Reactions of 5-substituted 3-alkyl- and 3-aryl-isoxazoles with tetrasulfur tetranitride antimony pentachloride complex (S_4N_4·$SbCl_5$): complete regioselective formation of 4-substituted 3-acyl- and 3-aroyl-1,2,5-thiadiazoles and their mechanism of formation

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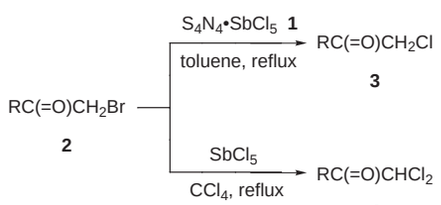
The reactions of 3-alkyl- 5a–f, 3-aryl- 5g–m, 3-acylamido- 5n,p, 3-benzamido- 5o and 3-arylamino- 5q -5-alkyl- and -5-aryl-isoxazoles with tetrasulfur tetranitride antimony pentachloride complex (S_4N_4·$SbCl_5$) in toluene at 90 °C to reflux temperature give 3-acyl- 6a–c, e, n–q and 3-aroyl-4-substituted-1,2,5-thiadiazoles 6d, f–m in 13 to 61% yields as single isomers. The same reactions of 3,4-dimethyl- 5s, 5v, 4-ethyl-3-methyl- 5t -5-alkyl- and/or 5-aryl-isoxazoles under the same conditions give 3-(1-acetyl-1-chloroethyl)- 8a, 3-(1-benzoyl-1-chloropropyl)- 8b, 3-(1-benzoyl-1-chloroethyl)- 8d, or 3-(1-benzoyl-1-chloroethyl)-4-methyl-1,2,5-thiadiazoles 8c, which are a new type of 1,2,5-thiadiazole derivatives. In addition the reactions with 5-aryl-4-bromoisoxazoles (5,w,y,z) having an electron-donating substituent such as methyl, 4-methylphenyl, and 4-methoxyphenyl groups at C3 under the same conditions afford 3-aroyl-4-substituted-1,2,5-thiadiazoles 6d, 6j and 6k, whereas the starting isoxazoles are recovered from the reactions with 5-aryl-4-bromoisoxazoles 5x,z′ having a phenyl or a 4-chlorophenyl group at C3. A plausible mechanism is proposed for the formation of the products.

Introduction

Tetrasulfur tetranitride antimony pentachloride complex (S_4N_4·$SbCl_5$) **1** is reported to be the most stable complex among the S_4N_4–Lewis acid complexes.[1] Its crystal structure was established by X-ray crystallography[2] and its many physical properties have been extensively studied.[1,3] On the other hand, its chemistry has received little attention. Recently[4] we have found that complex **1** is very effective for the conversion of α-(monobromo)methyl ketones **2** into α-chloro analogs **3**, whereas treatment of **2** with $SbCl_5$ gives α,α-di(chloro)methyl ketones **4** (Scheme 1).



Scheme 1

In a continuation of our study on the development of potential synthetic utilities of **1**, isoxazoles attracted our attention, owing not only to their synthesis from 1,3-diketones[5] which had been used as starting materials for the synthesis of 3,4-disubstituted 1,2,5-thiadiazoles,[6] but also due to their utilization as masked 1,3-diketones.[7] We have investigated the reactions of 5-substituted 3-alkyl- and 3-aryl-isoxazoles **5** with **1** in toluene at reflux with the expectation of ring cleavage of **5**, followed by successive reactions leading to new sulfur and nitrogen containing heterocyclic compounds. The results are described herein.

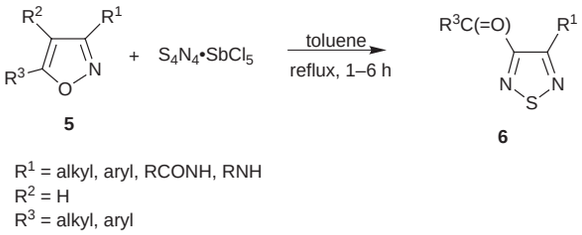
Results and discussion

Numerous isoxazoles **5** were prepared according to the literature procedures.[8a–m] From the reactions of **5** with **1** were isolated 4-substituted 3-acyl- and 3-aroyl-1,2,5-thiadiazoles **6** in fair to moderate yields (Scheme 2). Reaction times, yields and melting points of **6** are summarized in Table 1.

Compounds **6** are all new except for **6d**, **6g**, **6j** and **6l**. The structures of new compounds **6** were identified on the basis of their spectroscopic data and elemental analyses along with comparison of the spectroscopic data and melting points of **6d**, **6g**, **6j** and **6l** with those of the reported values.[6]

There are two reports on the synthesis of 3-alkyl-4-aroyl- and 3-aroyl-4-aryl-1,2,5-thiadiazoles **6**. The first one[6] involves the reactions of 1,3-diketones with S_4N_4 in toluene at reflux for 18 to 72 h. Very recently Rees and co-workers have prepared 3-aroyl-4-methyl- and 4-phenyl-1,2,5-thiadiazoles from 1,3-diketones and $(NSCl)_3$.[9] The reactions of S_4N_4 with various types of organic compounds have attracted much attention because sulfur(s) and nitrogen(s) containing heteroatom compounds and/or heterocyclic compounds can be prepared by a one step process,[10] although dried S_4N_4 is reported to be explosive by shock and at high temperature.[10a] However, the reactions of **5** with S_4N_4 did not occur at all. The reactions involving 1,3-diketones and S_4N_4 as reactants do not seem to be a promising method for the synthesis of **6** for three reasons. First, the reaction may give rise to a mixture of stereoisomers depending upon the substituents bonded to the 1,3-dicarbonyl groups. For example, a mixture of 3-(4-chlorobenzoyl)-4-phenyl- and 3-(4-chlorophenyl)-4-benzoyl-1,2,5-thiadiazoles was obtained in 9 and 17% yields, respectively, from the reaction of 1-benzoyl-1-(4-chlorobenzoyl)methane with S_4N_4.[6] In contrast, the R^3 substituent and the oxygen atom of **5** become either the acyl or aroyl group of compound **6** depending on the R^3 substituent. Therefore, a single stereoisomer is produced regardless of the R^1 substituent of **5**. Secondly, the reported reactions require a longer reaction time (18–72 h) than the reactions involving **1** (1–5 h). Thirdly, in spite of the shorter reaction times, yields of **6d**, **6g** and **6l** (43, 56 and 57%, respectively) (Table 1, entries 6, 10, 17), are higher than the corresponding reported yields of 12, 40 and 17%.[6]

Table 1 (entries 4–7) shows reaction times and yields of **6d** at four different temperatures. The reactions were monitored by the disappearance of the spot corresponding to **5** on TLC (R_f = 0.47, *n*-hexane–CH_3CO_2Et = 4 : 1). When compound **5d**



Scheme 2

Table 1 Reaction times, melting points and yields of **6**

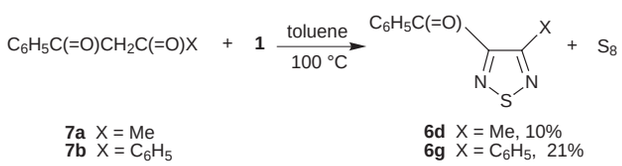
Entry	Compd.	R^1	R^2	R^3	*t*/h	*T*/°C	Product	Yield[a] (%)	Mp[b] (°C)
1	**5a**	Me	H	Me	1	90	**6a**	39	liquid
2	**5b**	Me	H	Et	1	100	**6b**	31	liquid
3	**5c**	Me	H	Pr^n	1	90	**6c**	33	liquid
4	**5d**	Me	H	C_6H_5	4	60	**6d**	33	74 (lit.,[6] 72–73)
5					1.5	90	**6d**	42	
6					1	reflux	**6d**	43	
7					0.5	100[c]	**6d**	36	
8	**5e**	Me	H	$C_6H_5CH_2CH_2$	1	100	**6e**	37	liquid
9	**5f**	Pr^i	H	C_6H_5	1	100	**6f**	46	liquid
10	**5g**	C_6H_5	H	C_6H_5	1	100	**6g**	56	80–81
11					1	reflux	**6g**	47[d]	(lit.,[6] 81–82)
12	**5h**	C_6H_5	H	4-MeC_6H_4	1	100	**6h**	33	128–129
13	**5i**	C_6H_5	H	4-FC_6H_4	1.5	reflux	**6i**	42	88–90
14	**5j**	4-MeC_6H_4	H	4-MeC_6H_4	1	100	**6j**	31	140–141 (lit.,[6] 137–138)
15	**5k**	4-$MeOC_6H_4$	H	4-$MeOC_6H_4$	1	100	**6k**	18	liquid
16	**5l**	4-ClC_6H_4	H	C_6H_5	2	100	**6l**	41[e]	86–88 (lit.,[6] 82–84)
17					3	reflux	**6l**	57	
18	**5m**	4-ClC_6H_4	H	4-ClC_6H_4	4	reflux	**6m**	61	130–131
19	**5n**	MeC(=O)NH	H	Me	1	100	**6n**	57	liquid
20	**5o**	$C_6H_5C(=O)NH$	H	Me	3	reflux	**6o**	56[f]	129–131
21	**5p**	$CF_3C(=O)NH$	H	Me	5	reflux	**6p**	24[g]	143–145
22	**5q**	$C_6H_5CH_2NH$	H	Me	1	100	**6q**	13	liquid
23	**5r**	Cl	H	C_6H_5	1	reflux	**6r**	0[h]	
24					3	reflux		0[i]	

[a] Isolated yields. [b] Solids **6** were recrystallized from *n*-hexane except for **6o** and **6p** (CCl_4) and liquids **6** were yellow in color except for **6f** (yellowish green). [c] 2 Equiv. of S_4N_4·$SbCl_5$ was used, otherwise 1 equiv. of S_4N_4·$SbCl_5$. [d] *p*-Xylene was used as the solvent. [e] Compound **5l** (10%) was recovered. [f] In addition, sulfur (8%) was isolated. [g] In addition, compound **5p** (20%) was recovered. [h] Compound **5r** (69%) was recovered. [i] Compound **5r** (20%) was recovered along with sulfur (5%).

was treated with an equimolar amount of **1**, reaction times decreased from 4 to 1 h when the reaction temperature was changed from 60 °C to reflux temperature, and yields of **6d** increased from 33 to 43% during such temperature changes. On the other hand, when the same reaction was carried out with two molar equivalent amounts of **1** at 100 °C under the same conditions, the reaction was completed in 30 min and **6d** was obtained in 36% yield. On the basis of these results, the rest of the reactions (except for the reactions of **5i**, **5l**, **5o**, **5p** and **5r** which were carried out at reflux temperature to accelerate the reactions) were performed at either 90 or 100 °C employing equimolar amounts of the starting materials *i.e.* **5** and **1**.

In order to examine the differences in reactivity between the two Lewis acids, S_4N_4·$SbCl_5$ and $SbCl_5$, **5d** was treated with an equimolar amount of $SbCl_5$ in CCl_4[11] for 1 h at reflux. The solution turned yellow and some yellow solids were formed. However, no further reaction was seen even after heating at reflux for 1 h. Upon addition of an equimolar amount of S_4N_4 to the yellow solution, the solution turned deep red, which was the same color as that of **1** in toluene. However, only **5d** was recovered in 84% yield after an additional 1 h heating at reflux. Treatment of **5d** with S_4N_4 in the presence of $AlCl_3$ in toluene at reflux for 3.5 h, however, gave only sulfur (6%) as an isolable product. These results indicate that **5d** does not react with either S_4N_4 or $SbCl_5$ alone. Furthermore, although complex **1** would be formed to some extent during the course of the reaction as indicated by the development of a deep red color (*vide supra*), it may not be either of sufficient quantity or purity to initiate the reaction. This view may be consistent with the observation that a reaction time of more than 14 h is needed for the preparation of **1** from S_4N_4 and $SbCl_5$.

Compounds **6**, albeit in low yields, were also formed by the reactions of 1,3-diketones **7** with **1** in toluene at 100 °C for 1 h (Scheme 3). Compounds **6d** (10%) and **6g** (21%) were isolated

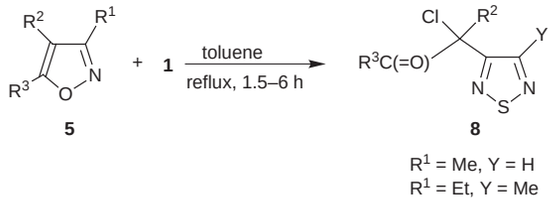


Scheme 3

from the reactions of benzoylacetone **7a** and dibenzoylmethane **7b**, respectively. Yields of **6d** are comparable with that (12%) obtained from the reaction of the same 1,3-diketone with S_4N_4 (ref. 6) but much lower than that obtained from the reaction of **5d** with **1** (Table 1, entry 4), and that (25%) obtained from the reaction of **7a** with $(NSCl)_3$.[9] In addition, compound **6g** has been prepared by the reactions of **7b** and benzylideneacetophenone with $(NSCl)_3$ in 41 and 60% yields, respectively.[9]

Unexpectedly, when compounds **5** have a substituent (R^2 = Me, Et) at C4 in addition to C3 and C5, 1,2,5-thiadiazoles **8** having a (1-acetyl-1-chloroethyl)-, (1-benzoyl-1-chloroethyl)-, or (1-benzoyl-1-chloropropyl)- group at C3 are formed (Scheme 4). Reaction times and yields of **8** are summarized in Table 2.

The structures of compounds **8** were determined based on their spectroscopic and mass spectral data and elemental

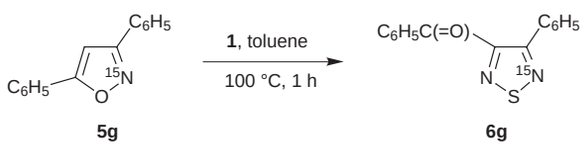


Scheme 4

Table 2 Reaction of isoxazoles **5s–z′** to give compounds **8**

Entry	Compd.	R^1	R^2	R^3	*t*/h	*T*/°C	Product	Yield[a] (%)
1	**5s**	Me	Me	Me	1.5	100	**8a**	14
2	**5t**	Me	Et	C_6H_5	3	reflux	**8b**	13
3	**5u**	Et	Me	C_6H_5	5	reflux	**8c**	36[b]
4	**5v**	Me	Me	C_6H_5	3	reflux	**8d**	21
5	**5w**	Me	Br	C_6H_5	6	reflux	**6d**	41[c]
6	**5x**	C_6H_5	Br	C_6H_5	3	reflux	**5x**	86
7	**5y**	4-MeC_6H_4	Br	4-MeC_6H_4	3	100	**6j**	75[d]
8	**5z**	4-$MeOC_6H_4$	Br	4-$MeOC_6H_4$	3	100	**6k**	42[e]
9	**5z′**	4-ClC_6H_4	Br	4-ClC_6H_4	3	reflux	**5z′**	81

[a] Isolated yields. Compounds **8** are colored liquids: **8a** (pale green); **8b** (green); **8c** (yellow); **8d** (pale yellow). [b] Compound **5u** (9%) was recovered. [c] Compound **5w** (30%) was recovered. [d] Compound **5y** (38%) was recovered. [e] Compound **5z** (28%) was recovered.



Scheme 5

Table 3 Mass spectral data of unlabeled and ^{15}N-labeled **5g** and **6g**

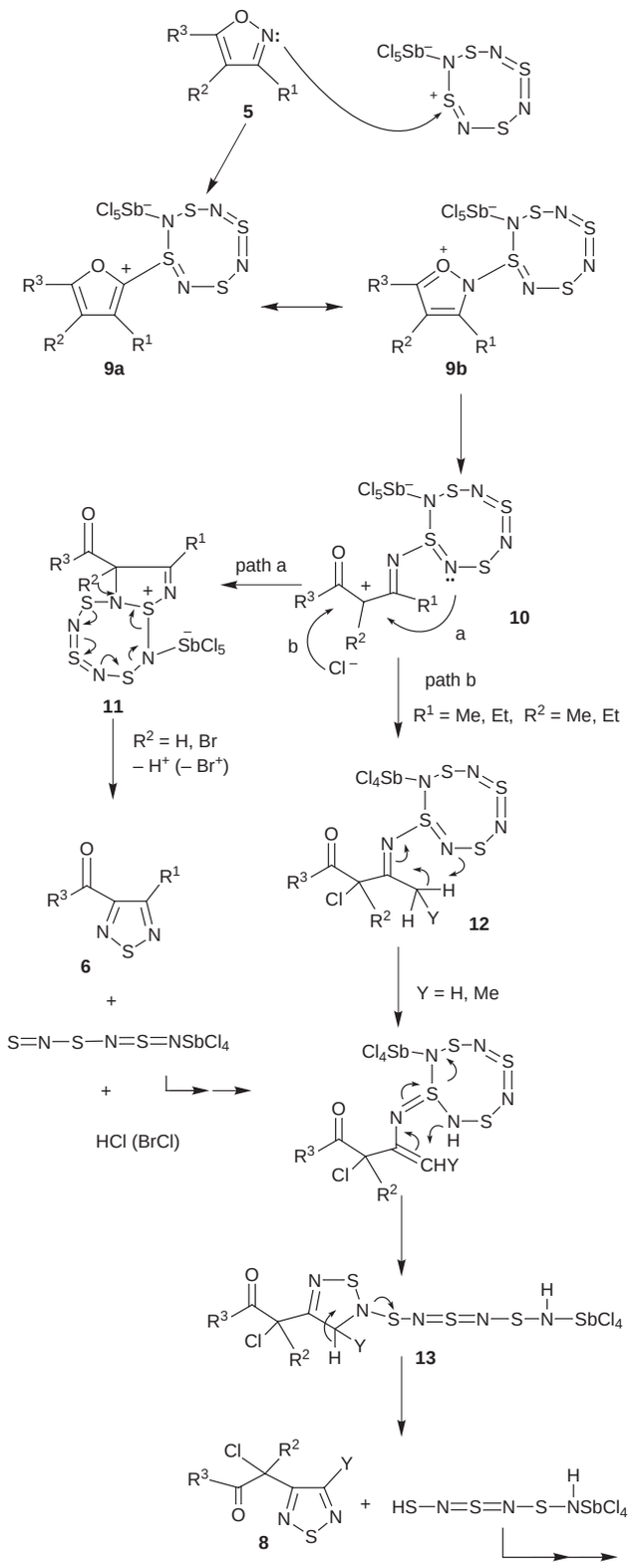
Compound	*m*/*z* (relative intensity)
5g	221 (M^+, 80.57%), 220 ($M^+ - 1$, 22.93), 193 (9.58), 165 (6.27), 144 (19.62), 116 (5.77), 105 (100)
^{15}N-labeled **5g**	222 (M^+, 69.04%), 221 ($M^+ - 1$, 20.08), 220 (6.64), 194 (6.82), 165 (4.81), 145 (16.45), 117 (4.75), 105 (100)
6g	266 (M^+, 85.20%), 265 ($M^+ - 1$, 42.99), 237 (27.58), 219 (5.78), 189 (2.51), 161 (2.39), 135 (10.97), 105 (100), 103 (8.41)
^{15}N-labeled **6g**	267 (M^+, 68.85%), 266 (41.95), 265 (5.24), 238 (21.64), 219 (5.13), 190 (2.70), 162 (1.91), 136 (8.37), 105 (100), 104 (7.55)

analyses. FAB Mass spectral data of **8b–d** showed molecular ion (M^+) peaks, but that of **8a** showed a ($M^+ - Cl$) peak. Compounds **8** were positive to the Beilstein test. To the best of our knowledge, 1,2,5-thiadiazoles having (1-acyl-1-chloro)- and (1-aroyl-1-chloro)-alkyl functionality at C3 have never been reported. Since the R^1 substituent at C3 of **5** is converted to a ring carbon in the 1,2,5-thiadiazoles **8**, compounds **5** having either a phenyl or a substituted phenyl group at C3 ($R^1 = C_6H_5$, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4) could not be converted to **8** (Table 2, entries 6–9) regardless of the R^2 substituent in **5**. In such cases, only isoxazoles were recovered from **5** having $R^1 = C_6H_5$ and 4-ClC_6H_4 (Table 2, entries 6 and 9). On the other hand, in the cases of R^1 = Me, 4-MeC_6H_4 and 4-$MeOC_6H_4$ with R^2 = Br (Table 2, entries 5, 7 and 8), 1,2,5-thiadiazoles **6d**, **6j** and **6k** were formed instead of the corresponding compounds **8** (Table 2, entries 1–4).

In order to identify the origin of the nitrogen atoms of the 1,2,5-thiadiazoles, **7b** was treated with $^{15}NH_2OH{\cdot}HCl$ (95 atom%) to give ^{15}N-labeled **5g** (92%). Mass spectral data showed that 96% of **5g** was labeled. By treatment of ^{15}N-labeled **5g** with **1** under the same conditions as those of unlabeled **5g**, ^{15}N-labeled **6g** was obtained (Scheme 5). Table 3 shows mass spectral data of unlabeled and labeled **5g** and **6g**. The peak at *m*/*z* 265 of ^{15}N-labeled **6g** is thought to originate from the ($M^+ - 1$) fragment of unlabeled **6g** in ^{15}N-labeled **6g**. Consequently, the ratio of ^{15}N-labeled **6g** to unlabeled **6g** is calculated to be 9:1. It is noteworthy that unlabeled **6g** did not show a peak at *m*/*z* 104, corresponding to PhC≡N^{15}, (ref. 12) in spite of exhibiting the corresponding fragment from ^{15}N-labeled **6g**. The results clearly show that the nitrogen atom of **5g** becomes the nitrogen atom at position 5 of **6g**.

The mechanism of the formation of compounds **6** and **8** may be rationalized by nucleophilic attack of the nitrogen atom of isoxazole **5** on a tetravalent sulfur atom of **1** to give a new complex **9a** which may be stabilized by resonance hybridization (Scheme 6). Cleavage of the N–O bond of **9b**, followed by electron delocalization, would give a cation **10**, which undergoes different reactions, depending on the R^2 substituent at C4 of **5**. In the case of R^2 = H, the cation formed α to the carbonyl group is expected to be unstable and a rapid intramolecular nucleophilic attack by the $S_4N_4{\cdot}SbCl_5$ moiety at the cation (path a) occurs to give **11**. Loss of a proton in the case of R^2 = H or that of a bromonium ion (Br^+) in the case of R^2 = Br gives **6**. On the other hand, in the case of R^2 = Me or Et, severe steric hindrance would be expected from nucleophilic attack by the bulky $S_4N_4{\cdot}SbCl_5$ moiety. Consequently, chloride ion attacks the tertiary cation to give a tertiary chloride **12**. Loss of a proton from the alkyl R^1 substituent, *i.e.* R^1 = Me, Et, followed by cyclization, gives an intermediate **13**, which undergoes aromatization to give compounds **8**.

Failure to form **6r** in the case of R^1 = Cl (Table 1, entries 23–24) may be explained by assuming either weak nucleophilicity of compound **5** due to the presence of a strong electron-withdrawing chlorine atom at C3 so that the initial interaction leading to an intermediate **9a** would not occur, or destabilization of the cation **10** due to the inductive electron-withdrawing effect by a chlorine atom α to the cationic center. Even though the formation of **6d** (Table 2, entry 5) at reflux temperature



Scheme 6

might be facilitated by the presence of an electron-withdrawing methyl group (R^1 = Me), it still resulted in 30% of **5w** being recovered. By introducing an electron-donating substituent, *e.g.* Me or MeO (Table 2, entries 7–8), the reactions proceeded at 100 °C to give **6j** and **6k** in 75 and 42% yields, respectively. The bromine atom (R^2 = Br) could be eliminated as a bromonium ion to give **6d**, **6j** and **6k** (entries 5, 7 and 8) whereas only **5x** and **5z**′ were recovered in the case of $R^1 = C_6H_5$, 4-ClC_6H_4 and R^2 = Br (Table 2, entries 6 and 9). The fact that the reactions with compounds **5** having $R^1 = R^3 = C_6H_5$ and 4-ClC_6H_4 afford only the starting materials, whereas those with $R^1 = R^3$ = 4-MeC_6H_4 and 4-$MeOC_6H_4$ give compound **6** supports the involvement of intermediates **9a** and **10**, which have a cationic center, stabilized by electron-donating substituents R^1 and R^3.

In summary, the reactions of 3,5-disubstituted isoxazoles with tetrasulfur tetranitride antimony pentachloride complex (S_4N_4·$SbCl_5$) in toluene at 90 °C to reflux temperature gave either 3-acyl- or 3-aroyl-4-substituted-1,2,5-thiadiazoles **6** or 3-(1-acyl-or 1-aroyl-1-chloroethyl)-4-substituted-1,2,5-thiadiazoles **8** as the major product depending on the substituents at C3, C4 and C5 of the starting isoxazoles. In particular, when the 4-methoxyphenyl or 4-methylphenyl group was substituted at C3 of an isoxazole, 1,2,5-thiadiazoles **6** were formed, whereas if a phenyl or 4-chlorophenyl group was placed at the same site, the reaction did not proceed. This may be due to either weak nucleophilicity of the corresponding isoxazoles or destabilization of the cationic intermediate **10** caused by an electron-withdrawing substituent at C3 of the starting isoxazoles.

Experimental

The ^{1}H NMR spectra were recorded at 80 MHz in $CDCl_3$ solution containing tetramethylsilane as an internal standard. IR Spectra were recorded in KBr or as thin films on KBr plates. Mass spectral data were obtained by electron impact at 70 eV at the Inter-University Center for Natural Sciences Research Facilities. Elemental analyses were determined by the Korea Basic Science Center. Column chromatography was performed using silica gel (70–230 mesh, Merck). Melting points are uncorrected.

Tetrasulfur tetranitride[9] and tetrasulfur tetranitride antimony pentachloride complex (S_4N_4·$SbCl_5$) **1**[1] were prepared according to the literature procedure.

Substituted isoxazoles **5a**–**z** were all known except for **5q**, **5t**, **5y**, **5z** and **5z**′ and were prepared by the literature procedures: 3,5-dimethylisoxazole **5a**, liquid,[8a] 5-ethyl-3-methylisoxazole **5b**, liquid;[8a] 3-methyl-5-(*n*-propyl)isoxazole **5c**, liquid;[8a] 3-methyl-5-phenylisoxazole **5d**, mp 64–65 °C (*n*-hexane) (lit.,[6] 62–64 °C); 3-methyl-5-(2-phenylethyl)isoxazole **5e**, liquid;[8a] 3-isopropyl-5-phenylisoxazole **5f**, liquid;[8b] 3,5-diphenylisoxazole **5g**, mp 143–145 °C ($CHCl_3$–CCl_4) (lit.,[8c] 141–142.5 °C); 5-(4-methylphenyl)-3-phenylisoxazole **5h**, mp 136–137 °C ($CHCl_3$) (lit.,[8d] 136 °C); 5-(4-fluorophenyl)-3-phenylisoxazole **5i**, mp 169–170 °C (lit.,[8e] 165–166 °C); 3,5-bis(4-methylphenyl)-isoxazole **5j**, mp 154–155 °C ($CHCl_3$–CCl_4) (lit.,[8f] 152–152.5 °C); 3,5-bis(4-methoxyphenyl)isoxazole **5k**, mp 175–176 °C (CCl_4–$CHCl_3$) (lit.,[8g] 176–177 °C); 3-(4-chlorophenyl)-5-phenylisoxazole **5l**, mp 176–178 °C ($CHCl_3$) (lit.,[8d] 178 °C); 3,5-bis(4-chlorophenyl)isoxazole **5m**, mp 193–194 °C (CCl_4–$CHCl_3$) (lit.,[8h] 192–194 °C); 3-acetamido-5-methylisoxazole **5n**, mp 178–180 °C (EtOH) (lit.,[8i] 179.5–181 °C); 3-benzamido-5-methylisoxazole **5o**, mp 163–164 °C (EtOH) (lit.,[8i] 162–163 °C); 3-trifluoroacetamido-5-methylisoxazole **5p**, mp 208–210 °C (EtOH) (lit.,[8j] 210–210.5 °C); 3-chloro-5-phenylisoxazole **5r**, mp 35–36 °C (*n*-hexane) (lit.,[8j] 36–37 °C); 3,4,5-trimethylisoxazole **5s**, liquid;[8k] 3-ethyl-4-methyl-5-phenylisoxazole **5u**, liquid;[8l] 3,4-dimethyl-5-phenylisoxazole **5v**, mp 47 °C (*n*-hexane) (lit.,[8l] 47–48 °C); 4-bromo-3-methyl-5-phenylisoxazole **5w**, liquid (lit.,[8m] 25–26 °C); 4-bromo-3,5-diphenylisoxazole **5x**, mp 133–134 °C (CCl_4) (lit.,[8m] 133–135 °C).

3-Benzylamino-5-methylisoxazole 5q

To a solution of 3-amino-5-methylisoxazole (1.50 g, 15.3 mmol) in water (50 ml) was added $NaHCO_3$ (402 mg, 4.78 mmol). The solution was heated at 90 °C and then benzyl chloride (483 mg, 3.83 mmol) was added dropwise. The mixture was additionally stirred for 3 h and then cooled to room temperature. The mixture was extracted with dichloromethane (100 ml × 2). The combined extracts were dried over $MgSO_4$. Removal of the solvent gave a residue, which was chromatographed on a silica gel column (2.5 × 7 cm). Elution with a mixture of *n*-hexane

and ethyl acetate (9:1) gave unreacted benzyl chloride. Elution next with the same solvent mixture (4:1) gave **5q** (584 mg, 81%) (liquid) (Found: C, 70.21; H, 6.41; N, 14.85. $C_{11}H_{12}N_2O$ requires C, 70.19; H, 6.43; N, 14.88%); ν_{max}(neat)/cm^{-1} 3296, 1619, 1539, 1443, 1386, 1350, 1027, 889, 771, 732, 691; δ_H(80 MHz; $CDCl_3$) 2.17 (3H, s, CH_3), 4.30 (2H, s, br, CH_2), 5.42 (1H, s, C4-H), 7.09–7.42 (6H, m, ArH, NH).

4-Ethyl-3-methyl-5-phenylisoxazole 5t

Compound **5t** was prepared according to the literature procedure[5] (liquid) (Found: C, 76.95; H, 6.98; N, 7.51. $C_{12}H_{13}NO$ requires C, 76.98; H, 7.00; N, 7.48%); ν_{max}(neat)/cm^{-1} 2960, 1619, 1436, 1414, 1059, 1011, 953, 908, 768, 713, 691; δ_H(80 MHz; $CDCl_3$) 1.18 (3H, t, *J* 8, CH_3CH_2), 2.27 (3H, s, CH_3), 2.59 (2H, q, *J* 8, CH_3CH_2), 7.30–7.79 (5H, m, ArH).

4-Bromo-3,5-bis(4-methylphenyl)isoxazole 5y

Compound **5y** was prepared according to the literature procedure:[8j] mp 175–177 °C (CCl_4) (Found: C, 62.14; H, 4.32; N, 4.30. $C_{17}H_{14}BrNO$ requires C, 62.19; H, 4.30; N, 4.27%); ν_{max}(KBr)/cm^{-1} 1603, 1580, 1555, 1491, 1411, 1369, 1177, 1100, 988, 924, 816, 720; δ_H(80 MHz; $CDCl_3$) 2.42 (6H, s, $2CH_3$), 7.30 (4H, d, *J* 7, ArH), 7.76 (2H, d, *J* 7, ArH), 7.98 (2H, d, *J* 7, ArH).

4-Bromo-3,5-bis(4-methoxyphenyl)isoxazole 5z

Compound **5z** was prepared according to the literature procedure:[8j] mp 146–147 °C (CCl_4) (Found: C, 56.70; H, 3.91; N, 3.88. $C_{17}H_{14}BrNO_3$ requires C, 56.67; H, 3.92; N, 3.89%); ν_{max}(KBr)/cm^{-1} 1600, 1491, 1417, 1372, 1292, 1251, 1177, 1100, 1020, 928, 828, 729; δ_H(80 MHz; $CDCl_3$) 3.84 (6H, s, $2CH_3O$), 7.00 (4H, d, *J* 7, ArH), 7.82 (2H, d, *J* 7, ArH), 8.04 (2H, d, *J* 7, ArH).

4-Bromo-3,5-bis(4-chlorophenyl)isoxazole 5z′

Compound **5z′** was prepared according to the literature procedure:[8j] mp 124–126 °C (CCl_4) (Found: C, 48.77; H, 2.19; N, 3.81. $C_{15}H_8BrCl_2NO$ requires C, 48.81; H, 2.18; N, 3.79%); ν_{max}(KBr)/cm^{-1} 1596, 1475, 1404, 1088, 1011, 931, 822, 723; δ_H(80 MHz; $CDCl_3$) 7.50 (4H, d, *J* 8, ArH), 7.81 (2H, d, *J* 8, ArH), 8.03 (2H, d, *J* 8, ArH).

General procedure for the synthesis of 4-substituted 3-acyl- and 3-aroyl-1,2,5-thiadiazoles 6 and 3-(1-acetyl-1-chloro- and 3-(1-benzoyl-1-chloro-alkyl)-1,2,5-thiadiazoles 8

To a solution of **5** (1.00–2.76 mmol) in toluene (30 ml) was added **1** (1.00–3.00 mmol), which was heated for the appropriate time. The color of the solution immediately turned dark. The reaction mixture was cooled to room temperature when a spot corresponding to **5** (R_f = 0.47, *n*-hexane–CH_3CO_2Et = 4:1) had disappeared on TLC. The reaction mixture was filtered to remove the toluene-insoluble solids. After removal of toluene *in vacuo*, the residue was chromatographed on a silica gel column (2.5 × 5 cm). Elution with *n*-hexane gave a trace amount of sulfur. Elution next with a mixture of *n*-hexane and benzene (3:1) gave unreacted S_4N_4 (less than 10 mg). Elution with the same solvent mixture (1:1) gave **6**. When compound **5** had a substituent (R^2 = Me, Et) at C4, elution with a mixture of CCl_4 and $CHCl_3$ (2:1) gave **8**. When R^2 was Br (**5x**), elution with a mixture of CCl_4 and $CHCl_3$ (2:1) gave the starting compound **5x** (30%). Elution with the same solvent mixture gave **6d** (41%). Consult Table 1 and Table 2 for the melting points of **6** and the reaction conditions and yields to form **6** and **8**, respectively.

3-Acetyl-4-methyl-1,2,5-thiadiazole 6a. (Found: C, 42.21; H, 4.26; N, 19.66; S, 22.58. $C_5H_6N_2OS$ requires C, 42.24; H, 4.25; N, 19.70; S, 22.55%); ν_{max}(neat)/cm^{-1} 1689, 1398, 1232, 1065, 947, 848, 828, 768, 617; δ_H(80 MHz; $CDCl_3$) 2.17 [3H, s, $CH_3C(=O)$], 2.81 (3H, s, CH_3).

3-Methyl-4-propanoyl-1,2,5-thiadiazole 6b. (Found: C, 46.11; H, 5.17; N, 17.88; S, 20.50. $C_6H_8N_2OS$ requires C, 46.14; H, 5.16; N, 17.93; S, 20.52%); ν_{max}(neat)/cm^{-1} 2960, 1689, 1398, 1194, 1075, 1008, 928, 828, 774; δ_H(80 MHz; $CDCl_3$) 1.20 (3H, t, *J* 8, CH_3CH_2), 2.80 (3H, s, CH_3), 3.20 (2H, q, *J* 8, CH_3CH_2).

3-(*n*-Butanoyl)-4-methyl-1,2,5-thiadiazole 6c. (Found: C, 49.41; H, 5.90; N, 16.44; S, 18.88. $C_7H_{10}N_2OS$ requires C, 49.39; H, 5.92; N, 16.46; S, 18.83%); ν_{max}(neat)/cm^{-1} 2960, 1697, 1452, 1398, 1190, 966; δ_H(80 MHz; $CDCl_3$) 0.97 (3H, t, *J* 8, CH_3CH_2), 1.72 (2H, quintet, *J* 8, $CH_3CH_2CH_2$), 2.78 (3H, s, CH_3), 3.13 (2H, t, *J* 8, $CH_3CH_2CH_2$).

3-Methyl-4-(3-phenylpropanoyl)-1,2,5-thiadiazole 6e. (Found: C, 62.10; H, 5.19; N, 12.03; S, 13.83. $C_{12}H_{12}N_2OS$ requires C, 62.05; H, 5.21; N, 12.06; S, 13.80%); ν_{max}(neat)/cm^{-1} 3008, 2912, 1686, 1484, 1398, 1027, 950, 828, 694; δ_H(80 MHz; $CDCl_3$) 2.77 (3H, s, CH_3), 3.05 (2H, t, *J* 8, PhCH_2), 3.48 (2H, t, *J* 8, CH_2CH_2), 7.23 (5H, s, ArH).

3-Benzoyl-4-isopropyl-1,2,5-thiadiazole 6f. (Found: C, 62.08; H, 5.20; N, 12.08; S, 13.84. $C_{12}H_{12}N_2OS$ requires C, 62.05; H, 5.21; N, 12.06; S, 13.80%); ν_{max}(neat)/cm^{-1} 2976, 1657, 1590, 1446, 1392, 1337, 1286, 1219, 1078, 912, 694; δ_H(80 MHz; $CDCl_3$) 1.34 (6H, d, *J* 8, $2CH_3$), 3.73 [1H, septet, *J* 8, $CH(CH_3)_2$], 7.38–7.68 (3H, m, ArH), 7.92–8.18 (2H, m, ArH).

3-(4-Methylbenzoyl)-4-phenyl-1,2,5-thiadiazole 6h. (Found: C, 68.50; H, 4.33; N, 10.01; S, 11.40. $C_{16}H_{12}N_2OS$ requires C, 68.55; H, 4.31; N, 9.99; S, 11.44%); ν_{max}(KBr)/cm^{-1} 1667, 1590, 1446, 1385, 1273, 1248, 1158, 1078, 1011, 896, 822, 688; δ_H(80 MHz; $CDCl_3$) 2.30 (3H, s, CH_3), 7.00–8.08 (9H, m, ArH).

3-(4-Fluorobenzoyl)-4-phenyl-1,2,5-thiadiazole 6i. (Found: C, 63.35; H, 3.18; N, 9.88; S, 11.30. $C_{15}H_9FN_2OS$ requires C, 63.37; H, 3.19; N, 9.85, S, 11.28%); ν_{max}(KBr)/cm^{-1} 1657, 1584, 1494, 1456, 1408, 1273, 1232, 1152, 896, 755, 694; δ_H(80 MHz; $CDCl_3$) 7.09–8.14 (9H, m, ArH).

3-(4-Methoxybenzoyl)-4-(4-methoxyphenyl)-1,2,5-thiadiazole 6k. (Found: C, 62.55; H, 4.30; N, 8.55; S, 9.85. $C_{17}H_{14}N_2O_3S$ requires C, 62.56; H, 4.32; N, 8.58; S, 9.82%); ν_{max}(neat)/cm^{-1} 1651, 1593, 1449, 1414, 1385, 1302, 1254, 1152, 896; δ_H(80 MHz; $CDCl_3$) 3.77 (3H, s, OCH_3 at C3), 3.84 (3H, s, OCH_3 at C4), 6.69–7.18 (4H, m, ArH), 7.52–8.17 (4H, m, ArH).

3-(4-Chlorobenzoyl)-4-(4-chlorophenyl)-1,2,5-thiadiazole 6m. (Found: C, 53.71; H, 2.42; N, 8.33; S, 9.52. $C_{15}H_8Cl_2N_2OS$ requires C, 53.75; H, 2.41; N, 8.36; S, 9.56%); ν_{max}(KBr)/cm^{-1} 1657, 1577, 1478, 1430, 1395, 1369, 1273, 1155, 1088, 1008, 892, 768; δ_H(80 MHz; $CDCl_3$) 7.20–8.00 (8H, m, ArH).

3-Acetamido-4-acetyl-1,2,5-thiadiazole 6n. (Found: C, 38.88; H, 3.80; N, 22.70; S, 17.35. $C_6H_7N_3O_2S$ requires C, 38.91; H, 3.81; N, 22.69; S, 17.31%); ν_{max}(KBr)/cm^{-1} 3296, 1699, 1670, 1523, 1488, 1417, 1369, 1235, 1081, 1014, 960, 876, 841, 688; δ_H(80 MHz; $CDCl_3$) 2.36 [3H, s, $CH_3C(=O)NH$], 2.75 [3H, s, $CH_3C(=O)$], 10.43 (1H, s, NH).

3-Acetyl-4-benzamido-1,2,5-thiadiazole 6o. (Found: C, 53.40; H, 3.66; N, 16.95; S, 12.99. $C_{11}H_9N_3O_2S$ requires C, 53.43; H, 3.67; N, 16.99; S, 12.97%); ν_{max}(KBr)/cm^{-1} 3296, 1692, 1664, 1529, 1491, 1379, 1321, 1248, 1104, 1056, 1020, 969, 832, 796, 704; δ_H(80 MHz; $CDCl_3$) 2.80 (3H, s, CH_3), 7.38–7.75 (3H, m, ArH), 7.86–8.19 (2H, m, ArH), 11.40 (1H, s, NH).

3-Acetyl-4-trifluoroacetamido-1,2,5-thiadiazole 6p. (Found: C, 30.15; H, 1.67; N, 17.55; S, 13.44. $C_6H_4F_3N_3O_2S$ requires C, 30.13; H, 1.69; N, 17.57; S, 13.40%); ν_{max}(KBr)/cm^{-1} 3264, 1744, 1670, 1542, 1494, 1296, 1136; δ_H(80 MHz; $CDCl_3$) 2.78 (3H, s, CH_3), 11.40 (1H, s, NH).

3-Acetyl-4-benzylamino-1,2,5-thiadiazole 6q. (Found: C, 56.60; H, 4.77; N, 18.05; S, 13.70. $C_{11}H_{11}N_3OS$ requires C, 56.63; H, 4.75; N, 18.01; S, 13.74%); ν_{max}(neat)/cm^{-1} 3376, 1664, 1542, 1484, 1372, 1017, 944, 729, 697, 624; δ_H(80 MHz; $CDCl_3$) 2.66 (3H, s, CH_3), 4.64 (2H, d, *J* 7, $ArCH_2$), 7.19–7.66 (6H, m, ArH, NH).

3-(1-Acetyl-1-chloroethyl)-1,2,5-thiadiazole 8a. (Found: C, 37.77; H, 3.68; N, 14.66; S, 16.85. $C_6H_7ClN_2OS$ requires C, 37.80; H, 3.70; N, 14.69; S, 16.82%); ν_{max}(neat)/cm^{-1} 1718, 1433, 1347, 1196, 1107, 1091, 1056, 960, 886, 838, 793, 742; δ_H(80

MHz; $CDCl_3$) 2.11 (3H, s, $CClCH_3$), 2.34 [3H, s, $CH_3C(=O)$], 8.74 (1H, s, C4-H).

3-(1-Benzoyl-1-chloropropyl)-1,2,5-thiadiazole 8b. (Found: C, 54.00; H, 4.14; N, 10.53; S, 12.05. $C_{12}H_{11}ClN_2OS$ requires C, 54.03; H, 4.16; N, 10.50; S, 12.02%); ν_{max}(neat)/cm^{-1} 2960, 1683, 1587, 1443, 1232, 1072, 1008, 982, 905, 822, 787, 694, 518; δ_H(80 MHz; $CDCl_3$) 0.94 (3H, t, *J* 8, CH_3CH_2), 2.59 (2H, q, *J* 8, CH_3CH_2), 7.17–7.82 (5H, m, ArH), 8.79 (1H, s, C4-H).

3-(1-Benzoyl-1-chloroethyl)-4-methyl-1,2,5-thiadiazole 8c. (Found: C, 54.05; H, 4.15; N, 10.51; S, 12.06. $C_{12}H_{11}ClN_2OS$ requires C, 54.03; H, 4.16; N, 10.50; S, 12.02%); ν_{max}(neat)/cm^{-1} 1686, 1436, 1235, 1081, 691, 627; δ_H(80 MHz; $CDCl_3$) 2.34 (3H, s, $CClCH_3$), 2.47 (3H, s, C4-CH_3), 7.24–7.86 (5H, m, ArH).

3-(1-Benzoyl-1-chloroethyl)-1,2,5-thiadiazole 8d. (Found: C, 52.22; H, 3.61; N, 11.07; S, 12.65. $C_{11}H_9ClN_2OS$ requires C, 52.28; H, 3.59; N, 11.08; S, 12.69%); ν_{max}(neat)/cm^{-1} 1689, 1587, 1440, 1248, 1100, 1052, 976, 950, 688; δ_H(80 MHz; $CDCl_3$) 2.18 (3H, s, CH_3), 7.19–7.87 (5H, m, ArH), 8.82 (1H, s, C4-H).

General procedure for the reactions of 1,3-diketones with 1

To a solution of a 1,3-diketone (1.4–1.5 mmol) in toluene (30 ml) was added **1** (1.4–1.5 mmol), which was heated for 1 h at 100 °C. The mixture was worked-up as described for the synthesis of **6**. From the reaction of benzoylacetone **7a** were isolated **6d** (10%) and sulfur (8%). Similarly, **6g** (21%) and a trace amount of sulfur were isolated from the reaction with dibenzoylmethane **7b**.

Reaction of 5d with antimony pentachloride ($SbCl_5$)

To a solution of **5d** (239 mg, 1.50 mmol) in CCl_4 (30 ml) was added $SbCl_5$ (449 mg, 1.50 mmol). Yellow solids immediately formed, and the mixture was heated for 1 h at reflux. TLC (R_f 0.47 *n*-hexane–CH_3CO_2Et = 4 : 1) showed only one spot corresponding to **5d**. Upon addition of S_4N_4 (216 mg, 1.50 mmol) to the yellow solution, the color of the solution turned immediately deep red. Additional heating for 1 h, following by work-up as usual gave **5d** (200 mg, 84%).

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