Synthesis of 4-Methylthio-2(1*H*)-pyridone Derivatives Using Ketene Dithioacetals

Yoshinori Tominaga*, Masanori Kawabe, and Akira Hosomi*

Faculty of Pharmaceutical Sciences, Nagasaki University, 1-14,
Bunkyo-machi, Nagasaki 852, Japan

Received April 20, 1987

Reaction of various active methylene compounds with ketene dithioacetals, bis(methylthio)methylenemalononitrile (**1a**) and bis(methylthio)methylenecyanoacetamide (**1b**) gave the corresponding 3-cyano-4-methylthio-2(1*H*)-pyridone derivatives. The transformation of 4-methylthio-2-oxo-2*H*-pyran-3-carbonitrile into 4-methylthio-2(1*H*)-pyridone derivatives was also described.

J. Heterocyclic Chem., **24**, 1325 (1987).

2(1*H*)-Pyridones are very important and interesting substances not only as intermediates for the synthesis of pyridine derivatives but also as the basic structural unit for the synthesis of pharmacological active compounds [1-3]. In particular, 4-methylthio-2(1*H*)-pyridone derivatives can be used as the starting materials for synthesis of pharmacologically active compounds, since it has been known that nucleophilic displacement of an alkylthio group on the similar heterocyclic compounds occurs smoothly [4,5]. The preparation of 4-methylthiopyridine derivatives using ketene dithioacetals has been reported hitherto in which α-oxoketene dithioacetals are usually used [6-11]. However, this method has some drawbacks, since it is necessary to prepare α-oxoketene dithioacetals in advance, some of which are inaccessible and, moreover, their acetals must display high reactivity toward nucleophiles. In this paper, we now wish to report an efficient method for the synthesis of 2(1*H*)-pyridone derivatives. This method provides the first example of the displacement of an acidic proton in active methyl or methylene compounds by ketene dithioacetal, followed by the ring transformation reaction of 6-substituted 3-cyano-2-pyrone derivatives into 2(1*H*)-pyridones. Ketene dithioacetals employed in this paper are bis(methylthio)methylenemalononitrile (**1b**) and bis(methylthio)methylenecyanoacetamide (**1b**) [12].

We have previously found that the ketene dithioacetals are useful and convenient reagents for the synthesis of the 2-pyrone derivatives [13-15], and that indeno[3,2-*b*]pyridin-2(1*H*)-one was synthesized by the displacement reaction of ketene dithioacetal with 1,3-indandione followed by the cyclization of the carbonyl group with cyano group in the presence of sodium hydride in dimethyl sulfoxide (DMSO) [16]. Thus functionalized ketene dithioacetals can be applied to prepare 2(1*H*)-pyridones. In particular, the nitrogen atom of cyanoketene dithioacetals is used for preparing nitrogen-containing heterocyclic compounds. Therefore, we first attempted the reaction of dicyanoketene dithioacetal (**1a**) with acetone (**2a**). When the reaction was conducted at room temperature in the presence of pulverized potassium hydroxide in DMSO followed by treatment with 10% hydrochloric acid, the expected 3-cyano-6-methyl-4-methylthio-2(1*H*)-pyridone (**3**) was obtained in 50% yield. Similarly, the reaction of **1a** with cyclohexane afforded the desired 2(1*H*)-pyridone, 3-cyano-1,2,5,6,7,8-hexahydro-4-methylthioquinolin-2-one (**4**), in 48% yield. Moreover 3-cyano-4-methylthio-2-oxo-2*H*-pyran-6-ylacetic acid (**5**) was obtained by the reaction of levulinic acid (**2c**) with **1a** in 34% yield, where the introduction of **1a** into the terminal methyl group of levulinic acid took place.

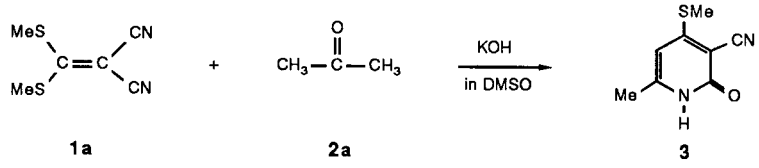
In contrast, the expected 2(1*H*)-pyridone **6a** was the minor product (2% yield), when **1a** was allowed to react with acetophenone (**2d**) under the similar conditions. The major product of this reaction was 4-methylthio-2-oxo-2*H*-pyran-3-carbonitrile (**7a**) [15]. Similar results are also observed for the reaction of **1a** with *p*-bromo- (**2e**) and *p*-chloroacetophenone (**2f**) [15].

The formation of 2(1*H*)-pyridones and 2-pyrones presumably proceeds *via* the intermediary formation of cyclized products, 2-imino-2*H*-pyrans, which undergo hydrolysis to give 2-pyrone derivatives and re-cyclization to 2(1*H*)-pyridone derivatives, successively, under an acidic conditions. Similarly, 3-benzoylpropionic acid (**2g**) was allowed to react with **1a** to give only 3-cyano-4-methylthio-6-phenyl-2-oxo-2*H*-pyran-5-ylacetic acid (**8**) in 34% yield. Thus, the present method is not necessarily suitable for the synthesis of 2(1*H*)-pyridones from **1a** except for 6-alkyl-2-(1*H*)-pyridones.

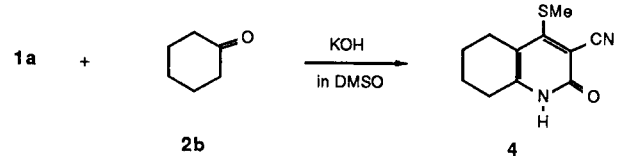
It is well known that the dehydrative condensation of an amide group with a carbonyl group gives the corresponding lactam compounds. Therefore ketene dithioacetal (**1b**) bearing a carbamoyl group should be an efficient and expedient reagent for the synthesis of 2(1*H*)-pyridone derivatives. In related works, Poetsh has reported the synthesis of several 3-cyano-4-alkylthio-2(1*H*)-pyridones by the reaction of enamines with **1b** [17].

Compound **1b** was allowed to react with various type of active methyl (**2a**, **d-f**, **h-k**) and active methylene compounds (**2b**, **l-q**) at room temperature or 60° in the

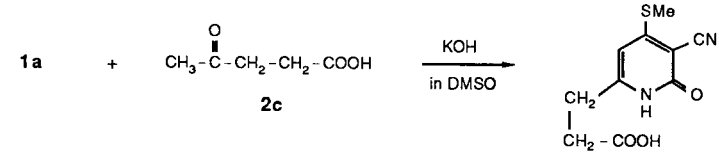
Chart 1



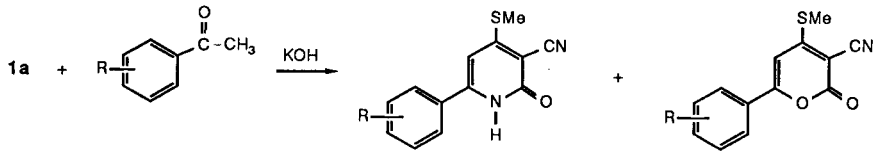
1a 2a 3



2b 4



2c 5

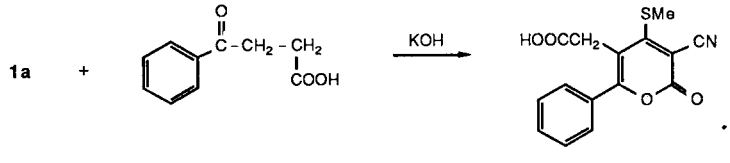


2d - f 6 a - c 7 a - c

2d, R = H
e, R = p-Br
f, R = p-OMe

a, R = H
b, R = p-Br
c, R = p-OMe

a, R = H
b, R = p-Br
c, R = p-OMe



2g 8

Chart 2

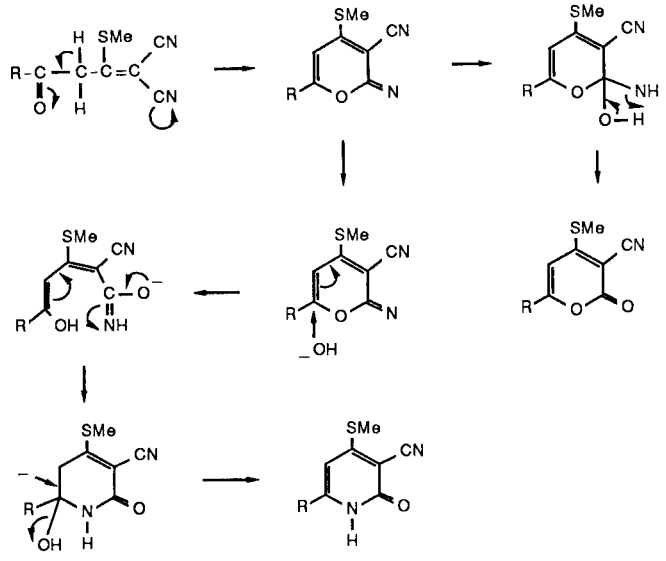
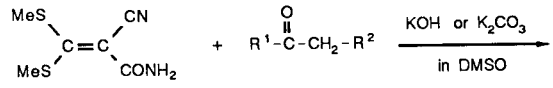


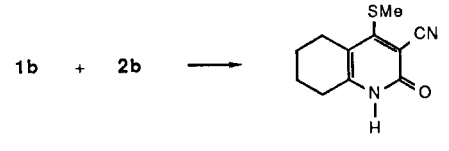
Table 1



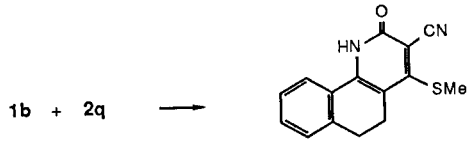
3, 5, 6a - c, 9a - i

entry	Ketone	products	R^1	R^2	Yields (%)
1	**2a**	**3**	Me	H	50
2	**2d**	**6a**	C_6H_5	H	26
3	**2e**	**6b**	p-Br-C_6H_4	H	38
4	**2f**	**6c**	p-MeO-C_6H_4	H	36
5	**2h**	**9a**	o-MeO-C_6H_4	H	33
6	**2i**	**9b**	3,4,5-$(MeO)_3$-C_6H_2	H	34
7	**2j**	**9c**	3,4-O-CH_2-O-C_6H_3	H	46
8	**2k**	**9d**	2-thienyl	H	36
9	**2l**	**9e**	C_6H_5	Me	38
10	**2m**	**9f**	C_6H_5	CH_2-COOH	25
11	**2n**	**9g**	C_6H_5	COOEt	63
12	**2o**	**9h**	Me	COOEt	77
13	**2p**	**9i**	Me	COMe	67
14	**2c**	**5**	CH_2-CH_2-COOH	H	27

Chart 3



4 24%



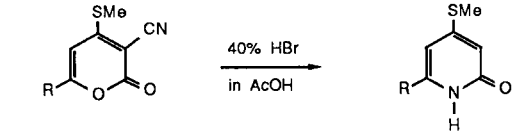
10 28%

presence of potassium hydroxide or potassium carbonate in DMSO to give the corresponding 2(1*H*)-pyridone derivatives (**3, 4, 6a-c, 9a-i, 10**) as shown in Table 1.

It is well known that the conversion of 2-pyrones to 2(1*H*)-pyridones occurs generally by the displacement of the oxygen atom in the 2-pyrone ring with the nitrogen atom of amines [18] and further that the 2-pyrone ring readily opens to give 1,4-dicarbonyl compounds in acidic or alkali medium. However, to our knowledge, the intramolecular conversion of 2-oxo-2*H*-pyran-3-carbonitrile to 2(1*H*)-pyridone using cyano group has not been reported hitherto.

Treatment of **6a-c** with hydrogen bromide solution in acetic acid gave the desired 3-methylthio-6-phenyl-2(1*H*)-pyridone derivatives **11a-c** in 24, 33, and 32% yield, respectively. Similarly, 6-methyl-4-methylthio-2-pyridone (**11d**) was prepared from 6-methyl-4-methylthio-2-oxo-2*H*-pyran-3-carbonitrile (**6d**) under the similar conditions in 24% yield. 6-Styryl-2(1*H*)-pyridone (**11e**) was also synthesized from the corresponding 2-styryl-2-pyrone (**6e**) [15]. Treatment of 3-methoxy-2-pyrone (**12**) with hydrogen bromide gave 4-hydroxy-2-pyridone (**13**) in 32% yield. The present reaction is a new type of ring transformation reaction, though the yield is not so good. Therefore we attempted the another transformation reaction. Thus, **6a-e** reacted with polyphosphoric acid to give 4-methylthio-2-oxo-2*H*-pyran-3-carboxamides **14a-e** which readily converted to 2(1*H*)-pyridones **11a-e** *via* ring cleavage reaction under stirring for 1 hour at 60° in the 10% sodium hydroxide solution.

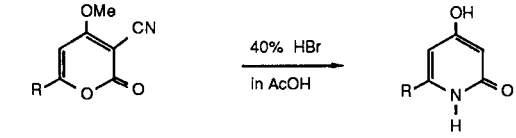
Chart 4



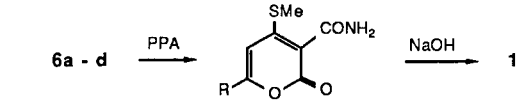
6a - e **11a - e**

a, R = C_6H_5
b, R = p-Br-C_6H_4
c, R = p-MeO-C_6H_4
d, R = Me
e, R = styryl

MeONa



12 **13**



14a - e

R

a, R = C_6H_5
b, R = p-Br-C_6H_4
c, R = p-MeO-C_6H_4
d, R = Me
e, R = styryl

R

a, R = C_6H_5
b, R = p-Br-C_6H_4
c, R = p-MeO-C_6H_4
d, R = Me
e, R = styryl

In conclusion, the reaction of ketene dithioacetals, **1b**, with active methyl or methylene compounds provides direct and efficient synthesis of 2(1*H*)-pyridones ring systems and opens the way to synthesis of various annelated 2-pyridones. It might be possible to prepare these analogs by using the reaction of **1a** or **1b** with substituted active methylene compounds and/or by the displacement of methylthio group on 2-pyridone rings with nucleophiles. These 2-pyridone derivatives are interesting from viewpoint of pesticides, pharmaceuticals, and also synthetic intermediates to those.

EXPERIMENTAL

All melting points were determined in a capillary tube and uncorrected. Infrared (ir) spectra were recorded in potassium bromide pellets on JASCO IRA-2 spectrometer and ultraviolet (uv) absorption spectra were determined in 95% ethanol on a Hitachi EP-S2 spectrometer. Nuclear magnetic resonance (nmr) spectra were obtained on JNM-PS-100 (100 MHz) and JNM-FX-90Q (90 MHz) spectrometers with tetramethylsilane as an internal standard. Mass (ms) spectra were recorded on a JEOL JMS-01SG mass spectrometer.

3-Cyano-6-methyl-4-methylthio-2(1*H*)-pyridone (**3**).

Method a. A mixture of 5.81 g (100 mmoles) of acetone (**2a**), 1.70 g (10 mmoles) of **1a** and 2.24 g (40 mmoles) of powdered potassium hydroxide was stirred in dimethyl sulfoxide (30 ml) at room temperature for 8 hours. The reaction mixture was poured into 200 ml of ice-water and acidified with 10% hydrogen chloride. The precipitate that appeared was collected by filteration and recrystallized from methanol to give colorless needles, mp 330° (lit **7**, mp 325°], in 50% yield.

Method b. A mixture of 5.81 g (100 mmoles) of acetone (**2a**), 1.88 g (10 mmoles) of **1b** and 2.24 g (40 mmoles) of powdered potassium hydroxide was stirred in dimethyl sulfoxide (30 ml) at room temperature for 8 hours. The reaction mixture was poured into 200 ml of ice-water and acidified with 10% hydrogen chloride. The resulting precipitate was collected by filteration and recystallized from methanol to give 0.90 g (5 mmoles) of colorless needles, mp 330°, in 50% yield; ir (potassium bromide: (ν max cm^{-1} 2195 (CN), 1640 (C=O); uv (ethanol): λ max nm 230, 300, 335; λ min nm 260, 316; ^{1}H nmr (deuteriochloroform): δ 2.57 (3H, s, 6-Me), 2.67 (3H, s, SMe), 2.66 (1H, s, 5-H).

1,2,5,6,7,8-Hexahydro-4-methylthio-2-oxoquinoline (**4**).

This compound was synthesized in 48% and 24% yield (method a and b, respectively) from 0.98 g (10 mmoles) of cyclohexanone and 10 mmoles of **1a** or **1b** in a similar manner to that described for the preparation of **3**. A pure sample was recrystallized from methanol to give 0.90 g (5 mmoles, 50%) as colorless needles, mp 294° [lit. **6**, mp 272°]; ir (potassium bromide): ν max cm^{-1} 2250 (CN), 1640 (C=O); uv (ethanol): λ max nm (log ϵ) 232 (4.13), 304 (3.90), 350 (3.98); ^{1}H nmr (trifluoroacetic acid): δ 1.98 (4H, bs, 6, 6', 7, 7'-H), 2.60-3.00 (4H, m, 5, 5', 8, 8'-H), 3.03 (3H, s, SMe).

3-Cyano-1,2-dihydro-4-methylthio-2-oxo-6-pyridylpropionic Acid (**5**).

This compound was synthesized in 34 and 27% yield (method a and b, respectively) from 1.16 g (10 mmoles) of levulinic acid and 1.70 g (10 mmoles) of **1a** in a similar manner to that described for the preparation of **3**. An analytical sample was recrystallized from methanol to give colorless needles, mp 245°; ir (potassium bromide): ν max cm^{-1} 2200 (CN), 1732 (C=O), 1623 (C=O); uv (ethanol): λ max nm (log ϵ) 238 (4.36), 303 (4.14), 337 (4.07); ^{1}H nmr (trifluoroacetic acid): δ 2.70 (3H, s, SMe), 2.92-3.28 (4H, m, $-CH_2-CH_2-$), 3.78 (1H, s, 5-H).

Anal. Calcd. for $C_{10}H_{10}N_2O_3S$: C, 50.41; H, 4.23; N, 11.76; S, 13.46. Found: C, 50.49; H, 4.18; N, 11.65; S, 13.41.

Reaction of Acetophenone Derivatives with **1a**.

A mixture of 5 mmoles of **1a**, 5 mmoles of active methyl compounds **2d-f**, 20 mmoles of powdered potassium hydroxide, and 30 ml of dimethyl sulfoxide was stirred at room temperature for 5 hours. The reaction mixture was poured into 200 ml of ice-water and then acidified with 10% hydrogen chloride. The precipitate that appeared was collected by filteration. A mixture of these products and 50 ml of methanol was refluxed for 1 hour. After removal of the solvent, the residue was recrystallized from appropriate solvent to give the corresponding 2-pyrones **7a-c** [15] and 2(1*H*)-pyridones **6a-c**. 2-Pyrone derivatives **7a-c** are readily dissolved in benzene, but 2-pyridone derivatives **6a-c** are dissolved hardly in benzene or methanol. Pure 2-pyridones were obtained by recrystallization using a large amount of methanol or methyl cellosolve. The yields of **7a-c** were 24, 35, and 50%, respectively, and these melting points were 201, 230, and 215°, respectively. 2(1*H*)-Pyridones **6a-c** were obtained in 2, 1, and 1% yields, respectively.

3-Cyano-1,2-dihydro-4-methylthio-2-oxo-6-phenyl-2*H*-pyran-5-ylacetic Acid (**8**).

A mixture of 1.78 g (10 mmoles) of benzoylpropionic acid (**2g**), 1.70 g (10 mmoles) of **1a**, 2.24 g (40 mmoles) of powdered potassium hydroxide, and 40 ml of dimethyl sulfoxide was stirred for 6 hours at room temperature. The reaction mixture was poured into 200 ml of ice-water and acidified with 10% hydrogen chloride. The precipitate that appeared was collected by filteration and recrystallized from methanol to give 0.75 g (2.5 mmoles, 25%) of colorless needles, mp 289°; ir (potassium bromide): ν max cm^{-1} 2205 (CN), 1740, 1684 (C=O); ^{1}H nmr (deuteriochloroform + trifluoroacetic acid): δ 3.03 (3H, s, SMe), 3.70 (2H, s, $-CH_2-COOH$), 7.51 (5H, s, phenyl-H).

Anal. Calcd. for $C_{15}H_{11}NO_4S$: C, 59.79; H, 3.68; N, 4.65; S, 10.64. Found: C, 59.78; H, 3.68; N, 4.51; S, 10.59.

3-Cyano-4-methylthio-6-phenyl-2(1*H*)-pyridone (**6a**).

A mixture of 0.60 g (5 mmoles) of acetophenone (**2d**), 0.85 g (5 mmoles) of **1b**, 1.12 g (20 mmoles) of powdered potassium hydroxide, and 30 ml of dimethyl sulfoxide was stirred for 8 hours. The reaction mixture was poured into 200 ml of ice-water and acidified with 10% hydrogen chloride. The precipitate was collected by filteration and recrystallized from a large amount of methanol to give 0.31 g (1.3 mmoles, 26%) of pale yellow needles, mp 290° [lit 7, mp 282°]; ir (potassium bromide): ν max cm^{-1} 3200-2800 (broad, NH or OH); 2205 (CN), 1630 (C=O); uv (ethanol): λ max nm (log ϵ) 225 (4.06), 252 (4.27), 324 (3.99), 356 (4.12); ^{1}H nmr (deuteriodimethylsulfoxide): δ 2.40 (3H, s, SMe), 6.10 (1H, s, 5-H), 7.36 (5H, s, phenyl-H).

6-(*p*-Bromophenyl)-3-cyano-4-methylthio-2(1*H*)-pyridone (**6b**).

This compound (0.58 g, 1.80 mmoles) was synthesized in 36% yield from *p*-bromoacetophenone (**2e**) (1.0 g, 5 mmoles) and **1b** in a similar manner to that described for the preparation of **6a**. The crude product was recrystallized from benzene + methanol to give pale yellow needles, mp 349°; ir (potassium hydroxide): ν max cm^{-1} 3200-2800 (broad, NH or OH), 2200 (CN), 1645 (C=O); uv (ethanol): λ max nm (log ϵ) 224 (4.33), 259 (4.37), 320 (shoulder, 4.11), 362 (4.29); ^{1}H nmr (deuteriodimethylsulfoxide): δ 2.69 (3H, s, SMe), 6.61 (1H, s, 5-H), 7.76 (4H, s, phenyl-H).

Anal. Calcd. for $C_{13}H_9BrN_2OS$: C, 48.61; H, 2.82; N, 8.72; S, 9.98. Found: C, 48.83; H, 2.88; N, 8.82; S, 10.42.

3-Cyano-6-(*p*-methoxy)phenyl-4-methylthio-2(1*H*)-pyridone (**6c**).

This compound (0.52 g, 1.90 mmoles) was synthesized in 38% yield from *p*-methoxyacetophenone (**2f**) (0.75 g, 5 mmoles) and **1b** in a similar manner to that described for the preparation of **6a**. A crude product was recrystallized from a large amount of methanol to give pale yellow needles, mp 303° [lit 7, mp 291°]; ir (potassium hydroxide): ν max cm^{-1} 3100-2800 (broad, NH or OH), 2200 (CN), 1625 (C=O); uv (ethanol): λ max nm 225, 244, 292, 320, 365; λ min 234, 270, 302, 330; ^{1}H nmr (deuteriodimethylsulfoxide): δ 2.70 (3H, s, SMe), 3.85 (3H, s, OMe), 6.62 (1H, s, 5-H), 7.15 (2H, d, J = 8.0 Hz, phenyl-H), 7.93 (2H, d, J = 8.0 Hz, phenyl-H).

3-Cyano-6-(*o*-methoxyphenyl)-4-methylthio-2(1*H*)-pyridone (**9a**).

This compound (0.48 g, 1.76 mmoles) was synthesized in 35% yield from *o*-methoxyacetophenone (**2h**) (0.75 g, 5 mmoles) and **1b** in a similar manner to that described for the preparation of **9a**. An analytical sample was recrystallized from methanol to give pale yellow needles, mp 288°; ir (potassium bromide): δ max cm^{-1} 3100-2800 (broad, NH or OH), 2205 (CN), 1645 (C=O); uv (ethanol): λ max nm (log ε) 221 (4.36), 239 (4.25), 310 (4.07), 353 (4.22); ^1H nmr (deuteriochloroform + trifluoroacetic acid 1:1): δ 2.73 (3H, s, SMe), 3.96 (3H, s, OMe), 6.88 (1H, s, 5-H), 7.10-7.25 (2H, m, phenyl-H), 7.53-7.73 (2H, m, phenyl-H).

Anal. Calcd. for $C_{14}H_{12}N_2O_2S$: C, 61.75; H, 4.44; N, 10.29; S, 11.77. Found: C, 61.70; H, 4.53; N, 10.24; S, 11.75.

3-Cyano-3,4,5-trimethoxyphenyl-4-methylthio-2(1*H*)-pyridone (**9b**).

This compound (0.56 g, 1.67 mmoles) was synthesized in 34% yield from 3,4,5-trimethoxyacetophenone (**2i**) (1.05 g, 5 mmoles) and **1b** in a similar manner to that described for the preparation of **3**. An analytical sample was recrystallized from methanol to give pale yellow needles, mp 285°; ir (potassium bromide): ν max cm^{-1} 3150-2800 (broad, NH or OH), 2200 (CN), 1620 (C=O); uv (ethanol): λ max nm (log ε) 230 (shoulder, 4.36), 248 (4.17), 320 (4.03), 364 (4.29); ^1H nmr (deuteriochloroform):δ 2.63 (3H, s, SMe), 3.93 (3H, s, OMe), 4.00 (6H, s, 2 x OMe), 6.36 (1H, s, 5-H), 6.94 (2H, s, phenyl-H).

Anal. Calcd. for $C_{16}H_{16}N_2O_4S$: C, 57.82; H, 4.85; N, 8.43; S, 9.65. Found: C, 57.65; H, 4.79; N, 8.33; S, 9.80.

3-Cyano-6-(3,4-methylenedioxyphenyl)-4-methylthio-2(1*H*)-pyridone (**9c**).

This compound (0.66 g, 2.31 mmoles) was synthesized in 46% yield from 3,4-methylenedioxyacetophenone (**2j**) (0.82 g, 5 mmoles) and **1b** in a similar manner to that described for the preparation of **3**. An analytical sample was recrystallized from methanol to give pale yellow needles, mp 314°; ir (potassium bromide): ν max cm^{-1} 3100-2700 (broad, NH or OH), 2210 (CN), 1630 (C=O); uv (ethanol): λ max nm 234, 315 (shoulder), 368; λ min nm 275; ^1H nmr (deuteriodimethylsulfoxide): δ 2.69 (3H, s, SMe), 6.12 (2H, s, O-CH_2-O), 6.53 (1H, s, 5-H), 7.04 (1H, dd, J = 1.1, 7.7 Hz, 5'-H), 7.41 (1H, dd, J = 2.0, 7.7 Hz, 6'-H), 7.46 (1H, s, 2'-H).

Anal. Calcd. for $C_{14}H_{10}N_2O_3S$: C, 58.73; H, 3.52; N, 9.78; S, 11.20. Found: C, 58.60; H, 3.50; N, 9.70; S, 11.54.

3-Cyano-4-methylthio-6-thien-2-yl-2(1*H*)-pyridone (**9d**).

This compound (0.62 g, 2.5 mmoles) was synthesizesd in 50% yield from 2-acetylthiophene (**2k**) (0.63 g, 5 mmoles) and **1b** in a similar manner to that described for the preparation **3**. An analytical sample was recrystallized from methanol to give colorless needles, mp 316°; ir (potassium bromide): ν max cm^{-1} 3075 (NH), 3000-2600 (NH or OH), 2205 (CN), 1635 (C=O); uv (ethanol): λ max nm 224, 264, 375; λ min nm 246, 304; ^1H nmr (deuteriodimethylsulfoxide): δ 2.68 (3H, s, SMe), 6.67 (1H, bs, 5-H), 7.23 (1H, dd, J = 3.7, 5.1 Hz, 4'-H), 7.87 (1H, dd, J = 1.1, 5.1 Hz, 5'-H), 8.00 (1H, dd, J = 1.1, 3.7 Hz, 3'-H).

Anal. Calcd. for $C_{11}H_8N_2OS_2$: C, 53.21; H, 3.25; N, 11.28; S, 25.82. Found: C, 53.05; H, 3.25; N, 11.31; S, 25.75.

3-Cyano-5-methyl-4-methylthio-6-phenyl-2(1*H*)-pyridone (**9e**).

This compound (0.49 g, 1.91 mmoles) was synthesized in 38% yield from propiophenone (**2l**) (0.67 g, 5 mmoles) and **1b** in a similar manner to that described for **3**. An analytical sample was recrystallized from methanol to give colorless needles, mp 208°; ir (potassium bromide): ν max cm^{-1} 3200-2800 (NH or OH), 2205 (CN), 1610 (C=O); uv (ethanol): λ max nm (log ε) 229 (4.22), 314 (3.90), 359 (4.10); ^1H nmr (deuteriochloroform): δ 2.11 (3H, s, 5-Me), 2.86 (3H, s, SMe), 7.36-7.58 (5H, m, phenyl-H).

Anal. Calcd. for $C_{14}H_{12}N_2OS$: C, 65.50; H, 4.71; N, 10.91; S, 12.49. Found: C, 65.65; H, 4.59; N, 11.02; S, 12.54.

3-Cyano-1,2-dihydro-4-methylthio-6-phenyl-2-oxo-5-pyridylacetic Acid (**9f**).

This compound (0.375 g, 1.25 mmoles) was synthesized in 25% yield from benzoylpropionic acid (**2m**) (0.89 g, 5 mmoles) and **1b** in a similar manner to that described for the preparation of **3**. An analytical sample was recrystallized from methanol to give colorless needles, mp 279°; ir (potassium hydroxide): ν max cm^{-1} 3200-2600 (NH or OH), 2210 (CN), 1700, 1619 (C=O); uv (ethanol): λ max nm (log ε) 228 (4.21), 243 (shoulder, 4.15), 358 (4.09).

Anal. Calcd. for $C_{15}H_{12}N_2O_3S$: C, 59.99; H, 4.03; N, 9.32; S, 10.68. Found: C, 59.96; H, 4.07; N, 9.46; S, 10.70.

Ethyl 3-Cyano-1,2-dihydro-4-methylthio-2-oxo-6-phenyl-5-pyridylcarboxylate (**9g**).

A mixture of 1.92 g (10 mmoles) of ethyl benzoylacetate (**2n**), 1.70 g (10 mmoles) of **1b**, 2.76 g (20 mmoles) of potassium carbonate, and 40 ml of dimethylsulfoxide was heated at 100° for 3 hours. The reaction mixture was poured into 200 ml of ice-water and acidified with 10% hydrogen chloride. The precipitate that appeared was collected by filteration and recrystallized from ethanol to give colorless needles (1.98 g, 6.31 mmoles, 63%), mp 172°; ir (potassium bromide): ν max cm^{-1} 3200-2700 (NH or OH), 2210 (CN), 1710, 1615 (C=O); uv (ethanol): λ max nm (log ε) 257 (4.23), 354 (4.06); ^1H nmr (deuteriochloroform): δ 1.02 (3H, t, J = 7.0 Hz, O-CH_2-Me), 2.79 (3H, s, SMe), 4.07 (2H, q, J = 7.0 Hz, O-CH_2-), 7.52 (5H, s, phenyl-H).

Anal. Calcd. for $C_{16}H_{14}N_2O_3S$: C, 61.13; H, 4.48; N, 8.91; S, 10.20. Found: C, 61.28; H, 4.48; N, 9.08; S, 10.08.

Ethyl 3-Cyano-1,2-dihydro-6-methyl-4-methylthio-2-oxo-5-pyridylcarboxylate (**9h**).

This compound (1.94 g, 7.70 mmoles) was synthesized in 77% yield from ethyl acetoacetate (**2o**) (1.30 g, 10 mmoles) and **1b** in a similar manner to that described for the preparation of **9g**. An analytical sample was recrystallized from benzene + ethanol to give yellow needles, mp 191°; ir (potassium bromide): ν max cm^{-1} 2980 (NH), 2900-2600 (NH or OH), 2205 (CN), 1718, 1655 (C=O); uv (ethanol): λ max nm (log ε) 252 (4.08), 340 (3.96); ^1H nmr (deuteriochloroform): δ 1.39 (3H, J = 7.0 Hz, O-CH_2-Me), 2.47 (3H, s, 6-Me), 2.76 (3H, s, SMe), 4.38 (2H, q, J = 7.0 Hz, O-CH_2).

Anal. Calcd. for $C_{11}H_{12}N_2O_3S$: C, 52.37; H, 4.79; N, 11.10; S, 12.79. Found: C, 52.26; H, 4.81; N, 11.21; S, 12.79.

5-Acetyl-3-cyano-6-methyl-4-methylthio-2(1*H*)-pyridone (**9i**).

This compound (1.49 g, 6.7 mmoles) was synthesized in 67% yield from acetyl acetone (**2p**) (1.0 g, 10 mmoles) and **1b** in a similar manner to that described for the preparation of **9g**. This compound was recrystallized from methanol to give pale yellow needles, mp 230°; [lit 19, mp 230°].

3-Cyano-1,2,9,10-tetrahydro-4-methylthio-2-oxobenzo[*h*]quinoline (**10**).

This compound (0.75 g, 2.80 mmoles) was synthesized in 28% yield from 1-tetralone (**2q**) (1.46 g, 10 mmoles) and **1b** in a similar manner to that described for the preparation. An analytical sample was recrystallized from methanol + benzene to give yellow needles, mp 268° [lit 8, mp 268°]; ir (potassium bromide): ν max cm^{-1} 3420 (NH or OH), 2210 (CN), 1640 (CO); uv (ethanol): λ max nm (log ε) 232 (4.16), 268 (4.09), 394 (4.21); nmr (deuteriodimethylsulfoxide): δ 2.68 (3H, s, SMe), 2.84 (4H, s, -CH_2-CH_2-), 7.24-7.47 (3H, m, aromatic-H), 7.92-8.85 (1H, m, aromatic-H).

6-Methyl-4-methylthio-2-oxo-2*H*-pyran-3-carbonitrile (**6d**).

A mixture of 5.06 g (100 mmoles) of acetone, 2.03 g (10 mmoles) of methyl 2-cyano-3,3-bis(methylthio)acrylate [12], 2.24 g (40 mmoles) of powdered potassium hydroxide, and 10 ml of dimethylsulfoxide was stirred for 5 hours at room temperature. The reaction mixture was poured into 300 ml of ice-water and the whole was stirred at room temperature for 4 hours. The precipitate that appeared was collected by filteration, washed with water and recrystallized from benzene + methanol to give 0.51 g (5 mmoles, 50%) of colorless needles, mp 198°; ir (potassium hydroxide): ν max cm^{-1} 2200 (CN), 1720 (C=O); uv (ethanol): λ max nm (log ε) 230 (4.16), 285 (4.13), 346 (3.99); ^1H nmr (deuteriochloroform + trifluoroacetic acid): δ 2.32 (3H, s, 6-Me), 2.56 (3H, s, SMe), 6.26 (1H, s, 5-H).

Anal. Calcd. for $C_8H_7NO_2S$: C, 53.04; H, 3.90; N, 7.70; S, 17.67. Found: C, 53.09; H, 3.88; N, 7.82; S, 17.84.

4-Hydroxy-6-phenyl-2(1*H*)-pyridone (**13**).

This compound (0.16 g, 0.86 mmoles) was synthesized in 17% yield from 4-methoxy-6-phenyl-2-oxo-2*H*-pyran-3-carbonitrile (**12**) [16] (1.14 g, 5 mmoles) in a similar manner to that described for the preparation of **11a** (method a). A crude product was recrystallized from methanol to give colorless needles, mp >350° [lit 20 mp >350°].

4-Methylthio-6-phenyl-2-oxo-2*H*-pyran-3-carboxamide (**14a**).

A mixture of 1.22 g (5 mmoles) of 4-methylthio-6-phenyl-2-oxo-2*H*-pyran-3-carbonitrile (**7a**) and 20 g of polyphosphoric acid (PPA) was heated at 100° for 5 hours. This reaction mixture was poured into 200 ml of ice-water. The tan precipitate that appeared was collected by filteration, washed with water and recrystallized from methanol to give 1.20 g (4.6 mmoles, 92%) of pale yellow leaflets, mp 254°; ir (potassium bromide): ν max cm^{-1} 3370, 3150 (NH_2), 1700, 1662 (C=O); uv (ethanol): λ max nm (log ϵ) 254 (4.28), 336 (4.31); ^1H nmr (deuteriochloroform + trifluoroacetic acid, 5:1): δ 2.64 (3H, s, SMe), 7.10 (1H, s, 5-H), 7.53-7.64 (3H, m, phenyl-H), 7.81-7.94 (2H, m, phenyl-H).

Anal. Calcd. for $C_{13}H_{11}NO_3S$: C, 59.76; H, 4.28; N, 5.36; S, 12.28. Found: C, 59.54; H, 4.12; N, 5.32; S, 12.21.

6-(*p*-Bromophenyl)-4-methylthio-2-oxo-2*H*-pyran-3-carboxamide (**14b**).

This compound (1.63 g, 4.8 mmoles) was synthesized in 96% yield from 6-(*p*-bromophenyl)-4-methylthio-2-oxo-2*H*-pyran-3-carbonitrile (**6b**) (1.61 g, 5 mmoles) in a similar manner to that described for the preparation of **14a**. An analytical sample was recrystallized from methanol to give yellow needles, mp 219°; ir (potassium bromide): ν max cm^{-1} 3370, 3160 (NH_2), 1700, 1660 (C=O); uv (ethanol): λ max nm (log ϵ) 242 (4.03), 261 (4.17), 337 (4.26); ^1H nmr (deuteriodimethylsulfoxide): δ 2.58 (3H, s, SMe), 7.15 (1H, s, 5-H), 7.48 (1H, bs, NH), 7.75 (2H, d, J = 9.0 Hz, phenyl-H), 7.94 (2H, d, J = 9.0 Hz, phenyl-H), 7.09 (1H, bs, NH).

Anal. Calcd. for $C_{13}H_{10}BrNO_3S$: C, 45.90; H, 2.96; N, 4.12; S, 9.42. Found: C, 45.74; H, 2.89; N, 9.32; S, 9.42.

4-Methylthio-6-(*p*-methoxyphenyl)-2-oxo-2*H*-pyran-3-carboxamide (**14c**).

This compound (1.10 g, 3.78 mmoles) was synthesized in 75% yield from 4-methylthio-6-(*p*-methoxyphenyl)-2-oxo-2*H*-pyran-3-carbonitrile (**6c**) (1.37 g, 5 mmoles) in a similar manner to that described for the preparation of **14a**. An analytical sample was recrystallized from methanol to give tan needles, mp 225°; ir (potassium bromide): ν max cm^{-1} 3380, 3160 (NH_2), 1700, 1655 (C=O); uv (ethanol): λ max nm (log ϵ) 245 (4.14), 346 (4.24), 382 (4.33); ^1H nmr (deuteriodimethylsulfoxide): δ 2.56 (3H, s, SMe); 3.85 (3H, s, OMe), 7.02 (1H, s, 5-H), 7.10 (1H, bs, NH), 7.42 (2H, d, J = 9.0 Hz, phenyl-H), 7.96 (2H, d, J = 9.0 Hz, phenyl-H), 8.28 (1H, bs, NH).

Anal. Calcd. for $C_{14}H_{13}NO_4S$: C, 57.72; H, 4.48; N, 4.81; S, 11.01. Found: C, 58.04; H, 4.45; N, 4.81; S, 11.04.

6-Methyl-4-methylthio-2-oxo-2*H*-pyran-3-carboxamide (**14d**).

This compound (1.9 g, 9.5 mmoles) was synthesized in 95% yield from 6-methyl-4-methylthio-2-oxo-2*H*-pyran-3-carbonitrile (**6d**) (1.8 g, 10 mmoles) in a similar manner to that described for the preparation of **14a**. An analytical sample was recrystallized from methanol to give tan leaflets, mp 232°; ir (potassium bromide): ν max cm^{-1} 3350, 3250 (NH_2), 1690, 1658 (C=O); uv (ethanol): λ max nm (log ϵ) 235 (4.23), 300 (4.07), 338 (4.06); ^1H nmr (deuteriochloroform): δ 2.32 (3H, s, SMe), 2.33 (3H, s, 6-Me), 5.57 (1H, bs, NH), 6.26 (1H, s, 5-H), 8.77 (1H, bs, NH).

Anal. Calcd. for $C_6H_9NO_3S$: C, 48.23; H, 4.55; N, 7.03; S, 16.07. Found: C, 47.90; H, 4.44; N, 6.94; S, 16.11.

4-Methylthio-6-styryl-2-oxo-2*H*-pyran-3-carboxamide (**14e**).

This compound (2.38 g, 8.3 mmoles) was synthesized in 83% yield from **6e** (2.69 g, 10 mmoles) in a similar manner to that described for the preparation of **14a**. An analytical sample was recrystallized from benzene to give yellow leaflets, mp 218°; ir (potassium bromide): ν max cm^{-1} 3400, 3180 (NH), 1690 (C=O); uv (ethanol): λ max nm (log ϵ) 242 (4.23), 248 (4.22), 270 (4.25), 276 (4.26), 366 (4.42), 384 (4.40), 402 (4.38); nmr (deuteriodimethylsulfoxide): δ 2.46 (3H, s, SMe), 6.84 (1H, s, 5-H), 7.12 (1H, d, J = 16.3 Hz, C=C-H), 7.38-7.75 (7H, m, C=C-H, phenyl-H, N-H), 8.12 (1H, bs, N-H).

Anal. Calcd. for $C_{15}H_{13}NO_3S$: C, 62.70; H, 4.56; N, 4.87; S, 11.16. Found: C, 62.68; H, 4.57; N, 4.79; S, 11.09.

4-Methylthio-6-phenyl-2(1*H*)-pyridone (**11a**).

Method a. A solution of 2.43 g (10 mmoles) of **6a** and 20 ml of 48% hydrogen bromide in 100 ml of acetic acid was refluxed for 15 hours. After evaporation of the hydrogen bromide solution and acetic acid, the residue was washed with 10% sodium carbonate and recrystallized from methanol to give 0.52 g (2.4 mmoles, 24%) of colorless needles, mp 189°.

Method b. A solution of 0.26 g (1 mmole) of **14a** in 10 ml of 10% sodium hydroxide was heated at 70° for 1 hour under stirring. The reaction mixture was poured into 30 ml of ice-water and appeared was collected by filteration and recrystallized from methanol to give 0.17 g (0.78 mmole; 78%) of **11a**, mp 189°; ir (potassium bromide): ν max cm^{-1} 3100-2700 (NH or OH), 1610 (C=O); uv (ethanol): λ max nm (log ϵ) 249 (4.34), 290 (3.98), 320 (4.39); ^1H nmr (trifluoroacetic acid): δ 2.66 (3H, s, SMe), 6.94 (1H, s, 3-H or 5-H), 7.12 (1H, s, 3-H or 5-H), 7.44-7.94 (5H, m, phenyl-H).

Anal. Calcd. for $C_{12}H_{11}NO$: C, 66.33; H, 5.10; N, 6.45; S, 14.76. Found: C, 66.03; H, 4.98; N, 6.35; S, 14.45.

6-(*p*-Bromophenyl)-4-methylthio-2(1*H*)-pyridone (**11b**).

This compound was synthesized from **6b** or **14b** in 33 and 80% yields, respectively, in a similar manner to that described for the preparation of **12a** by the method a or b. An analytical sample was recrystallized from methanol to give colorless needles, mp 248°; ir (potassium bromide): ν max cm^{-1} 3100, 2902 (NH or OH), 1610 (C=O); uv (ethanol): λ max nm (log ϵ) 255 (4.40), 324 (4.13); ^1H nmr (deuteriochloroform + trifluoroacetic acid): δ 2.61 (3H, s, SMe), 6.80 (1H, d, J = 1.7 Hz, 3 or 5-H), 7.04 (1H, d, J = 1.7 Hz, 3 or 5-H), 7.52 (2H, d, J = 8.9 Hz, phenyl-H), 7.74 (2H, d, J = 8.9 Hz, phenyl-H).

Anal. Calcd. for $C_{12}H_{10}BrNOS$: C, 48.66; H, 3.40; N, 4.73; S, 10.83. Found: C, 48.58; H, 3.28; N, 4.68; S, 10.58.

4-Methylthio-6-(*p*-methoxyphenyl)-2(1*H*)-pyridone (**11c**).

This compound was synthesized from **6c** or **14b** in 32 and 81% yields, respectively, in a similar manner to that described for the preparation of **11a** by the method a or b. An analytical sample was recrystallized from methanol to give colorless needles, mp 227°; ir (potassium bromide): ν max cm^{-1} 3120, 3075 (NH or OH), 1615 (C=O); uv (ethanol): λ max nm (log ϵ) 219 (4.34), 255 (4.31), 329 (4.20); ^1H nmr (deuteriochloroform): δ 2.45 (3H, s, SMe), 3.86 (3H, s, OMe), 6.17 (1H, d, J = 1.8 Hz, 3 or 5-H), 6.25 (1H, d, J = 1.8 Hz, 3 or 5-H), 6.99 (2H, d, J = 9.0 Hz, phenyl-H), 7.58 (2H, d, J = 9.0 Hz, phenyl-H).

Anal. Calcd. for $C_{13}H_{13}NO_2S$: C, 63.44; H, 5.30; N, 5.66; S, 12.96. Found: C, 62.89; H, 5.22; N, 5.59; S, 12.89.

6-Methyl-4-methylthio-2(1*H*)-pyridone (**11d**).

This compound was synthesized from **6d** or **14d** in 24 and 66% yields, respectively, in a similar manner to that described for the preparation of **11a** by the method a or b. An analytical sample was recrystallized from methanol to give colorless needles, mp 180°; ir (potassium bromide): ν max cm^{-1} 3220, 3040, 2880 (NH or OH), 1665, 1615 (C=O); uv (ethanol): λ max nm (log ϵ) 230 (4.32), 273 (4.09), 304 (3.83); ^1H nmr (deuteriochloroform): δ 2.25 (3H, s, 6-Me), 2.35 (3H, s, SMe), 5.89 (1H, s, 3 or 5-H), 6.65 (1H, s, 3 or 5-H).

Anal. Calcd. for C_7H_9NOS: C, 54.17; H, 5.84; N, 9.02; S, 20.66. Found: C, 53.82; H, 5.87; N, 9.09; S, 20.58.

4-Methylthio-6-styryl-2(1*H*)-pyridone (**11e**).

This compound was synthesized from **6e** or **14e** in 33 and 62% yields, respectively, in a similar manner to that described for the preparation of **11a** by the method a or b. An analytical sample was recrystallized from methanol to give yellow needles, mp 221°; ir (potassium bromide): ν max cm^{-1} 3100-2600 (NH or OH), 1630-1605 (C=O); uv (ethanol): λ max nm (log ϵ) 234 (4.28); 273 (4.37); 345 (4.35); ^1H nmr (deuteriochloroform + trifluoroacetic acid): δ 2.55 (3H, s, SMe); 6.59 (1H, s, 3 or 5-H), 6.80 (1H, s, 3 or 5-H), 6.84 (1H, d, J = 16.0 Hz, C=C-H), 7.40-7.64 (6H, m, phenyl-H, C=C-H); ms: m/z 243 (M^+).

Anal. Calcd. for $C_{14}H_{13}NOS$: C, 69.11; H, 5.39; N, 5.76; S, 13.18. Found: C, 68.75; H, 5.43; N, 5.65; S, 13.18.

Acknowledgment.

The work was supported to A. H. in part by the Ministry of Education, Science, and Culture, the Research Foundation of Pharmaceutical Sciences, the Houan-sha, and Yamada Science Foundation.

REFERENCES AND NOTES

[1] G. Jones, "Pyridines and their Benzo Derivatives: (V) Reactivity of Non-aromatics", in "Comprehensive Heterocyclic Chemistry", Vol **2**, A. R. Katrizky and C. W. Rees, eds, Pergamon Press Oxford, 1984, pp 395-510.

[2] P. Beak, J. B. Covington, S. G. Smith, J. White, and J. M. Zeigler, *J. Org. Chem.*, **45**, 1354 (1980).

[3] G. A. Youngdale and T. F. Oglia, *J. Med. Chem.*, **28**, 1790 (1985).

[4] Y. Tominaga and Y. Matsuda, *J. Heterocyclic Chem.*, **37**, 937 (1985).

[5] Y. Tominaga, S. Sakai, S. Kohra, J. Tsuka, and Y. Matsuda, and G. Kobayashi, *Chem. Pharm. Bull.*, **33**, 962 (1985).

[6] R. R. Rastogi, H. Ila, and H. Junjappa, *J. Chem. Soc., Chem. Commun.*, 645 (1975).

[7] S. M. S. Chauhan and H. Junjappa, *Tetrahedron*, **32**, 1779 (1976).

[8] R. R. Rastogi, A. Kumar, H. Ila, and H. Junjappa, *J. Chem. Soc., Perkin Trans. I*, 549 (1978).

[9] A. Kumar, H. Ila, and H. Junjappa, *J. Chem. Soc., Perkin Trans. I*, 858 (1978).

[10] R. K. Dieter, *Tetrahedron*, **42**, 3029 (1986).

[11] K. T. Potts, M. J. Cipullo, P. Ralli, and G. Theodoridis, *J. Am. Chem. Soc.*, **103**, 3585 (1981).

[12] R. Gompper and W. Topfel, *Chem. Ber.*, **95**, 2871 (1962).

[13] Y. Tominaga, A. Ushirogochi, Y. Matsuda, and G. Kobayashi, *Heterocycles*, **5**, 193 (1977).

[14] Y. Tominaga, Y. Matsuda, and G. Kobayashi, *Chem. Pharm. Bull.*, **32**, 1665 (1984).

[15] Y. Tominaga, A. Ushirogochi, Y. Matsuda, and G. Kobayashi, *Chem. Pharm. Bull.*, **32**, 3384 (1984).

[16] Y. Tominaga, H. Norisue, Y. Matsuda, and G. Kobayashi, *Yakugaku Zasshi*, **104**, 127 (1984).

[17] E. Poetsch, *German Offen.*, 1,809,467 (1968); *Chem. Abstr.*, **73**, P66443k (1970).

[18] G. P. Ellis, "Pyrans and Fused Pyrans: (ii) Reactivity" in "Comprehensive Heterocyclic Chemistry", Vol **3** by A. R. Katrizky and C. W. Rees, eds, 1984, pp 647-736.

[19] T. Hatada, M. Sone, Y. Tominaga, Y. Matsuda, and G. Kobayashi, *Yakugaku Zasshi*, **95**, 623 (1975).

[20] T. Kato, Y. Yamamoto, and M. Kondou, *Chem. Pharm. Bull.*, **23**, 1873 (1975).