A New Synthesis of Allethrolone

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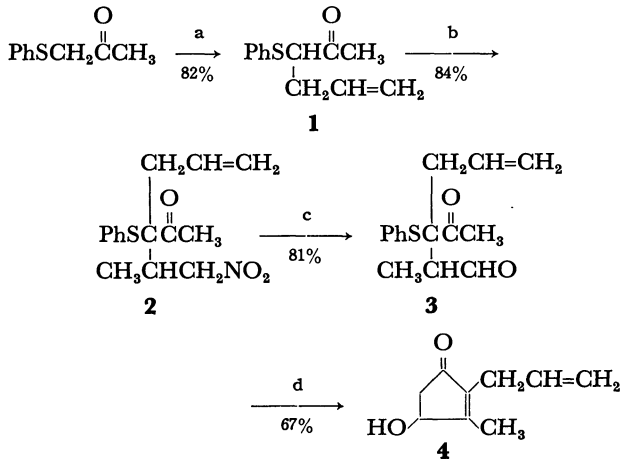
Synopsis. A new synthesis of 2-allyl-4-hydroxy-3-methyl-2-cyclopenten-1-one, so called allethrolone is described, in which the Michael addition of 3-phenylthio-5-hexen-2-one to 1-nitro-1-propene followed by conversion of the nitromethyl group in the adduct to an aldehyde function is involved as the key step.

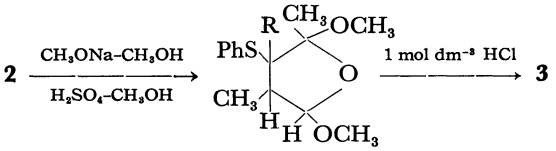
Allethrolone (**4**) is the alcohol component of the allethrine which is a commercially important synthetic homologue of natural occurring pyrethrines. Allethrolone is now prepared in industry by the method of Schechter, which starts from allyl chloride, methyl acetoacetate, and methylglyoxal.[1] Owing to low overall yield of this method, a new efficient method to prepare **4** is desired. Recently, some elegant methods have been devised by Büchi[2] or Schlessinger.[3] Though the yield has been greatly improved by these methods, they require rather expensive starting materials or reagents. This paper presents a new synthesis of **4** starting from readily available materials and by a simple procedure. This new method is outlined in Scheme 1.



a: CH_2=$CHCH_2Br$, 30% NaOH, b: NaH, CH_3CH=$CHNO_2$ in DMF, c: CH_3ONa-CH_3OH/H_2SO_4-CH_3OH, 1 mol dm^{-3} HCl, d: C_2H_5ONa-C_2H_5OH

Scheme 1. A new synthesis of allethrolone (**4**).

3-Phenylthio-5-hexen-2-one (**1**) was obtained in 82% yield by alkylation of α-(phenylthio)acetone with allyl bromide under phase transfer conditions. The Michael addition of **1** to 1-nitro-1-propene took place at 0 °C in DMF using sodium hydride as a base to give the adduct **2** in 84% yield. The key step of the new method is conversion of the nitromethyl group in **2** to an aldehyde function. In general, a Nef type reaction of 1-nitro-4-alkanones involves some difficulties due to formation of a stable cyclic intermediates.[4] After several unsuccessful trials,[5] **2** could be converted to γ-keto aldehydes (**3**) by treating the *aci*-nitro anion of **2** with sulfuric acid in methanol followed by hydrolysis of the crude product with 1 mol dm^{-3} hydrochloric acid. The conventional method to convert 1-nitro-4-alkanones to γ-keto aldehydes requires protection of the ketone function as an acetal before a Nef type reaction.[4] However, protection of the ketone function of **2** is not required in the present procedure, for the reaction proceeds *via* an intermediate **5** in which the ketone function is already protected.[6]



5 R= CH_2CH=CH_2

Finally, **4** was obtained in 67% yield on treatment of **3** with sodium ethoxide in ethanol.

The reactions devised here to prepare **4** can be applied to the synthesis of other related compounds: especially high reactivity of nitroolefins as Michael acceptors for ketone enolates and the simple method to prepare γ-keto aldehydes from 1-nitro-4-alkanones are of special use in organic synthesis.[7]

Experimental

NMR spectra were recorded on a JEOL PS-100 spectrometer. Chemical shift (δ) are given in ppm relative to an internal standard of TMS. IR spectra were recorded on a Hitachi 215 spectrometer, and MS on a Hitachi M-52 spectrometer with 20 eV.

3-Phenyltio-5-hexen-2-one (1). A mixture of α-(phenylthio)acetone[8] (10 g, 0.066 mol), allyl bromide (8.6 g, 0.072 mol), triethylbenzylammonium chloride (0.2 g) in 30% NaOH (100 ml) and benzene (100 ml) was stirred vigorously at 5—10 °C for 10 h. The reaction mixture was poured into water and worked up as usual. Distillation of the crude product afforded **1** (10.1 g, 82%), bp 120—121 °C/2 mmHg (1 mmHg=133.322 Pa); IR (neat) 1710 cm^{-1} (C=O); NMR (CCl_4) 2.20 (s, 3H), 2.4 (m, 2H), 3.60 (t, J=7.2 Hz, 1H), 4.9—5.2 (m, 2H), 5.5—6.0 (m, 1H), 7.5 (m, 5H). Found: C, 69.52; H, 6.82%. Calcd for $C_{12}H_{14}SO$: C, 69.86; H, 6.84%.

3-Allyl-4-methyl-5-nitro-3-phenylthio-2-pentanone (2). A solution of **1** (10 g, 0.048 mol) in 50 ml of DMF was added dropwise to a stirred suspension of NaH (0.05 mol, 50% dispersion in mineral oil) in 200 ml of DMF at room temperature, and the resulting mixture was kept stirring to cease evolution of hydrogen. A solution of 1-nitro-1-propene[9] (4.0 g, 0.048 mol) in 20 ml of DMF was added dropwise to the above DMF solution of the sodium salt of **1** under colling with an ice–salt bath (about −5 °C) and the resulting solution was stirred for 1 h at −5 °C, and then quenched with acetic acid (6 ml). After the usual work up, the crude product was subjected to column chromatography (sliica gel using benzene as an eluent) to give **2** (11.76 g, 84%): IR (neat)

1705 cm^{-1} (C=O), 1555, 1380 cm^{-1} (NO_2); NMR (CCl_4) 1.04, 1.14 (d, d, J=7.0 Hz, 3H), 2.30, 2.35 (s, s, 3H), 2.55 (m, 2H), 2.85 (m, 1H), 4.2—4.5 (m, 2H), 4.9—5.2 (m, 2H), 5.5—6.0 (m, 1H), 7.5 (m, 5H). The product was about 1: 1 mixture of two diasteroisomers and it was used for the next step without further purification.

3-Acetyl-2-methyl-3-phenylthio-5-hexenal (3). A solution of **2** (4.0 g, 0.014 mol) in 15 ml of methanol was added to a stirred solution of sodium methoxide (1 mol dm^{-3}, 16 ml) at −5 °C. The above solution of *aci*-nitro anion was added dropwise at a rate of one drop per second to a stirred solution of 30 ml of sulfuric acid in 120 ml of methanol at −5 °C. When the addition was complete the mixture was poured into 300 ml of dichloromethane and washed with ice water and dilute aqueous sodium hydroxide. The organic layer was dried over anhydrous magnesium sulfate and concentrated *in vacuo* to yield 3.9 g of the product **5**. The crude product was hydrolyzed with 1 mol dm^{-3} HCl (40 ml) at 50 °C for 1 h. After the usual work up, the crude product was subjected to column chromatography (silica gel using benzene as an eluent) to give **3** (2.9 g, 81%): IR (neat) 1720, 1700 cm^{-1} (C=O), NMR (CCl_4) 1.20, 1.38 (d, d, J=7.0 Hz, 3H), 2.40 (s, 3H), 2.55 (m, 2H), 2.8 (m, 1H), 4.9—5.1 (m, 2H), 5.8—6.0 (m, 1H), 7.3 (m, 5H), 9.55, 9.85 (s, s, 1H). The product was aboult 1: 1 mixture of two diastereoisomers.

Allethrolone (4). Compound **3** (2.62 g, 0.01 mol) was dissolved in 30 ml of ethanol which contained 0.01 mol sodium ethoxide. The resulting solution was stirred at room temperature for 1 h and quenched with 1 mol dm^{-3} HCl. After the usual work up, the crude product was subjected to column chromatography (silica gel using benzene–ether as an eluent) to give **4** (1.02 g, 67%); IR (neat) 3400 cm^{-1} (OH), 1720 cm^{-1} (C=O), 1650 cm^{-1} (C=C); NMR (CCl_4) 2.05 (s, 3H), 2.38 (m, 1H), 2.62 (m, 1H), 2.85 (m, 2H), 3.4 (s, 1H), 4.60 (m, 1H), 4.9—5.1 (m, 2H), 5.6—6.0 (m, 1H). MS m/e= 152 (M^+, 30), 137 (23), 124 (27), 123 (12), 111 (12), 109 (100). The spectral data of the product were identical in all respects with authetic allethrolone.

References

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5) Unsuccessful trials: Reductive method using $TiCl_3$, the classical procedure of a Nef reaction carried out in water, and oxidative methods. Recent development of this field is reviewed, D. Seebach, E. W. Colvin, F. Lehr, and T. Weller, *Chimica*, **36**, 1 (1979), N. Ono and A. Kaji, *Yuki Gosei Kyokai Shi*, **38**, 115 (1980).

6) R. M. Jacobsen, *Tetrahedron Lett.*, **1974**, 3215, where primary nitro compounds were converted to the acetals by a Nef reaction in methanol.

7) Synthetic utility of nitroolefins has been noted in recent years, see Ref. 5. 1-Nitro-1-propene is the best enolonium ion synthon ($CH_3\overset{+}{C}HCHO$) among those known to date. Other known synthons, for example, $CH_3CH{=}C(SCH_3)\overset{\overset{O}{\|}}{S}CH_3$ and $CH_3\underset{\underset{Br}{|}}{C}HCH(OCH_3)_2$ were inert to the sodium salt of **1**.

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