Pergamon

Tetrahedron Letters, Vol. 37, No. 26, pp. 4569-4572, 1996
Copyright © 1996 Elsevier Science Ltd
Printed in Great Britain. All rights reserved
0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)00848-9

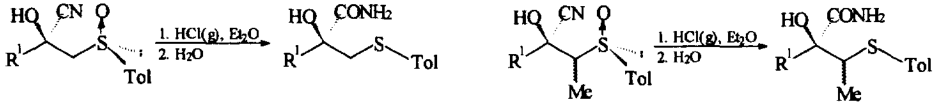
Anchimeric Assistance of the Sulfinyl Group in the Hydrolysis of Cyano Groups: A New Mild Method for the Reduction of Sulfoxides.

Jose L. García Ruano,* Ana M. Martín Castro, and Jesús H. Rodriguez Ramos*
Departamento de Química Orgánica, Universidad Autónoma de Madrid, Cantoblanco, 28049-Madrid. SPAIN

Abstract: *Conditions to achieve reductive hydrolysis of β-cyanosulfoxides into their corresponding β-sulfenylamides are reported. The anchimeric assistance of the sulfinyl oxygen in the hydrolysis of the cyano group is proposed to explain the mild conditions required to achieve it and several proofs supporting this assumption are indicated. From these results a new mild method to transform sulfoxides into sulfides has been developed.*

In the course of our studies on asymmetric hydrocyanation of sulfinylketones R^1-CO-CHR^2-SOTol with Et_2AlCN[1,2] and its application to the synthesis of chiral 2-alkylglycidic acid derivatives,[3] we found that the hydrolysis of the cyano group of β-sulfinylcyanohydrins into carboxamide took place in high yields (>80%) under unusually mild conditions (treatment with HCl(g) in anhydrous diethyl ether at 0°C). Concomitant reduction of the sulfinyl group was observed in all these reactions (Scheme 1). Taking into account the much stronger conditions required for the hydrolysis of nitriles into amides or carboxylic acids,[4] as well as the difficulties usually found when trying to stop the sequence at the amide stage (the hydrolysis of the latter is usually easier than that of the starting nitrile), our results prompted us to investigate the stereochemistry and mechanism of these reactions as well as their synthetic scope. In this paper we report the results obtained in the hydrolysis of several β-sulfinyl cyanohydrins under different conditions, propose a mechanistic pathway to explain the observed results, indicating several chemical proofs supporting it, and describe a mild general method for the reduction of sulfoxides to sulfides.

Sulfinylcyanohydrins **1a-1j** were synthesized by asymmetric hydrocyanation of the corresponding β–ketosulfoxides following previously described procedures.[1-3] Hydrolysis of substrates **1a-1j** was attempted under different acidic conditions (they decompose into the starting β-ketosulfoxides in basic medium).



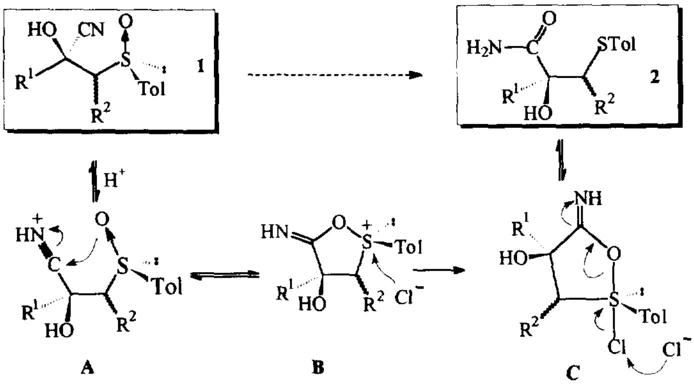
	R^1	Yield (%)	
1a	Ph	82	**2a**
1b	Me	73	**2b**
1c	Et	80	**2c**
1d	*n*-Pr	81	**2d**
1e	*t*-Bu	82	**2e**

	R^1	Yield (%)	
1f	Ph	95	**2f**
1g	Me	92	**2g**
1h	*n*-Pr	96	**2h**
1i	*i*-Pr	87	**2i**
1j	*t*-Bu	79	**2j**

Scheme 1

The best results, achieved by using a saturated solution of HCl(g) in Et_2O (0-4°C, 1-24 h) and further addition of H_2O (0-4°C, 1-2 h),[5] are indicated in Scheme 1 (concentrated HCl and mixtures of concentrated HCl-EtOH or HCl(g) in Et_2O-MeOH[6] were also used with poorer results). Under these conditions, sulfenylhydroxyamides **2f-2j** were obtained as the sole product[7] of their respective reactions. This behavior was also observed for **1a**, whereas cyanohydrins **1b**-**1e** afforded mixtures where sulfenylamides **2a**-**2e** were the main products in all cases. Thus, starting from **1b**-**1d**, 85:15 mixtures of sulfenylamides **2a**-**2e** and the corresponding sulfenylcyanohydrins were obtained after 24 h, whereas **1e** yielded a similar mixture where the proportion of the sulfenylcyanohydrin was dependent on the reaction time. It was practically as large as that of the carboxamide at short periods of time (30 minutes),[8] but for reaction times higher than 4 days decreased to reach a proportion similar to that attained in the other cases. Changes in the reaction medium avoided the formation of the sulfenylcyanohydrins. Thus, compound **1c** yielded only carboxamide **2c** (81% isolated yield) using EtOH instead of Et_2O as the solvent, and all substrates **1b**-**1e** were cleanly transformed into sulfenylcarboxamides **2b**-**2e** as the sole products by treatment with freshly distilled HBF_4 in anhydrous diethyl ether or CH_2Cl_2 at 0°C for 1-24 h, followed by NaI at 0°C for 1h.

The mild conditions required to achieve the hydrolysis of the cyano group and the fact that it took place with simultaneous reduction of the sulfinyl group, suggested the participation of the sulfinyl oxygen in the hydrolysis of the nitrile. A reasonable mechanism for the transformation of **1** into **2** is shown in Scheme 2.



Scheme 2

In the first step, the nucleophilic intramolecular attack of the sulfinylic oxygen on the cyano group, activated by association with the proton of the acid reagent (HCl(g) or HBF_4), would yield the cyclic oxysulfonium species **B**. The latter is able to react with the chloride anion present in the medium (or the iodide from NaI added later) giving rise to the sulfurane intermediate **C**,[9] bearing the most electronegative substituents at the apical possitions of a trigonal bipyramid.[10] The stability of this intermediate would be favored by its five-membered cyclic structure. The attack of a second chloride anion on the halogen at the sulfurane **C** would afford the sulfenylcarboxamide **2** with evolution of Cl_2.

We have several proofs supporting this mechanistic proposal.

i) Evolution of chlorine could be evidenced in the hydrolysis of compound **1c**.[11]

ii) The treatment of several commercially available nitriles and sulfoxides with HCl(g)/Et_2O or HBF_4 under the conditions used to transform **1a**-**1g**, resulted neither in the hydrolysis of the former ones nor in the reduction of the latter ones.

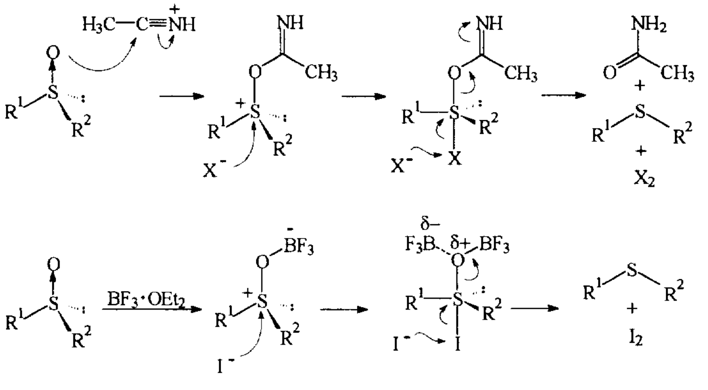
iii) The use of sulfinylcyanohydrin **1e** ^{18}O-labelled at the sulfinyl group[12] as the starting material, allowed us to obtain sulfenylcarboxamide **2e** bearing the ^{18}O-labelling at the amidic oxygen.[13]

The above results strongly support the participation of the sulfinyl group in the hydrolysis of the cyano group as well as the mechanistic pathway depicted in Scheme 2. It can be deduced that both processes (reduction of sulfoxides and hydrolysis of nitriles) could be independently achieved, which prompted us to look for the conditions required for both processes. All our efforts to find the conditions able to get the mild hydrolysis of nitriles with protonic or Lewis acids in DMSO have been so far unsuccessful. Conversely we have found a general procedure for the reduction of sulfoxides to sulfides, which involved addition of the sulfoxides into a HCl(g) saturated solution of acetonitrile.[14] The results obtained in the reduction of different representative sulfoxides are collected in table 1. As it can be seen, all the tested sulfoxides were reduced in high yields in short reaction times. The steric hindrance of *t*-Bu_2SO must be responsible for its lack of reactivity.

Table 1. Results obtained in the reduction of commercial sulphoxides (R^1-SO-R^2) with HCl(g)/CH_3CN at 0°

R^1	R^2	React. time	Yield (%)	R^1	R^2	React. time	Yield (%)
Me	*p*-Tol	1 h	85	Bn	Bn	1 h	84
n-Bu	*n*-Bu	1 h	82	Bn	*p*-Tol	1 h	86
i-Pr	*i*-Pr	1.5 h	78	*t*-Bu-CH_2	*p*-Tol	1.5 h	87
Ph	Ph	2.5 h	91	*t*-Bu	*t*-Bu	8 h	--

Deoxygenation of sulfur moiety would take place as a consequence of a nucleophilic attack of sulfinyl oxygen on the protonated nitrile group, followed by attack of Cl^- on sulphur (Scheme 3), according to a mechanism which is quite similar to that proposed for the hydrolysis of sulfinylcyanohydrins (Scheme 2). Isolation of acetamide (*ca.* 1 equiv) from the reaction media reinforces our mechanistic proposal.



Scheme 3

Taking into account that one of the most widely used and useful methods for the reduction of sulfoxides consists in their treatment with BF_3-OEt_2/NaI,[15] and that the conditions are similar to those herein reported [one acidic species —BF_3 and HCl(g), respectively— and one nucleophile —iodide or chloride], we have compared our mechanistic proposal with that reported in reference 15, which has also been depicted in Scheme 3. The only significant difference derives from the fact that, in this reference, the authors do not consider any role of CH_3CN, despite it is the solvent used in their reductions. Two different proofs have been made in order to clarify this point. First, the reaction of methyl *p*-tolyl sulfoxide with $BF_3.OEt_2$ and NaI in CH_2Cl_2 as the solvent, led to the unaltered starting material. Second, the study of the ^{1}H-NMR spectrum of the crude of the reaction of **1c** with $BF_3.OEt_2$ /CH_3CN and further treatment with NaI, in conditions identical to those reported allowed us to detect the formation of acetamide (*ca.* 1 equiv). It suggests, as the most probable pathway of these reductions, the reaction of the iodide with the oxysulfonium species resulting from the attack of the sulfinyl oxygen on the acetonitrile activated by association with BF_3 (instead of doing it on the sulfoxide associated to the Lewis acid).

In summary, we have reported the conditions to achieve inter and intramolecular reduction of sulfoxides to sulfides by reaction with protonated nitriles. We are currently working on the mechanism and synthetic scope of other reactions of sulfoxides with activated nitriles using as nucleophiles in the second step species different to halides.

Acknowledgement: We thank Dirección General de Investigación Científica y Técnica (Grant PB 92-0161) for financial support.

REFERENCES AND NOTES

1. García Ruano, J.L.; Martín Castro, A.M.; Rodriguez, J.H. *Tetrahedron Lett.* **1991**, *32*, 3195.
2. García Ruano, J.L.; Martín Castro, A.M.; Rodríguez, J.H. *J. Org. Chem.* **1992**, *57*, 7235.
3. García Ruano, J.L.; Martín Castro, A.M.; Rodríguez, J.H. *J. Org. Chem.* **1994**, *59*, 533.
4. Sarel, S.; Newman, M.S. *J. Am. Chem. Soc.* **1956**, *78*, 5416. Tsai, L.; Miwa, T.; Newman, M.S. *J. Am. Chem. Soc.* **1957**, *79*, 2530. Becke, F.; Fleig, H.; Pässler, P. *Liebigs Ann. Chem.* **1971**, *749*, 198. Houser, C.R., Hoffenberg, D.S. *J Org. Chem.* **1955**, *20*, 1448. Hauser, C.P.; Eby, C.J. *J. Am. Chem. Soc.* **1957**, *79*, 725.
5. The experimental procedure and physical and spectroscopical data of compounds **1** and **2** are described in refs. 1-3.
6. Herranz, R; Castro-Pichel, J.; Vinuesa, S.; García López, M.T. *J. Org. Chem.* **1990**, *55*, 2232.
7. In these reactions, **1f-1j** are used as mixtures of diastereomers (epimers at C-α) and, consequently, **2f-2j** are also obtained as mixtures of isomers in the same ratio than that of the corresponding starting products.
8. A small proportion of one sulfinyl carboxamide (which disappeared with the time) was also isolated under these conditions. As this compound has been also isolated under other hydrolysis conditions, we are currently elucidating its structure, optimizing the conditions required for its formation and investigating both the mechanism and the synthetic scope of this reaction.
9. Hayes, R.A. ; Martin, J.C. *Sulfurane Chemistry*, in *Organic Sulfur Chemistry*, Bernardi, F. ; Csizmadia, I.G. ; Mangini, A., Eds. Elsevier, Amsterdan, **1985**, 408.
10. Other alternative explanation would involve a S_N2 process at the sulfur atom, with concomitant formation of the Cl-S bond and breaking of the S-O bond, yielding the chlorosulfonium carboxamide. The evolution of this species would be similar to that proposed for the sulfurane **C** in Scheme 2.
11. The flask containing a solution of **1c** (R^1=Et, R^2=H) in diethyl ether, previously saturated with hydrogen chloride, under argon, was connected to a solution of sodium iodide in diethyl ether. As the chlorine evolved, the characteristic colour of iodine in the solution could be clearly detected.
12. It was prepared by condensation of the lithium anion derived from Me-S(^{18}O)-Tol (obtained in a 12.5% ^{18}O-content (MS) following the procedure described by Drabowicz J. ; Midura, W. ; Mikolajczyk M., *Synthesis Comm.*, **1979**, 39) with ethyl pivaloate and subsequent hydrocyanation of the resulting sulfinyl ketone with Et_2AlCN.
13. The presence of the ^{18}O in **2e** obtained from labelled **1e** was clearly evidenced by its mass spectrum regarding the higher intensity of the signal at m/z 269 (M^++2) than that of the same signal observed in the mass spectrum of **2e** obtained from an unlabelled **1e** sample, registered at the same conditions. The ^{18}O-labelled carboxamide moiety could be inferred from both the higher intensity of the signal at m/z 251 [isotopic peak of the fragment at m/z 249 (M^+-18)] in the spectrum obtained from the labelled sample, and the similar intensity of the signal at m/z 225 [isotopic peak of the fragment at m/z 223 (M^+-$CONH_2$)], in both spectra.
14. A solution of 1 mmol of sulfoxide in 3 mL of CH_3CN, previously saturated with hydrogen chloride, was stirred at 0°C. Water (1 mL) was added and the mixture stirred at 0°C for 1 h. The solvent was evaporated in vacuo. The residue was dissolved in CH_2Cl_2, washed with brine, and concentrated.
15. Vankar, Y.D.; Trinidha Rao, C. *Tetrahedron Lett.* **1985**, *26*, 2717.

(*Received in UK* 28 *March* 1996; *revised* 30 *April* 1996; *accepted* 3 *May* 1996)