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A new nitroxide radical derived from 2,2,4,6,6-pentamethyl-1,2,5,6-tetrahydro-pyrimidine and its conversion to 2,2,4,6,6-pentamethyl-1,2,5,6-tetrahydro-pyrimidine-1-oxyl

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Abstract

The new oxaziridine nitroxide, 2,2,4,4,6-pentamethyl-7-oxa-1,3-diaza-bicyclo[4.1.0]heptan-3-oxyl, has been obtained in 90% yield by oxidation of 2,2,4,6,6-pentamethyl-1,2,5,6-tetrahydro-pyrimidine with MCPBA in ether. This nitroxide is stable in the solid state or in non-protic solvents. It was converted to the known 2,2,4,6,6-pentamethyl-1,2,5,6-tetrahydro-pyrimidine-1-oxyl by successive reduction with $LiAlH_4$ and oxidation with Ag_2O, with a reproducible yield of 16% from the starting tetrahydropyrimidine. © 2000 Elsevier Science Ltd. All rights reserved.

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Recently, Volodarsky and Kosover[1] reported the preparation of 2,2,4,6,6-pentamethyl-1,2,5,6-tetrahydro-pyrimidine-1-oxyl **1** with yield varying from 24 to 50%, by direct oxidation of 2,2,4,6,6-pentamethyl-1,2,5,6-tetrahydro-pyrimidine **2** with hydrogen peroxide in the presence of sodium tungstate. This radical was found to decompose slowly in solution or in the pure state, but after conversion in 50% yield to the stable hydroxylamine **3** by hydrazine, it could be quantitatively recovered through a new oxidation by MnO_2 (Scheme 1).

Because of a reported application of **1** in living radical polymerization,[2] we investigated another preparation: when **2** (14 g) was treated with MCPBA (42 g) in ethyl ether (450 mL), **1** was not obtained, but the new oxaziridine nitroxide **4**[3] was isolated in 90% yield, no trace of **1** or the isomeric nitrone–nitroxide **5**[1,4] were detected. 1,2-Diphenylhydrazine selectively reduced the aminoxyl group to afford the new oxaziridine–hydroxylamine **6**[5] in 70% yield, while $LiAlH_4$ reduced both the aminoxyl and oxaziridine groups to **3**[6] in 36% yield. This hydroxylamine was then oxidized to **1** by Ag_2O in 50% yield.

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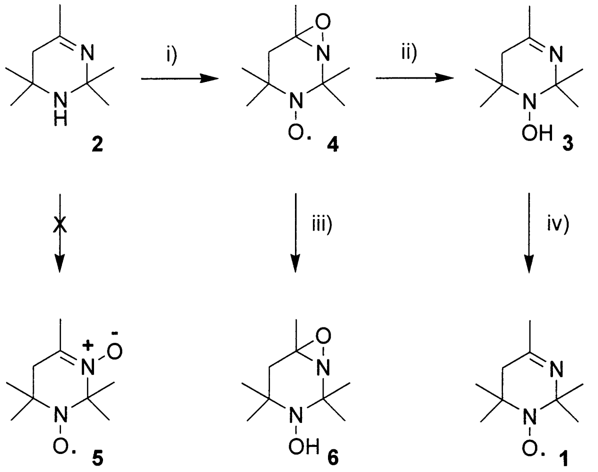

Scheme 1. (i) MCPBA (90%); (ii) $LiAlH_4$ (36%); (iii) 1,2-Diphenylhydrazine (72%); (iv) Ag_2O (50%)

Although **4** and **5** have similar ESR spectra and close mp,[4] they differ by the presence of two asymmetric carbon atoms in **4**. This structure was confirmed by partial resolution through complexation with β-cyclodextrin[7] and partial separation on chiral HPLC columns.[8] Similarly, the ^{13}C NMR spectrum of **6**[5] displays four non-equivalent methyl groups, thus excluding the isomeric hydroxynitrone structure.[1,4]

Crystalline **4** may be kept unchanged at room temperature. Its solutions in ethyl ether, petroleum ether, benzene, chloroform or cyclohexane did not show any decay of their ESR signals after a month at room temperature, but in water, methanol or ethanol, these signals disappeared within few days, probably because of hydrolysis of the oxaziridine ring.[9]

Although the conversion of oxaziridines to nitrones is well documented,[10] we could not transform **4** into **5** by thermal isomerization or by elution on silica gel.

Like other nitroxide radicals, **4** may be used in living radical polymerization; this is now being studied.

References

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2. Volodarsky, L.; Kosover, V. US Patent 5 847 035; Dec. 8, 1998.
3. 2,2,4,4,6-Pentamethyl-7-oxa-1,3-diaza-bicyclo[4.1.0]heptan-3-oxyl, **4**: Mp = 52–53°C (heptane); IR: absence of $\nu_{C=N}$ at 1670 cm^{-1}; anal. calcd for $C_9H_{17}N_2O_2$ (185.24): C, 58.35; H, 9.25; N, 15.12; O, 17.27. Found: C, 58.60; H, 9.36; N, 15.24; O, 17.54; esr (H_2O, LiCl): $a_N = 15.8$ G ($\Delta H_{pp} = 1.8$ G); UV: (ethanol) 410 nm ($\varepsilon = 10$ mol^{-1} cm^{-1}), 235 nm ($\varepsilon = 3490$ mol^{-1} cm^{-1}). In ethanol solution, both the esr signal and the UV absorption at 410 nm decay with a half life of ca. 17 h at room temperature.
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5. 2,2,4,4,6-Pentamethyl-7-oxa-1,3-diaza-bicyclo[4.1.0]heptan-3-ol, **6**: Mp = 98.5–99°C; ^1H NMR (250 MHz, $CDCl_3$) δ 1.16 (s, 3H), 1.25 (s, 3H), 1.41 (s, 3H), 1.53 (s, 6H), 2.06–2.28 (d, $J = 16$ Hz, 1H); ^{13}C NMR (250 MHz, $CDCl_3$) δ: 24.5, 24.9, 25.26, 27.4, 29.2, 40.6, 54.9, 77.4, 80.2.
6. Compound **3** (660 mg) was obtained from **2** (2 g) with $LiAlH_4$ (750 mg) in ethyl ether (20 mL): Mp = 156°C (lit.[1] 142–144°C, ethyl acetate); IR: 1670 cm^{-1}, (lit.[1] 1620 cm^{-1}); ^1H NMR (250 MHz, $CDCl_3$) δ 1.16 (s, 6H), 1.42 (s, 6H), 1.94 (s, 3H), 2.23 (s, 2H). ^{13}C NMR (250 MHz, $CDCl_3$) δ 25.6, 27.0, 27.45, 45.6, 54.8, 77.17, 161.6; anal. calcd for $C_9H_{18}N_2O$ (170.25): C, 63.49; H, 10.66; N, 16.45; O, 9.40. Found: C, 63.45; H, 10.87; N, 16.29; O, 9.44.

7. 1.6 g of **4** were added to a solution of 10 g of β-cyclodextrin in 200 mL of water. After 3 hours a precipitate appeared. The filtrate was extracted with ethyl ether, dried on sodium sulfate and evaporated, 700 mg of **4** was recovered. They were treated again with a solution of 4 g of cyclodextrin in 200 ml of water. After extraction, 210 mg of enantiomerically enriched nitroxide **4** was obtained. A solution (41 mg/mL) of this radical in cyclohexane (1 cm cell) shows $\Delta\varepsilon = 0.038$ mol^{-1} cm^{-1} at 456 nm. Determination of the e.e. was not possible: attempted resolution by HPLC on chiral columns (tris(phenylcarbamoyl)cellulose/SiO_2, triacetylcellulose, or tribenzoylcellulose) gave a clear indication of the chirality of **4**, but with only a weak separation of the enantiomers.
8. We thank Professor Mannschreck (University of Regensburg) for this analysis.
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