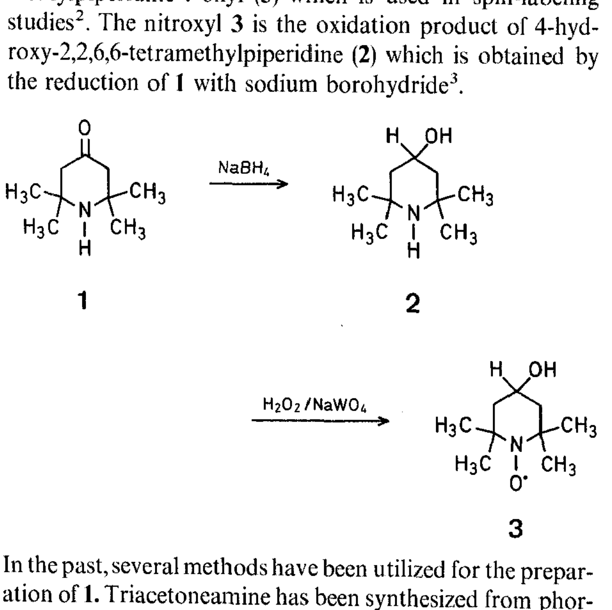
Preparation of Triacetoneamine (4-Oxo-2,2,6,6-tetramethylpiperidine), an Improved Method

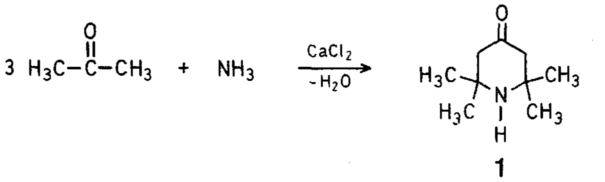
G. Sosnovsky*, M. Konieczny

Department of Chemistry, University of Wisconsin-Milwaukee, Milwaukee, Wisconsin 53201, USA

In the past decade there has been considerable interest in the preparation of triacetoneamine (4-oxo-2,2,6,6-tetramethylpiperidine, **1**), since it is the key intermediate in the preparation of the stable nitroxyl radical[1] 4-hydroxy-2,2,6,6-tetramethylpiperidine-1-oxyl (**3**) which is used in spin-labeling studies[2]. The nitroxyl **3** is the oxidation product of 4-hydroxy-2,2,6,6-tetramethylpiperidine (**2**) which is obtained by the reduction of **1** with sodium borohydride[3].



In the past, several methods have been utilized for the preparation of **1**. Triacetoneamine has been synthesized from phorone and ammonia[4-6], and from acetonin (2,2,4,4,6-pentamethyl-2,3,4,5-tetrahydropyrimidine) and acetone in the presence of catalysts[7]. However, the simplest and most frequently used method for the preparation of **1** remains the condensation of acetone with ammonia in the presence of calcium chloride[8-13].



In spite of these numerous reports on the preparation of **1** by this method, the yield of **1** reported has been low and varied from 20 to 32%, based on mol of acetone used. In the case that the unreacted acetone was recovered[11], the yield increased to 40%. In some cases[11,12] rather elaborate equipment was used.

We have now developed a simple method for the preparation of triacetoneamine (**1**) in higher yields (70–89% taking account of the recovered acetone) from acetone, ammonia, and calcium chloride using easily accessible laboratory equipment.

Until now, to the best of our knowledge, there has been no attempt made to investigate the influence of variables such as temperature, rate of stirring, amount of ammonia, particle size of calcium chloride, and acid catalysts such as ammonium chloride, and to monitor the reaction by analytical means[14]. We have now found (a) the temperature which is maintained during the introduction of ammonia and (b) the amount of ammonia introduced to be the two major factors influencing the yield and quality of **1**. If the amount of ammonia introduced is allowed to exceed 8.3 mol, a product of markedly inferior quality is obtained. Introduction of less than that amount decreases the weight yield of **1**. The reaction mixture was analyzed[14] by gas chromatography and found to contain, in addition to triacetoneamine, diacetone alcohol, diacetone amine, mesityl oxide, and acetonin. The purity of this crude material was 85% as determined by gas chromatography. Distillation was the preferred method for the isolation of pure **1**. The yield based on total acetone employed was 48%, whereas the yield rose to 70% on taking into account the recovered acetone. If pure **1** was obtained by solidification of the crude reaction mixture in carbon tetrachloride, the yield based on recovered acetone decreased to 34%. As much as 50% unrecoverable **1** remained in the filtrate. In the case that the temperature of the reaction mixture was maintained at 59 ± 1° during the introduction of ammonia, there was obtained **1** of higher purity (93%) though the weight yield was reduced. Thus the yield based on total acetone was 36%, whereas the yield rose to 89% on taking into account the recovered acetone. In fact, this product was of sufficient purity to be reduced to the corresponding 4-hydroxy-2,2,6,6-tetramethylpiperidine (**2**) in 85% yield without further purification[14].

Analytical Procedures:

All boiling points and melting points are uncorrected. An Aerograph A 90-P3 gas chromatograph with a thermal conductivity detector was used. The following overall conditions were maintained: injector temperature, 225°; detector temperature, 250°; bridge current, 150 ma; sample size, 5 μl with the appropriate attenuations. The column used was 20% Carbowax 20 M on 60/80 mesh acid washed Chromasorb W, 6 ft by $^{1}/_{4}$ in. Analyses were performed isothermally at 170°, with a flow rate of 60–65 ml of He/min. All identifications of products were made by the comparison of retention times and peak enhancement ("spiking") with authentic samples.

The reaction was performed in a 3-liter, 4-neck round-bottomed flask fitted with a thermometer, reflux condenser and drying tube, powerful overhead stirrer (average speed 300 rpm), and a gas inlet tube. The anhydrous ammonia was introduced from a lecture bottle. Thus the precise amount of gas added each time could be determined by difference in weight.

Preparation of Triacetoneamine (1); Reaction at Room Temperature:

Into a well-stirred mixture of reagent grade acetone (1000 g, 17.3 mol) and 4–20 mesh anhydrous calcium chloride (400 g) was introduced, over a period of 3 days, a total of 140 g (8.2 mol) anhydrous ammonia. No more than 2.0 mol of ammonia could be introduced on the first day. The remaining 6.2 mol were introduced on the second and third day in four approximately equal portions. The temperature of the reaction mixture during the introduction was not allowed to exceed 46°. Following the last introduction, stirring was discontinued, and the thickened reaction mixture was left to stand undisturbed at 23–25° for 4 days. Then, the setup was converted for distillation. The reaction mixture was stirred at 35° under reduced pressure (100 torr). The unreacted acetone was collected in two traps chilled by isopropyl alcohol/Dry Ice baths. All precautions were taken to exclude moisture from the system. In this manner was collected 310 g (31% based on mol initially used) acetone. To the remaining cake was added 500 ml of an aqueous solution containing 100 g sodium hydroxide. The mixture was well stirred. The oil was poured off, and the remaining aqueous slurry was extracted five times with a total of 1000 ml diethyl ether. The combined oil and ether extracts were dried over magnesium sulfate. Removal of the drying agent by filtration, and the solvent at 12 torr afforded crude **1**; yield: 644 g. The purity of **1** as determined by gas chromatography was 85%. Unreacted acetone, as determined by gas chromatography, plus that converted to **1** was accountable to 97%. Unreacted acetone recovered by distillation (310 g) plus that converted to **1** was accountable to 92%. Distillation of the crude reaction mixture under reduced pressure afforded **1**; yield: 430 g (70% taking into account the recovered acetone or 48% based on starting acetone); b.p. 50–56°/1 torr; m.p. 35–36°. Lit.[10] m.p. 34–36°.

The purity of **1** as determined by gas chromatography was 97%. Pure **1** can also be obtained by solidification in carbon tetrachloride. Thus, crude **1** of 85% purity (644 g) was mixed with an equal volume of carbon tetrachloride and stored at 0° overnight. The solid was collected by filtration and kept at 10 torr until all solvent was removed. In this manner was obtained **1**; yield: 210 g (34% taking into account the recovered acetone or 24% based on starting acetone); m.p. 34–36°.

Preparation of Triacetoneamine (1); Reaction at Elevated Temperature:

Into a well-stirred mixture of reagent grade acetone (1000 g, 17.3 mol) and 4–20 mesh anhydrous calcium chloride (400 g) was introduced, over a period of 4 days, a total of 140 g (8.2 mol) anhydrous ammonia, in six approximately equal portions. The pot temperature during the introduction was maintained at 59 ± 1°. Between the additions, the reaction mixture was kept at room temperature (23–25°). Following the last introduction, the thickened reaction mixture was left to stand undisturbed at 23–25° for 3 days. After the workup as described in the previous experiment there was recovered acetone (600 g, 60% based on mol initially used) and **1** (318 g, 89% yield taking into account the recovered acetone or 36% based on starting acetone); m.p. 33–34° (Lit.[10] m.p. 34–36°).

The purity of **1** as determined by gas chromatography was 93%. Unreacted acetone as determined by gas chromatography plus that converted to **1** was accountable to 98%. Unreacted acetone recovered by distillation (600 g) plus that converted to **1** was accountable to 94%.

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