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Synthesis of acetonine nitroxide radical and 1-hydroxy-2,2,4,6,6-pentamethyl-1,2,5,6-tetrahydropyrimidine

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Abstract

An oxidation of acetonine with hydrogen peroxide 30% in strong basic water media in the presence of sodium tungstate with subsequent reduction of reaction product with hydrazine hydrate afforded up to 50% yields of the title hydroxyderivative. Mild oxidation of this compound with MnO_2 in ether gave acetonine nitroxide radical quantitatively. © 1999 Elsevier Science Ltd. All rights reserved.

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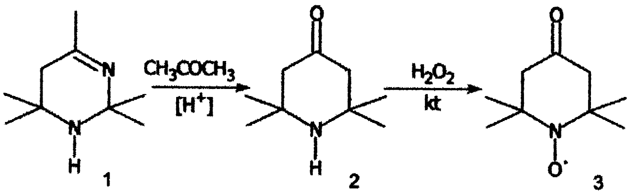
The 'acetonine', isolated from the reaction of acetone and ammonia, was finally identified as 2,2,4,6,6-pentamethyl-1,2,5,6-tetrahydropyrimidine **1**.[1] Excellent yields resulted when acetone and liquid ammonia were kept at 20°C for 24 h in the presence of calcium or ammonium chloride as a catalyst and other ammonium salts as promoters.[1] The synthesis of acetonine **1** can be also carried out without excess pressure of ammonia with good yield (82–88%), that is more convenient for the laboratory scale.[2] Acetonine **1** has attracted the attention of researchers and polymer companies as a basic compound for manufacturing triacetonamine **2** on an industrial scale;[3] **2** is widely used as an initial compound for the synthesis of light stabilizers and nitroxide radicals of the piperidine and pyrrolidine series. By reaction of **1** with acetone in the presence of Lewis acids, such as zinc, ammonium, or calcium chloride, triacetonamine **2** is formed in yields higher than 90% (Scheme 1).[3]



Scheme 1.

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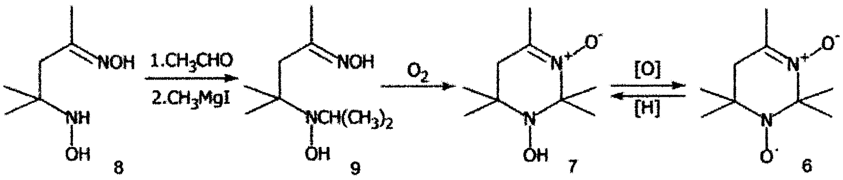
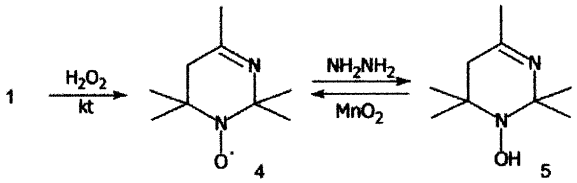
Acetonine forms a crystalline monohydrate in which the C=N and >NH< groupings still exist.[1] The similarity of the >NH< grouping and its surrounding in molecules **1** and **2** prompted us to search the possibility to oxidize acetonine **1** the same way as triacetonamine **2** was oxidized by hydrogen peroxide into stable nitroxide radicals **3** **(**Scheme 1**)**.[3] We could not find information about the synthesis of acetonine nitroxide radical **4** or corresponding hydroxylamine **5**. However it was evident that these compounds could be initial ones for a new series of derivatives, and would be an open challenge to combine the chemistry of nitroxide radicals with the chemistry of heterocyclic compounds (cf.[4]). This compound could be initial one for synthesis of spin labeled analogues of cytosine and thymine.

Nitroxide radical, 2,2,4,6,6-pentamethyl-1,2,5,6-tetrahydropyrimidine-3-oxide-1-oxyl **6** was synthesized by oxidation of 1-hydroxy-2,2,4,6,6-pentamethyl-1,2,5,6-tetrahydropyrimidine-3-oxide **7** with lead dioxide.[5] The synthesis of **7** was based on the condensation of prepared from mesityl oxide 1,3-hydroxylaminooxime **8** with acetaldehyde; subsequent interaction of the formed 1,3-oximinonitrone with methylmagnesium iodide gave *N*-isopropylhydroxylaminooxime **9.** A mild oxidation of **9** with air oxygen led to the cyclic compound **7**. Reduction of the unstable radical **6** by hydrazine in organic solvent also gave quantitatively stable hydroxylamine **7**, m.p. 156–158°C (Scheme 2).[5]



Scheme 2.

An oxidation of acetonine **1** with hydrogen peroxide 30% in strong basic water media in the presence of sodium tungstate at 20–40°C lead to nitroxide radical **4** with yields of 24 to 50% (GLC), which strongly depends on the temperature and the rate of work up.[6] The orange water solution was saturated with potassium carbonate and extracted with ether. As radical **4** in solution decomposes, an ether solution, containing **4**, was worked up with an excess of hydrazine which gave a colorless precipitate, 1-hydroxy-2,2,4,6,6-pentamethyl-1,2,5,6-tetrahydropyrimidine **5** with the same yield of 24 to 50% (Scheme 3).[6] Compound **5** is quite stable and has a comparatively high m.p. 142–144°C (ethylacetate). In its NMR spectrum ($CDCl_3$) there is a peak at 1.20 m.d. 6,6- $(CH_3)_2$, a peak at 1.67 m.d. 2,2- $(CH_3)_2$, a peak at 2.10 m.d. 4-CH_3, a peak at 2.46 m.d. CH_2 and a band with center at 9 m.d., which disappear in CD_3OD. In the IR spectrum of **5** (KBr) there is a weak band at 1620 sm^{-1} (C=N) and a broad band at 3300 sm^{-1} (OH). According to MS molecular weight of hydroxylamine **5** is 170 and of radical **4** is 169.



Scheme 3.

Pure radical **4** was prepared by oxidation of **5** with MnO_2 in ether at room temperature as a red oil.[6] In the refrigerator this oil gives red crystals of radical **4**, which melted at 20°C. During storage of liquid radical **4** or its saturated solution in organic solvent the crystals of hydroxylamine **5** separated out, evidently due to the redox reaction. During the storage of crystals of **5** in the presence of air in refrigerator for one month[6] orange color emerged and the substance had approximately 10% of radical **4** (GLC). However in absense of air compound **5** can be stored for months without any decomposition.

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