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Total synthesis of 3,3′:4′,3″-ter-1,2,5-thiadiazole using a synthetic utility of $S_4N_4 \cdot SbCl_5$ complex

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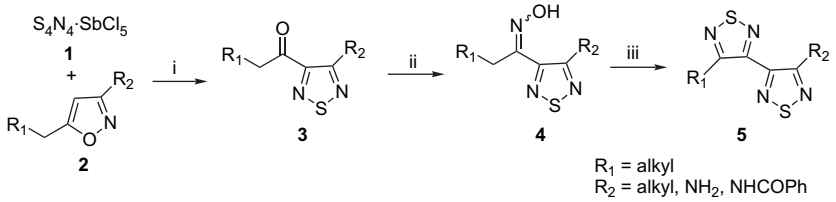
Abstract—3,3′:4′,3″-Ter-1,2,5-thiadiazole, an useful oligoheterocyclic compound, has been accomplished in seven steps from 1-(5-methyl-3-isoxazolyl)ethanone or diethyl acetylenedicarboxylate using a synthetic utility of tetrasulfur tetranitride antimony pentachloride ($S_4N_4 \cdot SbCl_5$) complex to make a 1,2,5-thiadiazole ring.

1. Introduction

The thiadiazole compounds have been broadly applied in the areas of electronics, nonlinear optics, sensors, or corrosion protection as well as pharmaceutical, agricultural, and polymer chemistries.[1] In particular, oligoheterocyclic compounds such as ter-1,2,5-thiadiazole have attracted much attention of both physical and organic chemists since they appear as nonlinear structural subunits in conducting polymer like polypyrroles and polythiophenes.[2] These are systems of growing interest in material science in view of the potential technological application in fields such as electronics, nonlinear optics, sensors, or corrosion protection.[3] However, there has been no general method to synthesize oligo-1,2,5-thiadiazole compound such as ter-1,2,5-thiadiazole, and as a result, its study has been restricted to computational chemistry without real substance. 3,4″-Diphenyl-3,3′:4′,3″-ter-1,2,5-thiadiazole prepared by very complex reaction of 1,6-diphenylhexa-1,3,5-triene with $(NSCl)_3$ is the only compound commented briefly on its preparation among other major works.[4] However, a detailed description about its reaction conditions and results was not shown.

We are interested in exploiting the potential synthetic utility of $S_4N_4 \cdot SbCl_5$ complex (**1**) in view of the synthesis of various heterocyclic compounds.[5] In particular, recently, we reported a new method to synthesize 4,4′-disubstituted-3,3′-bi-1,2,5-thiadiazoles (**5**) with ease using **1**, in which we showed two rings of bi-1,2,5-thiadiazole compound could be made one by one (Scheme 1).[6] It is a unique property of **1** unlike free S_4N_4 and other reagents utilized for the synthesis of heterocyclic compounds.

Based on those results, it was expected that if the substituents at C-4 or C-4′ contained ketone group, it could give another 1,2,5-thiadiazole ring by the reaction of its ketoxime with **1** to make ter-1,2,5-thiadiazole compound. The synthetic study of 3,3′:4′,3″-ter-1,2,5-thiadiazole (**16**), the simplest ter-1,2,5-thiadiazole compound, is described herein.



Scheme 1. Synthesis of bi-1,2,5-thiadiazole compound: (i) toluene, 100 °C, 1–8 h; (ii) $NH_2OH \cdot HCl$, methanol, reflux; (iii) **1**, toluene, 100 °C, 0.5 h.

Keywords: Tetrasulfur tetranitride antimony pentachloride; 3,3′:4′,3″-Ter-1,2,5-thiadiazole; Oligoheterocyclic; Oligo-1,2,5-thiadiazole.
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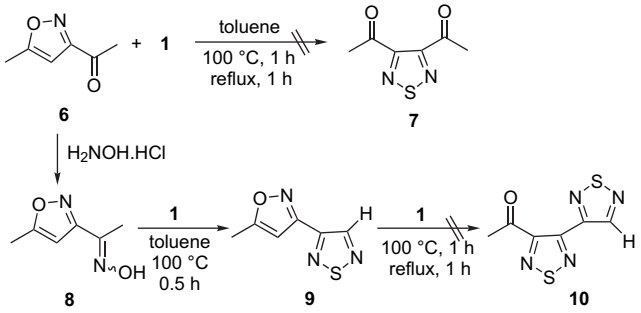
2. Results and discussion

2.1. Synthesis of 16 from 1-(5-methyl-3-isoxazolyl)-ethanone (6)

First, 1-(5-methyl-3-isoxazolyl)ethanone (**6**) was selected as a starting material for the synthesis of **16** because it was expected to make two acetyl groups after reaction with **1** (Scheme 2). However, **6** did not react with **1** at all, which might be due to the decreased nucleophilicity of the nitrogen atom of isoxazole by potential electron-withdrawing property of acetyl group. From the reaction, only reactant was recovered in 48% yield.



Scheme 2.

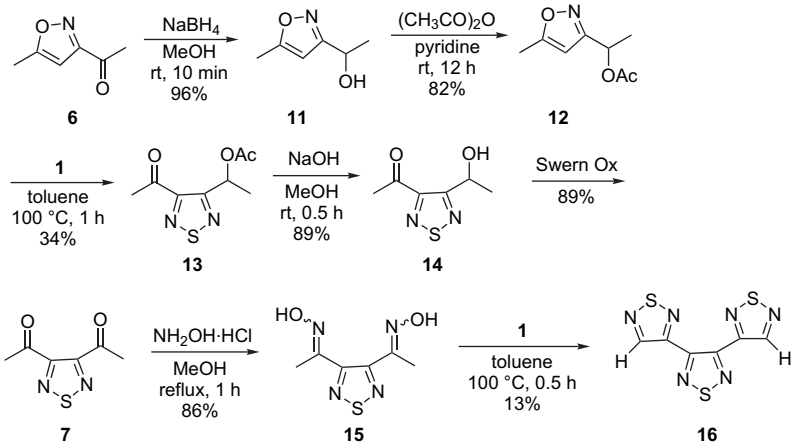
The same result was obtained from the reaction of 5-methyl-3-(3-1,2,5-thiadiazolyl)isoxazole (**9**), prepared by the reaction of 1-(5-methyl-3-isoxazolyl)ethanone oxime (**8**) with **1** in toluene at 100 °C for 0.5 h. In this case, the strong electron-withdrawing property of 1,2,5-thiadiazole ring was thought to prevent the reaction.

Subsequently, **6** was reduced to the corresponding alcohol **11** with $NaBH_4$ in methanol to remove the electron-withdrawing character of the substituent at C-3 (Scheme 3). Then the hydroxy group of **11** was protected with acetic anhydride to give 3-(1-acetyloxyethyl)-5-methylisoxazole (**12**) because complex **1** is known to be sensitive to hydroxy group. The protected **12** was reacted with **1** in toluene at 100 °C for 1 h to give 3-acetyl-4-(1-acetyloxyethyl)-1,2,5-thiadiazole (**13**) in 34% yield, which was a typical yield in the reaction of isoxazole compounds with **1**.[5c] After the acetyl group was removed with NaOH in methanol to give 3-acetyl-4-(1-hydroxyethyl)-1,2,5-thiadiazole (**14**), compound **14** was oxidized to 3,4-diacetyl-1,2,5-thiadiazole (**7**) according to Swern oxidation procedure.[7]

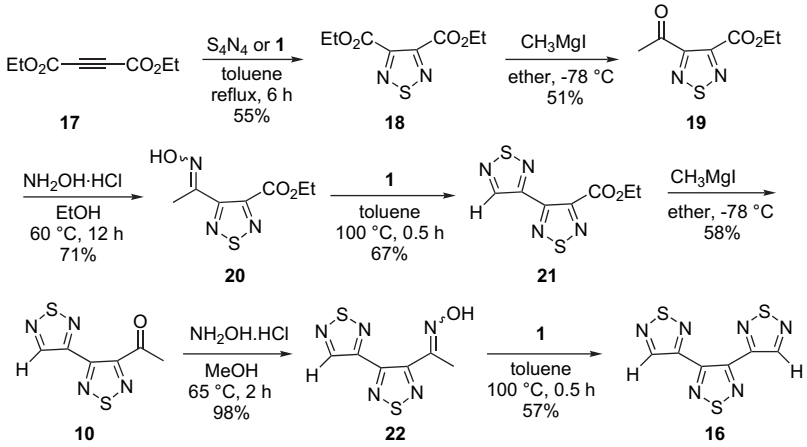
Diketoxime **15** obtained from the treatment of **7** with $NH_2OH{\cdot}HCl$ was reacted with **1** in toluene at 100 °C for 0.5 h to give **16** in 13% yield. Compound **16** was a pale yellow solid (mp 132–134 °C) and its structure was determined based on elemental analysis and spectroscopic and mass spectral data. The total yield of **16** was 2% after seven steps from this scheme. The most problematic step in yield was the last (13%), in which two 1,2,5-thiadiazole rings were formed at a time. There was no evidence on TLC to indicate a sequential formation of two 1,2,5-thiadiazole rings. As complex **1** was a bulky molecule, a simultaneous formation of two 1,2,5-thiadiazole rings at both sites did not seem to be a favorable process for yield. Therefore, we decided to make 1,2,5-thiadiazole ring one by one.

2.2. Synthesis of 16 from diethyl acetylene-dicarboxylate (17)

After many trials, we realized that it would be better to avoid hydroxyl group accompanied by its protecting and deprotecting processes because its stability could be affected by complex **1**, which might decrease the yields. Diethyl acetylenedicarboxylate (**17**) was selected as a new starting material because it had been known to afford 3,4-diethoxycarbonyl-1,2,5-thiadiazole (**18**) by the reaction with free S_4N_4 or **1** in moderate yield (Scheme 4).[8] Free S_4N_4 gave a better yield (55%) of **18** than complex **1** (20%) in refluxing toluene for 6 h. To make acetyl substituent, **18** was treated with 2.2 equimolar amounts of CH_3MgI, from which only one ester group was transformed to ketone in 51% yield. As the nucleophilic attack of organometallic species is possible with cleavage of the N–S bond, an excess amount of CH_3MgI was used.[9] After oximation of compound **19** with $NH_2OH{\cdot}HCl$, **20** was reacted with **1** in toluene at 100 °C for 0.5 h to give 4-ethoxycarbonyl-3,3′-bi-1,2,5-thiadiazole (**21**) in 67% yield. Then the other ester group of compound **21** was transformed to ketone with CH_3MgI in 58% yield. The yield of Grignard reaction depended mainly on the amount of CH_3MgI. Excess amounts (8–9 equimolar) of CH_3MgI were needed to proceed the reaction efficiently.



Scheme 3. Synthesis of **16** from 1-(5-methyl-3-isoxazolyl)ethanone.



Scheme 4. Synthesis of **16** from diethyl acetylenedicarboxylate.

The reaction did not proceed at all in the presence of 2 or 6 equimolar amounts of CH_3MgI, from which 95% of reactant was recovered. On the other hand, the use of 12 equimolar amounts of MeMgI gave unidentifiable products. Finally, compound **10** was transformed to the corresponding oxime (**22**) followed by the reaction with complex **1** to give **16** in 57% yield. The total yield (4%), though still low, increased by double compared to the first synthetic scheme.

As stated above, 4,4″-diphenyl-3,3′:4′,3″-ter-1,2,5-thiadiazole is to date the only one that contains ter-1,2,5-thiadiazole, which was produced at a time from the reaction of 1,6-diphenylhexa-1,3,5-triene with $(NSCl)_3$.[4] However, there was a comment without the reaction conditions and yield that the reaction produced a complex reaction mixture from which only the tris-1,2,5-thiadiazole had been isolated and characterized. The use of $(NSCl)_3$ for the synthesis of various ter-1,2,5-thiadiazole compound may not be desirable because it has been usually used in the reaction with substrate including inert substituents such as benzene or pyridine at the 3- and 4″-position.

3. Conclusion

In this paper, we have achieved two total synthetic scheme of 3,3′:4′,3″-ter-1,2,5-thiadiazole using $S_4N_4\cdot SbCl_5$ complex. It is very convenient to use complex **1** for elongating 1,2,5-thiadiazole ring one by one through the reaction with ketoxime and the reactions are complete in a very short time under mild conditions. It can provide any oligo-1,2,5-thiadiazole compound with three or more 1,2,5-thiadiazole rings if a proper synthetic scheme is available.

4. Experimental

4.1. General

IR spectra were obtained on a Shimadzu 470 spectrophotometer, in which s, m, and w in the parentheses mean strong, medium, and weak bands, respectively. ^1H and ^{13}C NMR spectra were measured on a Bruker AC 80 or 300 spectrometer using tetramethylsilane as an internal standard. MS spectra were obtained by electron impact at 70 eV using a VG 12-250 mass spectrometer. Elemental analyses were determined by the Korea Basic Science Center. Melting points were measured on a Fisher–Johns melting point apparatus and are uncorrected. Column chromatography was performed on a silica gel (Merck 70–230 or 240–400 mesh, ASTM). Tetrasulfur tetranitride (S_4N_4) and tetrasulfur tetranitride antimony pentachloride complex ($S_4N_4\cdot SbCl_5$) were prepared by the literature procedures.[10] A treatment of S_4N_4 requires special caution because of its explosive property. Solvents and diethyl acetylenedicarboxylate were purchased from Sigma–Aldrich (Milwaukee, WI, USA) and used without further purification unless stated otherwise. Compound **6** was prepared according to the literature.[11] All solids were recrystallized from *n*-hexane unless stated otherwise in parenthesis.

4.2. Synthesis of 16 from 1-(5-methyl-3-isoxazolyl)-ethanone

4.2.1. 5-Methyl-3-(3-1,2,5-thiadiazolyl)isoxazole (9). To a solution of **8** (141 mg, 1.00 mmol) in toluene (20 mL) was added **1** (483 mg, 1.00 mmol) and the mixture was heated at 100 °C. A spot corresponding to **8** (R_f=0.05, $CCl_4/CHCl_3$=2:1) disappeared on TLC in 0.5 h. The reaction mixture was cooled to room temperature followed by filtration to remove toluene-insoluble solids. After removal of toluene in vacuo, the residue was chromatographed on a silica gel column (70–230 mesh, 1.5×5.0 cm). Elution with *n*-hexane (50 mL) gave a trace amount of sulfur. Elution with a mixture of CCl_4 and $CHCl_3$ (1:2, 100 mL) gave pure product **9** (95 mg, 57%) as a pale yellow solid: mp 120–122 °C; δ_H (80 MHz, $CDCl_3$) 2.53 (s, 3H), 6.56 (s, 1H), 9.09 (s, 1H); ν_{max} (KBr/cm^{-1}) 3120 (w), 3072 (w), 1593 (s), 1446 (s), 1318 (m), 1180 (m), 1081 (w), 902 (s), 816 (s), 771 (m), 521 (s); MS (*m*/*z*) 167 (M^+, 98.11), 152 (100), 140 (2.48), 125 (36.12), 98 (15.38).

4.2.2. 1-(5-Methyl-3-isoxazolyl)ethanol (11). To a solution of **6** (1.66 g, 13.3 mmol) in methanol (10 mL) was added $NaBH_4$ (505 mg, 13.3 mmol) at room temperature, which was stirred for 10 min. After quenched with saturated NH_4Cl solution (50 mL), the reaction mixture was extracted with ethyl acetate (50 mL×2). The organic layer was

separated and dried over $MgSO_4$. After removal of solvent in vacuo, the product **11** (1.62 g, 96%) was obtained as a oil and used in the next step without further purification: δ_H (80 MHz, $CDCl_3$) 1.48 (d, J=7 Hz, 3H), 2.38 (s, 3H), 3.72 (d, J=9 Hz, 1H), 4.74–5.16 (m, 1H), 6.02 (s, 1H).[12]

4.2.3. 3-(1-Acetyloxyethyl)-5-methylisoxazole (12). To a solution of compound **11** (1.59 g, 12.5 mmol) in pyridine (20 mL) was added acetic anhydride (2.16 g, 21.2 mmol) dropwise at room temperature, which was stirred for 12 h. The reaction mixture was poured on ice (30 g) and extracted with CH_2Cl_2 (50 mL×2). The organic layer was separated and dried over $MgSO_4$. After removal of solvent in vacuo, the residue was chromatographed on a silica gel column (70–230 mesh, 2.5×5.0 cm). Elution with a mixture of *n*-hexane and ethyl acetate (5:1, 100 mL) gave pure 3-(1-acetyloxyethyl)-5-methylisoxazole (**12**) (1.74 g, 82%) as an oil: δ_H (80 MHz, $CDCl_3$) 1.57 (d, J=7 Hz, 3H), 2.08 (s, 3H), 2.39 (s, 3H), 5.76–6.18 (m, 2H); ν_{max} (neat/cm^{-1}) 3136 (w), 2976 (w), 1744 (s), 1603 (m), 1446 (m), 1369 (w), 1232 (s), 1145 (w), 1062 (w), 1033 (w), 940 (w), 896 (w), 851 (w), 800 (w). Anal. Calcd for $C_8H_{11}NO_3$: C, 56.80; H, 6.55; N, 8.28. Found: C, 56.75; H, 6.58; N, 8.33.

4.2.4. 3-Acetyl-4-(1-acetyloxyethyl)-1,2,5-thiadiazole (13). A solution of compound **12** (400 mg, 2.36 mmol) and **1** (1.14 g, 2.36 mmol) in toluene (30 mL) was heated at 100 °C for 1 h. The reaction mixture was cooled to room temperature when a spot corresponding to compound **12** had disappeared completely on TLC (R_f=0.05, CCl_4/$CHCl_3$=2:1). 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 (70–230 mesh, 2.5×5.0 cm). Elution with *n*-hexane (50 mL) gave a trace amount of sulfur. Elution with a mixture of CCl_4 and $CHCl_3$ (2:1, 50 mL) gave unreacted S_4N_4 (less than 10 mg). Elution with a mixture of *n*-hexane and ethyl acetate (4:1, 30 mL) gave pure product **13** (170 mg, 34%) as an oil: δ_H (80 MHz, $CDCl_3$) 1.61 (d, J=8 Hz, 3H), 2.07 (s, 3H), 2.74 (s, 3H), 6.41 (q, J=8 Hz, 1H); ν_{max} (neat/cm^{-1}) 2992 (w), 2912 (w), 1734 (s), 1692 (s), 1596 (w), 1443 (w), 1360 (m), 1241 (s), 1084 (s), 1052 (m), 1024 (m), 937 (m), 834 (m), 748 (m), 695 (m), 611 (m). Anal. Calcd for $C_8H_{10}N_2O_3S$: C, 44.85; H, 4.70; N, 13.08; S, 14.97. Found: C, 44.89; H, 4.73; N, 13.02; S, 15.02.

4.2.5. 3-Acetyl-4-(1-hydroxyethyl)-1,2,5-thiadiazole (14). To a solution of compound **13** (170 mg, 0.79 mmol) in methanol (10 mL) was added NaOH (40 mg, 1.00 mmol) at room temperature, which was stirred for 0.5 h. After quenched with saturated NH_4Cl solution (50 mL), the reaction mixture was extracted with ethyl acetate (50 mL×2). The organic layer was separated and dried over $MgSO_4$. After removal of solvent, the residue was chromatographed on a silica gel column (70–230 mesh, 1.5×10 cm). Elution with a mixture of *n*-hexane and ethyl acetate (5:1, 50 mL) gave pure product **14** (120 mg, 88%) as an oil: δ_H (80 MHz, $CDCl_3$) 1.62 (d, J=7 Hz, 3H), 2.80 (s, 3H), 4.31 (br, 1H), 5.09–5.47 (m, 1H); ν_{max} (neat/cm^{-1}) 3456 (s), 3024 (w), 2912 (m), 1686 (s), 1593 (w), 1484 (w), 1443 (m), 1056 (w), 1020 (w), 953 (w), 899 (w), 848 (w), 752 (s), 697 (s). Anal. Calcd for $C_6H_8N_2O_2S$: C, 41.85; H, 4.68; N, 16.27; S, 18.62. Found: C, 41.88; H, 4.70; N, 16.21; S, 18.69.

4.2.6. 3,4-Diacetyl-1,2,5-thiadiazole (7). Compound **7** was obtained as an oil from compound **14** according to Swern oxidation procedure:[7] δ_H (80 MHz, $CDCl_3$) 2.69 (s, 6H); ν_{max} (neat/cm^{-1}) 2924 (w), 2912 (m), 1702 (s), 1593 (m), 1484 (m), 1443 (m), 1401 (m), 1350 (m), 1248 (m), 1142 (m), 1014 (m), 944 (m), 748 (m), 697 (s), 627 (m). Anal. Calcd for $C_6H_6N_2O_2S$: C, 42.34; H, 3.55; N, 16.46; S, 18.84. Found: C, 42.28; H, 3.60; N, 16.42; S, 18.78.

4.2.7. 3,4-Diacetyl-1,2,5-thiadiazole dioxime (15). To a solution of compound **7** (75 mg, 0.44 mmol) at refluxing methanol (15 mL) was added $H_2NOH{\cdot}HCl$ (250 mg, 3.62 mmol), which was refluxed for 1 h. After cooled to room temperature, the reaction mixture was quenched with water (30 mL) and extracted with ethyl acetate (50 mL×2). The organic layer was separated and dried over $MgSO_4$. After removal of solvent, product **15** (76 mg, 86%) was obtained as an oil and used in the next reaction without further purification: δ_H (80 MHz, $CDCl_3$) 2.26 (s, 6H), 8.33 (br, 2H); ν_{max} (neat/cm^{-1}) 3312 (s), 3024 (w), 2912 (m), 1484 (w), 1443 (m), 1363 (w), 1017 (s), 940 (w), 905 (w), 841 (w), 752 (m), 697 (s).

4.2.8. 3,3′:4′,3″-Ter-1,2,5-thiadiazole (16). To a solution of compound **15** (48 mg, 0.24 mmol) in toluene (10 mL) was added **1** (260 mg, 0.54 mmol), which was heated at 100 °C. A spot corresponding to oxime disappeared on TLC (R_f=0.05, CCl_4/$CHCl_3$=2:1) after 0.5 h and the reaction mixture was cooled to room temperature followed by filtration to remove toluene-insoluble solids. After removal of toluene in vacuo, the residue was chromatographed on a silica gel column (70–230 mesh, 1.5×7.0 cm). Elution with *n*-hexane (50 mL) gave a trace amount of sulfur. Elution with a mixture of CCl_4 and $CHCl_3$ (1:1, 50 mL) gave pure product **16** (8 mg, 13%) as a pale yellow solid: mp 132–134 °C; δ_H (300 MHz, $CDCl_3$) 9.15 (s, 2H); ν_{max} (KBr/cm^{-1}) 1126 (w), 1040 (w), 886 (s), 832 (m), 768 (m), 527 (m), 499 (m); MS (*m/z*) 254 (M^+, 100), 227 (29.3), 196 (16.8), 168 (4.73), 143 (21.3), 116 (21.4), 84 (8.24), 64 (30.5). Anal. Calcd for $C_6H_2N_6S_3$: C, 28.34; H, 0.79; N, 33.05; S, 37.82. Found: C, 28.35; H, 0.81; N, 33.01; S, 37.77.

4.3. Synthesis of 16 from diethyl acetylenedicarboxylate

4.3.1. 3,4-Diethoxycarbonyl-1,2,5-thiadiazole (18). A mixture of compound **17** (1.65 g, 9.70 mmol) and S_4N_4 (920 mg, 5.00 mmol) in toluene (40 mL) was heated at reflux for 6 h. After removal of solvent in vacuo, the residue was chromatographed on a silica gel column (70–230 mesh, 2.5×10 cm). Elution with *n*-hexane gave a mixture of sulfur and a trace amount of 3,5-diethoxycarbonyl-1,2,4-thiadiazole. Elution with a mixture of *n*-hexane and ethyl acetate (15:1) gave 4,5-diethoxycarbonyl-1,3,6,2,7-trithiadiazine (186 mg, 7%) and 4-ethoxycarbonyl-1,3,6,2,5,7-trithiatriazine (93 mg, 4%). Further elution with the same solvent (10:1) gave pure product **18** (1.23 g, 55%).[8]

4.3.2. 3-Acetyl-4-ethoxycarbonyl-1,2,5-thiadiazole (19). To a solution of compound **18** (500 mg, 2.17 mmol) in ether (15 mL, dried over sodium) was added CH_3MgI (801 mg, 4.82 mmol) dropwise at −78 °C under nitrogen atmosphere. The reaction mixture turned to deep yellow color and was stirred for 10 min after addition. After warmed to 0 °C, the

reaction was quenched with saturated NH_4Cl solution (30 mL) followed by extraction with ether (50 mL×2). The organic layer was separated and dried over $MgSO_4$. After removal of solvent in vacuo, the residue was chromatographed on a silica gel column (70–230 mesh, 1.5×10 cm). Elution with a mixture of *n*-hexane and ethyl acetate (7:1, 20 mL) gave 3-ethoxycarbonyl-4-(1,1-hydroxymethylethyl)-1,2,5-thiadiazole (34 mg, 7%) as a minor and pure product **19** (220 mg, 51%) as an oil: δ_H (80 MHz, $CDCl_3$) 1.42 (t, J=8 Hz, 3H), 2.70 (s, 3H), 4.47 (q, J=8 Hz, 2H); ν_{max} (neat/cm^{-1}) 2992 (w), 1747 (s), 1699 (s), 1472 (w), 1408 (m), 1356 (w), 1267 (s), 1180 (s), 1052 (m), 1011 (w), 953 (w). Anal. Calcd for $C_7H_8N_2O_3S$: C, 41.99; H, 4.03; N, 13.99; S, 16.02. Found: C, 41.92; H, 4.01; N, 14.02; S, 16.00.

4.3.3. 3-Ethoxylcarbonyl-4-(1-(hydroxyimmino)ethyl)-1,2,5-thiadiazole (20). Oximation was performed according to the literature method:[13] Oil; δ_H (80 MHz, $CDCl_3$) 1.38 (t, J=6 Hz, 3H), 2.35 (s, 3H), 4.43 (q, J=6 Hz, 2H), 8.21 (s, 1H); ν_{max} (neat/cm^{-1}) 3408 (s), 1728 (s), 1440 (m), 1366 (s), 1296 (s), 1187 (m), 1056 (m), 1011 (w), 928 (w), 851 (w). Anal. Calcd for $C_7H_9N_3O_3S$: C, 39.06; H, 4.21; N, 19.52; S, 14.90. Found: C, 39.13; H, 4.24; N, 19.55; S, 14.85.

4.3.4. 4-Ethoxycarbonyl-3,3′-bi-1,2,5-thiadiazole (21). Compound **21** (98 mg, 67%) was obtained as an oil from the reaction of compound **20** (130 mg, 0.60 mmol) and **1** (350 mg, 0.73 mmol) according to the same procedure as **16**: δ_H (80 MHz, $CDCl_3$) 1.37 (t, J=6 Hz, 3H), 4.49 (q, J=6 Hz, 2H), 9.12 (s, 1H); ν_{max} (neat/cm^{-1}) 2976 (w), 1731 (s), 1456 (m), 1324 (w), 1299 (w), 1228 (m), 1148 (m), 1049 (m), 1008 (m), 928 (w), 848 (w), 780 (w). Anal. Calcd for $C_7H_6N_4O_2S_2$: C, 34.70; H, 2.50; N, 23.12; S, 26.47. Found: C, 34.65; H, 2.46; N, 23.10; S, 26.55.

4.3.5. 4-Acetyl-3,3′-bi-1,2,5-thiadiazole (10). To a solution of compound **21** (90 mg, 0.37 mmol) in ether (10 mL) was added CH_3MgI (534 mg, 3.21 mmol) dropwise at −78 °C. The reaction was monitored on TLC as CH_3MgI was added. When about 2.2 equiv amount of CH_3MgI was added, the spot corresponding to compound **22** (*n*-hexane/EtOAc=4:1) appeared on TLC. As CH_3MgI was added, the spot deepened more and more. However, when CH_3MgI was added completely, some tarry materials started to appear on TLC. After warmed to 0 °C, the reaction was quenched with saturated NH_4Cl solution (30 mL), which was extracted with ether (50 mL×2). The organic layer was separated and dried over $MgSO_4$. After removal of solvent in vacuo, the residue was chromatographed on a silica gel column (70–230 mesh, 2.5×15 cm). Elution with a mixture of *n*-hexane and ethyl acetate (15:1, 30 mL) gave unreacted compound **21** (31 mg, 34%). Elution with the same solvent gave pure product **22** (30 mg, 58%) as a pale yellow solid: mp 61–61.5 °C; δ_H (300 MHz, $CDCl_3$) 2.82 (s, 3H), 9.13 (s, 1H); ν_{max} (KBr/cm^{-1}) 1686 (s), 1395 (s), 1350 (w), 1209 (w), 1113 (w), 1046 (w), 956 (w), 912 (m), 835 (s), 780 (m), 617 (s), 512 (s). Anal. Calcd for $C_6H_4N_4OS_2$: C, 33.95; H, 1.90; N, 26.40; S, 30.21. Found: C, 33.99; H, 1.88; N, 26.45; S, 30.20.

4.3.6. 4-(1-(Hydroxyimmino)ethyl)-3,3′-bi-1,2,5-thiadiazole (22). Oximation was carried out according to the literature method:[13] mp 84–85 °C (CCl_4); δ_H (300 MHz, $CDCl_3$) 2.42 (s, 3H), 7.85 (s, 1H, OH), 9.00 (s, 1H); ν_{max} (KBr/cm^{-1}) 3264 (w), 1472 (w), 1420 (w), 1360 (w), 1324 (w), 1124 (w), 1017 (s), 953 (w), 905 (w), 854 (w), 780 (w), 512 (s). Anal. Calcd for $C_6H_5N_5OS_2$: C, 31.71; H, 2.22; N, 30.82; S, 28.22. Found: C, 31.73; H, 2.25; N, 30.80; S, 28.19.

4.3.7. Compound 16. To a solution of compound **22** (38 mg, 0.17 mmol) in toluene (15 mL) was added **1** (150 mg, 0.31 mmol), which was heated at 100 °C. The reaction mixture was cooled to room temperature when a spot corresponding to **22** (R_f=0.05, CCl_4/$CHCl_3$=2:1) had disappeared on TLC after 0.5 h. The reaction mixture was filtered to remove toluene-insoluble solids. After removal of toluene in vacuo, the residue was chromatographed on a silica gel column (70–230 mesh, 1.5×5.0 cm). Elution with *n*-hexane (50 mL) gave a trace amount of sulfur. Elution with a mixture of *n*-hexane and ethyl acetate (5:1, 10 mL) gave pure product **16** (24 mg, 57%).

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