REACTION OF AROMATIC N-OXIDES WITH DIPOLAROPHILES. XVII. CYCLOADDITION BEHAVIOR OF ALLENES TOWARD PYRIDINE N-OXIDES AND FORMATION OF AZETIDINE-TYPE CYCLOADDUCT

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Abstract — 3,5-Dimethylpyridine N-oxide was allowed to react with phenylsulfonylpropadiene in $CHCl_3$ at room temperature to give a mixture of the 1:1 [1,5] sigmatropic rearrangement product and the 1:2 azetidine-type cycloadduct. The structure of the azetidine-type cycloadduct was determined by single crystal X-ray analysis. The reaction behavior and the regioselectivity are discussed in terms of the frontier molecular orbital considerations.

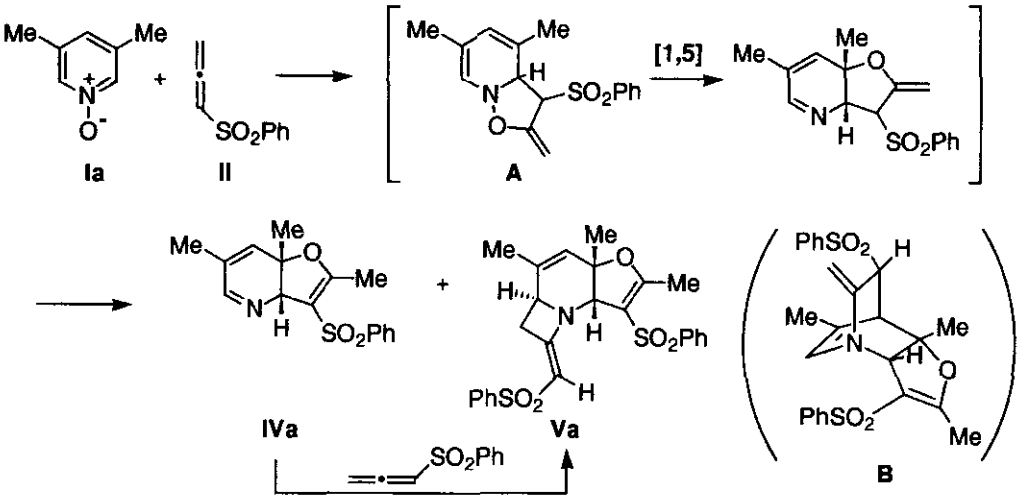
Pyridine N-oxides are versatile compounds showing high chemical reactivity in electrophilic and nucleophilic substitution reactions, molecular complex formations and catalytic reactions.[1a] However, although pyridine N-oxides have nitrone moiety, the 1,3-dipolar cycloadditions with unsaturated compounds have been scarcely known except for acetylenes[1b] and heterocumulenes[2a,b] because of the high degree of the ground-state stabilization arising from the aromaticity.[2]

In the past several years, we have examined the pericyclic reactions of pyridine N-oxides with various dipolarophiles and elucidated the mechanistic aspects of the reaction from the kinetic and frontier molecular orbital (FMO)[3] viewpoints.[2] Recently, we reported that dimethyl 2,3-pentadienedioate showed markedly high cycloaddtion reactivity toward pyridine N-oxides.[4] This paper deals with the pericyclic reaction of 3,5-disubstituted pyridine N-oxides with phenylsulfonylpropadiene (II).

RESULTS

Cycloaddition of 3,5-Dimethylpyridine N-Oxide (Ia) with Phenylsulfonylpropadiene (II) 3,5-Dimethylpyridine N-oxide (Ia) was allowed to react with phenylsulfonylpropadiene (II) in $CHCl_3$ at room temperature to give a mixture of two

products (IVa and Va). The products were separated by chromatography on silica gel. The mass spectrum (ms) of IVa showed a molecular peak (M^+) at *m/z* 303 and a fragment peak of M^+-$PhSO_2$ at *m/z* 162 suggesting the formation of 1:1 cycloadduct of Ia and II. The ^{1}H-nuclear magnetic resonance (^{1}H-nmr) spectrum of IVa exhibited three Me signals at 1.39, 1.85 and 2.18 ppm. The ^{13}C-nuclear magnetic resonance (^{13}C-nmr) spectrum of IVa showed two sp^3 carbons except for the three Me carbons. These facts suggest that the 1:1 cycloadduct is not the primary adduct (A) but the [1,5] sigmatropic rearrangement product (IVa).



Scheme 1

On the other hand, the ms of Va showed an M^+ at *m/z* 483 corresponding to an 1:2 adduct of Ia and II. As IVa reacted with II to give Va, we supposed Va as a hetero Diels-Alder reaction product (B) of IVa with II. However, the spectral data of Va could not sufficiently satisfy the structure. Therefore we performed the single X-ray crystal analysis of Va. The single crystals suitable for X-ray analysis were obtained by slow evaporation of a C_6H_6-AcOEt solution. The structure was solved by the direct method using the MULTAN78 programs[5] and refined by the block-diagonal least-square method. The final *R* value obtained was 0.038. The computer-generated drawing of Va with numbering sequence is depicted in Figure 1. As shown in Figure 1, Va is considered to be formally a [2+2] cycloadduct of IVa and II, in which the azetidine ring was formed *via* stereospecific attack of the terminal double bond of II toward the C=N bond of IVa from sterically less hindered site. The N13 is an sp^3 atom

forming planar azetidine ring. The exocyclic double bond between C10 and C11 and endocyclic double bond between C21 and C23 are 1.355Å and 1.336Å, respectively.

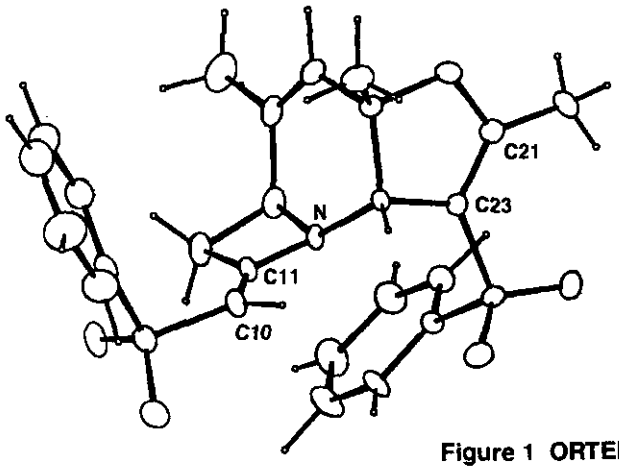
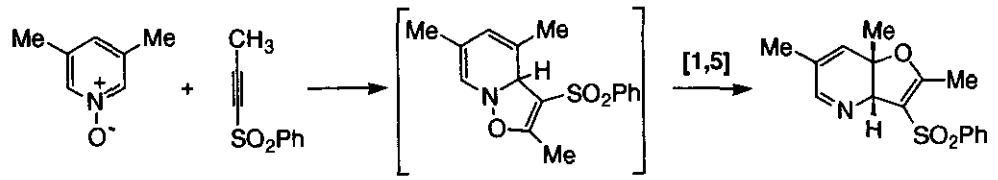


Figure 1 ORTEP Drawing of Va

Cycloaddition of 3,5-Dimethylpyridine N-Oxide (Ia) with 1-Phenylsulfonylpropyne (III) and 3-Phenylsulfonylpropyne (III') The reaction of Ia with III was examined to give IVa as a sole product in 41% yield. The formation of Va was not observed at all. Further, unactivated acetylene (III') ($PhSO_2CH_2C{\equiv}CH$) did not show any cycloaddition reactivity toward Ia and IVa.



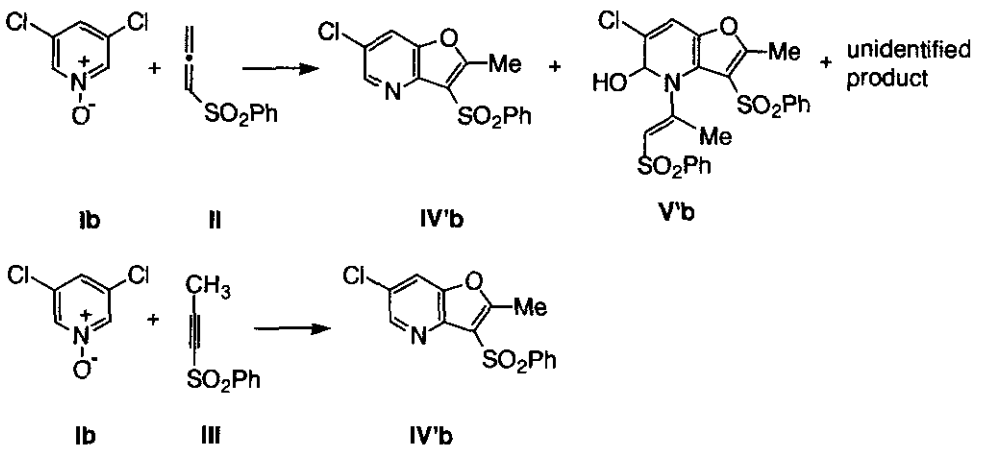
Ia III IVa

Scheme 2

Cycloaddition of 3,5-Dichloropyridine N-Oxide (Ib) with Phenylsulfonylpropadiene (II) and 1-Phenylsulfonylpropyne (III) 3,5-Dichloropyridine N-oxide (Ib) was allowed to react with II to give the aromatized product (IV'b), its N-vinyl derivative (V'b) and an unidentified product. On the other hand, Ib reacted with III at room temperature to give IV'b as a sole product in 57% yield.

The ms and ^{1}H-nmr spectral data indicated that IV'b is furopyridine-type compound resulted from the dehydrohalogenation of the [1,5] sigmatropic rearrangement product (the spectral data are given in experimental section). The ms of V'b showed an

M^+-H_2O at *m/z* 487 and 489 (relative intensity 3:1, 1:2 adduct-HCl). The ^{1}H-nmr spectrum showed the presence of two methyl groups, two phenyl groups and two olefinic protons. The D_2O exchangable OH proton appeared at 3.47 ppm. These spectral data suggest formation of the intermediary N-ylide derivative which undergoes addition reaction of H_2O to give V'b.



Scheme 3

DISCUSSION

The phenylsulfonylpropadiene (II) used here was generated *in situ* from 3-phenylsulfonylpropyne (III') according to the method of Stirling[6a] using triethylamine as catalyst. The heat of isomerization between acetylene and allene is relatively small (1.3 kcal/mol).[7] Therefore, we had a doubt that IVa and Va were arisen from the reaction of Ia with a small amount of III and III'. However, as described above, the product distribution for the reaction of Ia with II is quite different from the one for the reaction of III; the formation of Va was recognized only in the reaction of Ia with II. These facts support that in the synthetic conditions used, the equilibrium lies well over to the side of the allene (II) and Va was arisen from the reaction of Ia with II. As hitherto mentioned, II showed an interesting and high cycloaddition reactivity toward pyridine N-oxides (I) even at room temperature. To understand the reaction behavior, the modified neglect of diatomic overlap (MNDO) calculations[7] were performed. As can be seen in Figure 2, the important interaction will be HOMO (dipole) /LUMO (allene) ("normal-type reaction"),[3a] in which regiochemistry should follow in the usual way from the large-large/small-small interaction.[3b,c] Thus formed primary cycloadduct rearranges [1,5] sigmatropically to IVa,[2,4] followed by isomer-

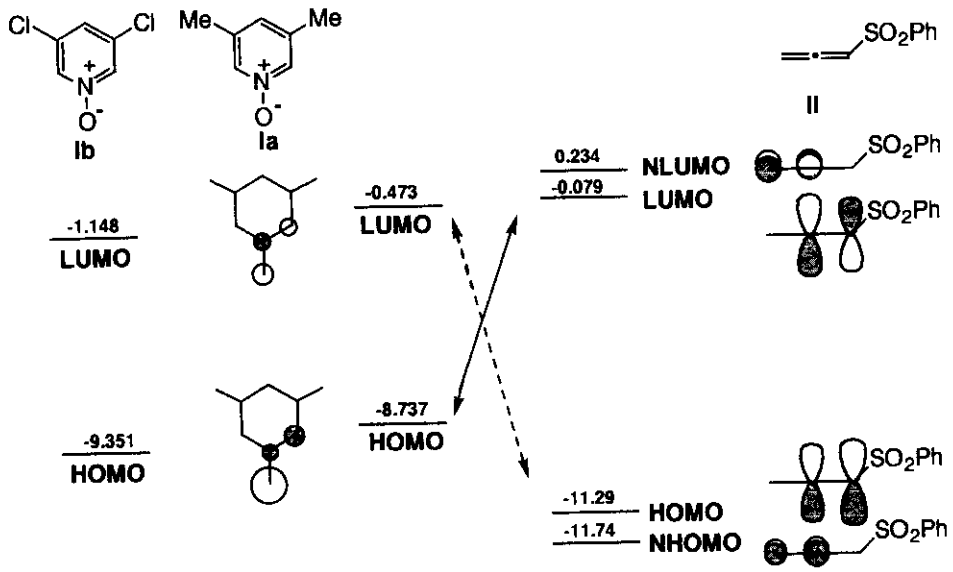


Figure 2 FMO Interactions between I and II

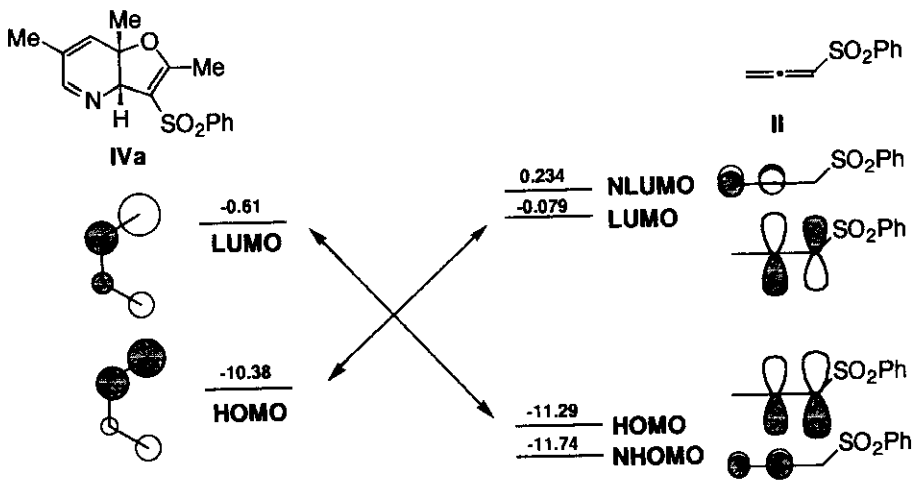
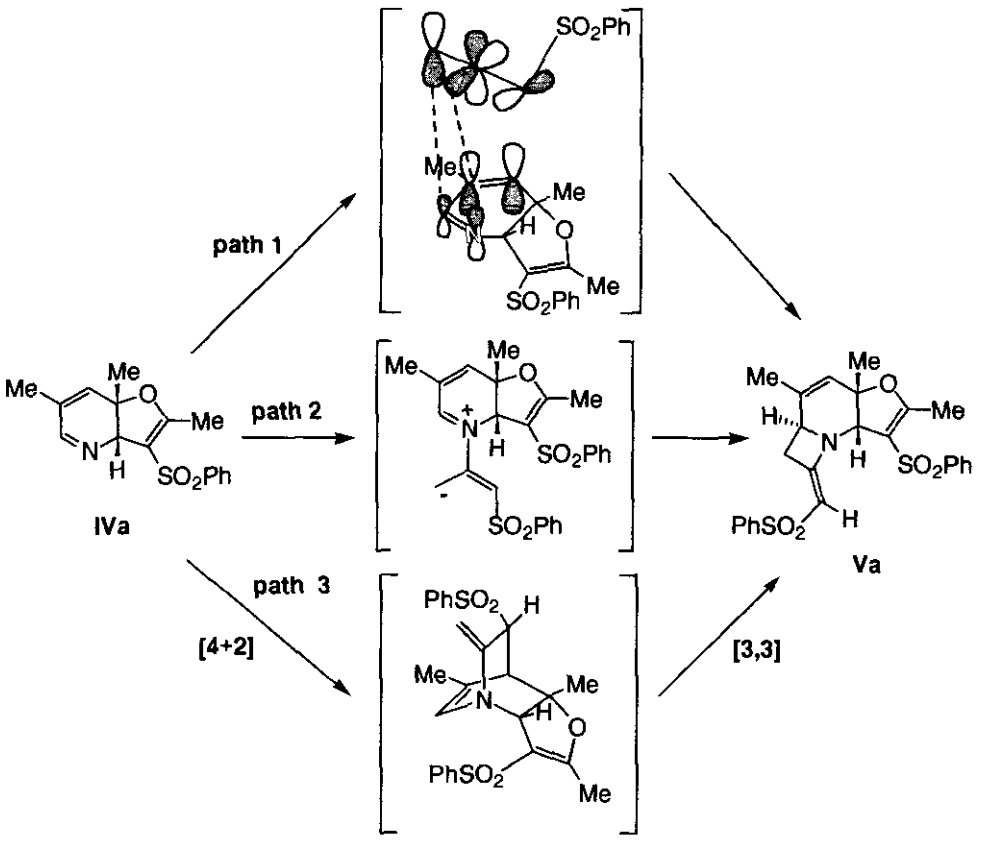


Figure 3 FMO Interactions between IVa and II



Scheme 4

ization of exocyclic double bond to endocyclic one. On the formation mechanism of Va from IVa and II, we supposed three possibile reaction pathways: 1) [2+2] cycloaddition of terminal double bond of II with C=N of IVa; 2) stepwise, ionic cycloaddition *via* ylide formation; 3) sequential pericyclic reaction (hetero Diels-Alder (DA) reaction - Cope rearrangement). Inspection of the MNDO calculation data of the [1,5] sigmatropic rearrangement product (IVa) implies that path 1 can be ruled out because the coefficients upon the C=N moiety are relatively small. The reaction of IVa with II was not affected by solvent polarity, ruling out path 2. Path 3 is considered to be the most plausible at present. The perturbation calculations on the hetero DA reaction of IVa with II suggest that both FMO interaction energies are almost identical ("neutral-type reaction"), indicating that the coulombic interaction plays a leading role in de-

termination of the regioselectivity, responsible for the observed regiochemistry of the hetero DA adduct.[3c]

The previous study of this series revealed that the reactivity of pyridine N-oxides toward olefins is considerably lower than the case of aliphtatic N-oxides because of the high degree of atomaticity.[2] The remarkably enhanced cycloaddition reactivity of electron-deficient allenes toward pyridine N-oxides may be arisen from an additional bonding overlap of the p_y orbitals of the both addends.[4] The details of the multistep pericyclic reaction mechanism will be reported elsewhere in near future.

EXPERIMENTAL

All melting points are uncorrected. ^{1}H-Nmr spectra were taken with Hitachi R-600 (60 MHz) and JEOL GX-400 (400 MHz) spectrometers for *ca.* 10 % (w/v) solution with tetramethylsilane (TMS) as an internal standard; chemical shifts are expressed in δ values. Ir spectra were recorded on a Hitachi 270-30 infrared spectrophotometer equipped with a double-blade grating. Ms were taken with a JEOL JMS-DX303HF double-focussing spectrometer operating at an ionization potential of 75eV. Molecular orbital calculations were performed on a FACOM M-780 computer at the Computer Center of Kumamoto University and on a Fujitsu S4/2 engineering work station (EWS). Graphic analysis of the MO calculation and X-ray data were performed on a Fujitsu S4/2 EWS and a Fujitsu FM R-60HD personal computer. All structure-solving programs were from the Computer Center of Kumamoto University with the Universal Crystallogra-phic Computation Program System (UNICS III).[8]

Materials 3,5-Dimethylpyridine N-oxide (Ia), 3,5-dichloropyridine N-oxide (Ib) were prepared according to the established methods.[1] *Phenylsulfonylpropadiene* (II), 1-phenylsulfonylpropyne (III) and 3-phenylsulfonylpropyne (III') were prepared according to the established method by Stirling[6a] and Sato[6b] from thiophenol and propargyl bromide.

Cycloaddition of 3,5-Dimethylpyridine N-Oxide (Ia) with Phenylsulfonylpropadiene (II) A solution of 3-phenylsulfonylpropyne (III') (0.8 g, 4.4 mmol) and triethylamine (1.6 ml) in 20 ml of $CHCl_3$ was stirred for 15 min at room temperature. After the disapperance of III' had been recognized by tlc, Ia (0.27 g, 2.2 mmol) was added and stirred for further 11 h. The solvent was removed *in vacuo* and the residue was purified by chromatography on silica gel using C_6H_6-AcOEt (5:1) as an eluent to give IVa (0.10 g, 14.9%, mp 117-120 °C, colorless prisms from C_6H_6-AcOEt) and Va (0.16 g, 15.0%, mp 227-229 °C, colorless prisms from C_6H_6-AcOEt). IVa; ^{1}H-nmr ($CDCl_3$): 1.39 (d, J=1.83 Hz, 3H, C_{7a}-Me), 1.85 (br s, 3H, C_6-Me), 2.18 (s, 3H, C_2-Me), 4.92 (br s, 1H, C_{3a}-H), 5.78 (d, J=1.83 Hz, 1H, C_7-H), 7.50 (m, 1H, C_5-H), 7.46 (m, 5H,

aromatic CH); ^{13}C-nmr ($CDCl_3$): 13.9 (q), 19.2 (q), 27.7 (q), 69.0 (d), 80.9 (s), 112.0 (s), 125.8 (d), 127.4 (d), 128.6 (d), 128.8 (s), 132.5 (d), 143.5 (s), 155.3 (d), 167.0 (s); EI-ms: *m/z*: 303 (M^+), 288 (M^+-Me), 162 (M^+-$PhSO_2$); ir (KBr) cm^{-1}: 1154 (SO_2), 1304 (SO_2), 1630 (C=C); *Anal.* Calcd for $C_{16}H_{17}NO_3S$: C,63.34; H, 5.65; N, 4.62. Found: C, 63.59; H, 5.73; N, 4.65. Va; ^{1}H-nmr ($CDCl_3$): 1.46 (s, 3H, C_{6a}-Me), 1.61 (d, *J*=1.47 Hz, 3H, C_7-Me), 2.25 (d, *J*=1.46 Hz, 3H, C_2-Me), 2.95 (m, 2H, C_6-H), 3.12 (m, 1H, C_{6a}-H), 4.49 (d, *J*=1.46 Hz, 1H, C_{3a}-H), 5.27 (d, *J*=1.47 Hz, 1H, C_5-H), 5.35 (dd, *J*=1.47, 1.46 Hz, 1H, C_8-H), 7.26 (m, 10H, aromatic CH); ^{13}C-nmr ($CDCl_3$): 14.2 (q), 18.0 (q), 27.8 (q), 34.3 (t), 55.0 (d), 63.2 (d), 82.2 (s), 92.5 (d), 106.5 (s), 122.9 (d), 126.0 (d), 127.1 (d), 128.7 (d), 129.0 (d), 132.1 (d), 132.9 (d), 138.4 (s), 142.1 (s), 145.2 (s), 163,8 (s), 167.4 (s); EI-ms: *m/z* 483 (M^+), 342 (M^+-$PhSO_2$); ir (KBr) cm^{-1}: 1136 (SO_2), 1300 (SO_2), 1626 (C=C); *Anal.* Calcd for $C_{25}H_{25}NO_5S_2$: C, 62.08; H, 5.22; N, 2.90. Found: C, 61.83; H, 5.06; N, 2.90.

Cycloaddition of 3,5-Dimethylpyridine N-Oxide (Ia) with 1-Phenylsulfonylpropyne (III) A solution of III (0.75 g, 4.17 mmol) and Ia (0.51 g, 4.17 mmol) in 8 ml of $CHCl_3$ was stirred for 11 h at room temperature. The solvent was removed *in vacuo* and the residue was purified by chromatography on silica gel using C_6H_6-AcOEt (5:1) as an eluent to give IVa (0.52 g, 40.8%, mp 117-120 °C, colorless prisms from C_6H_6-AcOEt).

Cycloaddition of IVa with Phenylsulfonylpropadiene (II) A solution of 3-phenylsulfonylpropyne (III') (0.12 g, 0.67 mmol) and triethylamine (0.25 ml) in 5 ml of $CHCl_3$ was stirred for 15 min at room temperature. After the disapperance of III' had been recognized by tlc, IVa (0.20 g, 0.67 mmol) was added and stirred further 48 h. The solvent was removed *in vacuo* and the residue was purified by chromatography on silica gel using C_6H_6-AcOEt (4:1) as an eluent to give Va (0.12 g, 37.5%, mp 227-229 °C, colorless prisms from C_6H_6-AcOEt).

Cycloaddition of 3,5-Dichloropyridine N-Oxide (Ib) with Phenylsulfonylpropadiene (II) A solution of 3-phenylsulfonylpropyne (III') (1.50 g, 8.3 mmol) and triethylamine (1.0 ml) in 10 ml of C_6H_6 was stirred for 15 min at room temperature. After the disapperance of III' had been recognized by tlc, Ib (0.68 g, 4.2 mmol) was added and stirred for further 48 h. The solvent was removed *in vacuo* and the residue was purified by chromatography on silica gel using $CHCl_3$-AcOEt (40:1) as an eluent to give IV'b (0.14 g, 11%, mp 141-143 °C, colorless prisms from C_6H_6-AcOEt) , V'b (0.24 g, 12%, oil) and 0.38 g of unidentified product. IV'b: ^{1}H-nmr ($CDCl_3$): 2.88 (s, 3H, C_2-Me), 7.70 (d, *J*=2.20 Hz, 1H, C_7-H), 8.57 (d, *J*=2.20 Hz, 1H, C_5-H), 7.48-7.59 (m, 3H, aromatic CH), 8.20-8.23 (m, 2H, aromatic CH); ^{13}C-nmr ($CDCl_3$): 14.3 (q), 118.5 (d),

118.9 (s), 128.3 (s), 127.6 (d), 129.1 (d), 133.6 (d), 141.8 (s), 141.9 (s), 146.1 (s), 146.4 (d), 165.0 (s); EI-ms: *m/z*: 307, 309 (M^+, relative intensity 3:1); ir (KBr) cm^{-1}: 1152 (SO_2), 1324 (SO_2); *Anal.* Calcd for $C_{14}H_{10}NO_3ClS$: C, 54.64; H, 3.26; N, 4.55. Found: C, 54.86; H, 3.26; N, 4.46. V'b; ^{1}H-nmr ($CDCl_3$): 1.75 (s, 3H, C_2-Me), 2.30 (s, 3H, C=C-Me), 3.47 (s, 1H, OH), 5.62 (s, 1H, C=C-H), 7.55 (m, 6H, aromatic CH), 7.87 (m, 4H, aromatic CH), 7.87 (d, *J*=2.20 Hz, 1H, C_7-H), 8.56 (d, *J*=2.20 Hz, 1H, C_5-H); ^{13}C-nmr ($CDCl_3$): 17.4 (s), 17.7 (s), 111.2 (d), 128.2 (s), 131.7 (s), 133.7 (s), 137.2 (d), 141.6 (s) 142.4 (s), 147.3 (d), 158.5 (s), 165.1 (s); EI-ms: *m/z*: 487, 489 (M^+-H_2O, relative intensity 3:1); ir (KBr) cm^{-1}: 1152 (SO_2), 1306 (SO_2), 1632 (C=C); Hrms Found: 488.0393. Calcd for $C_{23}H_{19}NO_5{}^{35}ClS_2$, M^+-OH, 488.0396

Cycloaddition of 3,5-Dichloropyridine N-Oxide (Ib) with 1-Phenylsulfonylpropyne (III) A solution of III (0.80 g, 4.4 mmol) and Ib (0.73 g, 4.4 mmol) in 4 ml of $CHCl_3$ was stirred for 46 h at room temperature. The solvent was removed *in vacuo* and the residue was purified by chromatography on silica gel using $CHCl_3$-C_6H_6 (1:1) as an eluent to give IV'b (0.77 g, 56.9%, mp 141-143 °C, colorless prisms from C_6H_6-AcOEt)

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