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LEAD TETRAACETATE OXIDATION OF KETOXIMES AND ALDOXIMES

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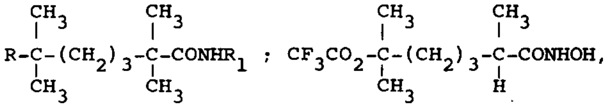
Oxidation of aliphatic ketoximes (1) and aldoximes (2) by lead tetraacetate ($Pb(OAc)_4$) has been reported to lead to unstable geminal nitrosoacetates and to dimeric nitrosoacetates, respectively, while α,β-unsaturated and arylaldoximes afforded oxime anhydride N-oxides and carbonyl compounds (3).

When applying this reaction to hindered ketoximes, we noted the formation of hydroxamic acid derivatives. 2,2,6,6-Tetramethylcyclohexanone oxime was chosen for a detailed study. Its reaction with an equimolar amount of $Pb(OAc)_4$ (10 min., room temperature, acetic acid as solvent) was found to produce the hydroxamic acid derivative I:



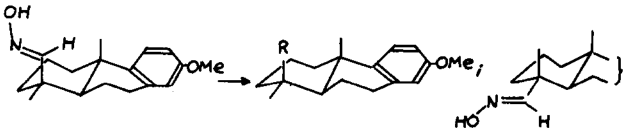
$$\text{R-}\underset{CH_3}{\overset{CH_3}{C}}\text{-}(CH_2)_3\text{-}\underset{CH_3}{\overset{CH_3}{C}}\text{-CONHR}_1\ ;\ CF_3CO_2\text{-}\underset{CH_3}{\overset{CH_3}{C}}\text{-}(CH_2)_3\text{-}\underset{H}{\overset{CH_3}{C}}\text{-CONHOH,}\quad \text{V}$$

I, $R = R_1 = OAc$; II, $R = OAc$, $R_1 = OH$; III, $R = CF_3CO_2$, $R_1 = OH$, IV, $R = R_1 = OH$.

Upon saponification with methanolic potassium carbonate (24hr., room temperature) I gave the ε-acetoxylhydroxamic acid II (84% based on oxime, m.p. 74-75° (hexane)). Oxidation of 2,2,6,6-tetramethylcyclohexanone oxime with an equimolar amount of $Pb(OAc)_4$ in trifluoroacetic acid for 10 seconds led to the ε-trifluoroacetoxylhydroxamic acid III (30%, m.p. 82° (hexane)). Compound III underwent facile hydrolysis in boiling water to the ε-hydroxylhydroxamic acid IV (94%, m.p. 112-113° (hexane/ether)).

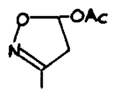
Oxidation of 2,2,6-trimethylcyclohexanone oxime with $Pb(OAc)_4$ in trifluoroacetic acid gave ε-trifluoroacetoxylhydroxamic acid V (54%, m.p. 78-80° (hexane)). A similar behaviour was observed for 2-methylcyclohexanone oxime which reacted in trifluoroacetic acid to yield approximately 40% hydroxamic acid and 60% 2-methylcyclohexanone. Analogous oxidative fragmentations were also observed for 3-oximes of 4,4-dimethylsteroids and camphor oxime. Investigations on unhindered ketoximes (4) indicated formation of geminal nitrosoacetates, carbonyl compounds, and nitric oxide; no hydroxamic acid derivatives could be detected.

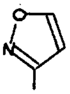
We next turned to the $Pb(OAc)_4$ oxidation of hindered aldoximes. As a convenient model for the study of this reaction syn-O-methylpodocarpinaldoxime ((5), m.p. 143°) was chosen (6). Reaction of this compound with $Pb(OAc)_4$ in methylene chloride (5 min., room temperature) yielded the nitrile oxide VI (94%, m.p. 132° (methanol)). Heating the nitrile oxide in acetic acid transformed it quantitatively to the hydroxamic acid derivative VII (m.p. 150° dec.) probably via rearrangement of the initial adduct VIIa (8).



, X

VI, R = -CNO; VIIa, R = -C(OAc)NOH; VII, R = -CONHOAc

VIII, R = 

; IX, R = 

Sodium borohydride reduction of VI afforded a quantitative yield of the starting aldoxime. The nitrile oxide proved to be stable at room temperature and could not be made to dimerize to the corresponding furoxan on heating. The nitrile oxide reacted readily with vinyl acetate affording a 1:1 mixture (9) of the diastereomeric 5-acetoxylisoxazolines VIII, which was converted by refluxing in acidic ethanol (10) to the expected isoxazole IX (80%, based on nitrile oxide, m.p. 104° (chloroform)).

When reacting dehydroabietinaldoxime and abietinaldoxime X (11) with Pb(OAc)$_4$ only hydroxamic acid derivatives corresponding to compound VII were formed. The stability of O-methylpodocarponitrile oxide is therefore, no doubt, due to severe steric hindrance.

In an attempt to generalize this reaction it was noted that only syn-aldoximes gave consistently high yields of products derivable from intermediate nitrile oxides. Thus syn-trimethylacetaldoxime (6) yielded with $Pb(OAc)_4$ in methylene chloride at room temperature N-acetoxyltrimethylacetohydroxamic acid (80%, m.p. 116.5° (hexane)) the structure of which was verified by independent synthesis by known procedures (8). The intermediacy of nitrile oxides was further demonstrated by scavenger experiments with vinyl acetate, which led to isoxazoline derivatives. The aldoximes were dissolved in a large excess of vinyl acetate (and methylene chloride when necessary) and reacted at -78° with an equimolar amount of $Pb(OAc)_4$ (10 min.) followed by addition of the stoichiometric amount of triethylamine to neutralize the acetic acid (12) liberated in the oxidation reaction. Trimethylacetaldoxime (100% syn), i-butyraldoxime (75% syn), and benzaldoxime (100% syn) were thus converted to 5-acetoxyl-3-t-butyl-2-isoxazoline (80%, m.p. 51° (hexane/ethanol)), 5-acetoxyl-3-i-propyl-2-isoxazoline (97%, based on syn-oxime, m.p. 33.5-34° (pentane)), and 5-acetoxyl-3-phenyl-2-isoxazoline (81%, m.p. 90-90.5° (13) (hexane/ethanol)), respectively.

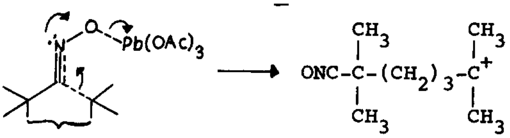
When anti-benzaldoxime was reacted with $Pb(OAc)_4$ in the presence of vinyl acetate and subsequent addition of triethylamine, a mixture of products was obtained from which could be isolated 5-acetoxyl-3-phenyl-2-isoxazoline (10%), benzaldoxime (15%), and benzaldehyde. Similar results were obtained for acetaldoxime (30% syn) which gave a product mixture containing not more than 20-30% of 5-acetoxyl-3-methyl-2-isoxazoline as estimated by infrared analysis. Anti-aldoximes, therefore, appear to follow a different reaction path, and we are presently engaged in investigations to obtain a satisfactory explanation for this behaviour.

Triethylamine was found to act merely as an acid scavenger since the oxidation in its absence also proceeded to isoxazoline derivatives, albeit in low yield, the main product of the reaction being the N-acetoxylhydroxamic acid. In the oxidation of trimethylacetaldoxime some (10%) of 1-acetoxyl-1-nitroso-2,2-dimethylpropane (14) was also detected which on refluxing with a catalytic amount of triethylamine in ethereal solution rearranged to N-acetoxyltrimethylacetohydroxamic acid. A similar reaction was observed previously (15) in the rearrangement of α-chloro-α-nitrosotoluene to benzohydroxamic acid chloride.

All compounds for which a melting point is recorded gave satisfactory elemental analyses. Spectral data (NMR, IR, UV) verifying the structure assignments of the new compounds were obtained in all cases.

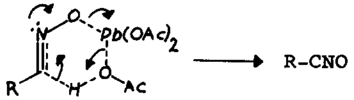
The experimental results so far obtained for the ketoxime oxidation indicate a mechanism proceeding via carbon-carbon bond fission to a nitrile oxide and a stabilized carbonium ion (A) with subsequent solvation by acetic acid and product formation.

A



$$\mathrm{ONC{-}\overset{\displaystyle CH_3}{\underset{\displaystyle CH_3}{C}}{-}(CH_2)_3{-}\overset{\displaystyle CH_3}{\underset{\displaystyle CH_3}{C^+}}}$$

B



The aldoxime oxidation likewise involves the intermediacy of a nitrile oxide. However, its formation might be the result of a concerted process for which a cyclic lead organic transition state is proposed (B).

Acknowledgements

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(1) Iffland, D.C., Criner, G.X., *Chem. Ind.*, **1956**, 176.

(2) Kropf, H., *Angew. Chem.*, **77**, 1030 (1965).

(3) Kropf, H., *Ibid.*, **77**, 1087 (1965).

(4) Cyclohexanone oxime, 3-methylcyclohexanone oxime, isophorone oxime, and cholestenone oxime were investigated.

(5) For the preparation of this compound cf.
(a) Bible, R.H., Burtner, R.R., *J. Org. Chem.*, **26**, 1174 (1961).
(b) Jones, W.H., Tristam, E.W. Benning, N.F., *J. Am. Chem. Soc.*, **81**, 2151 (1959)

(6) For configurational assignment of aldoximes by NMR, cf.
(a) Phillips, W.D., *Ann. New York Acad. Sci.*, **70**, 817 (1958).
(b) Pejković-Tadić, I., Hranisavljevic-Jakovljević, M., Nesić, S., Pascual, C., Simon, W., *Helv. Chim. Acta.*, **48**, 1159 (1965).

(7) (a) Smith, L.I., *Chem. Rev.*, **23**, 236 (1938).
(b) Grundmann, C., Dean, J.M., *J. Org. Chem.*, **30**, 2809 (1965).

(8) (a) Müller, E., Editor, Houben-Weyl, Methoden der organischen Chemie, Bd. VIII, Sauerstoffverbindungen III, Georg Thieme Verlag Stuttgart, 1952, p. 684.

(b) Yale, H.L., *Chem. Rev*. **33**, 209 (1943).

(9) As evidenced by the NMR spectrum which showed four methyl and two acetate singlets all of the same intensity.

(10) Paul, R., Tchelitcheff, S., *Bull. Chim. Soc. France*, **1962**, 2215.

(11) Fieser and Fieser, *Topics in Organic Chemistry*, New York, 1963, pp. 192-197.

(12) The acid scavenger $CaCO_3$ frequently used in $Pb(OAc)_4$ oxidations (cf. Partch, R.E., *J. Org. Chem*., **30**, 2498 (1965)) was found to be ineffective; similarly failed: Na_2HPO_4, $NaHCO_3$, and K_2CO_3.

(13) The material occurs in two crystal forms, one melts at 90-90.5° (hexane/ethanol), the other at 106° (vacuum sublimation).

(14) Identified by IR only; 1760, 1540, 1212 cm^{-1} (CCl_4), cf. reference (2).

(15) Müller, E., Metzger, H., *Chem. Ber*., **87**, 1282 (1954).