ORIGINAL

α -Alkylation of α, β -Unsaturated Ketones *via* *N, N*-Dimethylhydrazones*

New Synthesis of Dihydrojasmone and *cis*-Jasmone

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The alkylation of 3-methyl-2-cyclopenten-1-one *N, N*-dimethylhydrazone was investigated and was found to occur at the α -position of the α, β -unsaturated moiety of the hydrazone exclusively. By this method, dihydrojasmone and *cis*-jasmone were prepared in good yield.

Isophorone dimethylhydrazone was also alkylated at the α -position, but for ionone dimethylhydrazone, the reaction occurred at the α' -position (methyl carbon), not the α -position of the hydrazone.

1 Introduction

Cyclopentenone derivatives are very important compounds for fine chemical industry in order to produce agrochemicals, perfumes and pharmaceuticals. Undiminished efforts have been devoted to the syntheses of them. In the perfume industry, dihydrojasmone (1) and *cis*-jasmone (2), possessing the cyclopentenone structural unit, are significant raw materials. Many synthetic methods for their preparation have been reported¹⁾. However, base-catalyzed cyclization of 1,4-diketones such as 2,5-undecanedione and *cis*-8-undecene-2,5-dione is a general procedure. There have been few reports on the syntheses of (1) and (2) by α -alkylation of 3-methyl-2-cyclopenten-1-one (5), which is easily prepared from 2,5-hexanedione²⁾. In this paper, we wish to report a new synthesis of dihydrojasmone (1) and *cis*-jasmone (2) by the α -alkylation of (5) *via* *N, N*-dimethylhydrazone (6), and α -alkylation of the other components of essential oils such as isophorone and β -ionone, possessing α, β -unsaturated carbonyl moiety.

2 Results and Discussion

An approach to the synthesis of dihydrojasmone (1) is illustrated in **Scheme-1**. 3-Methyl-

2-cyclopenten-1-one (5), readily prepared from 2,5-hexane dione with base by means of intramolecular aldol condensation, reacted with *N, N*-dimethylhydrazine using trifluoroacetic acid as a catalyst by azeotropic distillation with benzene to give the corresponding hydrazone (6) in 84 % yield. NMR spectrum of (6) shows an olefinic methyl at 1.97 ppm, two methyl groups of hydrazone at 2.51 ppm and an olefinic proton at 6.02 and 6.43 ppm, respectively, suggesting the mixture of *syn* and *anti* isomers in the ratio of 1 : 2 or 2 : 1 by ¹H-NMR integral ratio of (6). To a lithium salt of the hydrazone (6), prepared from (6) (mixture of *syn* and *anti* isomers) and 1 equiv. of butyllithium in THF at -5°C, 1-iodopentane was added to give the 3-methyl-2-pentyl-2-cyclopenten-1-one dimethylhydrazone (7) in 56 % yield, which was readily converted to dihydrojasmone (1) by hydrolysis in 71 % yield. The compound (1) was identified by comparison of IR, NMR and mass spectra with those of an authentic sample. The results of alkylation of the hydrazone (6) with the other pentyl halides and tosylate were listed in **Table-1**.

The synthetic route of dehydrojasmone (3) is shown in **Scheme-2**. In a similar manner, treatment of the hydrazone (6) with 1 equiv. of *n*-butyllithium in THF at -5°C, followed by the addition of 3-bromo-1-propyne gave 3-methyl-2-(2-propynyl)-2-cyclopenten-1-one dimethylhy-

* Organic synthesis *via* dialkylhydrazones, Part 3. For Part 2, see *J. Jpn. Oil Chem. Soc. (Yukagaku)*, **35**, 1041 (1986)

Scheme-1

Table-1 Alkylation of the hydrazone (6) using pentyl halides and tosylate.

$\text{CH}_3(\text{CH}_2)_4\text{X}$	Yield (%) ^{a)}
I	56
Br	45
Cl	27
$\text{OTs}^{\text{b)}$	21

a) Isolated yield, b) $\text{Ts} = p\text{-CH}_3\text{C}_6\text{H}_4\text{SO}_2\text{-}$

drazone (8) in 25 % yield. Furthermore, deprotonation of (8) with 1 equiv. of butyllithium in THF at -5°C followed by treatment with iodoethane afforded 3-methyl-2-(2-pentynyl)-2-cyclopenten-1-one dimethylhydrazone (9) in 47 % yield, which was hydrolyzed under acidic condition to provide the desired dehydrojasnone (3) in 33 % yield. The product (3) was identified by IR, NMR and mass spectra. Partial hydrogenation of (3) to *cis*-jasnone (2) using Lindlar catalyst has been reported previously³⁾.

As mentioned above, judging from the NMR spectra, the hydrazone (6) was the mixture of *syn* and *anti* isomers. But the alkylation reaction occurred regioselectively at α -carbon atom of (6)

to form the α -alkylated hydrazones. The isomer which was expected to be alkylated at α' -carbon was not detected by TLC. This shows that the alkylation of (6) afforded α -alkylated hydrazones selectively starting from the *syn-anti* mixture of (6). Similar results were obtained in the alkylation of alkyl methyl ketone *N,N*-dimethyl hydrazone⁴⁾.

The procedure of regioselective α -alkylation as described above was also utilized for the synthesis of allethron (11) (Scheme-3). Treatment of the hydrazone (6) with butyllithium in THF at -5°C , followed by allylation with allyl bromide, resulted in the formation of (10) in 57 % yield. Hydrolysis of (10) with 1 mol·dm⁻³ hydrochloric acid gave allethron (11) in 54 % yield.

As shown in Scheme-4, isophorone (12), one of the α,β -unsaturated ketones possessing six-membered ring structure, also was α -alkylated by a sequence of reactions similar to synthesis of dihydrojasnone (1). To the THF solution of isophorone dimethylhydrazone (13), prepared from isophorone (12) and *N,N*-dimethylhydrazine in 98 % yield, was added 1 equiv. of butyllithium, followed by 1-iodopentane to pro-

Scheme-2

Scheme-3

Scheme-4

Scheme-5

vide the corresponding pentylated hydrazone, which was readily converted to 3,5,5-trimethyl-2-pentyl-2-cyclohexen-1-one (14) after hydrolysis in 12 % yield from (13)⁵.

On the other hand, β -ionone dimethylhydrazone (16), synthesized from β -ionone (15) by the same method described above in 88 % yield, was allowed to react with 1 equiv. of butyllithium in THF at -5°C , followed by iodomethane, to give the corresponding methylated hydrazone, which was readily converted to 1-(2,6,6-trimethyl-1-cyclohexenyl)-1-penten-3-one (17) after hydrolysis in 62 % yield from (16) (Scheme-5). In contrast to the alkylation reaction above-mentioned, this reaction occurred at α' -position instead of α -position of the hydrazone (16).

3 Experimental

The IR spectra were recorded on a Hitachi 260-10 Infrared Spectrophotometer. The NMR spectra were obtained with a Hitachi R-600 FT-NMR Spectrometer at 60 MHz, using tetramethylsilane ($\delta=0.00$ ppm) as an internal standard. Chemical shifts are given in ppm unit. The mass spectra (MS) were determined on a Hitachi

RM-50 GC-MS spectrometer. The analytical gas chromatography was carried out on a Yanagimoto G-8 gas chromatograph with a column of 10 % silicone gum SE-30 on Chromosorb. The preparative thin-layer chromatography (TLC) was performed on Merck Kieselgel 60 PF₂₅₄. All the yields are isolated ones unless otherwise noted.

3.1 Materials

Tetrahydrofuran (THF) was dried by distillation from lithium aluminum hydride under argon just before use. Ethanol and hexane were distilled over CaCl_2 . Benzene and methanol were used without further purification unless otherwise noted. Iodomethane, iodoethane, 1-iodopentane, 1-bromopentane, 1-chloropentane, 3-bromo-1-propyne, allyl bromide, 2,5-hexanedione, isophorone and β -ionone were all commercial products of the highest available purity. Pentyl *p*-toluenesulfonate was prepared from pentanol and *p*-toluenesulfonyl chloride. *N,N*-Dimethylhydrazine and trifluoroacetic acid were used without further purification. Butyllithium in hexane was also a commercial product and was titrated with 2-butanol using *o*-phenanthroline as an indicator just before use.

3·2 3-Methyl-2-cyclopenten-1-one (5).

The mixture of 2 % aqueous NaOH (15 mL), ethanol (20 mL) and 2,5-hexanedione (2.4 mL, 20 mmol) was refluxed for 3 h. After cooling to room temperature, the reaction mixture was extracted with ethyl acetate. The organic layer was washed with brine and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the residual liquid was distilled to give (5) (1.18 g, 62 % yield); Kugelrohr dist: bath temp. 150°C/22 Torr; NMR (CDCl₃) δ : 2.18 (3 H, d, CH₃), 2.35 (4 H, m, CH₂CH₂), 5.97 (1 H, q, =CH-); IR (neat): 1705, 1625, 1190, 970 cm⁻¹; MS m/z (%): 96 (M⁺, 100), 95 (29), 81 (40), 67 (43), 53 (38).

3·3 Preparation of 3-Methyl-2-cyclopenten-1-one Dimethylhydrazone (6).

The mixture of (5) (9.53 mmol), *N,N*-dimethylhydrazine (1.5 mL, 20 mmol), trifluoroacetic acid (0.04 mL, 0.5 mmol) and benzene (15 mL) was placed in a flask equipped with trap to remove water and heated under reflux for 6 h, followed by cooling to room temperature. To the reaction mixture was added NaCl aq, and the mixture was extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate. After removing the solvent *in vacuo*, the residue obtained was distilled by Kugelrohr to give the hydrazone (6) (1.1 g, 84 % yield); NMR (CDCl₃) δ : 1.96 (3 H, d, CH₃), 2.52 [6 H, s, N(CH₃)₂], 2.28-2.95 (4 H, m, CH₂CH₂), 6.02 and 6.43 (1 H, m, =CH-); IR (neat): 1630, 1190, 1155, 980, 970 cm⁻¹; MS m/z (%): 138 (M⁺, 100), 123 (22), 94 (20), 67 (21), 44 (62).

3·4 3,5,5-Trimethyl-2-cyclohexen-1-one Dimethylhydrazone (13).

NMR(CDCl₃) δ : 0.95 (3 H, s, CCH₃), 0.97 (3 H, s, CCH₃), 1.85 (3 H, d, =CCH₃), 2.48 [6 H, s, N(CH₃)₂], 2.00-2.70 (4 H, m, other CH₂), 6.00 and 6.57 (1 H, m, =CH-); IR (neat) 1640, 1595, 1160, 1135, 1025 cm⁻¹; MS m/z : 180 (M⁺).

3·5 1-(2,6,6-Trimethyl-1-cyclohexenyl)-1-buten-3-one Dimethylhydrazone (16).

NMR(CDCl₃) δ : 1.06 [6 H, s, C(CH₃)₂], 1.20-1.28 (2 H, m, CH₂), 1.54 (4 H, d, other CH₃), 1.73 (3 H, s, =CCH₃), 2.13 (3 H, s, N=CCH₃), 2.50 (3 H, s, NCH₃), 2.56 (3 H, s, NCH₃), 6.12 (1 H, d, =CH-), 6.60 (1 H, d,

=CH-); IR (neat): 1620, 1580, 1210, 1155, 1030, 980 cm⁻¹; MS m/z (%): 234 (M⁺, 10), 219 (67), 91 (54), 77 (48), 41 (100).

3·6 Representative Synthesis of 3-Methyl-2-pentyl-2-cyclopenten-1-one Dimethylhydrazone (7).

To the THF (20 mL) solution of the hydrazone (6) (6.6 mmol) was added dropwise with stirring *n*-butyllithium (7.7 mmol) *via* syringe at -5°C under argon atmosphere. After standing the mixture for 1 h, 1-iodopentane (7.0 mmol) was added. The mixture was stirred for 24 h at room temperature, added to NaCl aq, and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, filtered, and evaporated *in vacuo*. The preparative TLC of the crude residue (hexane-ethyl acetate 10:1) afforded pure product (7) (0.611 g, 56 %); NMR(CDCl₃) δ : 0.92 (3 H, t, CH₂CH₃), 1.25-1.64 [6 H, m, -(CH₂)₃-], 1.91 (3 H, s, CH₃), 2.53 [6 H, s, N(CH₃)₂], 2.10-2.75 (6 H, m, other methylene); IR (neat): 1740, 1615, 1085, 1020, 970 cm⁻¹; MS m/z (%): 208 (M⁺, 80), 193 (17), 179 (15), 165 (23), 152 (100).

3·7 3-Methyl-2-(2-propynyl)-2-cyclopenten-1-one Dimethylhydrazone (8).

NMR(CDCl₃) δ : 1.94 (1 H, t, $\equiv$ CH), 2.02 (3 H, s, CH₃), 2.30-2.75 (4 H, m, CH₂CH₂), 2.52 [6 H, s, N(CH₃)₂], 3.24 (2 H, broad s, -CH₂C $\equiv$); MS m/z : 176 (M⁺).

3·8 3-Methyl-2-(2-pentynyl)-2-cyclopenten-1-one Dimethylhydrazone (9).

NMR(CDCl₃) δ : 1.10 (3 H, t, CH₂CH₃), 2.13 (3 H, s, CH₃), 2.32 (6 H, m, other proton), 2.53 [6 H, s, N(CH₃)₂], 3.22 (2 H, broad s, -CH₂C $\equiv$); MS m/z : 204 (M⁺).

3·9 3-Methyl-2-(2-propenyl)-2-cyclopenten-1-one Dimethylhydrazone (10).

NMR(CDCl₃) δ : 1.92 (3 H, s, CH₃), 2.00-2.80 (4 H, m, CH₂CH₂), 2.54 [6 H, s, N(CH₃)₂], 3.08 (2 H, d, =CCH₂C=), 4.88-5.21 (2 H, m, =CH₂), 5.65-6.20 (1 H, m, =CH-); IR (neat): 1700, 1620, 1185, 1150, 1085, 1015, 995, 960, 905 cm⁻¹; MS m/z : 178 (M⁺).

3·10 Dihydrojasmane (1).

The hydrazone (7) (1.0 mmol) was refluxed in the mixture of 1 mol·dm⁻³ hydrochloric acid (10 mL) and methanol (10 mL) for 2 h. After cooling to room temperature, the organic material was extracted with ethyl acetate. The organic

layer was washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residual liquid was purified by preparative TLC (hexane-ethyl acetate 10:1) to afford dihydrojasnone (1) (0.118 g) in 71 % yield. This compound was identified by comparison of IR, NMR, and mass spectra with those of an authentic sample. NMR (CDCl_3) δ : 0.90 (3 H, t, CH_2CH_3), 1.10-1.80 [6 H, m, $(\text{CH}_2)_4$], 2.07 (3 H, s, CH_3), 2.07 (2 H, t, $=\text{CCH}_2-$), 2.33-2.60 (4 H, m, CH_2CH_2); IR (neat): 1700, 1650, 1185, 1080 cm^{-1} ; MS m/z (%): 166 (M^+ , 26), 151 (55), 137 (25), 123 (21), 110 (100).

3-11 Dehydrojasnone (3).

NMR(CDCl_3) δ : 1.10 (3 H, t, CH_2CH_3), 2.19 (3 H, s, CH_3), 2.05-2.57 (6 H, m, other methylene), 3.10 (2 H, broad s, $=\text{CCH}_2\text{C}\equiv$); MS m/z : 162 (M^+).

3-12 Allethrene (11).

NMR (CDCl_3) δ : 2.08 (3 H, s, CH_3), 2.30-2.63 (4 H, m, CH_2CH_2), 2.98 (2 H, d, $=\text{CCH}_2-$), 4.80-5.14 (2 H, m, $=\text{CH}_2$), 5.50-6.05 (1 H, m, $=\text{CH}-$); IR (neat): 1695, 1640, 1190, 1075, 1000, 920 cm^{-1} ; MS m/z (%): 136 (M^+ , 100), 121 (55), 92 (43), 88 (50), 86 (29).

3-13 3,5,5-Trimethyl-2-pentyl-2-cyclohexen-1-one (14).

The similar procedures as described above in the synthesis of the compound (7) or (1) were successively carried out in a one-pot to give (14) in 12 % yield from the hydrazone (13). NMR (CDCl_3) δ : 1.02 [6 H, s, $\text{C}(\text{CH}_3)_2$], 1.02 (3 H, t, CH_2CH_3), 1.18-1.83 [6 H, m, $(\text{CH}_2)_3$], 1.93 (3 H, s, $=\text{CCH}_3$), 2.24 (2 H, t, $=\text{CCH}_2\text{CH}_2$), 2.24 (4 H, s, other CH_2); IR (neat): 1670, 1635, 1195, 1150, 1105, 1015 cm^{-1} ; MS m/z (%): 208 (M^+ , 30), 193 (96), 152 (43), 109 (65), 96 (100).

3-14 1-(2,6,6-Trimethyl-1-cyclohexenyl)-1-penten-3-one (17).

The similar methods as described above in the

preparation of the compound (7) or (1) were continuously carried out in a one-pot to afford (17) in 62 % yield from the hydrazone (16). NMR(CDCl_3) δ : 1.05 [6 H, s, $\text{C}(\text{CH}_3)_2$], 1.12 (3 H, t, CH_2CH_3), 1.20-1.50 [6 H, m, $(\text{CH}_2)_3$], 1.75 (3 H, s, $=\text{CCH}_3$), 2.60 (2 H, q, COCH_2), 6.12 (1 H, d, $=\text{CH}-$), 7.35 (1 H, d, $=\text{CH}-$); IR (neat): 1690, 1660, 1600, 1190, 1105, 1035, 980 cm^{-1} ; MS m/z : 206 (M^+).

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N,N -ジメチルヒドラゾンを経る α,β -不飽和ケトンの α -アルキル化反応 ジヒドロジャスモン及び *cis*-ジャスモンの合成

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3-メチル-2-シクロペンテン-1-オン N,N -ジメチルヒドラゾンのアルキル化反応を検討した。アルキル化は、ヒドラゾンの α,β -不飽和部の α 位に選択的に起こった。この方法を用いて、ジヒドロジャスモン、*cis*-ジャスモンを良好な収率で合成した。

イソフォロンジメチルヒドラゾンもまた、 α 位がアルキル化されたが、ヨノンジメチルヒドラゾンでは α' 位(メチル炭素)にアルキル化が起こった。