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OXIDATION OF HYDROXYLAMINES TO NITROXYL RADICALS WITH FREMY'S SALT

NITROXYL ALDEHYDES

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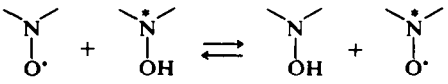
Abstract—Derivatives of 1-hydroxy-2,2,6,6-tetramethylpiperidine were oxidized by potassium nitrosodisulfonate (FREMY's salt) to 2,2,6,6-tetramethylpiperidine-1-oxyls. A triphenylphosphine-alkylene reaction, a Grignard reaction, and esterification resulted in derivatives with aldehyde groups.

Hydroxylamines and nitroxyl radicals interact in a redox equilibrium:[1,2]

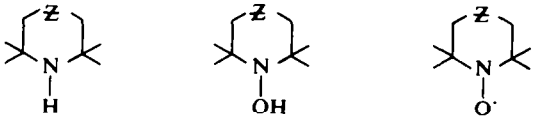


The mildest oxidation of a given hydroxylamine therefore uses as oxidant a nitroxyl from the more electropositive part of the redox scale of nitroxyl radicals.

Oxidations by FREMY's salt, $(KO_3S)_2NO$, an inorganic nitroxyl, have been reported for unsubstituted hydroxylamine[3] and for easy oxidisable substituted hydroxylamines[2] but a recent review[4] does not list oxidation of any other hydroxylamines.

Two advantages recommend its use: (1). Oxidations in aqueous solution may be homogenous, therefore no absorption by the oxidant or locally higher concentration of the oxidant occurs. (2). Reduced FREMY's salt is colourless, therefore excess of oxidant can be seen as a violet colour and can be avoided in the presence of other oxidisable groups.

Table 1 lists the formula of the substituted 2,2,6,6-tetramethylpiperidine derivatives of interest in this article.



amines **100** hydroxylamines **200** nitroxyls **300**

The hydroxylamines **200** were obtained in the usual way[5] by hydrogenation of the corresponding nitroxyls **300**.

The reaction cycle nitroxyl → hydroxylamine → nitroxyl can be used to perform reactions on functional groups of the hydroxylamines uncer conditions not favorable to nitroxyl groups like the acidic hydrolysis of acetal groups to free aldehydes. Nitroxyl groups react with acid by disproportionation.[6] Syntheses of nitroxyl aldehydes are reported either in low yield[8] or without experimental details.[9]

Free nitroxyl radicals with aldehyde groups are needed for spin labelling (for review see Ref 7) of compounds with carbonyl groups via hydrazone, azine-formation.

Syntheses of nitroxyls, not yet published. A possible synthesis of the aldehyde **304** via a triphenylphosphinealkylene reaction, would start with the ketone **303**. Phosphonatealkylenes add to the keto group in the nitroxyl **303** forming C—C bonds.[9] In addition, reduction of the nitroxyl group may occur.[9] A nitroxyl aldehyde withstanding lead dioxide has been reported.[9]

Triphenylphosphinemethoxymethylene added to the keto group in **303** to form the enol ether **305**. Acidic hydrolysis of the corresponding hydroxylamine **205** gave a mixture of 5 non-identified products. Alkaline hydrolysis[10] of the enol ether group in **305** could not be effected, in either methanolic or aqueous solution.

The nitroxyl acetal **306** was formed in the common peroxytungstate oxidation[11] of the corresponding amine **106**, which was synthesised from the amino ketone **103** with triphenylphosphine-methoxymethylene via the enol ether (**105**, not isolated) and acid catalysed addition of methanol. Hydrogenation of the acetal **306** to the hydroxylamine **206**, acidic hydrolysis and reoxidation with FREMY's salt yielded the free aldehyde **304**. Acidic hydrolysis of the amino acetal **106** yielded the amino aldehyde **104**, which gave upon peroxytungstate oxidation not the aldehyde **304** but in low yield the nitroxyl acid **307**.

Diazomethane does not attack the nitroxyl group.[12,13] Reaction with the ketone **303** therefore should give either the desired aldehyde **304**[14] or the epoxy compound **308** or ring expansion product(s). The only product from the reaction of

Table 1. Derivatives of 2,2,6,6-tetramethylpiperidine

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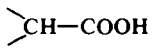
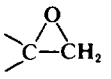
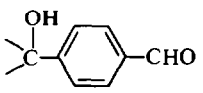
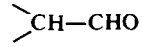
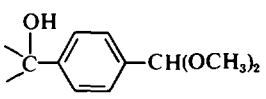
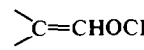
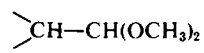
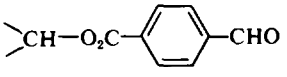
01		07	
02		08	
03		09	
04		10	
05			
06		11	

diazomethane with the ketone **303** was the epoxy compound **308**.

In a nitroxyl radical, alkyl Grignard reagents add either to a functional group[15] or to the nitroxyl group.[16] The Grignard reagent from *p*-bromobenzaldehyde dimethylacetal added to the keto group in **303** to give the acetal **310**. Hydrogenation to the hydroxylamine **210**, acidic hydrolysis of the acetal group and oxidation with FREMY's salt yielded the free aldehyde **309**. The aldehyde **311** could be synthesised by the common esterification method,[17] starting from the alcohol **302** and *p*-formylbenzo-benzoyl-chloride.

Spectroscopical data. UV (EtOH): All nitroxyls show absorption at ≈ 240 nm ($\epsilon \leq 2000$).[18]

IR (KI): The aldehyde groups in the compounds **104**, **204**, **209**, **211**, **304**, **309**, and **311** show CO absorption at 1720, 1700, 1685, 1695, 1720, 1695, and 1698 + 1708 cm^{-1} respectively. The CH-valence absorption at 2710–2730 cm^{-1}, characteristic for aldehydes, was given by the compounds **104**, **209**, **211**, **304**, and **307**. The carbonic acid **307** shows the characteristic broad OH band, overlapping the CH-valence band region: $\nu_{max} = 2980\ cm^{-1}$. ^{1}H-NMR ($CDCl_3$): All hydroxylamines **200** show sharp signals of all except the exchangeable H atoms. The aldehyde protons of the compounds **104**, **204**, **209**, and **211** were at 9·61 (d), 9·60 (s), 9·97 (s), and 10·09 (s) ppm. The epoxymethano hydrogens in compound **208** were at 2·64 (s, 2H), the ring protons at 1·68 (s, 4H) ppm.

ESR (MeOH): All nitroxyls show in 10^{-3} molar soln the characteristic[18] three line nitroxyl spectrum with $a_N = 15{\cdot}0$–$16{\cdot}5$ Gauss.

Mass spectra: All compounds gave the *m/e* signals for M^+. Nitroxyls showed the characteristic[19] $M^+ - 14$ (—CH_2) and $M^+ - 30$ (—NO) signals.

EXPERIMENTAL

All m.ps are uncorrected. Microanalyses were done by Alfred Bernhardt, Elbach, Germany and Ilse Beetz, Kronach, Germany.

Typical procedure[5]

Hydroxylamines **200** *by hydrogenation of nitroxyl radicals.* A soln of nitroxyl* (1–10 mmol) in EtOH (50–150 ml) was hydrogenated with PtO_2 at room temp until H_2 absorption stopped (30 min). The EtOH was removed *in vacuo*, the residue sublimed at 0·01–0·001 torr to yield a colourless crystalline hydroxylamine in almost quantitative yield. Table 2 lists examples of this procedure.

Nitroxyls **300** *by FREMY's salt oxidation of hydroxylamines* **200**. The hydroxylamine*(1 mmol), 0·1 molar aqueous dipotassium phosphate soln (35–50 ml) containing FREMY's salt (10 g per liter, iodometric titration[21] showed 0·03 molar soln, ESR amplitude decayed at 7%/h, prepared according to lit[22]), and chloroform (10 ml) were shaken for 2–10 min, depending on the water solubility of the hydroxylamine. The aqueous layer was extracted 4 times with chloroform (10 ml portions) and then remained slightly violet. The combined organic layers were dried with $MgSO_4$. The solvent was evaporated *in vacuo*, the residue sublimed at 0·01–0·001 torr, yields were from 90 to 100%. Table 3 lists examples of this procedure.

4-Methoxymethylene-2, 2, 6, 6-tetramethylpiperidine-1-oxyl **305**. To 1·2 molar phenyllithium in ether (42 ml, 50 mmol) THF (50 ml) was added with stirring at 0° under N_2, then triphenylphosphinemethoxymethylene hydrochloride[20] (15·5 g, 45 mmol) was added. After 10 min stirring, a soln of ketone **303**[25] (7·4 g, 44 mmol) in THF (20 ml) was added during 5 min at 0°. After stirring for 20 h at room temp, the solvents were removed at reduced pressure. The first destillation was carried out using an efficient high vacuum pump, maintaining less then 3×10^{-2} torr. The total condensate in the trap was redistilled at 10^{-3} torr and the fraction at 49–53° collected, yield: 6·2 g

*Synthesis described in this experimental part.

Table 2. Hydroxylamines by hydrogenation of nitroxyls

200	Hydroxylamine[a]	M.p.°	Analytical data % Calc. Found C	H	N	Ref
201	1-hydroxy-TEMP	40				20
202	1,4-dihydroxy-TEMP	158				20
203	1-hydroxy-4-oxo-TEMP	55, 90·5				20
204	1-hydroxy-4-formyl-TEMP	69	64·83	10·34	7·56	
			64·94	10·21	7·70	
205	1-hydroxy-4-methoxy-methylene-TEMP	41 – 42	66·29	10·62	7·05	
			66·12	10·53	7·21	
206	1-hydroxy-4-dimethoxy-methyl-TEMP	71 – 72	62·30	10·89	6·06	
			62·42	10·71	6·04	
208	1-hydroxy-4,4-epoxy-methano-TEMP	80 – 81	64·83	10·34	7·56	
			65·00	10·01	7·77	
209	1,4-dihydroxy-4(p-formyl-phenyl)-TEMP	120 – 128	69·28	8·36	5·05	
			69·24	8·32	5·02	
210	1,4-dihydroxy-4(p-dimetho-xymethyl-phenyl)-TEMP	124 – 126	66·84	9·04	4·33	
			66·67	8·86	4·43	
211	1-hydroxy-4(p-formyl-benzoyloxy)-TEMP	152 – 159	66·86	7·59	4·59	
			66·70	7·37	4·70	

[a]TEMP = -2,2,6,6-tetramethylpiperidine.

Table 3. Nitroxyls by oxidation of hydroxylamines

300	Nitroxyl[a]	m.p. °	Analytical data % Calc. Found C	H	N	Ref
301	TEMPO	35				23
302	4-hydroxy-TEMPO	71·5				24
303	4-oxo-TEMPO	36				25
304	4-formyl-TEMPO	79	65·18	9·85	7·60	*
			64·97	10·11	7·95	
305	4-methoxymethylene-TEMPO	28 – 30	66·63	10·17	7·06	*
			66·83	10·11	7·02	
306	4-dimethoxymetnyl-TEMPO	43	62·57	10·50	6·08	*
			62·52	10·46	6·01	
308	4,4-epoxymethano-TEMPO	65	65·18	9·85	7·60	*
			65·31	9·83	7·53	
309	4-hydroxy-4(p-formyl-phenyl)-TEMPO	127 – 128	69·54	8·02	5·07	*
			69·66	7·82	5·22	
310	4-hydroxy-4(p-dimetho-xymethyl-phenyl)-TEMPO	133	67·05	8·75	4·34	*
			66·84	8·63	4·49	
311	4-(p-formyl-benzoyloxy)-TEMPO	128	67·08	7·29	4·60	*
			67·02	7·22	4·59	

[a]TEMPO = – 2,2,6,6-tetramethylpiperidine-1-oxyl.

(71%) red oil. For analysis, distillation was done on a spinning band column with 70 plates, the fraction at 58·5°/0·15 torr was collected. Heating bath temps never exceeded 125°.[27]

4-Dimethoxymethyl-2,2,6,6-tetramethylpiperidine **106**. To 1·2 molar phenyllithium in ether (100 ml, 120 mmol) THF (100 ml) was added at 0° under N_2 with stirring and then triphenylphosphinemethoxymethylene hydrochloride[26] (37·6 g, 110 mmol) was added. After 10 min stirring, a soln of triacetoneamine **103**[28] (8·5 g, 55 mmol) in THF (20 ml) was added in 5 min at 0°. After stirring for 20 h at room temp, 4 N methanolic HCl (100 ml) was added in 2 min and the soln refluxed for 60 min, and then cooled to room temp. 4 N Na OMe in MeOH (about 50 ml required) was added (alkaline reaction), then water (200 ml), ether (200 ml), and AcOH (about 5 ml) were added to a pH 6–7. The ether phase contained the phosphorus compounds and was discarded. The aqueous phase was made alkaline with 10 M NaOH aq (15 ml), and then extracted 3 times with ether (200 ml portions). The combined ether phases were cleared with carboraffin, the

*Synthesis described in this experimental part.

ether removed *in vacuo*, and the residue distilled at a spinning band column with 70 plates, the colourless oil at 102°/15 torr collected, yield: 8·6 g (73%). (Found: C, 66·82; H, 11·71; N, 6·65; Calc. for $C_{12}H_{25}NO_2$ (215·3): C, 66·93; H, 11·70; N, 6·51%).

4-Formyl-2,2,6,6-tetramethylpiperidine **104**. A soln of the acetal **106*** (2·15 g, 10 mmol) in 2 N H_2SO_4 (20 ml) was kept at 70° for 45 min. The soln was cooled to room temp, 10 N NaOH (5 ml) was added, the soln extracted 5 times with ether (10 ml portions). The ether soln was dried with Na_2CO_3, and the solvent removed *in vacuo*, yield: 1·5 g (89%) of colourless crystals, m.p. 56°. They were sublimed for analysis at 30°/10^{-3} torr. (Found: C, 70·80; H, 11·42; N, 8·25. Calc for $C_{10}H_{19}NO$ (169·3): C, 70·96; H, 11·32; N, 8·28%).

4-Dimethyoxymethyl-2,2,6,6-tetramethylpiperidine-1-oxyl **306**. A soln of the acetal **106*** (2·15 g, 10 mmol) in MeOH (30 ml) was added at room temp to a soln of sodium tungstate (1 g), sodium ethylenediamine tetraacetate (1 g), water (100 ml), and 30% H_2O_2aq (20 ml) and kept in the dark. More H_2O_2aq (20 ml) was added after 2 days. After 5 days, the soln was extracted 3 times with chloroform (20 ml portions). The combined chloroform solns were dried with Na_2CO_3, and the solvent removed *in vacuo*, yield: 2·2 g (96%) of red crystals, m.p. 41–42°. These were sublimed for analysis at 30°/3 × 10^{-3} torr.

4-Formyl-2, 2, 6, 6-tetramethylpiperidine-1-oxyl **304**. A soln of the acetal **306*** (1·15 g, 5 mmol) in EtOH (50 ml) was hydrogenated over platinum catalyst.[5]. The solvent of the colourless soln was removed *in vacuo*. 2 N H_2SO_4 (50 ml) was added and the soln kept under N_2 at 70° for 45 min. After cooling to 10°, 1 molar tripotassiumphosphate soln (100 ml) containing FREMY's salt[22] (2·1 g, 7·8 mmol) was added and the soln again cooled to room temp. The soln was shaken for 3 min, then 3 times extracted with chloroform (50 ml portions). The combined chloroform solns were dried with $MgSO_4$, and the solvent removed *in vacuo*, yield: 900 mg (98%) of red crystals, m.p. 77–78°. These were sublimed for analysis at 35°/5 × 10^{-3} torr.

4-Carboxy-2,2,6,6-tetramethylpiperidine-1-oxyl **307**: A soln of the amino aldehyde **104*** (325 mg, 1·9 mmol) in MeOH (10 ml) was added at room temp to a soln of sodium tungstate (0·5 g), sodium ethylenediamine tetraacetate (0·5 g), water (50 ml), and 30% H_2O_2aq (10 ml) and kept in the dark. More H_2O_2 (10 ml) was added after 2 days. After 5 days, the soln was made acidic to pH 2 with 2 N H_2SO_4 (about 3 ml), then extracted 3 times with chloroform (10 ml portions). The chloroform solns were dried with $MgSO_4$, the solvent evaporateed *in vacuo*, and the residue sublimed at 60°/10 $^{-3}$ torr, yield: 80 mg (21%) red crystals, m.p. 150–155° dec. (Found: C, 60·45; H, 8·77; N, 7·14. Calc for $C_{10}H_{18}NO_3$ (200·3); C, 59·97; H, 9·06; N, 7·00).

4,4-Epoxymethano-2,2,6,6-tetramethylpiperidine-1-oxyl **308**. 1 molar soln of diazomethane in ether (90 ml, 90 mmol) was added at 0° to a soln of the ketone **303**[25] (8·0 g, 47 mmol) in ether (50 ml). The soln was kept for 4 days at 0° in the dark, then stirred with silicagel (1 g) at room temp until N_2 evolution stopped (about 30 min). The solvent was removed *in vacuo*, the residue chromatographed with EtOAc/hexane (1:4) on 600 cm^{-3} silicagel "Merck, 60". The first, red band yielded on evaporation of the solvent red crystals of epoxide **308**, yield: 3·3 g (38%), m.p. 64–65°. The second, orange band gave on evaporation of the solvent 4·6 g (57%) starting ketone **303**.

4-Hydroxy-4(p-dimethoxymethyl-phenyl)-2,2,6,6-tetramethylpiperidine-1-oxyl **310**. A mixture of ether/THF (1:1) was made anhydrous by distillation from a Grignard soln, e.g. EtMgBr. *p*-Bromo-benzaldehyde dimethylacetal[29] (29 g, 125 mmol) in ether/THF (50 ml) was added under N_2 to Mg turnings (4 g, 165 mg-atom) and ether/THF (175 ml) at reflux temp during 90 min. This Grignard soln was stirred and refluxed for a further 60 min, then added under N_2 during 10 min at 15° to a soln of the ketone **303**[25] (21·3 g, 125 mmol) in ether/THF (100 ml). After 12 h at room temp, excess water was added, the aqueous soln extracted once with benzene (200 ml) and the combined organic layers dried with Na_2CO_3. The solvent was removed *in vacuo*, and the residue dissolved in warm benzene (50 ml). Hexane was added to the soln within 16 h (portions of 50 ml, a total of 200 ml). The crystals lost solvent while being air dried, yield: 18 g (45%) pale red powder, m.p. 124–125°. These were sublimed for analysis at 110°/10^{-3} torr.

4-Hydroxy-4(p-formyl-phenyl)-2, 2, 6, 6-tetramethylpiperidine-1-oxyl **309**. A soln of the acetal **310*** (12·6 g, 39·5 mmol) in EtOH (400 ml) was hydrogenated over platinum catalyst.[5] 2 N H_2SO_4 (800 ml) was added and the colourless soln refluxed under N_2 for 45 min. After cooling to room temp, 10 N NaOH (190 ml) was added and the soln again cooled to 15°. Excess FREMY's salt[22] (more than 11 g) was added, the soln shaken for 10 min, then extracted 3 times with chloroform (250 ml portions). The combined chloroform extracts were dried with Na_2CO_3 and the solvent removed *in vacuo*. The residue was dissolved in EtOAc (20 ml) and hexane was added (50 ml portions, a total of 300 ml). The orange crystals were washed with hexane and air dried, yield: 9·8 g (90%), m.p. 124–127°. These were sublimed for analysis at 85°/10^{-3} torr.

4-(p-Formyl-benzoyloxy)-2,2,6,6-tetramethylpiperidine-1-oxyl **311**. A soln of *p*-formyl-benzoylchloride[30] (16·8 g, 100 mmol) in benzene (50 ml) was added to a soln of **302**[24] (15·5 g, 90 mmol), pyridine (8·7 ml, 110 mmol), and benzene (250 ml) at 4° during 10 min. The soln was kept at room temp for 20 h, then extracted 3 times with water (200 ml portions). The organic layer was cleared by addition of EtOAc (150 ml) and dried with $MgSO_4$. The solvent was removed *in vacuo*, the residue treated with EtOAc (25 ml). To the slurry hexane (250 ml in portions) was added the orange brown crystals washed with hexane and air dried, yield: 19·7 g (72%), m.p. 122–124°. These were sublimed for analysis at 85°/10^{-3} torr.

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*Synthesis described in this experimental part.

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