1,3-Dipolar Cycloaddition Reaction of Substituted Trimethylstannylacetylenes with Nitrile Oxides

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1,3-Dipolar cycloaddition reaction of trimethylstannylacetylene with nitrile oxides yielded 3-substituted 5-(trimethylstannyl)isoxazoles. On the other hand, the same reaction of (trimethylstannyl)phenylacetylene, -1-hexyne, and -(trimethylsilyl)acetylene gave 3,5-disubstituted 4-(trimethylstannyl)isoxazoles almost regioselectively. The regioselectivity of the cycloaddition reaction is interpreted by application of the frontier-electron theory.

Keywords 1,3-dipolar cycloaddition; nitrile oxide; trimethylstannylacetylene; trimethylstannylisoxazole; regioselectivity; MO calculation

In the previous papers, we have reported that the 1,3-dipolar cycloaddition reaction of tributylstannylacetylene with nitrile oxides, phenylsydnone, and diazoalkanes gave exclusively 3-substituted 5-(tributylstannyl)isoxazoles,[1,2] 1-phenyl-3-(tributylstannyl)pyrazole,[3] and 5-substituted 3-(tributylstannyl)pyrazoles.[3] The (tributylstannyl)isoxazoles and -pyrazoles are useful derivatives for the regioselective introduction of a functional group such as a halogen, aryl, or benzoyl group into these 1,2-azoles.

As described in a recent review,[4] no systematic study of the 1,3-dipolar cycloaddition reaction of nitrile oxides with asymmetrically 1,2-substituted acetylenes has been undertaken. In order to clarify the regioselectivity of the 1,3-dipolar cycloaddition reaction between unsymmetrically substituted acetylenes and nitrile oxides, the cycloaddition reaction of substituted trimethylstannylacetylenes with nitrile oxides was examined, and the regioselectivity was discussed on the basis of molecular orbital (MO) calculation.

First, the 1,3-dipolar cycloaddition reaction of trimethylstannylacetylene (**1a**) with acetonitrile oxide (**2a**), bezonitrile oxide (**2b**), and ethoxycarbonylnitrile oxide (**2c**) was examined. The cycloaddition reaction of **1a** with **2a** gave 3-methyl-5-(trimethylstannyl)isoxazole (**3a**) in 73% yield, but the product (**3b**) obtained from the reaction of **1a** with **2b** was easily hydrolyzed during purification by silica gel column chromatography using hexane–ethyl acetate as an eluent to give the detrimethylstannylated product, 3-phenylisoxazole (**4b**) in 62% yield. The product obtained from the reaction of **1a** with **2c** was purified by silica gel column chromatography to give ethylisoxazole-3-carboxylate (**4c**) in 79% yield together with a trace of ethyl 4-(trimethylstannyl)isoxazole-3-carboxylate (**14c**). Furthermore, the products from the reaction of **1a** and **2b, c** were treated with iodine to give 5-iodoisoxazoles (**5b, c**) as sole products, and no 4-iodoisoxazoles were detected. These results indicated that the reaction of **1a** with **2a—c** substantially proceeds regioselectively.

1-(Trimethylstannyl)-1-hexyne (**1b**) and (trimethylstannyl)phenylacetylene (**1c**) were less reactive than trimethylstannylacetylene (**1a**), and the yields of the products were generally low. The cycloaddition of **1b** with **2a** gave a mixture of 5-butyl-4-trimethylstannyl-(**6a**) and 4-butyl-5-trimethylstannyl-3-methylisoxazole (**8a**), which were difficult to separate by silica gel column chromatography. Then the crude products were detrimethylstannylated with concentrated sulfuric acid to give a mixture of 5-butyl-(**9a**) and 4-butyl-3-methylisoxazole (**11a**) in 11% yield. These products were also difficult to separate. The ratio of **9a** and **11a** was estimated to be 9 : 2 by analysis of the proton magnetic resonance (^{1}H-NMR) spectrum of the mixture.

On the other hand, the reaction of **1c** with **2a** gave 4-trimethylstannyl-3-methyl-5-phenylisoxazole (**7a**) as a sole product, but the yield was low. The reaction of **1b, c** and **2b** yielded 4-(trimethylstannyl)isoxazoles (**6b** and **7b**) which were contaminated with detrimethylstannylated derivatives (**9b** and **10b**) during purification by silica gel column chromatography. The crude products were detrimethylstannylated with concentrated sulfuric acid to give 5-butyl-3-phenylisoxazole (**9b**) and 3,5-diphenylisoxazole (**10b**) in 38 and 9% yields, and no regioisomers were detected.

The reaction of **1b, c** and **2c** gave a mixture of ethyl 5-substituted 4-(trimethylstannyl)isoxazoles (**6c** and **7c**) and the detrimethylstannylated derivatives (**9c** and **10c**), which were readily separated by column chromatography.

While the reaction of (trimethylstannyl)trimethylsilylacetylene (**1d**) with **2a, c** gave stable 5-trimethylsilyl-4-trimethylstannylisoxazoles (**12a, c**) in 63 and 95% yields, the same reaction with **2b** gave 3-phenyl-5-trimethylsilyl-4-(trimethylstannyl)isoxazole (**12b**) contaminated with 3-phenyl-5-(trimethylsilyl)isoxazole (**13b**) during purification by column chromatography. The crude product obtained from the reaction of **1d** and **2b** was treated with concentrated sulfuric acid to afford **13b** in 65% yield. The result suggests that 5-trimethylsilyl-4-(trimethylstannyl)isoxazoles (**12a, c**) could be selectively detrimethylstannylated in acidic media. Actually, treatment of **12a, c** with sulfuric acid gave detrimethylstannylated products (**13a, c**) in 60 and 55% yields.

On the contrary, **12a, c** were detrimethylsilylated by

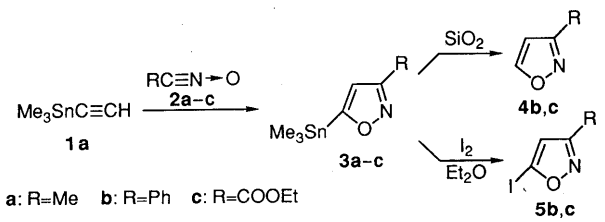

Chart 1

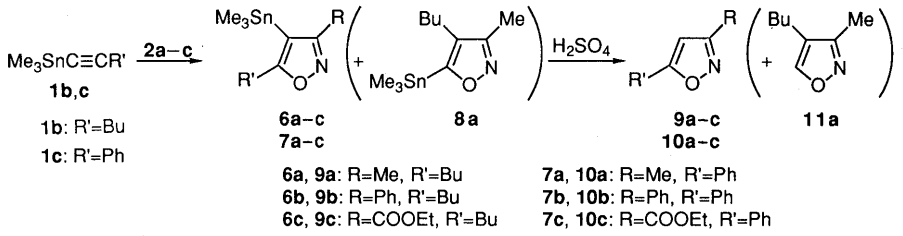

Chart 2

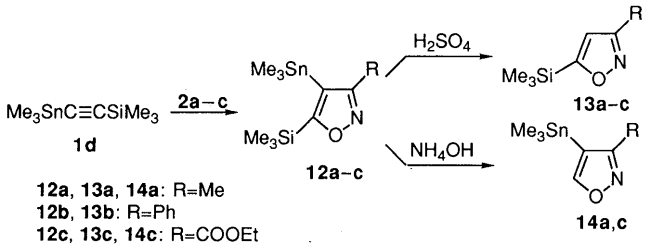

Chart 3

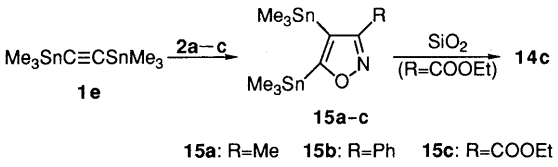

Chart 4

treatment with aqueous ammonia to give **14a, c** in 66 and 49% yields. These results show that 5-trimethylsilyl-4-(trimethylstannyl)isoxazoles could be useful intermediates for regioselective introduction of a functional group into the isoxazole ring.

Finally, the reaction of bis(trimethylstannyl)acetylene (**1e**) with **2a,b** gave 4,5-bis(trimethylstannyl)isoxazoles (**15a, b**) in 67 and 42% yields, and the reaction of **1e** with **2c** followed by purification by silica gel column chromatography gave ethyl 4-(trimethylstannyl)isoxazole-3-carboxylate (**16c**), which is the regioselectively detrimethylstannylated product at the 5-position in 89% yield.

In conclusion, the 1,3-dipolar cycloaddition reaction of **1a—d** with **2a—c** proceeded regioselectively except for a few cases, although the yields of the reaction using **1b, c** as dipolarophiles were low.

The regioselectivily described above may be rationalized by application of the frontier-electron theory. The highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) coefficients of the relevant compounds, calculated by the modified neglect of diatomic overlap, parametric method 3 (MNDO-PM3) method, where the geometries were fully optimized, are shown in Table I. Since it is considered that electrons move from the acetylenes (**1a—d**) to the nitrile oxides (**2a—c**) from the results shown in Table I, the HOMO coefficients of **1a—d** and the LUMO coefficients of **2a—c** are important. The HOMO coefficients of C^1 and C^2 of **1a—d** and C and O of **2a—c** are all the same in sign. This confirms that the reaction with electron flow from **1a—d** to **2a—c** may take place. Then, if one considers that the electron first moves from the larger site of the HOMO coefficients of **1a—d** to the larger site of the LUMO coefficients of **2a—c**, all regioselectivity data so far experimentally obtained are explained.

TABLE I. PM3/HOMO and LUMO Coefficients for Nitrile Oxides and Substituted Trimethylstannylacetylenes

	R–C≡N→O R=Me		R=Ph		R=COOEt	
	HOMO	LUMO	HOMO	LUMO	HOMO	LUMO
C	0.607	0.593	0.338	0.219	0.640	0.381
O	−0.659	0.306	−0.384	0.200	−0.653	0.293

	Me_3Sn–C^1≡C^2–R R=H		R=Bu		R=Ph		$R=SiMe_3$	
	HOMO	LUMO	HOMO	LUMO	HOMO	LUMO	HOMO	LUMO
C^1	0.345	0.000	0.515	0.004	0.409	0.346	0.460	0.004
C^2	0.377	0.000	0.468	−0.009	0.255	−0.243	0.402	−0.006

Experimental

Melting points were determined in capillary tubes and are uncorrected. Infrared (IR) spectra were measured on a JASCO IR-A1 spectrophotometer. ^{1}H-NMR spectra were recorded on a JEOL PMX-60 (60 MHz) using tetramethylsilane as an internal standard. Chemical shifts are expressed in δ (ppm) values, and coupling constants are expressed in hertz (Hz). The following abbreviations are used: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, and br=broad. Mass spectra (MS) and high resolution mass spectra (HRMS) were recorded on a JEOL JMS-DX303 spectrometer. Elemental analyses were performed by the staff of the Central Analysis Room of the Pharmaceutical Institute, Tohoku University.

General Procedure for the 1,3-Dipolar Cycloaddition Reaction Using Nitroethane A dry C_6H_6 (10 ml) solution of nitroethane (2.2 mmol) and phenyl isocyanate (4.4 mmol) was stirred at 50 °C for 5 min. To the mixture, a dry C_6H_6 (5 ml) solution of a trimethylstannylacetylene (2 mmol) and Et_3N (one drop) was added. The whole was stirred at 50 °C for 4 h, filtered, and concentrated under reduced pressure. The residue was chromatographed on a silica gel column with hexane–AcOEt (10:1) as an eluent to give 3-methylisoxazoles.

3-Methyl-5-(trimethylstannyl)isoxazole (**3a**): Yield 73%. bp 70—80 °C (3 mmHg). ^{1}H-NMR ($CDCl_3$): 0.40 (9H, s), 2.32 (3H, s), 6.27 (1H, s). *Anal.* Calcd for $C_7H_{13}NOSn$: C, 34.15; H, 5.28; N, 5.65. Found: C, 34.03; H, 5.28; N, 5.74.

3-Methyl-5-phenyl-4-(trimethylstannyl)isoxazole (**7a**): Yield 13%. bp 90—100 °C (2 mmHg). ^{1}H-NMR ($CDCl_3$): 0.25 (9H, s), 2.23 (3H, s), 7.2—7.7 (5H, m). HRMS Calcd for $C_{12}H_{11}NOSn$ (M^+−Me): 308.0097. Found: 308.0083.

3-Methyl-5-trimethylsilyl-4-(trimethylstannyl)isoxazole (**12a**): Yield 63%. bp 90—100 °C (3 mmHg). ^{1}H-NMR ($CDCl_3$): 0.36 (18H, s), 2.33 (3H, s). HRMS Calcd for $C_9H_{18}NOSiSn$ (M^+−Me): 304.0180. Found: 304.0164.

4,5-Bis(trimethylstannyl)-3-methylisoxazole (**15a**): Yield 67%. bp 100—110 °C (2 mmHg). ^{1}H-NMR ($CDCl_3$): 0.33 (9H, s), 0.42 (9H, s), 2.36 (3H, s). MS (*m/z*): 394 (M^+−Me).[5]

General Procedure for the 1,3-Dipolar Cycloaddition Reaction Using

Chlorooximes An ethereal (10 ml) solution of Et_3N (2.2 mmol) was added to an ethereal (10 ml) solution of a chlorooxime (2.2 mmol) and a trimethylstannylacetylene at room temperature. The mixture was stirred for 2—5 h, filtered, and concentrated under reduced pressure. The residue was chromatographed on a silica gel column with hexane–AcOEt (10 : 1) as an eluent to give a 3-phenylisoxazole or an ethyl isoxazole-3-carboxylate.

3-Phenylisoxazole (**4b**): Yield 62%. bp 90—100 °C (2 mmHg). Lit.[6] bp 40 °C (0.01 mmHg). ^{1}H-NMR ($CDCl_3$): 6.63 (1H, d, J=2), 7.3—8.0 (5H, m), 8.40 (1H, d, J=2).

Ethyl Isoxazole-3-carboxylate (**4c**): Yield 79%. bp 90 °C (32 mmHg). IR ν ($CHCl_3$): 1735 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 1.40 (3H, t, J=7), 4.50 (2H, q, J=7), 6.82 (1H, d, J=2), 8.55 (1H, d, J=2). *Anal.* Calcd for $C_6H_7NO_3$: C, 51.06; H, 4.96; N, 9.93. Found: C, 51.11; H, 5.07; N, 10.05.

Ethyl 5-Butyl-4-(trimethylstannyl)isoxazole-3-carboxylate (**6c**): Yield 32%. bp 100—110 °C (2 mmHg). IR ν ($CHCl_3$): 1722 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 0.33 (9H, s), 0.8—1.9 (10H, m), 2.7—3.0 (2H, m), 4.43 (2H, q, J=7). *Anal.* Calcd for $C_{13}H_{23}NO_3Sn$: C, 43.21; H, 6.37; N, 3.88. Found: C, 43.41; H, 6.32; N, 3.94.

Ethyl 5-Butylisoxazole-3-carboxylate (**9c**): Yield 5%. bp 75—85 °C (2 mmHg). IR ν ($CHCl_3$): 1732 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 0.7—2.0 (10H, m), 2.6—2.9 (2H, m), 4.42 (2H, q, J=7), 6.36 (1H, s). *Anal.* Calcd for $C_{10}H_{15}NO_3$: C, 60.91; H, 7.61; N, 7.11. Found: C, 60.93; H, 7.56; N, 7.14.

Ethyl 5-Phenyl-4-(trimethylstannyl)isoxazole-3-carboxylate (**7c**): Yield 26%. bp 130 °C (2 mmHg). IR ν ($CHCl_3$): 1730 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 0.22 (9H, s), 1.43 (3H, t, J=7), 4.44 (2H, q, J=7), 7.4—7.6 (5H, m). *Anal.* Calcd for $C_{15}H_{19}NO_3Sn$: C, 47.24; H, 4.99; N, 3.66. Found: C, 47.35; H, 5.05; N, 3.66.

Ethyl 5-Phenylisoxazole-3-carboxylate (**10c**): Yield 9%. mp 55—57 °C. Lit.[7] mp 52—53 °C. IR ν ($CHCl_3$): 1735 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 1.43 (3H, t, J=7), 4.47 (2H, q, J=7), 6.87 (1H, s), 7.3—8.0 (5H, m).

Ethyl 5-Trimethylsilyl-4-(trimethylstannyl)isoxazole-3-carboxylate (**12c**): Yield 95%. bp 135—140 °C (5 mmHg). IR ν ($CHCl_3$): 1725 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 0.33 (9H, s), 0.37 (9H, s), 1.42 (3H, t, J=7), 4.40 (2H, q, J=7). *Anal.* Calcd for $C_{12}H_{23}NO_3SiSn$: C, 38.30; H, 6.12; N, 3.72. Found: C, 38.28; H, 6.13; N, 3.76.

4,5-Bis(trimethylstannyl)-3-phenylisoxazole (**15b**): Yield 42%. mp 97—99 °C. ^{1}H-NMR ($CDCl_3$): 0.13 (9H, s), 0.50 (9H, s), 7.4—7.6 (5H, br s). *Anal.* Calcd for $C_{15}H_{14}NOSn_2$: C, 38.22; H, 4.88; N, 2.97. Found: C, 38.36; H, 4.87; N, 3.07.

Ethyl 4-(Trimethylstannyl)isoxazole-3-carboxylate (**14c**): Yield 89%. bp 120 °C (4 mmHg). IR ν ($CHCl_3$): 1725 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 0.34 (9H, s), 1.40 (3H, t, J=7), 4.45 (2H, q, J=7), 8.18 (1H, s). *Anal.* Calcd for $C_9H_{15}NO_3Sn$: C, 35.53; H, 4.93; N, 4.61. Found: C, 35.76; H, 4.78; N, 4.80.

General Procedure for the Reaction of Stannylisoxazoles with Iodine Iodine (2 mmol) in Et_2O (15 ml) was added dropwise to a solution of a crude trimethylstannylisoxazole in Et_2O (15 ml) with stirring at room temperature, and the mixture was stirred for 2 h. After addition of H_2O, the mixture was extracted with Et_2O. The ethereal extract was washed with aqueous $Na_2S_2O_3$, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was chromatographed on a silica gel column to give the iodoisoxazole.

5-Iodo-3-phenylisoxazole (**5b**): Yield 48%. mp 90—92 °C. ^{1}H-NMR ($CDCl_3$): 6.72 (1H, s), 7.3—7.9 (5H, m). *Anal.* Calcd for C_9H_6INO: C, 40.00; H, 2.22; I, 46.67; N, 5.19. Found: C, 39.77; H, 2.23; I, 46.77; N, 5.16.

Ethyl 5-Iodoisoxazole-3-carboxylate (**5c**): Yield 60%. mp 62—64 °C. IR ν ($CHCl_3$): 1738 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 1.42 (3H, t, J=7), 4.48 (2H, q, J=7), 6.87 (1H, s). HRMS Calcd for $C_6H_6INO_3$ (M^+): 266.9393. Found: 266.9393.

Detrimethylstannylation of the Trimethylstannylisoxazoles with Sulfuric Acid A mixture of a crude trimethylstannylisoxazole and concentrated H_2SO_4 was stirred for 0.5—2 h at room temperature, diluted with H_2O, and extracted with Et_2O. The ethereal extract was dried over $MgSO_4$, and concentrated under reduced pressure. The residue was chromatographed on a silica gel column to give the detrimethylstannylated isoxazoles.

5-Butyl-3-methyl- (**9a**) and 4-Butyl-3-methylisoxazole (**11a**): Yield 11%. bp 70 °C (45 mmHg). *Anal.* Calcd for $C_8H_{13}NO$: C, 69.06; H, 9.35; N, 10.07. Found: C, 68.78; H, 9.36; N, 10.05.

5-Butyl-3-phenylisoxazole (**9b**): Yield 38%. bp 100—110 °C (2 mmHg). ^{1}H-NMR ($CDCl_3$): 0.7—2.0 (7H, m), 2.6—3.0 (2H, m), 6.27 (1H, s), 7.3—8.9 (5H, m). *Anal.* Calcd for $C_{13}H_{15}NO$: C, 77.61; H, 7.46; N, 6.97. Found: C, 77.82; H, 7.50; N, 7.08.

Ethyl 5-Butylisoxazole-3-carboxylate (**9c**): Yield 85%.

3-Methyl-5-phenylisoxazole (**10a**): Yield 51%. mp 65—67 °C. Lit.[8] mp 65—66 °C. ^{1}H-NMR ($CDCl_3$): 2.36 (3H, s), 6.63 (1H, s), 7.3—7.9 (5H, m).

3,5-Diphenylisoxazole (**10b**): Yield 9%. mp 142—143 °C. Lit.[8] mp 141—143 °C. ^{1}H-NMR ($CDCl_3$): 6.80 (1H, s), 7.3—7.6 (6H, m), 7.7—8.1 (4H, m).

Ethyl 5-Phenylisoxazole-3-carboxylate (**10c**): Yield 70%.

3-Methyl-5-trimethylsilylisoxazole (**13a**): Yield 60%. bp 70—80 °C (35 mmHg). ^{1}H-NMR ($CDCl_3$): 0.33 (9H, s), 2.31 (3H, s). HRMS Calcd for $C_7H_{13}NOSi$ (M^+): 155.0766. Found: 155.0777.

3-Phenyl-5-trimethylsilylisoxazole (**13b**): Yield 65%. bp 110—120 °C (2 mmHg). Lit.[9] bp 80 °C (0.06 mmHg). ^{1}H-NMR ($CDCl_3$): 0.38 (9H, s), 6.73 (1H, s),7.3—7.6 (3H, m), 7.7—8.0 (2H, m).

Ethyl 5-Trimethylsilylisoxazole-3-carboxylate (**13c**): Yield 55%. bp 115—120 °C (27 mmHg). IR ν ($CHCl_3$): 1730 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 0.37 (9H, s), 1.40 (3H, t, J=7), 4.43 (2H, q, J=7), 6.83 (1H, s). *Anal.* Calcd for $C_9H_{15}NO_3$: C, 50.70; H, 7.04; N, 6.57. Found: C, 50.55; H, 6.93; N, 6.79.

Detrimethylsilylation of the 5-(Trimethylsilyl)isoxazoles with Aqueous Ammonia A mixture of a 5-(trimethylsilyl)isoxazole (0.25 mmol), aqueous NH_3 (2 ml) and EtOH (2 ml) was refluxed. After dilution with H_2O, the mixture was extracted with Et_2O. The ethereal extract was washed with H_2O, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was distilled under reduced pressure to give the detrimethylsilylated isoxazole.

3-Methyl-4-(trimethylstannyl)isoxazole (**14a**): Yield 66% (reflux for 1.5 h). bp 65—75 °C (3 mmHg). ^{1}H-NMR ($CDCl_3$): 0.33 (9H, s), 2.30 (3H, s), 8.03 (1H, s). HRMS Calcd for $C_6H_{10}NOSn$ (M^+): 231.9784. Found: 231.9784.

Ethyl 4-(Trimethylstannyl)isoxazole-3-carboxylate (**14c**): Yield 49% (reflux for 6 h).

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