Utilization of ultrasound for the synthesis of 4-substituted 2,2,6,6-tetramethylpiperidinyloxyls

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Dedicated to Professor Ing. J. Kováč, DrSc., in honour of his 60th birthday

Sonication facilitates the synthesis and accelerates the yields of 4-substituted 2,2,6,6-tetramethylpiperidinyloxyls. This effect is highly pronounced on the substrates with a long lipophilic chain in position 4. The influence of solvent and temperature on the yield of the reaction has been studied. H_2O_2 oxidation of the piperidine derivatives promoted by ultrasonic irradiation has been successful also without catalyst.

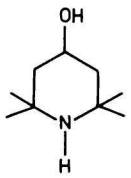
Обработка ультразвуком облегчает синтез и ускоряет выходы 4-замещенных-2,2,6,6-тетраметилпиперидинилоксилов. Этот эффект наиболее ярко выражен для субстратов с длинной липофильной цепью в положении 4. Изучено влияние растворителя и температуры на выход реакции. Окисление пиперидиновых производных перекисью водорода, промотированное ультразвуком, успешно проходило и без катализатора.

Nitroxyl radicals of sterically hindered secondary amines (stable compounds at room temperature) are a representative group of compounds which have been intensively studied [1—6]. *N*-Oxyl radicals of sterically hindered piperidines, pyrrolidines, and isoindolines are used as spin labels in the study of different biochemical processes in living organisms or model systems [7]. They are commonly prepared by the oxidation of the corresponding secondary amines with 30 % H_2O_2 (without solvent), using Na_2WO_4 as catalyst, at room temperature [3—8]. Sometimes $NaHCO_3$ can be used as a catalyst [9, 10]. Peroxy acids [11—13], Ag_2O [14], PbO_2 [15], ozone [16], dibenzoyl peroxide [17, 18] or di(*tert*-butyl) peroxide [19] can be used as oxidizing agents instead of H_2O_2.

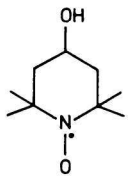
The H_2O_2 oxidation of sterically hindered secondary amines was in some cases rather slow, also producing low yields of *N*-oxyl radicals. As it was found

[20] that ultrasound accelerates the reaction course of different chemical reactions, the aim of this work was to study the influence of ultrasound on the H_2O_2 oxidation of sterically hindered piperidines.

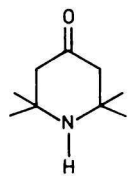
The influence of ultrasound on H_2O_2 oxidation of 2,2,6,6-tetramethyl-4--piperidinol (*I*) or 2,2,6,6-tetramethyl-4-piperidinone (*II*) (low molecular mass, water insoluble compounds) has not been observed. The reaction was reasonably fast without using ultrasound.



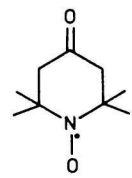
I



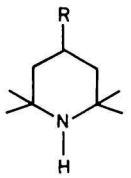
Ia

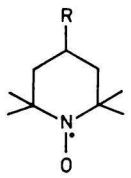


II



IIa

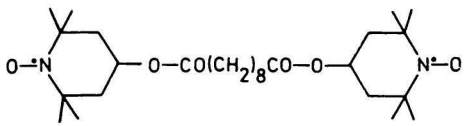




III, V *IIIa, Va*

III, IIIa: R = $NHCOC_6H_4OC_8H_{17}$-*p*

V, Va: R = $OCO(CH_2)_{16}CH_3$



IVa

Piperidines with a long lipophilic chain and higher molecular mass are more sensitive to sonication, *i.e.* (2,2,6,6-tetramethyl-4-piperidyl)-4-octyloxybenzamide (*III*) or bis(2,2,6,6-tetramethyl-4-piperidyl) esters of sebacic acid (*IV*) are almost unreactive without ultrasound (Table 1). The highest acceleration due to the ultrasound was observed in the case of oxidation of 2,2,6,6-tetramethyl-4--stearoyloxypiperidine (*V*). This reaction was therefore studied in most detail (Table 2).

As it is shown in Table 2, ultrasound accelerates the oxidation of 2,2,6,6-tetramethyl-4-stearoyloxypiperidine. This effect was most pronounced when the

Table 1

Results of oxidation of 4-substituted 2,2,6,6-tetramethylpiperidines by H_2O_2 with Na_2WO_4 catalyst and sonication

Product	Reaction time	Bath temperature/°C	Solvent	% *N*-oxyl
Ia	30 min	22	—	89
Ia	120 min	22	—	80
*Ia**	30 min	22	—	50
IIa	30 min	50	—	65
*IIa**	30 min	50	—	70
IIIa	20 h	50	C_2H_5OH	22
IVa	13 h	50	C_2H_5OH	37

* Without ultrasound.

Table 2

Results of oxidation of 2,2,6,6-tetramethyl-4-stearoyloxypiperidine (*V*) by H_2O_2 with Na_2WO_4 catalyst and sonication for 20 h

Experiment	Solvent	θ/°C	% *N*-oxyl
1	CH_3OH	50	78
2	CH_3OH^a	50	44
3	CH_3OH	22	25
4	CH_3OH^a	22	0
5	CH_3CH_2OH	50	84
6	CH_3CN	50	43
7	CH_3COOH^b	50	28
8	DMF^c	50	27
9	$CH_3CH_2OH^d$	50	31
10	$CH_3CH_2OH^e$	50	8

a) Without ultrasound; *b*) when the reaction was over, the mixture was neutralized with K_2CO_3 and the organic material was extracted into ether; *c*) when the reaction was over, the mixture was poured into water, saturated with K_2CO_3 and the organic material was extracted into ether; *d*) reaction without Na_2WO_4 as a catalyst; *e*) reaction in the presence of Na_2CO_3.

oxidation was carried out at lower temperature (22 °C). Under similar reaction conditions at 50 °C approximately twice the yield of *N*-oxyl radicals was obtained.

From the described results it is evident that ultrasound, catalyst, and temperature have beneficial effects on the course of the reaction (experiments *2*, *5*,

9). The effect of ultrasound is obviously due to accurate mixing and homogenization of the reaction mixture, while higher temperature increases the solubility of the starting lipophilic amine (experiments *2*, *4*). Therefore the solvent also must play an important role in these reactions, the best yield results being obtained in ethanol (84 %) and the lowest in acetic acid (28 %). Provisional experiments prove that Na_2WO_4 decomposes H_2O_2. From the results of experiment *9* (without Na_2WO_4) it follows that ultrasound also has the same effect. The question as to what extent ultrasound promotes the decomposition of H_2O_2 or whether it somehow activates the metallic catalyst, will be the subject of a later investigation.

Oxylation of 2,2,6,6-tetramethyl-4-stearoyloxypiperidine in an oxygen or argon atmosphere shows that the presence of the gas has no essential influence on the reaction course. The yields from these experiments are similar and 15 % lower than the yields of the experiments carried out in air.

Experimental

Ultrasound was generated by a 4 dm^3 ultrasonic cleaning bath Tesla UC 002 BM 1 (20 kHz, 160 W).

Concentrations of *N*-oxyl radicals of compounds *Ia* and *IIa* were determined by UV spectroscopy (calibration curve), of compounds *IIIa*, *IVa*, and *Va* by ESR spectroscopy. A calibration graph has been made by quantitative evaluation of the ESR signal (determination of intensity of the second peak of the triplet signal $a_N = 1.6$ mT, $g = 2.0057$) of benzene solution of 2,2,6,6-tetramethyl-4-stearoyloxypiperidinyl-1-oxyl (Fig. 1). The changes in intensity of ESR signals ΔI_{ESR} were measured on an ESR Spectrometer Bruker SRL-200 in the range x with 100 kHz modulation. UV spectra were measured on a Specord UV VIS instrument at $\lambda_{max} = 237$ nm (compound *IIa*) and at $\lambda_{max} = 243$ nm (compound *Ia*).

Starting compounds *I*, *II*, and *IV* were prepared by the known methods [1, 3]. (2,2,6,6-Tetramethyl-4-piperidyl)-4-octyloxybenzamide (*III*) was prepared in 33 % yield by the reaction of 4-amino-2,2,6,6-tetramethylpiperidine with 4-octyloxybenzoyl

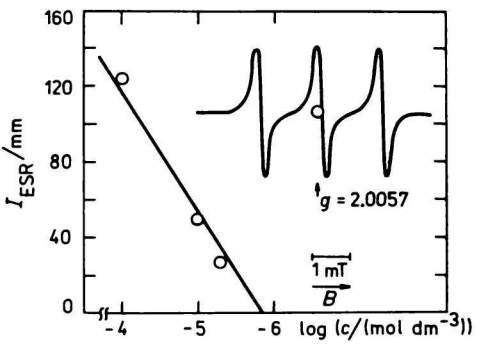


Fig. 1. ESR signal of 2,2,6,6-tetramethyl-4--stearoyloxypiperidine-*N*-oxyl in benzene solution at 23 °C, and dependence of signal intensity on the concentration.

chloride in anhydrous pyridine. After crystallization from hexane compound *III* (m.p. = 85.5—87.5 °C) was obtained. For $C_{24}H_{40}N_2O_2$ (M_r = 388.64) w_i(found): 74.33 % C, 10.66 % H, 7.21 % N; w_i(calc.): 74.17 % C, 10.43 % H, 7.21 % N.

2,2,6,6-Tetramethyl-4-stearoyloxypiperidine (*V*) (m.p. = 43.5—45.5 °C after recrystallization from acetone) was prepared in 15 % yield by the reaction of 2,2,6,6-tetramethyl-4-piperidinol and stearoyl chloride in anhydrous pyridine. For $C_{27}H_{53}NO_2$ (M_r = 423.79) w_i(found): 76.06 % C, 13.41 % H, 3.28 % N; w_i(calc.): 76.51 % C, 12.63 % H, 3.30 % N.

Preparation of 4-hydroxy-2,2,6,6-tetramethylpiperidinyloxyl (Ia)

A mixture of *I* (0.5 g; 0.3 mmol), $Na_2WO_4 \cdot 2H_2O$ (0.05 g; 0.15 mmol), Chelaton 3* (0.05 g; 0.15 mmol), H_2O (3 cm^3), and 30 % H_2O_2 (1 cm^3) in a 50 cm^3 Erlenmeyer flask was immersed in the ultrasonic cleaning bath and was sonicated. After the appropriate time the mixture was saturated with K_2CO_3 and the product was extracted into ether. After evaporation of the ether the content of *N*-oxyl radical in the residue was determined by UV spectroscopy (Table 1). The product (m.p. = 72—73 °C) was isolated by chromatography and crystallization (silica, benzene as eluent; benzene—petroleum ether for crystallization). For $C_9H_{18}NO_2$ (M_r = 172.26) w_i(found): 62.77 % C, 10.74 % H, 8.02 % N; w_i(calc.): 62.75 % C, 10.55 % H, 8.17 % N.

Preparation of 2,2,6,6-tetramethyl-4-oxopiperidinyloxyl (IIa)

Procedure as for *Ia:* reaction mixture: *II* (0.5 g; 3 mmol), $Na_2WO_4 \cdot 2H_2O$ (0.02 g; 0.06 mmol), Chelaton 3 (0.02 g; 0.06 mmol), H_2O (5 cm^3), and 30 % H_2O_2 (1 cm^3). The physical constants of *IIa* are in agreement with the literature data [10].

Preparation of 2,2,6,6-tetramethyl-4-stearoyloxypiperidinyloxyl (Va)

To *V* (1.0 g; 2.4 mmol) in 40 cm^3 of the appropriate solvent in an 100 cm^3 Erlenmeyer flask was added $Na_2WO_4 \cdot 2H_2O$ (0.05 g; 0.15 mmol), Chelaton 3 (0.05 g; 0.14 mmol), and 30 % H_2O_2 (3 cm^3). The flask was immersed into an ultrasonic cleaning bath and sonicated. After 20 h the solvent was removed, the residue was dissolved in benzene and the content of *N*-oxyl radical was determined by ESR (Table 2). The product (m.p. = 49—52 °C) was isolated by chromatography and crystallization. For $C_{27}H_{52}NO_3$ (M_r = 438.8) w_i(found): 76.80 % C, 12.45 % H, 3.40 % N; w_i(calc.): 76.70 % C, 12.39 % H, 3.31 % N.

* Chelaton 3 — disodium salt of ethylenediaminetetraacetic acid.

Preparation of 2,2,6,6-tetramethyl-4-(4-octyloxybenzamide) piperidinyloxyl (IIIa)

Procedure as for *Va*; reaction mixture: *III* (0.2 g; 0.5 mmol), $Na_2WO_4 \cdot 2H_2O$ (0.05 g; 0.15 mmol), Chelaton 3 (0.05 g; 0.14 mmol), and 30 % H_2O_2 (4 cm^3) in 10 cm^3 of ethanol. Product *IIIa* (m.p. = 82.5—84.5 °C) was obtained after recrystallization from benzene —petroleum ether. For $C_{24}H_{39}N_2O_3$ (M_r = 403.62) w_i(found): 70.90 % C, 9.92 % H, 6.60 % N; w_i(calc.): 71.41 % C, 9.77 % H, 6.94 % N.

Preparation of 2,2,6,6,2',2',6',6'-octamethyl-4,4'-sebacoyldioxydipiperidinyloxyl (IVa)

Procedure as for *Va;* reaction mixture: *IV* (0.5 g; 1 mmol), $Na_2WO_4 \cdot 2H_2O$ (0.04 g; 0.12 mmol), Chelaton 3 (0.04 g; 0.1 mmol), and 30 % H_2O_2 (1 cm^3) in 20 cm^3 of ethanol. Product *IVa* (m.p. = 120—124 °C) was obtained after recrystallization from benzene —petroleum ether. For $C_{28}H_{50}N_2O_6$ (M_r = 510.74) w_i(found): 65.49 % C, 10.24 % H, 5.43 % N; w_i(calc.): 65.84 % C, 9.88 % H, 5.49 % N.

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