734 *J. Org. Chem.* **1997,** *62,* 734−735

Hydrolysis of β,γ-Unsaturated Aldehyde Dimethylhydrazones with Copper Dichloride: A New Synthesis of Lavandulol†

Takashi Mino, Satoru Fukui, and Masakazu Yamashita*

Department of Molecular Science and Technology,
Faculty of Engineering, Doshisha University,
Tanabe, Kyoto 610-03, Japan

Received July 12, 1996

Lavandulol (**1**), a constituent of lavender oil,[1] possesses an unusual monoterpene skeleton and is used as an important additive in the perfume industry. This compound has also been isolated as a defensive pheromone of the red-lined carrion beetle.[2] Because of its importance, several syntheses of this compound have been reported.[3] However, these have required a complicated starting material[3b] or employed reaction of low regioselectivity.[3f]

In this paper, we wish to report on a new and convenient synthesis of lavandulol (**1**) by regioselective alkylation of 3-methyl-2-butenal dimethylhydrazone (**3**) with 1-bromo-3-methyl-2-butene and hydrolysis of the product, 2-isopropenyl-5-methyl-4-hexenal dimethylhydrazone (**4**), with copper dichloride without double bond migration from β,γ to α,β (Scheme 1). We also report additional examples of this mild hydrolysis procedure.

3-Methyl-2-butenal dimethylhydrazone (**3**) was easily prepared in 86% yield from 3-methyl-2-butenal (**2**) and *N*,*N*-dimethylhydrazine by using trifluoroacetic acid as a catalyst. After deprotonation of the dimethylhydrazone **3** with lithium diisopropylamide (LDA) in THF, the azaenolate of **3** was alkylated by 1-bromo-3-methyl-2-butene to give 2-isopropenyl-5-methyl-4-hexenal dimethylhydrazone (**4**) in 65% yield.[4] 2-Isopropenyl-5-methyl-4-hexenal (**5**) was obtained from the dimethylhydrazone **4** in 68% yield by hydrolysis in the presence of copper dichloride.[5] Reduction of **5** with sodium borohydride gave lavandulol (**1**) in 66% yield.

In this synthesis, one of the key steps is the hydrolysis of the dimethylhydrazone **4**. Although a variety of methods, such as using MMPP (magnesium monoperphthalate hexahydrate),[6] are available for the cleavage of ketone dimethylhydrazones,[7] few are satisfactory when applied to aldehyde dimethylhydrazones.

Scheme 1

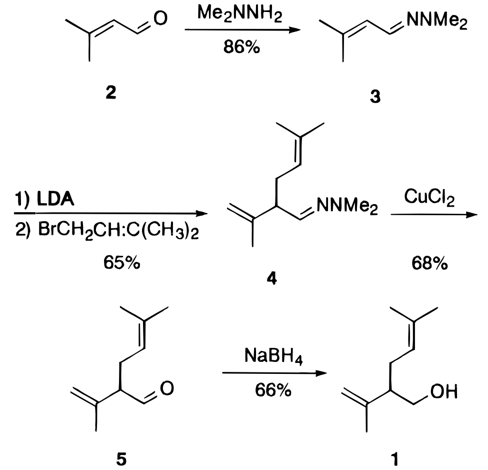
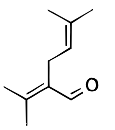
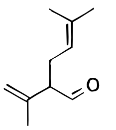
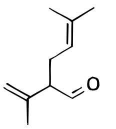
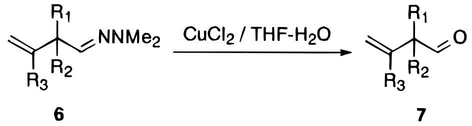


Table 1. Hydrolysis of Dimethylhydrazone 4

Entry	Condition	Product		yield / %[a]
1	1N-HCl aq., r.t.		**8**	23
2	1N-HCl aq.,0 °C		**5**	16
3	$CuCl_2$ aq., r.t.		**5**	68

[a] Isolated yield.

Scheme 2



R_1 : Alkyl
R_2 : H or Me
R_3 : H or Alkyl

We investigated the hydrolysis of 2-isopropenyl-5-methyl-4-hexenal dimethylhydrazone (**3**) under various conditions. Hydrochloric acid, which was previously used at room temperature in the synthesis of **7h**,[4] caused double-bond migration from β,γ to α,β in the case of **4** (entry 1, Table 1). At 0 °C (entry 2, Table 1), aldehyde **5** was found from **4** without double bond migration, but the yield was only 16%. On the other hand, when copper dichloride was used at room temperature, aldehyde **5** was obtained in good yield (entry 3, Table 1).

To test the generality of the method, various β,γ-unsaturated aldehyde dimethylhydrazones **6** were examined (Scheme 2). The results are listed in Table 2.

---

† Dedicated to Prof. Yoshito Kishi on the occasion of his 60th birthday.

(1) (a) Schinz, H.; Seidel, C. F. *Helv. Chim. Acta* **1942**, *25*, 1572. (b) Schinz, H.; Bourquin, J. P. *Helv. Chim. Acta* **1942**, *25*, 1591. (c) Bohlmann, F.; Zdero, C.; Faass, U. *Chem. Ber.* **1973**, *106*, 2904.

(2) Eisner, T.; Deyrup, M.; Jacobs, R.; Meinwald, J. *J. Chem. Ecol.* **1986**, *12*, 1407.

(3) (a) Schinz, H.; Schäppi, G. *Helv. Chim. Acta* **1947**, *30*, 1483. (b) Bertrand, M.; Gil, G.; Viala, J. *Tetrahedron Lett.* **1977**, 1785. (c) Ueno, Y.; Aoki, S.; Okawara, M. *J. Chem. Soc., Chem. Commun.* **1980**, 683. (d) Cookson, R. C.; Mirza, N. A. *Synth. Commun.* **1981**, *11*, 299. (e) Babin, D.; Fourneron, J. D.; Harwood, L. M.; Julia, M. *Tetrahedron* **1981**, *37*, 325. (f) Majewski, M.; Mpango, G. B.; Thomas, M. T.; Wu, A.; Snieckus, V. *J. Org. Chem.* **1981**, *46*, 2029. (g) Kramer, A.; Pfander, H. *Helv. Chim. Acta* **1982**, *65*, 293. (h) Takano, S.; Tanaka, M.; Seo, K.; Hirama, M.; Ogasawara, K. *J. Org. Chem.* **1985**, *50*, 931. (i) Celebuski, J.; Rosenblum, M. *Tetrahedron* **1985**, *41*, 5741. (j) Julia, M.; Schmitz, C. *Bull. Soc. Chim. Fr.* **1986**, 630. (k) Cardillo, G.; D'Amico, A; Orena, M.; Sandri, S. *J. Org. Chem.* **1988**, *53*, 2354. (l) McCullough, D. W.; Bhupathy, M.; Piccolino, E.; Cohen, T. *Tetrahedron* **1991**, *47*, 9727. (m) Piva, O. *J. Org. Chem.* **1995**, *60*, 7879.

(4) Yamashita, M.; Matsumiya, K.; Nakano, K. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 1759.

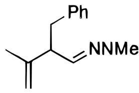
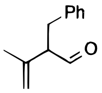
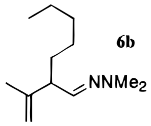
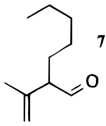
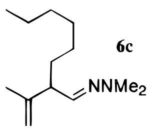
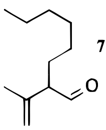
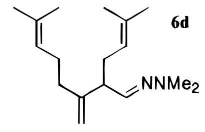
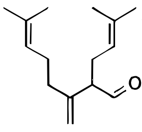
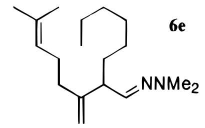
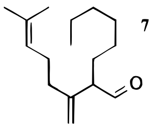
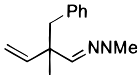
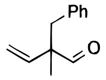
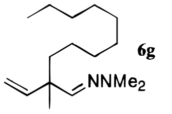
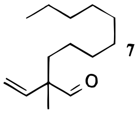
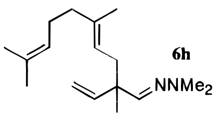
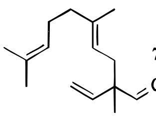
(5) To our knowledge, the hydrolysis of aldehyde dimethylhydrazone with copper dichloride was only applied to the cyclohexanecarboxaldehyde dimethylhydrazone and cinnamaldehyde dimethylhydrazone.[9]

(6) Enders, D.; Plant, A. *Synlett* **1990**, 725.

(7) Greene, T. W.; Wuts, P. G. M. In *Protective Groups in Organic Synthesis*; John Wiley & Sons, Inc.: New York, 1991; p 212 and references cited therein.

S0022-3263(96)01324-2 CCC: $14.00

Table 2. Hydrolysis of Dimethylhydrazone 6 with $CuCl_2$

Entry	Dimethylhydrazone **6**		Aldehyde **7**		Yield / %[a]
1		**6a**		**7a**	56
2		**6b**		**7b**	58
3		**6c**		**7c**	63
4		**6d**		**7d**	68
5		**6e**		**7e**	63
6		**6f**		**7f**	82
7		**6g**		**7g**	89
8		**6h**		**7h**	86 (76)[b]

[a] Isolated yield. [b] Value in parentheses is the yield using hydrochloric acid.

After workup and purification by flash column chromatography, β,γ-unsaturated aldehydes **7** were obtained in acceptable to good yields without double bond migration (entries 1−5, Table 2). As shown in entry 8 (Table 2), the copper dichloride method is more useful than the hydrochloric acid method even for the hydrolysis of β,γ-unsaturated aldehyde hydrazones, which have a quaternary carbon atom at the α-position.

Experimental Section

General Procedures. ^1H and ^{13}C NMR spectra were taken (at 400 MHz or 60 MHz) in $CDCl_3$ solvent and recorded in parts per million (ppm, δ) downfield from internal tetramethylsilane (Me_4Si). Column chromatography was performed on silica gel 60 (230−400 mesh), and thin-layer chromatography (TLC) was performed on silica gel 60 plates F_{254}. THF was dried and deoxygenated by distillation from potassium−benzophenone under an argon atmosphere just before use. Copper dichloride and sodium borohydride were commercial reagents of the highest available purity. Hydrazones **3**, **4**, and **6** were prepared according to methods reported previously.[4,8]

Hydrolysis of Dimethylhydrazone 4 with Hydrochloric Acid. To a solution of aqueous 1 N HCl (15 mL) was added a solution of hydrazone **4** (0.97 g, 5.0 mmol) in THF (15 mL) at room temperature. After being stirred for 8 h at room temperature, the reaction mixture was quenched with saturated $NaHCO_3$ (aq), diluted with ether, washed with brine, and dried over $MgSO_4$. Removal of solvents and column chromatography gave 2-isopropylidene-5-methyl-4-hexenal (**8**) (23%, 0.17 g, 1.11 mmol): IR (neat) 1670 (C=O) cm^{-1}; ^1H NMR (60 Mz, $CDCl_3$) δ 1.70 (s, 6H), 2.00 (s, 3H), 2.20 (s, 3H), 2.80−3.10 (m, 2H), 4.70−5.10 (m, 1H), 9.62−9.82 (m, 1H); MS *m/z* 152 (M^+, 74). Anal. Calcd for $C_{10}H_{16}O$: C, 78.90; H, 10.59. Found: C, 78.67; H, 10.59.

General Procedure for the Hydrolysis of Dimethylhydrazones with $CuCl_2$. To a solution of $CuCl_2$ (1.1 mmol, 0.15 g) in water (10.0 mL) was added a solution of hydrazone **4** or **6** (1.0 mmol) in THF (15 mL) at room temperature. After being stirred for 2.5 h at room temperature, the reaction mixture was quenched with aqueous 3 N NH_4OH, diluted with ethyl acetate, washed with brine, and dried over $MgSO_4$. Removal of the solvents and column chromatography gave the pure aldehyde **5** or **7**.

2-Isopropenyl-5-methyl-4-hexenal (5): IR (neat) 1742 (C=O) cm^{-1}; ^1H NMR (60 Mz, $CDCl_3$) δ 1.52 (s, 3H), 1.68 (s, 3H), 1.75 (s, 3H), 2.10−2.61 (m, 2H), 2.82−2.89 (m, 1H), 4.89 (s, 1H), 4.90−5.25 (m, 2H), 9.48 (s, 1H); ^{13}C NMR (100 Mz, $CDCl_3$) δ 17.88, 21.27, 25.74, 25.99, 60.69, 115.34, 120.64, 133.67, 140.27, 201.26; MS *m/z* 152 (M^+, 12). Anal. Calcd for $C_{10}H_{16}O$: C, 78.90; H, 10.59. Found: C, 79.04; H, 10.74.

2-Benzyl-3-methyl-2-hexenal (7a): IR (neat) 1722 (C=O) cm^{-1}; ^1H NMR (60 Mz, $CDCl_3$) δ 1.70 (s, 3H), 2.63−3.08 (m, 1H), 3.10−3.42 (m, 2H), 4.78 (s, 1H), 5.08 (s, 1H), 7.02−7.44 (br, 5H), 9.52 (s, 1H); ^{13}C NMR (100 Mz, $CDCl_3$) δ 21.36, 33.42, 62.03, 116.16, 126.31, 128.43, 128.84, 139.05, 139.74, 200.19; MS *m/z* 174 (M^+, 10). Anal. Calcd for $C_{12}H_{14}O$: C, 82.72; H, 8.10. Found: C, 82.58; H, 8.10.

Lavandulol (1). To a solution of aldehyde **5** (1.0 mmol, 0.152 g) in 10.0 mL of EtOH was added a solution of sodium borohydride (0.50 mmol, 0.02 g) in 1.0 mL of EtOH at room temperature. After 4 h, the reaction mixture was quenched with water, diluted with ethyl acetate, washed with brine, and dried over $MgSO_4$. After removal of the solvent, the residue was purified by silica gel column chromatography to give lavandulol (**1**) (0.66 mmol, 0.10 g, 66%): IR (neat) 3370 (OH) cm^{-1}; ^1H NMR (60 Mz, $CDCl_3$) δ 1.52 (br, 1H), 1.62 (s, 3H), 1.75 (s, 6H), 1.92−2.48 (m, 3H), 3.45−3.63 (m, 1H), 4.83 (s, 1H), 4.94 (s, 1H); MS *m/z* 136 ($M^+ - H_2O$, 8); TMS ether MS *m/z* 226 (M^+, 23).

Registry numbers provided by the author: 1, 1845-51-8; **3**, 16713-48-7; **4**, 119045-78-2; **5**, 75697-98-2; **7a**, 66730-46-9; **7f**, 68620-37-1; **7h**, 119045-67-9; **8**, 3304-28-7.

Supporting Information Available: Characterization data of compounds **7b−h** and copy of ^{13}C NMR spectra of **7f** (3 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO9613242

---

(8) Mino, T.; Yamashita, M. *J. Org. Chem.* **1996**, *61*, 1159.

(9) Corey, E. J.; Knapp, S. *Tetrahedron Lett.* **1976**, 3667.