Ring Cleavage Reaction of 1,3-Oxazine-2,4(3*H*)-dione Derivatives with Amines

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The reactions of 3,6-dimethyl [6-methyl-3-phenyl and 3-(4-chlorophenyl)-6-methyl]-1,3-oxazine-2,4(3*H*)-diones (1a, 1b, and 1c) with various amines were investigated under various conditions. Several reaction products were obtained such as the pyrimidines (3a, 3b, 3c, and 3d), the acetoacetamides (4a, 4b, and 4c), (4-chlorophenyl)urethane (5a), and ethyl acetoacetate (4d) with primary amines, and the acetoacetamides (4e and 4f), the urethanes (5a and 5b), the carboxamides (5c, 5d, 5e, and 5f), and the butenamides (7a, 7b, and 7c) with secondary amines. In the case of 1c with amine, alcohol used as a solvent reacted as a nucleophile to give the urethane (5a or 5b).

Keywords ring-cleavage reaction; 1,3-oxazine; amine; nucleophilic reaction; ring transformation; pyrimidine; solvolysis

The 1,3-oxazine-2,4(3*H*)-diones are useful materials for the regioselective preparation of 1-substituted uracils[1] by reaction with primary amines. Previously, 1-(2-hydroxyethyl)-3,6-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione (**3a**[2]), the key intermediate for the synthesis of dithiapyrimidinophane, was prepared by the reaction of 3,6-dimethyl-1,3-oxazine-2,4(3*H*)-dione (**1a**) with ethanolamine.

For the preparation of 1-(2-hydroxyethyl)-6-methyl-3-phenyl [and (4-chlorophenyl)]-2,4(1*H*,3*H*)-pyrimidinediones (**3b** and **3c**), 6-methyl-3-phenyl [and (4-chlorophenyl)]-1,3-oxazine-2,4(3*H*)-diones (**1b** and **1c**)[1d,3] were treated with ethanolamine in a similar manner. However, acetoacetanilides (**4a** and **4b**) and (4-chlorophenyl)urethane (**5a**) were obtained as major ring-cleaved products, while the desired pyrimidine derivatives (**3b** and **3c**) were isolated only in low yields.

Therefore, we searched for suitable reaction conditions for the preparation of pyrimidines (**3**) based on the ring-cleavage of 1,3-oxazine-2,4(1*H*)-diones (**1**) with amines (**2** and **6**). Reactions were carried out under various conditions and we obtained several new ring-cleaved products, which were different from the results of Ahmed *et al.*[1c] and Lacey.[1d] The results are summarized in Tables I and II.

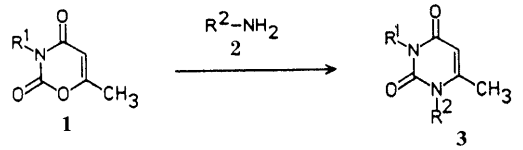
Reaction with Primary Amines Reaction of the oxazines (**1**) with the primary amines (**2**) gave a mixture of pyrimidines (**3**), the acetoacetamides (**4**), and a urethane (**5a**) (Chart 1 and Table I). Generally, the pyrimidines (**3b** and **3c**) were obtained in greater yields with increase in the molar ratio of ethanolamine (**2a**). However, acetoacetanilides (**4a** and **4b**) were isolated in almost the same yields (entries 1—4 and 6—9). In the case of **1c** with ethanolamine (**2a**), (4-chlorophenyl)urethane (**5a**) was obtained and the yield decreased with increase in the molar ratio of ethanolamine (entries 6—9). A similar tendency was observed in the reaction of compound **1c** with *n*-butylamine to give **3d**, **4b**, and **5** (entries 13 and 14). However, no pyrimidine derivative (**3**) was isolated in the reaction with *sec*-butylamine (entry 15).

When compound **1c** was refluxed in ethanol without amine, the starting material was recovered almost quantitatively (entry 16). However, (4-chlorophenyl)urethane (**5a**), 4′-chloroacetoacetanilide (**4b**), and ethyl acetoacetate

TABLE I. Reactions[a] of 1,3-Oxazine-2,4(3*H*)-diones (**1**) with Primary Amines

Entry No.	Oxazine	Amine (eq)	Solvent[b] (ml)	Products[c] (%) 3	4	5a
1	**1b**	**2a** (1.0)	A (10)	**b** 17	**a** 16	—
2	**1b**	**2a** (1.2)	A (10)	**b** 24	**a** 19	—
3	**1b**	**2a** (2.0)	A (10)	**b** 29	**a** 16	—
4	**1b**	**2a** (4.0)	A (10)	**b** 35	**a** 15	—
5	**1b**	**2a** (1.2)	B (10)	**b** 18	**a** 28	—
6	**1c**	**2a** (1.0)	A (15)	**c** 7	**b** 17	29
7	**1c**	**2a** (1.2)	A (15)	**c** 21	**b** 24	20
8	**1c**	**2a** (2.0)	A (15)	**c** 36	**b** 19	10
9	**1c**	**2a** (4.0)	A (15)	**c** 53	**b** 19	1
10	**1c**	**2a** (1.2)	B (10)	—	**b** 52	—
11	**1c**	**2a** (1.2)	C (25)	**c** 12	**b** 37	—
12	**1c**	**2a** (4.0)	C (25)	**c** 36	**b** 47	—
13	**1c**	**2b** (1.2)	A (15)	**d** 8	**b** 10	28
14	**1c**	**2b** (4.0)	A (15)	**d** 31	**b** 22	trace
15	**1c**	**2c** (4.0)	A (15)	—	**b** 8 **c** 40	56
16[d]	**1c**	—	A (15)	—	—	—
17	**1c**	1 ml[e]	A (15)	—	**b** 10 **d** 30	77

a) The reactions were carried out at 95—100 °C for 2 h. *b*) A, ethanol; B, dimethylformamide; C, acetonitrile. *c*) Yields are for the isolated pure products. *d*) Starting material (**1c**) was recovered in 95% yield. *e*) Triethylamine.



1	R^1
a	CH_3
b	C_6H_5
c	*p*-Cl-C_6H_4

2	R^2
a	$HOCH_2CH_2$
b	*n*-Bu
c	*sec*-Bu

3	R^1	R^2
a	CH_3	$HOCH_2CH_2$
b	C_6H_5	$HOCH_2CH_2$
c	*p*-Cl-C_6H_4	$HOCH_2CH_2$
d	*p*-Cl-C_6H_4	*n*-Bu

4	R^3
a	C_6H_5NH
b	*p*-Cl-C_6H_4NH
c	*sec*-BuNH
d	C_2H_5O

5	R^1	R^3
a	*p*-Cl-C_6H_4	C_2H_5O

Chart 1

(**4d**) were isolated as ring-opened products[4] by addition of triethylamine (entry 17).

When the reaction was carried out in an aprotic solvent (dimethylformamide or acetonitrile), increased yields of **4a** and **4b**, but decreased yields of the pyrimidines (**3b** and **3c**) were obtained (entries 5, 11, and 12).

Reactions with Secondary Amines For the further investigation of the ring-cleavage reaction, the oxazines (**1**) were treated with secondary amines (**6**, pyrrolidine and morpholine) which were expected to give not the pyrimidines (**3**), but new ring-cleavage products. As shown in Chart 2 and Table II, reaction of the oxazines (**1a**, **1b**, and **1c**) with amines (**6a** and **6b**) gave the acetoacetamides (**4e**[2,5]) and **4f**), the carboxamides (**5c**, **5d**, **5e**, and **5f**), the urethanes (**5a** and **5b**), and the butenamides (**7a**, **7b**, and **7c**). The compositions of reaction products depended on the combination of the oxazine and the amine, and were more complex than in the case of the primary amines.

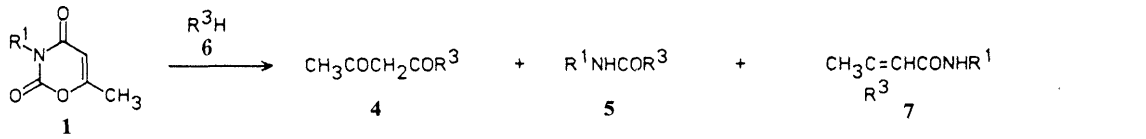
When the oxazines (**1a** and **1b**) reacted with pyrrolidine, butenamides (**7a** and **7b**) were obtained as major product accompanied with the acetoacetamide (**4e**) and the carboxamide (**5c**) (entries 1 and 2). On the other hand, **1c** and pyrrolidine gave the carboxamide **5d** and the urethane **5a** (entry 3). Reaction of **1a** with morpholine afforded the acetoacetamide (**4f**) and the carboxamide (**5e**), which would be counterparts of ring-cleavage products (entry 4). In the case of **1b** with morpholine, the butenamide **7c** was isolated with one exception (entry 5).

Compound **1c** was distinguished from other oxazines, namely **1c** could be treated in ethanol (or methanol) with an amine (pyrrolidine or morpholine) to give the urethane **5a** (or **5b**) in good yield (entries 3, 6 and 7). Clearly there were differences between pyrrolidine and morpholine: the former

TABLE II. Reactions of 1,3-Oxazine-2,4(3*H*)-diones (**1**) with Secondary Amines

Entry No.	Oxazine	Amine (eq)	Reaction[a] time (h)	Products[b] (%) 4	5	7
1	**1a**	**6a** (3.0)	10	**e** 4	—	**a** 45
2	**1b**	**6a** (3.3)	4	—	**c** 5	**b** 49
3	**1c**	**6a** (3.5)	2	—	**a** 61	—
					d 28	
4	**1a**	**6b** (3.3)	4	**f** 44	**e** 15	—
5	**1b**	**6b** (3.3)	4	**f** 44	**f** 13	**c** 32
6	**1c**	**6b** (3.5)	4	**f** 56	**a** 68	—
7	**1c**	**6b** (3.5)	5	**f** 61	**b** 70	—

a) Reactions were carried out in ethanol except entry No. 7 (methanol) and under reflux. *b*) Yields are for the isolated pure products.



1	R^1	6	R^3	4	R^3	5	R^1	R^3	7	R^1	R^3
a	CH_3	**a**	Pyrr	**e**	$NCOOC_2H_5$	**a**	*p*-Cl-C_6H_4	C_2H_5O	**a**	CH_3	Pyrr
b	C_6H_5	**b**	Mor		CH_3	**b**	*p*-Cl-C_6H_4	CH_3O	**b**	C_6H_5	Pyrr
c	*p*-Cl-C_6H_4			**f**	Mor	**c**	C_6H_5	Pyrr	**c**	C_6H_5	Mor
						d	*p*-Cl-C_6H_4	Pyrr			
						e	CH_3	Mor			
						f	C_6H_5	Mor			

Pyrr: 1-pyrrolidinyl
Mor: 4-morpholinyl

Chart 2

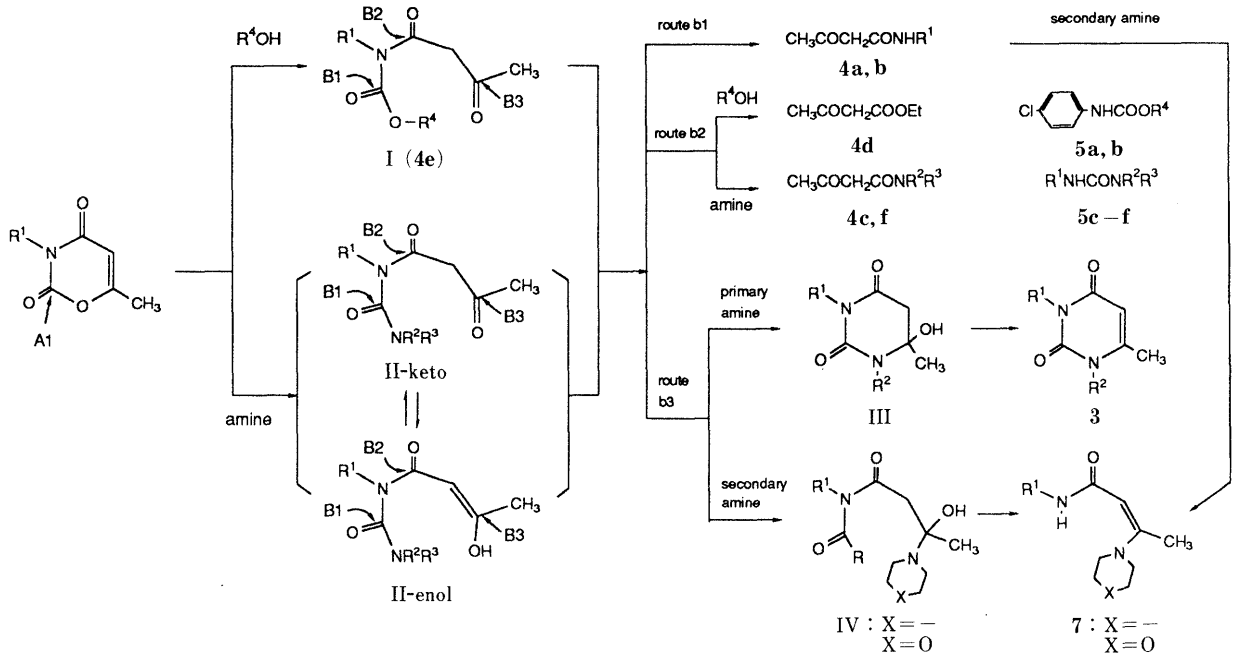


Chart 3

gave the corresponding butenamides while the latter afforded acetoacetamides and carboxamides.

On the basis of the above-mentioned results, the reaction pathways for the ring transformation and cleavage of the oxazines (**1**) are postulated to be shown in Chart 3. As is well-known,[1] an amine or alcohol initially attacks the A1 position of the oxazine competitively to give the intermediates I and/or II. The formation of I and II is supported by the isolation of cleaved counterparts: combinations of **4d–5a** (Table I, entry 17), **4f–5a**, **5b**, **5e**, and **5f** (Table II, entries 4—7). Moreover, as shown in entry 1 of Table II, **4e** (one of I) could be isolated, though in poor yield, and cleaved quickly to give the expected products.

There are three positions available (B1, B2, and B3) for the next nucleophilic attack on I and II, so three routes (b1, b2, and b3) can be considered for the next step and they are also competitive. The mechanism of ring transformation of oxazines to pyrimidine (**3**) has been reported,[1c] and Senda *et al.*[6] described isolation of the hydrated intermediate of type III.

Reactions of the oxazines with pyrrolidine give the butenamides **7**, and two routes can be considered: one of these involves the formation of acyclic IV (route B3), and the other is route b1. In the case of **1c** with morpholine, route b2 is predominant because only the counterparts of **5** and **4f** were isolated.

Experimental

All melting points were measured with a Laboratory Device Mel-temp capillary melting point apparatus or a Yanaco micro melting point apparatus, and are uncorrected. Infrared (IR) spectra were measured with a JASCO IR-810 or IRA-2 spectrophotometer. Ultraviolet (UV) spectra were recorded in ethanol on a Hitachi 323 spectrophotometer. NMR spectral measurements were carried out with a Hitachi R-600 Fourier-transform spectrometer (60 MHz, ^{1}H) or a JEOL JNM FX-90Q Fourier-transform spectrometer (90 MHz, ^{1}H). Chemical shifts are reported in ppm (δ) relative to tetramethylsilane (TMS) as an internal standard. Mass spectra (MS) were taken with a JEOL JMS-DX-303 and a JEOL JMA-DA-5000 data processor by the electron impact (EI) or fast atom bombardment (FAB) ionization method.

General Procedure A solution of an oxazine and an amine in a suitable solvent was treated under appropriate conditions. After removal of the solvent and excess amine *in vacuo*, the residue was extracted with $CHCl_3$. The combined extract was dried over $MgSO_4$ and the solvent was removed. The residue was dissolved in $CHCl_3$ and chromatographed on a silica gel column with $CHCl_3$ (gradient with CH_3CN).

1-(2-Hydroxyethyl)-6-methyl-3-phenyl-2,4(1*H*,3*H*)-pyrimidinedione (3b) mp 166—167 °C (colorless needles from acetone). *Anal.* Calcd for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73; N, 11.38. Found: C, 63.26; H, 5.74; N, 11.35. IR (KBr): 3555 (OH), 1704, 1650 (C=O) cm^{-1}. UV λ_{max}^{EtOH} nm (log ε): 270 (4.03). ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 2.31 (3H, s, C–CH_3), 3.78 and 3.97 (4H, A_2B_2 type m, CH_2CH_2), 5.68 (1H, s, ring olefin), 7.1—7.6 (5H, m, phenyl).

3-(4-Chlorophenyl)-1-(2-hydroxyethyl)-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione (3c) mp 147—148 °C (colorless needles from AcOEt). *Anal.* Calcd for $C_{13}H_{13}ClN_2O_3$: C, 55.62; H, 4.67; N, 9.98; Cl, 12.63. Found: C, 55.50; H, 4.59; N, 9.92; Cl, 12.83. IR (KBr): 3500 (OH), 1712, 1650 (C=O) cm^{-1}. UV λ_{max}^{EtOH} nm (log ε): 270 (4.03), 218 (sh). ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 2.34 (3H, s, C–CH_3), 3.8—4.1 (4H, m, CH_2CH_2), 5.70 (1H, s, ring olefin), 7.13 (2H, d, J=9.0 Hz, phenyl), 7.43 (2H, d, J=9.0 Hz, phenyl). FAB-MS m/z: 283, 281 [(M+1)$^+$].

1-*n*-Butyl-3-(4-chlorophenyl)-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione (3d) mp 144—145 °C (colorless needles from AcOEt). *Anal.* Calcd for $C_{15}H_{17}ClN_2O_2$: C, 61.54; H, 5.85; N, 9.57; Cl, 12.11. Found: C, 61.69; H, 5.83; N, 9.59; Cl, 11.96. IR (KBr): 1710, 1660 (C=O) cm^{-1}. UV λ_{max}^{EtOH} nm (log ε): 214 (4.55), 273 (4.34). ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 0.96 (3H, t, J=5.4 Hz, CH_2–CH_3), 1.2—1.8 (4H, m, 2×CH_2), 2.29 (3H, s, C(6)-CH_3), 3.84 (2H, t, J=7.8 Hz, N–CH_2), 5.69 (1H, s, C(5)-H), 7.35 (2H, d, J=9.0 Hz, phenyl), 7.42 (2H, d, J=9.0 Hz, phenyl).

***N*-(*sec*-Butyl)acetoacetamide (4c)** bp 160 °C/25 mmHg (Kugelrohr, pale yellow oil). *Anal.* Calcd for $C_8H_{15}NO_2$: C, 61.12; H, 9.62; N, 8.91. Found: C, 61.32; H, 9.52; N, 9.05. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 0.90 (3H, t, J=7.0 Hz, CH_2-CH_3), 1.14 (3H, d, J=7.3 Hz, CH–CH_3), 1.49 (2H, m, CH–CH_2–CH_3), 2.28 (3H, s, CO–CH_3), 3.40 (2H, s, CO–CH_2–CO), 3.91 (1H, m, CH_2–CH–NH), 6.85 (1H, br s, NH).

4-(1,3-Dioxobutyl)morpholine (4f) mp 69—70 °C (colorless needles from ether, lit.,[7] mp 64—68 °C. bp 124—127 °C/200 Pa).

(4-Chlorophenyl)carbamic Acid Ethyl Ester (5a) mp 66—67 °C (colorless needles from AcOEt or EtOH–H_2O, lit.,[8] mp 68—69 °C).

(4-Chlorophenyl)carbamic Acid Methyl Ester (5b) mp 116—117 °C (colorless plates from EtOH–H_2O or hexane, lit.,[9] mp 115—116 °C).

***N*-Phenyl-(1-pyrrolidine)carboxamide (5c)** mp 134—135 °C (colorless needles from AcOEt, lit.,[10] mp 136 °C). ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 1.97 (4H, m, CH_2CH_2), 3.46 (4H, m, 2×N–CH_2), 6.2 (1H, br, NH disappeared by D_2O), 7.0—7.6 (5H, m, phenyl). EI-MS m/z: 190 (M$^+$), 119 (PhN=C=O), 98 (pyrrolyl-C=O), 93 (aniline).

***N*-(4-Chlorophenyl)-1-pyrrolidinecarboxamide (5d)** mp 169—170 °C (colorless needles from AcOEt, lit.,[11] mp 167—168 °C).

***N*-Methyl-(4-morpholine)carboxamide (5e)** mp 85—87 °C (colorless needles from ether). *Anal.* Calcd for $C_6H_{12}N_2O_2$: C, 49.99; H, 8.39; N, 19.43. Found: C, 50.02; H, 8.42; N, 19.56. IR (KBr): 3350 (NH), 1633 (C=O) cm^{-1}. UV: no maxima. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 2.82 (3H, d, J=4.6 Hz, NH–CH_3), 3.33 (4H, m, 2×O–CH_2 or N–CH_2), 3.69 (4H, m, 2×N–CH_2 or O–CH_2), 4.5 (1H, br, NH).

***N*-Phenyl-(4-morpholine)carboxamide (5f)** mp 153—154 °C (colorless needles from AcOEt, lit.,[12] mp 162—163 °C). *Anal.* Calcd for $C_{11}H_{14}N_2O_2$: C, 64.06; H, 6.84; N, 13.58. Found: C, 64.35; H, 6.86; N, 13.74. IR (KBr): 3260, 3230 (NH), 1635 (C=O) cm^{-1}. UV λ_{max}^{EtOH} nm (log ε): 241 (4.321), 270 (sh). ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 3.45 (4H, m, CH_2CH_2), 3.70 (4H, m, 2×N–CH_2), 6.6 (1H, br, NH), 7.0—7.4 (5H, m, phenyl).

***N*-Methyl-3-(1-pyrrolidinyl)-2-butenamide (7a)** mp 183—185 °C (light yellow prisms from acetone). *Anal.* Calcd for $C_9H_{16}N_2O$: C, 64.25; H, 9.59; N, 16.65. Found: C, 64.24; H, 9.48; N, 16.46. IR (KBr): 3300 (NH), 1720 (sh, weak), 1628 (C=O) cm^{-1}. UV: no maximum. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 1.90 (4H, m, CH_2CH_2), 2.50 (3H, s, C–CH_3), 2.78 (3H, d, J=4.8 Hz, NH–CH_3), 3.23 (4H, m, 2×N–CH_2), 4.32 (1H, s, C–H), 5.1 (1H, br, NH).

***N*-Phenyl-3-(1-pyrrolidinyl)-2-butenamide (7b)** A solution of acetoacetanilide (**4a**) (100 mg, 0.57 mmol) and pyrrolidine (120 mg, 3 eq) in EtOH (5 ml) was refluxed for 1 h. After cooling, the separated crystals were collected and recrystallized from MeOH to give 108 mg (82.4%) of colorless needles, mp 209—210 °C. *Anal.* Calcd for $C_{14}H_{18}N_2O$: C, 73.01; H, 7.88; N, 12.17. Found: C, 72.93; H, 7.95; N, 12.35. IR (KBr): 3450 (NH), 1630 (C=O) cm^{-1}. UV λ_{max}^{EtOH} nm (log ε): 246 (4.15). ^{1}H-NMR (90 MHz, DMSO-d_6) δ: 1.86 (4H, m, CH_2CH_2), 2.43 (3H, s, C–CH_3), 3.24 (4H, m, 2×N–CH_2), 4.62 (1H, s, C–H), 6.83 (1H, tt, J=1.3, 7.3 Hz, phenyl), 7.17 (2H, dt, J=2.0, 7.3 Hz, phenyl), 7.54 (2H, td, J=1.2, 8.5 Hz, phenyl), 8.97 (1H, br s, NH).

3-(4-Morpholinyl)-*N*-phenyl-acetoacetamide (7c) mp 185—186 °C (colorless plates from MeOH, lit.,[13] mp 184—185 °C).

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