

Cascade Reaction of Imines with Phenylsulfinylallene. X-Ray Structure of the Product and Its Formation Mechanism

Shigeru OISO,^a Yasuyuki YOSHITAKE,^a Masashi ETO,^b and Kazunobu HARANO^{*,a}

^a Faculty of Pharmaceutical Sciences, Kumamoto University; 5-1 Oe honmachi, Kumamoto 862-0973, Japan; and ^b School of Agriculture, Kyushu Tokai University; 5435 Kawayo, Choyoson, Asogun, Kumamoto 869-1404, Japan.

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The structure of the product derived from the reaction of a dihydropyridine derivative with phenylsulfinylallene has been clarified by a single crystal X-ray analysis and the formation mechanism is discussed on the basis of the reaction-path calculations by semiempirical and *ab initio* molecular orbital methods.

Key words phenylsulfinylallene; dihydropyridine; imine; *ab initio*; PM3; X-ray analysis

Previously, we reported the reaction of phenylsulfonylallene (**2a**) with 6,7a-dimethyl-3-phenyl-3a,7a-dihydro-3H-oxazolo[4,5-*b*]pyridin-2-one (**1a**)¹ derived from the 1,3-dipolar reaction of lutidine *N*-oxide with phenyl isocyanate followed by the 1,5-sigmatropic shift gave the azetidine derivative (**3aa**). On the basis of the MO calculation of the reaction pathway, we proposed that the reaction of the imine with **2a** proceed *via* a nonconcerted two-step mechanism in which the allene attacks toward the lone pair of nitrogen atom of imine moiety. Isolation of two stereoisomeric 2 : 1 cycloadducts from the reaction of 3,3-dimethyl-3H-indole with phenylsulfonylallene strongly supports the presence of a zwitterionic reaction intermediate.²⁾

As an extension of this reaction, we also studied the reaction of **1a** with phenylsulfinylallene (**2b**).

However, we could not obtain a similar cycloadduct ascribable to the thermally-allowed pericyclic reaction. The structure and formation mechanism of the product were unsettled.

Recently, the structure of **3ab** was confirmed by X-ray analysis, indicating that **3ab** was produced *via* an interesting cascade-type reaction pathway. This prompted us to investigate the formation mechanism of **3ab**.

Results and Discussion

Inspection of the mass spectrum of the product indicated the 1 : 1 adduct and the presence of M⁺ - PhS (*m/z* 297) frag-

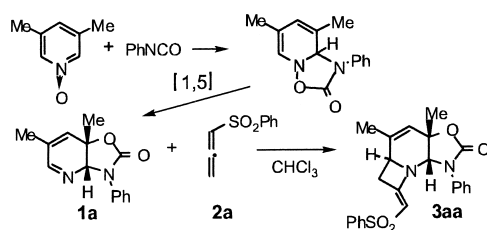


Chart 1

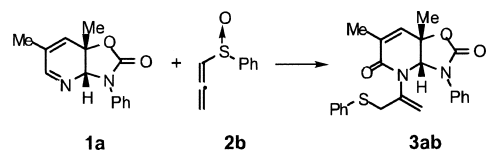


Chart 2

ment ion. The terminal vinyl proton signals (δ 5.40, 4.76) were found in the ¹H-NMR spectrum indicating that the double bond adjacent to the sulfoxide group reacted with the imine moiety. The ORTEP³⁾ drawing of **3ab** is depicted in Fig. 1.

As shown in Fig. 1, the product **3ab** is a dihydropyridone derivative, in which the sulfinyl oxygen and olefinic hydrogen intramolecularly migrate to separate positions. To clarify the formation mechanism, we performed the reaction-path calculation using a model reaction of dihydropyridine with methylsulfinylallene by MNDO-PM3 (PM3)⁴⁾ semiempirical molecular orbital technique. As pointed out in the preceding paper,²⁾ the reaction takes place *via* a stepwise pathway. The transition state of [4+2] π cycloaddition could not be located in various TS model structures but **TS1** leading to a zwitterionic intermediate (**IM1**) was obtained (Fig. 2).

The reaction-path calculation using the O \cdots C2 distance of **IM1** as a reaction coordinate gave the cyclic intermediate (**IM2**) *via* **TS2**. Then, **IM2** undergoes S-O bond scission and hydrogen migration to the α carbon of the sulfur atom to give the final product (**PDT**) *via* **TS3**. The intrinsic reaction coordinate (IRC) calculations using TS structures confirmed the proposed reaction pathway. The reaction is formally assumed to be a 4 π +2 π reaction of the =C=C-S \rightarrow O and -C=N- moieties.

The reaction barrier of the ring opening reaction for PM3 calculation is 25.0 kcal/mol. The *ab initio*⁵⁾ calculation at HF/6-31G* level supports the TS calculation of the semiempirical MO method, in which the S-O bond scission more advances than that of the semiempirical method, showing that the reaction barrier is 18.9 kcal/mol (Fig. 3).

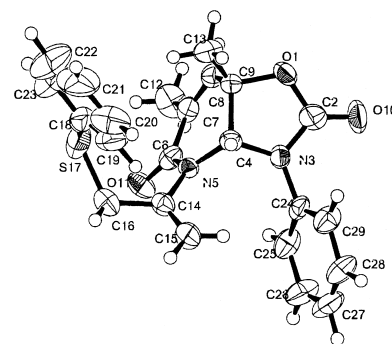


Fig. 1. ORTEP Drawing of **3ab**

* To whom correspondence should be addressed. e-mail: harano@gpo.kumamoto-u.ac.jp

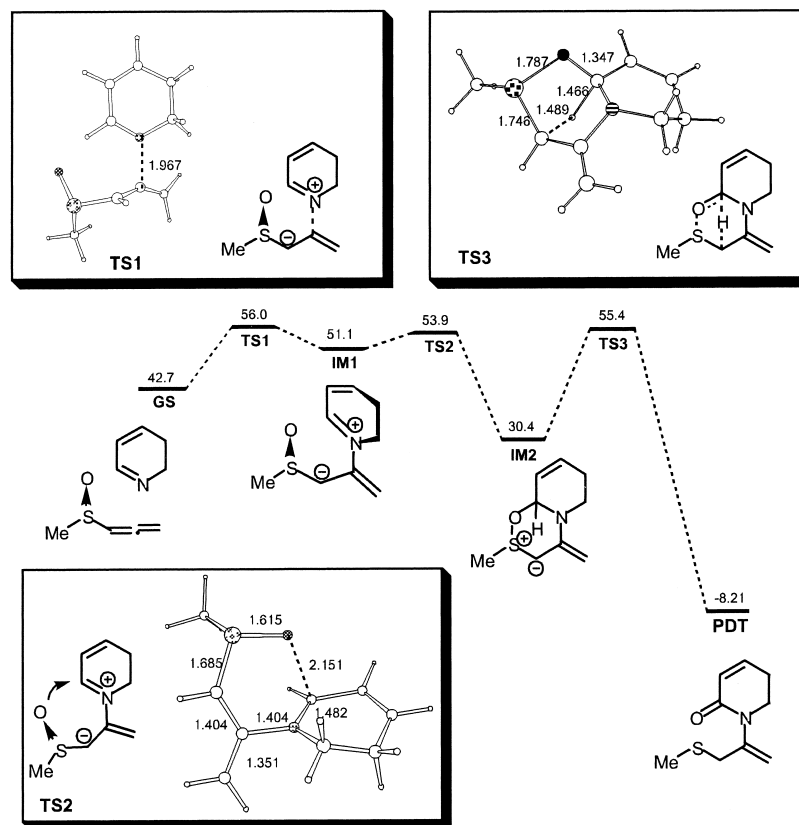


Fig. 2. PM3-Energy Profile for the Reaction of Dihydropyridine with Methylsulfinylallene
Heats of formation are given in kcal/mol and bond lengths are given in Å.

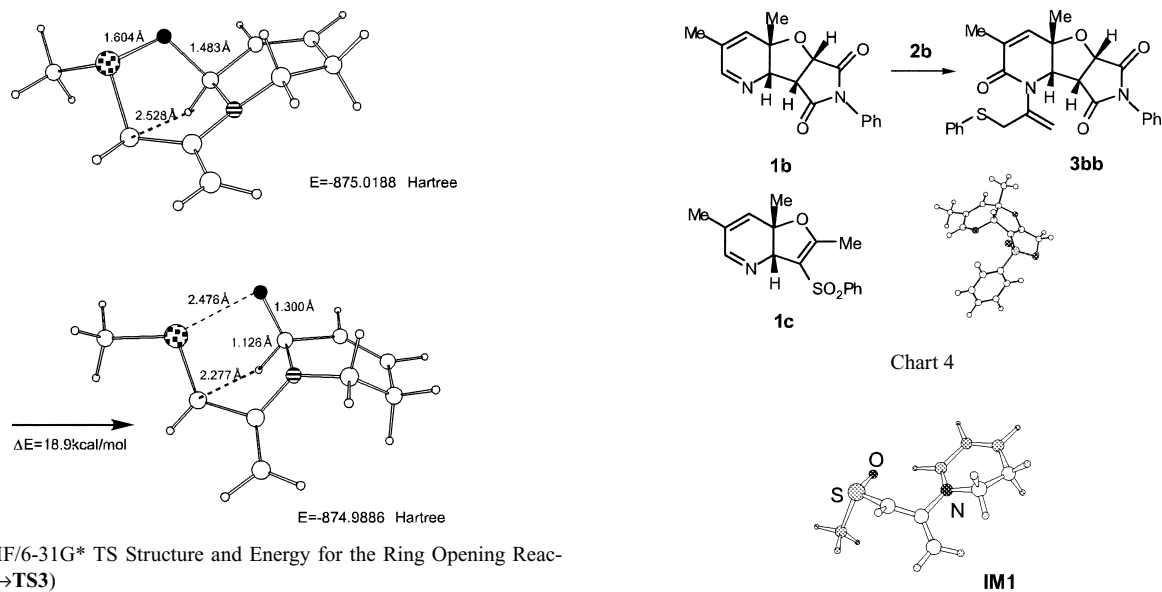
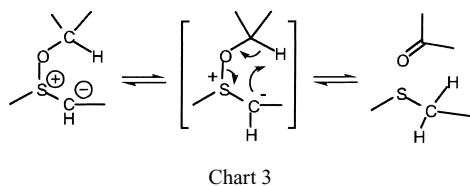


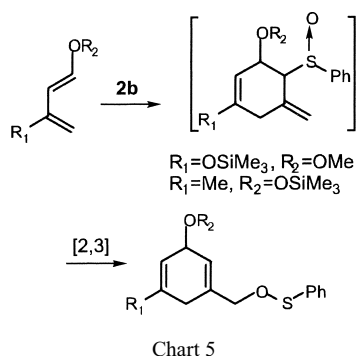
Fig. 3. HF/6-31G* TS Structure and Energy for the Ring Opening Reaction (IM2→TS3)



The reaction mechanism of the ring opening of the cycloadduct to the final product is considered to fall under the category of the elimination reaction of olefins from ylides.⁶⁾

The reaction of this type similarly occurred in the 1,3-dipolar reaction product **1b**⁷⁾ but not in **1c**,⁸⁾ in which the steric interference between the phenyl group of **1c** and **2b** seems to be serious, judging from the calculated conformation of **1c**.

On the basis of the frontier molecular orbital theory, an al-



ternative reaction pathway seems to be possible, in which the sulfoxide oxygen atom may migrate to the C2 carbon *via* a 1,5-sigmatropic shift. However, inspection of the **IM1** structure indicates that the geometrical requirement for the suprafacial orbital interaction seems to be unfavorable.

The reaction behavior of the present reaction is in sharp contrast to the known reaction of the butadiene derivatives with **2b** (Chart 5).⁹⁾ The difference in the reaction behavior is probably due to the nature of the HOMO. The HOMO of 1-azadiene localizes at the lone pair of the nitrogen atom leading to the stepwise reaction.

The present reactions occur in 3,3-dimethyl-3*H*-indole and some straight-chain imines, however the yields are poor.

In summary, the cycloaddition reaction of dihydropyridines with phenylsulfanylallene proceeds in a stepwise manner to give the six-membered cycloadduct which then undergoes O–S bond scission with hydrogen migration *via* a five-membered cyclic transition state to produce the pyridone derivative.

Experimental

Melting points were uncorrected. The IR spectra were taken with a Hitachi 270-30 spectrophotometer. ¹H- and ¹³C-NMR spectra were taken with JEOL JNM-EX 270 and JNM-A 500 spectrometers for *ca.* 10% solution (CDCl₃) with tetramethylsilane (TMS) as an internal standard. Chemical shifts are expressed as δ values and the coupling constants (*J*) are expressed in Hz. Mass spectra were obtained using a JEOL JMS-DX 303 instrument.

Molecular Orbital Calculation Semiempirical MO calculations were performed on a Compaq ML330 personal computer. The *ab initio* calculations were carried out on a HP Exemplar Technical Server TS VS2550 KS in the Kumamoto University Information Processing Center.

The ground states (GS) were optimized by the EF routine implemented in the WinMOPAC 3.0 program package using MNDO-PM3 (PM3) approximation. The transition states (TS) were located by the transition-state location routine.

The fully-optimized geometries calculated by PM3 method were used as starting geometries for the *ab initio* calculations. Graphical analysis of the MO calculation data was performed on a Macintosh G3 personal computer.

Material Phenylsulfanylallene (**2b**)⁹⁾ and 6,7a-dimethyl-3-phenyl-3a,7a-dihydro-3*H*-oxazolo[4,5-*b*]pyridin-2-one (**1a**)¹⁾ were prepared according to the reported methods.

Reaction of 2b with 1a A mixture of **1a** (484 mg, 2 mmol) and **2b** (656 mg, 4 mmol) in benzene (4 ml) was refluxed for 12 h. The solvent was removed under reduced pressure and the residual oil was purified by chromatography on silica gel. Elution with benzene–AcOEt (2 : 1) gave **3ab** as colorless prisms (171 mg, 21%). mp 143–145 °C (from EtOH). IR (KBr) cm^{-1} : 1760 (oxazolone >C=O), 1680 (dihydropyridone >C=O), 1642 (>C=CH₂). ¹H-NMR (270 MHz; CDCl₃) δ : 1.77 (3H, s, CH₃), 2.01 (3H, s, =C–CH₃), 3.34 (1H, d, *J*=15.2, –S–CH₂–), 3.85 (1H, s, >N–CH<), 3.95 (1H, d, *J*=15.2, –S–CH₂–), 4.76 (1H, s, =CH₂), 5.40 (1H, s, =CH₂), 6.23 (1H, m, =CH–C), 7.10–7.41 (10H, m, aromatic CH). ¹³C-NMR (125 MHz, CDCl₃) δ : 16.6, 23.0, 37.3, 77.2, 82.5, 113.8, 123.9, 126.4, 128.4, 128.9,

129.0, 129.1, 129.8, 130.9, 135.2, 135.5, 135.6, 144.6. MS *m/z*: 297 (M⁺–PhS), 253 (M⁺–PhS–CO₂). *Anal.* Calcd for C₂₃H₂₂N₂O₃S: C, 67.96; H, 5.45; N, 6.89. Found: C, 68.14; H, 5.46; N, 6.89.

Reaction of 2b with 1b A mixture of **1b** (296 mg, 1 mmol) and **2b** (328 mg, 2 mmol) in benzene (2 ml) was refluxed for 6 h. The solvent was removed under reduced pressure. The residue was recrystallized from acetone to give **3bb** as colorless prisms (322 mg, 70%). mp 228–230 °C (from acetone). IR (KBr) cm^{-1} : 1712 (imide >C=O), 1668 (dihydropyridone >C=O), 1632 (>C=CH₂). ¹H-NMR (500 MHz, CDCl₃) δ : 1.59 (3H, s, CH₃), 1.75 (3H, s, =C–CH₃), 3.72 (1H, dd, *J*=9.8, 8.3, >CH(C=O)–), 3.95 (1H, d, *J*=14.7, –S–CH₂–), 4.07 (1H, dd, *J*=9.8, 1.83, >N–CH–), 4.18 (1H, d, *J*=14.7, –S–CH₂–), 4.91 (1H, d, *J*=8.3, –O–CH(C=O)–), 5.21 (1H, s, =CH₂), 5.47 (1H, s, =CH₂), 6.21 (1H, s, =CH–C), 7.19–7.45 (10H, m, aromatic CH). ¹³C-NMR (125 MHz, CDCl₃) δ : 17.3, 24.5, 37.8, 47.1, 70.4, 75.5, 80.1, 113.3, 125.6, 126.4, 128.8, 129.0, 129.1, 129.5, 131.1, 132.7, 135.8, 138.7, 146.1, 162.2, 171.9, 173.7. MS *m/z*: 351 (M⁺–PhS). *Anal.* Calcd for C₂₆H₂₄N₂O₄S: C, 67.81; H, 5.25; N, 6.08. Found: C, 67.95; H, 5.27; N, 6.12.

Single Crystal X-Ray Analysis of 3ab The reflection data were measured on a RIGAKU AFC7R four-circle autodiffractometer with a graphite monochromated MoK α radiation ($\lambda=0.7107 \text{ \AA}$) and a rotating anode generator. The structures were solved by direct method. The hydrogen atoms were placed in calculated positions. The non-hydrogen atoms were refined anisotropically and the hydrogen atoms were refined isotropically. The final cycle of full-matrix least-square refinement was based on 1561 observed reflections (*I*_o >3.00 σ *I*) and converged with unweighted (*R*) and weighted agreement factors (*R*_w) of 0.039 and 0.053, respectively.

All calculations were performed on a Silicon Graphics O2 WS with the teXsan¹⁰⁾ Crystal Structure Analysis Package.

Crystal Data of **3ab**: C₂₃H₂₂N₂O₃S, *M*=406.5, orthorhombic, *a*=12.613 (17), *b*=19.837 (8), *c*=8.464 (7) \AA , *V*=2117 (2) \AA^3 , space group *P*2₁2₁1, *Z*=4, *D*_c=1.275, *D*_m=1.273 (g/cm³).

Supporting Information Available X-Ray crystallographic data for the structure **3ab** have been deposited at the Cambridge Crystallographic Data Center. The atomic coordinates of the MO-optimized structures are available from our web page (URL <http://yakko.pharm.kumamoto-u.ac.jp/>).

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References and Notes

- Matsuoka T., Shinada M., Suematsu F., Harano K., Hisano T., *Chem. Pharm. Bull.*, **32**, 2077–2090 (1984).
- Matsuoka T., Oiso S., Eto M., Harano K., *Tetrahedron Lett.*, **36**, 8031–8034 (1995).
- Johnson C. K., ORTEP ORNL-3794. Oak Ridge National Laboratory, Tennessee, U.S.A., 1965.
- PM3 calculations were performed using MOPAC 2000 ver. 1.11, Fujitsu Ltd., Tokyo, Japan, 1999.
- Gaussian 98, Revision A.6. Frisch M. J., Trucks G. W., Schlegel H. B., Scuseria G. E., Robb M. A., Cheeseman J. R., Zakrzewski V. G., Montgomery J. A. Jr., Stratmann R. E., Burant J. C., Dapprich S., Millam J. M., Daniels A. D., Kudin K. N., Strain M. C., Farkas O., Tomasi J., Barone V., Cossi M., Cammi R., Mennucci B., Pomelli C., Adamo C., Clifford S., Ochterski J., Petersson G. A., Ayala P. Y., Cui Q., Morokuma K., Malick D. K., Rabuck A. D., Raghavachari K., Foresman J. B., Cioslowski J., Ortiz J. V., Stefanov B. B., Liu G., Liashenko A., Piskorz P., Komaromi I., Gomperts R., Martin R. L., Fox D. J., Keith T., Al-Laham M. A., Peng C. Y., Nanayakkara A., Gonzalez C., Challacombe M., Gill P. M. W., Johnson B., Chen W., Wong M. W., Andres J. L., Gonzalez C., Head-Gordon M., Replogle E. S., Pople J. A., Gaussian, Inc., Pittsburgh, PA, 1998.
- Kano S., Yokomatsu T., Shibuya S., *Tetrahedron Lett.*, **19**, 4125–4128 (1978).
- Hisano T., Harano K., Matsuoka T., Yamada H., Kurihara M., *Chem. Pharm. Bull.*, **35**, 1049–1057 (1987).
- Matsuoka T., Hasegawa T., Eto M., Harano K., Hisano T., *J. Chem. Soc., Perkin Trans. 2*, **1993**, 1859–1865 (1993).
- Padwa A., Bullock W. H., Norman B. H., Perumattam J., *J. Org. Chem.*, **56**, 4252–4259 (1991).
- teXsan: Crystal Structure Analysis Package, Version 1.11. Molecular Structure Corporation, Rigaku Corporation, 2000.