The Synthesis of Dihydro-2(3*H*)-thiophenone Derivatives

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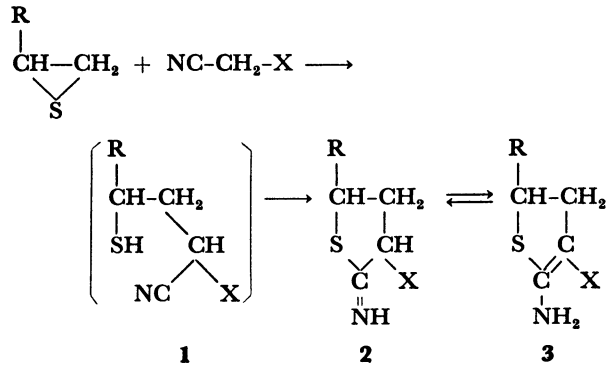
The reaction of 2,2-dimethylthiirane (**4**) with diethyl malonate (**5**) in the presence of sodium ethoxide gave 3-ethoxycarbonyl-5,5-dimethyl-dihydro-2(3*H*)-thiophenone (**6**) and a polymer. The yield of **6** could be increased to 65%. The reaction of thiirane, 2-methylthiirane, 2-butylthiirane, 2-hexylthiirane, 1,2-epithiocyclohexane, and 2-phenylthiirane with **5** also gave corresponding dihydro-2(3*H*)-thiophenone derivatives. Although the reaction of an alkyl-substituted thiirane with **5** selectively gave a product formed by an attack of a carbanion at the less-hindered carbon of the thiirane ring, the major product of the reaction of 2-phenylthiirane with **5** was an isomer formed by an attack at the more hindered carbon of the thiirane ring. The reaction of **4** with ethyl acetoacetate gave 3-acetyl-5,5-dimethyl-dihydro-2(3*H*)-thiophenone selectively. A product **6** was also obtained by a reaction of **4** with **5** by using sodium hydride instead of sodium ethoxide.

It was reported that a reaction of thiiranes with ethyl cyanoacetate[1] and malononitrile[2] in the presence of a base catalyst has dihydrothiophene derivatives (**3**). The first step of these reactions was considered to be the formation of an intermediate **1** by an attack of carbanion to the thiirane ring, and a following ring closure by the reaction of thiol **1** with



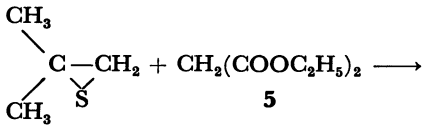
1 **2** **3**

the cyano group. This ring closure was considered to inhibit the polymerization of **1** with thiirane. Though it was reported[1] that the reaction of thiiranes with other active methylene compounds with cyano groups attached to the methylene gave only polymers, we expected that a ring closure similar to the condensation of **1** occured in the reaction of thiiranes with β-oxo-esters.

In this work, we found that the reaction of thiiranes with diethyl malonate (**5**) and ethyl acetoacetate gave dihydro-2(3*H*)-thiophene derivatives. The direction of the attack of carbanions to the thiirane rings, the effect of the structures of the thiiranes and the active methylene compounds, and the effect of the reaction conditions were studied.

Results and Discussion

The reaction of **4** with **5** in the presence of sodium ethoxide gave 3-ethoxycarbonyl-5,5-dimethyl-dihydro-2(3*H*)-thiophenone (**6**) selectively and did not give it's isomer, 3-ethoxycarbonyl-4,4-dimethyl-dihydro-2(3*H*)-thiophenone (**7**). This shows that the carbanion formed from **5** selectively attacked the sterically less-hindered terminal carbon of the thiirane; this selectivety is similar to that in a reaction of thiiranes with ethyl cyanoacetate,[1] malononitrile,[2] and the secondary amine.[6]



4 **5**

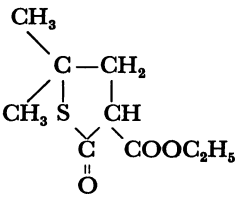


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Table 1 shows the effects of the reaction conditions on a reaction of **4** with **5**. A product which was insoluble in water and ether was obtained, and the ^{1}H NMR and IR spectra of this product showed that it was a polymer of **4** with a few carbonyl groups. The yield of **6** decreased and the ratio of the polymer to **6** increased at lower temperatures or by using more ethanol. By using less ethanol and a great exess of **5**, the yield of **6** increased to 65% (Run 7).

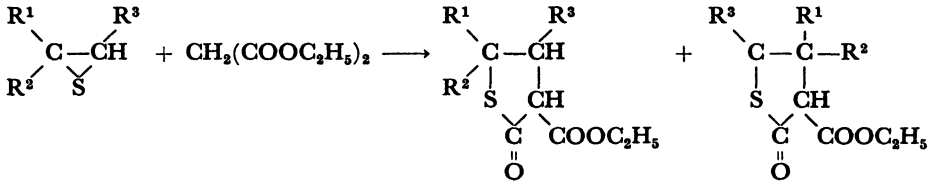
Table 2 shows the products and their yields in the reactions of various thiiranes with **5**. Thiiranes have a tendency to easily polymerize such molecules as thiirane, 2-methylthiirane and 1,2-epithiocyclohexane reacted with **5** to give corresponding dihydro-2(3*H*)-thiophenones in low yield. Although a reaction of alkyl-substituted thiiranes with **5** gave a product corresponding to **6**, selectively, the major product of a reaction of 2-phenylthiirane with **5** was 3-ethoxycarbonyl-4-phenyl-dihydro-2(3*H*)-thiophenone, corresponding to **7**. The different reactivity of 2-phenylthiirane from alkyl-substituted thiiranes was cosidered to be due to a polymerization of 2-phenylthiirane by the phenyl group.

Table 1. Effect of Reaction Conditions on the Reaction of 2,2-Dimethylthiirane with Diethyl Malonate[a)]

Run	Sulfide mmol	Malonate mmol	Sodium mmol	EtOH ml	Temp °C	Time h	Yield %	Solid[b)] g
1	10	20	15	50	Reflux	1	17	0.51
2	10	20	15	50	30	1	4	0.41
3	10	20	15	50	30	5	6	0.52
4	10	20	15	200	Reflux	1	2	0.24
5	10	20	15	10	Reflux	1	34	0.63
6	5	20	15	10	Reflux	1	46	0.11
7	5	40	30	20	Reflux	1	65	0.02

a) Nitrogen atmosphere. b) Polymer of 2,2-dimethylthiirane.

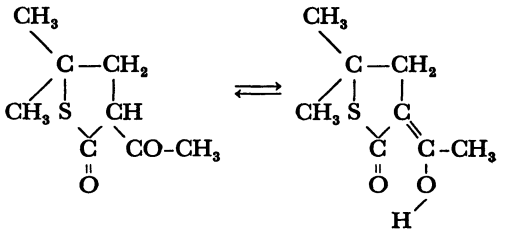
Table 2. The Reaction of Various Thiiranes with 5[a)]



R^1	R^2	R^3	Yield/% (A)	Yield/% (B)
H	H	H	38	
CH_3	H	H	48	—
CH_3	CH_3	H	65	—
n-C_4H_9	H	H	59	—
n-C_6H_{13}	H	H	58	—
H	$\{CH_2\}_4$		40	
C_6H_5	H	H	18	45

a) Same reaction conditions to Run 7 in Table 1 were used.

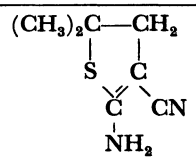
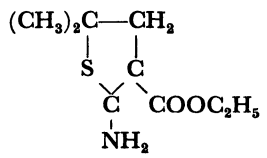
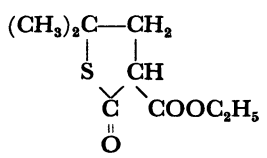
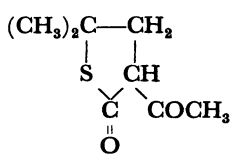
Table 3 shows the products and their yields in the reaction of **4** with malononitrile, ethyl cyanoacetate, and ethyl acetoacetate under the same reaction conditions as that of reaction of **4** with **5** (Run 1 and Run 7 in Table 1). The reaction of **4** with diethyl methylmalonate scarcely gave the corresponding dihydro-2(3*H*)-thiophenone. In the reaction of thiiranes with ethyl cyanoacetate, Snyder and Alexander[1)] could not determine the ratio of the tautomers, **2** and **3**. It was found that the equilibrium was shifted to **3** on the basis of a ^1H NMR analysis. It was also observed that the product of the reaction of **4** with ethyl acetoacetate was a tautomeric mixture, and the ratio of the tautomers **8** and **9** was about 6:4 from an analysis of the 400-MHz ^1H NMR and ^{13}C NMR.



8 **9**

A pronounced increase in the yield was observed in a reaction of **4** with active methylene compounds having ester groups (such as **5** and ethyl acetoacetate) when an active methylene compound was used in great exess (Yield II in Table 3).

Table 3. The Reaction of **4** with Active Methylene Compounds

Reactant		Yield/% I[a]	Yield/% II[b]
$CH_2(CN)_2$		50	62
$NCCH_2COOC_2H_5$		43	70
$CH_2(COOC_2H_5)_2$		17	65
$CH_3COCH_2COOC_2H_5$		8	27

a) Same reaction conditions to Run 1 in Table 1 were used. b) Same reaction conditions to Run 7 in Table 1 were used.

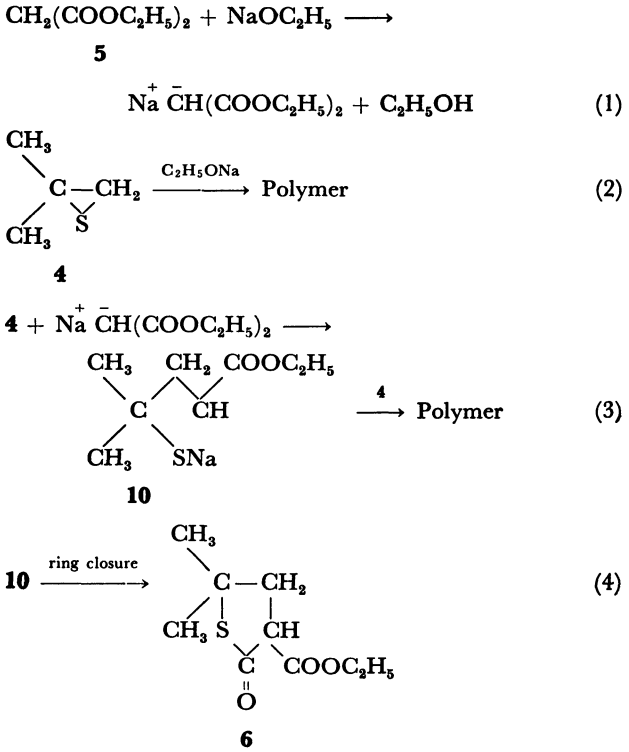
Table 4. Solvent Effect on the Reaction of **4** with **5**[a]

Solvent	Yield %	**5**[b] %	Solid[c] g
CH_3CN	16	38	0.36
DMSO	5	65	0.82
DMF	9	58	0.71
THF	21	38	—

a) Solvent, 15 ml; NaH, 15 mmol; **4**, 10 mmol; **5**, 20 mmol; reaction temperature, 80 °C; time, 3 h. b) Recovered after the reaction. c) Polymer of **4**.

Compound **6** could be obtained by using sodium hydride instead of sodium ethoxide. Table 4 shows the effects of a solvent on the reaction of **4** with **5** in the presence of sodium hydride. Polar solvents, such as DMF and DMSO, make the yield of **6** low, and make that of the polymer high. A better result was obtained when acetonitrile or THF was used as a solvent. The use of nonpolar solvents did not produce a good result since it could not dissolve the sodium salt of **5**. The yield in a reaction using sodium hydride was lower than that using sodium ethoxide.

The reaction of **4** with **5** was considered to involve three different reactions; 1) the polymerization of thiirane by sodium ethoxide (Eq. 2), 2) the polymerization of **8** with **4** (Eq. 3) and 3) the formation of **6** by a ring-closure reaction (Eq. 4). An intermediate **10** was very reactive and could not be detected through an analysis after the reaction. Although it was



presumed that a large amount of ethanol was favorable for an intramolecular condensation and

increased the yield of **6**, an opposite result occurred since the polymerization of **4** was accerelated by the sodium ethoxide (Eqs. 1, 2). When a large amount of active methylene compounds was used, higher effect was observed in the reaction of **4** with **5** or ethyl acetoacetate than these in the reaction of **4** with malononitrile and ethyl cyanoacetate. This was attributed to the fact that dihydro-2(3*H*)-thiophenone derivatives were more stable than dihydrothiophene derivatives having amino groups. Though **6** had active methine, and could possibly react with thiirane, its high steric hinderance was expected to disturb the reaction, because the reaction of **4** with diethyl methylmalonate scarcely gave the dihydro-2(3*H*)-thiophenone derivative.

Experimental

Measurement. GLC was carried out with a JEOL 20KF chromatograph equiped with 20% SE-30 columns. ^{1}H NMR spectra were measured with a Hitachi R-40 spectrometer. Mass spectra were measured with a JEOL D-300 GC-MS spectrometer using the CI(chemical ion) method with isobutane. IR spectra were obtained on a JASCO A302 spectrophotometer.

Materials. 2-Butylthiirane and 2-hexylthiirane were prepared as previously described.[3] 2,2-Dimethylthiirane-(4)[4], 1,2-epithiocyclohexane[4] and 2-phenylthiirane[5] were prepared according to a procedure described in the literature.

Reaction of Thiirane with 5. A typical procedure is as follows: To a solution prepared by disolving 0.70 g of sodium in 20 ml of absolute ethanol was added 6.40 g of **5** under a nitrogen atmosphere. This mixture was refluxed while 0.44 g of **4** was added dropwise over a period of one hour. Refluxing continued for more than one hour; then, the solution was poured into ice-cold water. The solution was acidified with dilute hydrochloric acid and extracted with ether. An insoluble polymeric material was filtered off and dried in vacuo. An organic layer was dried over anhydrous sodium sulfate and after the evaporation of solvent the residue was distilled in vacuo. This distillate was purified to give 3-ethoxycarbonyl-5,5-dimethyl-dihydro-2(3*H*)-thiophenone (**6**) by column chromatography on silica gel using a mixture of petroleum benzine (bp 50—90 °C) and ethyl acetate (100:1 v/v) as an eluent. IR: 1730 cm^{-1}, 1687 cm^{-1}, ^{1}H NMR δ=1.30 (t, 3H, CH_3), 1.57 (s, 3H, CH_3), 1.64 (s, 3H, CH_3), 2.17—2.76 (m, 2H, CH_2), 3.75—4.05 (quar, 1H, CH), 4.25 (quar, 2H, CH_2); QM$^+$: 203.

Thiirane, 2-methylthiirane, 2-butylthiirane, 2-hexylthiirane, 1,2-epithiocyclohexane, and 2-phenylthiirane were treated with **5**. The spectral data of these products are as follows:

3-Ethoxycarbonyl-dihydro-2(3*H*)-thiophenone. IR: 1740 cm^{-1}, ^{1}H NMR δ=1.29 (t, 3H, CH_3), 2.42—2.75 (m, 2H, CH_2), 3.20—3.70 (m, 3H, CH, SCH_2); QM$^+$: 175.

3-Ethoxycarbonyl-5-methyl-dihydro-2(3*H*)-thiophenone. IR, 1739 cm^{-1}, 1700 cm^{-1}, ^{1}H NMR δ=1.28 (t, 3H, CH_3), 1.47 (d, 1.5H, CH_3), 1.54 (d, 1.5H, CH_3), 1.80—2.95 (m, 2H, CHCO, CHS), 4.25 (quar, 2H, OCH_2); QM$^+$: 189.

5-Butyl-3-ethoxycarbonyl-2(3*H*)-thiophenone. IR: 1732 cm^{-1}, 1693 cm^{-1}, ^{1}H NMR δ=0.94 (t, 3H, CH_3), 1.30—2.00 (m, 6H, $(-CH_2-)_3$), 2.03—2.93 (m, 2H, CH_2), 3.47—3.80 (m, 1H, CHS), 3.75—4.10 (m, 1H, CHCO), 4.22 (quar, 2H, CH_2O); QM$^+$; 231.

9-Ethoxycarbonyl-7-thiabicyclo[4,3,0]nonane-8-one. IR: 1740 cm^{-1}, 1700 cm^{-1}, ^{1}H NMR δ=1.28 (t, 3H, CH_3), 1.05—2.70 (m, 9H, $(-CH_2-)_4$, CH), 3.05—3.65 (m, 2H, SCH, CHCO), 4.25 (quar, 2H, CH_2); QM$^+$: 229.

3-Ethoxycarbonyl-4-phenyl-2(3*H*)-thiophenone. IR: 1727 cm^{-1}, 1688 cm^{-1}, ^{1}H NMR δ=1.18 (t, 3H, CH_3), 3.40—4.40 (m, 4H, PhCH, CH_2S, CH_2), 7.33 (s, 5H, C_6H_5); QM$^+$: 251.

3-Ethoxycarbonyl-5-phenyl-2(3*H*)-thiophenone. IR: 1740 cm^{-1}, 1700 cm^{-1}, ^{1}H NMR δ=1.30 (t, 3H, CH_3), 2.25—3.15 (m, 2H, CH_2), 3.40—4.00 (m, 1H, CHCO), 4.25 (quar, 2H, CH_2), 4.80—5.10, 5.17—5.40 (m, 1H, PhCH), 7.25—7.60 (m, 5H, C_6H_5); QM$^+$: 251.

Reaction of 4 with Other Active Methylene Compounds. Compound **4** was reacted with ethyl cyanoacetate, malononitrile, and ethyl acetoacetate in a similar way to that for the reaction with **5**. The spectral data of these products are as follows:

2-Amino-3-ethoxycarbonyl-5,5-dimethyl-4,5-dihydrothiophene. IR: 3392 cm^{-1}, 1644 cm^{-1}, 1616 cm^{-1}, ^{1}H NMR δ=1.26 (t, 3H, CH_3), 1.51 (s, 6H, $2CH_3$), 2.83 (s, 2H, CH_2), 4.14 (quar, 2H, OCH_2), 6.00 (s, 2H, NH_2); QM$^+$: 155.

2-Amino-3-cyano-5,5-dimethyl-4,5-dihydrothiophene. IR: 3416 cm^{-1}, 1630 cm^{-1}, ^{1}H NMR δ=1.52 (s, 6H, $2CH_3$), 2.73 (s, 2H, CH_2), 4.80 (s, 2H, NH_2); QM$^+$: 202.

3-Acetyl-5,5-dimethyl-dihydro-2(3*H*)-thiophenone. IR: 1718 cm^{-1}, 1680 cm^{-1}, 1641 cm^{-1}, 1586 cm^{-1}, ^{1}H NMR (400 MHz): (keto type) δ=1.58 (s, 3H, CH_3), 1.62 (s, 3H, CH_3), 2.38 (s, 3H, $COCH_3$), 1.90—2.90 (m, 2H, CH_2), 3.90—4.20 (dd, 1H, CH). (enol type) δ=1.56 (s, 6H, $2CH_3$), 1.96 (s, 3H, CH_3–), 2.73 (s, 2H, CH_2); ^{13}C NMR: (keto type) δ=30.23, 31.25, 31.19, 42.23, 52.91, 65.77, 201.21, 202.07. (enol type) δ=19.91, 30.77(2C), 43.72, 52.63, 109.45, 166.11, 202.79; QM$^+$: 173.

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References

1) H. R. Snyder and W. Alexander, *J. Am. Chem. Soc.*, **70**, 217 (1948).
2) Hisamitsu Pharmceutical Co. Ltd., Japan Patent, 13164 (1974).
3) Y. Suhara and Y. Taguchi, *Yukagaku*, **25**, 848 (1976).
4) H. R. Snyder, J. M. Stewart, and J. B. Ziegler, *J. Am. Chem. Soc.*, **69**, 2672 (1947).
5) J. M. Stewart, *J. Org. Chem.*, **28**, 596 (1963).
6) Y. Taguchi and Y. Suhara, *Yukagaku*, **33**, 280 (1984).