Hypervalent Iodine Oxidation. Synthesis of Spin Labeled, 1-Oxyl-2,2,6,6-tetramethylpiperidine Derivatives

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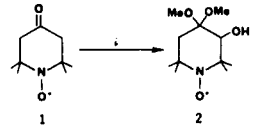
Received April 15, 1985

Oxidation of 1-oxyl-2,2,6,6-tetramethyl-4-piperidone (**1**) with [I,I-bis(acetoxy)iodo]benzene in methanolic potassium hydroxide yields 1-oxyl-4,4-dimethoxy-3-hydroxy-2,2,6,6-tetramethylpiperidine (**2**). Treatment of 2,2,6,6-tetramethyl-4-piperidone (**3**) with [I,I-bis(acetoxy)iodo]benzene in methanolic potassium hydroxide gave 3-methoxy-2,2,6,6-tetramethyl-4-piperidone (**4**) which on oxidation with 30% hydrogen peroxide and catalytic amount of sodium tungstate gave 1-oxyl-3-methoxy-2,2,6,6-tetramethyl-4-piperidone (**5**). The esr spectra of 1-oxyl-4,4-dimethoxy-3-hydroxy-2,2,6,6-tetramethylpiperidine (**2**) as well as 1-oxyl-3-methoxy-2,2,6,6-tetramethyl-4-piperidone (**5**) show three lines.

J. Heterocyclic Chem., **22**, 1581 (1985).

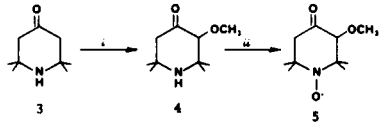
The success of spin labeling as applied to membranes, [1a-d], DNA, [2], RNA [3a-b] and other areas depends upon the ability of the spin label to be attached covalently to the substrate of interest. It is important to discover synthetic reactions under which the nitroxyl radical survives. Piperidine and pyrrolidine based nitroxyl radicals may be attached to amino acids *via* an amide linkage, *e.g.*, spin-labelled poly-L-lysine [4]. The nitroxyl radical is very susceptible to reduction to the hydroxylamine; for example, with ascorbic acid [5], phenylhydrazine [6] and copper(II) perchlorate [7] reduction occurs. Oxidation of the radical *via* a one electron process would lead to a dialkylnitrosonium system which could react further by fragmentation.

We report now the successful oxidation of a ketonic system to an α-hydroxydimethylacetal in a molecule containing the nitroxyl radical (**1** → **2**):



i $C_6H_5I(OAc)_2$-KOH/MeOH

Treatment of 2,2,6,6-tetramethyl-4-piperidone (**3**) with [I,I-bis(acetoxy)iodo]benzene in methanolic potassium hydroxide gave 3-methoxy-2,2,6,6-tetramethyl-4-piperidone (**4**). 1-Oxyl-3-methoxy-2,2,6,6-tetramethyl-4-piperidone (**5**) was obtained by the oxidation of **4** with 30% hydrogen peroxide and catalytic amount of sodium tungstate.



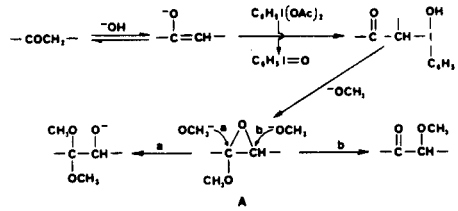
i $C_6H_5I(OAc)_2$-KOH/MeOH

ii 30% H_2O_2-Na_2WO_4/aq. MeOH

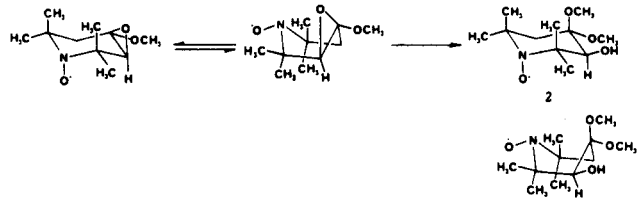
Disucussion.

The first point to be noticed is the fact that the nitroxyl radical is not oxidized by I(III). Secondly, the ketonic carbonyl in **1** behaves normally towards the hypervalent iodine; that is, iodosylbenzene in methanolic potassium hydroxide upon reaction with various ketones yields the corresponding α-hydroxydimethylacetal [8].

Furthermore, **3** → **4**, is different from: **1** → **2** in that the former yields the amino ketone. Mechanistically one may describe how products **2** and **4** form; however, a rationalization of the factors which cause the difference in reaction between **1** and **3** is less apparent. The mechanism for α-hydroxydimethylacetal formation is the following [8]:



Attack of methoxyl anion at the carbon bearing the methoxyl group in A, *route a*, yields the α-hydroxydimethylacetal [8]. Attack of methoxyl anion at the other carbon atom in A, *route b*, yields the α-methoxyketone. *Route a* is the normal and most frequently observed pathway: *route b* occurs in sterically hindered cases such as 17-ketosteroids [9]. Formation of **4** appears reasonable on the basis of steric strain. Formation of the very strained **2** is surprising, especially because attack of methoxyl anion at the more highly substituted carbon appears unfavorable.



Finally, returning to the original objective of the work, namely, providing novel functional groups on the nitroxyl radical molecule as potential points of attachment to substrates; the dimethyl acetal group in **2** offers the possibility of Mukaiyama type titanium tetrachloride, aldol, Claisen, and Michael type reactions [10].

EXPERIMENTAL

Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are uncorrected. The ir spectra were recorded on a Unicam SP1000 ir spectrophotometer. The nmr spectra were recorded on a Varian A-60. Varian E-4 spectrometer was used to record the esr spectra. Mass spectra were determined on a Hewlett Packard GC-MS 5985A spectrometer. Microanalyses were performed by Microtech labs, Skokie, Illinois.

1-Oxyl-4,4-dimethoxy-3-hydroxy-2,2,6,6-tetramethylpiperidine (**2**).

A solution of 1-oxyl-2,2,6,6-tetramethyl-4-piperidone [11] (3.06 g, 0.018 mole) in anhydrous methanol (30 ml) was added dropwise with stirring to a solution of potassium hydroxide (3 g, 0.54 mole) in methanol (50 ml) at 0-5°. After the addition, [I,I-bis(acetoxy)iodo]benzene (6.188 g, 0.019 mole) was added in several portions to the reaction mixture at 0-5°. The reaction mixture was stirred at 0-5° for 1 hour and at 23-25° for 15 hours. After the reaction, the reaction mixture was concentrated on a rotating evaporator at 40°/25 torr. The remaining residue was treated with water (50 ml) and saturated with potassium hydroxide (80 g). Then the solution was extracted with ether (4 × 30 ml). The combined ether extracts were dried over anhydrous sodium sulfate, filtered and the filtrate concentrated on a rotating evaporator at 25°/25 torr. The residue was purified by column chromatography on silica gel, using dichloromethane and diethyl ether (v/v 1:1) as an eluant to give a red oil, 1.67 g (40%); purity control by tlc (silica gel, dichloromethane:diethyl ether, 1:1) indicated one compound; ir (neat): 3480 cm^{-1} (br, OH stretching); ms: 232 (M^+, 7), 232 (7), 202 (1), 201 (2), 200 (2), 186 (3), 185 (2), 172 (2), 170 (2), 162 (2), 161 (26), 158 (2), 156 (2), 155 (12), 154 (4), 153 (2), 146 (3), 145 (4), 144 (3), 142 (2), 141 (2), 140 (12), 139 (6), 130 (39), 129 (100), 128 (23), 127 (11), 123 (5), 116 (8), 115 (96), 113 (10), 104 (5), 103 (14), 99 (12), 98 (26); esr: 3 lines, a_N = 13.5G.

Anal. Calcd. for $C_{11}H_{22}NO_4$: C, 56.89; H, 9.48; N, 6.03. Found; C, 56.75; H, 9.48; N, 5.60.

3-Methoxy-2,2,6,6-tetramethyl-4-piperidone (**4**).

To a cold solution (0-5°) of potassium hydroxide (6.72 g, 0.12 mole) in anhydrous methanol (80 ml), was added a solution of 2,2,6,6-tetramethyl-4-piperidone hydrochloride (5.76 g, 0.03 mole) in anhydrous methanol (30 ml). After the addition, [I,I-bis(acetoxy)iodo]benzene (10.95 g, 0.033 mole) was added to the reaction mixture in several portions. The reaction mixture was stirred at 0-5° for 2 hours and at 23-25° for 15 hours. After this time, the reaction mixture was concentrated on a rotating evaporator at 40°/22 torr. The remaining residue was treated with water (50 ml) and saturated with potassium hydroxide (80 g) and the aqueous saturated solution was extracted with ether (5 × 25 ml). The combined ether extracts were dried over anhydrous magnesium sulfate, filtered and the filtrate concentrated on a rotating evaporator at 25°/22 torr. The residue was purified by column chromatography on silica gel, using dichloromethane and diethyl ether (v/v 1:3) as an eluant to give 1.1 g (20%) of white solid crystalline product, mp 65-66°; ir (potassium bromide): 3320 cm^{-1} (NH, stretching), 1680 (>C=O), 1630 (NH, binding); nmr (deuteriochloroform): δ 1.33-1.65 (m, aliphatic protons, 14H), 3.55 (s, OCH_3, 3H), 5.66 (s, CH, 1H); ms: 185 (M^+ 1), 169 (2), 168 (20), 153 (4), 152 (3), 140 (12), 138 (2), 137 (2), 136 (3), 126 (6), 114 (4), 110 (3), 109 (3), 108 (11), 99 (5), 98 (6), 84 (8), 83 (100).

Anal. Calcd. for $C_{10}H_{19}NO_2$: C, 64.86; H, 10.27; N, 7.56. Found; C, 64.71; H, 9.97; N, 7.50.

1-Oxyl-3-methoxy-2,2,6,6-tetramethyl-4-piperidone (**5**).

Aqueous hydrogen peroxide (30%, 2.0 ml) was added dropwise with stirring at 0° to a solution of **4** (0.5 g, 0.0027 mole) and sodium tungstate (5 mg, 0.15 mmole) in aqueous methanol (45%, 8.0 ml). Following the addition, the solution was stirred at 23-25° for 50 hours, then diluted with water (10 ml), saturated with anhydrous potassium carbonate, and extracted with ethyl ether (3 × 10 ml). The combined ether extracts were dried over anhydrous magnesium sulfate, filtered and the solvent was removed on a rotating evaporator at 25°/20 torr. The remaining oily product was purified by column chromatography on silica gel, using dichloromethane as an eluant. Removal of the solvent gave 410 mg (76%) of pure yellow oil; purity control by tlc (silica gel, dichloromethane:hexane, 8:2) indicated one compound; ir (neat): 1720 cm^{-1} (>C=O); ms: 200 (M^+ 1), 183 (3), 169 (3), 168 (32), 153 (4), 152 (2), 142 (4), 141 (24), 140 (14), 136 (1), 114 (2), 112 (4), 111 (12), 110 (17), 98 (23), 97 (2), 88 (80); esr: 3 lines a_N = 14.5G.

Anal. Calcd. for $C_{10}H_{18}NO_3$: N, 7.00. Found: N, 6.88.

Acknowledgement.

We thank the USAMRDC and the Petroleum Research Fund for support of this work.

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