

Novel Syntheses of 5-Acetyl-2,3-dihydro-1,4-thiazine, a Very Intense Roasty, Popcornlike Odorant

Norbert G. De Kimpe* and Maria Teresa Rocchetti

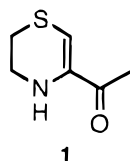
Department of Organic Chemistry, Faculty of Agricultural and Applied Biological Sciences,
University of Gent, Coupure Links 653, B-9000 Gent, Belgium

Two new synthetic pathways toward the new Maillard flavor compound 5-acetyl-2,3-dihydro-1,4-thiazine are disclosed. 1-Bromo-3,3-dimethoxy-2-butanone and *N*-protected 2-mercaptoethylamine are the key components in both synthetic routes. The first approach involves a one-step synthesis via nucleophilic substitution, followed by cyclization and hydrolysis. The second route entails a nucleophilic substitution, followed by TFA-deprotection of the primary amino function, which led to a spontaneous intramolecular transimination and hydrolysis of the acetal moiety to afford the desired flavor compound in very good yield.

Keywords: Popcorn flavor; roasty flavor; 5-acetyl-2,3-dihydro-1,4-thiazine; Maillard; flavor compound

INTRODUCTION

A variety of sulfur-containing heterocyclic compounds are distributed in food flavor, originating from the Maillard reaction between reducing sugars and cysteine (Hofmann and Schieberle, 1995). The most intense odorant in a thermally treated aqueous ribose/cysteine model system has recently been determined as 5-acetyl-2,3-dihydro-1,4-thiazine (**1**) (Hofmann and Schieberle,



1995). This compound elicits an intense roasty, popcornlike flavor at low odor thresholds of 0.06 ng/L of air and 0.6 µg/L of water (retronasally) (Hofmann et al., 1995), which is of the same order of magnitude as those reported in the literature for the roasty-smelling odorants 2-acetyl-1-pyrroline (Buttery et al., 1988) and 2-acetyl-2-thiazoline (Cerny and Grosch, 1993).

5-Acetyl-2,3-dihydro-1,4-thiazine (roasty), 2-furfurylthiol (roasty, coffeelike), 3-mercapto-2-pentanone (catty), 3-mercapto-2-butanone (sulfury, rotten), and 2-(1-mercaptoethyl)furan are the main contributors to the overall roasty, sulfury odor of the thermally treated glucose/cysteine mixture, and they are also important flavor contributors in the thermally treated mixture of rhamnose/cysteine (Hofmann and Schieberle, 1997). Only one synthesis of the flavor compound **1** has been reported in the literature. This synthetic process consisted of the condensation of an equimolar amount of cysteamine and 2,3-butanedione at 145 °C for 20 min in an autoclave, but the yield was disappointingly low (1%) (Hofmann et al., 1995).

In this paper, two new straightforward and attractive synthetic routes to 5-acetyl-2,3-dihydro-1,4-thiazine (**1**)

in very good yield are reported, using cheap basic chemicals which make this reaction amenable to a large scale synthesis of this potential flavor compound.

EXPERIMENTAL PROCEDURES

3,3-Dimethoxy-2-butanone (3). This compound was prepared by monoacetalization of diacetyl, as described in the literature (Harris, 1950; Braude and Timmons, 1953; Brodsky and Agosta, 1974).

***N*-(3,3-Dimethoxy-2-butyldene)isopropylamine (4).** The synthesis of this compound was performed following a procedure described in the literature (De Kimpe and Stevens, 1995).

***N*-(1-Bromo-3,3-dimethoxy-2-butyldene)isopropylamine (5).** At room temperature, a solution of 1.73 g (10 mmol) of compound **4** in 17 mL of CCl₄ was treated with 1.78 g (10 mmol) of *N*-bromosuccinimide, and the mixture was refluxed for 3 h. After the mixture was cooled, the succinimide was filtered off and washed with CCl₄, and the filtrate was evaporated in vacuo to give rise to 2.51 g of **5** (quantitative yield). ¹H NMR (270 MHz, CDCl₃) δ 1.21 (6 H, d, *J* = 6.27 Hz, CHMe₂), 1.51 (3 H, s, Me), 3.22 (6 H, s, (OMe)₂), 3.92 (2 H, s, CH₂Br), 3.94 (1 H, septet, CHMe₂). ¹³C NMR (68 MHz, CDCl₃) δ 16.8 (Me), 23.0 (CHMe₂), 49.1 (C(OMe)₂), 49.2 (CH₂Br), 51.8 (NCH), 102.3 (C(OMe)₂), 162.7 (C=N). IR (NaCl, cm⁻¹) 2850 (OMe), 1670 (C=N). Mass spectrum *m/z* (%) 253 [(M + 2)⁺, 0.6], 222 (3), 220 (3), 180 (2), 178 (2), 164 (1), 162 (2), 140 (4), 122 (3), 110 (2), 90 (5), 89 (100), 84 (7), 83 (5), 58 (2), 57 (3), 55 (2), 49 (3), 47 (3), 43 (28), 42 (26), 41 (8).

1-Bromo-3,3-dimethoxy-2-butanone (6). To a solution of 1.26 g (10 mmol) of oxalic acid dihydrate in 40 mL of H₂O was added a solution of 2.51 g (10 mmol) of *N*-(1-bromo-3,3-dimethoxy-2-butyldene)isopropylamine (**5**) in 40 mL of ether. The biphasic mixture was stirred for 1 h at reflux and poured into 50 mL of 1 N NaOH solution, extracted three times with CH₂Cl₂, and dried (K₂CO₃). Filtration and evaporation of the solvent in vacuo gave 1.87 g (yield 87%) of pure compound **6** (purity > 97%). ¹H NMR (270 MHz, CDCl₃) δ 1.44 (3 H, s, Me), 3.25 (6 H, s, (MeO)₂), 4.33 (2 H, s, CH₂Br). ¹³C NMR (68 MHz, CDCl₃) δ 20.3 (Me), 33.8 (CH₂Br), 49.8 (C(OMe)₂), 102.8 (C(OMe)₂), 200.0 (C=O). IR (NaCl, cm⁻¹) 2850 (OMe), 1740 (C=O). Mass spectrum *m/z* (%) no M⁺, 181 (18), 180 (5), 179 (19), 123 (5), 121 (1), 102 (5), 95 (5), 90 (6), 89 (100), 85 (7), 72 (5), 58 (4), 57 (20), 49 (6), 47 (13), 44 (9), 43 (89), 42 (13), 41 (6).

* Address correspondence to this author (fax 32 9 264 62 43; e-mail norbert.dekimpe@rug.ac.be).

5-Acetyl-2,3-dihydro-1,4-thiazine (1) (Method a, b). To a solution of 0.91 g (8.8 mmol) of 2-mercaptoethylamine hydrochloride in 20 mL of dimethylformamide (a) or acetonitrile (b) was added 1.68 g (8 mmol) of 1-bromo-3,3-dimethoxy-2-butanone (**6**) and the mixture was refluxed for 2 h (a) (for 3 h (b)). After the reaction mixture was cooled to room temperature, 10 mL of water were added to it, and stirring was continued for 15 min. This mixture was poured in 50 mL of 1 N NaOH and extracted with ether (3 × 50 mL). The combined extracts were dried (K₂CO₃) and filtered, and the solvent was removed in vacuo. To remove residual DMF (a), the crude mixture was evaporated at 0.01 mmHg (24 °C) to afford 0.55 g of pure 5-acetyl-2,3-dihydro-1,4-thiazine (**1**) (yield 48%, purity > 97% (a); yield 56% (b)). This compound was additionally purified (purity > 99%) by flash chromatography (silica gel) (rf_a = 0.25) with CH₂Cl₂/hexane (9:1) giving a 27% yield. The latter purification step is usually not necessary for further experiments. ¹H NMR (270 MHz, CDCl₃) δ 2.4 (3 H, s, Me), 3.0 (2 H, m, CH₂S), 3.5 (2 H, m, CH₂N), 4.6 (1 H, br s, NH), 6.2 (1 H, s, S-CH=). ¹³C NMR (68 MHz, CDCl₃) δ 23.3 (Me), 26.3 (CH₂S), 40.5 (CH₂N), 106.2 (S-CH=), 137.6 (N-C=), 190.0 (C=O). IR (NaCl, cm⁻¹) 3370 (NH), 1650 (CH=C-C=O). Mass spectrum *m/z* (%) 143 (M⁺, 100), 128 (17), 100 (35), 73 (26), 72 (20), 43 (62). These spectrometric data proved to be identical with those previously reported (Hofmann et al., 1995).

tert-Butyl-N-(2-mercaptoethyl)carbamate (8). A solution of 0.187 g (1.65 mmol) of 2-mercaptoethylamine hydrochloride (**9**) in 8 mL of CH₂Cl₂ was treated with 0.33 g (3.3 mmol) of Et₃N at room temperature. The mixture was stirred for 30 min at room temperature and was then treated with 0.38 mL (1.65 mmol) of *t*-Boc₂O and stirred for 2 h under a nitrogen atmosphere. The reaction mixture was poured in water (10 mL), extracted with ether (3 × 10 mL), dried (MgSO₄), and filtered, and the solvent was evaporated in vacuo to give 0.25 g (yield 85%) of compound **8** with a purity of 95% (GC). ¹H NMR (270 MHz, CDCl₃) δ 1.44 (9 H, s, *t*-Bu), 2.65 (2 H, m, CH₂N), 3.30 (2 H, m, CH₂S), 5.0 (1 H, br s, NH). ¹³C NMR (68 MHz, CDCl₃) δ 24.8 (CH₂S), 28.3 (*t*-Bu), 43.6 (CH₂N), 80.0 (OCMe₃), 155.8 (NHCOO). IR (NaCl, cm⁻¹) 3300 (NH), 1700 (C=O). Mass spectrum *m/z* (%) no M⁺, 121 (29), 104 (7), 74 (8), 62 (27), 61 (11), 60 (10), 59 (38), 58 (6), 57 (100), 56 (23), 55 (10), 44 (40), 43 (8), 42 (5), 41 (67), 40 (27).

tert-Butyl N-[2-(3',3'-Dimethoxy-2'-oxobutyl)mercaptoethyl]carbamate (7). A solution of 0.27 g (1.28 mmol) of 1-bromo-3,3-dimethoxy-2-butanone (**6**) in 5 mL of dry CH₂Cl₂ was treated with 0.25 g (1.4 mmol) of compound **8** and 0.14 g (1.4 mmol) of Et₃N at room temperature and then refluxed for 2 h. The reaction mixture was poured in 50 mL of H₂O and extracted with ether (3 × 50 mL). The combined extracts were dried (K₂CO₃) and evaporated in vacuo to afford 0.41 g of a mixture of compound **8** and compound **7** (ratio **8/7**, 17/83; ¹H NMR) with a yield of 86% of compound **7**. This mixture was used in the following step without separation of the two compounds. Spectroscopic data of compound **7**: ¹H NMR (270 MHz, CDCl₃) δ 1.44 (12 H, s, Me + *t*-Bu, overlap), 2.6 (2 H, t, CH₂CH₂S), 3.24 (6 H, s, (OMe)₂), 3.35 (2 H, m, CH₂N), 3.55 (2 H, s, COCH₂S), 5.0 (1 H, br s, NH). ¹³C NMR (68 MHz, CDCl₃) δ 20.5 (Me), 28.1 (CH₂CH₂S), 28.4 (*t*-Bu), 32.4 (COCH₂S), 36.8 (CH₂N), 49.7 (C(OMe)₂), 79.2 (OCMe₃), 102.7 (C(OMe)₂), 155.8 (NHCOO), 204.0 (C=O). IR (NaCl, cm⁻¹) 3363 (NH), 2835 (OMe), 1713 (C=O), 1690 (NHCOO). Mass spectrum *m/z* (%) no M⁺, 121 (4), 119 (4), 88 (10), 86 (61), 84 (100), 51 (5), 49 (22), 47 (22).

5-Acetyl-2,3-dihydro-1,4-thiazine (1) (Method c). A solution of 0.36 g (1.18 mmol) of compound **7** in 10 mL of dry CH₂Cl₂ was treated with 0.9 mL (12.8 mmol) of trifluoroacetic acid (TFA) at 0 °C and was stirred at room temperature for 3 h. The mixture was neutralized with a saturated solution of NaHCO₃ (30 mL) at 0 °C and then extracted with CH₂Cl₂ (3 × 50 mL). The combined extracts were dried (K₂CO₃) and filtered and the solvent was evaporated in vacuo to give 160 mg (yield 88%) of compound **1** (purity > 97%).

5-Acetyl-2,3-dihydro-1,4-thiazine Hydrochloride (1·HCl). A solution of 0.36 g (2.5 mmol) of compound **1** in 20 mL of dry ether was treated with saturated dry HCl in ether (6 mL). The

supernatant organic layer was decanted and the salt was washed with dry ether and dried in vacuo to afford a 0.39 g (yield 86%) of a light-yellow solid. Mp 171–172 °C. ¹H NMR (270 MHz, CDCl₃) δ 2.4 (3 H, s, Me), 3.31 (2 H, m, CH₂S), 3.61 (2 H, m, CH₂N), 7.95 (1 H, s, S-CH=). ¹³C NMR (68 MHz, CDCl₃) δ 23.68 (Me), 24.1 (CH₂S), 41.23 (CH₂N), 126.5 (=C_{quat}), 134.4 (S-CH=), 190 (C=O). IR (KBr, cm⁻¹): 3550–3400/2850–2400 (NH₂), 1650 (CH=C-C=O).

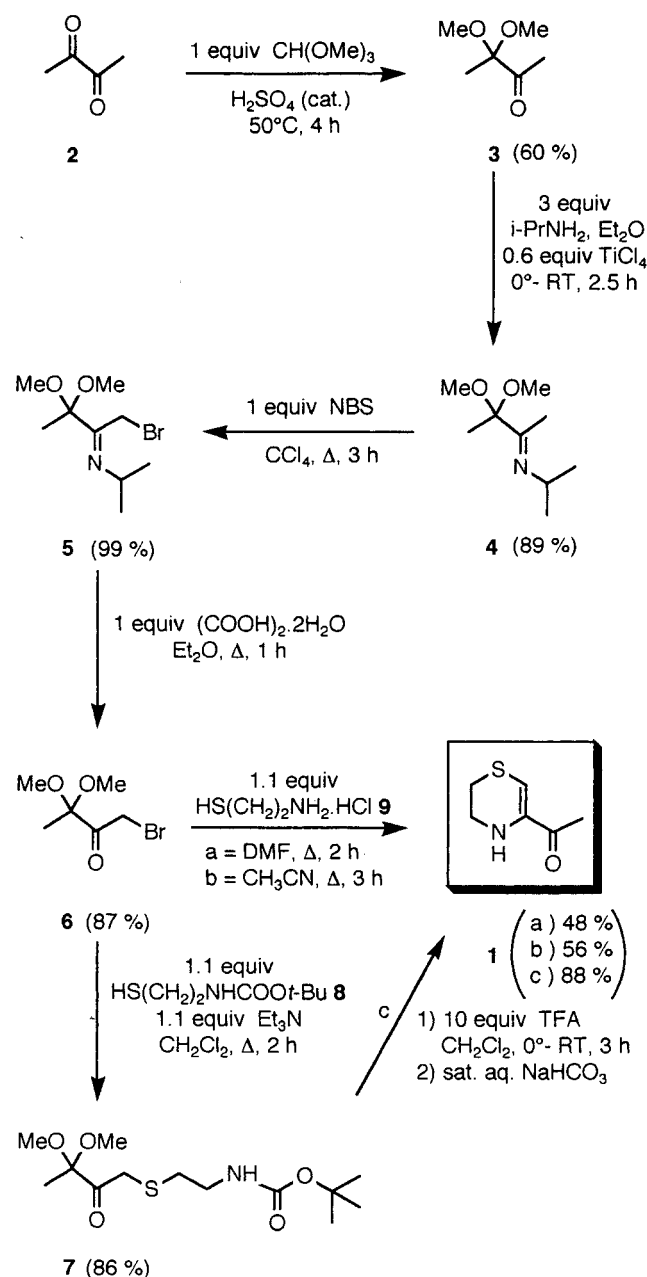
RESULTS AND DISCUSSION

To synthesize the new Maillard compound **1**, 1-bromo-3,3-dimethoxy-2-butanone (**6**) was reacted with a small excess of 2-mercaptoethylamine hydrochloride in dimethylformamide or acetonitrile at reflux. The reaction mechanism proceeds via nucleophilic substitution, followed by intramolecular transimination and successive hydrolysis of the acetal function. This process is finalized during the aqueous treatment, to give, after basic workup, 5-acetyl-2,3-dihydro-1,4-thiazine (**1**), free of side products and in good overall yields (48% in DMF; 56% in CH₃CN) (Scheme 1). The transimination reaction is most probably assisted by the basicity of the solvent, necessary for trapping the proton from the nucleophilic displacement and to liberate the primary amino function to allow the nitrogen atom to attack the carbonyl group. This reaction is best explained through an equilibrium between the protonated form of the solvent, the primary amino group of the mercaptoamine, and the oxygen of the carbonyl group (Scheme 2). During the aqueous treatment at room temperature the acetal function was completely hydrolyzed, after which the basic workup afforded the final products. Initially the imino form (**13**) of thiazine derivative **1** was probably formed but rapidly tautomerized to its free enamino form **1**. A similar tautomerism has been observed for the most important bread flavor compound 6-acetyl-1,2,3,4-tetrahydropyridine (De Kimpe and Stevens, 1995), which was detected (NMR) together with its imino form, 6-acetyl-2,3,4,5-tetrahydropyridine. In contrast to the analogous tetrahydropyridine, the imino tautomer (**13**) of the thiazine was never detected. This different behavior could be explained by a more extended conjugation of thiazine **1** compared to 6-acetyl-1,2,3,4-tetrahydropyridine, due to the sulfur atom.

The same reaction mixture from the reaction of 1-bromo-3,3-dimethoxy-2-butanone (**6**) with 2-mercaptoethylamine hydrochloride (**9**) in dimethylformamide was directly worked up with 1 N NaOH, affording a mixture, which mainly consisted of 5-acetyl-2,3-dihydro-1,4-thiazine (**1**), as well as some unidentified compounds. An acetal group could be distinguished in this mixture by ¹H NMR, perhaps the carbonyl-protected form of **1** (see **14**) and its imino tautomer (**12**).

The reaction mechanism was further unraveled by ¹H NMR experiments. 5-Acetyl-2,3-dihydro-1,4-thiazine (**1**) was found in the reaction mixture from the reaction of 1-bromo-3,3-dimethoxy-2-butanone (**6**) with 2-mercaptoethylamine hydrochloride (**9**) in acetonitrile, before (salt) as well as after the aqueous, and then basic, treatment. It proved that the cyclization reaction and the successive hydrolysis of the acetal function already occurred before the workup and came to completion during the workup. Moreover, the reaction of 1-bromo-3,3-dimethoxy-2-butanone (**6**) with 2-mercaptoethylamine hydrochloride was tried in other solvents, e.g., ether or dichloromethane, without any good result (probably because of the poor basicity/polarity of the solvent). In similar way, when a mixture of water/

Scheme 1

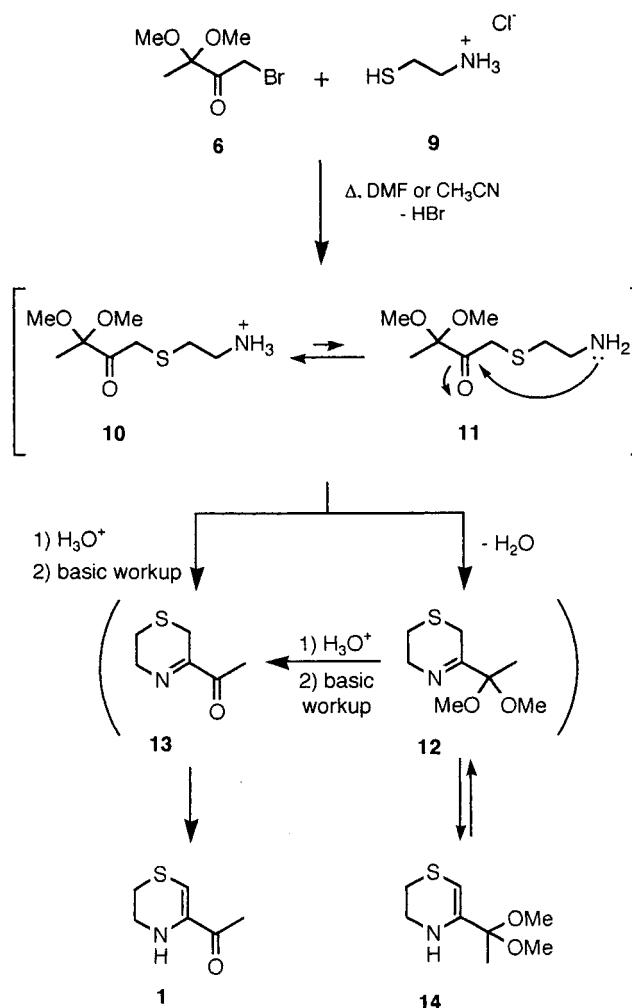


dioxane (4:1 ratio) or acetonitrile as solvents, in the presence of 2 equiv of base (sodium hydroxide and triethylamine, respectively), was used, a mixture containing a minor amount (about 2%) of the flavor compound **1** along with some unidentified compounds was obtained. Most probably, the basic medium liberates the free amino group of the 2-mercaptoethylamine and promotes the competitive nucleophilic attack of the bromide by the amino function.

The flavor compound **1** could be additionally purified by flash chromatography (silica gel) with dichloromethane/hexane (9:1), which resulted in a purity of >99%. Compound **1** was also transformed to the corresponding stable hydrochloride salt by reaction of **1** with dry hydrogen chloride in ether. The ammonium salt can be stored at -20°C for several months without decomposition.

Because of the relatively low yields of **1** in the above-described synthesis, a second route was disclosed using *tert*-butyl *N*-(2-mercaptoethyl)carbamate (**8**) (Saha and

Scheme 2



Roy, 1995; Lopez and Simons, 1991) as the nucleophilic reagent. This compound reacted smoothly with 1-bromo-3,3-dimethoxy-2-butanone (**6**) to give the intermediate *tert*-butyl *N*-(2-mercaptoethyl)carbamate derivative **7** (Scheme 1). *tert*-Butyl *N*-(2-mercaptoethyl)carbamate (**8**) is commercially available and is easily obtained by condensation of 2-mercaptoethylamine hydrochloride salt with Boc_2O in the presence of an excess of triethylamine in dichloromethane at room temperature. The intermediate functionalized carbamate **7** could be smoothly cleaved by an excess of trifluoroacetic acid in dichloromethane. Subsequent basic aqueous workup (saturated solution of NaHCO_3) afforded pure 5-acetyl-2,3-dihydro-1,4-thiazine (**1**) in 88% yield.

Also in this case, the reaction mechanism was unraveled by ^1H NMR experiments, which revealed the presence of the flavor compound **1** in its salt form in the reaction mixture before the basic aqueous workup. Although using an extra reaction step, this second method to synthesize the Maillard compound **1** can be the best way for a large-scale production of the flavor compound, due to the very good overall yield. The key reagent, 1-bromo-3,3-dimethoxy-2-butanone (**6**), of both syntheses of the flavor compound **1**, was synthesized in a three-step sequence involving: (i) imination of 3,3-dimethoxy-2-butanone (**3**) with isopropylamine in the presence of TiCl_4 (De Kimpe and Stevens, 1995), (ii) bromination of compound **4** with *N*-bromosuccinimide in carbon tetrachloride, and finally (iii) the selective

hydrolysis of the imino function of **5** with oxalic acid dihydrate in an ether–water biphasic system.

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