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Reactions of chiral ß-ketosulfoxides with Et_2AlCN: Asymmetric synthesis of cyanohydrin derivatives.

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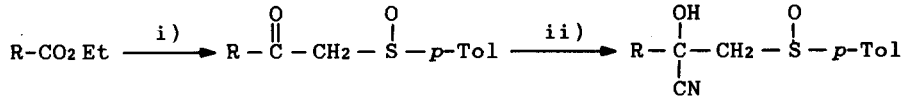
SUMMARY: The reaction of chiral *p*-tolylsulfinylmethyl ketones (R-CO-CH_2-SOTol, R=Ph, Et and *t*-Bu) with Et_2AlCN, yields almost optically pure sulfinyl cyanohydrins (d.e. ≥ 96%). The reaction was quicker in the presence of $ZnCl_2$, but the stereochemical results were identical. The cyanohydrins were transformed into the α-methyl α-hydroxyamides (e.e.≥92%) by hydrolysis of the CN group and subsequent hydrogenolysis of the C-S bond.

The easy transformation of cyanohydrins in biologically and pharmaceutically interesting organic groupings, such as α-hydroxyacids, vicinal diols, α-hydroxyketones, ethanolamines, amino acids, etc,[1] confers to those compounds a great importance as versatil starting materials in organic synthesis. Despite this interest, few methods have been reported to prepare chiral non racemic cyanohydrins,[1b,2] and none of them related to their α-methyl derivatives. The high stereoselectivity observed in DIBAL and DIBAL/$ZnCl_2$ reductions[3] of ß-ketosulfoxides was related to the ability of the aluminium to associate with any of the unshared electron pair at sulfinyl group, as a previous step to the intramolecular hydride transfer. A similar mechanism can be invoked to explain the high stereoselectivities found in the reactions of 2-*p*-tolylsulfinyl cycloalkanones with Me_3Al and $ZnCl_2/Me_3Al$.[4] These results suggested us the possibility of using the tricoordinate aluminium reagent Et_2AlCN to control the stereoselectivity of the cyanide addition on the chiral ß-ketosulfoxides. In this paper we report the excellent chemical and stereochemical results obtained in these reactions, starting from chiral phenyl or alkyl (ethyl and *t*-butyl) *p*-tolylsulfinylmethyl ketones, and the transformation of the resulting sulfinylcyanohydrins in their corresponding α-methyl α-hydroxycarboxamides, with high optical purity.

The reaction of (R)-(+)-methyl *p*-tolylsulfoxide with R-CO_2Et (R=Ph, Et and *t*-Bu) in the conditions reported by Solladié,[5] yield the (R)-ß-ketosulfoxides, R-CO-CH_2-SO-*p*-Tol (1 - 3).



R = Ph	1	4
R = Et	2	5
R = *t*-Bu	3	6

i) (R)-(+)-*p*-Tol-SO-Me/LDA/THF; ii) Et_2AlCN/Toluene

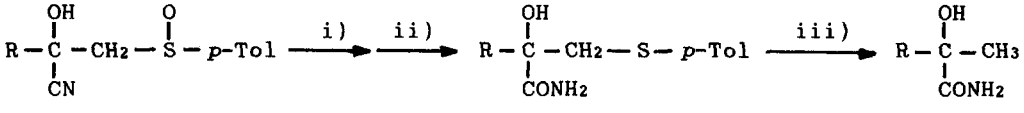
Scheme 1

The reaction of the ketosulfoxides 1-3 with diethylaluminium cyanide in toluene, afforded the cyanohydrins 4 - 6. In order to avoid the recovering of the starting material as the major component of the final mixture and to get good yields in cyanohydrins (~90%), it was necessary to modify the experimental procedure initially reported for the use of

Et_2AlCN,[6] being the main variation the inversion of the order in the addition of the reagents.[7] The reaction of compounds 1-3 with Et_2AlCN in the presence of $ZnCl_2$ was twice quicker but the stereochemical results and the yields were identical to those obtained in its absence.

The study of the ^1H-nmr spectra of the crude compounds 4-6[8] showed that only one diastereoisomer could be detected in the case of 4 and 6, but the signals corresponding to two epimers, 5 and 5' (98:2 ratio), were observed starting from 2. Therefore, it can be established that the d.e. of these reactions are higher than 96%.[9]

The hydrogenolysis of the CH_2-S bond in compounds 4-6 was not possible. The hydrolysis of the CN group in strong acidic conditions[10] determined the simultaneous reduction of the sulfinyl group. The so obtained sulfenyl hydroxyamides 7-10[11] reacted with Ni Raney yielding the α-hydroxyamides 10-12,[12] in 60-70% yield.



R=Ph	4	7	10
R=Et	5	8	11
R=Bu^t	6	9	12

i) HCl, Et_2O/MeOH(3:1), 0-4°, 24 h.; ii) H_2O, 0-4°, 24 h.; iii) Ni Raney/EtOH, 2 h. r.t.

Scheme 2

We assigned the (S) configuration to compound 10, and therefore to its precursos 4 and 7 (the reactions involved in the sequence 4 → 7 → 10 do not affect the configuration of the hydroxylic carbon), comparing the rotary power of 10 ($[\alpha]_D$ = -5.9°, acetone, c = 0.63) with that of the carboxamide ($[\alpha]_D$ = +6.3°, acetone, c = 0.63) obtained by us from enantiomerically pure (R)-atrolactic acid (available from Aldrich Co.). The same configuration (S) was assumed for the hydroxylic carbon of compounds in Scheme 2 in the view of the similar diastereoselectivities obtained in the hydrocyanation reactions (d.e. > 98%, Scheme 1). We can therefore conclude that the configuration induced at carbonyl carbon in rections of ß-ketosulfoxides with Et_2AlCN is only dependent on the sulfinyl sulfur configuration. In our starting (R)-sulfoxides, the configuration induced at carbon has been S, but the opposite must be expected starting from the (S)-enantiomers.

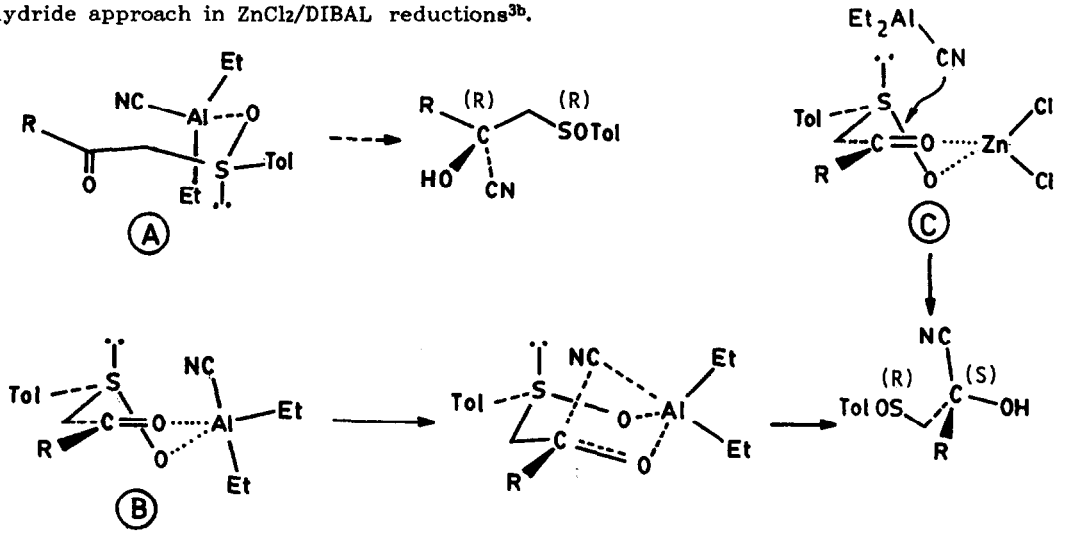
Additionally, we can estimate the optical purity of 10 from the indicated values for the rotary powers (e.e.= 92%). Taking into account the d.e. of the cyanohydrins, the slight decrease in the optical purity must be attributed to the epimerizating effect of the strong acidic conditions used in the hydrolysis, on the benzylic alcohol, which must be less important in the aliphatic alcohols. The study of compounds 10 -12 (and their corresponding racemics) by ^1H-nmr in the presence of the chiral shift reagent Eu(tfc)$_3$, did not allow us to detect the signals corresponding to the second enantiomer (unfortunately the signals of both enantiomers in compounds 10-12 did not appear perfectly separated). It suggested that the e.e. of 11 and 12 had to be, at least so high as that of 10, that is to say ≥92%.

When the reactions with Et_2AlCN were carried out in the presence of $ZnCl_2$, a slighly higher rate could be evidenced, but the stereochemical results were similar. The rotary power (and therefore the optical purity) of compound 10 obtained by this route was identical to that of the sample resulting from the cyanohydrin obtained without $ZnCl_2$.

The stereochemical results obtained in the cyanide addition to the carbonyl group of

ß-ketosulfoxides cannot be explained by assuming an intramolecular cyanide transfer from a tetracoordinated aluminium species A (Scheme 3) (like that postulated to explain the stereoselectivity of the DIBAL reductions[3b]). The evolution of species A would yield the cyanohydrin exhibiting the wrong configuration [(R) at sulfur would induce (R) at carbon instead the observed (S)]. The larger electronic defficience of the aluminium in Et_2AlCN, in respect to that in DIBAL, suggests that a double association of the aluminium with both oxygens in the substrate, like the one shown in the pentacoordinate intermediate B (Scheme 3), could be possible and even more stable than A. Assuming B as the most stable conformation of the substrate (with the *p*-tolyl group in a pseudoequatorial arrangement), the intramolecular transfer of the cyanide,[13] afforded the cyanohydrin with the right conformation throughout a like-chair transition state.

The fact that the configuration induced at carbonyl carbon during the methylation does not change in the presence of $ZnCl_2$ and that the reaction rate was increased, can be explained by assuming that this reagent acts as chelating agent. The presumably more stable half-chair conformation (C in Scheme 3) of this chelated species, undergo a cyanide attack from the upper face, favored by stereoelectronic and steric effects in a similar way to the hydride approach in $ZnCl_2$/DIBAL reductions[3b].



Scheme 3

ACKNOWLEDGEMENTS

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REFERENCES

1.- a) J. Fuhrhop, G. Penzlin, *Organic Synthesis, Concepts, Methods, Starting Materials.* Verlag Chemie, Weinheim. 1983, p. 47; b) J. Brussee, A. Van der Gen, *Eur. Pat. Appl.* EP 322,973 (Cl. C07C93/14), 5 Jul 1989.

2. J. Brussee, E.C. Roos, A. Van der Gen; *Tetrahedron Lett.* 1988, *29*, 4485; B.R. Matthews, W.R. Jackson, G.S. Jayatilake, C. Wilshire, H.A. Jacobs; *Aust. J. Chem.* 1988, *41*, 1697; J. Brussee, W.T. Loos, C.G. Kruse, A. Van der Gen; *Tetrahedron*, 1990, *46*, 979 (and references cited); J. Brussee, F. Dofferhoff, C.G. Kruse, A. Van der Gen; *Tetrahedron*, 1990, *46*, 1653.

3.- a) G. Solladié, G. Demailly, C. Greck; *J. Org. Chem.*, 1985, *50*, 1552; b) C. Carreño, J.L. García Ruano, A.M. Martín, C. Pedregal, J.H. Rodriguez, A. Rubio, J. Sanchez, G. Solladié; *J. Org. Chem.*, 1990, *55*, 2120;

4.- A.B. Bueno, M.C. Carreño, J. Fischer, J.L. García Ruano, L. Peñas and A. Rubio.

Tetrahedron Lett., submitted.

5.- G. Solladié, *Synthesis*, **1981**, 185. In this reference, the synthesis of compound 1 is reported. The same experimental conditions were used for the synthesis of compound 3 [m.p. 108-109ºC. [α]D +252º. ^{1}H-nmr: 7.60 and 7.33 (AA'BB' system, 4H, *aromatic protons*), 4.18 and 3.83 (AB system, 2H, J=15.2 Hz, C*H*$_2$), 2.42 (*s*, 3H, C*H*$_3$-Ar), 1.06 [*s*, 9H, (C*H*$_3$)$_3$C]; ^{13}C-nmr: 207, 142.0, 140.7, 130.0(2C), 124.3(2C), 65.3, 44.5, 25.5(3C)], but the synthesis of compound 2 [m.p. 78-79ºC. [α]D +253º. ^{1}H-nmr: 7.54 and 7.30 (AA'BB' system, 4H, *aromatic protons*), 3.89 and 3.77 (AB system, 2H, J=13.6 Hz, C*H*$_2$), 2.51 (*m*, 2H, C*H*$_2$-Me), 2.42 (*s*, 3H, C*H*$_3$-Ar), 1.01 (*t*, 3H, J=7.2, C*H*$_3$-C); ^{13}C-nmr: 204.3, 141.9, 139.5, 129.9(2C), 123.8(2C), 67.7, 38.1, 21.2, 6.9] required the modification of the relative concentration of base (1.25/4.62/1.00 : LDA/EtCO$_2$Et/methyl *p*-tolylsulfoxide) to get satisfactory results (92% yield).

6.- W. Nagata, M. Yoshioka, M. Murakami; *J. Am. Chem. Soc.*, **1972**, *94*, 4654. W. Nagata, M. Yoshioka, M. Murakami; *Org. Syn.*, **1972**, *52*, 96.

7.- A typical experimental procedure was used: A toluene solution of the ketosulfoxide (1 mmol) was added dropwise into other toluene solution of Et$_2$AlCN (2 mmol) and the mixture was stirred for 2 hours (the results obtained at 0ºC, -20ºC and -78ºC were similar). It was then added into a mixture of 25 ml of MeOH and 15 ml of concentrated HCl, vigorously stirred for 1 hour at -78ºC, poured into a mixture of 20 ml of concentrated HCl in 30 ml of ice water and extracted with CH_2Cl_2. The extracts were washed (30 ml of water), dried (Na_2SO_4), concentrated in vacuo below 40ºC (higher temperatures decompose the unstable cyanohydrins into the starting ketones) and purified by crystallization.

8.- Compound 4. Yellowish syrup, [α]D +85º ($CHCl_3$, c=1.0). ^{1}H-nmr: 7.64-7.57 (*m*, 4H, *aromatic protons*), 7.46-7.28 (*m*, 5H, *aromatic protons*), 3.18 and 3.11 (AB system, 2H, J=13.5 Hz, C*H*$_2$-S), 2.41 (*s*, 3H, C*H*$_3$-Ar); ^{13}C-nmr: 143.0, 138.4, 138.2, 130.3(2C), 129.4, 128.8(2C), 124.7(2C), 123.9(2C), 119.2, 72.5, 65.5, 21.3.

Compound 5. [α]D +243º ($CHCl_3$, c=1.0), m. p. 68-69º (recrystallized from Et$_2$O:hexane 1:2) ^{1}H-nmr: 7.59 and 7.39 (AA'BB' system, *aromatic protons*), 5.95 (*s*, 1H, O*H*), 3.02 and 2.93 (AB system, 2H, J=13.2 Hz, C*H*$_2$-S), 2.45 (*s*, 3H, C*H*$_3$-Ar), 1.87 (*m*, 2H, C*H*$_2$-Me), 1.14 (*t*, 3H, J=7.4 Hz, C*H*$_3$-CH$_2$); ^{13}C-nmr: 143.0, 139.3, 130.4(2C), 124.0(2C), 119.5, 71.7, 62.4, 34.9, 21.4, 7.7.

Compound 6. [α]D +245º ($CHCl_3$, c=1.0), m. p. 149:150º (recrystallized from acetone:hexane 1:2) ^{1}H-nmr: 7.61 and 7.40 (AA'BB' system, *aromatic protons*), 5.99 (*s*, 1H, O*H*), 2.96 and 2.89 (AB system, 2H, J=14.0 Hz, C*H*$_2$-S), 2.45 (*s*, 3H, C*H*$_3$-Ar), 1.09 [*s*, 9H, (C*H*$_3$)$_3$C]; ^{13}C-nmr: 143.0, 138.7, 130.4(2C), 123.9(2C), 119.2, 87.8, 58.5, 39.1, 24.2(3C), 21.4.

Compounds **4-6** gave satisfactory combustion analysis.

9.- The treatment of ketosulfoxide 2 with Et$_2$AlCN during 16 hours (only 2 h. in the standard conditions, see ref. 7) yielded a mixture that contained the starting product, 2 (26%), and the cyanohydrins 5 (45%) and 5' (29%), epimers at C-2. From the ^{1}H-nmr spectrum of this mixture, the signals corresponding to 5' could be easily identified, and later used to establish the ratio 5:5' obtained in the standard conditions (98:2, see text).

10.- We have tried many different hydrolysis conditions. The use of a saturated solution of HCl in Et$_2$O/MeOH (R. Herranz, J. Castro-Pichel, S. Vinuesa, M.T. García Lopez; *J. Org. Chem.*, **1990**, *55*, 2232) gave satisfactory results in all cases.

11.- Compound 7. ^{1}H-nmr: 7.59 and 7.03 (AA'BB' system, 4H, *aromatic protons*), 7.58-7.27 (*m*, 5H, *aromatic protons*), 6.74 and 6.02 (*broad singlets*, 2H, N*H*$_2$) 3.93 and 3.44 (AB system, 2H, J=13.6 Hz, C*H*$_2$-S), 3.85 (*s*, 1H, O*H*) and 2.28 (*s*, 3H, C*H*$_3$-Ar).

Compound 8. ^{1}H-nmr: 7.33 and 7.09 (AA'BB' system, *aromatic protons*), 6.69 and 5.51 (*broad singlets*, 2H, N*H*$_2$), 3.55 and 3.16 (AB system, 2H, J=13.8 Hz, C*H*$_2$-S), 2.31 (*s*, 3H, C*H*$_3$-Ar), 1.76 (*m*, 2H, C*H*$_2$-Me), 0.93 (*t*, 3H, J=7.4 Hz, C*H*$_3$-CH$_2$).

Compound 9. ^{1}H-nmr: 7.32 and 7.09 (AA'BB' system, *aromatic protons*), 6.76 and 5.83 (*broad singlets*, 2H, N*H*$_2$), 3.91 and 3.05 (AB system, 2H, J=13.3 Hz, C*H*$_2$-S), 3.39 (*s*, 1H, O*H*), 2.31 (*s*, 3H, C*H*$_3$-Ar), 1.05 [*s*, 9H, (C*H*$_3$)$_3$C].

12.- Compound 10: [α]D -5.9º (acetone, c=0.63); ^{1}H-nmr: 7.6-7.3 (*m*, 5H), 6.40 (*bs*, 1H), 5.80 (*bs*, 1H), 3.54 (*bs*, 1H), and 1.8 (*s*, 3H).

Compound 11: [α]D -5.2º (acetone, c=0.6); ^{1}H-nmr: 6.59 (*bs*, 1H), 5.68 (*bs*, 1H), 2.48 (*s*, 1H), 1.76 (*m*, 2H), 1.44 (*s*, 3H) and 0.94 (*t*, 3H, J= 7.4 Hz).

Compound 12: [α]D -5.4º (12:8 H$_2$O-acetone, c=0.7); ^{1}H-nmr: 6.58 (*bs*, 1H), 5.64 (*bs*, 1H), 1.42 (*s*, 3H), and 1.04 (*s*, 9H).

13.- The apical position of the cyanide in the trigonal bipyramidal structure B makes easier this transfer.

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