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# 1,3-Oxazines and Related Compounds. IX.[1] Alkylation, Acylation, and Cleavage Reaction of 6-Methyl-4-oxo-2-thioxo-3,4-dihydro-2*H*-1,3-oxazine

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Alkylation of the title compound (**2**) with alkyl halides in the presence of $Et_3N$ proceeded exclusively on the sulfur atom to give the *S*-alkyl-1,3-oxazine derivatives. Acylation with acyl chlorides took place regioselectively on the nitrogen atom, giving the *N*-acyl derivatives. 1,3-Oxazine **2** was found to undergo cleavage of the ring into acetylketene and thiocyanic acid. Hence, treatment of **2** with alkyl halides in the presence of $K_2CO_3$ gave alkyl thiocyanates; treatment with active methylene compounds afforded $\gamma$-pyrone derivatives. *N*-Acyl derivatives of **2** also underwent thermal cleavage of the ring, leading to the corresponding acyl isothiocyanates.

**Keywords**——2-thioxo-4-oxo-1,3-oxazine; acetylketene; thiocyanic acid; acyl isothiocyanate; alkyl thiocyanate; acylation; alkylation; substituted $\gamma$-pyrone

Various reactions, especially ring transformations, of 6-methyl-1,3-oxazin-2,4-dione (**1**) and its *N*-alkyl derivatives have been reported.[2] On the other hand, little is known concerning the chemical properties of an *S*-analogue of **1**, 6-methyl-4-oxo-2-thioxo-3,4-dihydro-2*H*-1,3-oxazine (**2**), which can be readily prepared from diketene and ammonium thiocyanate.[3] In the course of this series of studies, we became interested in comparing the chemical properties of **1** and **2**. We present herein details of the alkylation of **2** with alkyl halides, acylation with acyl chlorides, and reaction with some representative active methylene compounds to provide $\gamma$-pyrone derivatives.

## Reaction of 2 with Alkyl Halide (3)

Kato *et al.*[2] have demonstrated that reaction of **1** with alkyl halides such as methyl iodide (MeI, **3a**), ethyl iodide (EtI), and benzyl bromide ($PhCH_2Br$, **3b**) in acetone in the presence of potassium carbonate ($K_2CO_3$) yields the corresponding *N*-alkylated 1,3-oxazines in good yields. Analogous treatment of **2** with **3a** according to the reported procedure[2] gave only methyl thiocyanate (**4a**), instead of the expected 1,3-oxazine, in good yield. Similar treatment of **2** with **3b** gave the corresponding benzyl thiocyanate (**4b**) in good yield. Ethyl bromoacetate (**3c**) also reacted smoothly to give ethyl $\alpha$-thiocyanatoacetate (**4c**).

Alkylation of **2** was achieved by employing triethylamine ($Et_3N$) as a base and occurred predominantly at the sulfur atom of **2**; a solution of **2** in tetrahydrofuran (THF) was treated with **3a**—**c** from $-20$ °C to room temperature in the presence of $Et_3N$ to give **5a**—**c** in good yields. The product **5** was found to be very stable thermally. For instance, refluxing of a solution of the *S*-methyl derivative **5a** in acetone in the presence of $K_2CO_3$ or in xylene without any catalyst resulted in quantitative recovery of **5a**. Attempts to carry out regioselective alkylation at the nitrogen atom were unsuccessful.

On the other hand, the thioxo-1,3-oxazine **2** was found to be cleaved by $K_2CO_3$ catalysis through a retro-addition reaction to give acetylketene (**6**) and thiocyanic acid (HSCN). Generation of **6** *in situ* was confirmed as follows: an acetone solution of one equivalent each of

**2** and ethanol in the presence of $K_2CO_3$ was stirred for 1 h at room temperature to give ethyl acetoacetate (**7**) quantitatively. These findings suggest that **4** would be formed by the reaction between **3** and HSCN (and/or potassium thiocyanate) generated *in situ* as illustrated in Chart 1.

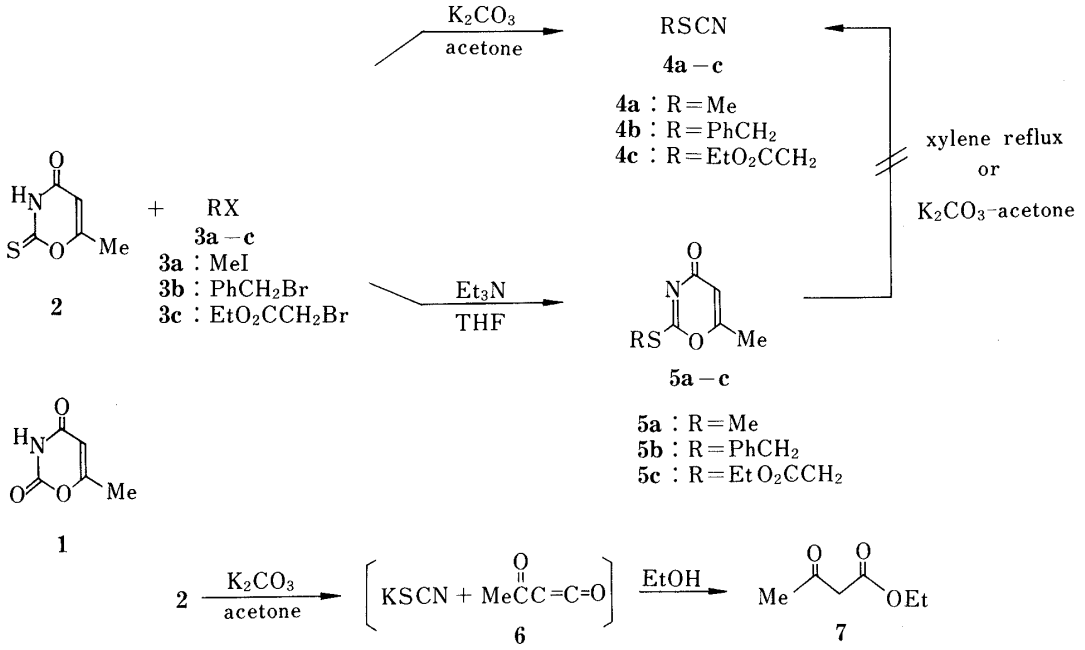



Chart 1

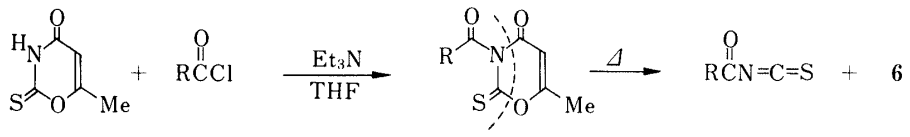
**Reaction of 2 with Acyl Chlorides (8)**

Thioxo-1,3-oxazine **2** smoothly reacted with acyl chlorides (**8**) to provide exclusively *N*-acyl derivatives (**9**). Acyl chlorides used were acetyl (**8a**), propionyl (**8b**), isobutyryl (**8c**), pivaloyl (**8d**), and benzoyl (**8e**) chlorides. Ethyl chloroformate (**8f**) was also employed. For example, treatment of **2** with **8a** in the presence of $Et_3N$ from $-20\,°C$ to room temperature gave *N*-acetylated **9a** in 85% yield. Infrared (IR) spectra of **9a—e** showed two characteristic bands due to C=O stretching at 1775 and 1700 $cm^{-1}$. Proton nuclear magnetic resonance ($^1$H-NMR) and mass spectra (MS) as well as analytical data supported the structures **9a—e** (Table III). Attempts at regioselective *S*-acylation were unsuccessful.

The *N*-acyl derivatives (**9a—e**) were found readily to undergo thermal cleavage, giving the corresponding acyl isothiocyanates (**10**) in good yields. When *N*-benzoyl-1,3-oxazine (**9e**) was heated for 1 h at 130—135 °C (bath temperature), benzoyl isothiocyanate (**10e**) was obtained in 71% yield; its IR spectrum showed a characteristic band due to the isothiocyanate group (–N=C=S) at 1950—1980 $cm^{-1}$, and it was identical with an authentic sample prepared by the reported procedure.[5] The results obtained are summarized in Table IV.

**Reaction of 2 with Active Methylene Compounds (11)**

Reactions of **2** with active methylene compounds such as malononitrile (**11a**), ethyl cyanoacetate (**11b**), ethyl acetoacetate (**11c**), and acetylacetone (**11d**) were carried out. For example, treatment of **2** with **11a** in the presence of sodium hydride (NaH) unexpectedly gave rise to 2-amino-3-cyano-6-methyl-4-pyrone (**12a**) in fair yield. Its IR spectrum was identical with that of an authentic sample prepared by the reported procedure.[7] Employing potassium hydride (KH) instead of NaH brought about almost the same result, but organic bases such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), 1,4-diazabicyclo[2.2.2]octane (DABCO), and 4-dimethylaminopyridine (DMAP) had little or no effect on the reaction.[10] Table V summarizes



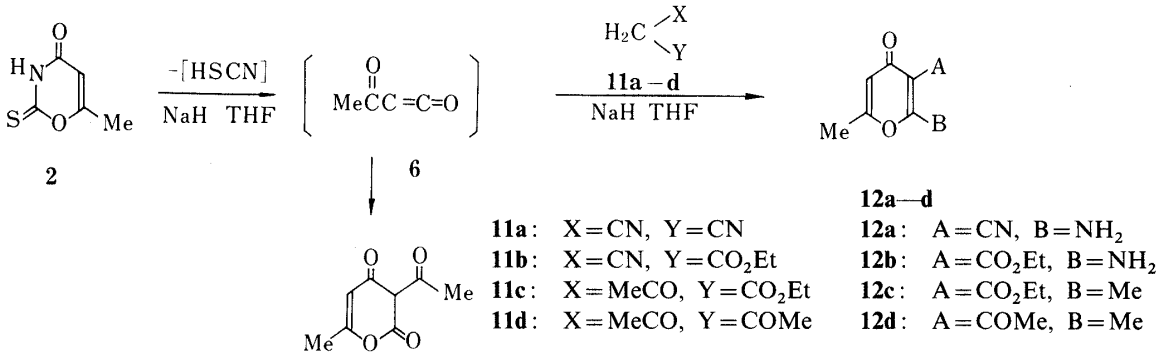
2 **8a—f** **9a—e** **10a—f**

**8a**: R=Me **8b**: R=Et **8c**: R=iso-Pr **8d**: R=*tert*-Bu **8e**: R=Ph **8f**: R=EtO

**9a**: R=Me **9b**: R=Et **9c**: R=iso-Pr **9d**: R=*tert*-Bu **9e**: R=Ph

**10a**: R=Me **10b**: R=Et **10c**: R=iso-Pr **10d**: R=*tert*-Bu **10e**: R=Ph **10f**: R=EtO

Chart 2



**11a**: X=CN, Y=CN **11b**: X=CN, Y=$CO_2$Et **11c**: X=MeCO, Y=$CO_2$Et **11d**: X=MeCO, Y=COMe

**12a—d**

**12a**: A=CN, B=$NH_2$ **12b**: A=$CO_2$Et, B=$NH_2$ **12c**: A=$CO_2$Et, B=Me **12d**: A=COMe, B=Me

Chart 3

the results of reactions between **2** and **11a—d**.

The γ-pyrones **12** are presumably formed from **11** and acetylketene (**6**), which is produced *in situ* by base-catalyzed cleavage of **2**, as shown in Chart 3. In fact, when a solution of **2** in THF was refluxed in the presence of NaH for 1 h, dehydroacetic acid (dimer of **6**) was obtained in 60% yield.

In summary, regioselective alkylation of **2** with **3** at the sulfur atom took place in the presence of $Et_3N$, whereas acylation with acyl chlorides (**8**) occurred exclusively at the nitrogen atom. The 1,3-oxazine ring of **2** readily underwent thermal cleavage to give HSCN and **6**. The acetylketene (**6**), generated *in situ*, reacted with active methylene compounds **11** to yield γ-pyrones **12**. Ring-opening of the *N*-acyl-1,3-oxazines **9** took place smoothly, leading to the isothiocyanates **10**.

## Experimental

Melting points were obtained in a Mel-Temp melting point apparatus with an open capillary tube, and are uncorrected. IR spectra were taken on a Shimadzu IR-400 or IR-430 s pectrometer. $^1$H-NMR spectra were measured on a JEOL JNM-PMX 60 instrument. Chemical shifts are reported in δ values downfield relative to internal tetramethylsilane or sodium 2,2-dimethyl-2-silapentane-5-sulfonate. The following abbreviations are used: s=singlet, d=doublet, t=triplet, m=multiplet, and br=broad. THF was distilled from $LiAlH_4$ directly before use.

**Reaction of 2-Thioxo-1,3-oxazin-4-one 2 with Alkyl Halides (3) in the Presence of $K_2CO_3$, Giving Alkyl Thiocyanates 4. General Procedure**——A mixture of **2** (1.43 g, 10 mmol), **3** (10 mmol), and anhyd. $K_2CO_3$ (4.14 g, 30 mmol) in acetone (30 ml) was magnetically stirred for 1 h at room temperature. Insoluble material was removed by filtration. The filtrate was concentrated under reduced pressure to give crude thiocyanate **4**, which was purified by distillation. The results obtained are summarized in Table I.

**Alkylation of 2-Thioxo-1,3-oxazin-4-one 2. General Procedure**——A solution of $Et_3N$ (1.11 g, 11 mmol) in THF (10 ml) and a solution of **3** (11 mmol) in THF (20 ml) were successively added dropwise to a solution of **2** (1.43 g,

TABLE I. Thiocyanates **4a**—**c** from **2** and **3a**—**c**

| Product No. | Yield (%) | bp (°C) (Torr) | IR[a] $cm^{-1}$ | NMR ($CDCl_3$) $\delta$ |
|---|---|---|---|---|
| **4a** | 64 | 130—131 | 2140 | 2.72 (3H, s) |
| **4b** | 80 | 120 (17) | 2140 | 4.03 (2H, s), 7.33 (5H, s) |
| **4c** | 76 | 90 (5.0)[b] | 2150 | 1.33 (3H, t, $J$=7 Hz), 3.80 (2H, s) |
| | | | 1740 | 4.26 (2H, q, $J$=7 Hz) |

*a*) Spectra of **4a**, **c** were taken neat and that of **4b** was taken in $CHCl_3$ solution.
*b*) Ref. 4, bp 119—120 °C (15 Torr).

TABLE II. *S*-Alkylated 1,3-Oxazine Derivatives **5a**—**c** from **2** and **3a**—**c**

| Product No. | Yield (%) | mp (°C) (Solvent) | Formula ($m/e$ $M^+$) | Analysis (%) Calcd (Found) C | H | N | IR (KBr) $cm^{-1}$ | NMR ($CDCl_3$) $\delta$ |
|---|---|---|---|---|---|---|---|---|
| **5a** | 67 | 81—83 | $C_6H_7NO_2S$ | 45.86 | 4.49 | 8.92 | 1660 | 2.23 (3H, s), 2.56 (3H, s) |
| | | ($Et_2O$) | (157) | (45.91 | 4.60 | 9.12) | | 5.90 (1H, s) |
| **5b** | 77 | 105—106 | $C_{12}H_{11}NO_2S$ | 61.80 | 4.75 | 6.01 | 1665 | 2.16 (3H, s), 4.33 (2H, s) |
| | | ($Et_2O$) | (233) | (61.95 | 4.55 | 6.16) | | 5.90 (1H, s), 7.32 (5H, s) |
| **5c** | 72 | 95—96 | $C_9H_{11}NO_4S$ | 47.16 | 4.84 | 6.11 | 1745 | 1.33 (3H, t, $J$=7 Hz), 2.33 (3H, s) |
| | | ($Et_2O$–$C_6H_6$) | (229) | (47.11 | 4.71 | 6.32) | 1670 | 3.96 (2H, s), 4.11 (2H, q, $J$=7 Hz) |
| | | | | | | | | 5.93 (1H, s) |

TABLE III. *N*-Acylated 1,3-Oxazine Derivatives **9a**—**e** from **2** and **8a**—**e**

| Product No. | Yield (%) | mp (°C) (Solvent) | Formula ($m/e$ $M^+$) | Analysis (%) Calcd (Found) C | H | N | IR (KBr) $cm^{-1}$ | NMR ($CDCl_3$) $\delta$ |
|---|---|---|---|---|---|---|---|---|
| **9a** | 85 | 83—84 (dec.) | $C_7H_7NO_3S$ | 45.41 | 3.81 | 7.57 | 1775 | 2.30 (3H, s), 2.63 (3H, s) |
| | | ($Et_2O$) | (185) | (45.38 | 3.92 | 7.59) | 1700 | 5.90 (1H, s) |
| **9b** | 78 | 85—86 (dec.) | $C_8H_9NO_3S$ | 48.24 | 4.56 | 7.03 | 1770 | 1.33 (3H, t, $J$=7 Hz), 2.30 (3H, s) |
| | | ($Et_2O$) | (199) | (48.48 | 4.53 | 6.92) | 1700 | 2.96 (2H, q, $J$=7 Hz), 6.00 (1H, s) |
| **9c** | 72 | 88—89 (dec.) | $C_9H_{11}NO_3S$ | 50.70 | 5.20 | 6.57 | 1770 | 1.30 (6H, d, $J$=7 Hz), 2.26 (3H, s) |
| | | ($Et_2O$) | (213) | (50.83 | 5.31 | 6.72) | 1700 | 3.20 (1H, m), 5.93 (1H, s) |
| **9d** | 66 | 84—85 (dec.) | $C_{10}H_{13}NO_3S$ | 52.86 | 5.77 | 6.17 | 1770 | 1.40 (9H, s), 2.30 (3H, s) |
| | | ($Et_2O$) | (227) | (52.81 | 5.83 | 5.99) | 1700 | 5.96 (1H, s) |
| **9e** | 76 | 118—120 (dec.) | $C_{12}H_9NO_3S$ | 58.30 | 3.67 | 5.67 | 1750 | 2.26 (3H, s), 5.96 (1H, s), |
| | | ($Et_2O$–$C_6H_6$) | (247) | (58.21 | 3.71 | 5.43) | 1700 | 7.50—8.12 (5H, m) |

10 mmol) in THF (20 ml) in an ice-salt bath. The reaction mixture was allowed to stand at room temperature. The precipitate formed was filtered off. The filtrate was concentrated under reduced pressure. The residual solid was purified by recrystallization from the solvent indicated in Table II.

**Reaction of 2-Thioxo-1,3-oxazin-4-one 2 with Acyl Halides (8). General Procedure**——A solution of $Et_3N$ (1.11 g, 11 mmol) in THF (10 ml) was added dropwise to a solution of **2** (1.43 g, 10 mmol) and **8** (11 mmol) in THF (20 ml) with stirring in an ice-salt bath. The reaction mixture was stirred at room temperature. In the case of **8d**, stirring was continued for 12 h at room temperature. The precipitate formed was removed by filtration. The filtrate was concentrated under reduced pressure to give crude **9**, which was purified from the solvent indicated in Table III. In the case of **8f**, the corresponding 1,3-oxazine **9f** was so unstable that attempts at its isolation failed.

**Cleavage Reaction of 9a—e to Acyl Isothiocyanates (10). General Procedure**——An *N*-acyl-1,3-oxazine **9a**—**e** (10 mmol) was heated alone at 10—15 °C beyond the decomposition temperature in an oil bath for 1 h. The resulting

TABLE IV. Acyl Isothiocyanates **10a—f** from **9a—f**

| Product No. | Yield (%) | bp (°C) (Torr)[a] | IR (neat) $cm^{-1}$ | NMR ($CDCl_3$) $\delta$ |
|---|---|---|---|---|
| **10a** | 54 | 50—55 (20)[b] | 1950—1980 (br)<br>1725 | 2.25 (3H, s) |
| **10b** | 52 | 70—75 (17)[c] | 1940—1980 (br)<br>1720 | 1.32 (3H, t, $J$=7 Hz)<br>2.93 (2H, q, $J$=7 Hz) |
| **10c** | 58 | 75—80 (17)[d] | 1950—1980 (br)<br>1720 | 1.28 (6H, d, $J$=7 Hz)<br>3.15 (1H, m) |
| **10d** | 62 | 90 (15)[e] | 1950—1980 (br)<br>1720 | 1.26 (9H, s) |
| **10e** | 71 | 67—70 (1.0)[f] | 1950—1980 (br)<br>1700 | 7.42—8.05 (5H, m) |
| **10f** | 66[h] | 80—85 (10)[g] | 1950—1980 (br)<br>1760 | 1.26 (3H, t, $J$=7 Hz)<br>4.23 (2H, q, $J$=7 Hz) |

*a*) Bath temperature, except in the case of **10e**.
*b*) Ref. 5, bp 39.5—40.5 °C (21 Torr). *c*) Ref. 6, bp 149—150 °C (760 Torr)
*d*) Ref. 6, bp 159—161 °C (760 Torr). *e*) Ref. 6, bp 163—166 °C (760 Torr).
*f*) Ref. 5, bp 102—103 °C (4.8 Torr). *g*) Ref. 5, bp 25.5—26.7 °C (1.8 Torr).
*h*) Yield from oxazine **2**.

TABLE V. γ-Pyrone Derivatives **12a—d** from **2** and **11a—d**

| Product No. | A | B | Yield (%) | mp (°C) (Solvent) or bp (°C) (Torr) | IR[a] $cm^{-1}$ | NMR[b] $\delta$ |
|---|---|---|---|---|---|---|
| **12a** | CN | $NH_2$ | 54 | 278—279 (dec.)[c]<br>(MeOH) | 3280<br>2240<br>1675 | 2.17 (3H, s), 5.86 (1H, s)<br>8.46 (2H, br) |
| **12b** | $CO_2Et$ | $NH_2$ | 36 | 166—168 (MeOH)[d] | 3480<br>3280<br>1685 | 1.23 (3H, t, $J$=7 Hz), 2.37 (3H, s)<br>4.18 (2H, q, $J$=7 Hz), 5.69 (1H, s)<br>8.42 (2H, br) |
| **12c** | $CO_2Et$ | Me | 30 | 125—127 (2.0)[e] | 1735<br>1670 | 1.33 (3H, t, $J$=7 Hz), 2.22 (3H, s)<br>2.33 (3H, s), 4.36 (2H, q, $J$=7 Hz)<br>6.10 (1H, s) |
| **12d** | COMe | Me | 21 | 92—95 (3.0)[f] | 1700<br>1670 | 2.23 (3H, s), 2.33 (3H, s)<br>2.50 (3H, s), 6.13 (1H, s) |

*a*) The spectrum of **12a** was taken in KBr and that of **12b** in $CHCl_3$ solution. Those of **12c, d** were taken neat.
*b*) DMSO-$d_6$ and $CDCl_3$–DMSO-$d_6$ were used as solvents in the cases of **12a** and **12b**, respectively, while $CDCl_3$ was used in the other cases.
*c*) Ref. 7, mp 275 °C (dec.). *d*) Ref. 7, mp 164—165 °C.
*e*) Ref. 8, bp 130—131 °C (4 Torr). *f*) Ref. 9, bp 107—112 °C (8 Torr).

liquid was purified by distillation. The results obtained are summarized in Table IV.

**Preparation of Benzoyl Isothiocyanate (10e)**——A solution of benzoyl chloride (2.8 g, 20 mmol) in acetone was treated with potassium thiocyanate (0.97 g, 10 mmol) according to the reported procedure[6] to give 1.1 g (68%) of **10e**, bp 68—70 °C (1 Torr). The IR spectrum was identical with that of the sample (**10e**) obtained in the above run.

**Reaction of 2 with 11 to Give the γ-Pyrones 12. General Procedure**——Sodium hydride (1.58 g, 33 mmol, in 50% mineral oil dispersion) was washed with three 10-ml portions of THF and suspended in 30 ml of THF. Solutions of **11** (10 mmol) and **2** (2.86 g, 20 mmol) in the same solvent were successively added dropwise with stirring to the above suspension in an ice-cooled bath. The reaction mixture was allowed to warm to room temperature, stirred for a further 3 h, neutralized with 10% HCl, and then concentrated under reduced pressure. The residue was extracted with $CHCl_3$. After being washed successively with 10% NaOH and water, the $CHCl_3$ layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by recrystallization or vacuum distillation as shown in Table V. The results obtained are summarized in Table V.

**Preparation of 2-Amino-3-cyano-6-methyl-4-pyrone (12a)**——2-Amino-3-cyano-6-methyl-4-pyrone (**12a**) was prepared from malononitrile (0.66 g, 10 mmol) and diketene (0.84 g, 10 mmol) in the presence of NaH in THF according to the procedure reported by Kato *et al.*[7] mp 278—279 °C (dec.). Yield; 1 g (73%).

**Cleavage Reaction of 2, Giving Dehydroacetic Acid**——Sodium hydride (0.53 g, 11 mmol, in 50% mineral oil dispersion) was washed with three 5-ml portions of THF and suspended in 20 ml of THF. A solution of **2** (1.43 g, 10 mmol) in THF (20 ml) was added dropwise with stirring. After completion of the addition, the reaction mixture was heated under reflux for 1 h. After acidification with 10% HCl, the whole was concentrated under reduced pressure and the residue was extracted with $CHCl_3$. The $CHCl_3$ layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give dehydroacetic acid, mp 109—111 °C. Yield: 0.5 g (60%). The IR spectrum was identical with that of an authentic sample.

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10) In the reactions of **2** with **11a** and **11d**, the use of DBU resulted in only 32 and 10% yields of the corresponding γ-pyrone derivatives. The use of DABCO or DMAP in the reaction with **11a** resulted in quantitative recovery of **2**.