2-Methylthiomethylation of 1,3-Dicarbonyl Compounds and Synthesis of 2-Methylene-1,3-dicarbonyl Compounds

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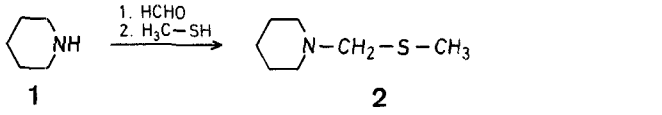
The introduction of methylene group into the α-position of carbonyl compounds is a key procedure in the syntheses of sesquiterpenes and antibiotics. When faced with the problem of preparing the enedione **1**[1], a 2-methylene-1,3-dicarbonyl compound, it was found that many of the existing synthetic methods for α-methylenation of monocarbonyl compounds[2] were not successful. We have thus focussed our attention on thiomethylation-oxidation-elimination sequences in order to introduce a methylene group into the 2-position of 1,3-dicarbonyl compounds. 2-Thiomethylations of 2-monosubstituted 1,3-dicarbonyl compounds have been long-established using chloromethyl sulfides and a base such as sodium[3] or sodium ethoxide[4] and give moderate yields. In the case of 2-unsubstituted 1,3-dicarbonyl compounds, Smissman et al.[5] reported that a satisfactory yield was obtained only with dimedone using piperidinomethyl thiobenzoate (or thioacetate) hydrochloride. We now report the successful preparation of 2-methylene-1,3-dicarbonyl compounds, useful synthetic intermediates, using *N*-methylthiomethylpiperidine hydrochloride[6] **(3)**, prepared from piperidine **(1)** as shown (Scheme **A**).

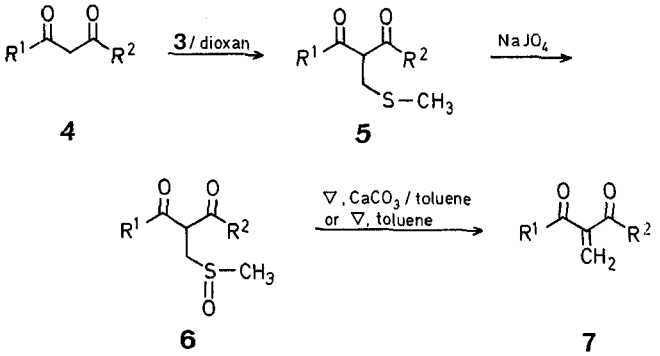


1 2 3

Scheme **A**

Compound **2** could also be prepared by treating piperidine **(1)** with chloromethyl methyl sulfide but the yield was lower.

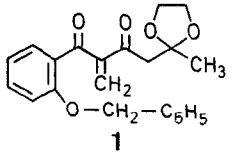
Methylthiomethylations were carried out by heating 1,3-dicarbonyl compounds **4** and 1.5 equivalents of **3** in dioxan for 24 h (Table 1). Acyclic (entries 3, 4) and cyclic (entry 6) keto esters also gave satisfactory yields of **5** (Scheme **B**). Acyclic diketones (entries 1, 2) gave good yields, while dimedone, a cyclic diketone, gave a trace of thiomethylated product (~5%). Diethyl malonate gave only recovered starting material under these reaction conditions. Oxidation of the 2-methylthiomethyl-1,3-dicarbonyl compounds **5** with sodium metaperiodate in methanol gave the 2-methylsulfinylmethyl-1,3-dicarbonyl compounds **6** (Table 2). High yields were obtained in the case of acyclic diketones (entries 1, 2) and keto esters (entries 3, 4), while acyclic keto amides and cyclic keto esters were decomposed under these reaction conditions. Pyrolysis of **6** furnished the 2-methylene-1,3-dicarbonyl compounds **7** (Table 3).



4 5 6 7

Scheme **B**

Two methods have been reported for preparation of 2-methylene-1,3-dicarbonyl compounds. Trahanovsky et al.[7] reported that the low-pressure gas-phase pyrolysis of 3-phenylpropargyl acetate or benzoate gave 1-phenyl-2-methylene-1,3-butanedione or 1,3-diphenyl-2-methylene-1,3-propanedione, respectively. Reich et al.[8] prepared 1-phenyl-2-methylene-1,3-butanedione from 2-methyl-1-phenyl-1,3-butanedione via a phenylselenenylation-oxidation-elimination sequence. However, these methods are not directly applicable to 2-unsubsti-



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tuted 1,3-dicarbonyl compounds. Our method is thus useful for the 2-methylenation of acyclic 2-unsubstituted 1,3-dicarbonyl compounds.

N-Methylthiomethylpiperidine Hydrochloride (3):
Methanethiol gas [generated by adding concentrated sulfuric acid (50 ml) to 15% aqueous sodium methanethiolate (150 ml)] is introduced to a homogeneous solution of piperidine (**1**; 16 g, 0.19 mol) and 37% aqueous formaldehyde (20 g) at 0 °C. As the reaction progresses an oil separates. The organic layer is extracted with ether (50 ml), dried with magnesium sulfate, and concentrated. The residual oil (19.5 g) is distilled to give *N*-methylthiomethylpiperidine **(2)**; yield: 16.6 g (61%); b.p. 92–95 °C/42 torr (Ref.[6], b.p. 82 °C/12 torr).

The ethereal solution of this amine is added dropwise to ether saturated with hydrogen chloride to afford *N*-methylthiomethylpiperidine hydrochloride **(3)**; yield: 20 g (58% from piperidine); m.p. 147–149 °C.

$C_7H_{16}ClNS$	calc.	C 46.26	H 8.89	N 7.71
(181.8)	found	45.93	8.73	7.84

2-Methylthiomethyl-1,3-dicarbonyl Compounds 5; General Procedure:
A mixture of the 1,3-dicarbonyl compound **4** (2.5 mmol), *N*-methylthiomethylpiperidine hydrochloride (**3**; 682 mg, 3.75 mmol) in anhydrous dioxan (50 ml) is stirred at 80–85 °C for 24 h. The reaction mixture is concentrated to one-third of its original volume under reduced pressure and the residue is diluted with water (5 volumes) and extracted with ethyl acetate (50 ml). The organic layer is washed with water (3 × 20 ml), dried with magnesium sulfate, and concentrated. The residual oil is subjected to column chromatography (Kieselgel 60, 70–230 mesh) eluting with *n*-hexane/benzene (1/1) to afford the 2-methylthiomethyl-1,3-dicarbonyl compound **5**.

2-Methylsulfinylmethyl-1,3-dicarbonyl Compounds 6; General Procedure:
A solution of sodium metaperiodate (8.4 g, 39 mmol) in water (85 ml) is added to a solution of the 2-methylthiomethyl-1,3-dicarbonyl compound **5** (7.9 mmol) in methanol (300 ml) at 0 °C within 10 min. After stirring at room temperature for 24 h, the reaction mixture is concentrated to one-fourth of its original volume under reduced pressure and extracted with ethyl acetate (80 ml). The ethyl acetate layer is washed with water (3 × 20 ml), dried with magnesium sulfate, and concentrated to afford the 2-methylsulfinylmethyl-1,3-dicarbonyl compound **6**.

Table 1. 2-Methylthiomethyl-1,3-dicarbonyl Compounds **5**

Entry	R^1	R^2	Yield[a] [%]	m.p. [°C] or b.p.[b] [°C]/torr	Molecular formula[c]	I.R. (Neat or KBr) ν [cm^{-1}]	^{1}H-N.M.R. (Solvent) δ [ppm]
1			95	260°/0.015	$C_{17}H_{16}O_2S$ (284.4)	1690, 1670, 1595	(CCl_4): 2.03 (s, 3H, SCH_3); 3.15 (d, 2H, J=6 Hz, —CH_2S—); 5.32 [t, 1H, J=6 Hz, —$CH(CO)_2$]; 7.2–7.6 (m, 6H_{arom}); 7.8–8.1 (m, 4H_{arom})
2	H_3C		79	205–210°/ 0.01	$C_{12}H_{14}O_2S$[d] (222.3)	1720, 1675, 1595	(CCl_4): (keto form): 2.08 (s, 6H, —$COCH_3$, and SCH_3); 3.01 (d, 2H, J=7 Hz, —CH_2S—); 4.58 [t, 1H, J=7 Hz, —$CH(CO)_2$]; 7.3–8.1 (m, 5H_{arom}) (enol form): 1.98 (s, 3H, SCH_3 or —$COCH_3$); 2.38 (s, 3H, —$COCH_3$ or SCH_3); 3.35 (s, 2H, —CH_2S—); 7.3–8.1 (m, 5H_{arom}); 16.95 (s, 1H, enolic H)
3		C_2H_5O	86	210–215°/ 0.04	$C_{13}H_{16}O_3S$ (252.4)	1735, 1685, 1593	(CCl_4): 1.17 (t, 3H, J=8 Hz, OCH_2CH_3); 2.07 (s, 3H, SCH_3); 3.05 (d, 2H, J=7 Hz, —CH_2S—); 4.08 (q, 2H, J=8 Hz, OCH_2CH_3); 4.48 [t, 1H, J=7 Hz, —$CH(CO)_2$]; 7.4–8.1 (m, 5H_{arom})
4	H_3C	i-$C_5H_{11}O$	77	205–210°/ 0.08	$C_{11}H_{20}O_3S$ (232.4)	1740, 1720, 1640	(CCl_4): 0.95 [d, 6H, J=6 Hz, —$CH(CH_3)_2$]; 1.4–1.8 [m, 3H, $OCH_2CH_2CH(CH_3)_2$]; 2.08 (s, 3H, SCH_3 or —$COCH_3$); 2.22 (s, 3H, —$COCH_3$ or SCH_3); 2.86 (d, 2H, J=7 Hz, —CH_2S—); 3.57 [t, 1H, J=7 Hz, —$CH(CO)_2$]; 4.13 (t, 2H, J=6 Hz, OCH_2CH_2—)
5	H_3C		74	205°/0.13	$C_{10}H_{17}NO_3S$ (231.3)	3550, 1730, 1710, 1655	($CDCl_3$): 2.13 (s, 3H, SCH_3 or —$COCH_3$); 2.20 (s, 3H, —$COCH_3$ or SCH_3); 3.03 (d, 2H, J=7 Hz, —CH_2S—); 3.67 [m, 8H, $N(CH_2CH_2)_2O$]; 3.85 [t, 1H, J=7 Hz, —$CH(CO)_2$]
6			85	156–159° (C_6H_6)	$C_{11}H_{10}O_3S$ (222.3)	3200, 1660, 1630	($CDCl_3$): 2.15 (s, 3H, SCH_3); 3.90 (s, 2H, —CH_2S—); 7.1–8.0 (m, 4H_{arom})

[a] Yields after column chromatography.
[b] Bath temperature of Kugelrohr apparatus.
[c] Satisfactory microanalyses obtained: C ±0.22, H ±0.22, N −0.06.
[d] Keto and enol isomers are separable.

Table 2. 2-Methylsulfinylmethyl-1,3-dicarbonyl Compounds **6**

Entry[a]	Yield[b] [%]	I.R. (Neat or KBr) ν [cm^{-1}]	^{1}H-N.M.R. (Solvent) δ [ppm]
1	91	1695, 1675, 1595	($CDCl_3$): 3.30 [s, 3H, S(O)—CH_3]; 4.08 [d, 2H, —CH_2S(O)—]; 5.64 [t, 1H, J=7 Hz, —$CH(CO)_2$]; 7.2–8.2 (m, 10H_{arom})
2	88	1720, 1675, 1595	(CCl_4): 2.10 (s, 3H, —$COCH_3$); 3.32 [s, 3H, S(O)—CH_3]; 3.6–4.2 [m, 2H, —CH_2S(O)—]; 4.7 [m, 1H, —$CH(CO)_2$]; 7.3–8.2 (m, 5H_{arom})
3	94	1745, 1690, 1600	($CDCl_3$): 1.17 (t, 3H, J=7 Hz, —OCH_2CH_3); 3.30 [s, 3H, S(O)—CH_3]; 3.84 [d, 2H, J=7 Hz, —CH_2S(O)—]; 4.09 (q, 2H, J=7 Hz, —OCH_2CH_3); 4.48 [t, 1H, J=7 Hz, —$CH(CO)_2$]; 7.4–8.1 (m, 5H_{arom})
4	80	1750, 1730, 1655	(CCl_4): 0.95 [d, 6H, J=6 Hz, —$CH(CH_3)_2$]; 1.3–1.9 [m, 3H, —$CH_2CH(CH_3)_2$]; 2.18 (s, 3H, —$COCH_3$); 3.27 [s, 3H, S(O)—CH_3]; 3.63 [s, 2H, —CH_2S(O)—]; 4.10 (t, 2H, J=7 Hz, —OCH_2—CH_2—)

[a] For R^1, R^2 see corresponding entries in Table 1.
[b] Yields are given for isolated crude products.

Table 3. 2-Methylene-1,3-dicarbonyl Compounds **7**

Entry[a]	Yield[b] [%] A	Yield[b] [%] B	b.p.[c] [°C]/torr	I.R. (Neat) ν [cm^{-1}]	^{1}H-N.M.R. (CCl_4) δ [ppm]	High-Resolution M.S.[d] *m/e*
1	89	91	250°/0.007	1675, 1597	6.15 (s, 2H, $=CH_2$); 7.2–7.9 (m, 10H_{arom})	236.0835 (M^+) (calc. for $C_{16}H_{12}O_2$: 236.0836)
2	86	95	195–200°/ 0.015	1670, 1595	2.27 (s, 3H, CH_3); 5.85 (s, 1H, $=CH_2$); 6.50 (s, 1H, $=CH_2$); 7.2–8.1 (m, 5H_{arom})	174.0669 (M^+) (calc. for $C_{11}H_{10}O_2$: 174.0680)
3	98	94	137–142°/ 0.005	1730, 1680, 1598	1.15 (t, 3H, J=8 Hz, CH_3); 4.11 (q, 2H, J=8 Hz, $-OCH_2-$); 5.95 (s, 1H, $=CH_2$); 6.56 (s, 1H, $=CH_2$); 7.2–8.2 (m, 5H_{arom})	204.0786 (M^+) (calc. for $C_{12}H_{12}O_2$: 204.0785)

[a] For R^1, R^2 see corresponding entries in Table 1.
[b] Yields are given for isolated products.
[c] Bath temperature of Kugelrohr apparatus.
[d] Satisfactory microanalyses could not be obtained due to unstability of **7**. The purity of **7** was established by spectral data (I.R., ^{1}H-N.M.R.) and G.L.C. (single peak for each) in combination with the high-resolution mass measurements.

2-Methylene-1,3-dicarbonyl Compounds 7; General Procedures:

Method A: A mixture of the 2-methylsulfinylmethyl-1,3-dicarbonyl compound **6** (6.0 mmol), a catalytic amount of calcium carbonate (~5 mg), and toluene (400 ml) is refluxed for 4 days. The solvent is evaporated under reduced pressure. The residue is diluted with benzene (80 ml), washed with water (2 × 20 ml), dried with magnesium sulfate, and concentrated to give the 2-methylene-1,3-dicarbonyl compound **7**.

Method B: A concentrated solution of the 2-methylsulfinylmethyl-1,3-dicarbonyl compound **6** (6.0 mmol) in toluene (0.5 ml) is heated at 130–135 °C for 1.5 h (entries 1, 2) or 6 h (entry 3). The reaction mixture is diluted with benzene (30 ml), washed with water (3 × 10 ml), dried with magnesium sulfate, and concentrated to give the 2-methylene-1,3-dicarbonyl compound **7**.

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