HETEROCYCLES, Vol. 55, No. 1, 2001, pp. 75 - 89, Received, 14th August, 2000

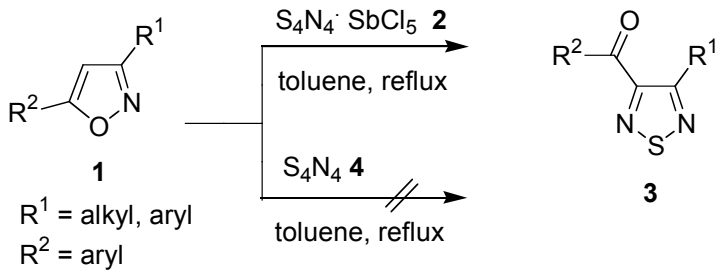
A MODIFIED PROCEDURE FOR THE SYNTHESIS OF 5-AMINO-3-ARYLISOXAZOLES AND THEIR REACTIONS WITH TETRASULFUR TETRANITRIDE ANTIMONY(V) CHLORIDE COMPLEX (S_4N_4•$SbCl_5$): NOVEL SYNTHESIS OF 3-ARYL-1,2,5-THIADIAZOLE-4-CARBOXAMIDES

Yung Cheol Kong,[a] Kyongtae Kim,[a,*] and Yung Ja Park[b]

[a]School of Chemistry and Molecular Engineering, Seoul National University, Seoul 151-742, Korea
[b]Department of Chemistry, Sook Myung Women's University, Seoul 140-724, Korea

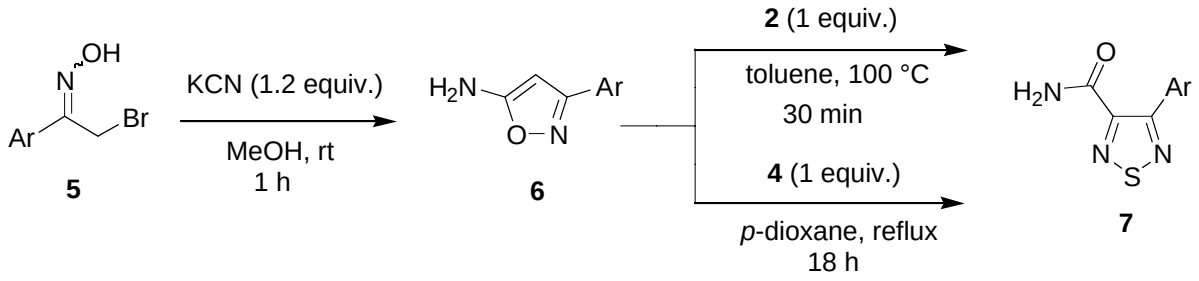
Abstract - Dropwise addition of a-bromo ketoximes to a solution of KCN in MeOH at room temperature gave 5-amino-3-arylisoxazoles in moderate to good yields. Treatment of the isoxazoles prepared with tetrasulfur tetranitride antimony (V) chloride complex (S_4N_4•$SbCl_5$) in toluene at 100°C afforded novel 3-aryl-1,2,5-thiadiazole-4-carboxamides.

Isoxazoles are an important class of heterocyclic compounds and their chemistry has been extensively studied.[1] Recently we have shown that treatment of 3-alkyl-5-aryl- and 3,5-diarylisoxazoles (**1**) with tetrasulfur tetranitride antimony(V) chloride complex (S_4N_4•$SbCl_5$) (**2**) in toluene at reflux gave 3-alkyl-4-aroyl- and 3-aroyl-4-aryl-1,2,5-thiadiazoles (**3**),[2] whereas compounds (**1**) did not react with tetrasulfur tetranitride (S_4N_4) (**4**) under the same conditions with quantitative recovery of **1** (Scheme 1).



Scheme 1

As part of our continuing effort to extend the methodology involving isoxazoles and compounds (**2**) or (**4**) to a synthesis of structually unequivocal 1,2,5-thiadiazoles, we were in need of 5-amino-3-arylisoxazoles (**6**). A survey of the literature shows that one of the existing methods for the synthesis of **6** consists of treatment of α-cyano ketones, prepared from esters and NaH in MeCN, with hydroxylamine hydrochlorides.[3] However, the success of this method depends on maintaining right pH through the reactions by using NaOEt or NaOH at reflux temperature. Otherwise, the cyano group is hydrolyzed first instead of forming cyano ketoximes. Alternatively treatment of olefins with NOCl, followed by addition of CN^- would give the desired compounds.[4] However, this method may not be suitable for the reactions of unsymmetric olefins owing to the formation of a mixture of stereoisomers when nitroso chlorides are formed. After some trial and error, we have found that dropwise addition of α-bromo ketoximes (**5**) (3.30 - 8.71 mmol) prepared from 1-aryl-2-bromoethanone and NH_2OH•HCl in the usual manner,[5] to a solution of KCN (3.96 - 10.45 mmol) in MeOH (20 - 55 mL) at room temperature gave 5-amino-3-arylisoxazoles (**6**) in moderate to good yields (Scheme 2). However, either stirring a mixture of **5** and KCN in MeOH or dropwise addition of a solution of KCN in MeOH to **5** in MeOH yielded a complicated mixture. Yields and physical properties of **6** are summarized in Table 1.



Scheme 2

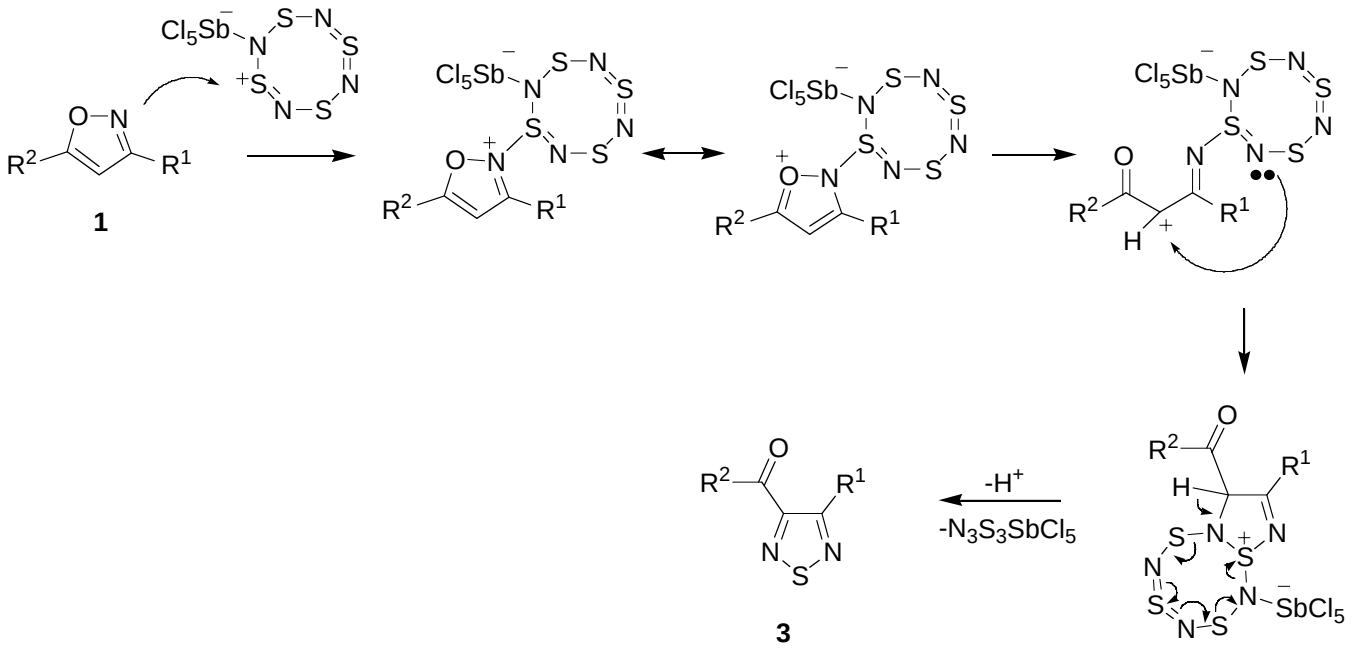
Since the formation of either the acyl or aroyl group of **3** is achieved by cleavage of the O-N bond of **1**, it is envisaged that 1,2,5-thiadiazoles with the desired substituents at C-3 and C-4 can be prepared stereoselectively *via* **1** as shown in Scheme 3.[2] For example, treatment of **6** with **2** would give 3-aryl-1,2,5-thiadiazole-4-carboxamides (**7**), which are not only hitherto unknown but also may be utilized as a good precursor for the synthesis of other 1,2,5-thiadiazoles having substituents difficult to access directly

Table 1. Yields and melting points of **6** and **7**

Compound	Ar	Yield[a] (%)	mp (°C)	Compound	Yield[b] (%)	mp (°C)
6a	C_6H_5	58	110-111 (lit.,[3c] 110-111)	**7a**	48 (35)	165-166
6b	4-FC_6H_4	64	104-105	**7b**	48 (12)	171-172
6c	4-ClC_6H_4	68	154-155 (lit.,[3b] 165-167)	**7c**	42 (34)	178-179
6d	4-BrC_6H_4	80	164-166	**7d**	45 (33)	183-185
6e	4-$O_2NC_6H_4$	35	163-165	**7e**	27 (26)	225-227
6f	4-MeC_6H_4	62	149-151	**7f**	51 (31)	196-198
6g	4-$MeOC_6H_4$	69	136-138	**7g**	57 (31)	188-189
6h	2-Naphthyl	55	126-128	**7h**	31 (18)	164-166
6i	2-Thienyl	44	sticky oil	**7i**	36 (21)	195-196

[a] Recrystallized yields except for **6i** (sticky). Compounds (**6a**-**c**) and (**6d**-**h**) were recrystallized from a mixture of CCl_4 and CH_2Cl_2, and CCl_4, respectively. **6a**, **6f**, **6g**: colorless; **6b**-**c**, **6h**-**i**: pale yellow; **6d**-**e**: brown. [b] Isolated yields. The numbers in parenthesis represent yields from the reactions with **4**. Compounds (**7a**-**d**), (**7g**-**i**), and (**7e**-**f**) were recrystallized from CCl_4, and a mixture of CCl_4 and CH_2Cl_2, respectively. Compounds (**7**) are colorless except for **7e** (pale yellow).

from **1**. The reaction of **6** (0.77 - 1.50 mmol) with **2** (1 equiv.) in toluene for 30 min at 100°C gave **7** as a major product. The structures of **7** were determined based on the spectroscopic (^{1}H and ^{13}C NMR, IR, MS) and analytical data. *X*-Ray crystallographic analysis of **7a** (Ar = Ph) (Figure 1) supports the structural assignments. Unexpectedly apart from the reactions of **1** with **4**, heating a mixture of **6** (1.05 - 2.25 mmol) and **4** (1 equiv.) in *p*-dioxane (5 - 10 mL) for 18 h at reflux gave **7** in lower yields compared with those from the reactions with **2** and an unknown mixture, presumably formed by decomposition of **6** because the same unknown mixture was obtained from heating **6** without **4** in *p*-dioxane at reflux. However, purification of the mixture has been unsuccessful owing to its instability.



Scheme 3

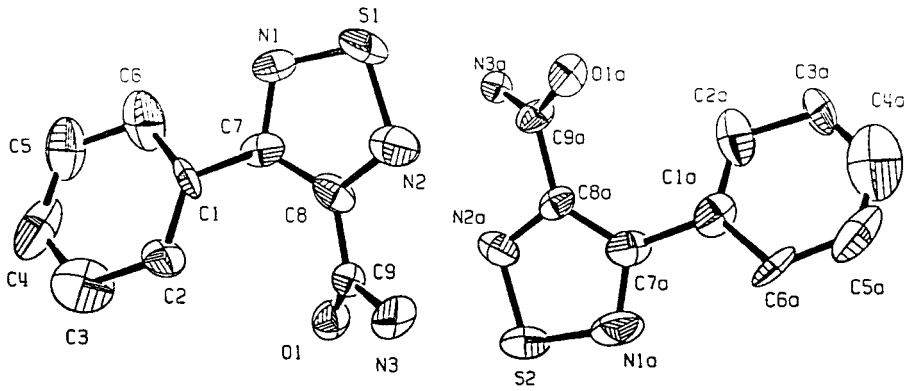
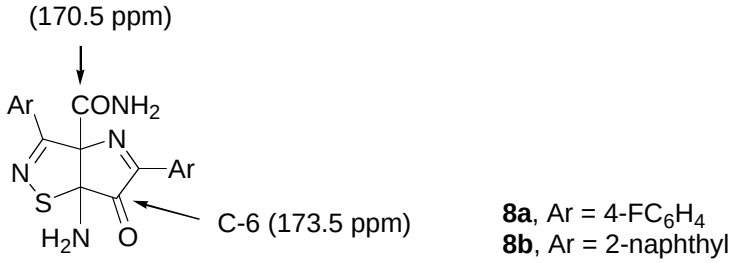


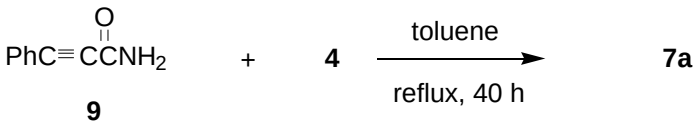
Figure 1 ORTEP drawing of 4-phenyl-1,2,5-thiadiazole-3-carboxamide (**7a**)

Interestingly, the reactions of compounds (**6b**) and (**6h**) with **4** gave additional compounds (**8a**) and (**8b**), respectively, as major products. The structures of **8a**-**b** were assigned based on the spectroscopic (^{1}H and



^{13}C NMR, IR, FAB MS) and analytical data: The ^{1}H NMR spectrum shows that the compound (**8a**) has two aryl groups and two different amino groups (7.25, 7.35, 7.43 ppm). The ^{13}C NMR spectrum exhibited two peaks at 50.5 and 72.4 ppm, corresponding to two quarternary carbons at the ring juncture. The HMBC spectrum shows that one of the amino groups (7.25, 7.43 ppm) correlates with one of the quarternary carbons (50.5 ppm) and a carbonyl carbon (170.5 ppm) but does not correlate with a carbonyl carbon at C-6 (173.5 ppm), whereas the other amino group (7.35 ppm) correlates with not only the other quarternary carbon (72.4 ppm) but also a carbonyl carbon at C-6. The observations are indicative of the presence of a carboxamido and a free amino groups, which is consistent with the IR data showing two C=O stretchings (1673, 1625 cm^{-1}) and NH stretchings (3440, 3296 cm^{-1}). On the other hand, purification of compound (**8b**) by repeated recrystallization was in vain. However, **8b** seems to be an analogous type of compound to **8a** in view of the ^{1}H NMR, IR, FAB MS, and HRFAB MS data although it has been unsuccessful to take the ^{13}C NMR and HMBC spectra of **8b** owing to its instability.

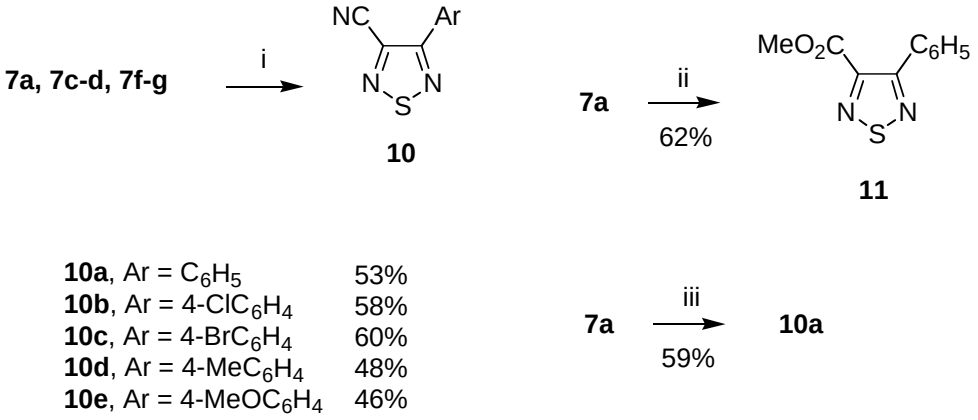
According to the documented procedure,[6] 3-phenylpropynecarboxamide (**9**) was treated with **4** (0.5 equiv.) in toluene for 40 h at reflux to give **7a** in 12% yield (Scheme 4). The result indicates that the present method involving **6** and **2** is preferable to the documented method involving 1,2-disubstituted acetylenes and **4** with respect to yield and reaction time.



Scheme 4

In order to see whether the carboxamido group of **7** might be utilized for the functional group transformation, the selected compounds (**7a**), (**7c**-**d**), and (**7f**-**g**) were subjected to various conditions.

Treatment of **7a**, **7c**-**d**, and **7f**-**g** with $SOCl_2$ in dried benzene (1 : 1, v/v) for 2 h at reflux gave cyano compounds (**10a**-**e**) in 46% to 60% yields (Scheme 5). The conversion may be through the enol form, with the dehydrating agent forming an ester with the OH group, RC(OSOCl)=NH, which undergoes



Reagents and Conditions: i. $SOCl_2$, PhH, reflux, 2 h. ii. $BF_3 \cdot Et_2O$, MeOH, reflux, 3 days. iii. P_4S_{10}, pyridine, reflux, 12 h.

Scheme 5

elimination by the E1 or E2 mechanism.[7] On the other hand, heating a mixture of **7a** and BF_3•OEt_2 in MeOH for 3 days at reflux afforded methyl ester (**11**) in 62% yield. The result is accord with the report in which amides are cleaved by methanolic boron trifluoride to methyl esters.[8] However, the reaction of **7a** with P_4S_{10} (1 equiv.) in pyridine at reflux did not yield the corresponding thioamide. Instead, **10a** was obtained in 59% yield. Since P_4S_{10} is one of the most useful reagents for replacing the oxygen of amides by sulfur[9] as well as a dehydrating agent,[10] the mechanism for the formation of **10a** from **7a** is uncertain. The scope of the reactions of isoxazoles (**1**) with **4** and further transformation of the functional group of **7** are currently under study.

EXPERIMENTAL

The ^1H and ^{13}C NMR spectra were recorded at 300 MHz and 75 MHz, respectively, in $CDCl_3$ containing Me_4Si as an internal standard. IR spectra were recorded in KBr or thin films on KBr plates. MS spectra were obtained by electron impact at 70 eV. Elemental analyses were measured by the Inter-University Center for Natural Science Research Facilities, SNU. Column chromatography was performed using

silica gel (70 - 230 mesh, Merck). Melting points are uncorrected. Tetrasulfur tetranitride (**4**) and tetrasulfur tetranitride antimony(V) chloride complex (**2**) were prepared by the documented procedure.[11]

General Procedure for the Preparation of 5-Amino-3-arylisoxazoles (6)

To a suspension of KCN (258 - 680 mg, 3.96 - 10.45 mmol) in MeOH (8 - 25 mL) was added dropwisely α-bromo ketoximes (**5**) (3.30 - 8.71 mmol) in MeOH (12 - 30 mL) at rt. The mixture was stirred for 30 min, followed by removal of KBr by filtration. Evaporation of the solvent in the filtrate gave a residue, which was recrystallized from the appropriate solvent except for **6i**. The solids were chromatographed on a silica gel (3 × 6 cm) using a mixture of EtOAc and *n*-hexane (1 : 1) as an eluent. Yields and melting points of **6** are summarized in Table 1.

5-Amino-3-phenylisoxazole (6a): ^{1}H NMR ($CDCl_3$, δ, ppm) 4.67 (2H, s, NH_2), 5.38 (1H, s, CH), 7.28-7.53 (3H, m, ArH), 7.55-7.87 (2H, m, ArH); IR (KBr) (ν, cm^{-1}) 3440, 3152, 1632, 1568, 1475, 1424, 732. *Anal.* Calcd for $C_9H_8N_2O$: C, 67.49; H, 5.03; N, 17.49. Found: C, 67.38; H, 5.02; N, 17.31.

5-Amino-3-(4-fluorophenyl)isoxazole (6b): ^{1}H NMR ($CDCl_3$, δ, ppm) 4.60 (2H, s, NH_2), 5.38 (1H, s, CH), 7.05-7.13 (2H, m, ArH), 7.66-7.72 (2H, m, ArH); IR (KBr) (ν, cm^{-1}) 3440, 3152, 1632, 1568, 1520, 1472, 1440, 1219, 1152, 838, 739. *Anal.* Calcd for $C_9H_7N_2OF$: C, 60.67; H, 3.96; N, 15.72. Found: C, 60.37; H, 3.92; N, 15.71.

5-Amino-3-(4-chlorophenyl)isoxazole (6c): ^{1}H NMR ($CDCl_3$, δ, ppm) 4.58 (2H, s, NH_2), 5.39 (1H, s, CH), 7.35 (2H, d, J = 8.6 Hz, ArH), 7.65 (2H, d, J = 8.6 Hz, ArH); IR (KBr) (ν, cm^{-1}) 3424, 3168, 1635, 1590, 1558, 1468, 1436, 1084, 828, 745. *Anal.* Calcd for $C_9H_7N_2OCl$: C, 55.54; H, 3.63; N, 14.39. Found: C, 55.39; H, 3.64; N, 14.29.

5-Amino-3-(4-bromophenyl)isoxazole (6d): ^{1}H NMR ($CDCl_3$, δ, ppm) 4.52 (2H, s, NH_2), 5.40 (1H, s, CH), 7.52-7.61 (4H, m, ArH); IR (KBr) (ν, cm^{-1}) 3456, 3184, 1632, 1587, 1557, 1472, 1433, 1065, 822,

729. *Anal.* Calcd for $C_9H_7N_2OBr$: C, 45.22; H, 2.95; N, 11.72. Found: C, 45.34; H, 2.98; N, 11.68.

5-Amino-3-(4-nitrophenyl)isoxazole (6e): ^{1}H NMR ($CDCl_3$-DMSO-d_6, δ, ppm) 5.45 (1H, s, CH), 5.75 (2H, s, NH_2), 7.89 (2H, d, *J* = 8.0 Hz, ArH), 8.27 (2H, d, *J* = 8.0 Hz, ArH); IR (KBr) (ν, cm^{-1}) 3424, 3184, 1635, 1577, 1507, 1468, 1337, 848, 736. *Anal.* Calcd for $C_9H_7N_3O_3$: C, 52.69; H, 3.44; N, 20.48. Found: C, 52.64; H, 3.44; N, 20.39.

5-Amino-3-(4-methylphenyl)isoxazole (6f): ^{1}H NMR ($CDCl_3$, δ, ppm) 2.38 (3H, s, CH_3), 4.48 (2H, s, NH_2), 5.41 (1H, s, CH), 7.22 (2H, d, *J* = 8.2 Hz, ArH), 7.61 (2H, d, *J* = 8.2 Hz, ArH); IR (KBr) (ν, cm^{-1}) 3440, 3152, 1635, 1587, 1558, 1465, 1440, 739. *Anal.* Calcd for $C_{10}H_{10}N_2O$: C, 68.95; H, 5.79; N, 16.08. Found: C, 68.85; H, 5.79; N, 15.99.

5-Amino-3-(4-methoxyphenyl)isoxazole (6g): ^{1}H NMR ($CDCl_3$, δ, ppm) 3.83 (3H, s, CH_3O), 4.55 (2H, s, NH_2), 5.36 (1H, s, CH), 6.93 (2H, d, *J* = 8.8 Hz, ArH), 7.65 (2H, d, *J* = 8.8 Hz, ArH); IR (KBr) (ν, cm^{-1}) 3456, 3152, 1632, 1587, 1520, 1465, 1446, 1251, 1177, 1017, 841, 745. *Anal.* Calcd for $C_{10}H_{10}N_2O_2$: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.08; H, 5.28; N, 14.69.

5-Amino-3-(2-naphthyl)isoxazole (6h): ^{1}H NMR ($CDCl_3$, δ, ppm) 4.54 (2H, s, NH_2), 5.57 (1H, s, CH), 7.49-7.52 (3H, m, ArH), 7.83-7.89 (3H, m, ArH), 8.16 (1H, s, ArH); IR (KBr) (ν, cm^{-1}) 3448, 3176, 1632, 1564, 1465, 1420, 735. *Anal.* Calcd for $C_{13}H_{10}N_2O$: C, 74.27; H, 4.79; N, 13.33. Found: C, 74.15; H, 4.65; N, 13.18.

5-Amino-3-(2-thienyl)isoxazole (6i): ^{1}H NMR ($CDCl_3$, δ, ppm) 4.55 (2H, s, NH_2), 5.38 (1H, s, CH), 7.06-7.12 (1H, m, ArH), 7.35-7.38 (2H, m, ArH); IR (KBr) (ν, cm^{-1}) 3440, 3168, 1628, 1580, 1456, 1225, 841, 704. *Anal.* Calcd for $C_7H_6N_2OS$: C, 50.59; H, 3.64; N, 16.86. Found: C, 50.38; H, 3.56; N, 16.69.

General Procedure for the Preparation of 3-Aryl-1,2,5-thiadiazole-4-carboxamides (7)

(i) Reactions of 6 with Tetrasulfur Tetranitride Antimony(V) Chloride Complex (S_4N_4•$SbCl_5$) (2). A mixture of **6** (0.77 - 1.50 mmol) and **2** (0.77 - 1.50 mmol) in toluene (5 - 7 mL) was heated for 30 min at 100°C by the time the spot corresponding to **6** (R_f = 0.6, EtOAc : *n*-hexane = 1 : 1) had disappeared on TLC. Removal of the solvent *in vacuo* gave a residue, which was chromatographed on a silica gel column (2 × 13 cm). Elution with *n*-hexane gave trace amount of sulfur. Elution with a mixture of EtOAc : *n*-hexane (1 : 1) gave **7**. Yields and melting points of **7** are summarized in Table 1.

4-Phenyl-1,2,5-thiadiazole-3-carboxamide (7a): ^{1}H NMR ($CDCl_3$, δ, ppm) 5.84 (1H, s, NH), 6.91 (1H, s, NH), 7.45-7.49 (3H, m, ArH), 7.80-7.83 (2H, m, ArH); ^{13}C NMR ($CDCl_3$, δ, ppm) 128.5, 129.9, 130.3, 132.5, 152.6, 162.1, 163.3; IR (KBr) (ν, cm^{-1}) 3304, 3160, 1651, 1462, 1430, 1337, 1116, 691; MS (EI) m/z 205 (M^+, 41%), 204 (100), 135 (17), 103 (11). *Anal.* Calcd for $C_9H_7N_3OS$: C, 52.67; H, 3.44; N, 20.47; S, 15.62. Found: C, 52.84; H, 3.12; N, 20.44; S, 15.27.

4-(4-Fluorophenyl)-1,2,5-thiadiazole-3-carboxamide (7b): ^{1}H NMR ($CDCl_3$, δ, ppm) 5.90 (1H, s, NH), 6.96 (1H, s, NH), 7.13 (2H, dd, *J* = 8.7, 8.8 Hz, ArH), 7.82-7.88 (2H, m, ArH); ^{13}C NMR ($CDCl_3$, δ, ppm) 115.2 (d, *J* = 21.9 Hz), 128.3, 131.8 (d, *J* = 8.6 Hz), 151.9, 161.7, 162.0 (d, *J* = 12.8 Hz), 165.4; IR (KBr) (ν, cm^{-1}) 3296, 3152, 1651, 1593, 1507, 1456, 1427, 1337, 1232, 1152, 1116, 835; MS (EI) m/z 223 (M^+, 59%), 153 (30), 121 (20). *Anal.* Calcd for $C_9H_6N_3OFS$: C, 48.42; H, 2.71; N, 18.82; S, 14.36. Found: C, 48.46; H, 2.71; N, 18.69; S, 14.25.

4-(4-Chlorophenyl)-1,2,5-thiadiazole-3-carboxamide (7c): ^{1}H NMR ($CDCl_3$, δ, ppm) 5.88 (1H, s, NH), 6.96 (1H, s, NH), 7.43 (2H, d, *J* = 8.7 Hz, ArH), 7.79 (2H, d, *J* = 8.7 Hz, ArH); ^{13}C NMR ($CDCl_3$, δ, ppm) 128.7, 131.0, 131.4, 136.6, 152.4, 161.9, 162.4; IR (KBr) (ν, cm^{-1}) 3280, 3168, 1651, 1459, 1427, 1337, 1177, 1088, 992, 822; MS (EI) m/z 239 (M^+, 57%), 169 (24), 137 (17). *Anal.* Calcd for $C_9H_6N_3OClS$: C, 45.10; H, 2.52; N, 17.53; S, 13.38. Found: C, 45.08; H, 2.24; N, 17.48; S, 13.64.

3-(4-Bromophenyl)-1,2,5-thiadiazole-4-carboxamide (7d): ^{1}H NMR ($CDCl_3$, δ, ppm) 5.30 (1H, s, NH),

6.98 (1H, s, NH), 7.58 (2H, d, *J* = 8.4 Hz, ArH), 7.70 (2H, d, *J* = 8.4 Hz, ArH); ^{13}C NMR ($CDCl_3$, δ, ppm) 125.0, 131.4, 131.6, 131.7, 152.3, 162.0, 162.3; IR (KBr) (ν, cm^{-1}) 3280, 3168, 1651, 1462, 1427, 1337, 1177, 1120, 1065, 992, 822; MS (EI) m/z 283 (M^+, 54%), 266 (5.9), 215 (19), 181 (13). *Anal.* Calcd for $C_9H_6N_3OBrS$: C, 38.04; H, 2.13; N, 14.79; S, 11.29. Found: C, 38.21; H, 2.16; N, 14.52; S, 11.08.

4-(4-Nitrophenyl)-1,2,5-thiadiazole-3-carboxamide (7e): ^{1}H NMR ($CDCl_3$, d, ppm) 5.83 (1H, s, NH), 7.04 (1H, s, NH), 8.02 (2H, d, *J* = 8.9 Hz, ArH), 8.32 (2H, d, *J* = 8.9 Hz, ArH); ^{13}C NMR ($CDCl_3$, d, ppm) 123.2, 130.9, 138.2, 148.5, 152.2, 160.8, 161.0; IR (KBr) (n, cm^{-1}) 3360, 3200, 1689, 1507, 1340, 1174, 1104, 992, 844; MS (EI) m/z 250 (M^+, 43%), 233 (4.4), 180 (4.4). *Anal.* Calcd for $C_9H_6N_4O_3S$: C, 43.20; H, 2.42; N, 22.39; S, 12.81. Found: C, 43.12; H, 2.42; N, 22.19; S, 12.64.

4-(4-Methylphenyl)-1,2,5-thiadiazole-3-carboxamide (7f): ^{1}H NMR ($CDCl_3$, δ, ppm) 2.40 (3H, s, CH_3), 6.90 (1H, s, NH), 7.25 (2H, d, *J* = 8.0 Hz, ArH), 7.38 (1H, s, NH), 7.72 (2H, d, *J* = 8.0 Hz, ArH); ^{13}C NMR ($CDCl_3$, δ, ppm) 21.4, 128.9, 129.2, 129.4, 139.9, 153.3, 162.0, 162.9; IR (KBr) (ν, cm^{-1}) 3296, 3152, 1651, 1456, 1427, 1337, 1174, 1116, 992, 857; MS (EI) m/z 219 (M^+, 60%), 202 (5.7), 149 (17), 116 (13). *Anal.* Calcd for $C_{10}H_9N_3OS$: C, 54.78; H, 4.14; N, 19.16; S, 14.62. Found: C, 54.74; H, 4.14; N, 18.98; S, 14.34.

4-(4-Methoxyphenyl)-1,2,5-thiadiazole-3-carboxamide (7g): ^{1}H NMR ($CDCl_3$, δ, ppm) 3.88 (3H, s, CH_3O), 5.94 (1H, s, NH), 6.96 (1H, s, NH), 6.99 (2H, d, *J* = 8.8 Hz, ArH), 7.83 (2H, d, *J* = 8.8 Hz, ArH); ^{13}C NMR ($CDCl_3$, δ, ppm) 55.4, 113.6, 124.6, 131.2, 151.8, 161.0, 162.0, 162.6; IR (KBr) (ν, cm^{-1}) 3296, 3152, 1651, 1600, 1507, 1456, 1420, 1337, 1248, 1171, 1027, 825; MS (EI) m/z 235 (M^+, 100%), 220 (12), 165 (27), 133 (24). *Anal.* Calcd for $C_{10}H_9N_3O_2S$: C, 51.05; H, 3.86; N, 17.86; S, 13.63. Found: C, 51.13; H, 3.84; N, 17.69; S, 13.29.

4-(2-Naphthyl)-1,2,5-thiadiazole-3-carboxamide (7h): ^{1}H NMR ($CDCl_3$, δ, ppm) 6.08 (1H, s, NH), 6.92 (1H, s, NH), 7.49-7.55 (2H, m, ArH), 7.84-7.91 (4H, m, ArH), 8.35 (1H, s, ArH); ^{13}C NMR ($CDCl_3$,

δ, ppm) 126.4, 126.6, 127.2, 127.67, 127.70, 128.8, 129.5, 129.7, 132.8, 133.9, 152.4, 162.0, 162.9; IR (KBr) (ν, cm^{-1}) 3312, 3152, 3056, 1651, 1456, 1424, 1331, 1260, 1120, 857; MS (EI) m/z 255 (M^+, 100%), 185 (15), 153 (38). *Anal.* Calcd for $C_{13}H_9N_3OS$: C, 61.16; H, 3.55; N, 16.46; S, 12.56. Found: C, 61.28; H, 3.58; N, 16.31; S, 12.27.

4-(2-Thienyl)-1,2,5-thiadiazole-3-carboxamide (7i): ^{1}H NMR ($CDCl_3$, δ, ppm) 7.11 (1H, dd, *J* = 3.8, 6.2 Hz, ArH), 7.38 (1H, s, NH), 7.51 (1H, d, *J* = 6.2 Hz, ArH), 7.65 (1H, s, NH), 8.16 (1H, d, *J* = 3.8 Hz, ArH); ^{13}C NMR ($CDCl_3$, δ, ppm) 127.7, 129.5, 130.3, 134.5, 152.4, 155.2, 162.9; IR (KBr) (ν, cm^{-1}) 3296, 3152, 1648, 1456, 1324, 1267, 1113, 848; MS (EI) m/z 211 (M^+, 100%), 141 (50), 109 (17). *Anal.* Calcd for $C_7H_5N_3OS_2$: C, 39.80; H, 2.39; N, 19.89; S, 30.36. Found: C, 39.68; H, 2.35; N, 19.65; S, 30.09.

(ii) Reactions of 6 with Tetrasulfur Tetranitride (S_4N_4) (4). A mixture of **6** (1.05 - 2.25 mmol) and **4** (1.05 - 2.25 mmol) in *p*-dioxane (5 - 10 mL) was heated for 30 min at reflux by the time the spot corresponding to **6** (R_f = 0.6, EtOAc : *n*-hexane = 1 : 1) had disappeared on TLC. Removal of the solvent *in vacuo* gave a residue, which was chromatographed on a silica gel column as in the reaction mixture obtained from the reaction with **2**. Elution with EtOAc gave fluorescent unknown mixtures and additional compounds (**8a**) (23%) and (**8b**) (18%) for the reactions of **6b** and **6h**, respectively. Yields and melting points of **7** are listed in Table 1.

6a-Amino-3,5-bis(4-fluorophenyl)-6-oxo-6,6a-dihydro-1-thia-2,4-diazapentalene-3a-carboxamide (8a): mp 191-193°C (EtOAc : *n*-hexane); ^{1}H NMR ($CDCl_3$-DMSO-d_6, δ, ppm) 7.17 (2H, t, *J* = 8.8 Hz, ArH), 7.25 (1H, br s, one of $CONH_2$), 7.33 (2H, t, *J* = 8.8 Hz, ArH), 7.35 (2H, s, NH_2), 7.43 (1H, br s, one of $CONH_2$), 7.60-7.63 (2H, m, ArH), 7.64-7.67 (2H, m, ArH); ^{13}C NMR ($CDCl_3$-DMSO-d_6, δ, ppm) 50.5, 72.4, 115.1 (d, *J* = 19 Hz), 116.5 (d, *J* = 19 Hz), 118.2, 125.4, 129.9 (d, *J* = 8 Hz), 132.2 (d, *J* = 8 Hz), 161.6, 162.2, 162.7 (d, *J* = 250 Hz), 165.1 (d, *J* = 250 Hz), 170.5, 173.5; IR (KBr) (ν, cm^{-1}) 3440, 3296, 3184, 1673, 1625, 1593, 1571, 1515, 1497, 1414, 1395, 1376, 1257, 1228, 1152, 835; FAB MS *m/z* 387 ($(M + 1)^+$, 22%), 154 (100), 122 (13). *Anal.* Calcd for $C_{18}H_{12}N_4O_2F_2S$: C, 55.95; H, 3.13; N, 14.50; S,

8.30. Found: C, 55.65; H, 3.09; N, 14.53; S, 7.99.

6a-Amino-3,5-dinaphthalen-2-yl-6-oxo-6,6a-dihydro-1-thia-2,4-diazapentalene-3a-carboxamide (8b): mp 154-156°C (EtOAc : *n*-hexane); ^{1}H NMR ($CDCl_3$, δ, ppm) 5.39 (1H, s), 5.70 (3H, s), 7.26-7.89 (13H, m, ArH), 8.13 (1H, s, ArH); IR (KBr) (ν, cm^{-1}) 3440, 3312, 3168, 3056, 2928, 1667, 1648, 1619, 1593, 1558, 1459, 1398, 1363, 1315, 1264, 892, 854; FAB MS *m/z* 451 ($(M + 1)^+$, 4.3%), 186 (3.8), 154 (100); HRFAB MS: Calcd *m/z* 451.1150 for $C_{26}H_{19}N_4O_2S$ $[M + 1]^+$. Found *m/z* 451.1216.

General Procedure for the Reactions 7 with $SOCl_2$

To a solution of **7** (0.15 - 0.47 mmol) in dried benzene (2 - 4 mL) was added $SOCl_2$ (1.8 - 5.6 g, 15 - 47 mmol) in benzene (2 - 4 mL). The mixture was stirred for 2 h at reflux, followed by removal of the solvent *in vacuo*. The residue was chromatographed on a silica gel column (2 × 8 cm). Elution with CH_2Cl_2 gave 3-aryl-1,2,5-thiadiazole-4-carbonitriles (**10**).

4-Phenyl-1,2,5-thiadiazole-3-carbonitrile (10a): mp 54-55°C (*n*-hexane) (lit.,[12] 55-56°C); ^{1}H NMR ($CDCl_3$, δ, ppm) 7.56-7.58 (3H, m, ArH), 8.10-8.13 (2H, m, ArH); IR (KBr) (ν, cm^{-1}) 3040, 2224, 1452, 1430, 1376, 1004, 860, 780; MS (EI) m/z 187 (M^+, 100%), 160 (26), 135 (68), 103 (27). *Anal.* Calcd for $C_9H_5N_3S$: C, 57.74; H, 2.69; N, 22.44; S, 17.13. Found: C, 57.76; H, 2.65; N, 22.38; S, 17.05.

4-(4-Chlorophenyl)-1,2,5-thiadiazole-3-carbonitrile (10b): oil; ^{1}H NMR ($CDCl_3$, δ, ppm) 7.54 (2H, d, *J* = 8.7 Hz, ArH), 8.08 (2H, d, *J* = 8.7 Hz, ArH); IR (KBr) (ν, cm^{-1}) 3056, 2224, 1587, 1494, 1398, 1372, 1091, 1001, 854, 838, 816; MS (EI) m/z 221 (M^+, 100%), 169 (72), 137 (46). *Anal.* Calcd for $C_9H_4N_3ClS$: C, 48.77; H, 1.82; N, 18.96; S, 14.47. Found: C, 48.62; H, 1.88; N, 18.72; S, 14.32.

3-(4-Bromophenyl)-1,2,5-thiadiazole-4-carbonitrile (10c): mp 85-87°C (*n*-hexane); ^{1}H NMR ($CDCl_3$, δ, ppm) 7.71 (2H, d, *J* = 8.6 Hz, ArH), 8.00 (2H, d, *J* = 8.6 Hz, ArH); IR (KBr) (ν, cm^{-1}) 3072, 2224, 1580, 1494, 1446, 1395, 1372, 1270, 1065, 998, 857, 835, 819; MS (EI) m/z 265 (M^+, 100%), 213 (49),

181 (31). *Anal.* Calcd for $C_9H_4N_3BrS$: C, 40.62; H, 1.52; N, 15.79; S, 12.05. Found: C, 40.09; H, 1.39; N, 15.64; S, 11.89.

4-(4-Methylphenyl)-1,2,5-thiadiazole-3-carbonitrile (10d): oil; ^{1}H NMR ($CDCl_3$, δ, ppm) 2.45 (3H, s, CH_3), 7.37 (2H, d, *J* = 8.0 Hz, ArH), 8.02 (2H, d, *J* = 8.0 Hz, ArH); IR (neat) (ν, cm^{-1}) 3040, 2224, 1603, 1446, 1372, 1184, 1030, 1004, 854, 819; MS (EI) m/z 201 (M^+, 100%), 174 (16), 149 (40), 117 (28). *Anal.* Calcd for $C_{10}H_7N_3S$: C, 59.68; H, 3.51; N, 20.88; S, 15.93. Found: C, 59.61; H, 3.55; N, 20.69; S, 15.84.

4-(4-Methoxyphenyl)-1,2,5-thiadiazole-3-carbonitrile (10e): oil; ^{1}H NMR ($CDCl_3$, δ, ppm) 3.90 (3H, s, CH_3O), 7.06 (2H, d, *J* = 9.0 Hz, ArH), 8.10 (2H, d, *J* = 9.0 Hz, ArH); IR (neat) (ν, cm^{-1}) 3056, 2928, 2224, 1596, 1510, 1494, 1417, 1376, 1299, 1251, 1174, 1027, 1014, 835; MS (EI) m/z 217 (M^+, 100%), 165 (29), 133 (38). *Anal.* Calcd for $C_{10}H_7N_3OS$: C, 55.29; H, H, 3.25; N, 19.34; S, 14.76. Found: C, 55.18; H, 3.21; N, 19.19; S, 14.39.

Reaction of 7a with BF_3•OEt_2

A mixture of **7a** (45 mg, 0.22 mmol) and BF_3•OEt_2 (156 mg, 1.10 mmol) in MeOH (3 mL) was stirred for 3 days at reflux. Removal of the solvent *in vacuo* gave a residue, which was chromatographed on a silica gel column (2 × 6 cm). Elution with CH_2Cl_2 gave methyl 4-phenyl-1,2,5-thiadiazole-3-carboxylate (**11**) (30 mg, 62%). mp 42-44°C (*n*-hexane) (lit.,[6] 45-46°C).

Reaction of 7a with P_4S_{10}

A mixture of **7a** (50 mg, 0.244 mmol) and P_4S_{10} (108 mg, 0.244 mmol) in pyridine (3 mL) was stirred for 12 h at reflux, followed by neutralization with 10% HCl. The mixture was extracted with CH_2Cl_2 (10 mL × 3). The combined extracts were dried over $MgSO_4$. After the solvent was stripped off, chromatography (2 × 6 cm) of the residue with *n*-hexane gave sulfur. Elution with CH_2Cl_2 gave 4-phenyl-1,2,5-thiadiazole-3-carbonitrile (**10a**) (27 mg, 59%).

***X*-Ray Structure Analysis of Compound (7a)**

Single crystals of **7a** were obtained from the concentrated solutions in CH_2Cl_2. The data were collected on an Enraf-Nomius CAD 4 diffractometer using graphite-monochromated Mo-K_a radiation. The structure was inferred by direct methods and subsequent Fourier maps. Refinements were carried out by full-matrix least-squares techniques. Non-hydrogen atoms were anisotropically refined. Atomic scattering factors were taken from the International Tables for *X*-ray Crystallography, Vol IV, 1974. All calculations and drawings were performed using a Micro VAX II Computer with an SDP system. Crystal data for $C_9H_7N_3OS$ **7a**: M = 205.24, orthorhombic, a = 9.636(5), b = 7.250(2), c = 27.312(4) Å, α = 90.00, β = 90.00, γ = 90.00 deg, V = 1908.0(12) $Å^{-3}$, space group Pca21, Z = 8, 2230 reflections measured, 1903 unique (R_{int} = 0.0503), $R1$ = 0.1067, $wR2$ = 0.2507, *Good F* = 1.084, largest diff. Peak 0.94 $eÅ^{-3}$.

ACKNOWLEDGEMENT

The authors are grateful for the financial support of the Korea Research Foundation made in the program of 1999.

REFERENCES AND NOTES

1. For a good review of isoxazoles: (a) S. A. Lang, Jr. and Y. -I. Lim, Comprehensive Heterocyclic Chemistry, Vol. 6, ed. by A. R. Katritzky and C. W. Rees, Pergamon Press, New York, 1984, pp. 1-130. (b) M. Sutharchanadevi and R. Murugan, Comprehensive Heterocyclic Chemistry II, Vol. 3, ed. by A. R. Katritzky, C. W. Rees, and E. F. V. Scriven, Elsevier Science Inc., New York, 1996, pp. 221-260.
2. K. -J. Kim and K. Kim, *J. Chem. Soc., Perkin Trans. 1*, 1998, 2175.
3. (a) A. Tashiro, A. Murabayashi, and S. Sumimoto, *Heterocycles* 1991, **32**, 1153. (b) T. Nishiwaki and T. Saito, *J. Chem. Soc., Chem. Commun.*, 1971, 3021. (c) I. Iwai and N. Nakamura, *Chem. Pharm. Bull.*, 1966, **14**, 1277.
4. M. Dines and M. L. Sheinbaum, *Tetrahedron Lett.*, 1969, 4817.

5. (a) J. H. Smith and E. T. Kaiser, *J. Org. Chem.*, 1974, **39**, 728. (b) J. H. Smith, J. H. Heidema, and E. T. Kaiser, *J. Am. Chem. Soc.*, 1972, **94**, 9274.
6. S. Mataka, K. Takahashi, Y. Yamada, and M. Tashiro, *J. Heterocycl. Chem.*, 1979, **16**, 1009.
7. B. Rickborn and F. R. Jensen, *J. Org. Chem.*, 1962, **27**, 4608.
8. D. J. Hamilton and M. J. Price, *J. Chem. Soc., Chem. Commun.*, 1969, 414.
9. W. Walter and J. Voss, The Chemistry of Amides, by J. Zabicky, John Wiley and Sons, New York, 1970, chap. 8, pp. 383-475.
10. (a) M. P. Cava and F. M. Scheel, *J. Org. Chem.*, 1967, **32**, 1304. (b) M. P. Cava and J. P. VanMeter, *J. Org. Chem.*, 1969, **34**, 538.
11. N. Baumann, B. Heibel, J. R. Jouanne, H. Keller-Rudek, and A. Kubny, Gmelin's Handbook of Inorganic Chemistry, Sulfur-Nitrogen Compounds, Part 2B; Springer-Verlag: Berlin, 1984; 8 th edn., 1984; chap. 5, p 128.
12. J. F. Engel and J. M. Puglis, *US Patent*, 4,555,521, Nov. 16, 1985, p. 8 (*Chem. Abstr.*, 1986, **104**, 64226b).