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# AUTOXIDATION OF LITHIO DERIVATIVE OF 2-ISOXAZOLINES

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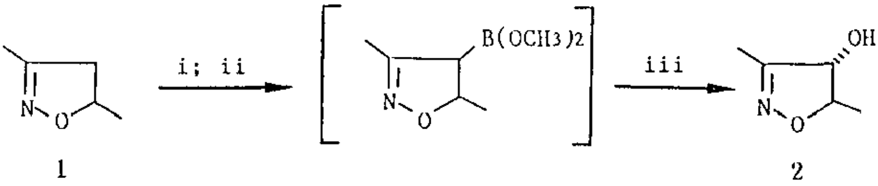
Abstract- 4-Lithio-2-isoxazolines are oxidized to the 4-peroxides or 4-hydroxy derivatives by air or oxygen at -80 °C. The concentration of oxygen in the solution is a decisive parameter. When it is bubbled into the lithium salt solution, the 4-hydroperoxide derivatives are mainly formed. However if oxygen is slowly absorbed in the liquid phase, 4-hydroxy derivatives predominate. In the reaction, the hydroperoxide anions has been confirmed to be the precursors of the 4-hydroxy-2-isoxazolines.

The isoxazole ring has received a great deal of attentions for its chemical properties related to its substitution and cleavage reactions[1]. In particular, 2-isoxazolines 1 give α,β-unsaturated ketoximes *via* a 4-endo anion[2] at room temperature, whereas below -78 °C the anionic species do not undergo the ring cleavage reaction but is subject to addition reactions at position 4[3]. Anion formation proceeds almost quantitatively and Schwab and Jäger have successfully applied the 4-hydroxylation of 2-isoxazolines[4] to the synthesis of many natural amino sugars[5].

Scheme 1

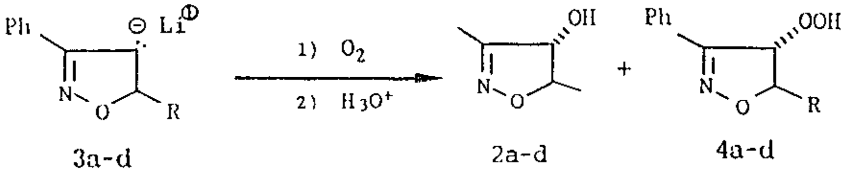


i) Lithium diisopropylamide, hexamethylphosphoric triamide, - 78 °C
ii) $B(OCH_3)_3$
iii)Oxidation

In the 4-hydroxy-2-isoxazolines thus obtained the trans-configuration predominates (>90:10). Moreover, oxidation is the crucial step of this process and the best results were obtained with concentrated oxidizing agents (hydrogen peroxide or tert-butyl hydroperoxide)[4].

In this report we describe a new method for the 4-hydroxylation of 3,5-disubstituted 2-isoxazolines, i.e. the oxidation of the 4-lithio derivative 3 with oxygen (Scheme 2).

Scheme 2



a, R=H; b, R=$CH_3$; c, R=n-$C_3H_7$; d, R=n-$C_5H_{11}$.

Almost only trans-isomers (>90:10) were formed according to the HPLC analyses and to the $^1$H-nmr spectra of the crude products[6].

The effects of the choice of temperature, oxygen and base concentration values, are as described below.

The reaction temperature should be below -78 °C due to its liability to the ring opening degradation as previously reported by Jäger[2].

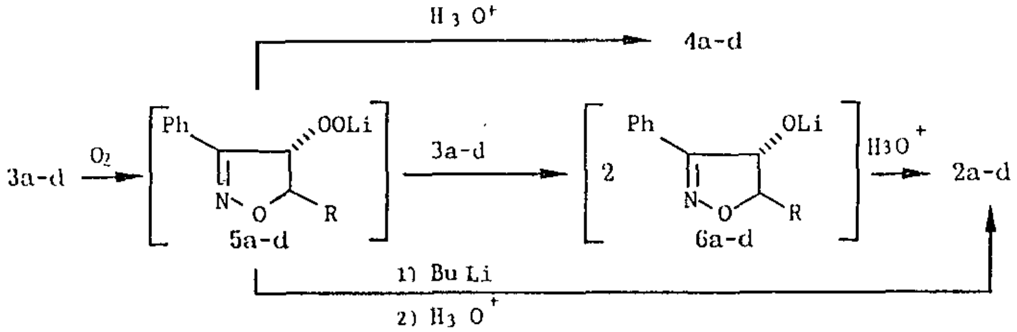
Operating in the usual conditions, with an excess of base, the formation of 2 decreases by increasing the amount of oxygen in the reaction medium. When oxygen was bubbled into the reaction mixture, the lithio derivative 3 is converted mainly to the 4-hydroperoxide 4.

The reaction was not affected by an increase of the amount of the base present.

DISCUSSION

The autoxidation of 2-isoxazolines in the presence of LDA, in the experimental conditions described, involves the reaction of the 4-lithio derivative 3 with oxygen. We propose (Scheme 3) that the reaction proceeds by direct formation of the hydroperoxide anion 5, which decomposes, with an excess of a base, to yield the 4-hydroxy anion 6; the latter gives 2, in the presence of acids.

Scheme 3

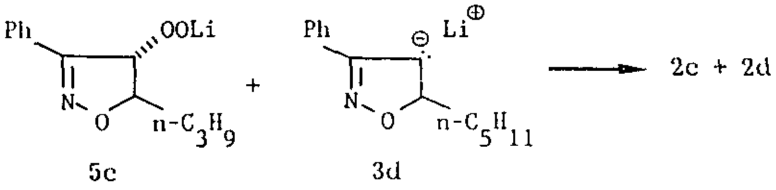


In fact, the reaction of 4-hydroperoxide 4c with BuLi or LDA (molar ratio 1:2), yields quantitatively 2c in both cases. Using BuLi, a quantitative amount of 1-butanol is detected, together with 2c.

The possibility that intermediate 3 can also undergo a straightforward reaction with 4-hydroperoxide anion 5 was confirmed by carrying out the reaction of 5c with a lithio salt of a differently substituted 2-isoxazoline 3d, under nitrogen.

This resulted in the formation of both the isoxazoline alcohols 2c and 2d in a 1:1 ratio (Scheme 4).

Scheme 4



However, when 3 was oxidized in the presence of either a large or a small amount of base, the formation of end products 2 or 4 was related only to the oxygen actually present. This can be explained taking into account that, if oxygen was bubbled into the solution of 3 , the reaction involves both 3 and LDA. A fast reaction with oxygen causes not only the formation of 4-hydroperoxide anion 5 but also the simultaneous disappearance of the excess of LDA, if present. Under these conditions, the reaction of 5 with a base (either LDA or 3) is not allowed; as a result, the formation of 4 takes place. Accordingly, even when oxygen is made to be slowly absorbed, the large or small amount of base was not an influent factor. This behaviour can be rationalized in terms of a slow formation of the 4-hydroperoxide-anion 5, when LDA (excess of base) or 3 (stoichiometric amount of base) are present, this allows conversion of 5 into 4-hydroxy anion 6 which in turn yields 2 with an acid.

In conclusion, autoxidation a 4-lithio derivatives of 2-isoxazolines allows one to obtain the corresponding 4-hydroperoxides or 4-hydroxy derivatives simply by bubbling oxygen in the reaction medium or by its absorption respectively.

## EXPERIMENTAL

Ir spectra were recorded on a Perkin-Elmer Mod. 177 instrument. $^1$H-Nmr spectra were determined on a Varian A 90 spectrometer, with TMS as an internal standard. Mass spectra were recorded with VG MM ZAB-2F instrument. Chromatographic separations were performed using Merck Kieselgel 60 F-254 (preparative tlc), and Merck Kieselgel 60 (column chromatography under atmospheric pressure or slightly above it). Mps are uncorrected. The reactions were run in dried vessels under a dry gas atmosphere (nitrogen, air, oxygen). All reagents and solvents were purified and dried by standard techniques; tetrahydrofuran (THF) was distilled prior to use from sodium-benzophenone ketyl.

_2-Isoxazolines 1a-d_. The 2-isoxazolines 1a-c were obtained as described in the literature[7].

5-Pentyl-3-phenyl-2-isoxazoline 1d was obtained by addition of benzonitrile oxide to 1-heptene: the stoichiometric amount of $NEt_3$ was slowly added under stirring to benzhydroxamic acid chloride dissolved in an excess of the heptene. The mixture was shaken with water and repeatedly extracted with diethyl ether; the extracts were separated and dried. Evaporation of the solvent under reduced pressure gave the isoxazoline 1d which was recrystallized from hexane (yield 86%). mp 42 °C; ir($cm^{-1}$) 1593, 1562; nmr($CDCl_3$, $\delta$,ppm) 7.22-7.82(m, 5H), 4.52-4.96(m, 1H), 3.36(dd,J=10.0 and 16.5, 1H), 2.92(dd, J=8.5 and 16.5, 1H), 1.10-1.90(m, 8H), 0.90(t, 3H). Found: C, 77.15; H, 8.96; N, 6.58 %. $C_{14}H_{19}NO$ requires: C, 77.38; H, 8.81; N, 6.45 %.

<u>4-Lithio-2-isoxazolines</u> <u>3a-d</u> <u>solution</u>. The solutions of 4-endo anions were obtained as described in the literature[3]: 1a-d dissolved in anhydrous THF, were slowly added dropwise at -78 °C to a solution of 1.2 equivalents of lithium diisopropylamide (from the amine in anhydrous THF and n-butyl lithium in hexane).

<u>4-Hydroxy-2-isoxazolines</u> <u>2a-d</u>. A: The 4-lithio-2-isoxazoline 3a-d solutions were left standing at -78 °C without stirring under dry air or oxygen dry atmosphere. After 15 h, into the reaction mixtures were added glacial acetic acid and then a saturated sodium chloride solution with cooling. The mixture was repeatedly extracted with diethyl ether and the combined extracts were dried and the solvent was evaporated in vacuo. The residues were chromatographed. B: oxygen was bubbled under stirring into a solution of 3a-d at -78 °C. After a few minutes the solution turned colourless and the oxygen was replaced by nitrogen, one equivalent of n-butylithium was added and, after 2 h, the mixtures were treated as in A. Yields 60-80 %.

2a:mp 96 °C(literature[4] 96 °C); ir($cm^{-1}$) 3280; $^1H$-nmr($CDCl_3$, $\delta$ , ppm) 8.10-7.20(m, 5H), 5.48(dd, J=3.0 and 7.5, 1H), 4.45(m, 2H), 3.10(s broad, 1H); ms m/z 163($M^+$,100), 120(75.0), 119(52.5), 104(37.5), 103(37.5). Found C, 66.32; H, 5.50; N, 8.39%. $C_9H_9NO_2$ requires: C, 66.24; H, 5.56; N, 8.58%.

2b: mp 98 °C(literature[4] 102-105 °C); ir($cm^{-1}$) 3280; $^1H$-nmr($CDCl_3$, $\delta$ , ppm) 7.80-7.20(m,5H), 4.99(d, J=3.0, 1H), 4.58(dd, J=3.0 and 6.8, 1H), 3.58(s broad, 1H), 1.28(d, J=6.8, 3H); ms m/z 177($M^+$, 17.7) 133(38.9), 120(19.5), 104(100). Found C, 67.72; H, 6.20; N, 8.01%. $C_{10}H_{11}NO_2$ requires: C, 67.78; H, 6.26; N, 7.91%.

2c: mp 43 °C; ir($cm^{-1}$) 3280; $^1H$-nmr($CDCl_3$, $\delta$ , ppm) 7.80-7.20(m, 5H), 5.06(d, J=3.3, 1H), 4.46(m, 1H), 3.68(s broad, 1H), 1.75-1.15(m, 4H), 0.9(t, J=7.2, 3H); ms m/z 205($M^+$, 22.6), 133(55.9), 104(100). Found: C, 70.38; H, 7.22; N, 6.98%. $C_{12}H_{15}NO_2$ requires C, 70.22; H, 7.37; N, 6.82%.

2d:mp 72 °C; ir($cm^{-1}$) 3280; $^1H$-nmr($CDCl_3$, $\delta$ , ppm) 7.80-7.20(m, 5H), 5.08(d, J=3.4, 1H), 4.40(m, 1H), 3.86(s broad, 1H), 1.80-1.05(m, 8H), 0.85(t, J=7.2, 3H); ms m/z 233($M^+$, 19.1), 162(26.3), 133(51.3), 104(100). Found: C, 72.24; H, 8.11; N, 6.31%. $C_{14}H_{19}NO_2$ requires C, 72.07; H, 8.21; N, 6.00%.

4-Hydroperoxy-2-isoxazolines 4a-d. Oxygen was bubbled into a stirred solution of 3a-d at -78 °C. After a few min the solution turned colourless and the mixture was hydrolized with glacial acetic acid and saturated sodium chloride solution with cooling as above. The mixture was repeatedly extracted with diethyl ether and the combined extracts were separated, dried and concentrated in vacuo. The residue was chromatographed to yield, yields 70-80%, respectively:

4a:mp 83°C; ir($cm^{-1}$) 3170; $^1H$-nmr($CDCl_3$, $\delta$, ppm) 9.10(s broad, 1H), 7.20-8.10(m, 5H), 5.85(dd, J=8.4 and 3.0, 1H), 4.80(dd, J=11.4 and 3.0, 1H), 4.35(dd, J=11.4 and 8.4, 1H); ms m/z 179($M^+$, 6.0), 163(22.5), 161(39.5), 120(17.5),119(14.0), 104(100). Found: C, 60.61; H, 4.99; N, 7.78%. $C_9H_9NO_3$ requires: C, 60.33, H, 5.06; N, 7.82 %.

4b: mp 102°C; ir($cm^{-1}$) 3170; $^1H$-nmr($CDCl_3$, $\delta$, ppm) 8.65(s broad, 1H), 7.3-7.95(m, 5H), 5.40(d, J=3.3, 1H), 5.00(d, J=3.3 and 6.5, 1H), 1.41(d, J=6.5, 3H); ms m/z 193($M^+$, 31.3), 175(16.1), 118(64.6), 104(86.8), 103(100). Found: C, 62.08; H, 5.88; N, 7.12%. $C_{10}H_{11}NO_3$ requires: C, 62.16; H, 5.74; N, 7.25%.

4c: mp 51°C; ir($cm^{-1}$) 3170; $^1H$-nmr($CDCl_3$, $\delta$, ppm) 8.40(s broad, 1H), 7.3-7.95(m, 5H), 5.45(d, J= 3.4, 1H), 4.90(m, 1H), 1.85-1,15(m, 4H), 0.98(t, J= 7.2, 3H); ms m/z 221($M^+$, 27.6), 205(18.1), 203(9.0), 133(25.5), 118(31.9), 104(100). Found: C, 65.03; H, 6.98; N, 6.24%. $C_{12}H_{15}NO_3$ requires: C, 65.14; H, 6.83; N, 6.33%.

4d: mp 40°C; ir($cm^{-1}$) 3170; $^1H$-nmr($CDCl_3$, δ, ppm) 7.95-7.3(m, 5H), 5.46(d, J=3.3, 1H), 4.88(m, 1H), 1.80-1.00(m, 8H), 0.90(t, J=7.2, 3H); ms m/z 249($M^+$,19.4), 233(32.8), 231(17.5), 162(38.8), 144(18.7), 133(21.6), 104(84.3), 103(100). Found: C, 67.26; H, 7.77; N, 5.43%. $C_{14}H_{19}NO_3$ requires: C, 67.44; H, 7.68; N, 5.62%.

Reaction between 4-hydroperoxy-2-isoxazoline 4c and n-BuLi. Two equivalents of n-butylithium in hexane were added at -78°C to a stirred solution of 4c in THF under nitrogen atmosphere. The mixture was left standing for five h, then hydrolized as usual. The mixture was extracted with diethyl ether and the extracts were analyzed by glc; stoichiometric amounts of the 4-hydroxy-2-isoxazoline 2c and 1-butanol were detected.

Reaction between 5c and 3d. A solution of one equivalent of 4-lithio-5-pentyl-3-phenyl-2-isoxazoline 3d was added, at -78 °C and under nitrogen atmosphere, to a 4-hydroperoxy-3-phenyl-5-propyl-2-isoxazoline anion 5c solution in THF (from 4c and one equivalent of BuLi in hexane). The mixture was left standing for 12 h, hydrolized, extracted as above, and the extracts analyzed by HPLC; an equivalent amount of both alcohols 2c and 2d was detected.

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6. The $^1$H-nmr spectra of the crude products show the presence of the *cis*-isomers with the protons in positions 4 and 5 of the ring coupled with a $J = 7.2$ Hz. In the case of 3c, the cis-isomer of the alcohol was isolated by chromatography of a large amount of crude product. The analiyical data are: mp 154 °C; ir (cm$^{-1}$) 3300; $^1$H-nmr(CDCl$_3$,$\delta$, ppm) 7.20-7.90(m, 5 H), 5.15(d, J= 7,2, 1 H), 4.25(q, J= 7.2, 1 H), 2.60(s broad, 1 H), 1.15-1.80(m, 4 H), 1.02(t, J= 7.2, 3 H); ms m/z 205(M$^+$, 8.0), 204(18.1), 186(54.5), 187(83.0), 172(45.3), 146(94.3), 104(100).

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