Organic Chemistry

Chemo- and regioselective nitration of geranylacetone by $NaNO_2$/AcOH. Synthesis of 6,10-dimethyl-9-methyleneundec-5*E*-en-2-one

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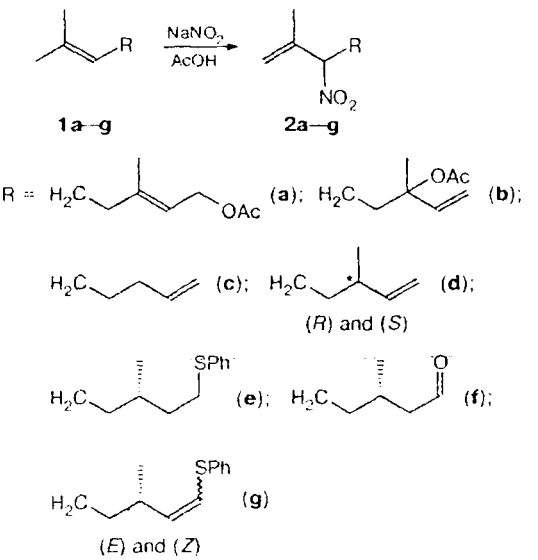
Treatment of geranylacetone with $NaNO_2$ in AcOH affords 6,10-dimethyl-9-nitroundeca-5*E*,10-dien-2-one as the major product. This product was used to synthesize 6,10-dimethyl-9-methyleneundec-5*E*-en-2-one, a component of the essential oil from the roots of the *Saussurea lappa* plant.

Key words: linear isoprenoid, geranylacetone, nitration, nitro derivative, Nef reaction, 6,10-dimethyl-9-methyleneundec-5*E*-en-2-one, essential oil component.

The range of methods for selective functionalization of an isopropylidene fragment in linear isoprenoids is currently limited to a few examples (*e.g.*, see Ref. 1 and references therein). Meanwhile, derivatives of this type are promising synthetic blocks for building molecules of natural compounds of the terpene series.[1] The smooth formation of nitro derivative **2a** (Scheme 1) as an intermediate, found by Corey *et al.*[2] in a study of the mechanism of degradation of the isopropylidene group in geranyl acetate **1a** into an ethynylidene group on treatment with $NaNO_2$ in AcOH, presents interest from this viewpoint.

We found that this transformation is chemoselective for a fairly representative series of isoprenoid substrates **1b**—**g**[3—6]; moreover, some of the nitro derivatives **2** proved to be convenient starting compounds for efficient synthesis of natural cyclopentanoids of the iridane series.[5,6] This communication presents a study of this approach in relation to commercially available geranylacetone (**3**), carried out in order to find new synthetic applications of the transformation in question (Scheme 2).

Scheme 1



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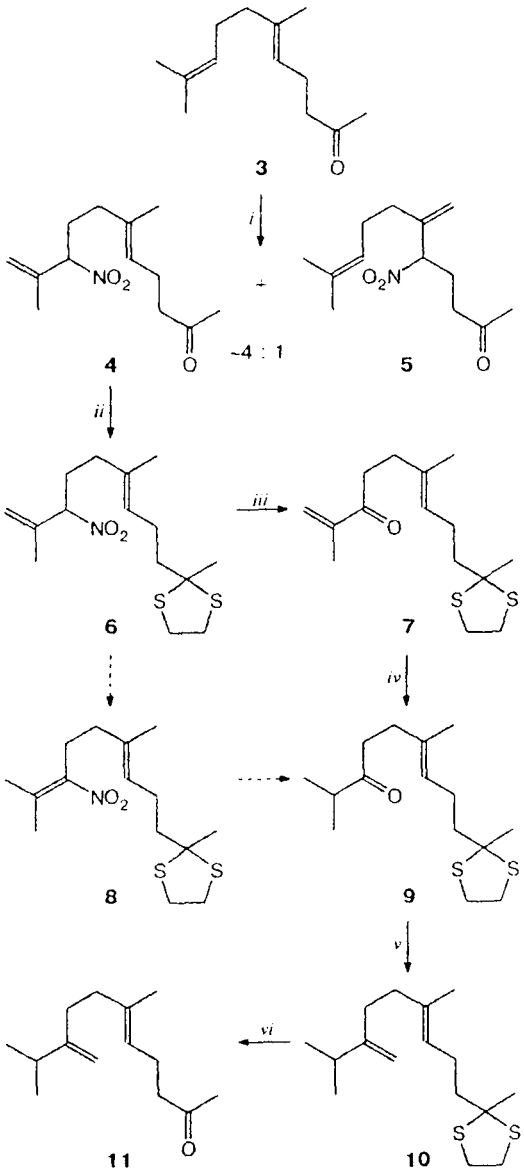
Scheme 2



Reagents and conditions: *i*. $NaNO_2/AcOH/Et_2O$, 5 °C.
ii. $HSCH_2CH_2SH/p$-TsOH/AcOH, 25 °C.
iii. $TiCl_3/NH_4OAc/MeOH$, 25 °C.
iv. $Na_2S_2O_4/n$-$Bu_4N^+Br^-/NaHCO_3/PhH/H_2O$, 80 °C.
v. Ph_3PCH_3Br/n-BuLi/THF, 68 °C.
vi. $AgNO_3/NCS/MeCN$, 10 °C.

The introduction of a nitro group into dienone **3** on treatment with $NaNO_2$ in AcOH was found to be less selective. In addition to the major product **4**, the reaction yields up to 20% of nitro compound **5** due to the involvement of the Δ^5-trisubstituted double bond of the starting diene **3**. The ratio of the components in this mixture was established by ^1H NMR spectroscopy (characteristic signals of compound **5**: δ 5.57 (m, 1 H, HC(9)) and δ 4.94 (m, 1 H, HC(5))) and by its separation by preparative HPLC.

The nitro derivative **4** thus obtained may be of interest as a starting compound for the synthesis of natural isoprenoids. As an illustration, we performed its five-step transformation into 6,10-dimethyl-9-methyleneundec-5*E*-en-2-one (**11**), a component of the essential oil from the roots of *Saussurea lappa*[7] (see Scheme 2).

In order to attain subsequent differentiation of functions, before transformation of the allylic nitro group into an enone group, ketone **4** had been protected by being transformed into dithiolane **6**. Treatment of the latter compound with $TiCl_3$ with pH control (*cf.* Ref. 8) afforded enone **7** in ~60% yield. It is noteworthy that compound **6** proved to be inert under other conditions used in the Nef reaction. Thus when dithiolane **6** is treated with $Pr^nONO/NaNO_2$ in DMSO (*cf.* Ref. 9), an aqueous solution of $TiCl_3$,[10] or cerium ammonium nitrate,[11] only the unreacted starting compound can be isolated from the reaction mixture.

Conjugate reduction of enone **7** by $Na_2S_2O_4$ (*cf.* Ref. 12) smoothly gave saturated ketone **9**. This product was methylenated under standard conditions and the dithiolane derivative **10** thus obtained was converted into the target ketone **11** by removing this protection at the final step.

Another attractive route for obtaining ketone **9** from nitro compound **6** could consist of direct transformation of the regioisomeric vinyl derivative **8** into the saturated ketone, as is known for related systems.[13] However, attempts to conjugate the multiple bond in allylic nitro derivative **6** by a catalytic amount of Et_3N in $CHCl_3$ or by excess Et_3N followed by treatment with AcOH (0 °C) (Ref. 14) did not give the desired isomerization product **8**, apparently, due to the unfavorable thermodynamics of this process, associated with the formation of a tetrasubstituted double bond.

The structures of newly obtained compounds **4**, **6**, **7**, **9**, and **10** were based on spectroscopic and elemental analysis; the spectral characteristics of natural ketone **11** synthesized in this way were virtually identical to those given in the literature.[7,15]

Experimental

IR spectra (ν/cm^{-1}) were recorded on a Specord M-80 instrument. ^1H NMR (δ) and ^{13}C NMR (δ) spectra for solutions in $CDCl_3$ were run on a Bruker AC-200 spectrometer (200.13 MHz and 50.32 MHz, respectively). ^1H and ^{13}C NMR chemical shifts were referred to the solvent signal (7.27 for ^1H and 77.0 for ^{13}C). Mass spectra (EI) were measured on a Varian MAT 311A instrument at 70 eV. The presented R_f values refer to a fixed SiO_2 layer (Silufol). HPLC was performed on a column with Silasorb-600 (10 μm, 250×24 mm), using a 95 : 5 heptane—AcOEt mixture, 7 mL min^{-1}, as the eluent and a refractometric detector. Commercially available (Fluka) $Me(Ph)_3P^+Br^-$ and a hexane solution of Bu^nLi were used.

6,10-Dimethyl-9-nitroundeca-5*E*,10-dien-2-one (4). Sodium nitrite (2.5 g, 34.2 mmol) was added in portions over a

period of 1 h to a solution of geranylacetone (**3**) (1 g, 5.2 mmol) in 12 mL of AcOH and 2.5 mL of Et_2O stirred at 5 °C. The reaction mixture was kept for 1 h at 10 °C, diluted with 10 mL of H_2O, and extracted with Et_2O (3×20 mL). The extract was washed with H_2O (3×5 mL), dried with $MgSO_4$, and concentrated *in vacuo*. The residue (~1 g) was chromatographed on 30 g of SiO_2. Gradient elution (hexane → hexane—AcOEt (75 : 15)) gave 0.82 g (66%) of a mixture of nitro derivatives **4** and **5** (~4 : 1) as a colorless oil, R_f 0.40 (hexane—AcOEt, 8 : 2). IR: 925, 1370, 1445, 1550, 1720, 2840—3000 (film). MS, *m/z*: 193 $[M - 46]^+$, 175, 163, 159. Found (%): C, 65.49; H, 8.89. $C_{13}H_{21}NO_3$. Calculated (%): C, 65.25; H, 8.84.

HPLC separation of compounds **4** and **5** gave 0.66 g of nitro derivative **4**. ^{1}H NMR: 1.61 (br.s, 3 H, MeC(6)); 1.80 (br.s, 3 H, MeC(10)); 1.80—2.50 (m, 8 H, 4 CH_2); 2.13 (s, 3 H, C(1)H_3); 4.80 (m, 1 H, HCN); 5.04 (m, 1 H, HC(5)); 5.10—5.15 (m, 2 H, H_2C(11)). ^{13}C: 15.7 (MeC(10)), 18.2 (MeC(6)), 22.2 (C-3), 29.1 (C-8), 29.3 (C-1), 35.6 (C-4), 43.3 (C-7), 92.1 (C-9), 118.4 (C-11), 124.8 (C-5), 133.7 (C-6), 138.7 (C-10), 210.0 (C-2).

10,10-(Ethylenedithio)-2,6-dimethyl-3-nitroundeca-1,6*E*-diene (6). *p*-TsOH · H_2O (0.19 g, 1 mmol) and $(CH_2SH)_2$ (0.21 g, 2.27 mmol) were added to a solution of nitroalkene **4** (0.51 g, 2.1 mmol) in 5 mL of AcOH (*cf.* Ref. 16). The mixture was stirred at 25 °C for 4 h and treated with Et_2O and H_2O. The aqueous layer was separated and extracted with Et_2O. The extract was washed with water and a saturated aqueous solution of $NaHCO_3$, dried with $MgSO_4$, and concentrated *in vacuo*. The residue (~0.7 g) was chromatographed on 30 g of SiO_2. Gradient elution (hexane → hexane—EtOAc (90 : 10)) gave 0.6 g (91%) of dithiolane **6** as a colorless oil, R_f 0.55 (hexane — AcOEt, 8 : 2). IR: 790, 860, 920, 1075, 1280, 1375, 1445, 1550, 2800—3000 (film). ^{1}H NMR: 1.65 (br.s, 3 H, MeC(6)); 1.78 (s, 3 H, C(11)H_3); 1.83 (br.s, 3 H, MeC(2)); 1.90—2.40 (m, 8 H, 4 CH_2); 3.20—3.40 (m, 4 H, $(CH_2S)_2$); 4.85 (m, 1 H, HCN); 5.10—5.20 (m, 3 H, C(1)H_2 and HC(7)). ^{13}C: 15.6 (MeC(2)), 18.4 (MeC(6)), 25.8 (C-8), 29.3 (C-4), 32.5 (C-11), 35.7 (C-9), 40.0 (CS), 45.5 (C-5), 66.6 (C-10), 92.6 (C-3), 118.4 (C-1), 125.7 (C-7), 133.1 (C-6), 138.9 (C-2). MS, *m/z*: 269 $[M - 46]^+$. Found (%): C, 57.22; H, 8.14; S 20.43. $C_{15}H_{25}NO_2S_2$. Calculated (%): C, 57.10; H, 7.99; S, 20.33.

10,10-(Ethylenedithio)-2,6-dimethylundeca-1,6*E*-diene-3-one (7). A solution of NH_4OAc (7.84 g, 103.6 mmol) in 22 mL of H_2O was added to 18 mL of an aqueous solution of $TiCl_3$* (containing 17.3 mmol of $TiCl_3$), thus bringing the pH to ~5.3. Bu^{t}OK (484 mg, 4.3 mmol) was added to a solution of nitro compound **6** (1.36 g, 4.3 mmol) in 40 mL of MeOH and the mixture was kept for 5 min. The resulting solution of nitronate was added dropwise over a period of 30 min to the solution of $TiCl_3$ stirred at 15 °C. The mixture was stirred at 25 °C for 1 h and treated with 20 mL of a saturated aqueous solution of $NaHCO_3$ and 50 mL of Et_2O. The aqueous layer was extracted with Et_2O (2×50 mL). The ethereal extract was washed with H_2O and a saturated aqueous solution of $NaHCO_3$, dried with $MgSO_4$, and concentrated *in vacuo*. The residue (~0.9 g) was chromatographed on 30 g of SiO_2. Gradient elution (hexane → hexane—AcOEt (90 : 10)) gave 0.71 g (58%) of unsaturated ketone **7** as a colorless oil, R_f 0.56 (hexane—AcOEt, 8 : 2). IR: 940, 1097, 1190, 1230, 1390, 1450, 1550, 1685, 1710, 2830—3020 (solution in $CHCl_3$). ^{1}H NMR: 1.63 (br.s, 3 H, MeC(6)); 1.74 (s, 3 H, C(11)H_3); 1.87 (br.s, 3 H, MeC(2)); 1.80—2.00 (m, 2 H, C(9)H_2); 2.10—2.35 (m, 4 H, C(5)H_2 and C(8)H_2); 2.73 (m, 2 H, C(4)H_2); 3.20—3.40 (m, 4 H, $(CH_2S)_2$); 5.12 (m, 1 H, HC(7)); 5.74 and 5.93 (both m, 2 H, HC(1)). ^{13}C NMR: 16.4 (MeC(2)), 18.1 (MeC(6)), 25.6 (C-8), 32.2 (C-11), 34.1 (C-4), 35.9 (C-9), 39.7 (CS), 45.4 (C-5), 66.5 (C-10), 123.7 (C-1), 124.9 (C-7), 134.4 (C-6), 144.3 (C-2), 201.6 (C-3). MS, *m/z*: 284 $[M]^+$, 256, 223. Found (%): C, 63.67; H, 8.68. $C_{15}H_{24}OS_2$. Calculated (%): C, 63.33; H, 8.50.

10,10-(Ethylenedithio)-2,6-dimethylundec-6*E*-en-3-one (9). $NaHCO_3$ (2 g, 23.8 mmol) and 5 mL of H_2O were added at 25 °C (Ar) to a solution of unsaturated ketone **7** (0.31 g, 1.1 mmol) in 5 mL of PhH. The mixture was heated to 100 °C (bath), and $Na_2S_2O_4$ (1.7 g, 9.8 mmol) was added to it in portions with vigorous stirring over a period of 2 h. Then the reaction mixture was cooled and treated with Et_2O and H_2O. The organic layer was separated, washed with a saturated aqueous solution of NaCl, dried with $MgSO_4$, and concentrated *in vacuo*. The residue (~0.3 g) was chromatographed on 30 g of SiO_2. Gradient elution (hexane → hexane—AcOEt (90 : 10)) gave 308 mg (98%) of ketone **9** as a colorless oil, R_f 0.55 (hexane—AcOEt, 8 : 2). IR: 1070, 1385, 1450, 1710, 2830—3010 (in $CHCl_3$). ^{1}H NMR: 1.10 (d, 6 H, Me_2CH, J = 6.5 Hz); 1.64 (br.s, 3 H, MeC(6)); 1.77 (s, 3 H, C(11)H_3); 1.70—2.70 (m, 9 H, CH, 4 CH_2); 3.30—3.40 (m, 4 H, $(CH_2S)_2$); 5.15 (m, 1 H, HC(7)). ^{13}C NMR: 16.1 (MeC(6)), 18.2 (Me_2CH), 23.2 (C-8), 26.0 (C-11), 32.3 (C-5), 33.4 (C-9), 38.7 (C-4), 39.9 (CS), 45.5 (C-2), 66.6 (C-10), 123.8 (C-7), 134.6 (C-6), 205.2 (C-3). MS, *m/z*: 286 $[M]^+$, 225, 207, 201. Found (%): C, 62.38; H, 8.58; S 21.99. $C_{15}H_{26}S_2O$. Calculated (%): C, 62.88; H, 9.15; S 22.38.

10,10-(Ethylenedithio)-2,6-dimethyl-3-methyleneundec-6*E*-ene (10). A 1.6 *M* solution of Bu^{n}Li (1.3 mL, 2.1 mmol) in hexane was added dropwise over a period of 5 min to a suspension of $Me(Ph)_3P^+Br^-$ (0.82 g, 2.3 mmol) in 6 mL of THF stirred at −30 °C (Ar). The resulting solution was stirred for 15 min at −10 °C; then a solution of ketone **9** (0.3 g, 1.05 mmol) in 2 mL of THF was added to it in one portion. The reaction mixture was refluxed for 4 h, cooled to 25 °C, treated with 2 mL of H_2O, and extracted with hexane. The extract was washed with brine, dried with $MgSO_4$, and concentrated *in vacuo*. The residue (~0.3 g) was chromatographed on 30 g of SiO_2. Gradient elution (hexane → hexane—AcOEt (90 : 10)) gave 280 mg (93%) of diene **10** as a colorless oil, R_f 0.66 (hexane—AcOEt, 8 : 2). IR: 900, 1390, 1460, 1640, 2830—3000 (in $CHCl_3$). ^{1}H NMR: 1.05 (d, 6 H, Me_2CH, J = 6.7 Hz); 1.67 (br.s, 3 H, MeC(6)); 1.78 (s, 3 H, C(11)H_3); 1.90—2.30 (m, 9 H, CH, 4 CH_2); 3.30—3.40 (m, 4 H, $(CH_2S)_2$); 4.65—4.70 (m, 2 H, H_2C=); 5.17 (m, 1 H, HC(7)). ^{13}C NMR: 16.1 (MeC(6)), 21.9 (Me_2CH), 23.4 (C-8), 25.6 (C-4), 26.0 (C-11), 31.2 (C-2), 38.4 (C-5), 39.8 (CS), 45.7 (C-9), 66.7 (C-10), 106.4 (H_2C=), 124.1 (C-7), 135.8 (C-6), 155.9 (C-3). MS, *m/z*: 284 $[M]^+$, 269, 256, 241. Found (%): C, 67.60; H, 9.65. $C_{16}H_{28}S_2$. Calculated (%): C, 67.54; H, 9.92.

6,10-Dimethyl-9-methyleneundec-5*E*-en-2-one (11). A solution of dithiolane **10** (10.1 mg, 0.035 mmol) in 2 mL of MeCN was added in one portion to a solution containing $AgNO_3$ (29.9 mg, 0.176 mmol) and *N*-chlorosuccinimide (NCS) (20.8 mg, 0.156 mmol) in 4 mL of MeCN and 1 mL H_2O and stirred at 10 °C (*cf.* Ref. 17). The reaction mixture was stirred for 10 min and treated successively with saturated

* The solution of $TiCl_3$ was prepared by gradual addition (Ar) of zinc dust (12.8 g, 0.19 mol) over a period of 1.5 h to a solution of $TiCl_4$ (6.35 g, 33 mmol) in 90 mL of 10% HCl stirred at ~5 °C followed by keeping the resulting mixture for 12 h at 25 °C.

solutions (0.2 mL each) of Na_2SO_3 and Na_2CO_3 and with 0.2 mL of brine. The product was extracted with 10 mL of a hexane—CH_2Cl_2 (1 : 1) mixture. The organic layer was separated, dried with $MgSO_4$, and concentrated *in vacuo*. The residue (~10 mg) was chromatographed on 10 g of SiO_2. Gradient elution (hexane → hexane—AcOEt (95 : 5)) gave 5.3 mg (72%) of diene **11** as a colorless oil, R_f 0.61 (hexane—AcOEt, 9 : 1). ^1H NMR: 1.05 (d, 6 H, $\underline{Me}_2CH$, J = 6.6 Hz); 1.63 (br.s, 3 H, MeC(6)); 2.13 (s, 3 H, HC(1)); 1.90—2.50 (m, 9 H, CH, CH_2); 4.67—4.75 (m, 2 H, H_2C=); 5.12 (m, 1 H, HC(5)).

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