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Synthesis and Stereoselective Reductions of Chiral ß-Iminosulfoxides

José L. García Ruano,* Antonio. Lorente and Jesús H. Rodríguez

Departamento de Química, Universidad Autónoma, Cantoblanco 28049-Madrid, SPAIN

Abstract Reaction of chiral non racemic ß-ketosulfoxides with amines or condensation of the imine enolates with (-)-menthyl sulfinate yield optically pure ß-iminosulfoxides. The second method requires the presence of an excess of $MgBr_2$ in order to avoid epimerization at sulfur. The highly diastereoselective reduction of these substrates can be successfully achieved only with DIBAL/$ZnBr_2$ (d.e.>97%). Hydrogenolysis of the C-S bond on the obtained ß-aminosulfoxides yields the protected primary amines with e.e. higher than 97%.

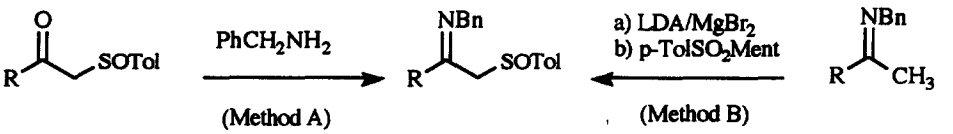
One of the most versatile methods to obtain acyclic chiral secondary methyl carbinols involves the reduction of the optically pure ß-ketosulfoxides with DIBAL and DIBAL/$ZnCl_2$, followed by desulfuration of the resulting ß-hydroxysulfoxides.[1] The scope of this methodology has been recently extended to other secondary alcohols by applying it to different a-alkylß-ketosulfoxides.[2] These excellent results suggested the possibility of using a similar methodology to synthesize enantiomerically pure acyclic amines from the corresponding ß-iminosulfoxides.[3] In order to find a general method to obtain the latter and to reduce them in a highly stereoselective way we have studied and optimized different methods and reagents. The most significant results obtained from these studies are reported hereby. Meanwhile, one paper concerning the synthesis and stereoselective reductions of ß-iminosulfoxides was published.[4] Despite the conditions indicated in it to prepare the a-sulfinylimines as well as the reagent proposed to get their stereoselective reductions had been considered in our study and disregarded because they were not satisfactory enough to be accepted as the general method that we were looking for, this paper prompted us to publish our results.

Several methods have been reported to synthesize ß-iminosulfoxides.[5] Nevertheless it seems that none of them is of general scope. In fact they have been used to prepare very specific series of compounds but failed, in many cases, when they were extended to other series. As we were interested in a general method to prepare enantiomerically pure ß-iminosulfoxides derived from ketones, we looked for one which could be applied to the synthesis of compounds **1-5** (Table 1), which are N-benzyl-1-R-2-(*p*-tolylsulfinyl)ethylidenamines, with R=methyl, primary (*n*-Pr), secondary (*i*-Pr), tertiary (*t*-Bu) and aromatic (Ph) groups.

We have used two successful methods to synthesize the optically pure a-sulfinylimines. The first involves the condensation of the chiral non racemic ß-ketosulfoxides (which were obtained from the reaction of esters with (***R***)-methyl *p*-tolyl sulfoxide)[6] with benzylamine in the presence of molecular shieves (3 A), using benzene as solvent (Method A, reaction time and temperature are indicated in table 1).[7] This method does not affect the configurational stability of the sulfur atom, yielding the ß-iminosulfoxides with the same optical purity as the one of the starting ketone. The second and shorter method consists on the condensation of the lithium N-benzylimine enolates (generated by reaction of LDA with the imines, which in turn were prepared by standard methods) with

(-)-menthyl sulfinate, affording the ß-iminosulfoxides in high yields (Method B).[8] The reactions had to be carried out in the presence of an excess of $MgBr_2$ in order to avoid the parcial epimerization of the sulfinyl sulfur.[9] Both methods yield products with high optical purity (e.e.>97%).[10] Significant data from these reactions are indicated in table 1.

Table 1. ß-Iminosulfoxides Prepared from Methods A and B



Comp.	R	Yield (%) [reaction time (h), T (°C)]		$[\alpha]_D^a$
		Method A	**Method B**	
1	Me	94 [12, r.t.]	83 [1, -48]	-8.0
2	*n*-Pr	90 [12, r.t.]	75 [1, -48]	-50.0
3	*i*-Pr	55 [72, r.t.]	81 [1, -48]	-66.1
4	*t*-Bu	55 [96, reflux]	40 [1, r.t.]	+145.0
5	Ph	65 [24, reflux]	92 [1, 0]	-120.7

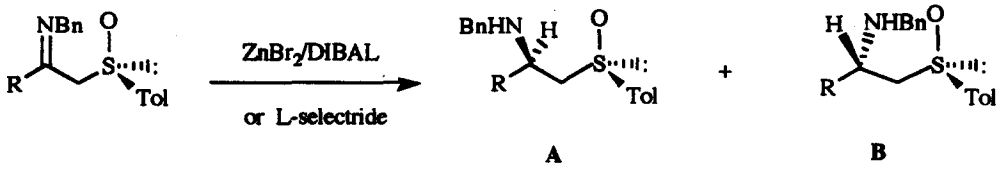
[a]These values (measured in CH_2Cl_2, c=1.0) are not constant in the time.

As we see, the yields are high except in the case of compound **4** (R=*t*-Bu), probably due to the steric effect of the *t*-butyl group. This large size could also be responsible for the fact that only substrate **4** mainly exists as iminic tautomer (Z regioisomer) whereas in the other ß-iminosulfoxides the enaminic structure is preferred. These properties are easily characterised by nmr.[11]

The yield and stereoselectivity of the reductions of ß-iminosulfoxides **1-5** with $NaBH_4$ or $LiAlH_4$ are only moderate.[12] The DIBAL reduction of these compounds was not possible but, in the presence of $ZnBr_2$, this hydride easily affords the aminosulfoxides **6A-10A**[11] (Table 2). High yields were obtained except for compound **10A**. The stereoselectivity is very high for all substrates. This behaviour can be explained by assuming that $ZnBr_2$ stabilizes the (**E**)-regioisomer of the ß-iminosulfoxide tautomer by formation of a chelate, which determines the shifting of the enamine-imine equilibrium towards the latter. This chelated tautomer is now easily reduced by DIBAL.[13] The instability associated of the (**E**)-regioisomer of compound **4** (R=*t*-Bu) justifies the increase of the reaction time and the decrease of the yield observed in the reduction of this substrate.

Compounds **1**, **2** and **5** were also reduced with L-Selectride using the conditions reported in ref. 4. As we see in table 2, the yields are only satisfactory when the size of R is small, precluding the use of L-selectride as a stereoselective reducing agent of β-iminosulfoxides. On the other hand, the major epimers (**6B** and **7B**)[11] are not the same as that obtained with DIBAL/$ZnBr_2$, which indicates that both must exhibit the opposite configuration at the carbon supporting the nitrogenated function.

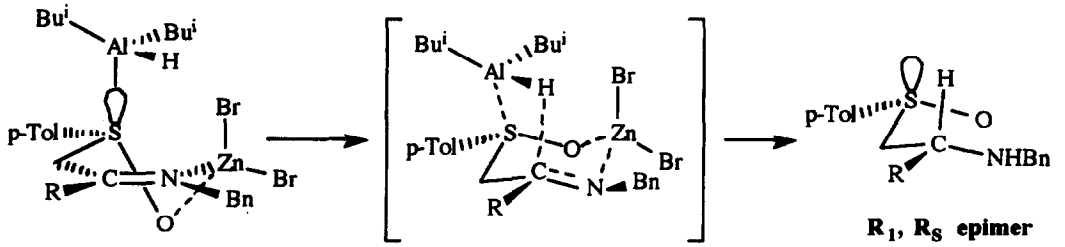
Table 2. Results Obtained in Reduction of **1-5** with $ZnBr_2$/DIBAL (-22°C) and L-Selectride.



A **B**

		$ZnBr_2$ / DIBAL			L-Selectride		
Subst.	Product	R. time (h)	Yield (%)	(A:B ratio)	R. time (h)	Yield (%)	(A:B ratio)
1	**6**	3	80	(>97 : <3)	12	50	(9 : 91)
2	**7**	3	72	(>97 : <3)	12	10	(<9 : >91)
3	**8**	3	82	(>97 : <3)			
4	**9**	48	15	(>97 : <3)			
5	**10**	4	75	(>97 : <3)	48	0	

The desulfinylation of the compound **10A** with Ra-Ni yielded the optically pure N-benzyl-1-phenylethylamine, the rotary power of which (-56°, c=1.07, EtOH) is identical but with the opposite sign to that of the (*S*)-enantiomer, previously reported.[14] This chemical correlation allowed us to state unequivocally the assignment of **10A**, the absolute configuration of which must be R_1,R_S. Therefore, configuration of **10B** must be S_1,R_S, and not the R_1,R_S one suggested by the authors in reference 4. A similar mechanism to that suggested for the reduction of ß-ketosulfoxides with $ZnCl_2$/DIBAL[15] can be invoked to explain the stereochemical course of the ß-iminosulfoxides with $ZnBr_2$/DIBAL. The upper face approach of the DIBAL on the most stable half-chair conformation of the chelated species (with the *p*-tolyl group in equatorial arrangement) is favoured with respect to the lower face approach on both steric (the chair-like transition state involved in the first, which is shown in Scheme 1, is more stable than the twist-like transition state of the latter) and stereoelectronic (stabilizing interactions between the lone electron pair at sulfur and the aluminium) grounds.



R_1, R_S epimer

Scheme 1

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2. Barros D.; Carreño M.C.; García Ruano J.L.; Maestro M.C. *Tetrahedron Lett.*, **1992**, *33*, 2733.
3. The synthesis of enantomerically pure cyclic β–iminosulfoxides and the study of their reduction whith diferent reducing agents has been recently reported by us (Carreño M.C.; Dominguez E.; García Ruano J.L.; Pedregal C.; Rodriguez J.H. *Tetrahedron*, **1991**, *47*, 10035). Despite the success obtained in the stereoselective reduction of these substrates, their behaviour with DIBAL and DIBAL/$ZnCl_2$ was not identical to that of the ketosulfoxides.
4. Ogura K.; Tomori H.; Fujita M. *Chemistry Lett.* **1991**, 1407.
5. a) See Baldenius K. U. ; Kagan H. B. *Tetrahedron Asymmetry*, **1990**, *1*, 597, and references cited therein. b) Hua D.H.;Bharathi S. N.; Panangadan J. A. K.; Tsujimoto A. *J. Org. Chem.*, **1991**, *56*, 6998.
6. García Ruano J.L.; Martín A.; Rodriguez J.H. *Tetrahedron Lett.* **1991**, *32*, 3195.
7. We have used the experimental method reported by Westheimer (Taguchi K.; Westheimer F.H. *J. Org. Chem.*, **1971**, *36*, 1570). We have also tried the conditions reported in ref. 4, but they were suitable only for compounds **1** and **2** (R=methyl or primary). The reaction of 2-(*p*-tolylsulfinyl)-1-phenyletanone with amines in the presence of $TiCl_4$ was used by Kagan to obtain β-iminosulfoxides of similar structure to that of **5** (see reference 5a), but the obtained yields were very poor (<30%).
8. n-Butyllithium (10.6 mmol) in hexane was added at -48°C to a stirred solution of di-isopropilamine (11 mmol) in THF (15 ml). The mixture was kept at -48° for 20 min and the imine (10 mmol) in THF (30 ml) was slowly added (70 min). After 15 min at -48°C, a freshly prepared solution of $MgBr_2$ in THF (43 ml, 0.28M) was added and the mixture stirred for 20 min. A THF solution (10 ml) of (-)- menthyl sulfinate (0.34 mmol) was then rapidly added and stirred for 1 h at room temperature. The reaction mixture was decomposed (saturated NH_4Cl, 30 ml) and extracted with CH_2Cl_2. The residue was purified by flash chromatography on silica gel (AcOEt/hexane/Et_3N). In the case of compound **5**, an increase of the temperature and imine concentration (4 equiv.) were necesary to obtain a high yield. A similar procedure (only differing in the molar ratio of the reagents and the reaction temperature) was successfully used to prepare β-iminosulfoxides derived from aldimines. (Annunziata R; Cinquini M.; Restelli A.; Cozzi F. *J. Chem. Soc. Perkin Trans. I*, **1982**, 1183) but the yield was poor when they applied it to one ketimine. It suggests that the mentioned differences must be critical to obtain high yields of the ketimine derivatives.
9. This requirement was also observed in the synthesis of other N-benzylated β-iminosulfoxides (see reference 3a). It can be explained by assuming a competition between the C-sulfinylation and the N-sulfinylation of the iminoenolate and the further attack of the enolate on the sulfinamide resulting in the N-sulfinylation.
10. The e.e. of compounds **1-5** were determined by comparison of the rotatory powers of their hydrolisys products with those of the optically pure starting β-ketosulfoxides.
11. Chemical shifts for the significant protons of the obtained compounds:

Comp.	CH-S[a]	CH_2S[b]	Comp.	CH-N	CH_2S	Comp.	CH-N	CH_2S
1[c]	5.10	3.83-3.72	**6A**	3.22	3.05-2.64	**6B**	3.30	2.85-2.81
2	5.07		**7A**	3.00	3.03-2.72	**7B**	3.20	2.88-2.75
3	4.95		**8A**	2.82	2.98-2.76			
4		4.05-3.67	**9A**	3.02	2.90-2.55	**9B**	3.02	2.96-2.58
5	5.35		**10A**	4.18	3.23-2.81			

[a] Enaminic form; [b] AB system of the iminic form; [c] enamine-imine ratio = 2.2:1

12. The preference of these substrates for the enaminic tautomer could be responsible for their low reactivity with nucleophilic hydrides. Compound **4** is easily reduced by $NaBH_4$, but the stereoselectivity is low (**9A**:**9b** = 1:1.5).
13. We have studied by nmr the influence of the Lewis acid on the imine-enamine equilibrium in the case of the compound **5**. We could observe that the initially formed enaminic tautomer was converted completely into the iminic form by addition of the $ZnBr_2$.
14. Park K. *J. Prakt. Chem.*,**1912**, *86*, 287.
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