

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

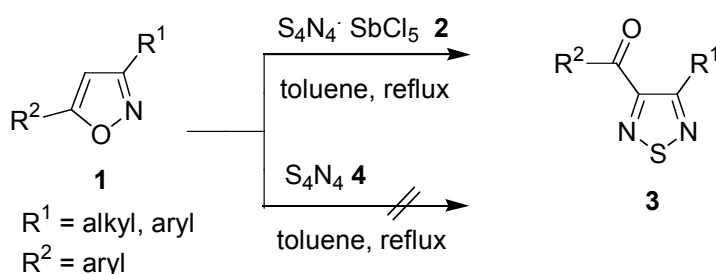
Yung Cheol Kong,^a Kyongtae Kim,^{a,*} and Yung Ja Park^b

^aSchool of Chemistry and Molecular Engineering, Seoul National University, Seoul 151-742, Korea

^bDepartment of Chemistry, Sook Myung Women's University, Seoul 140-724, Korea

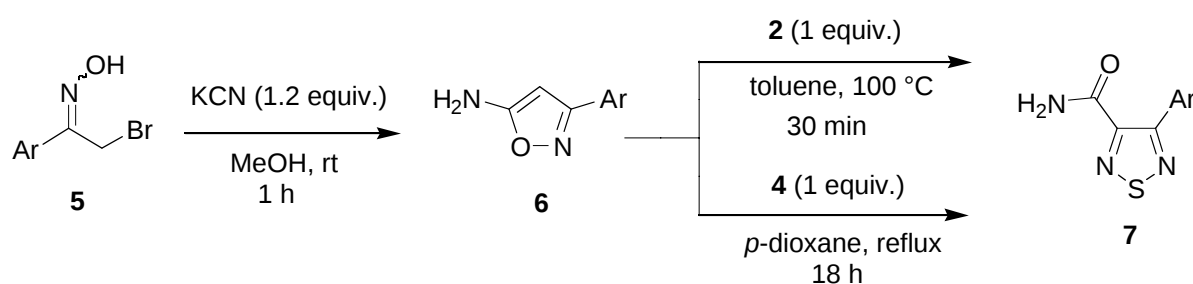
Abstract - Dropwise addition of α -bromo ketoximes to a solution of KCN in MeOH at room temperature gave 5-amino-3-arylisoxazoles in moderate to good yields. Treatment of the isoxazoles prepared with tetrasulfur tetranitride antimony(V) chloride complex ($S_4N_4 \cdot SbCl_5$) in toluene at 100°C afforded 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 ($S_4N_4 \cdot SbCl_5$) (**2**) in toluene at reflux gave 3-alkyl-4-aryloxy- and 3-aryloxy-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 structurally 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 $\text{NH}_2\text{OH}\cdot\text{HCl}$ 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

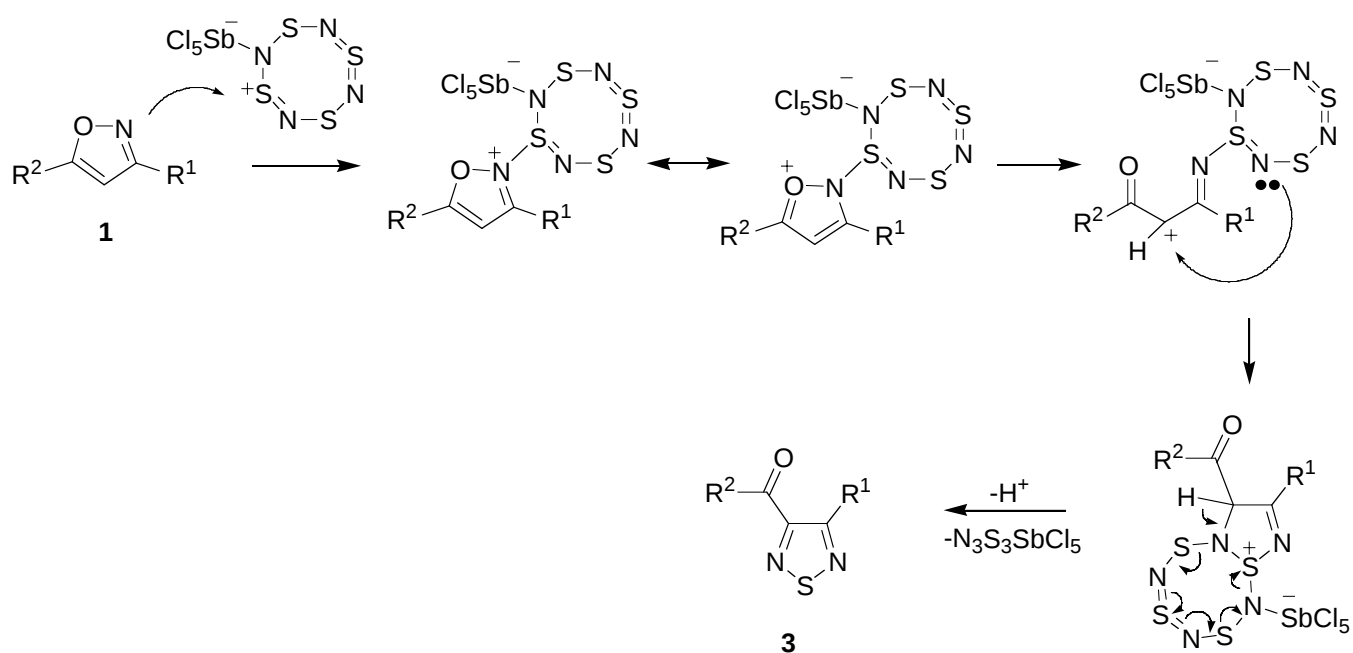
Since the formation of either the acyl or aroyl group of **3** is achieved by cleavage of the O-N bond of **1**, it is envisaged that 1,2,5-thiadiazoles with the desired substituents at C-3 and C-4 can be prepared stereoselectively *via* **1** as shown in Scheme 3.² For example, treatment of **6** with **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 ₆ H ₅	58	110-111 (lit., ^{3c} 110-111)	7a	48 (35)	165-166
6b	4-FC ₆ H ₄	64	104-105	7b	48 (12)	171-172
6c	4-ClC ₆ H ₄	68	154-155 (lit., ^{3b} 165-167)	7c	42 (34)	178-179
6d	4-BrC ₆ H ₄	80	164-166	7d	45 (33)	183-185
6e	4-O ₂ NC ₆ H ₄	35	163-165	7e	27 (26)	225-227
6f	4-MeC ₆ H ₄	62	149-151	7f	51 (31)	196-198
6g	4-MeOC ₆ H 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 CCl₄ and CH₂Cl₂, and CCl₄, 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 CCl₄, and a mixture of CCl₄ and CH₂Cl₂, 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 (¹H and ¹³C 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

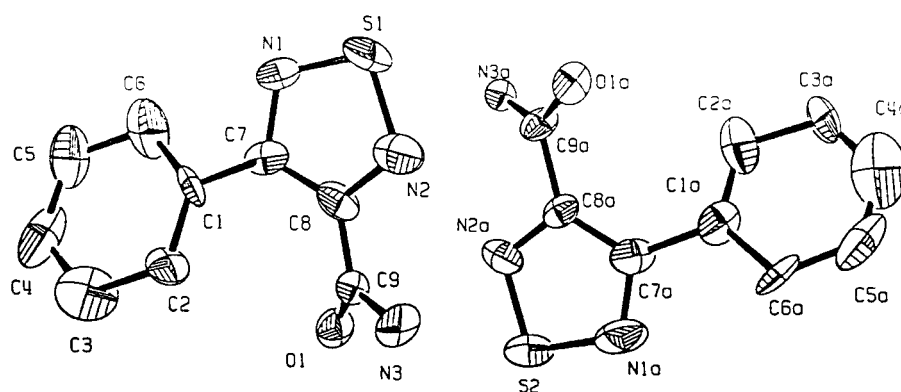
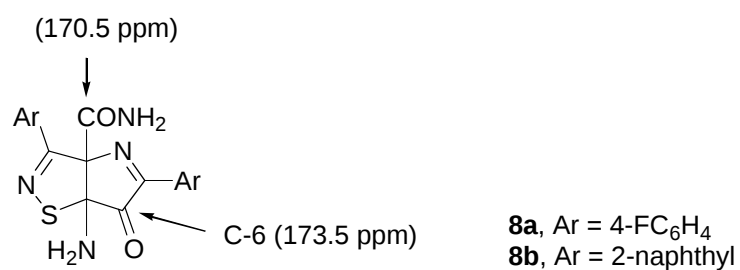


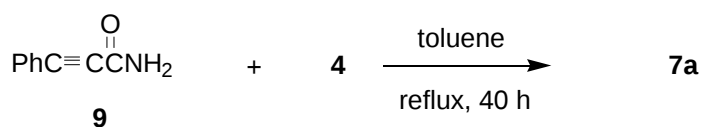
Figure 1 ORTEP drawing of 4-phenyl-1,2,5-thiadiazole-3-carboxamide (**7a**)

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 (^1H and



^{13}C NMR, IR, FAB MS) and analytical data: The ^1H 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 quaternary 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 quaternary 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 quaternary 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 $\text{C}=\text{O}$ stretchings ($1673, 1625\text{ cm}^{-1}$) and NH stretchings ($3440, 3296\text{ cm}^{-1}$). 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 ^1H 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.

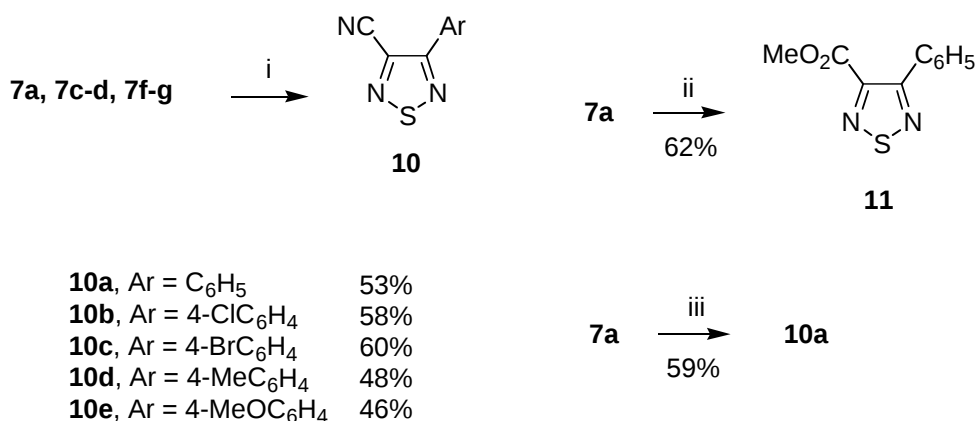
According to the documented procedure,⁶ 3-phenylpropynecarboxamide (**9**) was treated with **4** (0.5 equiv.) in toluene for 40 h at reflux to give **7a** in 12% yield (Scheme 4). The result indicates that the present method involving **6** and **2** is preferable to the documented method involving 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, $\text{RC}(\text{OSOCl})=\text{NH}$, which undergoes



Reagents and Conditions: i. SOCl₂, PhH, reflux, 2 h. ii. BF₃·Et₂O, MeOH, reflux, 3 days.

iii. P₄S₁₀, pyridine, reflux, 12 h.

Scheme 5

elimination by the E1 or E2 mechanism.⁷ On the other hand, heating a mixture of **7a** and BF₃·OEt₂ 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 P₄S₁₀ (1 equiv.) in pyridine at reflux did not yield the corresponding thioamide. Instead, **10a** was obtained in 59% yield. Since P₄S₁₀ is one of the most useful reagents for replacing the oxygen of amides by sulfur⁹ 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 ¹³C NMR spectra were recorded at 300 MHz and 75 MHz, respectively, in CDCl₃ containing Me₄Si 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-arylisoaxazoles (**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 $\times$ 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-phenylisoaxazole (6a): ¹H NMR (CDCl₃, δ , ppm) 4.67 (2H, s, NH₂), 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 C₉H₈N₂O: 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): ¹H NMR (CDCl₃, δ , ppm) 4.60 (2H, s, NH₂), 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 C₉H₇N₂OF: 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): ¹H NMR (CDCl₃, δ , ppm) 4.58 (2H, s, NH₂), 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 C₉H₇N₂OCl: 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): ¹H NMR (CDCl₃, δ , ppm) 4.52 (2H, s, NH₂), 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): 1H 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): 1H 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): 1H 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): 1H 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): 1H 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 ($S_4N_4 \cdot SbCl_5$) (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): 1H 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): 1H 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): 1H 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 $C_9H_6N_3OCIS$: 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): 1H 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 $\text{C}_9\text{H}_6\text{N}_3\text{OBrS}$: 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): ^1H NMR (CDCl_3 , δ , 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 , δ , ppm) 123.2, 130.9, 138.2, 148.5, 152.2, 160.8, 161.0; IR (KBr) (ν , 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 $\text{C}_9\text{H}_6\text{N}_4\text{O}_3\text{S}$: 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): ^1H 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 $\text{C}_{10}\text{H}_9\text{N}_3\text{OS}$: 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): ^1H 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 $\text{C}_{10}\text{H}_9\text{N}_3\text{O}_2\text{S}$: 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): ^1H 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 $\text{C}_{13}\text{H}_9\text{N}_3\text{OS}$: 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): ^1H 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 $\text{C}_7\text{H}_5\text{N}_3\text{OS}_2$: 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); ^1H 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 $\text{C}_{18}\text{H}_{12}\text{N}_4\text{O}_2\text{F}_2\text{S}$: 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); ¹H NMR (CDCl₃, 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 C₂₆H₁₉N₄O₂S [M + 1]⁺. Found *m/z* 451.1216.

General Procedure for the Reactions 7 with SOCl₂

To a solution of **7** (0.15 - 0.47 mmol) in dried benzene (2 - 4 mL) was added SOCl₂ (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 CH₂Cl₂ 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); ¹H NMR (CDCl₃, 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 C₉H₅N₃S: 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; ¹H NMR (CDCl₃, 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 C₉H₄N₃ClS: 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); ¹H NMR (CDCl₃, 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 C₉H₄N₃BrS: 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; ¹H NMR (CDCl₃, δ, ppm) 2.45 (3H, s, CH₃), 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 C₁₀H₇N₃S: 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; ¹H NMR (CDCl₃, δ, ppm) 3.90 (3H, s, CH₃O), 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 C₁₀H₇N₃OS: 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 BF₃•OEt₂

A mixture of **7a** (45 mg, 0.22 mmol) and BF₃•OEt₂ (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 CH₂Cl₂ 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 P₄S₁₀

A mixture of **7a** (50 mg, 0.244 mmol) and P₄S₁₀ (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 CH₂Cl₂ (10 mL × 3). The combined extracts were dried over MgSO₄. After the solvent was stripped off, chromatography (2 × 6 cm) of the residue with *n*-hexane gave sulfur. Elution with CH₂Cl₂ 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 CH₂Cl₂. The data were collected on an Enraf-Nomius CAD 4 diffractometer using graphite-monochromated Mo-K_α 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 C₉H₇N₃OS **7a**: $M = 205.24$, orthorhombic, $a = 9.636(5)$, $b = 7.250(2)$, $c = 27.312(4)$ Å, $\alpha = 90.00$, $\beta = 90.00$, $\gamma = 90.00$ deg, $V = 1908.0(12)$ Å³, space group Pca21, $Z = 8$, 2230 reflections measured, 1903 unique ($R_{\text{int}} = 0.0503$), $R1 = 0.1067$, $wR2 = 0.2507$, $\text{Good } F = 1.084$, largest diff. Peak $0.94 \text{ e}\text{\AA}^{-3}$.

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