Tetrahedron Letters,Vol.26,No.24,pp 2917-2920,1985 0040-4039/85 $3.00 + .00
Printed in Great Britain

REACTION OF N-ALKYLTHIAZOLIUM HALIDES, INCLUDING THIAMINE, WITH SUPEROXIDE ION. CHEMISTRY AND BIOLOGICAL IMPLICATIONS.

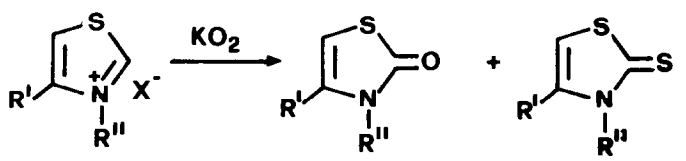
Alessandro Dondoni*, Guido Galliani*, Annarosa Mastellari, Alessandro Medici

Laboratory of Organic Chemistry, Faculty of Science, University of Ferrara, Ferrara, Italy

Summary: N-alkylthiazolium halides are transformed by KO_2 into the corresponding thiazolin-2-ones and thiazolin-2-thiones; the same reactions occur with thiamine, whose thiazolin-2-one pyrophosphate has been reported to be a strong inhibitor of pyruvic dehydrogenase.

The importance of the chemistry of superoxide ion $O_2^{\cdot-}$ and its use in organic synthesis are widely recognized[1], whereas the role of this ion in biological systems is still a matter of controversy[2,3]. Firmly established properties of $O_2^{\cdot-}$ are its relatively low basicity (pK = 4.8)[4] and its high nucleophilicity as shown in the reactions with alkyl halides[5] and carboxylic esters[6]. Therefore, a reactivity of $O_2^{\cdot-}$ can be forecast toward thiazolium salts for which reactions at C_2 with nucleophiles have been reported by others[7] and recently by us [8]. Here we describe the reaction of some N-alkylthiazolium halides (**1**) with potassium superoxide KO_2 and the biological implications thereby derived when a natural thiazolium salt, namely thiamine is considered.

Treatment of compounds (**1a-c**) with an excess of finely crushed KO_2 in benzene or DMSO gave after the appropriate work-up[9], two products in variable yields depending on the solvent[10], namely the N-alkylthiazolin-2-one (**2**) and the corresponding thio-analogue (**3**). Compounds (**2**) and (**3**) were



(1) (2) (3)

a; R^I=H, R^{II}=Me, X=I

b; R^I=R^{II}=Me, X=I

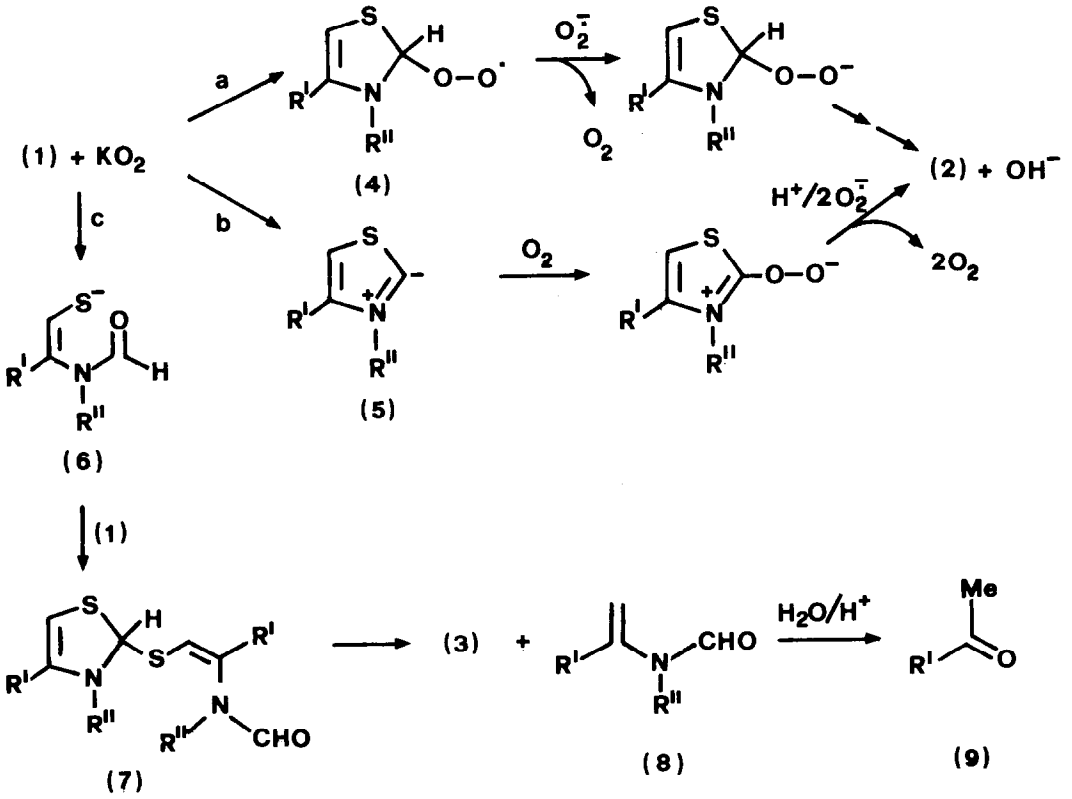
c; R^I=Me, R^{II}=$PhCH_2$, X=Cl

d; R^I=4,4'-C_6H_5-C_6H_5, R^{II}=Me, X=I

characterized by their spectroscopic data[10] and the X-ray analysis[11] of one of them, viz. (3b).

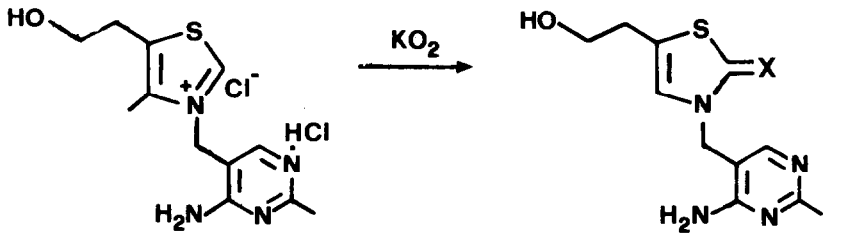
Two pathways can be envisaged for the formation of the thiazolinone (2), one involving as an initial step the attack of $O_2^{\cdot-}$ as a nucleophile at C_2 of (1) to give the thiazolinehydroperoxy radical (4) (**path a**), the other where $O_2^{\cdot-}$ acts as a base to give the N-thiazolium ylide (5) (**path b**)(Scheme 1). The former reaction is in line with the aforementioned properties[5,6] of $O_2^{\cdot-}$ and thiazolium salts[7,8]; the latter is consistent with the high kinetic acidity of the proton at C_2 in thiazolium salts [12] and the thermodynamic stability of the resulting ylide.[13] The evolution of intermediates (4) or (5) into the product (2) may involve a further amount of $O_2^{\cdot-}$ and/or molecular oxygen.A distinction between route a and b appears at present very difficult. For instance, although route a is supported by conversion of (1a) into the product (2a) and (3a) in the same ratio under

SCHEME 1



argon atmosphere as on exposure to air, route **b** cannot be ruled out because the molecular oxygen required in this sequence may be provided by one of the steps of route **a**. Compound (**3**) does not appear to derive from (**2**) since the ratio between these products (n.m.r.) was proved to be constant throughtout the entire reaction. On the other hand compound (**3**) can be rationalized to arise from the hydroxide ion induced[7] opening of the thiazole ring by C-S bond cleavage to give the α-formylaminothioenolate system (**6**) (**path c**). This is transformed by reaction with (**1**) into the adduct (**7**) which then fragments by S-C(vinyl) bond cleavage into the thiazoline thione (**3**) and the enamide (**8**). This Scheme is supported by some observations from the reaction of the thiazolium iodide (**1d**) with KO_2. In addition to thiazolines (**2d**) and (**3d**), a species was also detected by GLC-MS whose molecular peak (237 m/e) corresponds to (**8d**); the hydrolysis of this reaction mixture gave 4-phenylacetophenone (**9d**).

The conversion of thiazolium salts into thiazolin-2-ones is a potential obnoxious reaction in biological systems if one considers that thiamine thiazolone pyrophosphate has been shown to be a very strong inhibitor of pyruvic dehydrogenase, the enzyme utilizing thiamine pyrophosphate as a cofactor[14]. We have therefore turned our attention to thiamine and observed that in the form of its chloride hydrochloride (**1e**) it reacts readily (1g, DMSO, 0.5 h, r.t.) with KO_2 (0.5g) to give among several other unidentified products, the thiamine thiazolin-2-one[15] (**2e**) (TLC, HPLC, MS) and its thio-analogue[16] (**3e**) (MS). Unfortunately, potassium superoxide in DMSO appeared unsuitable as a model with thiamine pyrophosphate because of the dephosphorylation of the latter under these conditions. However thiazolines (**2e**) and (**3e**) were identified also in this case. Therefore, the actual conversion of thiamine pyrophosphate into its thiazolinone by superoxide ion and the eventual effects in vivo should be studied by rather a biochemical methodology then a refinement of the chemical model.



(**1e**) (**2e**) X=O (**3e**) X=S

References

1 For recents papers with leading references, see: G. Crank, M.I.H. Makin, Tetrahedron Lett., 1983, **24**, 3159; D.C. Neckers, G. Hauck, J. Org. Chem., 1983, **48**, 4691; G. Crank, M.I.H. Makin, J. Chem. Soc. Chem. Commun., 1984, 53; D. Vioril-Robert, M.T. Maurette, E. Oliveros, M. Hocquaux, B. Jacquet, Tetrahedron Lett., 1984, **25**, 529; H. Inoue, T. Nagano, M. Hirobe, Tetrahedron Lett., 1984, **25**, 317; T. Nagano, K. Yokookji, M. Hirobe, Tetrahedron Lett., 1984, **25**, 965; A.R. Forrester, V. Purushotham, J. Chem. Soc. Chem. Commun., 1984, 1505; T.S. Calderwood, D.T. Sawyer, J. Am. Chem. Soc., 1984, **106**, 718.

2 I. Fridovich, Science, 1978, **201**, 875; I. Fridovich, Acc. Chem. Res., 1982, **15**, 200.

3 D.T. Sawyer, J.S. Valentine, Acc. Chem. Res., 1981, **14**, 393; D.T. Sawyer, J.S. Valentine, Acc. Chem. Res., 1982, **15**, 200.

4 D. Behar, G. Czapski, J. Rabani, L.M. Dorfman, H.A. Schwartz, J. Phys. Chem., 1970, **74**, 3209.

5 M.V. Merritt, D.T. Sawyer, J. Org. Chem., 1970, **35**, 2157.

6 J. San Filippo Jr., L.J. Romano, C.I. Chern, J.S. Valentine, J. Org. Chem., 1976, **41**, 586.

7 D.J. Adam, H. Wharmby, Tetrahedron Lett., 1969, 3063; H.J. Federsel, J. Bergman, ibid., 1980, **21**, 2429.

8 A. Medici, M. Fogagnolo, P. Pedrini, A. Dondoni, J. Org. Chem., 1982, **47**, 3844; A. Dondoni, T. Dall'Occo, G. Fantin, M. Fogagnolo, A. Medici, Tetrahedron Lett., 1984, **25**, 3633; A. Dondoni, T. Dall'Occo, G. Galliani, A. Mastellari, A. Medici, ibid, 1984, **25**, 3637.

9 In Benzene: stirring (r.t.,12h) a suspension of (**1**) (ca. 1g) and KO_2 (2 equiv) in 70 ml of solvent containing 50 mg of 18-crown-6. The solution was washed with a concentrated aqueous solution of NH_4Cl, and extracted with chloroform. In DMSO: stirring (r.t.,0.5h) in 50 ml of solvent and evaporation under vacuum. The products were separated by column chromatography (silica) eluents: **a**, CH_2Cl_2-AcOEt 4:1; **b**, CH_2Cl_2-AcOEt-n--hexane 1:1:2; **c**, CH_2Cl_2-cyclohexane 3:1. (**2e**) and (**3e**) were separated by preparative TLC and identified by MS.

10 (**2a**) (benzene, 21%; DMSO, 12%) oil, MS, m/e 115 (M^+, 100%); IR, 1660 cm^{-1}; ^1H NMR: δ 3.3 (s, 3H), 6.1 (d, 1H), 6.6 (d, 1H). (**3a**) (benzene, 9%; DMSO, 30%) m.p. 55°C, MS, m/e 131 (M^+, 100%); IR, 1130, 1330 cm^{-1}; ^1H NMR, δ 3.7 (s, 3H), 6.7 (d, 1H), 7.1 (d, 1H). (**2b**) (benzene, 12%; DMSO, 27%) oil, MS, m/e 129 (M^+, 100%); IR, 1660 cm^{-1}; ^1H NMR: δ 2.2 (d, 3H), 3.3 (s, 3H), 5.8 (q, 1H). (**3b**) (benzene, 6%; DMSO, 5%) m.p. 111°C, MS, m/e 145 (M^+, 100%); IR, 1100, 1310 cm^{-1}; ^1H NMR δ 2.3 (d, 3H), 3.7 (s, 3H), 6.4 (q, 1H). (**2c**) (benzene, 18%; DMSO, 31%) deliq. solid, MS, m/e 205 (M^+, 100%); IR, 1660 cm^{-1}; ^1H NMR δ 2.0 (d, 3H), 4.9 (s, 2H), 5.8 (q, 1H), 7.3 (m, 5H). (**3c**) (benzene, 8%) m.p. 79°C, MS, m/e 221 (M^+, 20%), 91 (100); IR, 1180, 1350 cm^{-1}; ^1H NMR δ 2.1 (d, 3H), 5.5 (s, 2H), 6.2 (q, 1H), 7.3 (m, 5H).

11 G.D. Andreetti, and F. Ugozzoli, to be published.

12 P. Haake, Tetrahedron Lett., 1981, **22**, 2939; P. Haake, J. Phys. Chem., 1968, **72**, 2213; M.M.E. Scheffers-Sap, H.M. Buck, J. Am. Chem. Soc., 1979, **101**, 4807.

13 R. Breslow, J. Am. Chem. Soc., 1958, **80**, 3719; P. Haake, L.P. Bansher, W.B. Miller, J. Am. Chem. Soc., 1969, **91**, 1113.

14 J.A. Gutowski, G.E. Lienhard, J. Biol. Chem., 1976, **251**, 2863.

15 P.Sykes, A.R. Todd, J. Chem. Soc., 1951, 534.

16 H. Neef, K.D. Kohnert, A. Schellenberger, J. Prakt. Chem., 1973, **315**, 701.

(Received in UK 1 April 1985)