J. Indian Inst. Sci., Sept.–Oct. 1994, **74**, 627–631
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Mild and efficient synthesis of isoprenoidal α-oxoketene dithioacetals†

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Received on February 15, 1994.

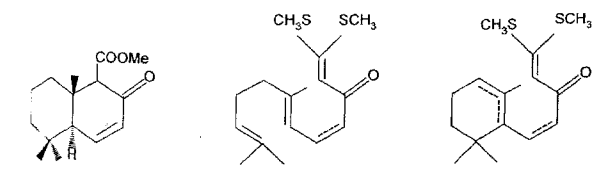
Abstract

The reaction of α-ionone (**4**) and β-ionone (**5**) with sodium hydroxide powder, carbon disulphide and methyl iodide yielded α-oxoketene dithioacetals **11** and **12** with 70 and 95% yield, respectively. Under identical conditions, ketones **6**, **7**, **8**, **9** and **10** yielded **13**, **14**, **15**, **16** and **17** with respectable yields.

Keywords: Isoprenoidal α-oxoketene dithioacetal, sodium hydroxide powder, ionones.

1. Introduction

Several naturally occurring diterpenoids having decalin skeleton possess important biological activities[1]. Trimethyl-(*trans*)-decahydronaphthalene-8-one (**1**) is an important terpene synthon used in the synthesis of deoxoforskolin[2] and related labdane diterpenoids[3]. Decalone (**1**) has been synthesized *via* biomimetic cyclization of acyclic β-keto esters[4] and monocyclic β-keto esters[5]. In view of the synthetic potential of **1**, we visualized substrates **2** and **3** for the biomimetic cyclization. In this communication, we report on efficient preparation of **11**, **12** and related compounds.



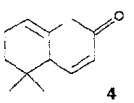
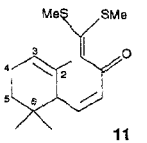
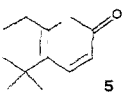
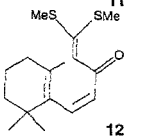
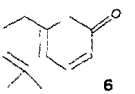
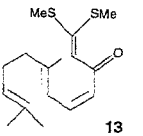
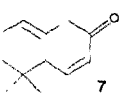
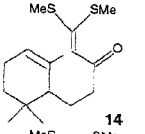
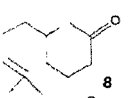
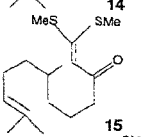
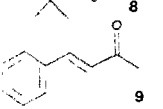
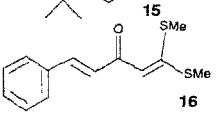
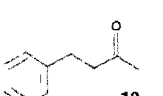
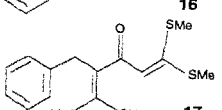
1 **2** **3**

Fig. 1

α-Oxoketene dithioacetals have proved useful in the synthesis of a variety of compounds[5, 6]. They are generally prepared by *bis*-alkylation of dithioacid salts. Many

†CDRI Communication No. 4921.
*For correspondence.

Table 1

Entry	Substrate	Product	Reaction time (h)	Yield (%)
1	 **4**	 **11**	24	70*
2	 **5**	 **12**	24	95*
3	 **6**	 **13**	24	58
4	 **7**	 **14**	48	40*
5	 **8**	 **15**	48	54
6	 **9**	 **16**	24	56
7	 **10**	 **17**	24	57*

*On the basis of recovered starting material

hindered bases have been used for their preparation, *e.g.*, sodium *tert*-amylate[6], sodium 2,6-di-*tert*-butyl-4-methyl-phenoxide[7], lithium dialkylamide[8], potassium *tert*-butoxide[9] and potassium fluoride on alumina[10]. However, these bases proved less effective on α and β ionones. Recently, we have found that sodium hydroxide powder is an effective base for the preparation of allylic xanthates[11] and alkylation of acid labile hemiketals[12]. This base also proved effective in the preparation of α-oxoketene dithioacetals of α- and β-ionones.

The reaction of α-ionone (**4**) with sodium hydroxide powder and carbon disulphide, followed by alkylation with methyl iodide (Table I, entry 1) yielded α-oxoketene dithioacetal **11** with 70% yield. Under the reaction conditions, the α-ionone double bond was not shifted to the β-position. The ^{1}H NMR spectrum of **11** displayed a multiplet at 6.70 for the H-5 proton, another multiplet at 6.20 for the H-4 proton, a singlet at 6.10 for the H-2 proton, multiplet at 5.50 for the H-3′ proton and a six-proton singlet at 2.50 ppm for the two thiomethyl groups. The reaction of β-ionone (**5**) under identical reaction conditions yielded α-oxoketene dithioacetal **12** as a pale yellow crystalline solid, melting point (m.p.) 79–80°C, with significant yield (Table I, entry 2). The reaction of citrylidene acetone (**6**) under identical reaction conditions yielded α-oxoketene dithioacetal **13** with 58% yield (Table I, entry 3). The yields of α-ionone (**4**) and citrylidene acetone (**6**) were on the lower side compared to β-ionone (**5**), and longer reaction time and excess reagent did not help in the improvement of yields.

The dihydro-α-ionone (**7**) and tetrahydro-citrylidene acetone (**8**) were made available from α-ionone (**4**) and citrylidene acetone (**6**) by Birch reduction followed by PCC oxidation. The reaction of dihydro-α-ionone (**7**) with sodium hydroxide powder, carbon disulphide, followed by alkylation with methyl iodide, yielded α-oxoketene dithioacetal **14** with 40% yield (Table I, entry 4). Under identical reaction conditions, the reaction of tetrahydro-citrylidene acetone (**8**) yielded α-oxoketene dithioacetal **15** with 54% yield Table I, entry 5). The yields of dihydro-α-ionone (**7**) and tetrahydro-citrylidene acetone (entries 4 and 5) were on the lower side compared to α- and β-ionone (entries 1 and 2), and excess reagent and extended reaction time did not help in the improvement of yields but resulted in excessive formation of the *bis*-thio-alkylated products.

The benzylidene acetone (**9**) under identical reaction conditions yielded **16** with 56% yield (Table I, entry 6). However, dihydrobenzylidene acetone (**10**) yielded only *bis*-thioalkylated product **17** with 57% yield (Table I, entry 7).

The present method is more efficient and economically viable for sensitive ketones.

Experimental

The reported melting point values (°C) are the uncorrected ones. The infrared spectra were recorded in KBr on a Perkin–Elmer model-157 infrared spectrometer. NMR spectra were obtained in $CDCl_3$ (with Me_4Si internal standard, Aldrich) and are reported in parts per million downfield from Me_4Si. Proton NMR were recorded on Perkin–Elmer R-32 (90 MHz), Varian EM-360 (60 MHz) and Brucker WM-400 instruments, carbon NMR on

a Varian CFT-20 (20 MHz) or a Brucker WM-400 instrument. Mass spectra were recorded on Jeol D-300 mass spectrometer (70 eV, 200°C).

2.1. *1,1-Dimethylmercapto-5-(2′, 6′, 6′-trimethyl-cyclohex-2′-en-1′-yl)-penta-1,4(z)-dien-3-one* (**11**)

To a solution of α-ionone (4) (0.25 g, 1.30 mmol) in dry THF (10.00 ml) were added sodium hydroxide powder (0.20 g, 5.00 mmol) and carbon disulphide (0.15 g, 2.00 mmol) and stirred at ambient temperature for 15 min. Methyl iodide (0.56 g, 3.90 mmol) was added and the stirring was continued at the same temperature for 24 h. The reaction mixture was poured into water and extracted with ethyl acetate (3 × 50 ml). The combined extract was washed with water (3 × 50 ml) and brine solution (50 ml), and dried (Na_2SO_4); the solvent was removed *in vacuo* to afford a pale brown liquid (0.32 g). The total crude product was chromatographed (SiO_2, 60–120 mesh, 15.00 g). Elution with ethyl acetate : hexane (5:95) yielded unreacted **4** as a colourless liquid (0.06 g, 15%). Further elution with ethyl acetate : hexane (10:90) yielded **11** as a thick yellow liquid (0.21 g, 55%): IR (neat, cm^{-1}) 3000, 1660, 1620, 1500, 1380, 1270, 1140, 1000; ^1H NMR ($CDCl_3$, 90 MHz) δ 0.85 (*s*, 6H), 5.50 (*m*, 1H), 6.10 (*s*, 1H), 6.20 (*m*, 1H), 6.70 (*m*, 1H); *m/z* 296 (M^+).

2.2. *1,1-Dimethylmercapto-5-(2′, 6′, 6′-trimethyl cyclohex-1′-en-1′-yl)-penta-1,4(z)-dien-3-one* (**12**)

m.p. 79–90°C; IR (KBr, cm^{-1}) 2900, 1690, 1620, 1560, 1465, 1260, 1080; ^1H NMR ($CDCl_3$, 90 MHz) δ 1.05 (*s*, 6H), 1.50 (*m*, 4H), 1.75 (*s*, 3H), 2.10 (*m*, 2H), 2.45 (*s*, 6H), 6.10 (*s*, 1H), 6.10 (*d*, J = 16.00 Hz, 1H), 7.30 (*d*, J = 16.00 Hz, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 14.88 (*q*), 17.03 (*q*), 18.80 (*t*), 21.60 (*q*), 2 × 28.65 (*q*), 33.39 (*t*), 33.97 (*s*), 39.64 (*t*), 113.39 (*d*), 130.94 (*d*), 134.86 (*s*), 136.40 (*s*), 140.86 (*d*), 163.99 (*s*), 184.13 (*s*); MS (*m/z*) 296 (M^+), 281 (M^+-CH_3), 249 (M^+-SCH_3).

2.3. *1,1-Dimethylmercapto-7,11-dimethyl-1,4(z), 6(E), 10-dodeca-tetraen-3-one* (**13**)

IR (neat, cm^{-1}) 2950, 1600, 1500, 1380, 1250, 1120, 970; ^1H NMR ($CDCl_3$, 90 MHz) δ 1.45 (*s*, 3H), 1.55 (*s*, 3H), 1.75 (*s*, 3H), 2.00 (*m*, 4H), 2.35 (*s*, 6H), 4.95 (*m*, 1H), 6.00 (*m*, 3H), 7.30 (*dd*, J = 12.00, 5.00 Hz, 1H); MS (*m/z*) 296 (M^+).

2.4. *1,1-Dimethylmercapto-5-(2′, 6′, 6′-trimethyl cyclohex-2′-en-1′-yl)-penta-1-en-3-one* (**14**)

IR (neat, cm^{-1}) 3000, 1770, 1660, 1540, 1430, 1200, 1160; ^1H NMR ($CDCl_3$, 90 MHz) δ 0.90 (*s*, 6H), 1.70 (*s*, 3H), 2.00 (*m*, 8H), 2.45 (*s*, 3H), 2.50 (*s*, 3H), 5.30 (*m*, 1H), 6.00 (*s*, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz) 14.80 (*q*), 17.02 (*q*), 22.90 (*t*), 23.40 (*q*), 25.36 (*t*),

27.43 (*q*), 27.62 (*q*), 31.57 (*t*), 32.51 (*s*), 43.12 (*t*), 48.59 (*d*), 112.78 (*d*), 114.51 (*s*), 120.70 (*d*), 135.80 (*s*), 195.39 (*s*); MS (*m/z*) 298 (M^+).

2.5. 1,1-Dimethylmercapto-7,11-dimethyl-dodeca-1,-10-dien-3-one **(15)**

IR (neat, cm^{-1}) 3000, 1770, 1660, 1540, 1430, 1200, 1160; ^1H NMR ($CDCl_3$, 90 MHz) δ 1.26 (*bs*, 6H), 1.60 (*bs*, 3H), 2.10 (*m*, 10H), 2.40 (*s*, 6H), 5.00 (*m*, 1H), 6.00 (*s*, 1H); MS (*m/z*) 300 (M^+).

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