Lead tetraacetate oxidation of hindered alicyclic ketoximes

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Lead tetraacetate oxidation of 2,2,6,6-tetramethylcyclohexanone oxime and structurally related ketoximes caused C—C bond fission to yield acetyl hydroxamates. Severely hindered ketoximes gave nitrile oxides as intermediates which were trapped by 1,3-dipolar cycloaddition reaction.

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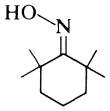
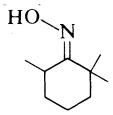
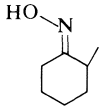
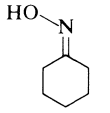
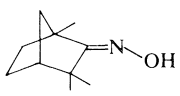
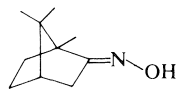
In our preliminary communication, we reported about a facile oxidative cleavage reaction of 2,2,6,6-tetramethylcyclohexanone oxime (**1**) and structurally related ketoximes with lead tetraacetate (1). A mechanism was proposed involving the intermediacy of nitrile oxides. We now wish to report about the spectroscopic detection and trapping of these intermediates.

Lead tetraacetate oxidation of sterically hindered cyclohexanone oximes in acetic acid gave mainly acetyl hydroxamates. Equation [1][2] shows two plausible mechanisms to account for the reaction products, and Table 1 gives a summary of the results.

Low temperature oxidation of ketoxime **1** in the presence of excess methyl acrylate produced the adducts **2**, **3***a*, and **3***b*, thus providing evidence for mechanism *a* (2). Isolation of the adducts was effected by thin-layer chromatography (t.l.c.). The nuclear magnetic resonance (n.m.r.) spectra of **2**, **3***a*, and **3***b* are diagnostic. The isopropylidene groups adjacent to the isoxazoline and acetate group in **2** appear as two singlets at 1.20 (6H) and 1.37 p.p.m. (6H), respectively. A singlet at 1.92 p.p.m. (3H) was assigned to the acetate group. The methylene protons appear as a complex multiplet from 1.2 to 2 p.p.m. Two almost superimposed doublets centered at 3.13 p.p.m. (2H) were assigned to the methylene group in the isoxazoline ring. The other ring proton gives rise to a set of two doublets centered at 4.85 p.p.m. (1H) showing coupling constants of 8.0 and 9.1 Hz. A singlet at 3.75 p.p.m. (3H) was assigned to the carbomethoxy group. The olefinic components **3***a* and **3***b* could not be separated by t.l.c. and the mixture was analyzed. Spectral data arising from the isoxazoline and saturated hydrocarbon portion of **3***a* and **3***b* are almost identical to those of compound **2**. The vinylic protons of **3***a* appear as a poorly resolved triplet centered at 4.64 p.p.m. (J_{gem} = 0.8 Hz) while the olefinic proton of **3***b* appears as a partly resolved triplet centered at 5.05 p.p.m. (J_{vic} = 6.0 Hz). Integration of the two

TABLE 1
Oxidative cleavage of ketoximes

Ketoxime	Solvent	% Cleavage*
	CH_3COOH	90
	CF_3COOH	>90 (30)†
	CH_3COOH	<10
	CF_3COOH	54†
	CH_3COOH	Not detected
	CF_3COOH	30
	CH_3COOH	Not detected
	CF_3COOH	Not detected
	CH_3COOH	>90
	CH_2Cl_2	>90
	CH_3COOH	70

*Estimate based on spectral analysis (i.r., n.m.r.).
†Analytically pure material.

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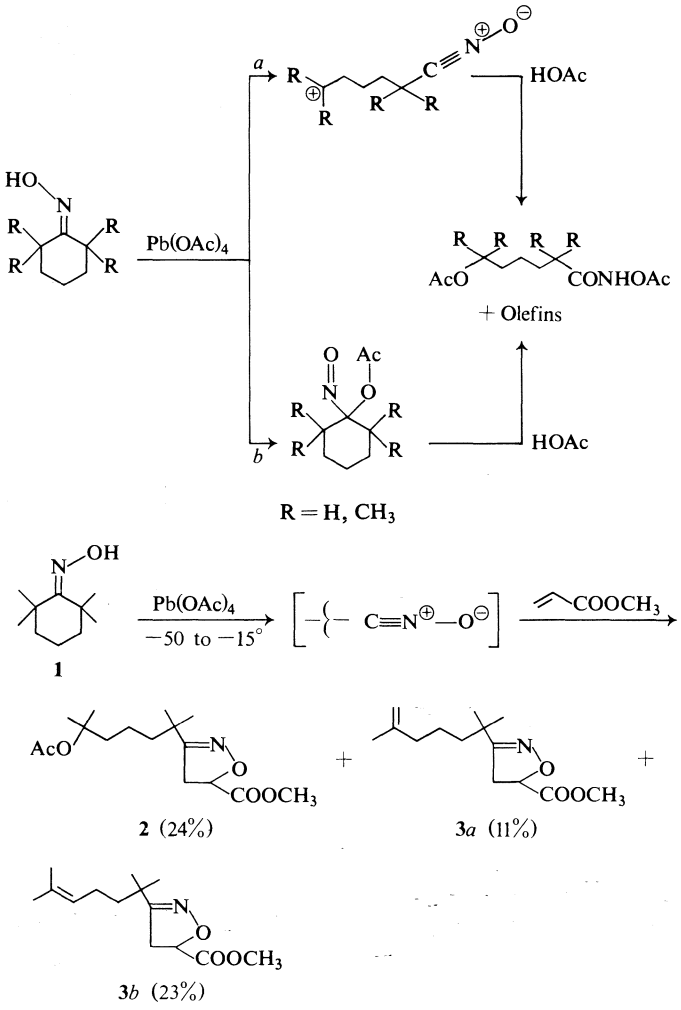
[2]Analogous considerations apply to camphor and fenchone oxime.

[1]

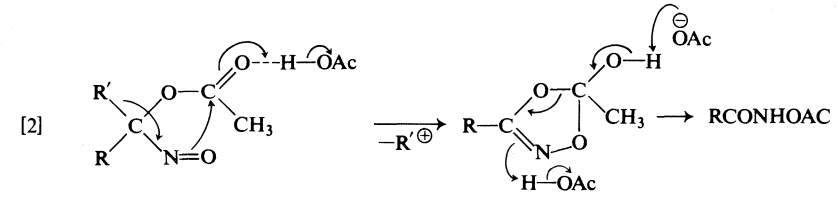


MECHANISM *a*

signals indicated for **3***a* and **3***b* a ratio of 1:2. Two slightly broadened singlets at 1.58 and 1.66 p.p.m. were assigned to the methyl groups which are attached to the double bond of **3***a* and **3***b*.

Interception of the nitrile oxide was also achieved with vinyl acetate. However, the instability of the resulting isoxazolinyl acetates permitted only spectral characterization (3). While reaction in methylene chloride caused very little cleavage, the extent of cleavage increased with acetic acid concentration. When a mixture of acetic acid and methylene chloride was used, and work-up was conducted below 0°, the resulting product mixture contained a substantial amount of material which showed a strong infrared (i.r.) band at 2280 cm^{-1}. This band is indicative of nitrile oxides.

Interception of a nitrile oxide and its i.r. spectroscopic detection was also realized in the oxidation of fenchone oxime. No such intermediate, however, was detected for camphor oxime although ring cleavage did occur to give mainly acetyl hydroxamates. Oxidation of camphor oxime was accompanied by formation of a deep blue color which was stable below 0°, but faded at room temperature. The rate of fading was accelerated by addition of acetic acid. This observation suggests the intermediacy of a geminal nitroso-acetate of the type found in the oxidation of unhindered aliphatic ketoximes (4), and would satisfy reaction path *b* (eq. [1]). A possible mechanism for the rearrangement of the nitroso-acetate to give acetyl hydroxamates is shown in eq. [2].



Common to all lead tetraacetate oxidations of the ketoximes investigated was the occurrence of a green color which appeared at about −70° and was accompanied by formation of a heavy white precipitate which was assumed to be lead diacetate. This color faded irreversibly when raising the temperature above −30°. Electron spin resonance measurements (5) have shown that iminoxyl radicals are formed in the lead tetraacetate oxidation of oximes, and it is conceivable that these radicals are intermediates in the oxidative cleavage reaction. This mechanistic assumption could also explain the oxidation products obtained from aromatic ketoximes (*6a–d*). A discussion of these results was published in a previous paper (*6d*).

Experimental

Melting points were measured in a capillary tube in a sulfuric acid bath and are corrected. Analyses were performed by Beller Mikroanalytisches Laboratorium, Göttingen, and Bernhard Mikroanalytisches Laboratorium, Mühlheim, Germany. The n.m.r. spectra were recorded on a Varian A-60 spectrometer with tetramethylsilane serving as internal standard. The i.r. spectra were recorded on Perkin–Elmer Infracord, 337, and 521 spectrometers. Ultraviolet (u.v.) spectra were recorded with a Beckmann DK spectrometer.

Lead Tetraacetate

The lead tetraacetate (Matheson, Coleman, and Bell) contained 4–7% acetic acid and was used as such for all oxidations.

Ketoximes

2,2,6,6-Tetramethylcyclohexanone oxime (m.p. 151.5°) was prepared from 2-methylcyclohexanone by exhaustive methylation (7), followed by oximation (8). All other ketoximes were prepared from commercially available ketones using standard procedures (9).

Oxidation of 2,2,6,6-Tetramethylcyclohexanone Oxime (1) in Acetic Acid

Lead tetraacetate (6.036 g, 13.6 mmoles) was added with stirring to a solution of **1** (2.000 g, 11.8 mmoles) in acetic acid (10 ml). After 5 min, acetic acid was removed by distillation (20°/0.1 mm), affording a pale green oil and lead diacetate which was suspended in a mixture of chloroform and ether (1:2) and filtered. The filtrate was washed with cold saturated sodium bicarbonate solution, dried ($MgSO_4$), and freed of solvent (40°/20 mm) to give 3.39 g of a pale green oil. Titration with 0.1 *N* sodium hydroxide solution indicated 90 ± 5% of acetyl 6-acetoxy-2,2,6-trimethylheptanohydroxamate (**4**): the n.m.r. ($CDCl_3$) δ 1.20 [s, 6H, $(CH_3)_2CCO$], 1.36 [s, 6H, $(CH_3)_2COAc$], 1.90 (s, 3H, *Ac*OC), 2.17 (s, 3H, *Ac*ON), and 9.5 (s, 1H, NH, exchangeable) p.p.m.; i.r. (CCl_4) 3350 (NH), 1790 (*N*-acetate C=O), 1740 (ester C=O) and 1720 (hydroxamate C=O) cm^{-1}. The material gave a negative ferric chloride test.[3]

Hydrolysis of Hydroxamate 4

A methanolic solution of 341 mg of **4** was neutralized at room temperature with 2 *N* aqueous potassium carbonate solution. After stirring for 24 h, solvent was removed (20°/0.2 mm) and the residue was dissolved in water (10 ml) and ether (50 ml), then acidified with a drop of dilute acetic acid. The aqueous phase was separated and extracted with ether. The combined ether extracts were dried ($MgSO_4$) and freed of solvent (30°/20 mm) to produce 320 mg of crystalline material. Recrystallization from hexane gave 245 mg (1.0 mmoles, 84%) of 6-acetoxy-2,2,6-trimethylheptanohydroxamic acid: m.p. 74–75°; n.m.r. ($CDCl_3$) δ 1.18 [s, 6H, $(CH_3)_2$-CCO], 1.41 [s, 6H, $(CH_3)_2COAc$], 1.98 (s, 3H, *Ac*O), and 9.0 (s,[4] 2H, *NHOH*, exchangeable) p.p.m.; i.r. (CCl_4) 3450 and 3290 (*NHOH*), 1730 (ester C=O), and 1660 (hydroxamic acid C=O), cm^{-1}.

Anal. Calcd. for $C_{12}H_{23}NO_4$: C, 58.75; H, 9.45; N, 5.71. Found: C, 59.07; H, 9.46; N, 6.22.

Oxidation of Ketoxime 1 in Trifluoroacetic Acid

Lead tetraacetate (21.0 g, 47.4 mmoles) was dissolved in 210 ml of trifluoroacetic acid and stirred for 1 h. This reagent was added to a solution of 7.20 g (42.5 mmoles) of **1** in 35 ml of trifluoroacetic acid. The reaction mixture was stirred at room temperature for 0.5 h, then diluted with cold water followed by extraction with ether. The combined extracts were washed with saturated sodium bicarbonate solution and water, then dried ($MgSO_4$), and freed of solvent (40°/20 mm) to give 9.39 g of crystalline material. Repeated recrystallization from hexane afforded 3.82 g (12.8 mmoles, 30%) of 6-trifluoroacetoxy-2,2,6-trimethylheptanohydroxamic acid (**5**): m.p. 81.5–82°; n.m.r. ($CDCl_3$) δ 1.18 [s, 6H, $(CH_3)_2CCO$], 1.53 [s, 6H, $(CH_3)_2COCOCF_3$], and 9.0 (s, 2H, *NHOH*, exchangeable) p.p.m.; i.r. (CCl_4) 3450 and 3250 (NHOH),

[3]All subsequently described hydroxamic acids gave a positive ferric chloride test.

[4]The 2-proton peak was resolved in $(CD_3)_2SO$ solution into 2 signals: 8.43 (s, 1H, *NH*) and 10.23 (s, 1H, *NOH*) p.p.m.; analogous resolution was achieved for other hydroxamic acids given.

1780 (ester C=O), and 1660 (hydroxamic acid C=O) cm^{-1}; u.v. max (95% C_2H_5OH) 211 mμ (ε 1550).

Anal. Calcd. for $C_{12}H_{20}F_3NO_4$ (299.29): C, 48.17; H, 6.74; F, 18.90; N, 4.68. Found ((mass spectrum) 299): C, 48.57; H, 6.71; F, 19.25; N, 4.80.

Hydrolysis of Hydroxamic Acid **5**

A solution of 36.0 mg (0.1204 mmoles) of **5** in water (2 ml) was boiled for 10 min, then cooled to room temperature and saturated with ammonium sulfate. Ether extraction afforded 23.0 mg (0.1134 mmoles, 94%) of 6-hydroxy-2,2,6-trimethylheptanohydroxamic acid: m.p. 112–113°; n.m.r. ($CDCl_3$) δ 1.20 [s, 12H, $(CH_3)_2$-COH, and $(CH_3)_2CCO$], 6.3[5] (s, 3H, *OH* and *NHOH*, exchangeable) p.p.m.; i.r. ($CHCl_3$) 3605 (OH), 3455 and 3300 (NHOH), and 1655 (hydroxamic acid C=O) cm^{-1}; u.v. max (95% C_2H_5OH) 212 mμ (ε 1520).

Anal. Calcd. for $C_{10}H_{21}NO_3$: C, 59.08; H, 10.40; N, 6.89. Found: C, 59.60; H, 10.51; N, 6.77.

Oxidation of 2,2,6-Trimethylcyclohexanone Oxime (6)

Lead tetraacetate (670 mg, 1.52 mmoles) was dissolved in 10 ml of trifluoroacetic acid, stirred for 1 h, and then added to a solution of 180 mg (1.16 mmoles) of ketoxime **6** in 2 ml of trifluoroacetic acid. The reaction was completed within a few seconds at room temperature. Trifluoroacetic acid was removed by distillation (20°/0.5 mm), and to the oily distillation residue was added cold saturated sodium bicarbonate solution, followed by ether extraction. The combined ether extract gave 247 mg of a colorless oil. Crystallization from pentane afforded 180 mg (0.631 mmoles, 54%) of 2,6-dimethyl-6-trifluoroacetoxyheptanohydroxamic acid: m.p. 79.5–80.5°; n.m.r. ($CDCl_3$) δ 1.14 (d, 3H, J = 6.7 Hz, $HCCH_3$), 1.54 [s, 6H, $(CH_3)_2COCOCF_3$], and 8.5 (s, 2H, *NHOH*) p.p.m.; i.r. (CCl_4) 3430 and 3210 (NHOH), 1790 (ester C=O), and 1660 (hydroxamic acid C=O) cm^{-1}.

Anal. Calcd. for $C_{11}H_{18}F_3NO_4$: C, 46.30; H, 6.36; N, 4.96. Found: C, 46.52; H, 6.27; N, 4.92.

Nitrile Oxide Interception in the Oxidation of Ketoxime **1**

A mixture of 1.00 g (5.90 mmoles) of ketoxime **1**, 15 ml of methyl acrylate, 15 ml of methylene chloride, and 6 ml of acetic acid was cooled to −50° and a cold (−50°) solution of 3.08 g (6.9 mmoles) of lead tetraacetate in 20 ml of methylene chloride and 1 ml of acetic acid was slowly added with stirring. The reaction mixture was kept at −50° for 1.5 h, then the temperature was raised to −15° within 0.5 h. The solution was re-cooled to −50° and 20 ml of cold triethylamine was added dropwise with stirring. The temperature was raised to 25° and 100 ml of ether was added, followed by extraction with water. The organic phase was dried ($MgSO_4$) and freed of volatile material (30°/20 mm and 85°/0.005 mm) to yield 1.405 g of a yellow oil. Separation by t.l.c. [SiO_2, hexane/ether (30%) as solvent] gave 2 oily fractions. These were rechromatographed on precleaned (methanol) plates, affording 445 mg (1.42 mmoles, 24%) of isoxazoline **2** and 500 mg (1.98 mmoles, 34%) of isoxazolines **3***a* and **3***b*. Compound **2** did not crystallize; distillation at 140–145° (bath)/0.0005 mm caused partial decomposition to give **3***a* and **3***b*. Isoxazoline **2** was, therefore, analyzed as such: n_D^{20} 1.4632; i.r. (neat) 1730 (ester C=O) cm^{-1}.

Anal. Calcd. for $C_{16}H_{27}NO_5$: C, 61.32; H, 8.68; N, 4.47. Found: C, 61.15; H, 8.72; N, 4.65.

Compounds **3***a* and **3***b* were distilled at 110–115° (bath)/0.0005 mm to give a colorless oil: n_D^{20} 1.4752; i.r. (neat) 1740 (ester C=O), 1650 and 1615 (C=C) cm^{-1}.

Anal. Calcd. for $C_{14}H_{23}NO_3$: C, 66.37; H, 9.15; N, 5.53. Found: C, 66.15; H, 9.23; N, 5.65.

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[5]In $(CD_3)_2SO$ the *tert* OH appeared as 1-H singlet at 3.95 p.p.m.