INTRAMOLECULAR CYCLIZATION REACTION OF AMIDO-UREIDO (OR THIOUREIDO)-ACETALS

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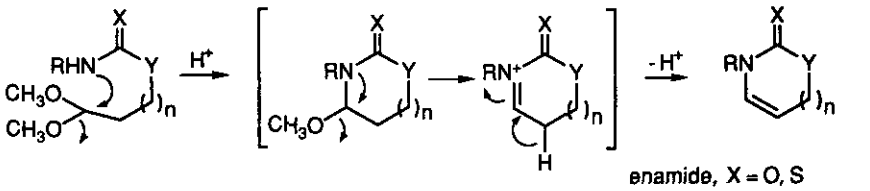
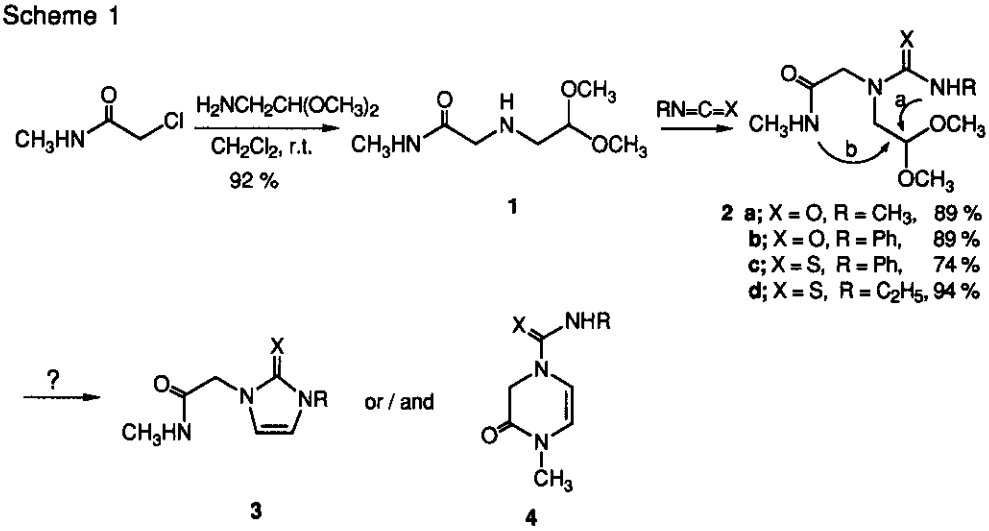
Abstract---Intramolecular cyclization reaction of the compound having amide, urea and acetal functional groups was investigated under various conditions. In acidic conditions, the cyclization reaction of *N*-methyl-*N'*-(2,2-dimethoxyethyl)-*N'*-(alkyl- or phenylcarbamoyl)glycine amide proceeded only to afford imidazolinone derivative *via* an acyliminium ion intermediate formed by intramolecular amidoalkylation reaction of amide and acetal functional groups. However, the corresponding compounds having thiourea functional group resulted in the formation of iminothiazolidine derivatives as major product and pyrazinone compounds as minor product. In nearly neutral or basic conditions, both of ureido- or thioureidoacetals afforded hydantoin or thiohydantoin derivatives, respectively, in excellent yield.

An intramolecular cyclization *via* *N*-acyliminium ion has proven to be a useful method for the synthesis of heterocyclic systems.[1] *N*-Acyliminium ions are generally formed by way of heterolysis of α-substituted amides. α-Substituted amides are mostly prepared by the intra-



molecular reaction of amides with aldehydes (or ketones),[2] or partial reduction of cyclic imides.[3] *N*-Acyliminium ion, generated *in situ* as an intermediate readily reacts with nucleophile in an irreversible process to yield the product. An important side reaction in *N*-acyliminium ion chemistry is the formation of enamide.[4] Accordingly, *N*-acyliminium ions may be transformed to enamide *via* loss of a proton if there is no nucleophile in the molecule to trap an *N*-acyliminium ion. As part of a research program aimed at developing new methodology for the synthesis of heterocyclic compounds using site-selective *N*-acyliminium ion cyclization,[5] we studied intramolecular amidoalkylation of a compound having amide, urea (or thiourea) and acetal moiety for obtaining enamide-type heterocyclic systems in a selective manner. We herein report the mode of reaction and the ratio of the products when the amido-ureido(or thioureido)acetal (**2**) is subjected to the intramolecular cyclization reaction (Scheme 1).

Scheme 1



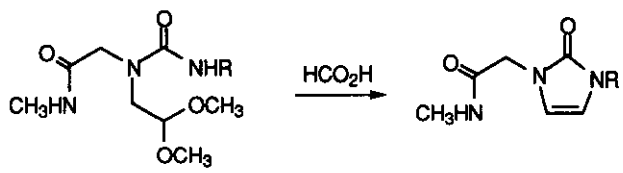
In order to examine the selectivity for intramolecular amidoalkylation, we have chosen amido-ureido (or thioureido)-acetal (**2**) bearing both amide and urea (or thiourea) nucleophile in the same molecule.

Amido-ureido-acetals (**2**) were prepared as follows; Treatment of N-methyl chloroacetamide with 2 equiv. of aminoacetaldehyde dimethyl acetal afforded *N*-methyl-*N'*-(2,2-dimethoxyethyl)glycine amide (**1**) in 92 % yield. Reaction of glycine amide (**1**) with methyl or

phenyl isocyanate at room temperature in methylene chloride gave *N*-methylcarbamoylglycine amide (**2a**) or *N*-phenylcarbamoylglycine amide (**2b**). Reaction of glycine amide (**1**) with ethyl and phenyl isothiocyanate at - 10 °C afforded the corresponding thiocarbamoylglycine amide (**2c**) and (**2d**), respectively. Since **2c** and **2d** are unstable under recrystallization or column chromatography, these compounds were isolated by direct solidification from the reaction mixture by using ethyl acetate - ether (1 : 1) as solvent and were used without further purification.

The selectivity in intramolecular amidoalkylation reaction to afford enamide-type heterocycles was examined initially under acidic conditions. When the amido-ureido-acetals (**2a**, **2b**) were reacted in formic acid, imidazolinones (**3a**) and (**3b**) were obtained in 69 % and 94 % yields, respectively (Scheme 2). On the other hand, pyrazinone (**4**), formed by the intramolecular amidoalkylation of amide and acetal moiety, was not detected at all. Several attempts to obtain pyrazinone under various acidic conditions were fruitless. It implicates that nitrogen nucleophiles in the urea group are more reactive than those in the amide group toward protonated acetal in amidoalkylation reaction.

Scheme 2

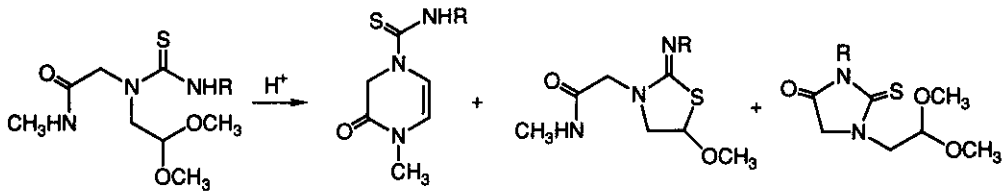


2 a,b **3 a**; R = CH_3, 69 %
b; R = Ph, 94 %

However, when amido-thioureido-acetals (**2c**, **2d**) were subjected to various acidic conditions, interesting results were obtained (Table 1). The amidoalkylation reaction of the thiourea group with acetal did not occur to give the imidazolinone compound in contrast to that of amido-ureido-acetals (**2a**, **2b**). But, iminothiazolidine derivatives (**5c**, **5d**) were obtained as major products with pyrazinone derivatives (**4a**, **4c**), which were not formed under the same reaction condition in amido-ureido-acetals (**2a**, **2b**). The formation of iminothiazolidine can be explained that nucleophilic attack of sulfur nucleophile in the thiourea is more favorable than that of nitrogen

toward protonated acetal. The ratio of the products obviously displays higher nucleophilicity of sulfur than nitrogen toward protonated acetal.

Table 1. The products ratio in intramolecular alkylation reaction of amido-thioureido-acetals **(2c, d)**



2 c,d **4 c,d** **5 c,d** **6 c,d**

c; R=Ph,
d; R=C_2H_5

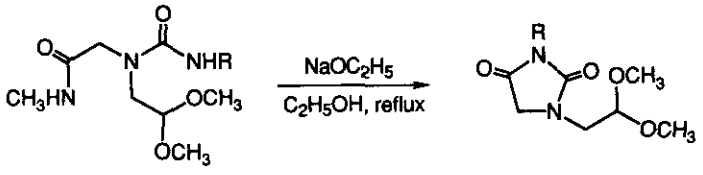
entry	R	reaction condition[a]	ratio (**4** / **5** / **6**)[b]		
1	Ph	CH_3SO_3H (cat.) / CH_2Cl_2	-	1.6	1
2	Ph	CH_3SO_3H (0.2 ml) / CH_2Cl_2	1	1.1	trace
3	Ph	CH_3SO_3H (1 ml) / CH_2Cl_2	1	8.8	-
4	Ph	CH_3SO_3H (5 ml) / CH_2Cl_2	-	only	-
5	C_2H_5	CH_3SO_3H (cat.) / CH_2Cl_2	1	1.5	0.1
6	C_2H_5	CH_3SO_3H (1 ml) / CH_2Cl_2	1	23	-
7	C_2H_5	CH_3SO_3H (2 ml) / CH_2Cl_2	1	34	-
8	C_2H_5	CH_3SO_3H (5 ml) / CH_2Cl_2	-	only	-
9	Ph	pH 6.4 Phosphate buffer sol.[c]	-	1	7.3
10	Ph	$NaOC_2H_5$ (cat.)[d]	-	-	only
11	C_2H_5	$NaOC_2H_5$ (cat.)[d]	-	-	only

a. Cyclization reactions were carried out with 0.1 g of starting materials in 15 ml of solvent at 14 °C for 12 h; b. The ratio of the products was determined by the integration of characteristic peaks of the products in the ^{1}H-Nmr spectra of the reaction mixture; c. Reaction was carried out at reflux temperature; d. Cyclization reaction was carried out in ethanol at reflux temperature.

In nearly neutral or basic conditions (entries 9~11), thiohydantoin **(6)** was obtained as a major product in consequence of unexpected nucleophilic attack of nitrogen nucleophile in the urea group to the amide carbonyl group. A plausible explanation for this result is that under these circumstances acetal can not be activated by protonation to proceed amidoalkylation to form *N*-acyliminium ion intermediate. It has been proven by the fact that the amido-ureido-acetals (**2a** and

2b) were also converted to hydantoin derivatives (**6a**) and (**6b**) in 100 % and 73 % yields, respectively, in the presence of 1 equivalent of sodium ethoxide at the reflux temperature in ethanol (Scheme 3). The ratio of the products was determined by ^{1}H-nmr integration of the CH_3OCHS (iminothiazolidine), NCH_2CO (pyrazinone), and $CH(OCH_3)_2$ (thiohydantoin).

Scheme 3



2 a,b

6 a; R = CH_3, 100 %
b; R = Ph, 73 %

In conclusion, the intramolecular cyclization reaction of the amido-ureido-acetal compounds (**2a**, **2b**) is preferred to form imidazolinone (**3**) rather than pyrazinone (**4**) under acidic conditions. However, in the case of amido-thioureido-acetals (**2c** and **2d**), the cyclization reaction did not proceed in the same manner as in the compounds (**2a**) and (**2b**). From these findings we can synthesize either imidazolinone, hydantoin (or thiohydantoin), or iminothiazolidine derivatives with good selectivity from amido-ureido (or thioureido)-acetals under acidic or nearly neutral, or basic condition.

EXPERIMENTAL

Melting points were determined with a Thomas-Hoover melting point apparatus and were uncorrected. Infrared spectra were recorded on FX-6160 FT-IR spectrophotometer. ^{1}H-Nmr spectra were recorded on JEOL PMX-60 NMR Spectrometer. Chemical shifts are in ppm relative to TMS.

***N*-Methyl-*N'*-(2,2-dimethoxyethyl)glycine amide (1):** To a solution of aminoacetaldehyde dimethyl acetal (13.96 g, 0.13 mol) in methylene chloride (40 ml) was added a solution of *N*-methyl chloroacetamide (6.86 g, 0.064 mol) in methylene chloride (20 ml) and stirred at room temperature for 6 h. The resulting solid was removed by filtration and the filtrate

was concentrated to one half volume and cooled in refrigerator. The resulting solid was removed again. The filtrate was concentrated to give **1** (10.35 g, 92 %) as an oil. The crude **1** was used in next step without purification. Ir (KBr) 3250, 2900, 1650, 1540, 1420 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ 2.75 and 2.83 (3H, two s, NCH_3), 3.33 (2H, d, J=6 Hz, $CH_2CH(OCH_3)_2$, 3.37 (6H, s, OCH_3), 3.43 (2H, s, COCH_2), 4.70 (1H, t, J=6 Hz, $CH(OCH_3)_2$), 4.83 (1H, s, amine *NH*), 7.94 (1H, br s, amide *NH*).

***N*-Methyl-*N'*-(2,2-dimethoxyethyl)-*N'*-methylcarbamoylglycine amide (2a):** To a stirred solution of **1** (12.34 g, 0.07 mol) in methylene chloride (100 ml) was added dropwise methyl isocyanate (6.2 ml, 0.11 mmol) at 0 °C. The reaction mixture was stirred for 2 h and warmed to room temperature. After 30 min, the mixture was concentrated and purified by recrystallization from ethyl acetate to afford **2a** (16.41 g, 89 %) as a white solid. mp 135-136 °C; ir (KBr) 3300, 2940, 1670, 1640, 1550, 1410 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ 2.77, 2.78, 2.83 and 2.84 (6H, four s, amide and urea *NH*CH_3), 3.38 (2H, d, J= 5 Hz, $CH_2CH(OCH_3)_2$), 3.45 (6H, s, OCH_3), 3.90 (2H, s, COCH_2), 4.50 (1H, t, J=5 Hz, CH(OCH_3)$_2$), 5.63 (1H, br s, urea *NH*), 7.06 (1H, br s, amide *NH*); Anal. Calcd for $C_9H_{19}N_3O_4$: C 46.34, H 8.21, N 18.01. Found C 46.56, H 8.41, N 17.93.

***N*-Methyl-*N'*-(2,2-dimethoxyethyl)-*N'*-phenylcarbamoylglycine amide (2b):** By the use of the procedure described above for **2a**, this compound was prepared using phenyl isocyanate. Yield 89 %. mp 162-163 °C; ir (KBr) 3293, 1661, 1639, 1590, 1500 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ 2.74 and 2.81 (3H, two s, NHCH_3), 3.37 (2H, d, J=5 Hz, $CH_2CH(OCH_3)_2$), 3.43 (6H, s, OCH_3), 3.93 (2H, s, COCH_2), 4.50 (1H, t, J=5 Hz, $CH(OCH_3)_2$), 7.20 (5H, m, *phenyl-H*), 7.13 (1H, br s, amide *NH*); Anal. Calcd for $C_{14}H_{21}N_3O_4$: C 56.94, H 7.17, N 14.23. Found C 56.90, H 7.17, N 14.10.

***N*-Methyl-*N'*-(2,2-dimethoxyethyl)-*N'*-phenylthiocarbamoylglycine amide (2c):** To a stirred solution of **1** (3 g, 0.017 mol) in mixed solvent of ethyl acetate and diethyl ether (6 ml, 1:1) was added dropwise phenyl isothiocyanate (2.44 ml, 0.020 mmol) at -10 °C. The reaction mixture was stirred for 1 h and diluted with ether (10 ml). The precipitate was filtered and washed with ether (10 ml) and dried in vacuo to give **2c** (5 g, 94 %) as a white solid. The crude **2c** was used in next step without purification and stored in refrigerator. mp 89-90 °C; ir (KBr) 3280, 1599, 1518, 1410, 1122 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ 2.73 and 2.80 (3H, two s,

NHCH$_3$), 3.50 (6H, s, OCH$_3$), 3.78 (2H, d, J=5 Hz, CH$_2$CH(OCH$_3$)$_2$), 4.47 (2H, s, COCH$_2$), 4.58 (1H, t, J=5 Hz, CH(OCH$_3$)$_2$), 7.23 (5H, m, *phenyl-H*), 9.27 (1H, br s, amide *NH*).

***N*-Methyl-*N'*-(2,2-dimethoxyethyl)-*N'*-(ethylthiocarbamoyl)glycine amide (2d):** By the use of the procedure described above for **2c**, this compound was prepared using ethyl isothiocyanate and used in next step without purification. Yield 74 %. mp 57-60 °C; ir (KBr) 3317, 1670, 1532 cm^{-1}; ^{1}H-nmr (CDCl$_3$) δ 1.23 (3H, t, J=8 Hz, CH$_2$CH$_3$), 2.73 and 2.79 (3H, two s, NHCH$_3$), 3.30-3.83 (4H, m, CH$_2$CH$_3$, CH$_2$CH(OCH$_3$)$_2$), 4.39 (2H, s, COCH$_2$), 4.50 (1H, t, J=5 Hz, CH(OCH$_3$)$_2$), 5.63 (1H, br s, urea *NH*), 7.26 (1H, br s, amide *NH*).

1-Methyl-3-(*N*-methylcarbamoylmethyl)-4-imidazolin-2-one (3a): A solution of **2a** (5 g, 0.021 mol) in formic acid (25 ml) was stirred at room temperature for 5 h. The solution was evaporated and the residue was recrystallized from ethanol and ethyl acetate to afford **3a** (2.52 g, 69 %) as a white solid. mp 126-128 °C; ir (KBr) 3200, 1650, 1529, 1470, 1420 cm^{-1}; ^{1}H-nmr (CDCl$_3$) δ 2.70 and 2.78 (3H, two s, amide NHCH$_3$), 3.22 (3H, s, NCH$_3$), 4.20 (2H, s, COCH$_2$), 6.12 (1H, d, J=3 Hz, *vinyl-H*), 6.26 (1H, d, J=3 Hz, *vinyl-H*), 7.00 (1H, br s, amide *NH*); Anal. Calcd for C$_7$H$_{11}$N$_3$O$_2$: C 49.70, H 6.55, N 24.84. Found C 49.59, H 6.52, N 24.78.

1-Phenyl-3-(*N*-methylcarbamoylmethyl)-4-imidazolin-2-one (3b): By the use of the procedure described above for **3a**, this compound was prepared from **2b**. Yield 94 %; mp 173-174 °C; ir (KBr) 3200, 1650, 1529, 1470, 1420 cm^{-1}; ^{1}H-nmr (CDCl$_3$) δ 2.70 and 2.80 (3H, two s, amide NHCH$_3$), 4.30 (2H, s, COCH$_2$), 6.46 (1H, d, J=3 Hz, *vinyl-H*), 6.59 (1H, d, J=3 Hz, *vinyl-H*), 6.80 (1H, br s, amide *NH*), 7.20-7.57 (5H, m, *phenyl-H*); Anal. Calcd for C$_{12}$H$_{13}$N$_3$O$_2$: C 62.33, H 5.67, N 18.17. Found C 62.40, H 5.63, N 18.20.

Intramolecular cyclization of *N*-methyl-*N'*-(2,2-dimethoxyethyl)-*N'*-phenylthiocarbamoylglycine amide (2c): To a solution of **2c** (3.40 g, 10.91 mmol) in methylene chloride (15 ml) was added methanesulfonic acid (0.2 ml) and stirred at room temperature for 12 h. The mixture was cooled to 0 °C and neutralized with saturated aqueous Na$_2$CO$_3$ solution. The organic layer was separated and the aqueous layer was washed with methylene chloride (15 ml). The combined organic layer was dried (MgSO$_4$) and purified on silica gel (ethyl acetate-hexane, 1:1) to afford thiohydantoin (**6c**) (20 mg, 0.7 %), pyrazinone (**4c**) (190 mg, 7 %), and

iminothiazolidine (**5c**) (1.76 g, 58 %) respectively. **6c** : R_f 0.5 (ethyl acetate-hexane, 1:1); mp 125-126 °C; ir (KBr) 1770, 1510, 1490, 1380 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ 3.42 (6H, s, O*CH*$_3$), 3.88 (2H, d, J=5 Hz, *CH*$_2$CH(OCH$_3$)$_2$), 4.28 (2H, s, CO*CH*$_2$), 4.63 (1H, t, J=5 Hz, *CH*(OCH$_3$)$_2$), 7.16-7.52 (5H, m, *phenyl-H*); Anal. Calcd for $C_{13}H_{16}N_2O_3S$: C 55.70, H 5.75, N 9.99, S 11.44. Found C 55.88, H 5.84, N 9.94, S 11.23. **4c** : R_f 0.3 (ethyl acetate-hexane, 1:1); mp 95-97 °C; ir (KBr) 3452, 1750, 1436, 1380, 1224 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ 3.83 (3H, s, N*CH*$_3$), 4.97 (2H, s, CO*CH*$_2$), 6.93 (2H, s, *vinyl-H*),7.40-7.70 (5H, m, *phenyl-H*); Anal. Calcd for $C_{12}H_{13}N_3OS$: C 58.28, H 5.30, N 16.99, S 12.96. Found C 58.18, H 5.25, N 16.87, S 12.91. **5c** : R_f 0.1 (ethyl acetate-hexane, 1:1); mp 118-119 °C; ir (KBr) 3235, 2935, 1678, 1612, 1583, 1549, 1250 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ 2.78 and 2.86 (3H, two s, amide NH*CH*$_3$), 3.32 (3H, s, O*CH*$_3$), 3.77-4.50 (4H, m, N*CH*$_2$CHS), N*CH*$_2$CO), 5.18 (1H, m, S*CH*OCH$_3$), 6.83-7.50 (5H, m, *phenyl-H*); Anal. Calcd for $C_{13}H_{17}N_3O_2S$: C 55.89, H 6.13, N 15.04, S 11.48. Found C 56.01, H 6.15, N 14.96, S 11.43.

Intramolecular cyclization of *N*-methyl-*N'*-(2,2-dimethoxyethyl)-*N'*-ethylthiocarbamoylglycine amide (2d): By the use of the procedure described above for **2c**, thiohydantoin (**6d**), pyrazinone (**4d**), and thiazolidine (**5d**) were obtained from **2d**. **6d** : R_f 0.8 (ethyl acetate-hexane, 1:1); ir (KBr) 2978, 1669, 1491, 1414, 1368, 1260 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ 1.22 (3H, t, J=7 Hz, CH$_2$*CH*$_3$), 3.40 (6H, s, O*CH*$_3$), 3.67-3.88 (4H, m, *CH*$_2$CH(OCH$_3$)$_2$, *CH*$_2$CH$_3$), 4.08 (2H, s, CO*CH*$_2$), 4.57 (1H, t, J=5 Hz, *CH*(OCH$_3$)$_2$); Anal. Calcd for $C_9H_{16}N_2O_3S$: C 46.53, H 6.94, N 12.06, S 13.80. Found C 46.70, H 7.01, N 11.98, S 13.80. **4d** : R_f 0.4 (ethyl acetate-hexane, 1:1); mp 65-67 °C; ir (KBr) 1683, 1571, 1217 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ 1.33 (3H, t, J=7 Hz, CH$_2$*CH*$_3$), 3.67 (3H, s, N*CH*$_3$), 4.03 (2H, q, J=7 Hz, *CH*$_2$CH$_3$), 4.80 (2H, s, CO*CH*$_2$), 6.67 (2H, s, *vinyl-H*); Anal. Calcd for $C_8H_{13}N_3OS$: C 48.22, H 6.58, N 21.09, S 16.09. Found C 48.12, H 6.56, N 20.98, S 16.03. **5d** : R_f 0.1 (ethyl acetate-hexane, 1:1); mp 154-156 °C; ir (KBr) 3310, 2970, 1641, 1414, 1270, 1212 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ 1.13 (3H, t, J=7 Hz, CH$_2$*CH*$_3$), 2.67 and 2.75 (3H, two s, *CH*$_3$NH), 3.16 (2H, q, J=7 Hz, *CH*$_2$CH$_3$), 3.35 (3H, s, O*CH*$_3$) 3.77-4.33 (4H, m, N*CH*$_2$CHS, N*CH*$_2$CO), 5.27 (1H, m, S*CH*OCH$_3$), 7.13 (1H, br s, amide CH$_3$*NH*); Anal. Calcd for $C_9H_{17}N_3O_2S$: C 46.73, H 7.41, N 18.18, S 13.83. Found C 46.84, H 7.42, N 18.21, S 13.85.

The general procedure for the cyclization reaction of amido-ureido (or thioureido)-acetal compounds (2a ~ d) to form hydantoin or thiohydantoin derivatives (6a ~ d) in basic condition: *N*-Methyl-*N'*-(2,2-dimethoxyethyl)-*N'*-methylcarbamoylglycine amide (**2a**, 0.64 g, 2.72 mmol) was dissolved to a solution of sodium ethoxide (0.04 g, 2.72 mmol) in ethanol (30 ml). After refluxing for 2 h, the reaction mixture was evaporated to dryness. The residue was dissolved in methylene chloride (10 ml) and washed with water. The organic layer was dried ($MgSO_4$), concentrated, and purified by column chromatography (ethyl acetate-hexane, 1:2) to give 1-(2,2-dimethoxyethyl)-3-methylhydantoin (**6a**, 0.55 g, quantitative) as an oil. Ir (KBr) 1750, 1680, 1460 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ 3.00 (3H, s, NCH_3), 3.42 (6H, s, OCH_3), 3.49 (2H, d, J=5 Hz, $CH_2CH(OCH_3)_2$), 3.98 (2H, s, $COCH_2$), 4.47 (1H, t, J=5 Hz, $CH(OCH_3)_2$); Anal. Calcd for $C_8H_{14}N_2O_4$: C 47.52, H 6.98, N 13.85. Found C 47.50, H 6.95, N 13.81.

1-(2,2-Dimethoxyethyl)-3-phenylhydantoin (6b): By the use of the procedure described above for **6a**, this compound was prepared from **2b** using 3 equivalents of sodium ethoxide. Yield 73 %. Ir (KBr) 1774, 1723, 1500, 1459, 1422, 1378 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ 3.45 (6H, s, OCH_3), 3.54 (2H, d, J=5 Hz, $CH_2CH(OCH_3)_2$), 4.13 (2H, s, $COCH_2$), 4.50 (1H, t, J=5 Hz, $CH(OCH_3)_2$), 7.40 (5H, s, *phenyl-H*); Anal. Calcd for $C_{13}H_{16}N_2O_4$: C 59.08, H 6.10, N 10.60. Found C 58.97, H 6.12, N 10.54.

1-(2,2-Dimethoxyethyl)-3-phenylthiohydantoin (6c): By the use of the procedure described above for **6a**, this compound was prepared from **2c** using 0.1 equivalent of sodium ethoxide. Yield 90 %.

1-(2,2-Dimethoxyethyl)-3-ethylthiohydantoin (6d): By the use of the procedure described above for **6a**, this compound was prepared from **2d** using 0.1 equivalent of sodium ethoxide. Yield 82 %.

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