylic alcohols.

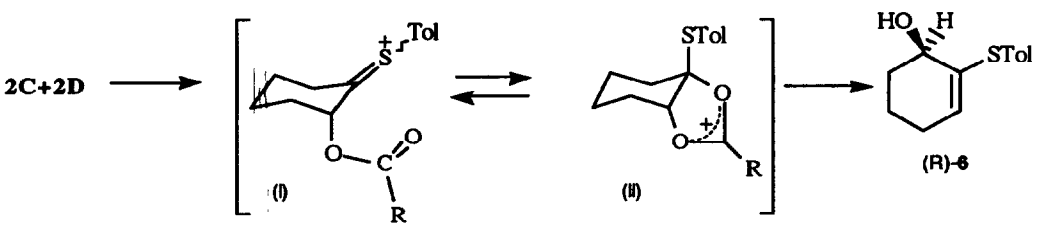
Acknowledgements

We thank *DGICYT* (Grant PB88-0176) for financial support.

REFERENCES AND NOTES

1.- M.C. Carreño, J.L. García Ruano and A. Rubio, *Tetrahedron Lett.* **1987**, *28*, 4861.
2.- A.B. Bueno, M.C. Carreño, J. Fischer, J.L. García Ruano, B. Peña, L. Peñas, and A. Rubio, *Tetrahedron Lett.* **1991**, *32*, 3191.
3.- S. Iriuchijima, K. Maniwa, G. Tsuchihashi, *J. Am. Chem. Soc.*, **1974**, *96*, 4280.
4.- This behaviour has been observed in other substrates (P.J. Brown D.N. Jones, M.A. Khow, N.A. Meanwell, *J. Chem. Soc., Perkin Trans. I*, **1984**, 2049).
5.- Compound 6: **^{1}H-nmr** ($CDCl_3$): 7.26 and 7.11 (AA'BB' system), 6.16 (*t*, 1H, J=4.0 Hz), 4.03 (*m*, 1H, CH-O) 2.32 (*s*, 3H, CH_3-Ar), 2.33-1.51 (*m*, 6H). **^{13}C-nmr**: 137.1, 135.4, 131.1 (2C), 130.5, 129.9 (2C), 128.7, 65.8, 31.2, 27.1, 21.0 and 17.6. (*S*)-enantiomer: $[\alpha]_D$=-215 (c=1.2, $CHCl_3$); (*R*)-enantiomer: $[\alpha]_D$=+213 (c=1.5, $CHCl_3$)

6.- The hydrolysis of **4** with $HgCl_2$ in aqueous acetonitrile (E.J. Corey and J.I. Shulman, *J. Org. Chem.*, **1970**, *35*, 777) did not lead to the expected hydroxyketone, despite long reaction times. Equally unsuccessful was the addition of dry HCl to **4** and further reaction of the chlorinated intermediate with $HgCl_2$ in aqueous THF (A.J. Mura Jr, G. Magetich, P.A. Grieco and T. Cohen, *Tetrahedron Lett.*, **1975**, 4437), or the treatment of **5** with $TiCl_4$ and further hydrolysis with H_2O (T. Mukaiyama, K. Kamio, S. Kobayashi, and H. Takei, *Bull. Chim. Soc. Jpn.*, **1972**, *45*, 3723.; T. Mukaiyama, M. Shiono, and T. Sato, *Chem. Lett.* **1974**, 37). The reactions used in reference 4 to hydrolyze the vinylic thioethers to the ketones were not fruitful. The only method yielding trace amounts of adipoin and trifluoroacetoxy adipoin, involved the reaction of **4** with TFA in $CHCl_3$ (D.H. Hua, S. Venkataraman, M.J. Coulter and G. Sinai-Zingde, *J. Org. Chem.*, **1987**, *52*, 719). Unfortunately, this reaction evolved with racemization and the isolated α-hydroxycyclohexanone exhibited almost no optical rotation. The unexpected evolution of the substrates under the Pummerer conditions and the low reactivity of the obtained vinyl thioethers can be explained as a consequence of the anchimeric assistance of the trifluoroacetoxy group at C-1. Thus, the sulphenium salt **I**, intermediate in the Pummerer reactions, is intramolecularly attacked by the carboxylate, yielding the intermediate **II**. This evolution is entropically favored with respect to any attack of the external nucleophiles. Further transformation of the intermediates **I** or **II** is only possible by the action of a base, which yields the sulfenyl derivatives **4** or **5**. Intermediates such as **II** might be also responsible of the lack of reactivity of the vinylic thioethers.



7.- The reaction was also carried out on diastereomerically pure **3C** and **3D**. The obtained results were identical to those from their mixture.

8.- Compound **7**: ^{1}H-nmr ($CDCl_3$): 7.1 (AA'BB' system), 5.40 (*m*, 1H,CHO), 2.30 (*s*, 3H, CH_3-Ar) 2.05 (*bs*, 3H, CH_3-C=), 2.00-1.70 (*m*, 6H). Compound **8**: ^{1}H-nmr ($CDCl_3$): 7.07 and 7.00 (AA'BB' system), 4.05 (*m*, 1H, CHOH), 2.30 (*s*, 3H, CH_3-Ar), 1.98 (*d*, 3H, J=1.0 Hz, CH_3-C=), 2.20-1.50 (*m*, 7H). ^{13}C-nmr: 146.0, 135.5, 132.0,129.6, 128.4 (2C), 127.2, 66.8, 33.1, 31.0, 21.9, 20.8 and 17.8.

9.- The reaction of 2-*p*-tolylsulfinylcycloheptanone with $ZnCl_2/Me_3Al$ gave a mixture of two methylcarbinols, the treatment of which with $(CF_3CO)_2O$/Pyr yielded a mixture of compounds. Two of them were characterized as 3-methyl and 1-methyl 2-*p*-tolylsulfenyl-2-cycloheptenyl trifluoracetates (the rearranged product and its precursor). Despite the fact that the configuration of all these products has not yet been unequivocally established both alcohols reinforce the proposed mechanism.

10.-L.E. Overman, C.B. Campbell and F.M. Knoll, *J. Am. Chem. Soc.*, **1978**, *100*, 4822.
11.-S.J. Danishefsky, M.P. Kabal and K. Chow, *J. Am. Chem. Soc.*, **1989**, *111*, 3456.
12.-W.S. Trahanovsky and P.W. Mullen, *J. Am. Chem. Soc.*, **1972**, *94*, 5086.