

Practical Synthesis of 3-Methylnonane-2,4-dione, an Intense Strawlike and Fruity Flavored Compound

Yasushi Kato and Yoshifumi Yuasa*

Technical Engineering Department, Fine Chemical Division, Takasago International Corporation, 1-5-1 Nishiyawata, Hiratsuka, Kanagawa 254-0073, Japan

A practical synthesis of 3-methylnonane-2,4-dione, which is an intense strawlike and fruity flavored compound, has been performed by the aldol condensation of *n*-hexanal and methyl ethyl ketone, followed by oxidation using sodium hypochlorite in the presence of 4-benzoyloxy-2,2,6,6-tetramethylpiperidine-*N*-oxide in an overall yield of 59%. The purification of 3-methylnonane-2,4-dione with high purity was performed via copper complexes.

Keywords: Aldol condensation; 3-methyl-4-hydroxy-2-nonanone; 3-methylnonane-2,4-dione; 4-benzoyloxy-2,2,6,6-tetramethylpiperidine-*N*-oxide; copper bis(3-methylnonane-2,4-dionate)

INTRODUCTION

3-Methylnonane-2,4-dione (**1**) has been found in reverted soybean oil (*1*). It has also been identified by aroma extract dilution analysis as one of the odorant compounds of the volatiles of green and black tea samples (*2*), and its odor threshold was reported to be low (0.007–0.0014 ng/L) in air (*1*). Recently, **1** was reported to strongly contribute to the reversion flavor and the strawlike and fruity flavor of oxidized soybean oil (*3*).

Previous synthetic methods for the preparation of **1** have been the condensation of *n*-caproic anhydride and methyl ethyl ketone in 64% yield with BF₃ gas (*4*, *5*) and the methylation of 2,4-nonanedione by methyl iodide and purification by preparative GC (*1*). However, these reported methods are considered to be unsuitable for economical and large-scale production. In contrast, the aldol condensation of aliphatic aldehydes and ketones, which produces a β -hydroxyketone, has been illustrated in many examples (*6*). The β -hydroxyketone produced by the aldol condensation can then be oxidized to the corresponding β -diketone with many oxidation reagents.

To develop a practical synthesis of **1**, we have studied this procedure and we now report a practical synthetic route to **1** that is an efficient, safe, and cost-effective process. Thus, **1** was obtained in high purity by the aldol condensation of *n*-hexanal and methyl ethyl ketone, followed by oxidation using sodium hypochlorite in the presence of 4-benzoyloxy-2,2,6,6-tetramethylpiperidine-*N*-oxide (BzOTEMPO) and purification of the copper complexes of the β -diketone.

MATERIALS AND METHODS

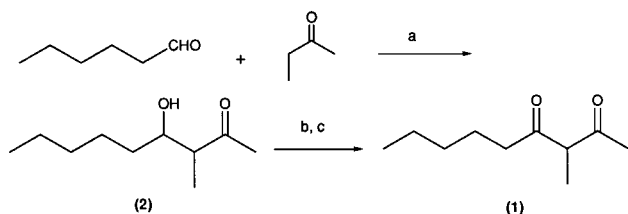
Chemicals. All reagents and solvents were obtained from Sigma-Aldrich Japan, Inc. (Tokyo, Japan), Wako Pure Chemical Industries, Ltd. (Tokyo, Japan), and Nacalai Tesque (Kyoto, Japan) and used without further purification.

* Author to whom correspondence should be addressed [telephone 81-(0)463-21-7150; fax 81-(0)463-23-1655; e-mail TIC00488@nifty.ne.jp].

Instruments. For determination of the melting points, a Yanagimoto micro melting apparatus was used, and the values are uncorrected. NMR spectra were obtained with a Bruker DRX-500. The ¹H and ¹³C NMR spectra were measured at 500 and 125 MHz, respectively, in CDCl₃ with tetramethylsilane (TMS) as the internal standard. The chemical shifts are given in δ (parts per million). The IR spectra were obtained with a Nicolet Avatar 360 FT-IR. Mass spectra (electronic impact) were obtained with a Hitachi M-80A mass spectrometer. GC analysis was performed with a Shimadzu GC-14A with an FID detector (column, Neutrabond-1, *df* = 0.15 μ m, 0.25 mm i.d. \times 30 m; carrier gas, N₂, 0.1 MPa; oven temperature, 100–200 °C programmed at 10 °C/min; injection temperature, 230 °C; detector temperature, 230 °C).

3-Methyl-4-hydroxy-2-nonanone (2). *n*-Hexanal (100 g, 1 mol) was added dropwise to the mixture of 2% aqueous sodium hydroxide (200 mL, 4 mol) and methyl ethyl ketone (288.5 g, 4 mol) at 20–25 °C for 8 h. The reaction mixture was stirred at the same temperature for 15 h, and the organic layer was separated and washed with a 5% NaCl solution. The solvent was removed under vacuum, and the residue was distilled under reduced pressure to give a threo/erythro mixture of 3-methyl-4-hydroxy-2-nonanone (**2**) (118.7 g, 69%). The purity was 93% (as threo/erythro mixture) by GC: bp 52–57 °C/0.2 Torr; IR (neat) 3446, 2933, 2860, 1705, 1420 cm⁻¹; ¹H NMR (threo/erythro mixture) 0.89 (t, *J* = 6.9 Hz, 3H), 1.06 and 1.07 (each t, *J* = 7.4 Hz, 3H), 1.22–1.53 (m, 6H), 2.19 and 2.20 (each s, 3H), 2.58–2.73 (m, 3H), 3.69 and 3.95 (each br s, 1H); ¹³C NMR (threo/erythro mixture) 10.33 (CH₃), 14.43 (CH₃), 14.62 (CH₃), 23.21 (CH₂), 23.23 (CH₂), 25.78 (CH₂), 26.33 (CH₂), 29.76 (CH₃), 30.41 (CH₃), 32.39 (CH₂), 32.41 (CH₂), 34.68 (CH₂), 35.15 (CH₂), 51.60 (CH), 52.86 (CH), 71.65 (CH), 74.05 (CH), 214.44 (C=O), 214.60 (C=O); MS, *m/z* 172 (100) (M⁺), 155 (70), 113 (7), 101 (26), 83 (15), 73 (89), 61 (19).

3-Methylnonane-2,4-dione (1). Sodium bicarbonate (11.7 g, 0.14 mol) and potassium bromide (6.91 g, 58 mmol) were dissolved in water (135 mL). 3-Methyl-4-hydroxy-2-nonanone (100 g, 0.581 mol) in dichloromethane (500 mL) and 4-benzoyloxy-2,2,6,6-tetramethylpiperidine-*N*-oxide (24.1 g, 87 mmol) were added to the solution at 5 °C. Sodium hypochlorite (2 mol/L; 864 mL, 1.74 mol) was added dropwise to the mixture at 5 °C for 1.5 h and stirred for an additional 30 min. Sodium sulfite (11 g, 87 mmol) was added to the mixture, and the organic layer was separated and then washed with water. The solvent was concentrated under vacuum, and the residue was distilled under reduced pressure to give 3-methylnonane-2,4-dione (84.2 g, 85%). The purity was 96% by GC. The distillate was dissolved in methanol (85 mL), and copper(II) acetate



Reagents: a) 2% NaOH aq. r.t., 24 h, 69%. b) 3 eq. 2N NaOCl, 15 mol% BzOTEMPO, KBr, NaHCO₃, CH₂Cl₂, 5 °C, 5 h, 85%. c) 0.6 eq. Cu(OAc)₂·H₂O, MeOH/H₂O, and then 10% H₂SO₄, 87%.

Figure 1. Synthetic route to 3-methylnonane-2,4-dione (**1**).

Table 1. Result of Aldol Condensation of *n*-Hexanal and Methyl Ethyl Ketone Using a Variety of Bases^a

base	conversion of <i>n</i> -hexanal ^b (%)	selectivity of 2 ^b (%)	yield of 2 ^c (%)
NaOH	95	79	69
KOH	79	86	67
Ba(OH) ₂	83	85	65
Na ₂ CO ₃	35	80	28

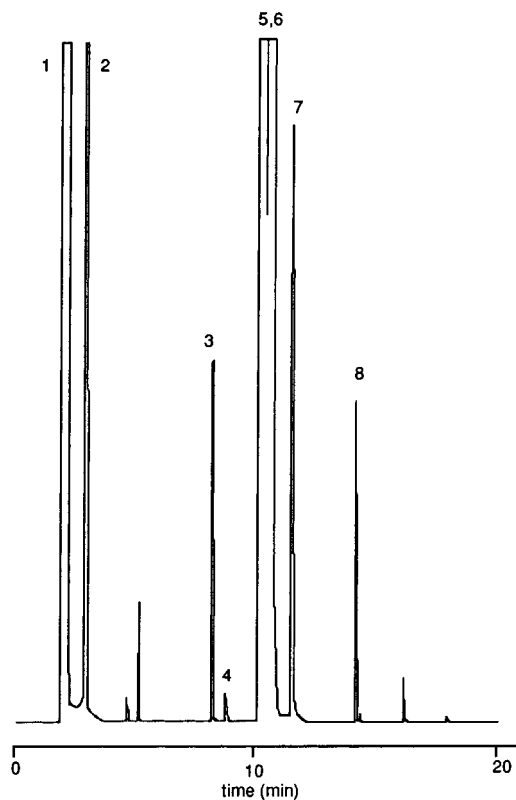
^a Reaction conditions: 10 mol % of 2% solution of base, 4 mol equiv of methyl ethyl ketone for *n*-hexanal; reaction temperature, 20–25 °C; reaction time, 8 h. ^b The conversion and selectivity of **2** were measured by GC. ^c The yield is shown as an isolated yield.

monohydrate (59 g, 0.296 mol) dissolved in water (500 mL) was added at 60 °C; the mixture was cooled to room temperature. The gray crystalline solid was filtered and washed with water (200 mL) and then with *n*-heptane (200 mL). The gray crystalline solid was recrystallized from 95% ethanol: mp 126–126.5 °C [lit. 122–124 °C (**5**)]; NMR data were not recorded because the measurement of the copper complex in CDCl₃ or DMSO-*d*₆ gave broad peaks; IR (CHCl₃) 2959, 2931, 1568, 1469, 1429 cm⁻¹; MS, *m/z* 403 (**5**) (M⁺ + 2), 401 (11) (M⁺), 233 (65), 231 (100), 161 (6), 134 (3), 99 (24), 43 (7).

The crystalline solid was suspended in toluene (300 mL), and a 10% sulfuric acid solution (274 g) was added dropwise at room temperature. The organic layer was separated and washed with water, and the solvent was removed in a vacuum. The residue was distilled under reduced pressure to give 3-methyl-2,4-nonanedione (72.6 g, 87%). The purity was 99% by GC, and the keto/enol isomer ratio was 60:40 by ¹H NMR: bp 57–59 °C/0.1 Torr [lit. 120–123 °C/20 Torr (**5**)]; IR (neat) 2957, 2933, 1726, 1702, 1604 cm⁻¹; ¹H NMR (keto/enol mixture) 0.83 (t, *J* = 7.2 Hz, 3H), 1.26 (d, *J* = 7.1 Hz, 3H), 1.18–1.31 (m, 5H), 1.50–1.58 (m, 3H), 1.79 (s, 2H), 2.07 and 2.13 (each s, 3H), 2.32–2.49 (m, 3H), 3.63 (q, *J* = 7.1, 14.2 Hz, 1H); ¹³C NMR (keto/enol mixture) 12.39 (CH₃), 12.54 (CH₃), 13.72 (CH₃), 13.78 (CH₃), 22.28 (CH₂), 22.34 (CH₂), 23.00 (CH₂), 23.26 (CH₃), 24.80 (CH₂), 28.35 (CH₃), 31.09 (CH₂), 31.45 (CH₂), 35.73 (CH₂), 41.55 (CH₂), 61.24 (CH), 104.25 (C), 190.12 (C), 193.39 (C), 204.98 (C=O), 207.19 (C=O); MS, *m/z* 170 (100) (M⁺), 99 (95), 71 (7).

RESULTS AND DISCUSSION

3-Methylnonane-2,4-dione (**1**) was synthesized via the route shown in Figure 1. Several inorganic bases were examined for the aldol condensation of *n*-hexanal and methyl ethyl ketone, and the best result was obtained when NaOH was used as the alkaline solution (Table 1). The aldol condensation of *n*-hexanal and methyl ethyl ketone was carried out in aqueous NaOH solution at room temperature for 8 h to give a threo and erythro mixture of 3-methyl-4-hydroxy-2-nonanone (**2**) with 95% conversion based on the *n*-hexanal and 79% selectivity (Table 1, run 1). With no water present, using only a methanol solvent, for example, 3-methyl-3-nonen-2-one (**4**) was predominantly produced. In this aldol condensation, the byproducts were 5-hydroxy-3-decanone (**3**), 3-methyl-3-nonen-2-one (**4**), 4-decen-3-one (**5**), and the



Peak No.	Compound
1	Methyl ethyl ketone
2	<i>n</i> -hexanal
3	(4)
4	(5)
5, 6	(2) threo/erythro isomer
7	(3)
8	<i>n</i> -hexanal dimer
others	unknowns

Figure 2. GC chromatogram of the aldol condensation of *n*-hexanal and methyl ethyl ketone.

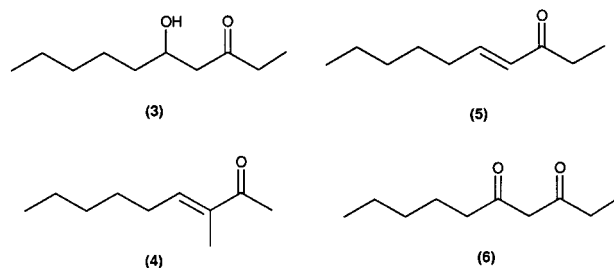


Figure 3. Byproducts of aldol condensation and oxidation.

n-hexanal dimer (Figures 2 and 3). These byproducts could not be isolated, but the structures were inferred on the basis of GC-MS. The major byproduct was **3**, and the ratio of **2** to **3** was 92:8. After the workup, the products were distilled under reduced pressure to give **2** with 93% purity in 69% yield. The threo/erythro ratio was 56:44 by NMR.

We next investigated the oxidation of **2** initially by the Swern oxidation (7 and references cited therein), but the yield was unsatisfactory at 36%. The Collins or Jones oxidation using chromium(VI) oxide was not examined due to environmental concerns. Although oxidation by sodium hypochlorite in the presence of 2,2,6,6-tetramethylpiperidine-*N*-oxide (TEMPO) is well-known (8, 9 and references cited therein), only a few

Table 2. Results of the Oxidation of 2 Using a Variety of Solvents and Catalysts^a

solvent	catalyst	conversion of 2 ^b (%)	selectivity of 1 ^b (%)	yield of 1 ^c (%)
CH ₂ Cl ₂	TEMPO	79	91	69
CH ₂ Cl ₂	BzOTEMPO	100	93	85
AcOEt	BzOTEMPO	69	88	58
toluene	TEMPO	57	79	43
toluene	BzOTEMPO	55	63	31

^a Reaction conditions: 10 mol % of 2% NaHCO₃aq, 4 equiv mol of KBr for **2**; reaction temperature, 5 °C; reaction time, 2 h. ^b The conversion and selectivity of **1** were measured by GC. ^c The yield is shown as an isolated yield.

examples of the oxidation of β -hydroxyketones via this method have been reported, and we therefore tried this oxidant. Thus, **2** and 15 mol % of TEMPO were added to a mixture of 2% NaHCO₃ and 10 mol % of an aqueous KBr solution, and then 2 mol/L sodium hypochlorite was added dropwise at 5 °C. The reaction mixture was checked by GC, and the conversion and selectivity were 79 and 91%, respectively (Table 2, run 1). The effects of different TEMPO reagents and solvent are shown in Table 2. The best result was obtained using 4-benzoyloxy-2,2,6,6-tetramethyl-piperidine-*N*-oxide (BzOTEMPO) and dichloromethane as the solvent. In this oxidation, 3,5-decanedione (**6**), which would come from **3**, was not detected by GC-MS; it was probably easily chlorinated by sodium hypochlorite. After workup, the products were distilled under reduced pressure to give **1** with 96% purity in 85% yield.

To obtain **1** in high purity, the distillate was treated with a 0.6 mol equiv of copper acetate monohydrate to give a quantitative yield of copper bis(3-methylnonane-2,4-dionate) (**5**). The crystalline solid was treated with 10% sulfuric acid to decompose the complex, and a simple distillation afforded 99% purity of **1** in 87% yield. **1** was found to be a mixture of the keto/enol tautomers, and the ratio was 60:40 by NMR.

LITERATURE CITED

- (1) Guth, H.; Grosch, W. 3-Methylnonane-2,4-dione—An intense odour compound formed during flavour reversion of soybean oil. *Fat Sci. Technol.* **1989**, *91*, 225–230.
- (2) Guth, H.; Grosch, W. Identification of potent odourants in static headspace samples of green and black tea powders on the basis of aroma extract dilution analysis (AEDA). *Flavour Fragrance J.* **1993**, *8*, 173–178.
- (3) Kao, J.-W.; Wu, X.; Hammond, E. G.; White, P. J. The impact of furanoid fatty acids and 3-methylnonane-2,4-dione on the flavor of oxidized soybean oil. *J. Am. Oil Chem. Soc.* **1998**, *75*, 831–835.
- (4) Hauser, C. R.; Adams, T. The acylation of certain unsymmetrical aliphatic ketones with acetic anhydride in the presence of boron trifluoride. *J. Am. Chem. Soc.* **1944**, *66*, 345–349.
- (5) Adams, J. T.; Hauser, C. R. The arylation of ketones with aliphatic anhydrides by means of boron trifluoride. Synthesis of β -diketones. *J. Am. Chem. Soc.* **1945**, *67*, 284–286.
- (6) Nielsen, A. T.; Houlihan, W. J. The aldol condensations. In *Organic Reactions*; Adams, R., et al., Eds.; Wiley: New York, 1968; Vol. 16.
- (7) Mancuso, A. J.; Swern, D. Activated dimethyl sulfoxide: Useful reagents for synthesis. *Synthesis* **1981**, 165–185.
- (8) Anelli, P. L.; Banfi, S.; Montanari, F.; Quici, S. Oxidation of diols with alkali hypochlorites catalyzed by oxammonium salts under two-phase conditions. *J. Org. Chem.* **1989**, *54*, 2970–2972.
- (9) de, Nooy, A. E. J.; Besemer, A. C.; van Bekkum, H. On the use of stable organic nitroxyl radicals for the oxidation of primary and secondary alcohols. *Synthesis* **1996**, 1153–1174.

Received for review January 24, 2001. Revised manuscript received May 18, 2001. Accepted May 18, 2001.

JF0100954