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A TOTAL SYNTHESIS OF ISOSOLANONE

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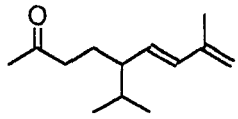
Summary: Nitroaldol reaction of acetone with nitromethane in the presence of base to give a nitroalcohol **3**, followed by acetylation, and subsequent reduction of the resultant acetate **4** with $NaBH_4$ gave 2-methyl-1-nitropropane **5**. Michael reaction of **5** in base with acrylonitrile to give nitronitrile **6**, and Nef conversion of the nitro group resulted in the corresponding ketonic nitrile **7**. Wittig olefination of the ketonic nitrile with 3-methyl-2-butenyl triphenylphosphonium bromide **8** gave dienenitrile **9**, which upon treatment with MeLi, followed by acidic work up, provided isosolanone **2**.

Solanone (**1**) and isosolanone (**2**) are members of terpeniods and represent unique structures in that they apparently violate the isoprene rule. They are clear, colorless, mobile oil with a faint aroma reminiscent of carrots. They have been detected in the Burley,[1] Greek[2] tobacco and marijuana.[3] In spite of their valuable odor characteristics, they are unfortunately not readily available commercially.

Recently, we reported[4a-f] several syntheses of terpene perfumery compounds, such as jasmone, jasmonate, damascenone, nuciferal, and damascone. In the present paper, we wish to report a synthesis of isosolanone (**2**), a more stable

isomer of solanone, for it is similarly important as solanone in the perfumery industry. Although the synthesis of solanone has been reported by some workers,[5] that of isosolanone has never been reported, and this is the first total synthesis of isosolanone, which is reasonably short and inexpensive.



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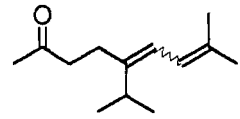
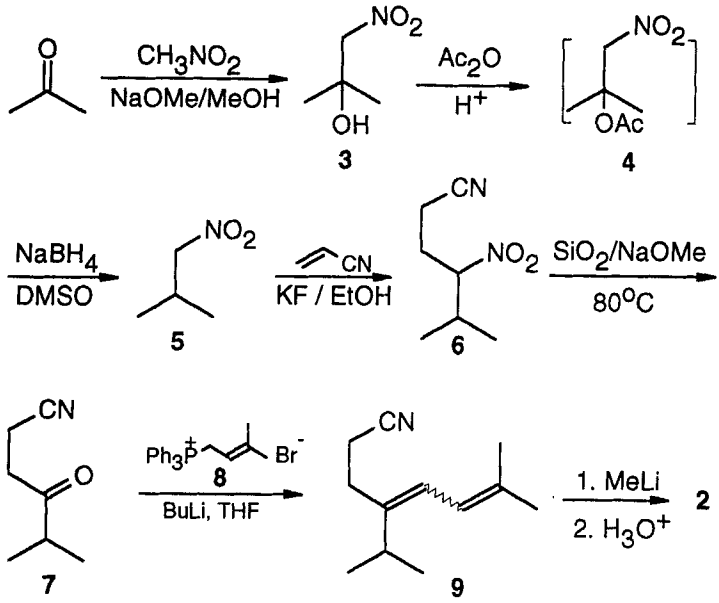


2

Our route leading to isosolanone **2** is outlined in Scheme I, which begins with nitroaldol reaction of acetone. Treatment of nitromethane with sodium methoxide in methanol, followed by reaction of the resultant nitroenolate with dry acetone, gave nitroalcohol **3**.[6] Acetylation of nitroalcohol **3** with acetic anhydride to give acetate **4**, followed by reduction, without separation, with sodium borohydride in DMSO, provided 2-methyl-1-nitropropane **5**.[7]

In the preparation of nitronitrile **6**, the reaction are carefully examined by the use of various bases, since acrylonitrile, the Michael acceptor, is very susceptible to polymerization depending on the strength of the base. It has been known by recent reports about Michael reaction of nitroalkane that the more subtle reactions became possible by use of very mild bases, such as $(n\text{-Bu})_4NF$,[10,11] PBu_3,[12] DBU,[13,14] Et_3N,[15,16] basic alumina,[17-20] KF/EtOH,[8] and KF/18-C-6.[21,22] Of the bases, by far the best one was potassium fluoride (KF). Treatment of **5** with KF (0.2 mole %) in ethanol, and reaction of the resultant nitroenolate with acrylonitrile at 80 °C yielded nitronitrile **6**[8] in reasonable yield (60%).

The nitro group in **6** was converted by Nef reaction[9, 23-26] to carbonyl. Treatment of **6** at 80 °C with activated sodium methoxide adsorbed on silica gel ($NaOMe/SiO_2$)[9] gave ketonic nitrile **7** in good yield (93%). Treatment of a



Scheme I

Wittig salt, 3-methyl-2-butenyl triphenylphosphonium bromide **8**, with *n*-BuLi, followed by reaction of the resultant phosphonium ylide with **7**, provided Wittig olefination product **9** in 71% yield. Although the exact mass (M^+ 177.1524) of this product was agreed with calcd value for $C_{12}H_{19}N$ (177.1519), the ^{13}C NMR spectrum displayed 20 resonances that are twice the number of carbon atoms of different environment, but the half of them were much weaker. This suggested that the Wittig product was a mixture of two geometrical isomers, one of which was major product and the other minor. The major product may be regarded as *E*-isomer; in previous work,[27] the Wittig reaction between methyl isopropyl ketone and triphenylphosphonium ethylidene resulted in the mixture of an approximate 9:1 ratio of *E* and *Z* isomers. The mixture was difficult to separate cleanly by ordinary chromatography, and was used directly to the next reaction.

Reaction of dienenitrile **9** with methyllithium, followed by hydrolytic workup, afforded 88% yield of isosolanone **2**. The exact mass (M^+ 194.1683) found by HRMS was agreed with calcd value for $C_{13}H_{22}O$ (M 194.1671), but ^{13}C NMR spectrum gave 21 signals, but 9 of which were much weaker than the others, suggesting the product to be a mixture of geometrical isomers. Gas chromatography also demonstrated that the product was an approximate 3:1 mixture of isomers. The formation of isomer mixture of **2** was also observed[5a] when solanone **1** was treated with mineral acid. Complete separation of the mixture was difficult, but repeated separation (glc) afforded almost pure major product, which may be regarded as *E*-form.

Experimental Part

2-Methyl-1-nitro-2-propanol (3). To a solution of MeONa, prepared by dissolving metallic Na (2.0 g, 87 mmol) in MeOH (50 mL), was added CH_3NO_2 (122 g, 2 mol) with stirring at room temperature. To this white, milky solution was added pure, well-dried acetone (600 mL). The mixture was stirred for 3 d at room temperature and quenched with a solution of AcOH (8 mL) in water (100 mL). The reaction mixture was evaporated under reduced pressure to remove MeOH, unreacted CH_3NO_2, and excess acetone. The crude product was extracted with CH_2Cl_2, the organic layer was washed with water, dried over anhydrous $MgSO_4$, and evaporated *in vacuo*. The crude product was vacuum-distilled to give 69 g (29%) of title compound **3** as a colorless oil at 82-84 °C (6 torr). IR (neat, NaCl disc) 3400 (O-H), 2960, 2930, 1550 and 1370 (NO_2), 1460, 1430, and 1320 cm^{-1}; ^1H NMR ($CDCl_3$/TMS, 80 MHz) δ 1.34 (s, 6 H, $2CH_3$), 3.38 (s, 1 H, OH), and 4.41 (s, 2 H, CH_2NO_2); ^{13}C NMR($CDCl_3$) δ 26.73, 69.61, and 85.07.

2-Methyl-1-nitropropane (5). To a mixture of Ac_2O (58.0 g, 569 mmol) and nitroalcohol **3** (66.7 g, 561 mmol), cooled in an ice-bath, was added conc. H_2SO_4

(5 drops) with stirring. Stirring was continued for more than 30 min at 0 °C and the mixture was allowed to warm to room temperature. To this mixture was added a suspension of $NaBH_4$ (7 g, 185 mmol) in DMSO (100 mL), and the mixture was stirred for 4 h. The reaction mixture was quenched with aqueous NH_4Cl, extracted several times with Et_2O, the combined organic layer was washed with water, and dried over anhydrous $MgSO_4$. After removed the solvent by simple distillation, the crude product was purified by fractional distillation using 20-cm Vigreux column, to give 38.7 g (67%) of the title compound **5** as an oil at 136-138 °C. IR (neat, NaCl disc) 2960, 2870, 1550 and 1370 (NO_2), 1460, 1440, 1230, and 1140 cm^{-1}; ^1H NMR ($CDCl_3$/TMS, 80 MHz) δ 1.04 (d, J = 6.4 Hz, 6 H, 2 CH_3), 2.19-2.75 (m, 1 H, CH), and 4.22 (d, J = 7.2 Hz, 2 H, CH_2NO_2); ^{13}C NMR($CDCl_3$) δ 19.02, 27.67, and 82.43.

5-Methyl-4-nitrohexanenitrile (6). A mixture of nitropropane **5** (4.2 g, 40.8 mmol), acrylonitrile (12.5 g, 236 mmol) and catalytic amount of KF (0.20 g) in EtOH (50 mL) was refluxed for 15 h, and the solvent was evaporated *in vacuo* to give a brown oil. After addition of aqueous NH_4Cl, the mixture was extracted with Et_2O, the organic layer was washed with water, and dried over anhydrous $MgSO_4$. After evaporated the solvent, the crude product was chromatographed on a silica gel column eluting with CH_2Cl_2, to give yellowish oil of Michael adduct **6** in 60% yield. IR (neat, NaCl disc) 2960, 2870, 2250 (C≡N), 1550 and 1370 (NO_2), and 1460 cm^{-1}; ^1H NMR ($CDCl_3$/TMS, 80 MHz) δ 1.03 (two d, J = 6.4 Hz, 6 H, 2 CH_3), 1.98-2.61 (m, 5 H, CH_2CN, CH_2 and CH), and 4.17-4.48 (m, 1 H, $CHNO_2$). ^{13}C NMR($CDCl_3$) δ 14.10, 17.99, 18.33, 25.99, 31.77, 92.25, and 117.76; EIMS *m/z* (relative intensity) 110 (M^+ - NO_2, 100), 93 (13.29), 86 (33.72), and 84 (58.52),

Preparation of Basic Silica Gel. In a 500-mL round-bottomed flask was dissolved metallic Na (24 g) in MeOH (200 mL), followed by addition of silica

gel (152 g). The mixture was well mixed and the solvent was evaporated to dryness *in vacuo*. The silica gel-sodium methoxide mixture was heated for 4 h at 200-300 °C in a furnace to give an activated basic silica gel.

5-Methyl-4-oxohexanenitrile (7). A mixture of nitronitrile **6** (1.40 g, 8.97 mmol) and basic silica gel (14 g) was heated at 80 °C in an oven for 15 h. The reaction mixture was extracted with CH_2Cl_2. After evaporated the solvent, the crude product was chromatographed on a silica gel column eluting with CH_2Cl_2 to give title compound **7** as an oil in 93% yield. IR (neat, NaCl disc) 3400, 2970, 2880, 2250 (C≡N), 1710 (C=O), 1460, and 1080 cm^{-1}; ^1H NMR ($CDCl_3$/TMS, 80 MHz) δ 1.14 (d, J = 5.5 Hz, 6 H, $2CH_3$), and 2.41-2.98 (m, 5 H, CH_2CN, CH_2, CH); ^{13}C NMR($CDCl_3$) δ 11.05, 17.60, 35.01, 40.09, 118.94, and 209.73; EIMS *m/z* 125 (M^+), 110, 95, and 82; HRMS found M^+ 125.0885, calcd for $C_7H_{11}ON$ M 125.0841.

3-Methyl-2-butenyltriphenylphosphonium Bromide (8). A mixture of 4-bromo-2-methyl-2-butene (4.0 g, 26.8 mmol) and $(C_6H_5)_3P$ (6.8 g, 26.0 mmol) dissolved in anhydrous benzene (20 mL) was stirred at reflux for 2 h. After cooled the reaction mixture, the phosphonium salt was filtered, and recrystallized from a mixed solvent (EtOH-Et_2O) to give 8.5 g (80 %) of Wittig salt **8** as a white solid, mp. 139-140 °C, which was dried over P_2O_5 in a vacuum oven at 100 °C. IR (KBr pellet) 3380, 3040, 2980, 2880, 1585, 1435, 1115, and 895 cm^{-1}; ^1H NMR ($CDCl_3$/TMS, 80 MHz) δ 1.32 (d, J = 4.2 Hz, 3 H, CH_3 *cis* to vinyl proton), 1.67 (d, J = 5.8 Hz, 3 H, CH_3 *trans* to vinyl proton), 4.40-4.79 (m, 2 H, CH_2P), 4.98-5.23 (m, 1 H, vinyl proton), and 7.80-8.05 (m, 15 H, Ar*H*).

4-Isopropyl-7-methyl-4,6-octadienenitrile (9). To a solution of Wittig salt **8** (2.63 g, 6.40 mmol) in anhydrous THF (20 mL), cooled to 0 °C, was added an equiv amount of *n*-BuLi (2 *M* in hexane, 3.1 mL) under nitrogen at 0 °C, then the

bright yellow solution was turned to red. To this solution was added dropwise, at gentle reflux, a solution of cyanoketone **7** (0.40 g, 3.2 mmol) in THF (5 mL). After stirring for 15 h at gentle reflux, the reaction mixture was quenched with aqueous NH_4Cl, and the solvent was removed *in vacuo*. The aqueous layer was extracted with Et_2O, the organic layer was washed with water, and dried over anhydrous $MgSO_4$. The crude product was chromatographed on silica gel eluting with CH_2Cl_2 to give 400 mg (71%) of dienenitrile **9** as an oil. IR (neat, NaCl disc) 2960, 2920, 2870, 2240 (C≡N), 1610, 1460, 1440, and 850 cm^{-1}; ^1H NMR ($CDCl_3$/TMS, 80 MHz) δ 1.04 (two d, J = 7.2 Hz, 6 H, 2 CH_3), 1.78 (d, J = 4 Hz, 6 H, 2 CH_3), 2.12-2.58 (m, 5 H, CH_2CN, CH_2, CH), and 6.02 (two d, J = 9.5, 3.4 Hz, 2 H, vinyl protons); ^{13}C NMR spectrum gave 20 resonances, which are twice the number of carbon atoms of different environment, showing a mixture of two geometrical isomers: δ 140.40, 130.19, 134.53, 134.04, 120.60, 120.08, 119.09, 118.87, 118.44, 33.94, 27.69, 26.49, 25.36, 24.56, 20.90, 20.02, 17.16, 17.06, 16.37, and 16.09; EIMS *m/z* 177 (M^+), 162, 121, 95, and 81; HRMS found M^+ 177.1524, calcd for $C_{12}H_{19}N$ M 177.1519.

Isosolanone (2) In a 50-mL three-necked round-bottomed flask, fitted with a dropping funnel, a reflux condenser and a nitrogen inlet, was placed Li-shavings (300 mg, 43 mmol) and anhydrous Et_2O (10 mL). To this stirred mixture was added dropwise, under nitrogen, a solution of MeI (1.50 g, 10.6 mmol) in anhydrous Et_2O (10 mL) at room temperature. When dropping was proceeded, the surface of lithium shavings became bright and the solution became cloudy. After the addition of MeI, the reaction mixture was stirred for 2 h to complete the formation of a lithio reagent, MeLi.

To a solution of octadienenitrile **9** (200 mg, 1.13 mmol) in anhydrous Et_2O (15 mL), cooled to 0 °C, was added an excess MeLi prepared above under

nitrogen, and the mixture was stirred overnight at room temperature, then the solution became turbid. The reaction mixture was quenched with aqueous NH_4Cl, extracted with Et_2O, the organic layer was washed with water, and dried over anhydrous $MgSO_4$. The crude product was purified by chromatography on silica gel eluting with CH_2Cl_2 to give 190 mg (88%) of isosolanone **2** as an oil. This flavoring product was a mixture of two geometrical isomers. Repeated separation (glc) afforded a major isomer, but in low yield (less than 10% of the mixture). IR (neat, NaCl disc) 3020, 2960, 2920, 2870, 1718, 1610, 1460, 1440, and 850 cm^{-1}; ^1H NMR ($CDCl_3$/TMS, 80 MHz) δ 1.03 (two d, J = 7.2 Hz, 6 H, 2 CH_3), 1.77 (d, J = 3.5 Hz, 6 H, CH_3), 2.14 (s, 3 H, CH_3CO), 2.23-2.54 (m, 5 H, CH_2CO, CH_2, CH), and 5.82-6.18 (m, 2 H, vinyl protons); ^{13}C NMR ($CDCl_3$) δ 208.17, 144.29, 133.67, 120.65, 119.11, 43.66, 35.18, 29.66, 26.23, 23.46, 21.90, and 17.97; EIMS *m/z* 194 (M^+), 179, 121, 93, and 81; HRMS found M^+ 194.1683, calcd for $C_{13}H_{22}O$ M 194.1671.

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