A Convenient Synthesis of 6-Acetyl-1,2,3,4-tetrahydropyridine, the Principle Bread Flavor Component

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Introduction

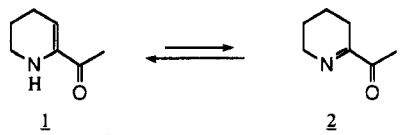
Flavor and aroma play a pronounced role in the food industry. A variety of heterocyclic compounds are distributed in food flavors. These compounds originate from (a) enzymatic reactions of several substrates, e.g., polyphenols, lipids, and proteins, and (b) nonenzymatic browning reactions between α-amino acids and reducing sugars. The latter process is referred to as the Maillard reaction, which gains in importance with increasing temperatures. During the Maillard reaction of L-proline and reducing sugars, more than 100 proline-specific compounds are formed, depending on the reaction conditions and the sugars used.[1,2] Many of these compounds, such as 6-acetyl-1,2,3,4-tetrahydropyridine (1), display extremely strong cracker-like odor characteristics. This cyclic enamine, which occurs in tautomeric equilibrium with its imino tautomer 2 (Scheme I), has been identified in freshly baked bread[3] and in the crust of freshly baked rye bread.[4,5] 6-Acetyl-1,2,3,4-tetrahydropyridine is a labile compound, which is currently considered as the most significant bread flavor component. A synthesis of 6-acetyl-1,2,3,4-tetrahydropyridine (1) in an unspecified yield has been reported from the thermal condensation of proline with 1,3-dihydroxy-2-propanone in the presence of sodium bisulfite.[3,6,7] An improved synthesis was published later, utilizing hydrogenation of 2-acetylpyridine over an expensive rhodium catalyst and oxidation of the resulting amino alcohol with a large excess of a silver reagent.[8] 6-Acetyl-1,2,3,4-tetrahydropyridine (1) has been stabilized as the bisulfite adduct and the hydrochloride. Both derivatives were proposed as flavoring agents for bread and bakery products.[3,6,7]

Herein, we report a novel straightforward synthesis of this potential bread flavor component 1.

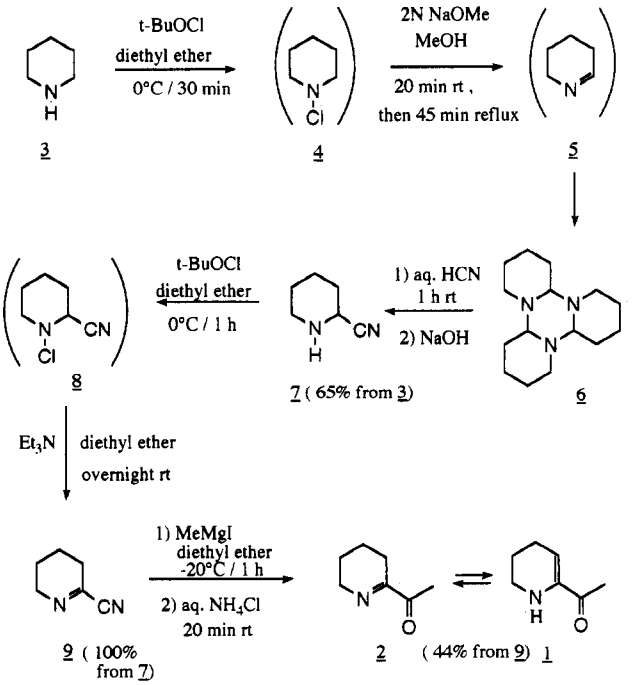
Results and Discussion

According to literature procedures, cyanation of piperidine (3) into 2-cyanopiperidine (7) can be accomplished in a two-step process by oxidation of piperidine into 1-piperideine (5), which trimerizes readily into hexahydro-1,3,5-triazine derivative 6,[9-11] and subsequent addition of aqueous hydrogen cyanide.[12,13] The first step comprises N-chlorination of piperidine with calcium hypochlorite

Scheme I



Scheme II



to form *N*-chloropiperidine (4) in situ and subsequent dehydrochlorination with ethanolic potassium hydroxide.[9] The procedure utilizing calcium hypochlorite is lengthy due to a time-consuming filtration and an overnight trimerization step. Alternative procedures for the N-chlorination of piperidine include the treatment of piperidine with *N*-chlorosuccinimide,[14,15] *tert*-butyl hypochlorite,[16,17] or sodium hypochlorite.[18] The dehydrochlorination of *N*-chloropiperidine can be accomplished using alcoholic potassium hydroxide[9,11,18] or potassium superoxide in ether.[16] In order to avoid the above-mentioned disadvantages, a modified procedure was worked out in which tripiperideine (6), i.e., dodecahydro-1*H*,6*H*,11*H*-tripyrido-[1,2-*a*:1′,2′-*c*:1″,2″-*e*][1,3,5]triazine, was prepared in a more convenient way (Scheme II). In addition, the crude tripiperideine (6) was directly converted into 2-cyanopiperidine (7) with an overall yield of 65%, as compared to the 39–48% yield of tripiperideine in the reported procedure.[9] The improved procedure consists of the N-chlorination of piperidine 3 with *tert*-butyl hypochlorite in ether at 0 °C and dehydrochlorination of the resulting *N*-chloropiperidine (4) with sodium methoxide in methanol under reflux. The resulting 1-piperideine trimerized immediately to form tripiperideine (6), which was isolated as a light-yellow solid. Tripiperideine (6) was obtained in pure form (95–97% purity) and was shown to consist of

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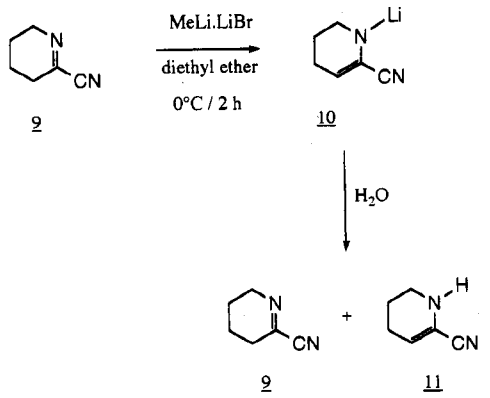
Scheme III



α-tripiperideine, based on ^{13}C NMR spectroscopy.[19] This procedure allows the isolation of α-tripiperideine in pure form, which might be an advantage over such methods which utilize in situ formed solutions.[15,17] Tripiperideine (6) was treated directly with aqueous hydrogen cyanide to afford 2-cyanopiperidine (7), which was isolated after basification of the aqueous solution (overall yield 65%).

2-Cyanopiperidine (7) was then oxidized into imidoyl cyanide 9 by N-chlorination with *tert*-butyl hypochlorite in ether and subsequent dehydrochlorination of the in situ formed 1-chloro-2-cyanopiperidine (8) with triethylamine in ether. Imidoyl cyanide 9 was obtained in quantitative yield. It is important to keep the freshly prepared imidoyl cyanide 9 for the shortest period of time under neat form, that is to say after removal of triethylamine hydrochloride and evaporation of the solvent and 2-methyl-2-propanol. Otherwise, substantial amounts of the corresponding enamine 11 are formed, resulting in less favorable results in the next step. The last reaction step consists of the addition of methylmagnesium iodide to imidoyl cyanide in ether at −20 °C, followed by hydrolysis of the N-unsubstituted ketimine moiety by aqueous ammonium chloride at room temperature. After workup, 6-acetyl-2,3,4,5-tetrahydropyridine (2) is obtained in 44% yield (purity ≥98%) from imidoyl cyanide (9). The freshly prepared flavor compound occurred as a 4:1 mixture of the imino form 2 and the enamine form 1 (^1H NMR; $CDCl_3$). On standing, this ratio gradually changed to a ratio in favor of the enamino form (up to 1:2). When imidoyl cyanide 9 was reacted with methyllithium–lithium bromide complex in ether at 0 °C for 2 h, a yellow precipate readily formed. Aqueous workup regenerated imidoyl cyanide 9, which occurred in equilibrium with the enamine 11 (ratio 85:15, respectively). Preparative gas chromatographic analysis of this reaction mixture revealed one peak which consisted of a 1:1 ratio of imidoyl cyanide 10 and α-cyano enamine 11 (^1H NMR, $CDCl_3$). Presumably, the yellow solid was the lithium salt 10 (Scheme III), which proved to be stable at elevated temperature in ether (reflux 1 h).

The freshly prepared flavor compound (1, 2) is rather labile in neat form and should therefore be kept in diluted solution (pentane, CH_2Cl_2) at −20 °C. After standing for several months or even 2 years at −20 °C, these solutions still contained the flavor compound and there was no sign of decomposition (GC, ^1H NMR). Alternatively, the stable hydrochloride salt can be prepared by reacting the flavor compound with dry hydrogen chloride at 0 °C in ether.[8] This hydrochloride is stable for years as a free flowing powder when kept at −20 °C, protected from moisture.

As 6-acetyl-1,2,3,4-tetrahydropyridine (1) is the major contributor to the flavor of bread due to its pronounced cracker-like aroma, it possesses a great potential for use in bread and especially bakery products. This pronounced potential originates from the extremely low odor threshold values, i.e., the minimum physical intensity detection where the subject is not required to identify the stimulus but just to detect the existence of the stimulus.[20] The odor threshold value of 6-acetyl-1,2,3,4-tetrahydropyridine (1) was established as 1.4 ppb.[20] Because of this interesting flavor characteristic, this compound is of major interest for the flavor industry.

In conclusion, a straightforward and attractive synthetic route to 6-acetyl-1,2,3,4-tetrahydropyridine (1) is described, utilizing cheap and basic chemicals. This process is amenable to large-scale production of the flavor material.

Experimental Section

Synthesis of 2-Cyanopiperidine (7). A stirred solution of 17.0 g (0.2 mol) of piperidine in 130 mL of dry ether was treated dropwise with 21.70 g (0.2 mol) of *tert*-butyl hypochlorite at 0 °C. Stirring was continued at this temperature for 30 min. Three-fourths of the solvent was evaporated in vacuo (<30 °C), and the residual product, i.e., *N*-chloropiperidine (4) in ether, was triturated with 130 mL of 2 N sodium methoxide in methanol (0.26 mol). In most cases, a vigorous reaction started after several minutes. After this vigorous reaction ceased or after an additional 20 min at room temperature, the mixture was stirred under reflux for 45 min. The precipitate was then filtered and washed with a little dry methanol, after which the solvent was removed in vacuo. The residual light-yellow solid consisted of pure tripiperideine (6), mp 59–60 °C (lit.[9] mp 58–61 °C). ^{13}C NMR ($CDCl_3$): [19] 22.37, 25.82, and 29.19 (each t, each CH_2); 46.39 (t, NCH_2); 81.94 (d, NCHN). The solid tripiperideine (6) was treated directly with aqueous hydrogen cyanide, prepared from 26.0 g (0.4 mol) of potassium cyanide and 100 mL of aqueous 4 N hydrogen chloride (0.4 mol) (this procedure should be performed in a well-ventilated hood). If necessary, some additional 12 N HCl was added dropwise in order to acidify the solution (water bath cooling). The mixture was stirred at ambient temperature for 1 h, and afterwards, sodium hydroxide pellets were added under cooling until the mixture was alkaline. The aqueous phase was extracted three times with CH_2Cl_2, and the organic phases were dried ($MgSO_4$) and evaporated in vacuo to leave a clear oil, which was distilled in vacuo to afford 14.3 g (65%) of pure 2-cyanopiperidine (7), bp 91–95 °C/12 mmHg (lit.[10] bp 90–92 °C/12 mmHg). ^{13}C NMR ($CDCl_3$): δ 21.58 (t, CH_2); 25.31 (t, CH_2); 29.05 (t, CH_2); 43.42 (t, CH_2N); 46.68 (d, CHN); 120.14 (s, C≡N).

Synthesis of 6-Cyano-2,3,4,5-tetrahydropyridine 9. A solution of 4.4 g (0.04 mol) of 2-cyanopiperidine (7) in 50 mL of dry ether was treated dropwise with 4.34 g (0.04 mol) of *tert*-butyl hypochlorite at 0 °C. After the solution was stirred for 1 h at room temperature, 4.04 g (0.04 mol) of triethylamine was added and stirring was continued for overnight. The precipitated triethylamine hydrochloride was filtered and washed with dry ether, and the filtrate and washings were evaporated in vacuo without heating. The remaining 2-methyl-2-propanol was evacuated under high vacuum (0.05 mmHg) for 30 min. The remaining imidoyl cyanide 9 was obtained in quantitative yield. It was essential to avoid elevated temperatures as otherwise tautomerism to the corresponding enamine 11 occurred. This tautomerism seemed to have a negative influence on the elaboration of this compound in the next step. As expected, distillation of imidoyl cyanide 9 caused partial isomerization into the corresponding

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enamine (ratio imine/enamine 44/56; ^{1}H NMR $CDCl_3$). Bp: 97–99 °C/10 mmHg.

6-Cyano-2,3,4,5-tetrahydropyridine (9). ^{1}H NMR ($CDCl_3$): δ 1.8 (4 H, m, CH_2CH_2), 2.4 (2 H, m, CH_2C=N), 3.8 (2 H, m, CH_2N). ^{13}C NMR ($CDCl_3$): δ 18.21 (CH_2), 20.98 (CH_2), 30.75 (CH_2C=N), 50.99 (CH_2N), 116.12 (C≡N), 148.41 (C=N). IR (NaCl): 2220 (C≡N), 1635 cm^{-1} (C=N). Mass spectrum *m/z*: 108 (M^+, 42), 107 (14), 80 (100), 66 (10), 55 (28), 54 (20), 53 (48), 52 (20), 41 (36), 39 (28). Anal. Calcd for $C_6H_8N_2$: N, 25.90. Found: N, 25.71.

6-Cyano-1,2,3,4-tetrahydropyridine (11). ^{1}H NMR ($CDCl_3$): δ 1.7 (2 H, m, CH_2), 2.2 (2 H, m, CH_2C=C), 3.2 (2 H, m, CH_2N), 5.40 (1 H, t, *J* = 4 Hz, CH=C). IR (NaCl): 3370 (NH), 2230 cm^{-1} (C≡N). ^{13}C NMR ($CDCl_3$): δ 20.98 and 22.32 (each t, CH_2CH_2C=C), 41.61 (t, CH_2N), 114.41 (d, CH=C), 117.00 (s, CH=*C*), 118.25 (s, *C*≡N). These data are taken from a sample consisting of a mixture of 6-cyano-2,3,4,5-tetrahydropyridine (**9**) and the corresponding enamine **11**, obtained after distillation, bp 97–99 °C/10 mmHg (imine/enamine 44/56; ^{1}H NMR, $CDCl_3$).

Synthesis of 6-Acetyl-1,2,3,4-tetrahydropyridine (1). Freshly prepared 6-cyano-2,3,4,5-tetrahydropyridine (**9**) (4.32 g; 0.04 mol), obtained in quantitative yield as described above, was dissolved in 20 mL of dry ether, and this solution was added dropwise to a vigorously stirred solution of freshly prepared methylmagnesium iodide in ether at −20 °C (the Grignard reagent was prepared from 2.92 g (0.12 g atom) of magnesium turnings and 17.0 g (0.12 mol) of iodomethane in 120 mL of ether under reflux for 1 h). After complete addition of the imidoyl cyanide **9**, stirring was continued for 1 h. The supernatant was cautiously poured into a stirred and ice-cold aqueous ammonium chloride solution in an Erlenmeyer flask. The viscous residue remaining in the reaction flask was treated with the latter ice-cold mixture from the Erlenmeyer flask. The clear organic and aqueous layers were stirred vigorously for 20 min at ambient temperature. The organic layer was isolated, and the aqueous phase was extracted twice with ether. The combined extracts were dried ($MgSO_4$) for 30 min. The drying agent was filtered off and replaced for a fresh portion of $MgSO_4$. After being dried overnight at 5 °C, the drying agent was filtered and the solvent was removed in vacuo without heating to afford 2.2 g (44%) of light-yellow oil (purity 98%; GC). The freshly prepared compound occurred as a 4:1 mixture of the imino form **2** and the enamino form **1** (^{1}H NMR; $CDCl_3$). On standing, this ratio gradually changed to a ratio in favor of the enamino form (up to 1:2). The freshly prepared bread flavor compound (**1**, **2**) is rather labile in neat form and should therefore be kept in diluted solution (CH_2Cl_2, preferably pentane) at −20 °C.

6-Acetyl-2,3,4,5-tetrahydropyridine (2). ^{1}H NMR ($CDCl_3$): δ 1.4–2 (4 H, m, CH_2CH_2); 2.3 (2 H, m, CH_2C=N); 3.5–4 (2 H, m, CH_2N); 2.37 (3 H, s, CH_3CO). IR (NaCl): 1700 (C=O), 1660 cm^{-1} (C=N). ^{13}C NMR ($CDCl_3$): δ 18.70 and 21.58 (each t, CH_2CH_2); 23.71 (t, CH_2C=N); 50.26 (t, CH_2N); 24.35 (q, CH_3C=O); 167.26 (s, C=N); 200.46 (s, C=O). MS *m/z*: 125 (M^+, 62); 124 (12); 92 (10); 83 (40); 82 (76); 55 (64); 54 (72); 53 (10); 43 (100); 42 (8); 41 (22); 40 (32).

6-Acetyl-1,2,3,4-tetrahydropyridine (1). These data were deduced from a sample consisting of a mixture of imine **2** and enamine **1** in a 1:2 ratio, respectively. ^{1}H NMR ($CDCl_3$): δ 2.2 (4 H, m, CH_2CH_2); 3–3.3 (2 H, m, CH_2N); 2.38 (3 H, s, CH_3C=O); 5.64 (2 H, t, *J* = 4 Hz, CH=C); 4.0 (1 H, broad, NH). IR (NaCl): 3420 (NH); 1670 (C=O); 1630 cm^{-1} (C=C). ^{13}C NMR ($CDCl_3$): δ 21.72 and 22.70 (each t, CH_2CH_2); 40.92 (t, CH_2N); 23.86 (q, CH_3C=O); 109.52 (d, CH=C); 141.99 (s, C=*C*–N); 194.57 (s, C=O).