

STEREOCHEMISTRY OF THE REACTIONS OF β -HALOTHIOETHERS WITH NaCN AND AgCN

J.C. Carretero and J.L. García Ruano*

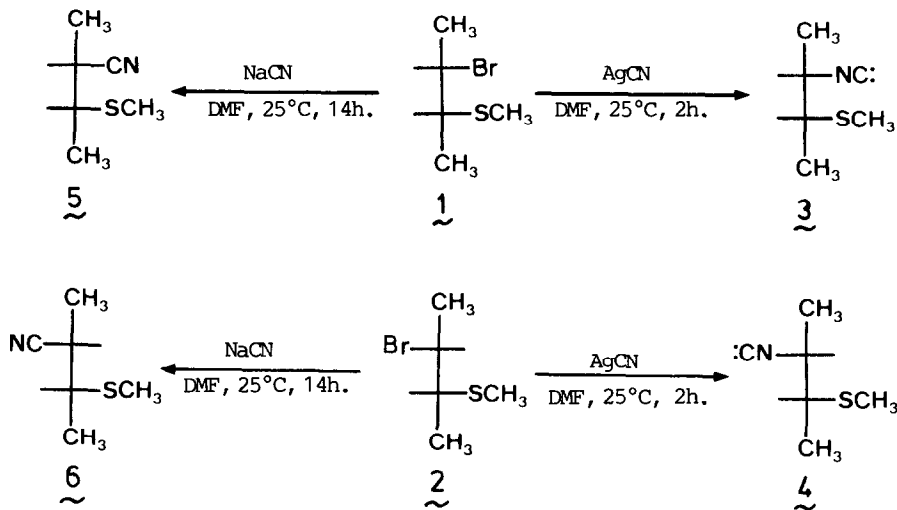
Depto. Química Orgánica, Universidad Autónoma de Madrid, 28049 Madrid, Spain.

The S_N reactions of NaCN and AgCN with erythro and threo-2-methylthio-3-halobutanes are reported. The stereochemistry of the resulting nitriles and isonitriles demonstrates that total retention in configuration has taken place in these processes. This disagrees with the accepted explanation for the regioselectivity of these reactions.

The reactions of alkyl halides with NaCN and AgCN are traditional methods for the synthesis of nitriles¹ and isonitriles², respectively. At present the course of these processes is usually explained accepting that the cyanide ion is the ambident reagent with two nucleophilic ends of different hardness in both cases. The different nature of the two metallic cations modifies the hardness of the electrophilic carbon through its interactions with the halogen of the substrate. This modification enables us to explain the regioselectivity in the attack of the cyanide ion. Through this explanation these reactions became one of the classic examples to illustrate the application of the Klopman and Salem equation and are discussed in the majority of books and articles on the subject³. We believe that we have some conclusive results that put in doubt this justification and agree with other older hypotheses which suggest that the formation of isonitriles from AgCN is due to the participation of a species (non free CN^-) in which the Ag^+ is bonded to the carbon atom⁴. Although these are in no way underrated, they have been consigned to a secondary position and are frequently omitted.

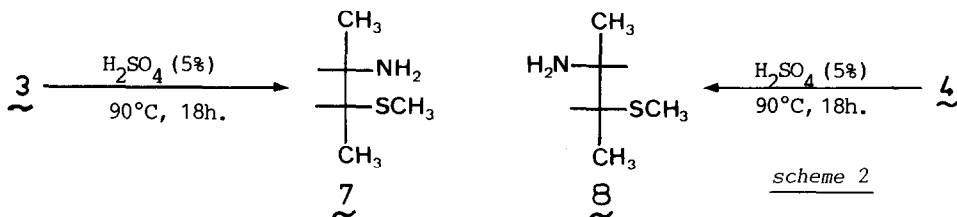
The extraordinary ability of the SMe group as an anchimeric assistant notably facilitates the S_N process in β -halothioethers, which takes place through the intermediate thiiranium salt⁵. If the reactions of these substrates with NaCN and AgCN follow a similar pattern and if the initially indicated justification were correct, in both cases the same reagent (ambident cyanide ion) would have to act on the episulphonium intermediate, which must be unaffected by the nature of the metal cation. Therefore, the results obtained in the reactions of both cyanides with β -halothioethers would have to be identical.

The reaction of erythro-2-methylthio-3-bromobutane⁵ (1) with AgCN yields only the isonitrile (3) ($\nu_{max} = 2205\text{ cm}^{-1}$), while the threo-diastereoisomer (2) gives the compound (4) ($\nu_{max} = 2205\text{ cm}^{-1}$), which is an isomer of (3). Identical results (differing only in the reaction time) are obtained in reactions starting with the corresponding chloro or iodothioethers. On the other hand, the reactions of (1) with an excess of NaCN yields a ~97:3 mixture (measured by ¹H-RMN) of the nitrile (5) ($\nu_{max} = 2250\text{ cm}^{-1}$) and the isonitrile (3). In similar conditions, (2) gives a ~96:4 mixture of the nitrile (6) ($\nu_{max} = 2250\text{ cm}^{-1}$) and the isonitrile (4). The configuration (erythro or threo) of compounds (3)-(6) indicated in scheme 1 could not be established from their spectroscopic



data (see table 1). Therefore, their correlation by chemical methods, with compounds of a known configuration was attempted.

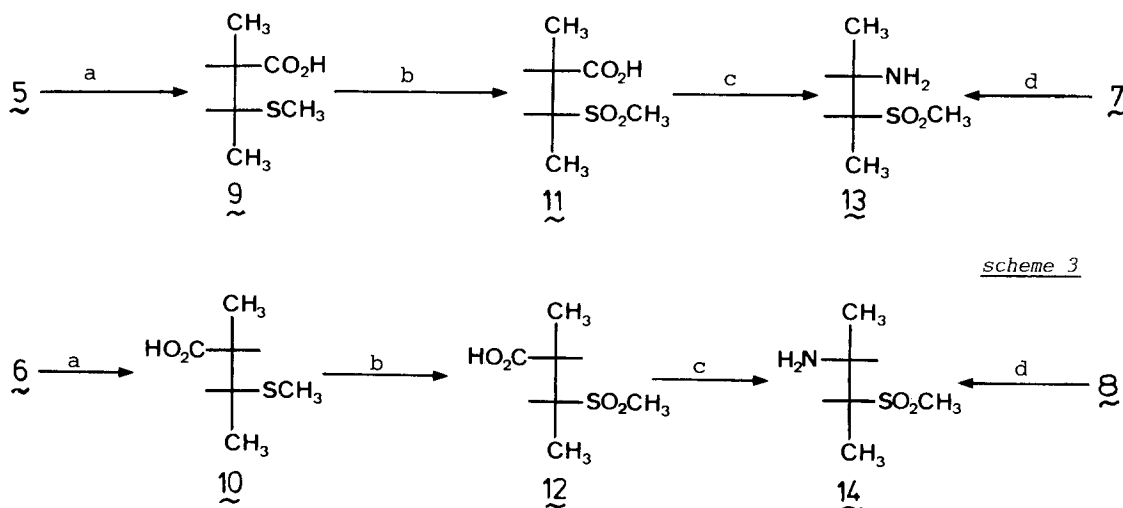
The acid hydrolysis of compound (3) gives *erythro*-3-methylthio-2-butanamine⁵ (7) which demonstrates that the configuration of (3) is also *erythro*. In a similar fashion, (4) yields *threo*-3-methylthio-2-butanamine⁵ (8) which again shows that halogen substitution by the $-N=C:$ group was accomplished with total retention of the configuration (scheme 2).



The stereochemical assignment of the nitriles was more difficult. As isonitrile \rightarrow nitrile rearrangement⁶ was unsuccessful, further efforts on the transformation of the CN group into NH_2 were undertaken. As the trials involving the transformation of the CN group into $CONH_2$ and the subsequent correlation through the Hoffman rearrangement (using basic conditions) were also unsuccessful, we thought that a similar process could take place in acid medium. In this sense the Schmidt rearrangement, which required the previous transformation of nitriles in carboxylic acids, was attempted.

Under suitable conditions, the hydrolysis of (5) and (6) afforded the acids (9) and (10), respectively. When these substrates were treated with NaN_3/H_2SO_4 they yielded a complex mixture of compounds⁷, probably due to the ability of the unshared electron pair on sulphenylic sulphur to act as a trap for nitrenes to give sulphimides⁸, which easily yield sulphoxides and amides by hydrolysis⁹ and sulphoximides by oxidation¹⁰.

As the sulphone group has no unshared electron pair, the 2-methyl-3-methylsulphonylbutanoic acids (**11**) and (**12**) seem to be the adequate substrates for achieving the correlation reaction. When the sulphones (**11**) and (**12**) (obtained from (**9**) and (**10**) by oxidation with NaIO_4) react with $\text{NaN}_3/\text{H}_2\text{SO}_4$ they yield β -aminosulphones (**13**) and (**14**), respectively. The oxidation of *erythro*-thioether (**7**)⁵ gives (**13**), while *threo*-(**8**) yields (**14**). No single reaction in this sequence affects the configuration of the compounds, indicating that the synthesis of the cyanides (**5**) and (**6**) from the haloderivatives (**1**) and (**2**) has taken place with retention of the configuration (scheme 3).



a: HCl (15%), 100°C , 48h.; b: NaIO_4 (2eq.), 50°C , 18h.; c: NaN_3 ($\text{H}_2\text{SO}_4\text{-CHCl}_3$), 50°C , 30min; d: MCPBA (CHCl_3), 0°C , 10 min.

The retention of the configuration in the reactions of β -halothioethers with AgCN and NaCN indicates that the S_N process takes place through the intermediate thiiranium salt. This agrees with the mild conditions and high yields. The metal cations, which affect the formation rate of thiiranium salts (reactions with AgCN are faster), cannot interact with these intermediates once formed. This assumption is based in the fact that stable thiiranium salts have been isolated from reactions of β -halothioethers with some silver salts (AgBF_4 ¹¹, AgSbF_6 ¹², etc) suggesting that the Ag^+ does not interact with the unshared electron pair on sulphur. This is in accordance with the positive character of both species (Ag^+ and thiiranium salt) and with the supposedly large energy difference between the HOMO in the thiiranium salts (evaluated at -11.16eV ¹³ in Me_3S^+) and the LUMO in the Ag^+ . (-2.82eV ³). Therefore, the observed regioselectivity with both metal cyanides (identical to other alkyl halides without the SMe group in β position) cannot be explained as variations in the hardness of the electrophilic carbon induced by the interactions between the metal cation and the halogen, as is commonly accepted³. Therefore, one has to assume that the nucleophilic species varies, depending on the metal cyanide used. The HOMO (anion)-LUMO (cation) interaction has a much more stabilizing effect with CN^-/Ag^+ ($\Delta E = 5.96\text{eV}$)³ than with CN^-/Na^+ ($\Delta E = 8.78\text{eV}$)³. Thus, these variations could determine that the AgCN acts as a not completely dissociated species, in which the Ag^+ is partially bonded to the carbon atom (that is the end of the cyanide ion with larger coefficient in the HOMO). Hence the nitrogen is the only atom exhibiting

nucleophilic properties and AgCN cannot be considered as an ambident nucleophile¹⁴.

Our findings suggest that the generally accepted explanation³ for the results obtained from reactions between alkyl halides and metal cyanides is not truly satisfactory. It is therefore not a good example for illustrating the Klopman and Salem equation.

compound	δ_1	δ_2	δ_3	δ_4	δ_{SMe} (ppm)	J_{12}	J_{23}	J_{34} (Hz)
(3)	1.42	2.89	2.76	1.44	2.16	7.0	5.7	6.8
(4)	1.40	2.89	2.89	1.40	2.17	7.1	4.7	6.9
(5)	1.51	3.91	2.79	1.39	2.17	6.8	5.5	7.0
(6)	1.52	4.01	2.94	1.39	2.19	6.8	4.4	7.0
(9)	1.30	2.60	2.99	1.37	2.10	6.9	7.0	7.0
(10)	1.23	2.71	3.08	1.27	2.11	6.9	6.6	6.9
(11)	1.44	3.08	3.41	1.54	2.93	7.2	4.3	7.2
(12)	1.35	3.31	3.61	1.44	2.92	7.2	4.8	7.1
(13)	1.21	3.84	2.92	1.41	2.95	6.7	1.7	7.1
(14)	1.27	3.57	3.05	1.40	2.98	6.6	6.5	6.9

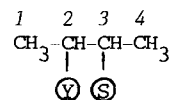
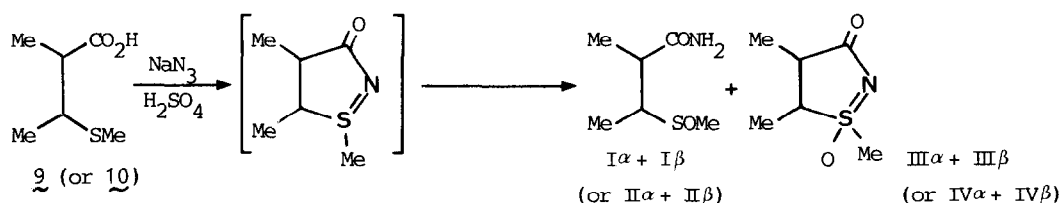


Table 1:
¹H-NMR parameters in CDCl₃
 of compounds (3)-(14)³

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- 2) L.L. Jackson and Mc. Kusick, *Org. Synth.*, IV, 438.
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- 5) J.C. Carretero, J.L. García Ruano, J.H. Rodríguez and M.C. Martínez, *J. Chem. Research*, (S), 1985, 6; (M), 1985, 172.
- 6) J. Casanova, "The Chemistry of the Cyano Group", Z. Rappoport, Interscience, New York (1970), p. 885.
- 7) The reaction of (9) with NaCN/H₂SO₄ yielded a mixture of four compounds. The first two are the 2-methyl-3-methylsulphonylbutanamides (I α + I β) which are epimers in sulphur. The other two are the diastereomeric mixtures of sulphoximides III α + III β . The behaviour of compound (10) was similar. The structures of all these compounds were established from their spectroscopic data and could be confirmed by synthesis.



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- 10) C.R. Johnson, "Comprehensive Organic Chemistry", S. Barton and W.D. Ollis, Pergamon Press, Oxford (1979), Vol. 3, p. 219. In our case H₂SO₄(c) could be the oxidizing agent.
- 11) W.A. Smit, M.Z. Krimer and E.A. Vorob'eva, *Tetrahedron Lett.*, 1975, 2451.
- 12) W.A. Smit, A.S. Gybin and V.S. Bogdanov, *Tetrahedron Lett.*, 1978, 1085.
- 13) M. Simonetta and A. Gavezzotti, "The Chemistry of the Sulphonium Group", C.J.M. Stirling and S. Patai, John Wiley & Sons, New York (1981), p. 11.
- 14) The reactions of bromides (1) and (2) with equimolecular quantities of AgCN also only yielded isonitriles. This indicates that the cyanide anion does not exist as a free nucleophile in the medium (this would determine the formation of mixtures of nitriles and isonitriles) and suggest that species as (Br-Ag-CN)⁻ (also with the nitrogen as the only atom exhibiting nucleophilic properties) could be the attacking reagent.