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Acid and Base Catalyzed Intramolecular Cyclizations of *N*-Benzoylthiocarbamoyl-acetals

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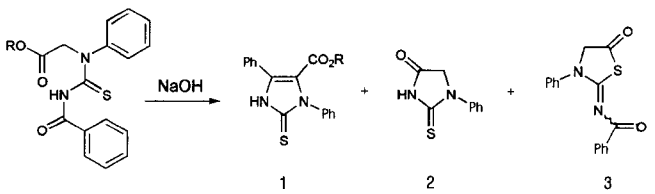
Acid and base catalyzed intramolecular cyclizations of *N*-benzoylthioureidoacetal, containing four functional groups adjacent to thiourea such as benzocarbamoyl, acetal, thioure and amide, were investigated. The condensation reaction of *N*-benzoyl thiocarbamoylglycine amide in the presence of 10% aqueous NaOH provided 1-(2,2-dimethoxy)ethyl-imidazolidine-2-thione exclusively. In the presence of pyridine, it was transformed to 2-thiohydantoin. *N*-Benzoyl thiocarbamoyl glycine amide was completely transformed to an iminothiazolidine exclusively in the presence of Lewis acid such as borontrifluoride etherate or trimethylsilyl iodide. 1-(2,2-Dimethoxy)ethyl-imidazolidine-2-thione was transformed to imidazole[2,1-*b*]thiazole and pyrazino[5,1-a]imidazole in the presence of $BF_3.Et_2O$ and formic acid, respectively.

Key words: *N*-benzoylthiocarbamoyl glycine amide, 1-(2,2-Dimethoxy)ethyl-imidazolidine-2-thione, Iminothiazolidine, Imidazo[2,1-*b*]thiazole, Imidazo[5,1-a]pyrazine, Acid catalyzed intramolecular cyclization, Acetal, urea, thiourea

INTRODUCTION

As shown in Scheme 1, it was reported that thioureido containing *N*-phenyl *N*-benzoyl thiocarbamoyl glycine was transformed to three heterocycles **1, 2, 3** in basic condition due to the unselective nucleophilic attacks of N or S atom of thiocarbamoyl group (Viski *et al.*, 1983) (Fig. 1). 4-(Dimethoxyethyl)-5-thioxo-1,2,4-triazoles **4** was reported to undergo the Lewis acid mediated intramolecular cyclization resulting in methoxythiazolidine fused heterocycles **5** (Lee *et al.*,1991). It was also reported that 5% hydrochloric acid catalyzed intramolecular condensation



1 2 3

Fig. 1. Diverse Ring Formation of *N*-Benzoyl Thiocarbamoyl-Glycine

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of 5-thioxo-4,5-hydro-1,2,4-triazole **6** bearing acetal and aminocarbonyl moieties gave 2-methyl-8-oxo-3-thioxo-2,3,7,8-tetrahydro-1,2,4-triazolo[4,3-*a*]pyrazines **7** (Lee *et al.*, 1989, & 1993) (Fig. 2). The cyclization of *N*-methyl-*N'*-(2,2-dimethoxyethyl)-*N'*-(ethyl or phenylthiocarbamoyl) glycine amide in acidic condition resulted in the formation of iminothiazolidine derivatives as a major product and pyrazone compounds as a minor product (Lee *et al.*, 1994). Even these intramolecular cyclizations were investigated only in the presence of one or two functional groups, they provided multiple products. In spite of usefulness of oxonium ion of acetal in preparation of heterocycles, only a few intramolecular cyclization of thiocarbamoylacetals between acetal and hetero atoms had been reported probably due to its complexity in formation of heterocycles (Barkoczy *et al.*, 1991). As reported, the stable oxonium anoion of acetal formed by the assistant of acid catalysis provide a good opportunity to be attacked by nucleophiles (Lee *et al.*, 1994). Therefore, it is very desirable if the formation of heterocycles from *N*-benzoylthioureidoacetal could be exclusively controlled depend on the kinds of acid or base.

In this article, we introduce the formations of heterocycles via oxonium ion of acetal by acid or base catalyzed intramolecular cyclizations of *N*-benzoylthioureidoacetal **9**, in which there are four functional groups

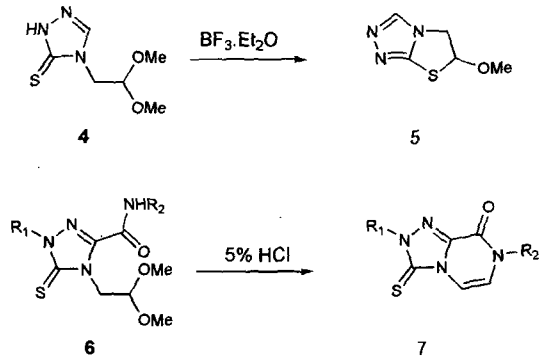


Fig. 2. Acid Catalyzed Cyclization of Thiocarbamoyl-Acetals

adjacent to thiourea such as benzocarbamoyl, acetal, thioure and amide.

MATERIALS AND METHODS

General experiment

Melting points were uncorrected. The infrared spectra of solids (potassium bromide) were recorded on a Shimadzu IR-435 spectrometer (Shimazu Corporation, Japan). The 1H-NMR spectra were recorded on a Varian VXR 5200S 200MHz instrument (Varian Associates Inc., CA, USA) in $CDCl_3$ solution and chemical shifts(δ) are expressed in ppm relative to tetramethylsilane as an internal standard. Thin layer chromatography was performed on pre-coated plates of silica gel 60 F 254 (Merck KGaA, Germany) and the spots visualized using an ultraviolet lamp or iodine vapor. E.Merck silica gel 60 F (70-230 mesh) was used for silica-gel column chromatography. All chemicals and solvents were purchased from Aldrich Co. (Aldrich Chemical Company Inc., Wisconsin, USA), and used without further purification.

N-Methyl- *N'*-(2,2-dimethoxy)ethyl- *N''*-benzoylthiocarbamoyl glycine amide (9)

To a solution of ammonium thiocyanate (1.7 g) in dry acetone was added benzoylchloride (2.3 mg). After 30 min stirring at room temperature, N-methyl-N'-(2,2-dimethoxy)ethyl glycine amide (3.5 g) was added to the reaction mixture containing benzoylisothioscyanate. After stirring for 1 h, the resulting ammonium chloride was filtered off. The filtrate was concentrated in vacuo. The concentrated residue was diluted with ethyl acetate (200 ml), washed with distilled water, brine and distilled water. The organic phase was dried over sodium sulfate and concentrated in vacuo. The resulting solid was recrystallized from chloroform to give **9** as a white crystal in the yield of 64%. m.p 195°C; IR (KBr) 3330 (NH), 1680 (C=O) cm^{-1}; 1H NMR (CDCl3) δ 2.85 (d, 3H, NCH_3), 3.42 (s, 6H, 2 × OCH_3), 7.40-7.80 (m, 5H, C_6H_5); TLC (EtOAc/n-hexane=1/1) Rf=0.29.

1-(2,2-Dimethoxy)ethyl-4-phenyl-5-(*N* -methylcarbamoyl)-imidazole-2-thione (10)

A solution of *N*-methyl-*N'*-(2,2-dimethoxy)ethyl-*N''*-benzoylthiocarbamoyl glycine amide (6.8 g) in 10% aqueous NaOH (30 ml) was heated at reflux temperature for 30 min. After cooling to room temperature, the reaction mixture was neutralized with 10% HCl. The aqueous layer was extracted three times with ethyl acetate. The organic layer was dried over anhydrous $MgSO_4$ and concentrated in vacuo. The resulting precipitate was recrystallized from ethyl acetate to give **10** as a white crystal (5.6g, 87%). m.p 234-235°C; IR (KBr) 3310 (NH), 1640 (C=O), 1490 (C=S) cm^{-1}; TLC (EtOAc/MeOH= 20/1) Rf=0.5.

1-(2,2-Dimethoxy)ethyl-2-thiohydantoin (11)

A solution of *N*-methyl-*N'*-(2,2-dimethoxy)ethyl-*N''*-benzoylthiocarbamoyl glycine amide (2.1 g) in pyridine (30 ml) was stirred for 3 h at reflux temperature. After cooling to room temperature, pyridine was removed in vacuo. The residue was dissolved in ethyl acetate, and washed with water, 5% HCl, brine and water. The organic phase was dried over anhydrous Na_2SO_4. After concentration in vacuo, the residue was purified by silcagel column chromatography (n-hexane/EtOAc=2/1) to give white solid in the yield of 77%. m.p 68-69°C; IR (KBr) 1752 (C=O), 1499(C=S) cm^{-1}; 1H NMR ($CDCl_3$) δ 3.45 (s, 6H, 2 × OCH_3), 3.85 (d, 2H, NCH_2CO), 4.25 (s, 2H, $COCH_2$), 4.65 (t, 1H, NCCHO), 9.30 (s, 1H, NH); TLC (EtOAc/n-Hx=1/1) Rf=0.72.

1-(*N*-methylcarbamoyl)methyl-2-(*N*-benzoyl)imino-4-methoxy-thiozolidine (12)

A solution of *N*-methyl-N'-(2,2-dimethoxy)ethyl-N''-benzoylthiocarbamoyl glycine amide (6.49 g, 20 mmol) in borontrifluoride etherate (30 ml) was stirred for 20 min at room temperature. The reaction was quenched with water (50 ml), neutralized with 10% $NaSO_4$, and extracted with dichloromethane (20 ml). The organic phase was dried over anhydrous $MgSO_4$ and concentrated in vacuo to give a solid. The solid was recrystallized from ethyl acetate to give **11** as a white crystal (5.15 g, 89%).m.p 148°C; IR (KBr) 3330 (NH), 1630 (C=O) cm^{-1}; 1H NMR ($CDCl_3$) δ .80 (d, 3H, NCH_3), 4.40 (s, 3H, OCH_3), 4.3-5.05 (m, 2H, CH_2), 5.90 (d, 1H, CHO), 7.50 (m, 5H, C_6H_5); TLC (EtOAc only) Rf=0.35.

1,2,6,7-Tetrahydro-2-methyl-8-phenyl-1-oxo-5-thionoimidazo-[5,1-a]pyrazine (13)

A solution of 1-(2,2-dimethoxy)ethyl-4-phenyl-5-(N-methylcarbamoyl)-imidazole-2-thione (6.49 g, 20 mmol) in 98%

formic acid (30 ml) was stirred for 30 min at 60°C. The resulting yellow precipitate was collected and washed with ethyl ether to remove formic acid and then dried in vacuo to give the desired product (13) (3.8 g, 74%).

A solution of 2,3-dihydro-6-phenyl-5-(N-methylcarbamoyl)-2-methoxyimidazo[2,1-b]thiazole (0.9 g) in 98% formic acid (30 ml) was stirred for 30 min at 60°C. The resulting yellow precipitate was collected and washed with ethyl ether to remove formic acid and then dried in vacuo to give the same product (13). m.p >300°C; IR (KBr) 1655 (C=O), 1495 (C=C) cm^{-1}; 1H NMR (CDCl3) δ 3.30 (s, 3H, NCH_3), 6.90 (d+d, 2H, HC=CH), 7.3-8.0 (m, 5H, C_6H_5); TLC (EtOAc/MeOH=20/1) Rf=0.79.

2,3-Dihydro-6-phenyl-5-(*N*-methylcarbamoyl)-2-methoxyimidazo[2,1-*b*]thiazole (14)

After stirring a solution of 1-(2,2-dimethoxy)ethyl-4-phenyl-5-(N-methylcarbamoyl)-imidazole-2-thione (6.42 g, 20 mmol) in $BF_3.Et_2O$ (30 ml) for 20 min at room temperature, the reaction was quenched with water (50 ml), neutralized with 10% $NaSO_4$, and extracted with dichloromethane (20 ml). The organic phase was dried over anhydrous $MgSO_4$ and concentrated in vacuo to give a solid. The solid was recrystallized from ethyl acetate to give a white crystal (5.15 g, 89%). m.p 170-170.5°C; IR (KBr) 3330 (NH), 1630 (C=O) cm^{-1}; 1H NMR ($CDCl_3$) δ 2.80 (d, 3H, NCH_3), 4.40 (s, 3H, OCH_3), 4.3-5.05 (m, 2H, CH_2), 5.90 (d, 1H, CHO), 7.50 (m, 5H, C_6H_5); TLC (EtOAc/MeOH=20/1) Rf=0.45.

1-(2,2-Dimethoxy)ethyl-2-methylthio-4-phenylimidazole (15)

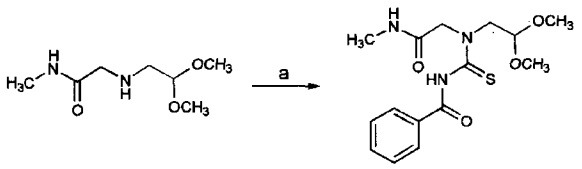
To a solution of 1-(2,2-dimethoxy)ethyl-4-phenyl-5-(N-methylcarbamoyl)-imidazole-2-thione (1.61 g, 5 mmol) in 1N-NaOH (7.5 ml) was added methyl iodide (0.5 ml). To the reaction mixture was added ethyl alcohol (15 ml) to dissolve the resulting precipitate. After stirring for 24 hr at room temperature, the reaction was poured into ice-cold water with stirring. The precipitate was collected and dried in vacuo. The solid was recrystallized from a co-solvent of ethyl acetate and n-hexane to give **15** as a white crystal (0.8 g, 48%). m.p 120-122°C; IR (KBr) 3290 (NH), 1635 (C=O) cm^{-1}; 1H NMR ($CDCl_3$) 2.66 (s, 3H, S-CH_3), 2.80 (d, 3H, N-CH_3), 3,41 (s, 6H, 2 × OCH_3), 4.41 (d, 2H, NCH_2), 4.70 (t, 1H, CH), 7.45 (m, 5H, C_6H_5); TLC (EtOAc/MeOH=20/1) Rf=0.79.

7,8-Dihydro-3-methylthio-7-methyl-1-phenyl-8-oxo-imidazo[1,5-*a*]pyrazine (16)

A solution of 1-(2,2-dimethoxy)ethyl-2-methylthio-4-phenylimidazole (0.7 g) in 98% formic acid (10 ml) was stirred for 30 min at 60°C. The resulting yellow precipitate was collected and washed with ethyl ether to remove formic acid and then dried in vacuo to give the desired product **16** in the yield of 81%. m.p 123-125°C; IR (KBr) 1669 (C=O), 1641 (HC=CH) cm^{-1}; 1H NMR ($CDCl_3$) δ 2.75 (s, 3H, S-CH_3), 3.43 (s, 3H, NCH_3), 6.40-6.95 (d+d, 2H, CH=CH), 7.2-8.5 (m, 5H, C_6H_5);

RESULTS AND DISCUSSION

For the synthesis of 1-(2,2-dimethoxy)ethyl-imidazolidine-2-thione, the starting material, glycine amide **8** was synthesized by the reported method (Lee *et al.*, 1994). It was reacted with benzoylisothiocyanate to provide *N*-benzoylthiocarbamoyl glycine amide **9** in 64% yield.



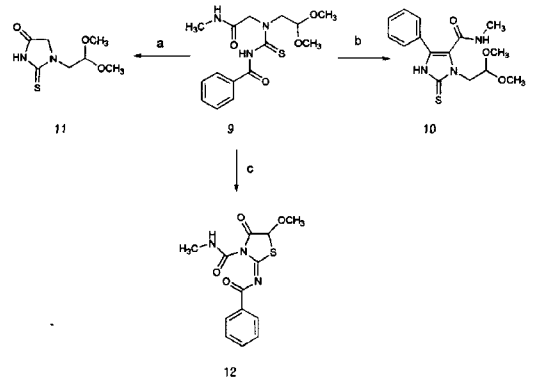
Scheme 1. Synthesis for *N*-benzoyl thiocarbamoylglycinamide

Benzoyl isothiocyanate was prepared *in situ* from benzoylchloride and ammonium thiocyanate (Horning *et al.*, 1955). The condensation reaction of *N*-benzoylthiocarbamoyl glycine amide **9** in the presence of 10% aqueous NaOH at the reflux temperature for 30 min provided 1-(2,2-dimethoxy)ethyl-imidazolidine-2-thione **10** exclusively in 84% yield. While benzoyl group attached to a thiourea is considered to be hydrolyzed in aqeous NaOH, the activation of a-carbon of glycine amide by NaOH induced a Knoevenagel condensation between α-carbon of glycine amide and carbonyl of benzamide.

On the otherhand, in the presence of organic base, pyridine, *N*-benzoylthiocabamoyl glycine amide **9** selectively transformed to 2-thiohydantoin **11**. It is speculated that the formation of acylpyridine produced by the nucleophilic attack of nitrogen in pyridine to benzoyl group enhanced the nucleophilicity of nitrogen of thiourea. The nucleophilic attack of nitrogen of thiourea against the carbonyl of glycine amide gave selectively 2-thiohydantoin **11**.

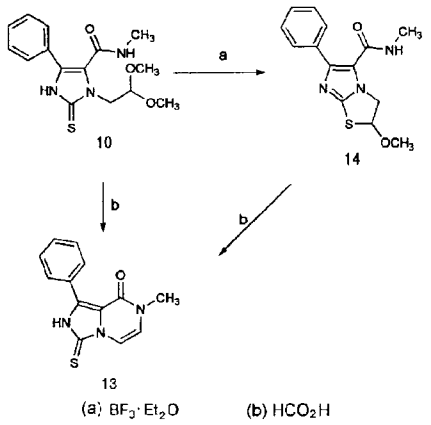
While *N*-benzoylthiocarbamoyl glycine amide **9** was transformed to imidazole-2-thione **10** or 2-thiohydantoin **11** in basic conditions, it was completely transformed to iminothiazolidine **12** exclusively in the presence of Lewis acid such as boron trifluoride etherate or trimethylsilyl iodide.

The acid catalyzed nucleophilic cyclization of imidazole-2-thione **10** produced different bicyclic com-pounds depending on the kinds of acid catalysis. The reaction of imidazole-2-thione 10 in formic acid at 60°C provided imidazo[5,1-a]pyrazine **13** exclusively in the yield of



Scheme 2. Acid and base catalyzed intramolecular cyclization

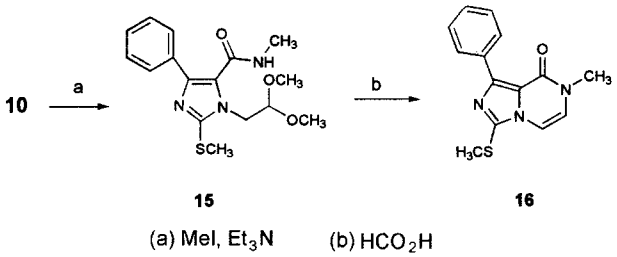
74%. However, in the presence of borontrifluoride etherate or trimethylsilyl iodide as acid catalysis, it transformed to imidazolidine [2,1-*b*] thiazole **14** exclusively in the yield of 89%. It is speculated that iodide or fluoride ion resulting from oxonium ion formation between acetaldehyde dimethylacetal and Lewis acid abstracts the proton of thiourea, and then the electrons of thiocarbonyl attack to the oxonium ion. Finally, iminothiazole ring **14** was formed by the removal of one molecule methoxy group. In consideration of the fact that the nucleophilicity of sulfur is stronger than that of nitrogen based upon the stable tautomeric structure of thioureido, imidazo[5,1-*a*]pyrazine **13** is thought to be produced via imidazolidine[2,1-*b*]thiazole 14. In order to confirm this hypothesis, imidazolidine[2,1-*b*]thiazole **14** was treated with formic acid at 60°C. As expected, imidazolidine[2,1-*b*]thiazole 14 was completely transformed to imidazo [5,1-*a*]pyrazine **13**.



Scheme 3. Bicyclic ring formation

This two-step acid catalyzed cyclization seem to be occurred by the *S*-nucleophilic attack against oxocarbonium ion formed by the protonation of acetal group by acid catalysis. After formation of oxocarbonium ion of acetal, the counter base abstracts a proton from 3-NH of imidazole-2-thione **10** to enhance the nucleophicity of S of 2-sulfone, and then nucleophilic attacks by the activated sulfur against oxocarbonium ion of acetal resulting in imidazolidine[2,1-*b*]thiazole **14** with releasing a molecule of methanol. The nucleophic attack of amide -NH against another oxocarbonium ion formed by formic acid resulted in imidazo[5,1-*a*]pyrazine **13** via *N*-acyliminium ion.

After blocking of *S*-nucleophilicity by *S*-methylation, formic acid catalyzed cyclization of the resulting imidazolidine **15** gave only *S*-methylated imidazo[5,1-*a*]pyrazine **16**.



Scheme 4. Ring fromation of *S*-Masked imidazole

In conclusion, acid and base catalyzed intramolecular cyclizations of *N*-benzoylthioureidoacetal containing four functional groups adjacent to thiourea such as benzocarbamoyl, acetal, thioure and amide, had been successfully investigated. The condensation reaction of *N*-benzoyl thiocarbamoylglycine amide in the presence of 10% aqueous NaOH provided 1-(2,2-dimethoxy) ethyl-imidazolidine-2-thione exclusively. In the presence of pyridine, it was transformed to 2-thiohydantoin. *N*-Benzoyl thiocarbamoyl glycine amide was completely transformed to iminothiazolidine derivatives exclusively in the presence of Lewis acid such as borontrifluoride etherate or trimethylsilyl iodide. 1-(2,2-Dimethoxy)ethyl-imidazolidine-2-thione was transformed to imidazole [2, 1-*b*]thiazole and pyrazino[5,1-a]imidazole in the presence of $BF_3.Et_2O$ and formic acid, respectively.

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