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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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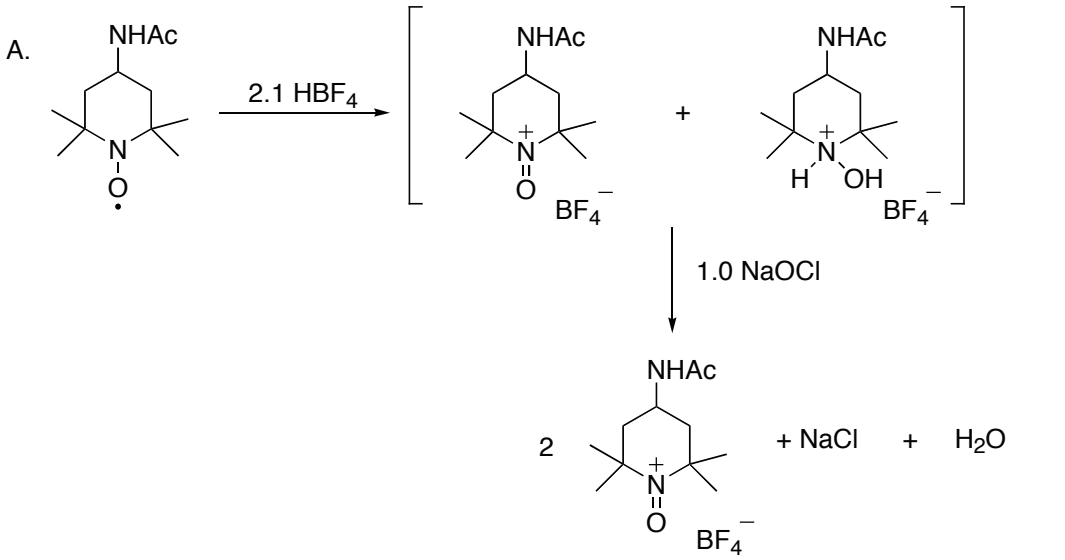
PREPARATION OF 4-ACETYLAMINO-2, 2, 6, 6-TETRAMETHYLPIPERIDINE-1-OXOAMMONIUM TETRAFLUOROBORATE, AND THE OXIDATION OF GERANIOL TO GERANIAL

(2,6-Octadienal, 3,7-dimethyl-, (2E)-)



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Discussion Addendum *Org. Synth.* **2013**, *90*, 215

1. Procedures (Note 1)

A. 4-Acetylamino-2,2,6,6-tetramethylpiperidine-1-oxoammonium tetrafluoroborate. In a 250-mL one-necked, round-bottomed flask equipped with a 3-cm magnetic stirring bar, 4-acetylamino-2,2,6,6-tetramethyl-1-piperidinyloxy (4-acetamido-TEMPO) (25.0 g, 0.117 mol) (Note 2) and water (50.0 mL) are added. An aqueous solution of HBF_4 (48% aqueous solution, 17.7 mL, 0.135 mol) (Note 3) is charged into a 25-mL dropping funnel and added dropwise over 30 min to the vigorous stirring orange

mixture. A dark brown solution is formed initially, followed by formation of a yellow precipitate. The yellow slurry is stirred for an additional 30 min. Commercial sodium hypochlorite (Chlorox® bleach, 6.00 % NaOCl) (65.5 mL, 0.058 mol) is transferred into a 100-mL dropping funnel and added dropwise over a 1 hr period to the heterogeneous mixture (Note 4). The yellow slurry is then cooled to 0 °C and stirred at this temperature for 2 hrs. The mixture is filtered and the yellow solid washed with cooled water (4 °C, 2 x 20 mL) (Note 5) and dichloromethane (3 x 20 mL) to remove sodium chloride and unreacted 4-acetamido-TEMPO, respectively. The bright yellow salt is compressed with a spatula to remove additional solvent, transferred into a 100-mL round-bottomed flask and dried under high vacuum at room temperature overnight (Note 6). The product is obtained as a bright yellow solid (27.4 g, 78%, 98% purity) (Note 7).

B. The oxidations of a number of alcohols with 4-acetylamino-2,2,6,6-tetramethylpiperidine-1-oxoammonium perchlorate have been described on a 10 mmol scale.[2] The oxoammonium perchlorate salt detonated when a 9 g sample was dried at 40 °C under high vacuum, after being apparently stable for several years.[3] Thus, attention has been shifted to development of the oxoammonium tetrafluoroborate salt. In all cases investigated, the oxidative properties of the two salts are identical.

Oxidation of geraniol to geranial. Into a 500-mL one-necked, round-bottomed flask are added geraniol (7.70 g, 50.0 mmol) (Note 8) and dichloromethane (400 mL). 4-Acetylamino-2,2,6,6-tetramethylpiperidine-1-oxoammonium tetrafluoroborate (16.5 g, 55.0 mmole, 1.10 eq) and 2 g of silica gel are added to the solution (Note 9). The flask is equipped with a mechanical stirrer and the reaction mixture is vigorously stirred at room temperature for 6 h. The reaction begins immediately, and the yellow slurry turns gradually to the off-white color of the reduced oxidant. A 1-cm thick pad of silica gel is placed in a fritted glass funnel (*ca*. 7 cm in diameter), wetted with dichloromethane and covered with a piece of filter paper. The slurry is carefully poured onto the silica gel pad and filtered (Note 10). The pad is washed with four successive 50 mL portions of dichloromethane (Note 11). The solvent is evaporated under vacuum (room temperature) to give 7.08 g (93%) of geranial (98% purity by GC analysis) as a colorless oil (Note 12). The hydroxylamine-silica gel precipitate can be processed to obtain 4-acetamido-TEMPO for recycling (Note 13).

2. Notes

1. No professional safety check has been carried out to determine the stability of 4-acetylamino-2,2,6,6-tetramethylpiperidine-1-oxoammonium tetrafluoroborate salt. All the procedures herein described have been carried out behind a safety shield.

2. 4-Acetamido-TEMPO was purchased from TCI and used without further purification; however, submitters report that it can readily be prepared from 4-amino-2,2,6,6-tetramethylpiperidine (Fluka). In their original procedure for the preparation of 4-acetamido-TEMPO,[2] potassium carbonate was used to basify 4-acetylamino-2,2,6,6-tetramethylpiperidinium acetate; however, due to its insolubility the potassium tetrafluoroborate can accumulate in the salt. Therefore, sodium carbonate should be used and all potassium salts should be avoided. Sodium tetrafluoroborate is quite water-soluble.

3. Tetrafluoroboric acid (48% aqueous solution) was purchased from ACROS.

4. Slow addition is necessary since the tetrafluoroborate oxoammonium salt reacts with excess bleach to produce undesired byproducts.

5. The oxoammonium tetrafluoroborate salt is fairly soluble in pure water (6 g/100 mL at 0 °C, 8 g/100 mL at 20 °C and >100 g/100 mL at 100 °C), so care must be taken during the washes.

6. The oxoammonium tetrafluoroborate salt reacts, albeit slowly, with hot water. If the wet salt is dried in an oven, some decomposition will take place.

7. The melting point of the oxoammonium tetrafluoroborate salt is a vigorous, instantaneous decomposition in a capillary tube: mp 184-185 °C (dec.). The submitters report that the observed melting point can vary from 180 °C to 194 °C, even though the purity is about the same. Since the melting points are ambiguous, the purity of the salt was measured by oxidation of a known quantity of 1-decanol with a known, limited amount of salt. The conversion of 1-decanol to 1-decanal was quantified using ^{1}H NMR (300 MHz, $CDCl_3$). The C-2 proton NMR signal (triplet) at 2.43 ppm (decanal) and the C-1 proton signal (triplet) at 3.65 ppm (1-decanol) are integrated and the percentage of conversion is compared with the theoretical value. In a 25-mL round-bottomed flask 1-decanol (0.079 g, 0.50 mmol), dichloromethane (7.0 mL), silica gel (0.10 g) and 4-acetylamino-2,2,6,6-

tetramethylpiperidine-1-oxoammonium tetrafluoroborate (0.075 g, 0.25 mmol, 0.50 eq) were added and the resulting slurry left under stirring at room temperature for 12 h. The mixture was filtered through a 1-cm silica gel pad and subsequently washed with dichloromethane (25 mL). The solvent was removed under vacuum at room temperature to give a mixture of 1-decanol and decanal as a colorless oil.

8. Geraniol (99% purity) was purchased from ACROS and used without further purification.

9. The amount of silica gel and the reaction time depend on the alcohol being oxidized. Geraniol, an allylic alcohol, requires less silica gel and takes less time. Primary aliphatic alcohols will require twice as much silica gel and longer reaction times.[2]

10. If the slurry is filtered without the pad of clean silica gel, a small amount of nitroxide will contaminate the product; however, some product loss occurs due to its incomplete removal from the silica gel.

11. The submitters report that this solution can be used for various reactions, without actual isolation of the carbonyl compound. Reactions reported include Wittig, Grignard, and Baylis-Hillman reactions, as well as cyanohydrin and acetal formation.

12. The crude aldehyde can be distilled at 20 mm and 115-120 °C (lit.[4] 117 °C at 20 mm) to give 6.53 g (89 %) of geranial with spectral and chromatographic properties identical with the undistilled product: colorless oil, IR (KBr) [cm^{-1}]: 2967, 2918, 2836, 1676, 1633, 1444, 1381, 1194, 1121; EI-MS: *m/z* (%) = 153 (7), 152 (24), 137 (19), 123 (19), 109 (29), 94 (39), 84 (51), 69 (100); ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ 1.62, (s, 3H), 1.69 (s, 3H), 2.18 (s, 3H), 2.21-2.28 (m, 4H), 5.05-5.10 (m, 1H), 5.87-5.91 (m, 1H), 10.00 (d, J = 8.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.4, 17.6, 25.5, 25.6, 40.5, 122.5, 127.3, 132.7, 163.5, 191.0. GC-Analysis was performed with a EC-1 column of 30 m /0.32 mm ID and a T-ramp of 70 °C to 240 °C in 15 °C/min, providing a retention time for geraniol of 6.94 min.

13. The submitters report that the spent oxidant consisting of a mixture of hydroxylamine tetrafluoroborate and silica gel can be collected from several oxidations and processed as follows to give 4-acetamido-TEMPO for recycling: The mixture is washed with several portions of warm water to extract hydroxylamine tetrafluoroborate salt from the silica gel. The aqueous solution is basified with $NaHCO_3$ to pH 7 and treated with an excess of H_2O_2 (30% aqueous solution). The 4-acetamido-TEMPO can be extracted with dichloromethane. Recrystallization from boiling water or

boiling ethyl acetate provides purified 4-acetamido-TEMPO, which tends to be quite soluble at the boiling point of either solvent and precipitates quickly upon cooling. The resulting 4-acetamido-TEMPO should melt above 144 °C to be judged suitable for further use.

Safety and Waste Disposal Information

All hazardous materials should be handled and disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995. If all of the materials are recycled as described, the only waste products are NaCl and $NaBF_4$.

3. Discussion

Oxoammonium salts are stable, non heavy-metal, specific oxidizing agents for the preparation of aldehydes or ketones from alcohols.[5] Under normal conditions,[2] the reactions are nearly quantitative; the reactions are colorimetric; and product isolation is simple. Anhydrous conditions may be used, but are not necessary.

Oxoammonium salt oxidations are actually the stoichiometric version of nitroxide-catalyzed oxidations using a secondary oxidant such as bleach, as described in a previous *Organic Syntheses* procedure.[6] Disadvantages of the catalyzed oxidations are that a two phase system is generally used and that the secondary oxidant can cause undesired reactions. Catalytic reactions are, however, more suitable for large-scale reactions. On the other hand, stoichiometric oxidations undergo fewer side reactions, but are more appropriate on a 1-50 mmol scale.

Other than convenience, two major advantages of oxoammonium salt reactions are that phenolic alcohols can be oxidized without protecting the phenol[2,7] and allylic alcohols can be oxidized without isomerization of double bonds.[2, 8, 9]

Many oxoammonium salts are known with various substitution patterns and different anions.[5] The properties vary tremendously, being especially important with respect to their hygroscopic nature and their rates of reaction. 4-Acetylamino-2,2,6,6-tetramethylpiperidine-1-oxoammonium perchlorate and tetrafluoroborate salts were described in our preliminary publication,[2] and the perchlorate was used exclusively for the oxidations. However, the perchlorate proved to be unstable and its use was

discontinued.[3] All further work has been done with the tetrafluoroborate oxoammonium salt, which is a bright yellow crystalline material, completely non-hygroscopic and stable indefinitely. Its solubility and oxidation properties appear to be identical with those of the perchlorate.

The tetrafluoroborate salt possesses sufficient solubility in dichloromethane to react easily, and its reduced form, 4-acetylamino-2,2,6,6-N-hydroxypiperidinium tetrafluoroborate is colorless and essentially insoluble in this solvent. Thus, it can be removed by filtration, leaving a quantitative yield of aldehyde or ketone in solution.

Reaction rates vary, allylic and benzylic alcohols being fast (1-3 hr), acetylenic and secondary alcohols next (4-6 hr) and primary aliphatic alcohols being slowest (2-3 days without silica gel).[2] Silica gel is an effective catalyst and may also assist in the purification of the products. When silica gel is used, primary aliphatic alcohols are oxidized in 10-15 hr and allylic and benzylic alcohols require a lower catalyst loading. Completion of the oxidation can be easily monitored colorimetrically, since the yellow tetrafluoroborate oxoammonium salt starting material is converted to its white reduced form.

The most serious side reaction is the rapid oxidation of amines, a reaction that is not well understood.[2,5] Two slow competing reactions, the oxidation of benzyloxy groups[10] and the addition to activated double bonds,[2,11] can result in side product formation, particularly when slowly oxidized substrates (primary aliphatic alcohols) are used. Several other side reactions have been documented for oxoammonium salts,[5] but most are slow and of lesser importance, especially when the anion is tetrafluoroborate.

For reasons that are not understood, alcohols with a β-oxygen (in any functional group) or β-nitrogen (as amide) react so slowly with the oxidant as to be useless. Interestingly, this limitation is apparently not true for nitroxide-catalyzed reactions.[6]

Oxidations in dichloromethane are slightly acidic, due to the reduced oxidant, which has a pKa of about 5.6.[2] For this reason, simple acetal groups and such acid labile protecting groups as the *tert*-butyldimethylsiloxy group are slowly cleaved, although the *tert*-butyldiphenylsiloxy group seems to be stable.

Stoichiometric oxidations can be carried out in the presence of a base such as pyridine, although only one paper has appeared on the subject.[12] The reaction takes place in a different manner with two equivalents of oxidant and pyridine being required. The products are the desired oxidation

product, pyridine tetrafluoroborate, and nitroxide. Under these conditions, acetal groups are stable, and β-oxygenated materials are oxidized.

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Appendix
Chemical Abstract Nomenclature (Registry Number)

4-Acetylamino-2,2,6,6-tetramethylpiperidine-1-oxoammonium tetrafluoroborate: Piperidinium, 4-(acetylamino)-2,2,6,6-tetramethyl-1-oxo-, tetrafluoroborate(1-) (9); (219543-09-6)
4-Acetylamino-2,2,6,6-tetramethylpiperidine-1-oxoammonium perchlorate: (219543-08-5)
4-Acetamido-TEMPO: 1-Piperidinyloxy, 4-(acetylamino)-2,2,6,6-tetramethyl- (9); (14691-89-5)
Tetrafluoroboric acid: Borate(1-), tetrafluoro-, hydrogen (8,9); (16872-11-0)
Sodium hypochorite (Clorox®); (7681-52-9)
1-Decanol: 1-Decanol (9); (112-30-1)
Decanal: Decanal (8,9); (112-31-2)
Hydrogen peroxide: Hydrogen peroxide (9); (7722-84-1)
4-Amino-2,2,6,6-tetramethylpiperidine: 4-Piperidinamine, 2,2,6,6-tetramethyl- (9); (36768-62-4)
4-Acetylamino-2,2,6,6-tetramethylpiperidinium acetate: Acetamide, N-(2,2,6,6-tetramethyl-4-piperidinyl)-, monoacetate (9); (136708-43-5)
Geraniol: 2,6-Octadien-1-ol, 3,7-dimethyl-, (2E)-; (106-24-1)
Geranial: 2,6-Octadienal, 3,7-dimethyl-, (2E)-; (141-27-5)

DAm-0128A (CDCl3): OS#3036 (geranial, distilled)