

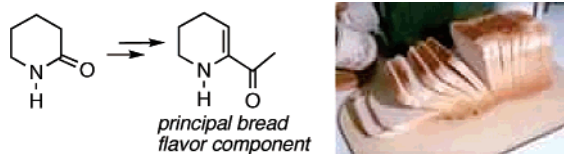
An Expedient, High-Yielding Construction of the Food Aroma Compounds 6-Acetyl-1,2,3,4-tetrahydropyridine and 2-Acetyl-1-pyrroline

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Received September 15, 2005



The key compound responsible for the aroma of bread, 6-acetyl-1,2,3,4-tetrahydropyridine (**1**), has been constructed in an efficient three-step procedure from 2-piperidone in an overall yield of 56%. Compound **1** was liberated in the final step under basic conditions. A related synthetic route produced 2-acetyl-1-pyrroline (**2**), the principal component of cooked rice, in 10% overall yield.

Simple heterocycles are formed by the nonenzymatic browning reaction between reducing sugars and free amine functions during the cooking process (the Maillard reaction).¹ Although present in relatively small quantities, these compounds can exhibit strong flavoring and odorant properties. Two such compounds, 6-acetyl-1,2,3,4-tetrahydropyridine (**1**) and 2-acetyl-1-pyrroline (**2**), are believed to be responsible for the biscuit or cracker-like odor present in baked goods,² popcorn,³ tortilla products,⁴ and aromatic varieties of cooked rice,⁵ respectively (Figure 1). The odor thresholds for **1** and **2** have been determined to be 0.06 ng/L^{3b} (in air) and 0.02 ng/L^{3c} (in air), respectively. As such, these and related compounds have significant practical interest as additives in the food industry.

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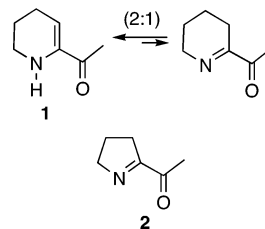


FIGURE 1. Structures of bread and rice flavor components **1** and **2**.

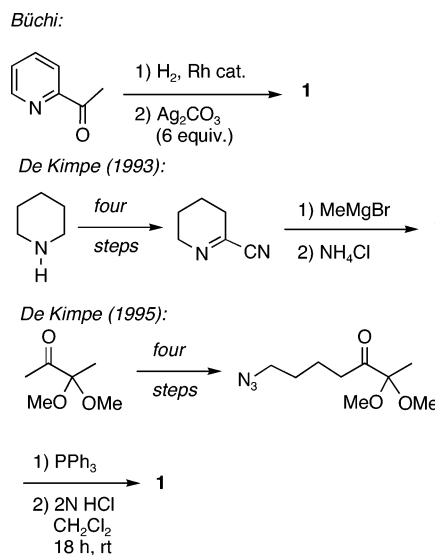
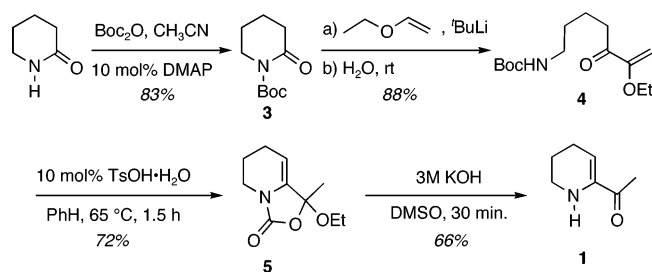


FIGURE 2. Representative synthetic routes to **1**.

We learned of these compounds through literature searches related to the preparation of substrates for an unrelated research project ongoing in our laboratory.⁶ Although a number of practical synthetic routes have been disclosed for these flavor components **1** and **2**, these published routes all suffer to some extent from lengthy reaction sequences or costly reagents (Figure 2).^{7,8} It has previously been reported that **1** interconverts with its tautomer and rapidly decomposes when isolated neat.^{7g} It is also known that enamines and related structures are sensitive to acid.⁹ Consequently, it should be advantageous to minimize exposure of **1** to acid. In addition,

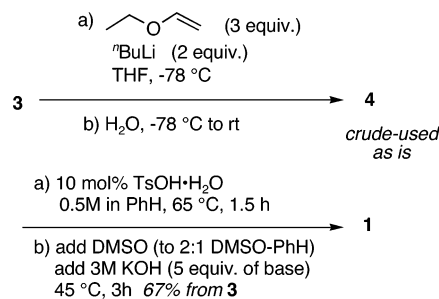
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SCHEME 1



the ketone function was typically protected as its corresponding ketal in intermediates toward **1**,^{7a,e,8f} and the requirement for acidic conditions in the final steps of published synthetic routes were detrimental to overall yields. An alternative route where **1** was produced with use of basic conditions could be an important solution. These compounds and their corresponding challenge of a concise, potentially scalable construction intrigued us. In addition, the lessons learned in the course of this exercise would prove valuable for the synthesis of structurally related compounds.

We focused on the construction of **1**. Criteria under consideration were (a) brevity for the overall sequence and (b) avoiding acidic conditions in the reaction that would ultimately produce **1**. To that end, we developed the following sequence (Scheme 1). The reaction of 2-piperidone and di-*tert*-butyl dicarbonate provided imide **3**.¹⁰ Subjecting **3** to 1-ethoxy-1-lithioethene (produced by metalation of ethyl vinyl ether with *tert*-butyllithium in THF^{8e,11} at $-78\text{ }^{\circ}\text{C}$) produced ketone **4** after aqueous workup. Reformation of the heterocycle occurred with use of 10 mol % *p*-toluenesulfonic acid in benzene at $65\text{ }^{\circ}\text{C}$ after 1.5 h to produce enecarbamate **5**. We did not make a concerted effort to use alternate solvents in this reaction, although reactions in THF or toluene do proceed. The use of benzene is precluded in industrial processes. Importantly, the ketone function is now protected as a derivative that can be released with use of basic hydrolysis conditions. We parenthetically note that **5**, as it possesses a strong, pleasant smell of “seasoning salt on popcorn”, may have its own uses as a flavor additive. Barium hydroxide in THF was initially used to carry out the final transformation, giving rise to 30–40% conversions of **1**. In comparison, aqueous potassium hydroxide in THF afforded only trace amounts of **1** after extended reaction times. Optimization of the reaction conditions revealed that potassium hydroxide in DMSO was sufficient to remove the carbamate function and produce **1** in 66% yield. From a practical perspective, conditions with barium hydroxide in either THF or

SCHEME 2. Telescoped Sequence to **1**

DMSO tended to be “messier” and required a more involved workup procedure.

Although the route was reasonably short, we were interested in minimizing isolation steps to produce **1** as efficiently as possible. To that end, optimization of the sequence produced the following protocols (Scheme 2). The reaction of **3** with the organolithium reagent produced from 3 equiv of ethyl vinyl ether and 2 equiv of *tert*-butyllithium occurred smoothly in THF at $-78\text{ }^{\circ}\text{C}$. The purity of **4** was acceptable after workup and solvent removal to be used directly in the next reaction. It should be noted that **4** does not store well; this material should be carried on to the next reaction as soon as possible. Addition of benzene (to produce a 0.5 M solution) and 10 mol % of *p*-TsOH·H₂O followed by warming at $65\text{ }^{\circ}\text{C}$ for 1.5 h resulted in the production of **5** according to thin-layer chromatography. Cooling of the reaction mixture to $45\text{ }^{\circ}\text{C}$ and direct addition of DMSO to produce a 2:1 DMSO/PhH solvent mixture was followed by the addition of 5 equiv of aqueous potassium hydroxide solution. After 3 h and following workup and isolation, the desired bread flavor component **1** was formed in 67% yield. As previously reported, **1** was found to equilibrate to a 2:1 mixture of tautomers.

We also applied this sequence to the rice flavor component **2** using 2-pyrrolidinone as a starting material (Scheme 3). In this context, a major complication could arise. In the transformation of **7** to **8**, the nitrogen atom of the carbamate function presumably can react with either the ketone function to form a five-membered ring (desired) or the oxocarbenium ion produced from the enol ether to form a six-membered ring (undesired). In the event, only a 48% yield of **8** is obtained in the two-step procedure. No byproducts containing a six-membered ring were obtained. This compound, which smells of “buttery caramel corn”, can be deprotected by using trifluoroacetic acid in dichloromethane to produce **2** in 22% isolated yield.

It should be noted during the deprotection step that (a) lengthy reaction times should be avoided, (b) cooling the reaction mixture is necessary during the workup procedure, and (c) a room temperature bath is used when concentrating **2** in vacuo. Straying from these procedures leads to the formation of an inseparable contaminant in varying amounts whose ¹H NMR spectrum matches that of **9** as described by De Kimpe and Keppens.^{7d}

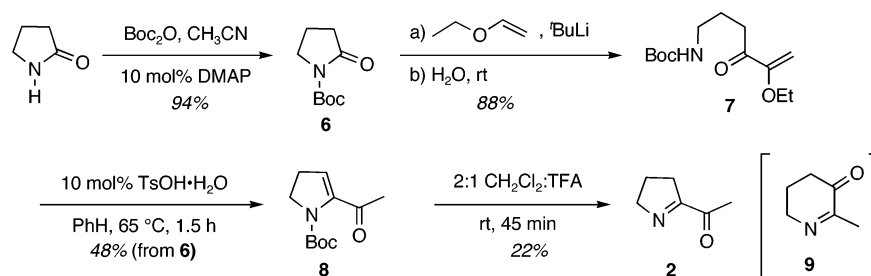
In summary, a short construction of the bread flavor component **1** has been established. A key feature is the release of a “carbamate-ketal” function under basic conditions to ultimately produce **1**.

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SCHEME 3



Experimental Section

Procedure for the Conversion of 3 to 1. To a solution of 1.44 mL of ethyl vinyl ether (15.0 mmol) in 25 mL of THF at $-78\text{ }^{\circ}\text{C}$ was added 6.6 mL of a solution of *tert*-butyllithium (1.53 M in pentane, 10.0 mmol) dropwise. The bright yellow reaction mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for 30 min and then warmed to $0\text{ }^{\circ}\text{C}$ for 10 min. The resulting pale yellow solution was cooled back down to $-78\text{ }^{\circ}\text{C}$ for 15 min and to this reaction mixture was added a solution of 0.983 g of **3** (4.94 mmol) in 5 mL of THF. The reaction was stirred for 45 min before being quenched with 10 mL of H_2O and 20 mL of diethyl ether. The organic phase was washed twice with a saturated aqueous solution of sodium bicarbonate. The combined aqueous fractions were extracted once with diethyl ether. The combined organic fractions were washed with a saturated aqueous brine solution and then dried over sodium sulfate and concentrated by rotary evaporation in vacuo to afford 1.49 g of **4** as a pale yellow oil.

To a solution of 1.49 g of crude **4** in 10 mL of benzene was added 95 mg of *p*-toluenesulfonic acid (0.50 mmol) and the reaction mixture was stirred at $65\text{ }^{\circ}\text{C}$ for 1.5 h. The reaction temperature was cooled to $45\text{ }^{\circ}\text{C}$ and 20 mL of dimethyl sulfoxide was added followed by 9 mL of an aqueous 3 M NaOH solution (27.0 mmol). The red reaction mixture was stirred for 3 h before being cooled to room temperature and diluted with a saturated aqueous solution of ammonium chloride. The mixture was extracted four times with diethyl ether. The combined organic fractions were washed four times with a saturated aqueous brine

solution, dried over magnesium sulfate, and concentrated by rotary evaporation in vacuo to afford an orange oil. Purification by column chromatography on a thin band of triethylamine washed silica gel (3:1 petroleum ether:diethyl ether) afforded 411 mg (67%) of the title compound **1** as a yellow oil.

IR (film): 3407, 2942, 1697, 1667, 1630, 1254 cm^{-1} . ^1H NMR (400 MHz, CDCl_3): δ (A) 5.57 (t, $J = 4.6$ Hz, 1H), 4.15 (s, 1H), 3.10 (t, $J = 5.5$ Hz, 2H), 2.22 (s, 3H), 2.17–2.24 (m, 2H), 1.70–1.80 (m, 2H); (B) 3.77 (m, 2H), 2.30 (s, 3H), 2.27–2.34 (m, 2H), 1.58–1.67 (m, 2H), 1.50–1.58 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3): δ 200.4, 194.5, 167.1, 141.8, 109.5, 50.1, 40.8, 24.3, 23.7, 23.6, 22.5, 21.6, 21.4, 18.6. MS (ESI): 126 ($\text{M} + \text{H}^+$).

Acknowledgment. The authors thank the University of British Columbia, the Natural Sciences and Engineering Research Council (NSERC) of Canada, Glaxo Smith Kline, and Merck-Frosst for the financial support of our programs.

Supporting Information Available: Experimental procedures and characterization data for compounds **1–9**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

JO051940A