

# Synthesis of 2-[(Methylthio)methyl]-2-butenal, a Characteristic Flavor Component of Potato Chips, Krill Seasoning, Roasted Coffee, and Yeast Extracts

Norbert G. De Kimpe\* and Wim A. Aelterman

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

A straightforward three-step synthesis of the characteristic flavor impact compound 2-[(methylthio)methyl]-2-butenal starting from crotonaldehyde is described. The synthetic route comprised (i) imination of crotonaldehyde with *tert*-butylamine, (ii)  $\alpha$ -alkylation of the resulting imine with chloromethyl methyl sulfide, and (iii) final acid hydrolysis of the  $\beta,\gamma$ -unsaturated imine to the desired flavor compound.

**Keywords:** 2-Alkenal; potato chips; 2-[(methylthio)methyl]-2-butenal; chips flavor

## INTRODUCTION

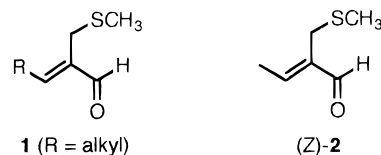
A large number of aldehydes contribute significantly to the flavor of foodstuffs, e.g. coffee, cocoa, and tea (Flament, 1989) and onions (Furia and Bellanca, 1971; Grosch, 1982). Branched 2-alkenals are formed during roasting of foods and contribute as such significantly to the flavor characteristics of foodstuffs.  $\alpha,\beta$ -Unsaturated aldehydes have a pronounced industrial use as synthetic flavor additive of candies, baked goods, ice cream, and dairy products (Furia and Bellanca, 1971; Grosch, 1982; Pickenhagen and Velluz, 1980). In addition, 2-alkenals have a potential use as artificial flavor compounds with a characteristic floral and jasmine-like odor (Furia and Bellanca, 1971). A peculiar class of enals are sulfur-containing  $\alpha,\beta$ -unsaturated aldehydes, which have a major flavor impact on several foodstuffs. The methional-derived 2-[(methylthio)methyl]-2-alkenals **1** are of special interest (Chart 1). 2-[(Methylthio)methyl]-2-butenal (**2**) especially has interesting flavor characteristics and contributes significantly to the total aroma of potato chips (Chart 1) (Buttery, 1973).

In addition, the latter compound has been identified as an odorant in the liquid seasoning of the hydrolysate of Antarctic krills (Kubota et al., 1981; Takasaki et al., 1986) and as a flavor component in yeast extracts (Werkhoff et al., 1991), roasted coffee (Tressl et al., 1982), and cocoa (Baltes, 1992). The flavor compound **2** has been known as a flavoring agent in food to impart a tomato-like and meat-like flavor (Yanai et al., 1986).

2-[(Methylthio)methyl]-2-butenal (**2**) has been synthesized by aldol condensation of methional with acetaldehyde resulting in low yields and impure compounds due to expected self-condensation of the reactants (Buttery, 1973; Yanai et al., 1986). This condensation reaction regularly leads to about 25% yield of product but requires purification by preparative gas chromatography (Buttery, 1973). In our hands the aldol condensation of methional with acetaldehyde also turned out to be unsuccessful in terms of a ready access to this flavor substance.

In the present paper a new straightforward synthesis of the major flavor impact compound 2-[(methylthio)-

## Chart 1



methyl]-2-butenal (**2**) is disclosed, making available this substance in substantial quantities for further flavor evaluation.

## EXPERIMENTAL PROCEDURES

**N-(2-Buten-1-ylidene)-*tert*-butylamine (4).** This compound was prepared from crotonaldehyde **3** and *tert*-butylamine (1 equiv) in benzene utilizing a Dean-Stark trap for the azeotropic removal of water (3 h reflux) (Crawford et al., 1977): yield 74%; bp 36–38 °C (11 mmHg).

**N-[2-[(Methylthio)methyl]-3-buten-1-ylidene]-*tert*-butylamine (5).** A solution of lithium diisopropylamide was freshly prepared from 1.31 g (13 mmol) of diisopropylamine in 15 mL of THF to which 4.8 mL of 2.5 M *n*-butyllithium was added at 0 °C under a nitrogen atmosphere. The aldimine **4** (1.25 g, 10 mmol) was dissolved in THF (10 mL) and added dropwise. The solution was stirred for 10 min at 0 °C after which time it was cooled to –78 °C and further stirred for 30 min. At –78 °C a solution of 0.97 g (10 mmol) of chloromethyl methyl sulfide in 10 mL of THF was added via syringe and the solution was further stirred for 4 h at –78 °C, after which time the reaction was quenched with 20 mL of saturated  $\text{NH}_4\text{Cl}$  solution. This solution was added to ice-cooled 0.5 N NaOH (30 mL) and extracted with diethyl ether (3  $\times$  15 mL). After drying ( $\text{K}_2\text{CO}_3$ ) and concentration *in vacuo*, 1.85 g (yield 100%) of  $\beta,\gamma$ -unsaturated aldimine **5** was obtained, which was used as such in the next step:  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  1.19 (9H, s,  $\text{CMe}_3$ ), 2.10 (3H, s, SMe), 2.62–2.82 (2H, m,  $\text{SCH}_2$ ), 3.12–3.24 (1H, m,  $\text{CHCH}_2$ ), 5.05–5.20 (2H, m,  $\text{CH}=\text{CH}_2$ ), 5.83 (1H, d,  $J = 17.4$  Hz,  $J = 10.2$  Hz,  $J = 6.8$  Hz,  $\text{CH}=\text{CH}_2$ ), 7.47 (1H, d,  $J = 5.94$  Hz,  $\text{HC}=\text{N}$ );  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ )  $\delta$  15.76 (SMe), 29.56 ( $\text{Me}_3\text{C}$ ), 36.37 ( $\text{CH}_2\text{S}$ ), 48.97 ( $\text{CHCH}_2$ ), 57.03 ( $\text{Me}_3\text{C}$ ), 116.92 ( $\text{CH}_2=\text{CH}$ ), 136.96 ( $\text{CH}=\text{CH}_2$ ), 158.34 ( $\text{CH}=\text{N}$ ); IR (NaCl) 1633, 1665  $\text{cm}^{-1}$  ( $\text{C}=\text{N}$  and  $\text{C}=\text{C}$ ); mass spectrum,  $m/z$  (%) 185 ( $\text{M}^+$ , 34), 170 (42), 152 (14), 139 (17), 138 (6), 128 (7), 122 (13), 116 (9), 114 (100), 96 (9), 87 (12), 83 (30), 82 (26), 81 (15), 80 (24), 67 (9), 61 (6), 58 (6), 57 (49), 55 (12), 54 (11), 53 (13), 48 (8), 47 (12), 45 (9), 44 (28), 43 (11), 42 (13), 41 (46).

**2-[(Methylthio)methyl]-2-butenal (2).** To a solution of 1.18 g (6.4 mmol) of  $\beta,\gamma$ -unsaturated imine **5** in 10 mL of ether was added an equal volume of a buffered aqueous acetic acid

\* Author to whom correspondence should be addressed (fax 32 9 264 62 43; e-mail norbert.dekimpe@rug.ac.be).

solution prepared from acetic acid (5 mL), water (5 mL), and sodium acetate (2.16 g). This mixture was stirred for 2 h at room temperature. The organic layer was separated and the water phase extracted with diethyl ether (2 × 10 mL). The combined organic phases were washed with saturated NaHCO<sub>3</sub> solution and dried (MgSO<sub>4</sub>). After evaporation of the solvent, 0.83 g (yield 99%) of crude aldehyde **2** was obtained. Purification of 290 mg of the reaction mixture by flash chromatography on silica gel using diethyl ether/hexane (1:4) as eluent resulted in 140 mg (yield 48%) of pure *Z*-2-[(methylthio)methyl]-2-butenal **2**. *Z*-(**2**): <sup>1</sup>H NMR (C<sub>6</sub>D<sub>6</sub>) δ 1.43 (3H, d, *J* = 7.0 Hz, MeCH=C), 1.78 (3H, s, SMe), 3.14 (2H, s, CH<sub>2</sub>S), 5.84 (1H, q, *J* = 7.0 Hz, CH=C), 9.13 (1H, s, CH=O); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 15.24 (MeCH=C), 15.76 (SMe), 25.39 (CH<sub>2</sub>S), 141.27 (CH=C), 151.41 (CH=C), 193.53 (C=O); IR (NaCl) 1670–1690 (C=O), 1642 cm<sup>-1</sup> (C=C); mass spectrum, *m/z* (%) 130 (M<sup>+</sup>, 46), 115 (6), 101 (2), 97 (2), 87 (5), 86 (2), 85 (6), 84 (5), 83 (22), 82 (100), 81 (8), 71 (2), 69 (2), 65 (2), 61 (14), 59 (5), 58 (3), 55 (29), 54 (72), 53 (41), 52 (3), 51 (10), 50 (5), 49 (8), 48 (11), 47 (15), 46 (7), 45 (20), 44 (11), 43 (6), 41 (6). *E*-(**2**): <sup>1</sup>H NMR (C<sub>6</sub>D<sub>6</sub>) δ 1.44 (3H, d, *J* = 7.3 Hz, MeCH=C), 1.71 (3H, s, SMe), 3.06 (2H, s, CH<sub>2</sub>S), 5.98 (1H, q, *J* = 7.3 Hz, CH=C), 9.85 (1H, s, CH=O); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 12.97 (MeCH=C), 15.56 (SMe), 32.97 (CH<sub>2</sub>S), 136.69 (CH=C), 145.17 (CH=C), 189.68 (C=O); mass spectrum, *E* and *Z* isomers were not separated by GC/MS.

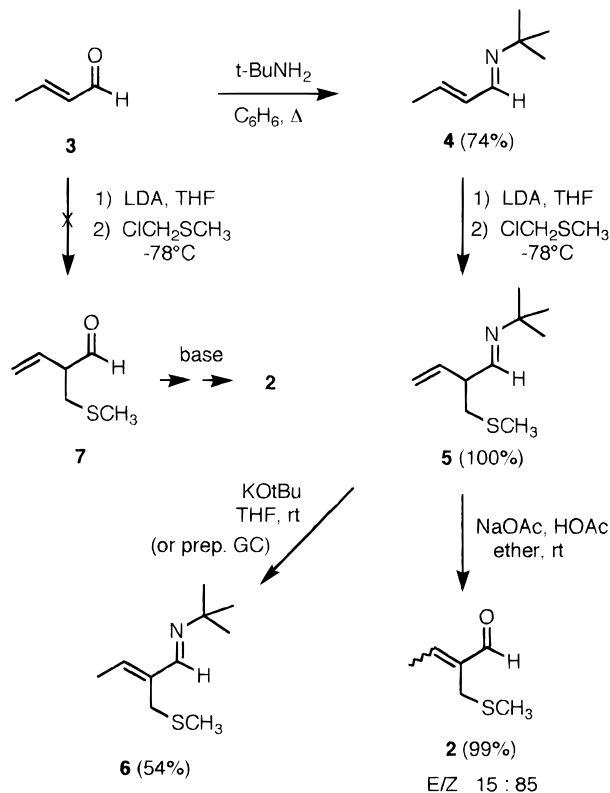
***N*-[2-[(methylthio)methyl]-2-buten-1-ylidene]-*tert*-butylamine (**6**)**. Purification of the β,γ-unsaturated aldimine **5** by preparative gas chromatographic analysis resulted in a conjugated compound **6**. The α,β-unsaturated imine **6** could also be obtained by base treatment of the vinylaldehyde **7**. To a solution of 3.00 g (16.2 mmol) of aldimine **5** in 30 mL of THF was added 0.18 g (1.62 mmol) of potassium *tert*-butoxide. After 2 weeks of stirring at room temperature, the mixture was poured into water and extracted three times with diethyl ether. The combined ether extracts were dried with MgSO<sub>4</sub>, filtered, and concentrated *in vacuo*. The residue was distilled (37–38 °C at 0.03 mmHg) to afford 1.62 g (yield 54%) of **6** as a light yellow oil: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.19 (9H, s, Me<sub>3</sub>C), 1.91 (3H, d, *J* = 7.1 Hz, MeCH=C), 2.10 (3H, s, SMe), 3.54 (2H, s, CH<sub>2</sub>S), 6.02 (1H, q, *J* = 7.1 Hz, CH=C), 7.78 (1H, s, CH=N); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 14.43 (MeCH=C), 15.99 (SMe), 27.13 (CH<sub>2</sub>S), 29.70 (Me<sub>3</sub>C), 56.58 (CMe<sub>3</sub>), 136.35 (CH=C), 139.15 (C=CH), 156.92 (CH=N); IR (NaCl) 1626, 1640 cm<sup>-1</sup> (C=N and C=C); mass spectrum, same as for compound **5**.

## RESULTS AND DISCUSSION

First of all, the direct conversion of crotonaldehyde **3** to the flavor compound via the intermediacy of 2-[(methylthio)methyl]-3-butenal (**7**) was tried. It is known that α,β-unsaturated carbonyl compounds, e.g. ketones (Baltrop and Day, 1961) and esters (Herrmann et al., 1973), can be alkylated at the α-position under basic conditions, resulting in α-alkyl-β,γ-unsaturated carbonyl compounds, which can be isomerized into the conjugated isomers. It has also been reported that direct alkylation of α-substituted α,β-unsaturated aldehydes gives α- and *O*-alkylated products as well as unreacted starting material (De Graaf, 1974). This procedure did not work for crotonaldehyde, which gave a mixture of several compounds after deprotonation and reaction with chloromethyl methyl sulfide. The unsuccessful synthesis of compound **7** precluded a direct access to the flavor compound **2** upon base treatment (Scheme 1).

Alternatively, the *N-tert*-butylimine of crotonaldehyde **4** was used as a masked form, which proved to be easier to handle and more reliable than the reported *N*-cyclohexyl analogue in deconjugative α-alkylations (Kieczykowski et al., 1976; Takabe et al., 1975). Deprotonation of *N*-(2-buten-1-ylidene)*tert*-butylamine (**4**) with lithium diisopropylamide in THF at 0 °C (10 min) and then at -78 °C (30 min) produced the delocalized

## Scheme 1



γ-deprotonated intermediate which was reacted with the electrophile, i.e. chloromethyl methyl sulfide, at -78 °C to afford, after quenching with aqueous ammonium chloride, *N*-[(2-methylthio)methyl]-3-buten-1-ylidene-*tert*-butylamine (**5**) in essentially quantitative yield. This compound **5** isomerized in the conjugated enamine **6** upon treatment with catalytic potassium *tert*-butoxide in tetrahydrofuran for 2 weeks at room temperature. Preparative gas chromatographic analysis of the α-vinylaldehyde **5** resulted in a complete rearrangement in the conjugated compound **6**. The β,γ-unsaturated aldimine **5** was converted in one step into the flavor compound **2** by reaction with sodium acetate and acetic acid in ether at room temperature, during which the isomerization to the conjugated form and the imine hydrolysis took place (Scheme 1).

2-[(Methylthio)methyl]-2-butenal (**2**) was obtained as a mixture of *E* and *Z* isomers in a ratio of 15:85, respectively. The stereochemistry of compound **2** was established by NOE NMR experiments (<sup>1</sup>H NMR, 270 MHz, C<sub>6</sub>D<sub>6</sub>). Irradiation of the proton at C3 of the minor isomer resulted in a NOE at the methylene protons of the methylthiomethyl group, implicating *E* configuration for this minor isomer. The major isomer showed a NOE enhancement at the C4 methyl protons when irradiated at the methylene protons of the methylthiomethyl group, implicating *Z* configuration for this isomer.

Comparison between the spectral data of the isolated potato chip flavor **2** (Buttery, 1973) and our stereochemical studies (NOE experiments) suggests the *Z* configuration for the title flavor compound **2**.

In conclusion, a highly reproducible synthesis of the title flavor compound, which is of importance to potato chips, krill seasoning, roasted coffee, and yeast extracts, has been developed, making available this flavor compound in pure form for the first time according to a reaction sequence amenable to large scale production.

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