A Selective Synthesis of 2-Arylamino-4*H*-1,3,4-thiadiazino[5,6-*b*]-quinoxalines and Mesoionic Triazolo[4,3-*a*]quinoxaline

Ho Sik Kim*, Tong Eun Kim, Sam Tag Kwag, Yong Tae Park [1a], and Young Seuk Hong [1b]

Department of Chemistry, Catholic University of Taegu-Hyosung, Gyongsan 713-702, Korea

Yoshihisa Okamoto

Division of Chemistry, Center of Liberal Arts and Sciences, Kitasato University, Kitasato, Sagamihara, Kanagawa 227, Japan

Yoshihisa Kurasawa*

School of Pharmaceutical Sciences, Kitasato University, Shirokane, Minato-ku, Tokyo 108, Japan

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The reaction of the 6-chloro-2-(1-methyl-2-thiocarbamoylhydrazino)quinoxaline 4-oxides **3a-d** with trifluoroacetic anhydride gave the 2-(*N*-aryl)trifluoroacetamido-8-chloro-4-methyl-4*H*-1,3,4-thiadiazino-[5,6-*b*]quinoxalines **7a-d**, respectively, while the reflux of compounds **3a-c** in *N,N*-dimethylformamide afforded the mesoionic triazolo[4,3-*a*]quinoxaline **4**. Hydrolysis of compounds **7a-d** with triethylamine/water provided the 2-arylamino-8-chloro-4-methyl-4*H*-1,3,4-thiadiazino[5,6-*b*]quinoxalines **8a-d**, respectively.

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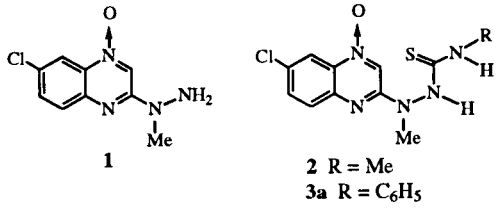
In a previous paper [2], we reported that the reaction of 6-chloro-2-(1-methylhydrazino)quinoxaline 4-oxide **1** with methyl or phenyl isothiocyanate gave 6-chloro-2-[1-methyl-2-(*N*-methylthiocarbamoyl)hydrazino]quinoxaline 4-oxide **2** or 6-chloro-2-[1-methyl-2-(*N*-phenylthiocarbamoyl)hydrazino]quinoxaline 4-oxide **3a**, respectively

Chart 1



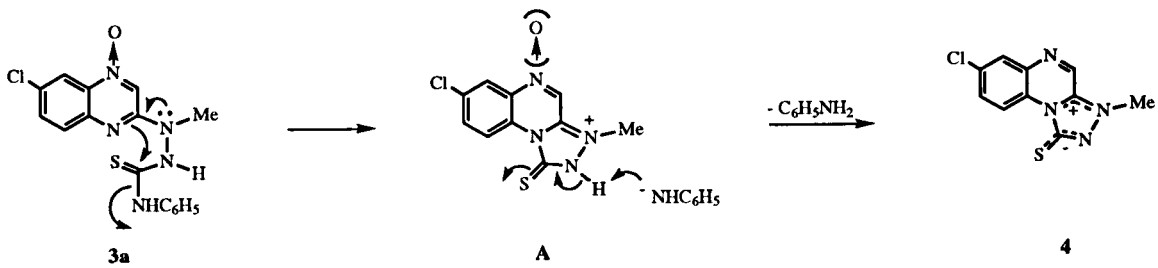
1

2 R = Me

3a R = C_6H_5

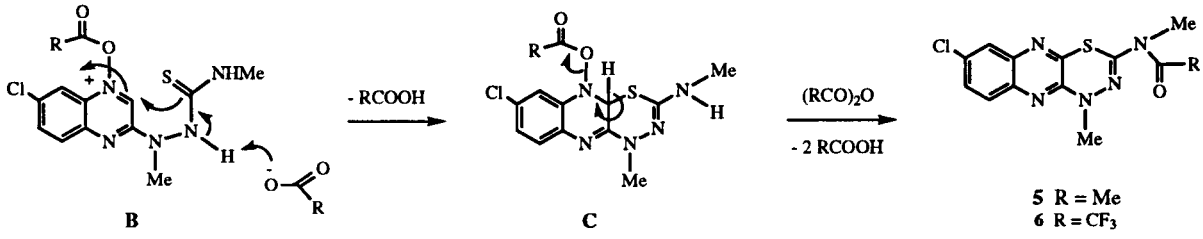
(Chart 1). Moreover, the methyl derivative **2** was stable under reflux in *N,N*-dimethylformamide, but the phenyl derivative **3a** was labile under reflux in *N,N*-dimethylformamide to change into the mesoionic triazolo[4,3-*a*]-quinoxaline **4** presumably *via* an intermediate **A** (Scheme 1) [3]. On the other hand, we have recently reported that the reaction of the methyl derivative **2** with acetic anhydride or trifluoroacetic anhydride conveniently furnished the 4*H*-1,3,4-thiadiazino[5,6-*b*]quinoxaline **5** or **6**, respectively, presumably *via* intermediates **B** and **C** (Scheme 2) [4]. However, it has not been clarified yet whether the reaction of the phenyl derivative **3a** with acyl anhydride would afford the mesoionic triazolo[4,3-*a*]-quinoxaline **4** or 4*H*-1,3,4-thiadiazino[5,6-*b*]quinoxalines **7** (Scheme 3). It was interesting for us to study such an alternative cyclization reaction, and hence we investigated the reaction condition to convert the aryl derivatives **3a-d** into the mesoionic triazolo[4,3-*a*]quinoxaline **4** or 4*H*-1,3,4-thiadiazino[5,6-*b*]quinoxalines **7**. As the result, we found that the reflux of the aryl derivatives **3a-c** in *N,N*-dimethylformamide produced the mesoionic triazolo[4,3-*a*]-quinoxaline **4**, while the reaction of compounds **3a-d** with trifluoroacetic anhydride provided the 4*H*-1,3,4-thiadiazino[5,6-*b*]quinoxalines **7a-d**, respectively. In contrast, the reaction of compounds **3a-d** with acetic anhydride did not give the 4*H*-1,3,4-thiadiazino[5,6-*b*]quinoxalines **9**. This paper describes the selective cyclization of compounds **3**

Scheme 1



3a **A** **4**

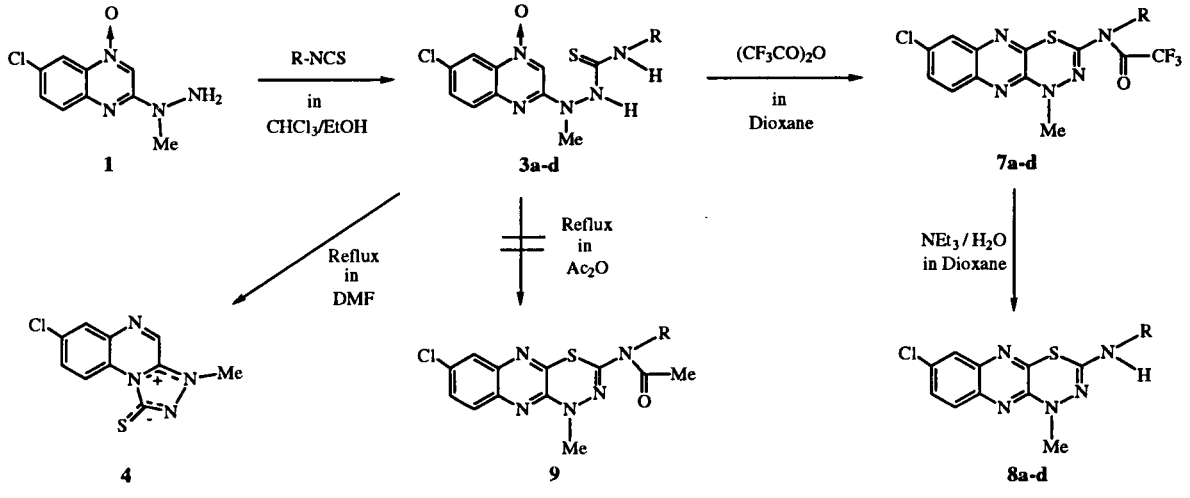
Scheme 2



into the mesoionic triazolo[4,3-*a*]quinoxaline **4** and 4*H*-1,3,4-thiadiazino[5,6-*b*]quinoxalines **7**.

methyl **2**, benzyl **3d**, and aryl **3a-c** derivatives into the 4*H*-1,3,4-thiadiazino[5,6-*b*]quinoxaline ring system.

Scheme 3



	R	Yield of **4** from **3**	Yield of **7** from **3**	Yield of **8** from **7**
a	C_6H_5	32% [Ref 3]	83%	66%
b	C_6H_4-*p*-Cl	63%	61%	65%
c	C_6H_4-*p*-Br	51%	53%	74%
d	$CH_2C_6H_5$	---	38%	71%

The conversion of the phenyl derivative **3a** into the mesoionic triazolo[4,3-*a*]quinoxaline **4** has already been reported in a previous paper [3], and the reflux of the *p*-chlorophenyl **3b** or *p*-bromophenyl **3c** derivative in *N,N*-dimethylformamide similarly afforded the mesoionic triazolo[4,3-*a*]quinoxaline **4** (Scheme 3). However, the benzyl derivative **3d** was not cyclized into compound **4**. These data indicate that the methyl or benzyl derivative does not cyclize into the mesoionic triazolo[4,3-*a*]quinoxaline **4**.

On the other hand, the reaction of compounds **3a-d** with trifluoroacetic anhydride conveniently resulted in cyclization to provide the 2-(*N*-aryl)trifluoroacetamido-8-chloro-4-methyl-4*H*-1,3,4-thiadiazino[5,6-*b*]quinoxalines **7a-d**, respectively, whose hydrolysis gave the 2-arylamino-8-chloro-4-methyl-4*H*-1,3,4-thiadiazino[5,6-*b*]quinoxalines **8a-d**, respectively. However, the reaction of compounds **3a-d** with acetic anhydride afforded neither 4*H*-1,3,4-thiadiazino[5,6-*b*]quinoxalines **9** nor mesoionic triazolo-[4,3-*a*]quinoxaline **4**. Thus, it was found that trifluoroacetic anhydride was a suitable annelation agent of the Acetic anhydride was effective only in the annelation of the methyl derivative **2** into the 4*H*-1,3,4-thiadiazino-[5,6-*b*]quinoxaline **5**.

EXPERIMENTAL

All melting points were determined on a Yazawa micro melting point BY-2 apparatus and are uncorrected. The ir spectra (potassium bromide) were recorded with a JASCO IRA-1 spectrophotometer. The nmr spectra were measured in deuteriodimethyl sulfoxide with a Varian XL-400 spectrometer at 400 MHz. The chemical shifts are given in the δ scale. The mass spectra (ms) were determined with a JEOL JMS-01S spectrometer. Elemental analyses were performed on a Perkin-Elmer 240B instrument.

6-Chloro-2-[2-(*p*-chlorophenylthiocarbamoyl)-1-methylhydrazino]quinoxaline 4-Oxide **3b**.

A solution of compound **1** (10 g, 44.5 mmoles) and *p*-chlorophenyl isothiocyanate (9.05 g, 53.4 mmoles) in chloroform (150

ml)/ethanol (100 ml) was refluxed on a boiling water bath for 1 hour to precipitate colorless needles of **3b**, which were collected by suction filtration to provide an analytically pure sample (12.23 g). Evaporation of the filtrate *in vacuo* gave colorless crystals of **3b**, which were triturated with ethanol/*n*-hexane and then collected by suction filtration (3.12 g), total yield, 15.35 g (85%).

Compound **3b** had mp 206-207°; ir: ν cm^{-1} 3280, 1580, 1540; ms: m/z 393 (M^+), 395 ($M^+ + 2$); pmr: 10.21 (s, 2H, NH), 8.26 (d, J = 1.0 Hz, 1H, C_5-H), 8.13 (s, 1H, C_3-H), 7.83 (d, J = 10.0 Hz, 1H, C_8-H), 7.78 (dd, J = 10.0, 1.0 Hz, 1H, C_7-H), 7.56 (d, J = 8.5 Hz, 2H, aromatic), 7.38 (d, J = 8.5 Hz, 2H, aromatic), 3.35 (s, 3H, CH_3); ^{13}C-nmr: 180.8 (C=S).

Anal. Calcd. for $C_{16}H_{13}Cl_2N_5OS$: C, 48.64; H, 3.32; Cl, 17.98; N, 17.76; S, 8.13. Found: C, 48.81; H, 3.36; Cl, 18.04; N, 17.90; S, 8.09.

2-[2-(*p*-Bromophenylthiocarbamoyl)-1-methylhydrazino]-6-chloroquinoxaline 4-Oxide **3c**.

A solution of compound **1** (10 g, 44.5 mmoles) and *p*-bromophenyl isothiocyanate (14.30 g, 66.8 mmoles) in chloroform (150 ml)/ethanol (100 ml) was refluxed on a boiling water bath for 2 hours to precipitate yellow needles of **3c**, which were collected by suction filtration and washed with ethanol and then *n*-hexane to give an analytically pure sample (13.12 g). Evaporation of the filtrate *in vacuo* afforded yellow crystals of **3c**, which were collected by suction filtration and washed with ethanol (1.42 g), total yield, 14.54 g (74%).

Compound **3c** had mp 216-217°; ir: ν cm^{-1} 3280, 1580, 1530; ms: m/z 437 (M^+), 439 ($M^+ + 2$); pmr: 10.23 (br, 2H, NH), 8.26 (s, 1H, C_5-H), 8.11 (s, 1H, C_3-H), 7.81 (d, J = 9.0 Hz, 1H, C_8-H), 7.78 (d, J = 9.0 Hz, 1H, C_7-H), 7.50 (s, 4H, aromatic), 3.34 (s, 3H, CH_3); ^{13}C-nmr: 180.8 (C=S).

Anal. Calcd. for $C_{16}H_{13}BrClN_5OS$: C, 43.80; H, 2.99; N, 15.96; S, 7.31. Found: C, 44.02; H, 2.95; N, 16.00; S, 7.45.

2-(2-Benzylthiocarbamoyl-1-methylhydrazino)-6-chloroquinoxaline 4-Oxide **3d**.

A solution of compound **1** (10 g, 44.5 mmoles) and benzyl isothiocyanate (9.95 g, 66.8 mmoles) in dioxane (200 ml) was refluxed in an oil bath for 2 hours. Evaporation of the solvent *in vacuo* gave yellow crystals of **3d**. Recrystallization from dioxane/ethanol afforded yellow needles of **3d**, which were collected by suction filtration (12.70 g). Evaporation of the filtrate *in vacuo* provided yellow crystals of **3d**, which were triturated with ethanol and then collected by suction filtration (2.73 g), total yield, 15.43 g (93%).

Compound **3d** had mp 226-227°; ir: ν cm^{-1} 3280, 1585, 1550; ms: m/z 373 (M^+), 375 ($M^+ + 2$); pmr: 9.95 (br, 1H, NH), 9.12 (br, 1H, NH), 8.25 (d, J = 2.0 Hz, 1H, C_5-H), 8.00 (s, 1H, C_3-H), 7.81 (d, J = 9.0 Hz, 1H, C_8-H), 7.78 (dd, J = 9.0, 2.0 Hz, 1H, C_7-H), 7.43-7.16 (m, 5H, aromatic), 4.72 (s, 2H, CH_2), 3.34 (s, 3H, CH_3); ^{13}C-nmr: 181.9 (C=S).

Anal. Calcd. for $C_{17}H_{16}ClN_5OS$: C, 54.62; H, 4.31; Cl, 9.48; N, 18.73; S, 8.58. Found: C, 54.60; H, 4.34; Cl, 9.46; N, 18.71; S, 8.84.

7-Chloro-3-methyl-1,2,4-triazolo[4,3-*a*]quinoxalin-3-ium-1-thioate **4**.

General Procedure.

A solution of the appropriate compound **3** (1 g) in *N,N*-dimethylformamide (30 ml) was refluxed in an oil bath for 5 hours. Evaporation of the solvent *in vacuo* gave orange crystals of **4**, which were triturated with hot ethanol and then collected by suction filtration. The ir spectra of compound **4** obtained in the present investigation were identical with the ir spectrum of an authentic sample [2].

8-Chloro-4-methyl-2-(*N*-phenyl)trifluoroacetamido-4*H*-1,3,4-thiadiazino[5,6-*b*]quinoxaline **7a**.

A solution of compound **3a** (10 g) and trifluoroacetic anhydride (20 ml) in dioxane (400 ml) was refluxed in an oil bath for 2 hours. Evaporation of the solvent *in vacuo* afforded an oily residue, which was crysrtallized from ethanol/water to furnish yellow crystals (10.13 g, 83%). Recrystallization from ethanol afforded yellow needles of **7a**, mp 139-140°; ir: ν cm^{-1} 3060, 2930, 1710; ms: m/z 437 (M^+), 439 ($M^+ + 2$); pmr: 7.61-7.44 (m, 8H, aromatic), 3.31 (s, 3H, CH_3); ^{13}C-nmr: 156.5 (C=O).

Anal. Calcd. for $C_{18}H_{11}ClF_3N_5OS$: C, 49.38; H, 2.53; N, 16.00; S, 7.32. Found: C, 49.47; H, 2.54; N, 16.27; S, 7.18.

8-Chloro-2-[*N*-(*p*-chlorophenyl)trifluoroacetamido]-4-methyl-4*H*-1,3,4-thiadiazino[5,6-*b*]quinoxaline **7b**.

A solution of compound **3b** (5 g) and trifluoroacetic anhydride (10 ml) in dioxane (200 ml) was refluxed in an oil bath for 2 hours. Evaporation of the solvent *in vacuo* afforded an oily product, which was crystallized from ethanol/*n*-hexane to provide yellow crystals of **7b** (3.68 g, 61%). Recrystallization from dioxane/ethanol gave yellow needles of **7b**, mp 151-152°; ir: ν cm^{-1} 3120, 2950, 1720; ms: m/z 471 (M^+), 473 ($M^+ + 2$); pmr: 7.65 (d, J = 8.5 Hz, 2H, aromatic), 7.61 (dd, J = 2.0, 0.5 Hz, 1H, C_9-H), 7.58 (d, J = 8.5 Hz, 2H, aromatic), 7.56 (dd, J = 8.5 , 0.5 Hz, 1H, C_6-H), 7.52 (dd, J = 8.5, 2.0 Hz, 1H, C_7-H), 3.32 (s, 3H, CH_3); ^{13}C-nmr: 156.5 (C=O).

Anal. Calcd. for $C_{18}H_{10}Cl_2F_3N_5OS$: C, 45.78; H, 2.13; N, 14.83; S, 6.79. Found: C, 45.79; H, 2.15; N, 15.02; S, 6.99.

2-[*N*-(*p*-Bromophenyl)trifluoroacetamido]-8-chloro-4-methyl-4*H*-1,3,4-thiadiazino[5,6-*b*]quinoxaline **7c**.

A solution of compound **3c** (5 g) and trifluoroacetic anhydride (10 ml) in dioxane (200 ml) was refluxed in an oil bath for 2 hours. Evaporation of the solvent *in vacuo* gave an oily product, whose crystallization from ethanol afforded yellow needles of **7c** (3.11 g, 53%), mp 169-170°; ir: ν cm^{-1} 3080, 2920, 1700; ms: m/z 515 (M^+), 517 ($M^+ + 2$); pmr: 7.72 (d, J = 8.5 Hz, 2H, aromatic), 7.60 (dd, J = 2.0, 0.5 Hz, 1H, C_9-H), 7.58 (d, J = 8.5 Hz, 2H, aromatic), 7.52 (dd, J = 8.5, 0.5 Hz, 1H, C_6-H), 7.51 (dd, J = 8.5, 2.0 Hz, 1H, C_7-H), 3.32 (s, 3H, CH_3); ^{13}C-nmr: 156.5 (C=O).

Anal. Calcd. for $C_{18}H_{10}BrClF_3N_5OS$: C, 41.85; H, 1.95; N, 13.55; S, 6.20. Found: C, 41.95; H, 1.99; N, 13.53; S, 6.45.

2-(*N*-Benzyl)trifluoroacetamido-8-chloro-4-methyl-4*H*-1,3,4-thiadiazino[5,6-*b*]quinoxaline **7d**.

A solution of compound **3d** (5 g) and trifluoroacetic anhydride (10 ml) in dioxane (200 ml) was refluxed in an oil bath for 2 hours. Evaporation of the solvent *in vacuo* gave an oily product. Crystallization from ethanol/*n*-hexane with cooling in a refrigerator afforded yellow needles of **7d**, which were collected by suction filtration and washed with ethanol/*n*-hexane (1:2) (2.26 g, 38%), mp 109-110°; ir: ν cm^{-1} 1710; ms: m/z 451 (M^+), 453 ($M^+ + 2$); pmr: 7.66 (dd, J = 2.0, 1.0 Hz, 1H, C_9-H), 7.55 (dd, J = 8.5, 1.0 Hz, 1H, C_6-H), 7.52 (dd, J = 8.5, 2.0 Hz, 1H, C_7-H), 7.40-7.26 (m, 5H, aromatic), 4.85 (s, 2H, CH_2), 3.25 (s, 3H, CH_3); ^{13}C-nmr: 156.6 (C=O).

Anal. Calcd. for $C_{19}H_{13}ClF_3N_5OS$: C, 50.51; H, 2.90; N, 15.50; S, 7.10. Found: C, 50.53; H, 2.88; N, 15.59; S, 7.08.

8-Chloro-4-methyl-2-phenylamino-4*H*-1,3,4-thiadiazino[5,6-*b*]-quinoxaline **8a**, 8-Chloro-2-(*p*-chlorophenylamino)-4-methyl-4*H*-1,3,4-thiadiazino[5,6-*b*]quinoxaline **8b**, 2-(*p*-Bromophenylamino)-8-chloro-4-methyl-4*H*-1,3,4-thiadiazino[5,6-*b*]quinoxaline **8c**, and 2-Benzylamino-8-chloro-4-methyl-4*H*-1,3,4-thiadiazino[5,6-*b*]quinoxaline **8d**.

A solution of compound **7a** (2 g) in dioxane (35 ml)/water (5 ml)/triethylamine (1 ml) was refluxed in an oil bath for 30 minutes. After cooling to room temperature, the solution was filtered, and water was added to the solution with stirring on a boiling water bath. Then, the solution was allowed to stand at room temperature to precipitate analytically pure orange needles of **8a**, which were collected by suction filtration (1.26 g, 66%).

A similar reaction of compound **7b** (2 g) in dioxane (35 ml)/water (5 ml)/triethylamine (1 ml), compound **7c** (1.5 g) in dioxane (25 ml)/water (5 ml)/triethylamine (1 ml), or compound **7d** (1 g) in dioxane (20 ml)/water (5 ml)/triethylamine (1 ml) afforded compound **8b** (orange needles, 1.02 g, 65%), compound **8c** (orange needles, 0.89 g, 74%), or compound **8d** (orange needles, 0.56 g, 71%), respectively.

Compound **8a** had mp 226-227°; ir: ν cm^{-1} 3260, 1620, 1590, 1530, 1510; ms: m/z 341 (M^+), 343 ($M^+ + 2$); pmr: 9.22 (s, 1H, NH), 7.61 (dd, J = 2.0, 1.0 Hz, 1H, C_9-H), 7.50 (dd, J = 8.5, 1.0 Hz, 2H, *o*-H), 7.48 (dd, J = 8.5, 1.0 Hz, 1H, C_6-H), 7.44 (dd, J = 8.5, 2.0 Hz, 1H, C_7-H), 7.25 (dddd, J = 8.5, 7.5, 1.0, 1.0 Hz, 2H, *m*-H), 6.94 (dddd, J = 7.5, 7.5, 1.0, 1.0 Hz, 1H, *p*-H), 3.34 (s, 3H, CH_3).

Anal. Calcd. for $C_{16}H_{12}ClN_5S$: C, 56.22; H, 3.54; Cl, 10.37; N, 20.49; S, 9.38. Found: C, 56.20; H, 3.53; Cl, 10.29; N, 20.62; S, 9.23.

Compound **8b** had mp 249-250°; ir: ν cm^{-1} 1635, 1590; ms: m/z 375 (M^+), 377 ($M^+ + 2$); pmr: 9.37 (s, 1H, NH), 7.65 (dd, J = 2.0, 0.5 Hz, 1H, C_9-H), 7.52 (dd, J = 8.5, 0.5 Hz, 1H, C_6-H), 7.51 (d, J = 9.0 Hz, 2H, aromatic), 7.48 (dd, J = 8.5, 2.0 Hz, 1H, C_7-H), 7.29 (d, J = 9.0 Hz, 2H, aromatic), 3.36 (s, 3H, CH_3).

Anal. Calcd. for $C_{16}H_{11}Cl_2N_5S$: C, 51.07; H, 2.95; Cl, 18.85; N, 18.61; S, 8.52. Found: C, 51.26; H, 3.08; Cl, 19.06; N, 18.67; S, 8.33.

Compound **8c** had mp 254-255°; ir: ν cm^{-1} 1635, 1585; ms: m/z 419 (M^+), 421 ($M^+ + 2$); pmr: 9.34 (s, 1H, NH), 7.61 (d, J = 2.0 Hz, 1H, C_9-H), 7.48 (d, J = 8.5 Hz, 1H, C_6-H), 7.44 (d, J = 9.0 Hz, 2H, aromatic), 7.44 (dd, J = 8.5, 2.0 Hz, 1H, C_7-H), 7.39 (d, J = 9.0 Hz, 2H, aromatic), 3.34 (s, 3H, CH_3).

Anal. Calcd. for $C_{16}H_{11}BrClN_5S$: C, 45.68; H, 2.64; N, 16.65; S, 7.62. Found: C, 45.83; H, 2.73; N, 16.71; S, 7.40.

Compound **8d** had mp 128-129°; ir: ν cm^{-1} 1605, 1510; ms: m/z 355 (M^+), 357 ($M^+ + 2$); pmr: 7.56 (dd, J = 2.0, 1.0 Hz, 1H, C_9-H), 7.43 (dd, J = 8.5, 1.0 Hz, 1H, C_6-H), 7.40 (dd, J = 8.5, 2.0 Hz, 1H, C_7-H), 7.36-7.19 (m, 5H, aromatic), 4.31 (d, J = 5.5 Hz, 2H, CH_2), 3.23 (s, 3H, CH_3). The NH proton signal was overlapped with the aromatic proton signals.

Anal. Calcd. for $C_{17}H_{14}ClN_5S$: C, 57.38; H, 3.97; Cl, 9.96; N, 19.68; S, 9.00. Found: C, 57.57; H, 4.11; Cl, 10.01; N, 19.66; S, 8.74.

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REFERENCES AND NOTES

[1] Present address: [a] Department of Chemistry, Kyungpook National University, Taegu 702-701, Korea; [b] Department of Chemistry, Keimyung University, Taegu 704-701, Korea.

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