DOI: 10.1002/ejoc.200600257

Formation of 4*H*-Azepine by the Electrophilic Reaction of a 2-Methoxyazepinium Ion and Analysis of the Sigmatropic Isomerization

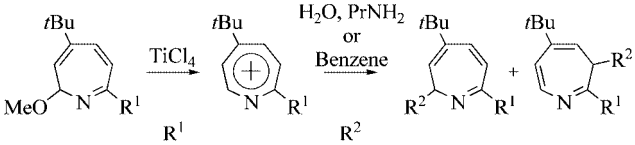
Christopher E. J. Cordonier,[a] Kyosuke Satake,*[a] Hideki Okamoto,[a] and Masaru Kimura[a]

Keywords: Azepinium / 4*H*-Azepine / Density functional calculations / Heterocycles / 1,5-Hydrogen shift

2-Aryl-2*H*-, 3-aryl-3*H*-, and 4-aryl-4*H*-azepine were formed by the novel, electrophilic, π_{LUMO}-controlled reaction of the 2-methoxyazepinium ion, generated in situ by the reaction of $TiCl_4$ with 2,7-dialkoxy-2*H*-azepine and an aryl compound, for which the kinetic parameters of the sigmatropic hydrogen rearrangement of the 4*H*-azepine was measured. The substitution and hydrogen shift of the azepinium ion were analyzed with DFT studies.

Introduction

In relation to the hydrocarbon analogue cycloheptatriene (CHT),[1,2] reaction pathways that involve azepine compounds have been a long-studied field of fundamental chemistry, although vastly limited to theoretical studies as experimental results have been rare. Among these pathways, of particular interest are those that involve the aromatic azepinium cation[3] and sigmatropic isomerization of the azepine ring.[4,5] Recently, attention has been drawn to the role of azepinium ions as intermediates in the reactions of nitrenium ions with aryl compounds.[6] For the first time, azepinium ions **2a**,**b** have been generated in solution by the dealkoxylation of 2*H*-azepines **1a**,**b** with titanium tetrachloride ($TiCl_4$).[7] In the same account, they were reported to react electrophilically with water and an amine in situ to give the corresponding 2-substituted 2*H*-azepines **1c**,**d** (Scheme 1).



1a	*t*Bu	**2a**			
1b	OMe	**2b**	OH	**1c** (45%)	
1b	OMe	**2b**	NHPr	**1d** (85%)	
1b	OMe	**2b**	Ph	**1e** (49%)	**3a** (5%)

Scheme 1.

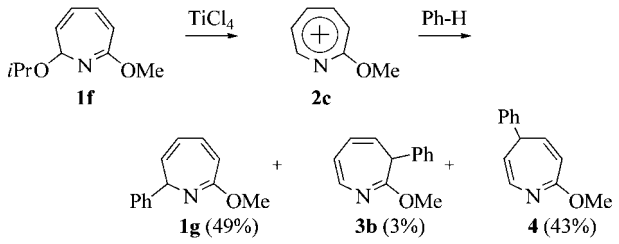
Investigation of the reactive properties of azepinium ions could lead to a deeper understanding of them and provide further evidence for the character of this new family of aromatic cations. The reaction with hard nucleophiles has been confirmed,[7] and the reaction with soft nucleophiles, as in the Friedel–Crafts reaction, could also generate valuable information on the electrophilic character of these delocalized cations. We recently reported the reaction via **2b** with various aromatic compounds, including benzene, where 2-phenyl-2*H*-azepine **1e** and 3-phenyl-3*H*-azepine **3a** were formed as shown in Scheme 1.[8] In order to attain a deeper and more fundamental view of the azepinium ion character, analysis of a less substituted cation free of bulky ring substituents must be conducted.

Results and Discussion

Reaction of 2-*iso*propoxy-7-methoxy-2*H*-azepine (**1f**) with $TiCl_4$ in the presence of benzene gave a mixture of 7-methoxy-2-phenyl-2*H*-azepine (**1g**), 2-methoxy-3-phenyl-3*H*-azepine (**3b**), and 7-methoxy-4-phenyl-4*H*-azepine (**4**) (Scheme 2). This reaction presumably occurs with the initial formation of the 2-methoxyazepinium ion (**2c**) followed by electrophilic addition to benzene and then deprotonation. The azepinium ring structure was confirmed by comparison of the ^1H- and ^{13}C NMR signals of **2c** and the previously reported *tert*-butyl-substituted analogues **2a** and **2b**,[7] listed in Table 1, in which chemical shifts coincided.

The minimal substitution and lack of steric restriction of the azepinium ring in **2c** offers a more fundamental example of its reactivity and electrophilic character. Lack of a substituent at the 5-position of the 2-methoxyazepinium ring not only allowed for the clear experimental observation of the π_{LUMO} character, but also the formation of rare 4*H*-azepines.[12] 2-Isopropoxy-2*H*-azepine **1f** was prepared in high yield from nitrobenzene by using the established methods,[13,14] and the products **1g**, **3b**, and **4** were easily sepa-

[a] Department of Chemistry, Faculty of Science, Okayama University,
3-1-1, Tsushima-Naka, Okayama, 700-8530 Japan
Fax: +81-86-251-7841
E-mail: satake@cc.okayama-u.ac.jp
Supporting information for this article is available on the WWW under http://www.eurjoc.org or from the author.



Scheme 2.

Table 1. ^{13}C- and ^{1}H NMR chemical shifts observed for the ring atoms of azepinium ions in $CDCl_3$.[a]

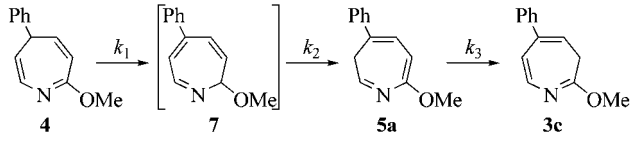
Compound	^{13}C Chemical shift [ppm]					
	C2	C3	C4	C5	C6	C7
2a	187.5	133.1	150.0	180.0	133.7	158.6
2b	176.0	131.0	150.8	181.2	134.5	170.2
2c	176.9	132.7	151.3	152.7	139.5	170.9
	^{1}H Chemical shift [ppm]					
	C3–H	C4–H	C5–H	C6–H	C7–H	
2a	8.11	8.78	–	8.10	9.24	
2b	7.81	8.61	–	8.19	9.36	
2c	8.04	8.76	8.76	8.48	9.66	

[a] Peak assignments were made on the basis of HMQC and HMBC NMR correlations.

rated from the reaction mixture by medium-pressure liquid chromatography on silica gel at 0 °C. The structures of all the new compounds were confirmed by the analysis of the characteristic $^{3}J_{H,H}$ coupling constants, from which the connectivity of the azepine ring could be unambiguously determined.

Compounds **1g** and **4** were formed and isolated in good yields, which enabled the easy preparation of the 2*H*- and 4*H*-azepines. Because 2*H*- and 4*H*-azepines isomerize by a [1,5] sigmatropic H shift, a characteristic feature of the azepine ring,[4] to give their more stable 3*H*- form, synthetic examples are rare. While accounts of the shift in 2*H*-azepines have been reported, along with their kinetic analyses,[15] there have been no accounts of the kinetic analysis on the isomerization of 4*H*-azepines.[12a]

Isomerization of **4** apparently occurs as a two-step reaction from **4** first to 7-methoxy-4-phenyl-3*H*-azepine (**5a**) and then to 2-methoxy-5-phenyl-3*H*-azepine (**3c**). If the isomerization occurs by a 1,5-H shift, then the step from **4** to **5a** is a two-step reaction followed by one final reaction from **5a** to the most thermally stable **3c**, as illustrated in Scheme 3, where the second reaction is very fast. The time-dependent concentration of **4**, **5a**, and **3c** closely fit those expected for a two-step first-order reaction system. The first rate constant, k_1, was estimated from the first-order reaction equation and k_3 was estimated from the best fit line of the equation for a two-step first-order reaction system, with an overall rate constant given by k_1, to the experimental data. The experimental data for the isomerization of **4** at 160 °C is compared to the simulation for $k_1 = 1.73 \cdot 10^{-5}$ s^{-1} and $k_3 = 1.00 \cdot 10^{-4}$ s^{-1} in Figure 1, for which a good correlation is observed. Experimentally determined values of k_1 and k_3 are listed in Table 2. The kinetic parameters listed in Table 3 for both observed steps (**4** to **5a** and **5a** to **3c**) were estimated from the Arrhenius plots of k_1 and k_3.



Scheme 3.

The product distribution of the substitution reaction can be best explained by an electrophilic substitution reaction controlled by the azepinium π_{LUMO} as opposed to a thermodynamically controlled reaction. For analysis of this reaction, the azepinium π_{LUMO} (Figure 2) and the potential

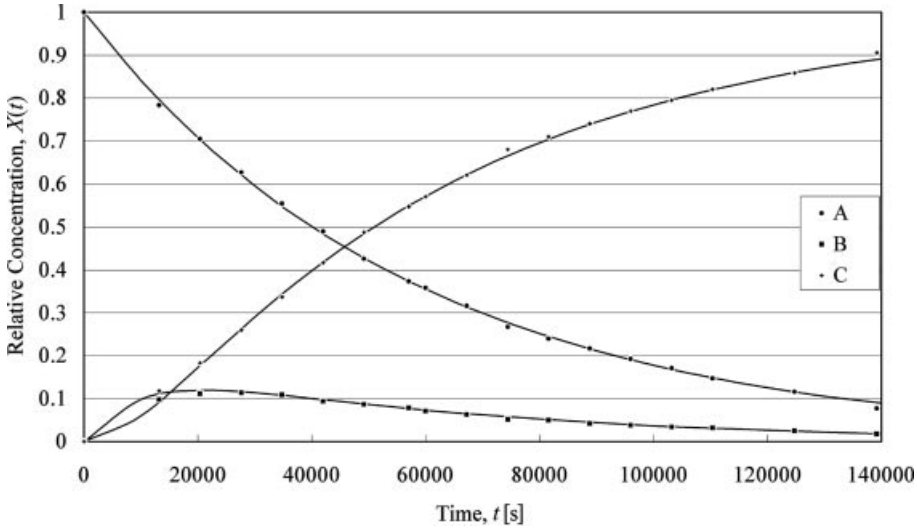


Figure 1. Isomerization of **4** at 162 °C. Points denote A = [**4**], B = [**5a**] and C = [**3c**] observed by ^{1}H NMR spectroscopy. Solid lines represent simulation of two consecutive reactions for $k_1 = 1.73 \cdot 10^{-5}$ and $k_3 = 1.00 \cdot 10^{-4}$ s^{-1}.

Table 2. Rate constants at temperature T of the isomerization of **4**.

T [°C]	k_1[a] [s^{-1}]	k_3[b] [s^{-1}]
132	$1.84 \cdot 10^{-6}$	$1.40 \cdot 10^{-5}$
140	$4.60 \cdot 10^{-6}$	$3.00 \cdot 10^{-5}$
150	$1.00 \cdot 10^{-5}$	$6.15 \cdot 10^{-5}$
162	$1.73 \cdot 10^{-5}$	$1.00 \cdot 10^{-4}$
170	$4.59 \cdot 10^{-5}$	$3.00 \cdot 10^{-4}$

[a] k_1 was determined from the linear correlation of time versus ln[**4**] at T. [b] k_3 was determined by fitting the two consecutive reaction linear equation, given k_1, to the time dependent [**5a**] and [**3c**] determined by ^{1}H NMR spectroscopy.

Table 3. Kinetic parameters of [1,5] sigmatropic hydrogen shifts.[a]

Reaction	E_a [kJ/mol]	ln A	$\Delta H^{\neq}$ [kJ/mol]	$\Delta S^{\neq}$ [J/mol]	$\Delta G^{\neq}$ [kJ/mol]
4 → **5a**	117.0	21.6	114.5	–73.3	136.3
5a → **3c**	110.4	21.7	108.0	–73.2	129.8

[a] Calculated from the Arrhenius equation, $\ln k = E_a/RT - \ln A$, for the experimentally observed correlation of $\ln k$ and T^{-1}.

energies of the possible substitution products (Figure 3) were calculated by DFT studies at the B3LYP/6-31G(d,p)[9] level with Gaussian 03.[10] The relative stabilities of the products decrease in the order: **3b** > **1g** > **4** > **5b** > **6a**, as was predicted, and thus the experimental results are in contradiction with those expected for a thermodynamically controlled substitution. On the other hand, the π_{LUMO} lobe coefficients of **2c** are position-dependent and decrease in size in the order: 7-position ≥ 5-position > 3-position, where 7-position >> 6-position and 5-position >> 4-position, which correlates to the experimental product distribution. The π_{LUMO} coefficient ratios and molar product ratios were found to be close to each other, which suggests a kinetic control of the reaction. In a resonance theory, consideration of azepinium ion **2c** for the resonance structures where the imino–ether moiety exists, a positive charge is located at the 3-, 5-, and 7-positions (Scheme 4). Thus, a stabilizing effect of the imino–ether form may explain the product distribution. Similarly, the higher stability of the imino–ether-bearing products, **1g**, **3b**, and **4** in Figure 3 compared with those without the imino–ether group, **5b** and **6a**, may also result from stabilization by the imino–ether form. Substitution of benzene by the azepinium ion illustrates the relative increase in electrophilicity of the ion compared to the hydrocarbon analogue, tropylium bromide, which did not react.[11]

Again to confirm the experimental findings, the potential energy surface of the [1,5] sigmatropic H-shift from **4** was calculated at the B3LYP/6-31G(d,p)[9] level, shown in Figure 4, for which a correlation with the experimental data was found. Transition states were all found to be the expected 6-membered 4π + 2σ electron cyclic states. The activation energy, E_a, of **4** to **TS1** was calculated to be 148.8 kJ/mol, of **7** to **TS2** 97.7 kJ/mol, and of **5a** to **TS3** 139.7 kJ/mol; therefore, as observed experimentally, k_2 is expected to be very large in comparison to k_1 and k_3, and k_3 is expected to be larger than, but comparable to, k_1.

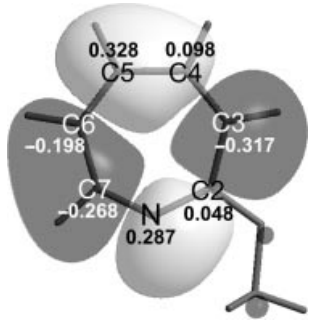


Figure 2. The B3LYP/6-31G(d,p) calculated π_{LUMO} and eigenvectors of the $2p_z$ orbital for the ring atoms of the aromatic methoxyazepinium cation **2c**.

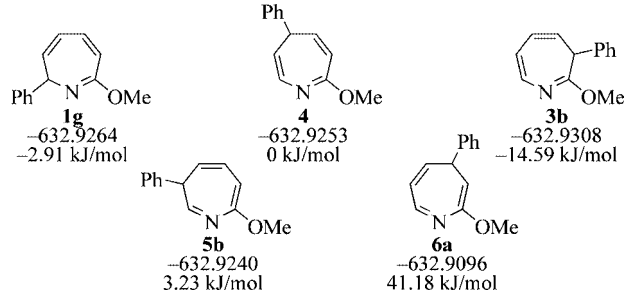
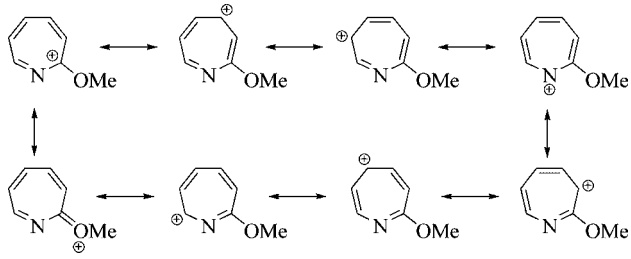


Figure 3. Zero-point-corrected B3LYP/6-31G(d,p) energies (in a.u.) and relative energies for the possible substitution products of benzene by **2c**.



Scheme 4.

Thermodynamic isomerization of **4** to the more stable intermediate **8**, as opposed to the least stable intermediate **7**, could be expected as depicted in Figure 4, but isomerization via **7** is experimentally observed. The largest E_a in the system for the transition of **8** to **TS6** (170.1 kJ/mol) could present a larger barrier to this pathway, although from **8**, barrierless enamine–imine isomerization directly to the 3*H*-azepine **3c** may be anticipated. Preference for the reaction via **7** can be considered a result of the difference in E_a in the kinetically controlled reaction from **4** to **TS1** as opposed to **TS7** (164.4 kJ/mol). This difference can be elegantly explained in terms of the frontier molecular orbital theory,[16] by the MO interaction between the σ_{LUMO} of the C–H bond and the π_{HOMO} of the reacting diene moiety. The π_{HOMO} energies of 2-methoxy-1-azadiene and 1-methoxy-2-azadiene are 10.163 eV and –9.365 eV, respectively, as calculated byAM1.[17] The reacting diene moiety in the transition from **4** to **TS1** is thus the more reactive 1-methoxy-2-azadiene.

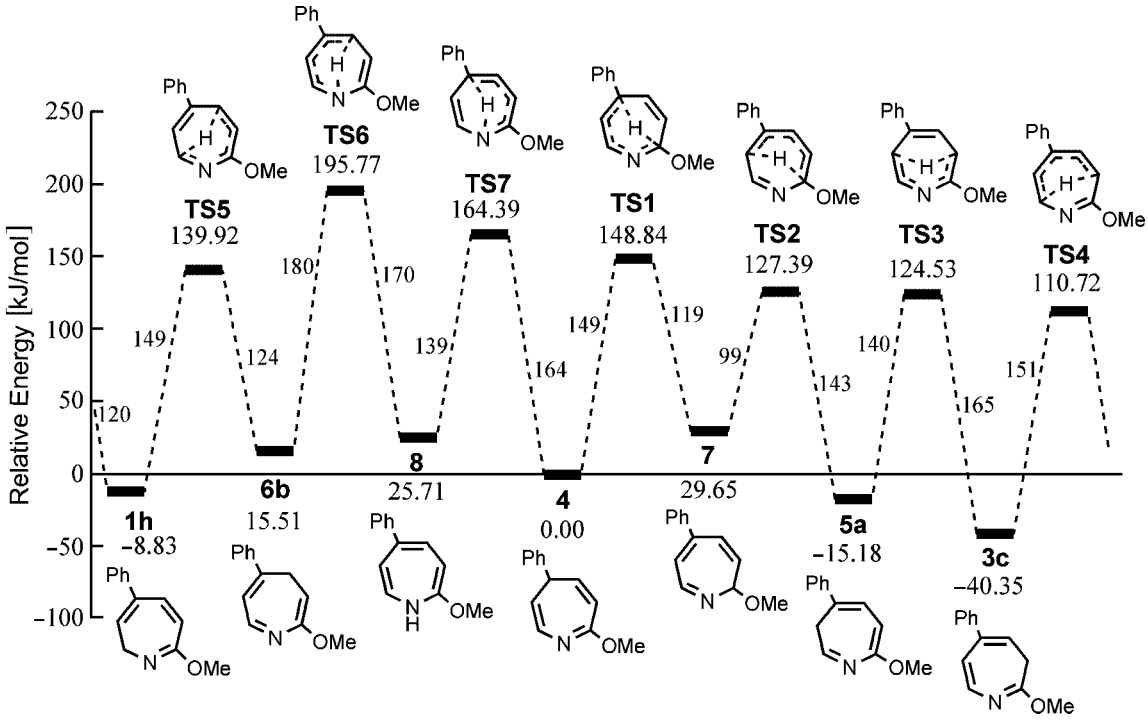


Figure 4. Isomerization pathway of 7-methoxy-4-phenyl-4*H*-azepine (**4**), calculated at the B3LYP/6-31G(d,p) level of theory.

As displayed in Figure 4, the most stable transition state is that in which the imino–ether moiety is intact, **TS4**. The higher E_a requirement in the isomerizations of **4** to **5a** and **5a** to **3c** in Table 3 and Figure 4, as opposed to that of **1h** to **3c** in Figure 4, may also be a consequence of the disruption of the imino–ether conjugation. Azepinium substitution and 1,5-H isomerization of the azepine ring present elegant examples of the correlation between experimental data and DFT predictions.

Conclusions

The simplest form of azepinium so far, **2c**, was synthesized and the analysis of the electrophilic reactivity gave an elegant example of the character of the π_{LUMO}, for which experimental data and DFT predictions coincide. The novel 4*H*-azepine **4** was one of the major products of the reaction of **2c** with benzene, providing a new synthetic route to this rare class of compounds.

The kinetic analysis of the 1,5-hydrogen shift of **4**, which was the first reported for a 4*H*-azepine, was conducted and correlated well with the model estimated by the B3LYP theory with the 6-31G(d,p) basis set.

Experimental Section

Reaction of 1f with $TiCl_4$ in the Presence of Benzene: $TiCl_4$ (5.69 g, 30.0 mmol) was added to a solution of **1f** (1.81 g, 10.0 mmol) in benzene (40 mL) cooled in an ice bath. The reaction mixture was then stirred at room temp. for 15 h before quenching with aq. K_2CO_3 (8.3 g, 60 mmol). Salts formed were removed by vacuum filtration. The aqueous phase was then separated from the organic phase and washed three times with CH_2Cl_2. The organic liquors were dried with $MgSO_4$, then the volatile components were removed. The phenyl-substituted compounds were separated from the remaining nonvolatile component by MPLC on ICN 32–63 silica gel at 0 °C eluted by 1:9 v/v AcOEt/hexane. The following were isolated: 970 mg (49%) of 7-methoxy-2-phenyl-2*H*-azepine (**1g**) as a colorless oil [^{1}H NMR (600 MHz, $CDCl_3$): δ = 3.82 (s, 3 H), 4.29 (d, J = 5.4 Hz, 1 H), 5.95 (dd, J = 9.8, 5.4 Hz, 1 H), 6.24 (dd, J = 9.8, 5.4 Hz, 1 H), 6.66 (d, J = 11.5 Hz, 1 H), 6.86 (dd, J = 11.5, 5.4 Hz, 1 H), 7.33 (d, J = 7.6 Hz, 1 H), 7.44 (dd, J = 7.6, 7.1 Hz, 2 H), 7.67 (d, J = 7.1 Hz, 2 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 53.7 (q), 58.1 (d), 125.9 (d), 126.2 (d), 126.68 (d), 126.70 (d), 128.3 (d), 137.6 (d), 137.9 (d), 144.3 (s), 161.7 (s) ppm], 56 mg (3%) of 2-methoxy-3-phenyl-3*H*-azepine (**3b**) as a colorless oil [^{1}H NMR (600 MHz, $CDCl_3$): δ = 3.31 (d, J = 6.4 Hz, 1 H), 3.68 (s, 3 H), 5.57 (dd, J = 9.0, 6.4 Hz, 1 H), 6.06 (dd, J = 8.1, 5.9 Hz, 1 H), 6.36 (dd, J = 9.0, 5.9 Hz, 1 H), 7.03 (d, J = 8.1 Hz, 1 H), 7.28–7.32 (m, 3 H), 7.36 (dd, J = 7.8, 7.6 Hz, 2 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 50.2 (d), 55.3 (q), 114.6 (d), 121.4 (d), 126.6 (d), 127.0 (d), 128.2 (d), 129.0 (d), 137.0 (d), 137.2 (s), 150.1 (s) ppm], and 854 mg (43%) of 7-methoxy-4-phenyl-4*H*-azepine (**4**) as a colorless oil [^{1}H NMR (600 MHz, $CDCl_3$): δ = 3.49–3.52 (m, 1 H), 3.81 (s, 3 H), 5.10 (ddd, J = 7.1, 5.1, 1.0 Hz, 1 H), 5.90 (dd, J = 10.0, 1.7 Hz, 1 H), 6.13 (ddd, J = 10.0, 5.9, 1.0 Hz, 1 H), 6.66 (dd, J = 7.1, 1.7 Hz, 1 H), 7.29 (t, J = 7.3 Hz, 1 H), 7.32 (dd, J = 7.8, 7.3 Hz, 2 H), 7.37 (d, J = 7.8 Hz, 2 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 42.8 (d), 52.4 (q), 116.9 (d), 117.3 (d), 126.8 (d), 127.4 (d), 128.7 (d), 134.2 (d), 142.5 (d), 142.5 (s), 163.7 (s) ppm].

Supporting Information (see footnote on the first page of this article): Experimental procedures for, characterization and spectral assignments of compounds **1f**, **1g**, **2c**, **3b**, **3c**, **4**, and **5a**. Kinetic analysis of the 1,5-hydrogen shift of **4**, including calculations used.

Acknowledgments

The authors thank the SC-NMR Laboratory of Okayama University for the service of NMR spectroscopy. This work is in part supported by JSPS, Grant-in-aid for Scientific Research (C) 16550039.

[1] W. Von E. Doering, L. H. Knox, *J. Am. Chem. Soc.* **1954**, *76*, 3203–3206.
[2] T. Okajima, K. Imafuku, *J. Org. Chem.* **2002**, *67*, 625–632.
[3] D. A. Smith, J. Bitar, *J. Org. Chem.* **1993**, *58*, 6–8.
[4] R. K. Smalley, *Comprehensive Heterocyclic Chemistry*, Pergamon Press, Oxford, **1984**, vol. 7, p. 481.
[5] a) K. Satake, R. Okuda, M. Hashimoto, Y. Fujiwara, H. Okamoto, M. Kimura, S. Morosawa, *J. Chem. Soc., Perkin Trans. 1* **1994**, 1753–1757; b) K. Satake, R. Okuda, M. Hashimoto, Y. Fujiwara, I. Watadani, H. Okamoto, M. Kimura, S. Morosawa, *J. Chem. Soc., Chem. Commun.* **1991**, 1154–1156.
[6] M. Di Stefano, M. Rosi, A. Sgamellotti, F. Negri, *Chem. Phys.* **2004**, *302*, 295–308.
[7] K. Satake, Y. Kubota, C. E. J. Cordonier, H. Okamoto, M. Kimura, *Angew. Chem. Int. Ed.* **2004**, *43*, 736–738.
[8] Y. Kubota, K. Satake, H. Okamoto, M. Kimura, *Org. Lett.* **2005**, *7*, 5215–5218.
[9] a) A. D. Becke, *J. Chem. Phys.* **1993**, *98*, 5648–5652; b) M. J. Frisch, J. A. Pople, J. S. Binkley, *J. Chem. Phys.* **1984**, *80*, 3265–3269.
[10] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery Jr, T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez, J. A. Pople, Gaussian, Inc., Pittsburgh PA, **2003**.
[11] D. Bryce-Smith, N. A. Perkins, *J. Chem. Soc.* **1962**, 5295–5297.
[12] a) U. Goeckel, U. Hartmannsgruber, A. Steigel, J. Sauer, *Tetrahedron Lett.* **1980**, *21*, 595–598; b) W. Steglich, H. Bauer, M. Grosse-Bley, R. Jeschke, J. Josten, J. Klein, *J. Heterocycl. Chem.* **1990**, *27*, 107–110.
[13] C. E. J. Cordonier, K. Satake, M. Atarashi, Y. Kawamoto, H. Okamoto, M. Kimura, *J. Org. Chem.* **2005**, *70*, 3425–3436.
[14] M. Masaki, K. Fukui, J. Kita, *Bull. Chem. Soc. Jpn.* **1977**, *50*, 2013–2016.
[15] a) D. Hamprecht, J. Josten, W. Steglich, *Tetrahedron* **1996**, *52*, 10883–10902; b) D. W. Jones, M. Thornton-Pett, *J. Chem. Soc., Perkin Trans. 1* **1995**, 809–815.
[16] a) K. Fukui, *Science* **1982**, *218*, 747–754; b) K. Fukui, *Angew. Chem.* **1982**, *94*, 852–861; c) K. Fukui, *Acc. Chem. Res.* **1971**, *4*, 57–64.
[17] M. J. S. Dewar, E. G. Zoebisch, E. F. Healy, J. J. P. Stewart, *J. Am. Chem. Soc.* **1985**, *107*, 3902–3909.

Received: March 23, 2006
Published Online: July 25, 2006

