Synthesis of TEMPO from Over-the-Counter Materials

By Cheddite Cheese

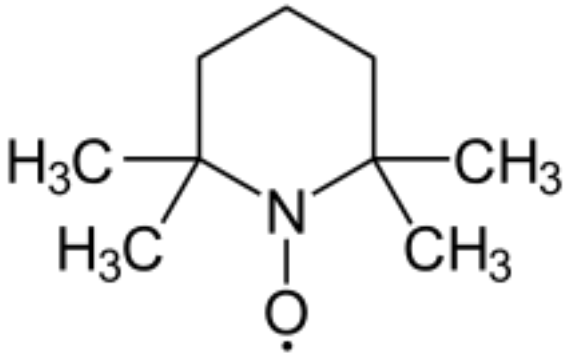
In November 2014, member Etaoin Shrdlu posted a challenge to synthesize TEMPO, a stable free radical used as an oxidation catalyst, from starting materials either available to the general public, or easily made from generally available materials. This challenge was, unsurprisingly, challenging; as member Chloric1 put it in 2005, TEMPO "is an exotic catalyst that is virtually unavailable to most home experimenters." Nonetheless, I decided to attempt it. It took me six months of research and lab work (albeit working discontinuously) and, quite frankly, the yields are horrible. However, the starting materials are quite cheap, and most importantly, easy to come by.

Materials List:

Reagents (* denotes amount less than 1 gram):
Ammonium Chloride
Acetone
Sodium Hydroxide
Hydrochloric Acid
Mercury*
Nitric Acid*
Zinc
Sodium Tungstate*
Hydrogen Peroxide

Solvents:
Methanol
Isopropanol
Water
Toluene
Ethyl Acetate
Chloroform

Target Compound:
TEMPO (2,2,6,6-tetramethylpiperidinyl 1-oxyl)



Step 1: Synthesis of triacetonamine (2,2,6,6-tetramethylpiperidinone) hydrochloride

117.29 g ammonium chloride was placed in a double-necked flask. One neck of the flask was fitted with an addition funnel with 220 ml of 10M sodium hydroxide solution. A fritted gas dispersion tube was connected to the other neck of the flask. The sodium hydroxide was slowly added over the course of 1 hour, and the ammonia gas produced was run through a solution of 1.93 g ammonium chloride in 175 ml of acetone and 25 ml of methanol chilled to 0 °C.

The solution was then warmed to 50 °C and stirred for overnight, during which time it developed a red-orange color. The excess acetone and methanol were removed by evaporation under vacuum to yield a slushy red residue. The residue was acidified with 12M hydrochloric acid until it tested acidic with litmus paper (ph 4~5). Excess water and hydrochloric acid were removed by evaporation under vacuum. The residue, now a dark red solid, was dissolved in hot isopropanol, with insoluble impurities removed by filtration. The solution was concentrated and chilled to 0 °C, whereupon reddish-brown solids with small colorless crystals precipitated.

The solids (19.87 g) were collected by filtration, and recrystallized again from isopropanol to yield 12.61 g colorless crystals.

Step 2: Synthesis of 2,2,6,6-tetramethylpiperidine hydrochloride by Clemmensen reduction

In a test tube, 0.514 g mercury was dissolved in 0.7 ml 90% nitric acid.

Then, 4.960 g of the product from Step 1 was dissolved in a flask with 25 ml methanol. 17.053 g zinc powder, the mercuric nitrate solution, and a magnetic stir bar were added to the flask, which was fitted with a reflux condenser and an addition funnel containing 45 ml 12M hydrochloric acid. The flask was heated to reflux, and then 10 ml of the acid were added quickly. The rest of the acid was added slowly over 3 hours, with vigorous magnetic stirring.

Over this time, all of the zinc dissolved, and the mercury was reduced back to metallic form. When the reaction mixture had cooled, it was decanted from the mercury, and 10M sodium hydroxide solution was added until it was basic to litmus paper (pH ~9). A white precipitate of zinc hydroxide formed. The precipitate was filtered out, and the solution was extracted with 3 10 ml portions of toluene. Then, the toluene solution was extracted with 3 5 ml portions of 3M hydrochloric acid. The acid was evaporated under vacuum to give 1.658 g white powder. The powder was recrystallized from isopropanol to give 1.194 g colorless crystals.

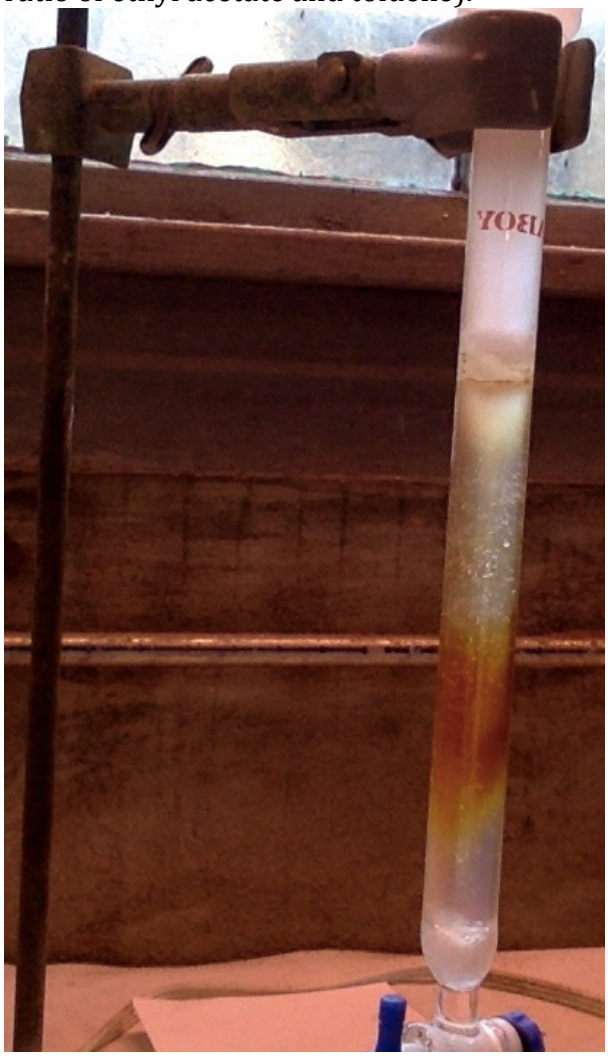
TLC evaluation of Clemmensen reduction:

The products from steps 1 and 2 were spotted on a silica gel TLC plate, which was eluted with 40% acetone, 59% toluene, 1% triethylamine. The plate was stained with potassium permanganate. The Rf for the product from Step 1 was 0.46, and the Rf for the product from step 2 was 0.69.

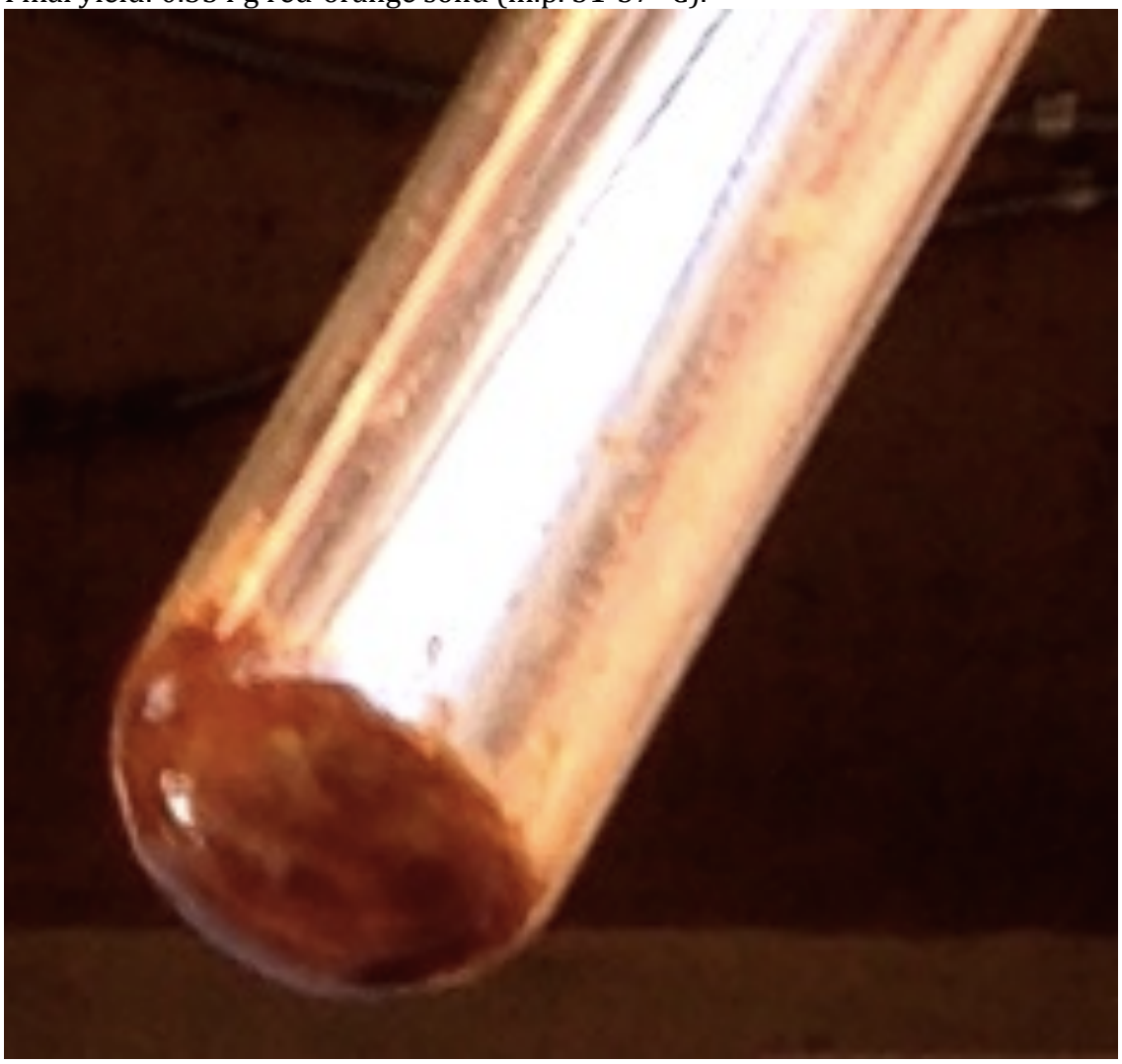
Step 3: Synthesis of TEMPO by oxidation with peroxide and tungstate

0.987 g of the product from Step 2 and 0.468 g sodium tungstate dihydrate were dissolved in 10 ml methanol and 4 ml water. 10M sodium hydroxide solution was added until the reaction mixture tested basic to litmus paper (pH ~9). 3.4 ml of 30% hydrogen peroxide solution were added, and the reaction mixture was mechanically stirred at room temperature for 24 hours, during which time it developed a red-orange color. The reaction mixture was extracted with 3 5 ml portions of chloroform, and the chloroform was removed by evaporation under vacuum to yield 0.535 g red-orange viscous oil.

The oil was purified by column chromatography (200 mesh silica gel, eluent 1:1 ratio of ethyl acetate and toluene).



Final yield: 0.354 g red-orange solid (m.p. 31-37 °C).



For further reading (list of most useful source for each step):

Member Klute's work with triacetonamine, and related US patents:
https://www.sciencemadness.org/whisper/viewthread.php?tid=3960

The Clemmensen Reduction (Organic Reactions series, from Wiley Online Library)

Science of Synthesis: Houben-Weyl Methods of Molecular Transformations Vol. 40b: Amine N-Oxides, Haloamines, Hydroxylamines and Sulfur Analogues, and Hydrazines