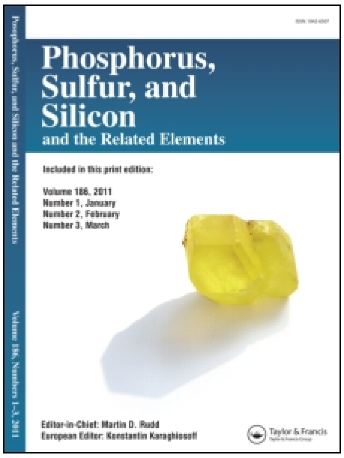

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# A SYNTHETIC ROUTE TO 3-METHYLTHIO-2-ALKANONES STARTING FROM 3-ALKYL-2,4-PENTANEDIONES

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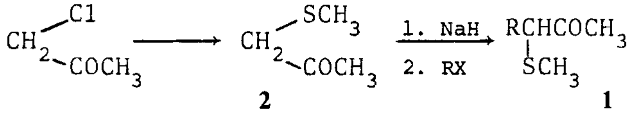
An efficient preparation of a 3-methylthio-2-alkanone (**1**) has been realized by the reaction of a 3-alkyl-2,4-pentanedione (**8**) with one mol-equiv of *S*-methyl methanethiosulfonate (**4**) in the presence of excess EtONa in EtOH. Furthermore, treatment of **8** with **4** and $K_2CO_3$ in refluxing acetone, followed by addition of MeOH and heating the resulting mixture, gave **1** in a high yield. These methods were applied to synthesis of pseudoionone.

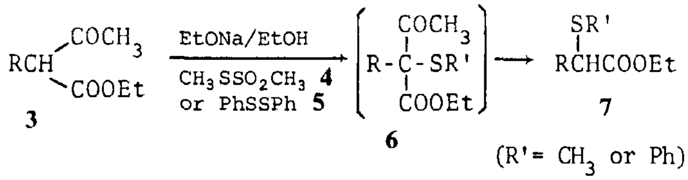
## INTRODUCTION

A title compound, 3-methylthio-2-alkanone (**1**), is a useful synthetic precursor of a 3-alken-2-one[1] and 3-methylthio-3-alken-2-one.[2] Alkylation of 1-methylthio-2-propanone (**2**) is one of the methods for making **1**, and there have been two reports on this alkylation.[2,3] Both of them utilized NaH as a base for generating the carbanion of **2**, and the subsequent alkylation of the carbanion was reported to suffer from contamination of inseparable impurities or relatively low yields. The low yields are probably due to competitive dialkylation and *O*-alkylation.



SCHEME 1

Recently, we disclosed an efficient and convenient method for preparation of 2-(methyl or phenylthio)alkanoic ester (**7**) from 2-acetylalkanoic ester by the use of a sulfenylating reagent, *S*-methyl methanethiosulfonate (**4**) or diphenyl disulfide (**5**), as shown in Scheme 2.[4] In this method, easily removable acetyl group serves for stabilization of the adjacent carbanion to permit utilization of EtONa as a base and for protection of the methine carbon of **7** from further alkylation. As being apparently suggested from Scheme 2, exchange of ethoxycarbonyl group for acetyl group in the starting material can provide a new method for synthesizing **1**. Hence, we initiated our investigation to survey the reaction conditions for conversion of 3-alkyl-2,4-pentanedione (**8**) to the desired **1**. Now we wish to describe highly



SCHEME 2

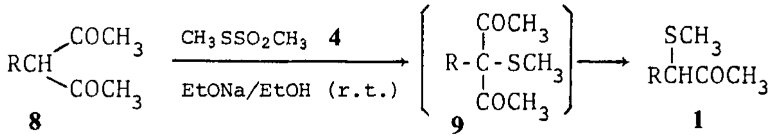
selective and convenient methods for preparation of **1**, where either $K_2CO_3$ or EtONa can be employed as a base, together with their application to synthesis of pseudoionone (**13**, 6,10-dimethyl-3,5,9-undecatrien-2-one).

## RESULTS AND DISCUSSION

First, a 3-alkyl-2,4-pentanedione, 3-benzyl-2,4-pentanedione (**8a**), was treated with 1.2 mol-equiv of *S*-methyl methanethiosulfonate (**4**) in the presence of excess EtONa (1.4 equiv) in EtOH at room temperature. These conditions were similar to those for the efficient transformation of **3** into **7** (*R'* = Me) in Scheme 2. Although sulfenylation of **8a** leading to 3-benzyl-3-methylthio-2,4-pentanedione (**9a**), the subsequent deacetylation took place smoothly to afford **1a** in 86% yield and the formation of 3,3-bis(methylthio)-4-phenyl-2-butanone (8% yield) was observed. As a result of examining various reaction conditions, we found that the amount of the sulfenylating reagent (**4**) was crucial to the yield of **1** and use of just one mol-equiv of **4** gave the best result without formation of the disulfenylated product. The results are summarized in Table I. It should be noted that diphenyl disulfide (**5**), which could be preferably employed for synthesis of **7** (*R'* = Ph) in Scheme 2, is not suitable for the present conversion. In the reaction of **8a** with **5** (2 mol-equiv) and EtONa (1.3 equiv) in EtOH (at room temperature for 48 h), 4-phenyl-2-butanone was obtained in 40% yield together with **1a** (48% yield).[5]

Since acetyl group stabilizes an adjacent carbanion more strongly than ethoxycarbonyl group, the 3-position of **8** is more acidic than the 2-position of the corresponding **3**. Therefore, it is anticipated that a weaker base can be used for sulfenylation of **8** and deacetylation of **9**. In fact, treatment of **8a** with 1.4 mol-equiv of **4** and 1.6 mol-equiv of $K_2CO_3$ in refluxing acetone for 6 h gave **9a** in 96% yield. When a mixture of **9a** and $K_2CO_3$ (0.5 mol-equiv) in acetone-MeOH (1 : 1) was stirred at room temperature, the expected **1a** was obtained in 97.5% yield. Further, we examined the possibility of performing these reactions, **8** → **9** and **9** → **1**, in one flask. To a solution of **8a** in acetone, were added **4** (1.5 mol-equiv) and $K_2CO_3$ (1.2 mol-equiv), and the mixture was heated under a reflux for 7 h. Then, MeOH was added and the resulting mixture was further heated under a reflux for 30 min. The usual work-up afforded **1a** in 97% yield. In analogous manners, 3-methylthio-2-decanone (**1b**) and 3-methylthio-2-pentadecanone (**1c**) were prepared in high yields (see Table I). It is noteworthy that any amount of the disulfenylated product, 3,3-bis(methylthio)-2-alkanone, was not detected in the reaction mixture though excess **4** was used. This may be explained in terms of the basicity of $K_2CO_3$ which cannot abstract the proton at the 3-position of **1**, but that of **8**.

[Method A]



$$\mathrm{RCH(COCH_3)_2}\ (\mathbf{8}) \xrightarrow[\text{EtONa/EtOH (r.t.)}]{\mathrm{CH_3SSO_2CH_3}\ \mathbf{4}} \left[\mathrm{R\text{-}C(SCH_3)(COCH_3)_2}\ (\mathbf{9})\right] \longrightarrow \mathrm{RCH(SCH_3)COCH_3}\ (\mathbf{1})$$

[Method B]

$$\mathbf{8} \xrightarrow[\text{K}_2\text{CO}_3\text{/acetone (reflux)}]{\mathrm{CH_3SSO_2CH_3}\ \mathbf{4}} \mathbf{9} \xrightarrow[\text{then reflux}]{\text{addition of MeOH,}} \mathbf{1}$$

a: R = $PhCH_2$ b: R = $n\text{-}C_7H_{15}$ c: R = $n\text{-}C_{12}H_{25}$

SCHEME 3

TABLE I

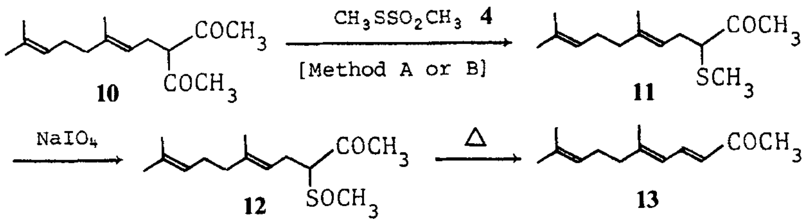
Yield (%) in conversion of **8** to **1**

| R | [Method A][a] | [Method B][a] |
|---|---|---|
| $PhCH_2$ | 92 | 97 |
| $n\text{-}C_7H_{15}$ | 94 | 95 |
| $n\text{-}C_{12}H_{25}$ | 92 | 95 |
| geranyl | 90 | 89 |

[a] See Scheme 3 and Experimental Section.

Thus, we have established a novel method for preparation of **1** from **8** using inexpensive EtONa [Method A] or $K_2CO_3$ [Method B] as summarized in Scheme 3 and Table I.

Finally, we would like to describe the application of the present methods to synthesis of pseudoionone (**13**). As outlined in Scheme 4, the starting material is 3-geranyl-2,4-pentanedione (**10**), which is readily prepared from geraniol (see Experimental Section). When **10** was subjected to the reaction with **4** according to Method A or Method B of Scheme 3, 6,10-dimethyl-3-methylthio-5,9-undecadien-2-one (**11**) was produced in 90% or 89% yield, respectively. Oxidation of **11** with $NaIO_4$ in MeOH—$H_2O$ gave the corresponding sulfoxide (**12**), and refluxing the solution of **12** in toluene containing $CaCO_3$ resulted in formation of **13** in 92% overall yield from **11**.



SCHEME 4

## EXPERIMENTAL

NMR spectra were obtained on a Hitachi R-600 spectrometer. Infrared spectra were determined with a JASCO A-200 spectrometer. Mass spectra were recorded on a Hitachi RMU 7M high-resolution spectrometer.

*Preparation of 3-methylthio-4-phenyl-2-butanone* **1a**. *A Typical Procedure.* (*a*) [*Method A*]. To a solution containing 3-benzyl-2,4-pentanedione (**8a**) (290 mg : 1.52 mmol) and *S*-methyl methanethiosulfonate (**4**) (194 mg : 1.54 mmol) in EtOH (1 ml), was added 0.70 M ethanolic solution (2.7 ml) of EtONa, and the resulting solution was stirred at room temperature for 1 h. After addition of aqueous $NH_4Cl$ solution and extraction with $CH_2Cl_2$, the extract was dried over anhydrous $Na_2SO_4$, evaporated, and column-chromatographed on silica gel [elution with benzene–hexane (1 : 1)] to give **1a** (253 mg, 96% yield) as a colorless oil, which was further purified by a short-path distillation (bath temperature: 119–122°C/1 mmHg): NMR ($CDCl_3$) $\delta$ 1.90 (3 H, s), 2.12 (3 H, s), 2.61–3.54 (3 H, m), and 7.13 (5 H, s); IR (neat) 1705 $cm^{-1}$. *Anal.* Calcd. for $C_{11}H_{14}OS$: C, 68.02; H, 7.26. Found: C, 67.89; H, 7.14.

(*b*) [*Method B*]. To a solution of **8a** (333 mg : 1.75 mmol) in acetone (12 ml), were added $K_2CO_3$ (290 mg) and **4** (334 mg : 2.65 mmol), and the resulting mixture was heated under a reflux for 7 h. Then, MeOH (10 ml) was added and the reaction mixture was further heated under a reflux for 30 min. After evaporation, addition of water, and extraction with $CH_2Cl_2$, the organic layer was dried over anhydrous $Na_2SO_4$ and evaporated. The residue was subjected to column-chromatography on silica gel using hexane–benzene (5 : 1) as an eluent to give **1a** (329 mg, 97% yield).

Analogously, 3-methylthio-2-decanone (**1b**) and 3-methylthio-2-pentadecanone (**1c**) were obtained.

**1b**: a colorless oil which was purified by column-chromatography and a short-path distillation (bath temperature: 98–100°C/1 mmHg); NMR ($CDCl_3$) $\delta$ 0.63–2.10 (15 H, m), 1.92 (3 H, s), 2.27 (3 H, s), and 3.16 (1 H, t, J = 7.2 Hz); IR (neat) 1710 $cm^{-1}$. *Anal.* Calcd. for $C_{10}H_{22}OS$: C, 65.29; H, 10.96. Found: C, 65.02; H, 10.78.

**1c**: a colorless oil which was purified by column-chromatography and a short-path distillation (bath temperature: 152–158°C/1 mmHg); NMR ($CDCl_3$) $\delta$ 0.65–1.80 (25 H, m), 1.91 (3 H, s), 2.25 (3 H, s), and 3.15 (1 H, t, J = 6.9 Hz); IR (neat) 1710 $cm^{-1}$. *Anal.* Calcd. for $C_{15}H_{32}OS$: C, 70.53; H, 11.84. Found: C, 70.47; H, 11.69.

*Synthesis of 3-Benzyl-3-methylthio-2,4-pentanedione* (**9a**). To a solution of **8a** (387 mg : 2.03 mmol) in acetone (20 ml), were added **4** (366 mg : 2.90 mmol) and $K_2CO_3$ (450 mg : 3.26 mmol), and the resulting mixture was heated under a reflux for 6 h. Then, $CH_2Cl_2$ was added and the insoluble solid was filtered off. The filtrate was evaporated and subjected to column-chromatography on silica gel using hexane–benzene (1 : 1) as an eluent to afford **9a** (459 mg, 96% yield) as colorless crystals: mp 70–71°C (from diethyl ether); NMR ($CDCl_3$) $\delta$ 1.94 (3 H, s), 2.11 (6 H, s), 3.27 (2 H, s), and 7.22 (5 H, s); IR (KBr) 1730 and 1705 $cm^{-1}$. *Anal.* Calcd. for $C_{13}H_{16}O_2S$: C, 66.06; H, 6.84. Found: C, 66.02; H, 6.82.

*Conversion of* **9a** *to* **1a**. To a solution of **9a** (517 mg : 2.19 mmol) in acetone (2.5 ml) and MeOH (2.5 ml), was added $K_2CO_3$ (160 mg, 1.16 mmol), and the resulting mixture was stirred at room temperature for 1 h. After addition of $CH_2Cl_2$, an insoluble solid was removed by filtration and the filtrate was evaporated. The residual oil was separated by column-chromatography on silica gel using hexane–benzene (2 : 1) as an eluent to give **1a** (415 mg, 98% yield).

*Synthesis of 6,10-Dimethyl-3-methylthio-5,9-undecadien-2-one* (**11**). The starting material, 3-geranyl-2,4-pentanedione **10**, was prepared by the following manner. To a solution containing geraniol (22.20 g : 0.144 mol) and $Et_3N$ (20 ml) in diethyl ether (100 ml), was dropwise added $SOCl_2$ (11 ml) under keeping the reaction temperature between −5 and +5°C by cooling with ice-salt bath. Then, the reaction mixture was stirred at room temperature for 12 h and evaporated to remove diethyl ether and excess $Et_3N$. After addition of water and extraction with $CH_2Cl_2$, the extract was dried over anhydrous $Na_2SO_4$ and evaporated to yield an oil (27.21 g) which was shown by an NMR analysis to consist of geranyl chloride and its $\gamma$-isomer (3-chloro-3,7-dimethyl-1,6-octadiene) in the ratio of *ca.* 2 : 1. This oil (10.52 g : *ca.* 61 mmol) was dissolved in EtOH (35 ml), and 2,4-pentanedione (16 ml : 123 mmol) as well as NaI (9.0 g) was added. After 1.49 M ethanolic solution (35 ml) of EtONa was added, the resulting mixture was stirred at room temperature for 2 days, and then EtOH was removed by evaporation. After addition of aqueous $NH_4Cl$ solution and extraction with $CH_2Cl_2$, the organic layer was evaporated and distilled under reduced pressure to give **10** (8.437 g, 64% overall yield from geraniol) as a colorless oil having bp 123–126°C/7 mmHg.

To a solution of **10** (1.569 g : 6.64 mmol) and **4** (836 mg : 6.63 mmol) in EtOH (12 ml), was added 0.61 M ethanolic solution (13 ml) of EtONa, and the mixture was stirred at room temperature for 1 h. After removal of EtOH by evaporation, addition of aqueous $NH_4Cl$ solution, and extraction with $CH_2Cl_2$, the extract was dried over anhydrous $Na_2SO_4$, evaporated, and column-chromatopgraphed on silica gel [elution with hexane–benzene (1 : 1)] to give **11** (1.441 g, 90% yield) as a colorless oil, which was further purified by a short-path distillation (bath temperature: 127–129°C/1 mmHg; lit.[3] bp 118–120°C/0.35 mmHg): NMR ($CDCl_3$) $\delta$ 1.65 (9 H, br s), 1.8–2.6 (6 H, m), 1.95 (3 H, s), 2.25 (3 H, s), 3.19 (1 H, t, $J = 7.2$ Hz), and 4.8–5.4 (2 H, m); IR (neat) 1710 $cm^{-1}$; exact mass for $C_{14}H_{24}OS$ ($M^+$) m/e 240.1547, found 240.1566 [relative intensity to the base peak ($C_5H_9$): 15%]; exact mass for $C_{14}H_{25}OS$ ($MH^+$) m/e 241.1624, found 241.1609 (4.5%).

To a solution of **10** (465 mg : 1.97 mmol) and **4** (299 mg : 2.37 mmol) in acetone (20 ml), was added $K_2CO_3$ (330 mg), and the resulting mixture was heated under a reflux for 7 h. Then, methanol (10 ml) was added and the mixture was further heated under a reflux for 30 min. After removal of the solvents by evaporation, addition of water, and extraction with $CH_2Cl_2$, the organic layer was dried over anhydrous $Na_2SO_4$, evaporated, and column-chromatographed on silica gel to afford **11** (418 mg, 89% yield).

*Transformation of* **11** *into Pseudoionone* (**13**). To a solution of **11** (1.070 g : 4.45 mmol) in MeOH (25 ml), was dropwise added aqueous solution of $NaIO_4$ (955 mg/15 ml) under cooling with ice-water, and the resulting mixture was stirred at room temperature for 24 h. After removal of an insoluble solid by filtration, evaporation of MeOH, addition of brine, and extraction with diethyl ether, the extract was dried over anhydrous $Na_2SO_4$ and evaporated to give crude 6,10-dimethyl-3-methylsulfinyl-5,9-undecadien-2-one **12** (1.106 g). This crude sulfoxide (388 mg) was dissolved in toluene (30 ml), and then $CaCO_3$ (180 mg) was added. The resulting mixture was heated under a reflux for 24 h. After filtrating an insoluble solid off, the filtrate was concentrated and chromatographed on silica gel (elution with benzene) to afford **13** (277 mg, 92% overall yield from **11**) as an oil, the IR and NMR spectra of which were in complete agreement with those of the authentic sample prepared from citral and acetone.[6]

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