Heteroatom Chemistry
Volume 5, Number 3, 1994

Prior Ligand Exchange, Followed by Ligand Coupling in the Reaction of 2-Pyridyl 2-Thienyl Sulfoxide with 2-Thienyllithium or 2-Selenophenyllithium

Shigeru Oae*

Institute of Heteroatom Chemistry, 2509 Hirao, Mihara-cho, Minamikawachi-gun, Osaka, 587, Japan

Yoichi Inubushi and Masakuni Yoshihara

Department of Applied Chemistry, Kinki University, Higashi Osaka City, 577, Japan

Received 1994

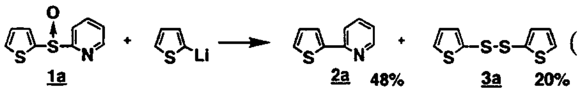
ABSTRACT

2-Pyridyl 2-thienyl sulfoxide was found to react with variously substituted 2-thienyllithiums and 2-selenophenyllithium, exclusively affording 2-(2-pyridyl)thiophenes and 2-(2-pyridyl)-selenophene and the disulfides derived from the substituted thiophenes and selenophene. Apparently, ligand exchange precedes ligand coupling. The coupling product always involved the pyridine nucleus, but no bithienyl-type products were formed.

INTRODUCTION

Since the introduction of the concept of the ligand coupling within sulfurane intermediates [1–3], numerous studies have been carried out, mainly by us. From an early period, there were numerous questions regarding the abilities of many different ligands for coupling and exchange. We have known for years [2–14] that heteroaromatic ligands, such as pyridyl, thienyl and furanyl, undergo both ligand coupling themselves and ligand exchange, presumably from an axial position. However, we did not know the controlling factors for the ligand exchange or coupling of these heteroaromatics.

We have shown that treatment of 2-pyridyl 2-thienyl sulfoxide with 2-thienyllithium affords 2-(2-pyridyl)thiophene, as shown in Equation 1 [15]. However, we could not observe the formation of 2,2′-bipyridyl or 2,2′-bithienyl in spite of the possibility of ligand exchange. The reactions of di-2-pyridyl and di-2-thienyl sulfoxides with an organolithium reagent easily give these bipyridyl and bithienyl coupling products [15]. Thus, in order to shed some light on the mechanism of the reactions of these thiophene derivatives, we have now carried out new reactions and found a few interesting results.



(1)

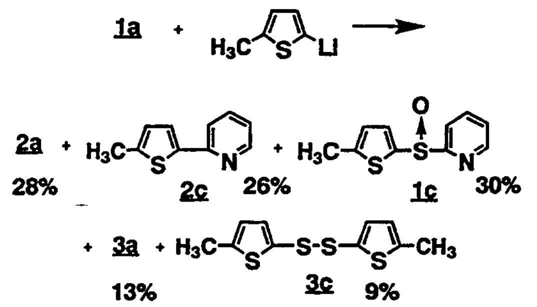
RESULTS AND DISCUSSION

The treatment of 2-pyridyl 2-thienyl sulfoxide **1a** with 3-methyl-2-thienyllithium gave both 3-methyl-2-(2-pyridyl)thiophene **2b** and 2-(2-pyridyl)thiophene **2a** in addition to di-2-thienyl disulfide **3a** and bis-(3-methyl-2-thienyl) disulfide **3b**. A large amount of the exchange product, 3-methyl-2-thienyl 2-pyridyl sulfoxide **1b**, was also obtained, as shown in Equation 2.

Dedicated to Prof. Adrian Gibbs Brook on the occasion of his seventieth birthday.

*To whom correspondence should be addressed.

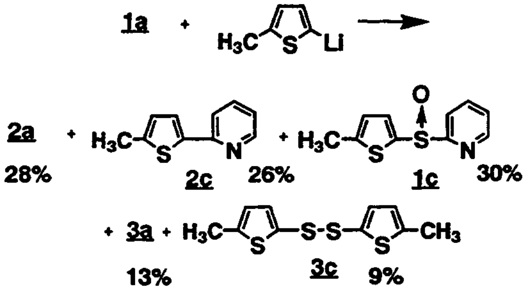
1042-7163/94/$5.00 + .25



(2)

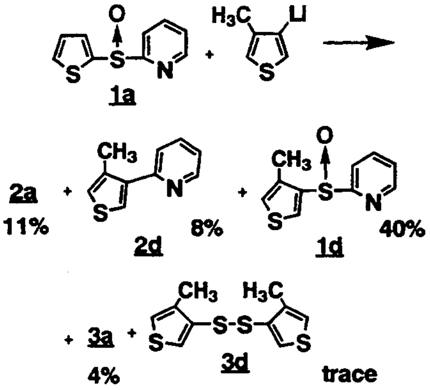
In spite of extensive ligand exchange, no evidence of any formation of 2,2′-bipyridyl or 3,3′-dimethyl-2,2′-bithienyl was found.

5-Methyl-2-thienyllithium behaved in exactly the same way. Products of the reaction with **1a** were the two coupling products [5-methyl-2-(2-pyridyl)thiophene **2c** and **2a**] and the two disulfides, [bis-(5-methyl-2-thienyl) disulfide **3c** and di-2-thienyl disulfide **3a**] as well as the exchange product, 5-methyl-2-thienyl 2-pyridyl sulfoxide **1c**, as shown in Equation 3. However, here again, there was no formation of 2,2′-bipyridyl or 2,2′-bithienyl.



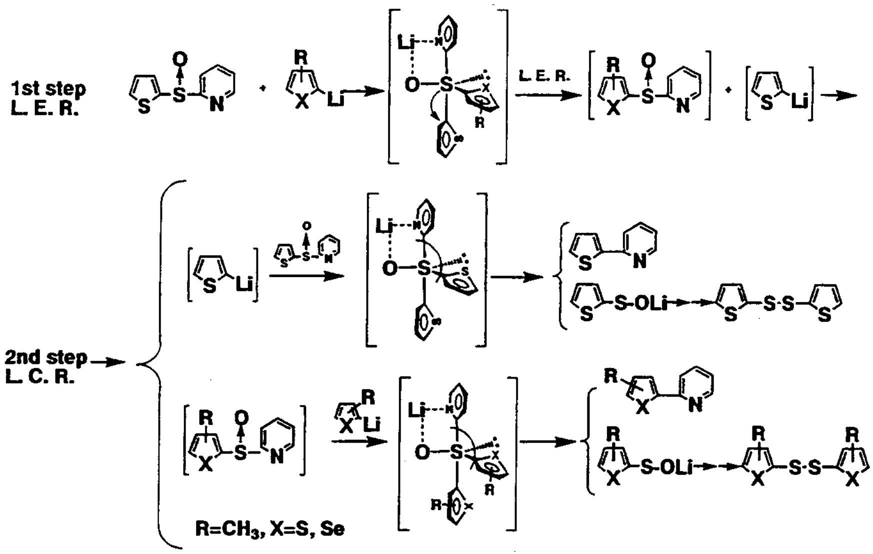
(3)

The reaction of a 3-thienyllithium was also examined. Even in the reaction of **1a** with 4-methyl-3-thienyllithium, the ligand coupling product, 4-methyl-3-(2-pyridyl)thiophene **2d**, was obtained together with **2a**, the two disulfides (**3a** and **3d**), and the exchange product (4-methyl-3-thienyl 2-pyridyl sulfoxide **1d**), as shown in Equation 4.



(4)

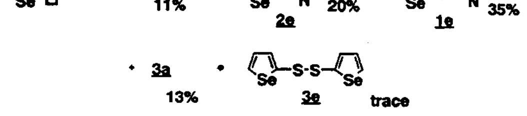
When an alkyl-substituted 2-thienyllithium was reacted with **1a**, however, we isolated two coupling products involving a pyridine nucleus together with two thienyl disulfides and the exchange product, the alkylthienyl 2-pyridyl sulfoxide. Thus, the mechanism for this reaction can be described as illustrated by Equation 5.



(5)

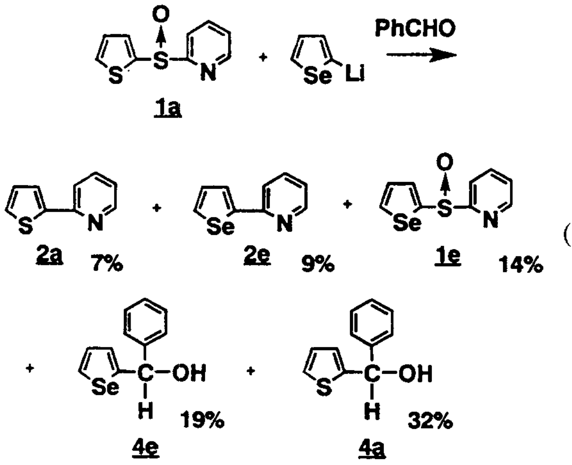
A recent MO [20] calculation has also suggested that there is a strong interaction between the axial and equatorial ligands.

Similar reactions were observed between **1a** and 2-selenophenyllithium. Two coupling products (**2a** and **2e**) and two disulfides (**3a** and **3e**) as well as the exchange product, 2-pyridyl 2-selenophenyl sulfoxide **1e**, were isolated, as shown in Equation 6.



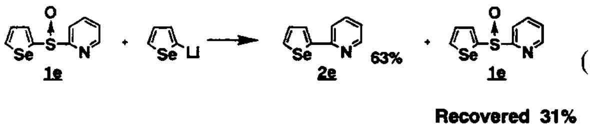
(6)

In order to detect the exchanged lithium compound, we have carried out a trapping experiment by treating **1a** with 2-selenophenyllithium in the presence of benzaldehyde. In addition to the normal reaction products, phenyl 2-selenophenylcarbinol **4e** and phenyl 2-thienylcarbinol **4a** were indeed isolated (Equation 7), showing the formation of 2-thienyllithium, the counterpart of the exchange product **1e**. However, phenyl 2-pyridylcarbinol could not be found by this trapping experiment, indicating that only the 2-thienyl group, which is less electronegative than 2-pyridyl, undergoes the ligand exchange. Similar trapping of exchanged reagents by the aldehyde was previously observed during the reaction of alkyl 2-pyridyl or di-2-pyridyl sulfoxide with a Grignard reagent [4–14, 16–19].



(7)

In order to further clarify this reaction to give 2-(2-pyridyl)-selenophene **2e**, we carried out the reaction of 2-pyridyl 2-selenophenyl sulfoxide **1e** with 2-selenophenyllithium and indeed isolated **2e**, while the original sulfoxide **1e** was also recovered, as shown in Equation 8.

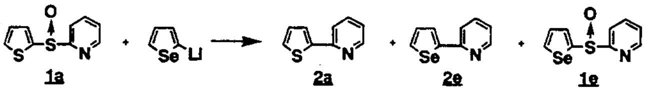


(8)

The effect of temperature was examined to clarify the relative ease of the ligand exchange and coupling reactions in Equation 6. The results are given in the Table 1.

Except for Run No. 6, the yield of **2e** was always larger than that of **2a**, but when a 1.5 molar amount of 2-selenophenyllithium was used (No. 6), the yield of **2e** was smaller than that of **2a**. This result also seems to indicate that the first step is the ligand exchange to form 2-thienyllithium, and the ligand coupling proceeds after the exchange.

TABLE 1 Temperature Effect of the Reaction of **1a** with 2-Selenophenyllithium



Number	Temperature (°C)	Yield (%) 2a	2e	1e	Poportion 2a/2e
1	−78	11	20	35	0.55
2	−40	18	34	5	0.52
3	0	21	35	0	0.60
4	25	19	27	0	0.70
5	66	19	33	0	0.57
6[a]	−78	8	2	48	4.00
7[b]	−78	19	25	15	0.33

[a] 0.5 molar amount of 2-selenophenyllithium was used per molar amount of **1a**.

[b] 1.5 molar amount of 2-selenophenyllithium was usedper molar amount of **1a**.

It is noteworthy that we could successfully isolate two coupling products and two disulfides in all cases, and the exchanged sulfoxide was also obtained, while **1a** was not recovered. All these observations can be accommodated by the reaction mechanism illustrated in Equation 5. Initially, the ligand exchange reaction of 2-pyridyl 2-thienyl sulfoxide **1a** with the substituted thienyl- or 2-selenophenyllithium takes place to afford 2-thienyllithium and the exchanged sulfoxide. The 2-thienyllithium thus formed reacts with the original sulfoxide **1a** to give one coupling product **2a**, and the newly formed sulfoxide also gives another coupling product. A similar mechanism of ligand exchange and coupling was previously proposed for the reaction of methyl 2-pyridyl sulfoxide with Grignard reagents [4–14, 16–19].

EXPERIMENTAL

General

All the melting points were uncorrected and were taken on a Yanagimoto melting-point apparatus. IR spectra were obtained on Jasco-IRA-202 and Perkin Elmer FT-IR 1760X spectrometers. NMR spectra were obtained on a JEOL-PMX60SI or a JEOL-GSX-270 FT-NMR spectrometer in $CDCl_3$ using TMS as an internal standard. All the reactions were monitored by TLC (Merck, Kieselgel 60 F254), GLC (Hitachi 163 and 663-30, using a 3% silicon OV-17 chromosorb W, a 30% silicon gum SE-30, or a 30% polyethylene glycol 20 M on 60–80 mesh), and HPLC (Shimadzu SPD-6A, OD-ST). The silica gel used for column chromatography was Wakogel C-200 and C-300. Mass spectra were taken with a Shimadzu GCMS-QP1000(A) mass spectrometer. Elemental analyses were carried out at the Elemental Analysis Center of Wako Pure Chemical Industries, Ltd.

Materials

All reagents were obtained from Wako Pure Chemical Industries Ltd., Tokyo Kasei Co., or Aldrich Chemical Co. The reagents and reaction solvents used were further purified by general methods.

Preparation of 2-Pyridyl 2-Selenophenyl Sulfoxide **1e**

A typical experimental procedure is as follows. A solution of 2-selenophenyllithium was prepared by adding 1.1 mmol of *n*-BuLi (as a 1.60 M solution in *n*-hexane) to a solution of selenophene (53 μL, 1 mmol) in THF (10 mL) under a nitrogen atmosphere at −78°C, with a reaction period of 30 minutes. The solution was added to a stirred solution of di-2-pyridyl disulfide (220 mg, 1 mmol) in THF (20 mL) at RT under a nitrogen atmosphere. The reaction mixture was stirred at RT for 1 hour. The solution turned yellow. After 1 hour, water was added to the reaction mixture. The product was extracted with ether three times. The combined ether layer was washed with water and dried over anhyd $MgSO_4$. After the solvent had been evaporated, the residue was purified by silica gel column chromatography with eluting by *n*-hexane and ether (5:5) to give 2-pyridyl 2-selenophenyl sulfide in 85% (205 mg) yield.

2-Pyridyl 2-selenophenyl sulfide Oil; H NMR (δ): 6.90–7.04 (selenophene H_3, pyridine H_5, 2H, m), 7.33 (selenophene H_4, 1H, dd, *J* = 4.5 Hz, 5.4 Hz), 7.45–7.54 (pyridine $H_{3,4}$, 2H, m), 8.26 (selenophene H_5, 1H, d, *J* = 5.4 Hz), 8.43 (pyridine H_6, 1H, d); ^{13}C NMR (DEPT, δ): 78.51, 119.92, 120.15, 130.09, 133.60, 136.78, 138.08, 138.96, 149.06 (ipso position in selenophene ring), 161.63 (ipso position in pyridine ring); MS (*m/z*): 240 (M^+), 215, 160, 117. To a solution of the 2-pyridyl 2-selenophenyl sulfide (205 mg, 0.8 mmol) in CH_2Cl_2 (30 mL) was added a solution of *m*-chloroperbenzoic acid (147 mg, 0.8 mmol) in CH_2Cl_2 (50 mL) at 0°C. The mixture was stirred at 0°C. After 4 hours, aq $Na_2S_2O_3$ soln and aq NaOH soln were added. The product was extracted with $CHCl_3$ three times. The combined $CHCl_3$ layer was washed with water and dried over anhyd $MgSO_4$. After the solvent had been evaporated, the residue was purified by silica gel column chromatography to give 2-pyridyl 2-selenophenyl sulfoxide in 98% (250 mg) yield. Mp: 65.5–66.0°C; ^1H NMR (δ): 7.31 (pyridine H_5, 1H, t), 7.37 (selenophene H_4, 1H, t), 7.88 (selenophene H_3, 1H, d), 7.94 (pyridine H_4, 1H, t, *J* = 7.8 Hz), 8.12 (pyridine H_3, 1H, d, *J* = 7.8 Hz), 8.30 (selenophene H_5, 1H, d), 8.60 (pyridine H_6, 1H, d); ^{13}C NMR (DEPT, δ): 118.22, 124.83, 129.44, 132.97, 137.75, 138.15, 149.71, 152.51 (ipso position in selenophene ring), 165.69 (ipso position in pyridine ring); MS (*m/z*): 256 (M^+), 240, 209, 176, 149, 117, 78; IR: 1088 (cm^{-1})($S \to O$); HRMS: calcd for C_9H_7NOSe, 256.941; anal., 256.947.

Reaction of Sulfoxide **1a** *with 3-Methyl-2-thienyllithium*

A typical experimental procedure is as follows. To a solution of **1a** (627 mg, 3.0 mmol) in THF (10 mL), 3-methyl-2-thienyllithium, which had been prepared from 2-bromo-3-methylthiophene (337 μL, 3.3 mmol) and *n*-BuLi (2.1 mL, 3.3 mmol) in THF (5 mL), was added at −78°C under a nitrogen atmosphere. After 10 minutes, water was added to the reaction mixture. The product was extracted with ether three times. The combined ether layer was washed with water and dried over anhyd $MgSO_4$. After the solvent had been evaporated, the residue was purified by silica gel column chromatography with eluting by *n*-hexane and ether to give **2a**, **3a**, **2b**, **3b**, and **1b**. Yields of obtained compounds were determined by glc analysis using *n*-pentadecane 2-(3-Methyl-2-thienyl)pyridine **2b** [21], as an internal standard, as shown in Equation 2. MS (*m/z*): 177 (M^+), 149, 130, 97. bis-(3-Methyl-2-thienyl)disulfide **3b**. Mp: 62.5–63.0°C; ^1H NMR (δ): 2.04 ($-CH_3$, 6H, s), 6.87 (thiophene H_4, 2H, d, *J* = 5.1 Hz), 7.37 (thiophene H_5, 2H, d, *J* = 5.1 Hz); ^{13}C NMR (DEPT, δ): 14.13 (CH_3), 129.04 (Ar, C_3), 129.92, 130.28, 145.47 (Ar, C_2), MS (*m/z*): 258 (M^+), 129.

3-Methyl-2-thienyl 2-pyridyl sulfoxide **1b** ^1H NMR(δ); 2.60 ($-CH_3$, 3H, s), 6.87 (thiophene H_4, 1H, d, *J* = 4.8 Hz), 7.37 (pyridine H_5, 1H, t, *J* = 7.9 Hz), 7.46 (thiophene H_5, 2H, d, *J* = 4.8 Hz), 7.97 (pyridine H_4, 1H, t, *J* = 7.9 Hz), 8.19 (pyridine H_3, 1H, d), 8.58 (pyridine H_6, 1H, d), ^{13}C NMR (DEPT, δ); 14.63 (CH_3), 119.26, 124.80, 130.23, 131.28, 138.02, 139.91, 144.41 (ipso position in thiophene ring), 149.76, 165.44 (ipso position in pyridine ring), MS (*m/z*): 223 ($M^+ + 1$), 222 (M^+), 206, 190, 97, 78; IR: 1052 (cm^{-1})($S \to O$).

Reaction of Sulfoxide **1a** *with 5-Methyl-2-thienyllithium*

A similar procedure to that described previously was followed with **1a** (627 mg, 3.0 mmol), THF (10 mL), 2-bromo-5-methylthiophene (359 μL, 3.3 mmol), *n*-BuLi (2.1 mL, 3.3 mmol), and THF (5 mL) to give **2a**, **3a**, **2c**, **3c**, and **1c**. Yields of obtained compounds were determined by glc analysis using *n*-pentadecane as an internal standard, as shown in Equation 3. 2-(5-Methyl-2-thienyl)pyridine **2c**. Mp: 82.0–83.0°C [22] bis-(5-Methyl-2-thienyl) disulfide **3c**. Mp: 38.5–40.0°C [23]

Reaction of Sulfoxide **1a** *with 4-Methyl-3-thienyllithium*

A similar procedure to that described previously was followed with **1a** (626 mg, 3.0 mmol), THF (10 mL), 3-bromo-4-methylthiophene (353 μL, 3.3 mmol), *n*-BuLi (2.1 mL, 3.3 mmol), and THF (5 mL) to give **2a**, **3a**, **2d**, **3d**, and **1d**. Yields of obtained compounds were determined by glc analysis using *n*-pentadecane as an internal standard, as shown in Equation 4. **2d**: MS (*m/z*): 174 ($M^+ - 1$), 161, 117, 51. **1d**: MS (*m/z*): 223 (M^+ +), 206, 190, 174, 129, 97, 78, 45.

Reaction of Sulfoxide 1a *with 2-Selenophenyllithium*

A similar procedure to that described previously was followed with **1a** (625 mg, 3.0 mmol), THF (10 mL), selenophene (300 μL, 3.3 mmol), *n*-BuLi (2.1 mL, 3.30 mmol), and THF (5 mL) at −78, −40, 0, 25, and 66°C, respectively, to give **2a**, **3a**, **2e**, **3e** and **1e**. Yields of obtained compounds were determined by glc analysis using *n*-pentadecane as an internal standard, as shown in Equation 6.

2-(2-Selenophenyl)pyridine 2d

Oil; ^{1}H NMR(δ); 7.14 (pyridine H_5, 1H, t), 7.37 (selenophene H_4, 1H, dd, J = 4.5, 6.2 Hz), 7.65–7.70 (pyridine $H_{3,4}$, 2H, m), 7.75 (selenophene H_3, 1H, d, J = 4.5 Hz), 8.06 (selenophene H_5, 1H, d, J = 6.2 Hz), 8.53 (pyridine H_6, 1H, d); ^{13}C NMR (δ); 117.86, 121.94, 126.17, 130.75, 132.91, 136.62, 147.18, 149.57, 153.96. MS (*m/z*): 209 (M^+), 128, 78.

Reaction of Sulfoxide 1a *with 2-Selenophenyllithium in the Presence of Benzaldehyde*

A typical experimental procedure is as follows. To a solution of **1a** (209 mg, 1 mmol) in THF (5 mL), 2-selenophenyllithium, which had been prepared from selenophene (100 μL, 1.1 mmol) and *n*-BuLi (1.5 mL, 1.1 mmol) in THF (10 mL), was added at −78°C under a nitrogen atmosphere. After 5 minutes, benzaldehyde (159 μL, 1.5 mmol) was added to the reaction mixture, and the solution was stirred at −78°C.

After 10 minutes, water was added to the reaction mixture. The products were extracted with ether three times. The combined ether layer was washed with water and dried over anhyd $MgSO_4$. After the solvent had been evaporated, the residue was purified by the silica gel column chromatography to give **2a**, **2e**, **1e**, **4a**, and **4e**. Yields of obtained compounds were determined by actual isolations, as shown in Equation 7.

Phenyl 2-thienylmethanol **4a**. Oil; ^{1}H NMR(δ); 2.38 (–OH, 1H, b), 6.05 (–CH–, 1H, s), 6.86–6.96 (thiophene $H_{3,4}$, 2H, m), 7.23–7.48 (phenyl, thiophene H_5, 6H, m).

Phenyl 2-selenophenylmethanol **4e**. Oil; ^{1}H NMR(δ); 2.68 (–OH, 1H, b), 5.97 (–CH–, 1H, s), 7 (selenophene H_3, 1H, d, J = 4.7 Hz), 7.14 (selenophene H_4, 1H, dd, J = 4.7, 6 Hz), 7.24–7.45 (phenyl H, 5H, m), 7.92 (selenophene H_5, 1H, d, J = 6 Hz)^{13}C NMR (δ); 73.89, 126.13, 126.53, 127.78, 128.37, 128.95, 130.53, 143.36, 155.69.

Reaction of Sulfoxide 1e *with 2-Selenophenyllithium*

A similar procedure to that described previously was followed with **1e** (88.3 mg, 0.34 mmol), THF (5 mL), selenophene (37 μL, 0.4 mmol), *n*-BuLi (0.3 mL, 0.4 mmol), and THF (5 mL) to give **2e**. Yields of obtained compounds were determined by actual isolations, as shown in Equation 8, with sulfoxide **1e** used as a starting material being recovered in a yield of 31%.

REFERENCES

[1] S. Oae, *Croat, Chem. Acta*, *59*, 1986, 129.

[2] S. Oae, *Phosphorus and Sulfur*, *27*, 1986, 13.

[3] S. Oae, *Reviews on Heteroatom Chemistry*, MYU, Tokyo, vol. 1, p. 304 (1988).

[4] S. Oae: *Reviews on Heteroatom Chemistry*, MYU, Tokyo, vol. 4, p. 195 (1991).

[5] T. Kawai, Y. Kotera, N. Furukawa, S. Oae, M. Ishida, T. Takeda, S. Wakabayashi, *Phosphorus and Sulfur*, *34*, 1987, 139.

[6] S. Wakabayashi, M. Ishida, T. Takeda, S. Oae, *Tetrahedron Lett.*, *29*, 1988, 4441.

[7] S. Oae, T. Takeda, S. Wakabayashi, *Tetrahedron Lett.*, *29*, 1988, 4445.

[8] T. Kawai: Ph.D. Thesis, University of Tsukuba, Tsukuba, Japan, 1985.

[9] N. Furukawa, T. Shibutani, H. Fujiwara, *Tetrahedron Lett.*, *29*, 5845.

[10] T. Shibutani, H. Fujiwara, N. Furukawa, S. Oae, *Heteroatom Chem.*, *2*, 1991, 521.

[11] M. Yoshihara, M. Kakumoto, T. Maeshima, S. Oae: ICHAC-Kobe-87, July 19–24, 1987.

[12] S. Oae, T. Kawai, N. Furukawa, *Tetrahedron Lett.*, *25*, 1984, 69.

[13] S. Oae, T. Kawai, N. Furukawa, F. Iwasaki, *J. Chem. Soc., Perkin Trans., 2*, 1987, 405.

[14] Y. Uchida, T. Takaya, S. Oae, *Heterocycles*, *30*, 1990, 347.

[15] S. Oae, Y. Inubushi, M. Yoshihara, *Heteroatom Chem.*, *4*, 1993, 185.

[16] T. Kawai, N. Furukawa, S. Oae, *Tetrahedron Lett.*, *25*, 1984, 2546.

[17] S. Oae, T. Kawai, N. Furukawa, *Phosphorus and Sulfur*, *34*, 1987, 123.

[18] S. Oae, Y. Uchida, *Acct. Chem. Res.*, *24*, 1991, 202.

[19] S. Oae: *Organic Sulfur Chemistry—Structure and Mechanism*, CRC Press, Boca Raton, FL, ch. 5, p. 183 (1991).

[20] J. Moe, A. E. Dorigo, K. Morokuma, *Chem. Phys. Lett., 204*, 1993, 65.

[21] D. D. Perrin: *Dissociation Constants of Organic Bases in Aqueous Solution*, Butterworth and Co. Ltd., London.

[22] M.-J. Shiao, L.-H. Shih, W.-L. Chia, T.-Y. Chau, *Heterocycles, 32(11)*, 1991, 2111.

[23] M. A. Kalik, M. L. Kirmalova, *Izr. Akad. Nauk. SSSR. Ser. Khim., 9*, 1964, 1675.