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Improved Synthesis of 1-Hydroxy-2,2,5,5-tetramethyl-3-imidazoline 3-Oxide (HTIO)

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Abstract: A simple, efficient, mild, and reproducible method for the synthesis of 1-hydroxy-2,2,5,5-tetramethyl-3-imidazoline 3-oxide is described. The method is based on the condensation of 2-hydroxyamino-2-methylpropanal oxime with 2,2-diethoxypropane in the presence of an equimolar quantity of acetic acid. Cost-effectiveness of the condensation procedure could be also achieved by replacing 2,2-diethoxypropane with less expensive 2,2-dimethoxypropane.

Keywords: Aldonitrone, 2,2-dialkoxypropane, HTIO, 3-imidazoline 3-oxide, nitroxide

INTRODUCTION

1-Hydroxy-2,2,5,5-tetramethyl-3-imidazoline 3-oxide **2**,[1] abbreviated as HTIO,[2] is a compound whose molecular structure combines an aldonitrone and sterically hindered hydroxylamino groups. HTIO is widely used as a precursor for 1-oxyl-2,2,5,5-tetramethyl-3-imidazoline 3-oxide **3** (OTIO), the stable nitroxide bearing aldonitrone group.[1] An unique combination of these groups makes OTIO a useful starting compound in a series of chemical

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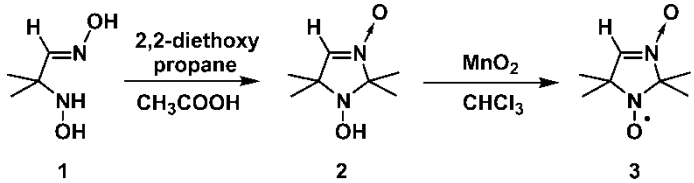
transformations. OTIO was shown to be the only one of its kind capable for spin-labeling through the 1,3-dipolar cycloaddition reaction to the compounds with unsaturated carbon–carbon bonds.[3] An elegant approach to the synthesis of 4-R-amino-2,2,5,5-tetramethyl-3-imidazoline 1-oxyls—nitroxides with pH-dependent electron paramagnetic resonance (EPR) spectra (pH-sensitive spin probes)—was elaborated through the 1,3-dipolar cycloaddition of OTIO to isocyanates.[4] HTIO was utilized in the synthesis of paramagnetic chelate[5] and imidazoline disulfide biradical[6]—the thiol-specific reagent for EPR determination of SH-groups in high- and low-molecular-weight compounds. HTIO was shown to be of great effectiveness in the redox-based EPR method for peroxidase activity determination.[2] More than decade ago, HTIO has appeared in the list of commercially available products,[7] evidence of its practical utility.

In spite of extensive synthetic and analytical applications of the titled compound, only one procedure that describes the preparation of HTIO has been reported.[1] The procedure involves the condensation of 2-hydroxyamino-2-methylpropanal oxime **1** (HAO) with 2,2-diethoxypropane (DEP) (Scheme 1).[1]

The desired product was obtained in a low yield of 25%. Unfortunately, no data indicate whether the reported yield is given for a solid product precipitated from the reaction mixture or for the isolated compound.[1] To our knowledge, the contamination of the product with 2,2,5,5-tetramethyl-2,5-dihydropyrazine 1,4-dioxide is an unavoidable feature of the synthesis. As follows from our own experience, the success of the reported procedure substantially depends on whether the desired product precipitates. Otherwise, the reaction mixture has to be discarded without chance for product recovery. Another procedure for the synthesis of 1-hydroxy-4-R-2,2,5,5-tetramethyl-3-imidazoline 3-oxides, the condensation of α-hydroxyamino oximes with acetone in the sealed ampule at high temperature,[1] has been reported, but it was found to be inappropriate for HTIO preparation. It has been shown recently that NH_4OAc promotes the condensation of α-hydroxyamino oximes with ketones,[8] but in the case of HAO **1** this finding does not work either. These prerequisites prompted us to focus our efforts on improving the procedure involving the condensation of HAO **1** with acetone acetals.

Use of HAO acetates in the reaction with DEP instead of free HAO results in increasing yield of the condensation product.[1] To the best of our knowledge, the acetate salt of HAO **1** has never been utilized in HTIO preparation.



Scheme 1.

RESULTS AND DISCUSSION

Herein we report our results on HTIO preparation. We suggest a simple, efficient, and reproducible procedure to obtain HTIO through the condensation of HAO **1** with 2,2-dialkoxypropanes in the presence of an equimolar amount of acetic acid. To the best of our knowledge, the method suggested here is the most efficient one.

At first, we have shown that the condensation of HAO with DEP in the presence of an equimolar amount of glacial CH_3COOH readily affords the desired product in a good yield (about 45%). To make the procedure more convenient, we modified it so that it does not depend on whether the desired product precipitates. We found that the solvent removal at reduced pressure with the following triturating of the residue with ether repetitively yields crystalline solid with high content of **2** (96% according to HPLC). Recrystallization of the resulting solid from the water gives analytically pure HTIO (98+% according to HPLC), which melts in the range of 172–174°C (lit.[1] 162–163°C). However, the overpriced cost of DEP makes this synthesis economically unfavorable in day-to-day laboratory practice. As we discovered, the replacement of DEP with less expensive 2,2-dimethoxypropane (DMP) readily affords the desired product in moderate yield (30%). No literature data shows that DMP has ever been introduced into condensation with α-hydroxyamino oximes. Typically, refluxing of the mixture of HAO, CH_3COOH, and DMP yields the solid product with 83% HTIO content (according to HPLC) after the work-up procedure. Recrystallization of the crude solid from water gives 96% pure HTIO (according to HPLC). Furthermore, the acid-catalyzed condensation suggested here allows one to use 2,2-dialkoxypropane in less excess as compared with the published procedure (1.6 equiv. vs. 2.3 equiv.[1]). The lower yield and the main compound content as compared with the case when DEP (bp 115°C) was utilized are most likely the result of the lower boiling point of DMP (bp 83°C). Table 1 summarizes results on the condensation of HAO **1** with 2,2-dialkoxypropanes depending on the amount of **1** and the 2,2-dialkoxypropane used.

When optimizing condensation conditions, we found that refluxing the reaction mixture over the critical time results in increasing the 2,2,5,5-tetramethyl-2,5-dihydropyrazine 1,4-dioxide content. Using acetic acid in a less than equimolar amount increases the total reaction time and also results in further contamination of the product with 2,2,5,5-tetramethyl-2,5-dihydropyrazine 1,4-dioxide. The optimized condensation conditions are given in the Experimental section.

Note that the reported yield for preparation of **3** by oxidation of HTIO does not exceed 35%.[1] The procedure described here provides compound **2** of sufficient purity to be used directly in the oxidation step. We have shown that oxidation of the crude **2** (83% of the main compound content) with MnO_2 in $CHCl_3$ affords **3** in 66% yield (after purification by column chromatography).

Table 1. Condensation of 2-hydroxyamino-2-methylpropanal oxime with 2,2-dialkoxypropanes

Entry	Amount of **1** (g)	2,2-Dialkoxy-propane	Amount of solid precipitated (g)	Yield (%)[a]
1	5	DMP	1.9	23.6
2	10	DMP	4.4	26.8
3	10	DMP	3.9	23.9
4	10	DMP	4.0	24.8
5	20	DMP	9.3	28.8
6	20	DMP	7.8	24.2
7	50	DMP	28.7	35.6
8	5	DEP	3.1	44.2
9	10	DEP	6.0	42.8

[a]Based on the main compound content obtained from the HPLC data.

In conclusion, this improved procedure provides 1-hydroxy-2,2,5,5-tetramethyl-3-imidazoline 3-oxide in a yield higher than the reported one. The ease and reproducibility of the condensation procedure, the simplicity of workup procedure and product purification, and mild reaction conditions indicate this is a promising alternative to the existing method. The cost-effectiveness of the procedure could be also achieved when 2,2-dimethoxypropane instead of more expensive 2,2-diethoxypropane is utilized.

EXPERIMENTAL

The IR spectra were recorded with a Bruker Vector 22 FT-IR spectrometer in KBr pellets (the concentration was 0.25%; the pellet sickness was 1 mm). NMR spectra were recorded on a Bruker AC-200 spectrometer operating at 200.132 MHz for ^{1}H and 50.323 MHz for ^{13}C in DMSO-d_6 using residual solvent signal as internal standard ($\delta_H = 2.50$ ppm, $\delta_C = 39.51$ ppm). High Performance Liquid Chromatography (HPLC) data were acquired with a Milichrom A-02 EcoNova chromatograph. A 70% H_2O–30% CH_3OH mixture was used as a mobile phase. Mass spectrum was obtained with a Finnigan MAT 8200 spectrometer. The spectroscopic characteristics of compounds **2** and **3** are identical with those reported in the literature.[1] Elemental analyses are correct.

Condensation of 2-Hydroxyamino-2-methylpropanal Oxime with 2,2-Dialkoxypropanes (General Procedure)

HAO **1** (0.01 mol) and 2,2-dialkoxypropane (0.016 mol) were placed into a round-bottomed flask equipped with a magnetic stirrer, and glacial

CH_3COOH (0.01 mol) was added dropwise to the mixture upon stirring. The flask was fitted with a condenser and placed into a preheated (T = 110–115°C) oil bath. After complete dissolution of HAO, the resulting mixture was refluxed for 20 min and cooled to the ambient temperature. The solvents were removed under reduced pressure. The residue was triturated with dry ether; the precipitate formed was collected on the filter and washed with ether twice to give 1-hydroxy-2,2,5,5-tetramethyl-3-imidazoline 3-oxide **2**. Colorless crystals, mp 172–174°C (water) (lit.[1] 162–163°C); HPLC: 99.05%; Prontosil 120-5C18AQ column, retention time 3.087 min; IR (KBr): 1603 (C═N); ^{1}H NMR (DMSO-d_6), $\delta = 1.23$ (s, 6H, $2CH_3$), 1.34 (s, 6H, $2CH_3$), 6.92 (s, 1H, H), 8.12 (s, 1H, OH). ^{13}C NMR (DMSO-d_6), $\delta = 23.64$, 24.23 (CH_3), 64.19 (C-5), 91.43 (C-2), 134.16 (C═N). Anal. calcd. for $C_7H_{14}N_2O_2$: C, 53.16; H, 8.86; N, 17.72. Found: C, 53.04; H, 8.66; N, 17.63.

Oxidation of 1-Hydroxy-2,2,5,5-tetramethyl-3-imidazoline 3-Oxide

MnO_2 (0.035 mol) was added to a suspension of HTIO (0.01 mol) in 30 ml of $CHCl_3$, and the resulting mixture was vigorously stirred for 1 h. The course of the reaction was monitored by chromatography on thin layer chromatography (TLC) plates (SiO_2, $CHCl_3 + 2\%$ CH_3OH). The oxidant was filtered off, and the solvent was removed under reduced pressure. The solid residue was purified by chromatography on silica gel (eluting with $CHCl_3$) to give 2,2,5,5-tetramethyl-3-imidazoline-1-oxyl 3-oxide **3** (66% yield, lit.[1] 35%). Orange crystals, mp 116–118°C (hexane–EtOAc) (lit.[1] 100–103°C); $R_f = 0.75$ (SiO_2, $CHCl_3 + 2\%$ CH_3OH); HPLC: 96.4%, ZORBAX Eclipse XDB C8 column, retention time was 3.848 min; IR (KBr): 1588 (C═N), 3168 (═C-H); anal. calcd. for $C_7H_{13}N_2O_2$: C, 53.50; H, 8.28; N, 17.83. Found: C, 53.57; H, 8.55; N, 17.44. Mass spectrum (M^+) calcd. for $C_7H_{13}N_2O_2$: 157.09770. Found: 157.09742.

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