Diels–Alder Reaction of 2(1*H*)-Pyridones Acting as Dienes

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Received October 31, 2007; accepted January 21, 2008; published online January 23, 2008

Diels–Alder reactions between *N*-phenylmaleimide, acting as the dienophile, and 2(1*H*)-pyridones having a methoxy or a chloro substituent, were carried out, under atmospheric and high pressure conditions, to give the corresponding isoquinuclidine derivatives. Stereoselectivity of the Diels–Alder reactions was studied using molecular orbital calculations.

Key words Diels–Alder reaction; isoquinuclidine; methoxy-2(1*H*)-pyridone; chloro-2(1*H*)-pyridone; *N*-phenylmaleimide; molecular orbital calculation

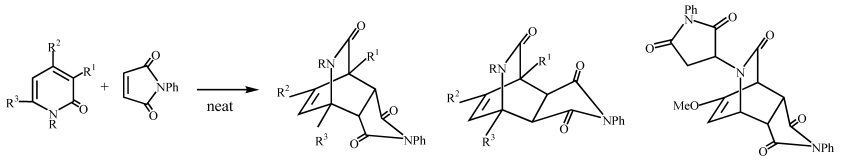
Preparation of isoquinuclidines *via* Diels–Alder (DA) reaction between a dienophile and 2(1*H*)-pyridone, acting as the diene, would be highly useful towards possible intermediates in the synthesis of iboga alkaloids.[1)] Accordingly, we have developed the synthesis of isoquinuclidines bearing various substituents such as Me, COOMe, COMe, and Ph.[2—8)] As an extension of our synthetic methodology, we present the DA reactions between *N*-phenylmaleimide (as the dienophile), and 1-substituted or 1-unsubstituted 2(1*H*)-pyridones having a methoxy or chloro substituent at 3—6 positions (as the diene). In addition to atmospheric (AP) conditions, the reactions were also performed under high pressure (HP), which has proven to be effective in overcoming the energy barriers imposed by steric and electronic effects of DA reactions.[9)] Furthermore, the stereoselectivities of the DA reactions of the 2(1*H*)-pyridones and Michael addition reactions of 1-unsubstituted 2(1*H*)-pyridones were determined using molecular orbital (MO) calculations.

DA Reactions between 2(1*H*)-Pyridones and *N*-Phenylmaleimide As listed in Table 1, the DA reactions were initially investigated using methoxypyridones (**1a**—**c**, **2a**—**c**)[10—13)] and a large excess *N*-phenylmaleimide (**3**) under AP at 110 °C for 3 d. For the 1-substituted methoxypyridones, the DA reaction of 3-methoxypyridone (**1a**) afforded *endo*-DA-adduct (**4a**, 36%) and *exo*-DA-adduct (**6a**, 23%), whereas the DA reactions of 4-methoxypyridone (**1b**) and 6-methoxypyridone (**1c**) gave only the *endo*-DA-adducts (**4b**, 93% and **4c**, 44%), respectively. For the 1-unsubstituted 3-methoxypyridone (**2a**) and 4-methoxypyridone (**2b**) afforded *endo*-DA-adducts (**5a**, 89% and **8**, 51%), in contrast, the reaction between **2c** and **3** did not afford any DA-adducts, and **2c** was recovered.

Next, as listed in Table 2, DA reactions were carried out using chloropyridones (**9a**—**d**, **10a**—**d**)[14—18)] and a large excess **3**. In the cases of 3-chloropyridone (**9a**) and 4-chloropyridone (**9b**), the DA reactions with **3** gave *endo*-DA-adducts (**11a**, 73% and **11b**, 77%), and *exo*-DA-adducts (**13a**, 10% and **13b**, 19%), respectively. In contrast, the reaction using 5-chloropyridone (**9c**) gave only *endo*-DA-adduct (**11c**, 88%), whereas 6-chloropyridone (**9d**) did not afford any DA-adducts, and **9d** was recovered. For the 1-unsubstituted pyridones (**10a**—**d**), only the reactions of 4-chloropyridone (**10b**) and 5-chloropyridone (**10c**) were successful the former afforded *endo*-DA–Michael-adduct (**15**, 84%), whereas the latter gave *endo*-DA-adduct (**12c**, 79%). The configurations of the two substituents at the 5- and 6-positions for *endo*-DA-adducts (**4a**—**c**, **5a**, **8**, **11a**—**c**, **12c**, **15**), and *exo*-DA-adducts (**6a**, **13a**—**c**) were determined based on the coupling constants of their ^{1}H-NMR spectra. For isoquinuclidine derivatives, the coupling constant between the bridge-head protons and H_{exo} is generally 3.5—4.5 Hz, and for H_{endo}, less than 3.5 Hz.[2—8)]

Finally, as listed in Table 3, HP DA reactions between a excess **3** and **1a**—**c**, **2a**—**c**, **9a**—**d**, and **10a**—**d** were carried

Table 1. DA Reaction of **1**, **2** with **3** in Sealed Tube



1a-c **2a-c** **3** **4a-c** *endo* **5a, c** **6a-c** *exo* **7a-c** **8** *endo*

Entry	Pyridone	R	R^1	R^2	R^3	Temp. (°C)	Time (d)	Adduct	Yield (%) *endo*	Adduct	Yield (%) *exo*
1	**1a**	Me	OMe	H	H	110	3	**4a**	36	**6a**	23
2	**1b**	Me	H	OMe	H	110	3	**4b**	93	**6b**	0
3	**1c**	Me	H	H	OMe	110	3	**4c**	44	**6c**	0
4	**2a**	H	OMe	H	H	110	3	**5a**	89	**7a**	0
5	**2b**	H	H	OMe	H	110	3	**8**	51	**7b**	0
6	**2c**	H	H	H	OMe	110	3	**5c**	0	**7c**	0

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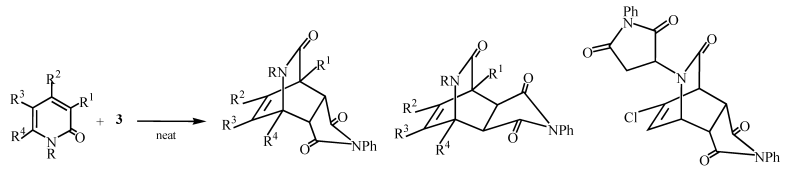
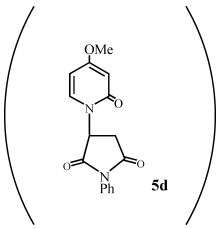
Table 2. DA Reaction of **9**, **10** with **3** in Sealed Tube



Entry	Pyridone	R	R^1	R^2	R^3	R^4	Temp. (°C)	Time (d)	Adduct	Yield (%) *endo*	Adduct	Yield (%) *exo*
1	**9a**	Me	Cl	H	H	H	110	3	**11a**	73	**13a**	10
2	**9b**	Me	H	Cl	H	H	110	3	**11b**	77	**13b**	19
3	**9c**	Me	H	H	Cl	H	110	3	**11c**	88	**13c**	0
4	**9d**	Me	H	H	H	Cl	110	3	**11d**	0	**13d**	0
5	**10a**	H	Cl	H	H	H	110	3	**12a**	0	**14a**	0
6	**10b**	H	H	Cl	H	H	110	3	**15**	84	**14b**	0
7	**10c**	H	H	H	Cl	H	110	3	**12c**	79	**14c**	0
8	**10d**	H	H	H	H	Cl	110	3	**12d**	0	**14d**	0

Table 3. DA Reaction of **1**, **2**, **9** and **10** with **3** under 10 kbar in CH_2Cl_2

Entry	Pyridone	Temp. (°C)	Time (d)	Adduct	Yield (%) *endo*	Adduct	Yield (%) *exo*
1	**1a**	90	2	**4a**	31	**6a**	0
2	**1b**	90	2	**4b**	35	**6b**	0
3	**1c**	90	2	**4c**	21	**6c**	0
4	**2a**	90	2	**5a**	63	**7a**	0
5	**2b**	90	2	**5d**	33	**7b**	0
6	**2c**	90	2	**5c**	0	**7c**	0
7	**9a**	90	2	**11a**	80	**13a**	0
8	**9b**	90	2	**11b**	60	**13b**	0
9	**9c**	90	2	**11c**	81	**13c**	5
10	**9d**	90	2	**11d**	0	**13d**	0
11	**10a**	90	2	**12a**	0	**14a**	0
12	**10b**	90	2	**15**	18	**14b**	0
13	**10c**	90	2	**12c**	75	**14c**	0
14	**10d**	90	2	**12d**	0	**14d**	0



out under 10 kbar at 90 °C for 2 d in CH_2Cl_2. In the case of **9c**, the HP DA reaction resulted in both *endo*-adduct **11c** and *exo*-adduct **13c**; in contrast, **13c** was not obtained under AP conditions. For the HP DA reaction of **2b**, Michael-adduct **5d** was the sole product, which implies that *endo*-DA–Michael-adducts **8** and **15** are derived from the Michael-adducts of **3** with **2b** or **10b**, respectively. Based on the yields of the adducts produced under AP conditions and those formed under HP conditions, the HP DA reactions did not exhibit significant increases in the yields of the adducts.

Theoretical Studies Using MO Method Theoretical studies were carried out for the DA reaction of pyridones **1a**—**c**, **2a**—**c**, **9a**—**d**, and **10a**—**d** with **3**. For each reaction, two transition states (TS), which were related to the *endo*- and *exo*-adducts, were selected; upon optimization of the selected structures, the activation energies (*Ea*) were calculated using PM5 method.[19] The optimized TS structures are shown in Fig. 1, and the calculated *Ea* values are listed in Table 4, together with the experimental yields of the adducts. As shown in Table 4, the *Ea* values of TS that lead to the *endo*-adducts are lower than those leading to the *exo*-adducts, which is consistent with the experimental results showing that the main products are the *endo*-adducts. The retro-DA reactions are not thought to occur, because calculated *Ea* values of the retro-DA reactions are about 30 kcal/mol greater than those of the forward reactions. For example, the *Ea* values of the retro-DA reactions (Entry 1 of Table 4) are 54.51 kcal/mol (*endo*) and 55.45 kcal/mol (*exo*).

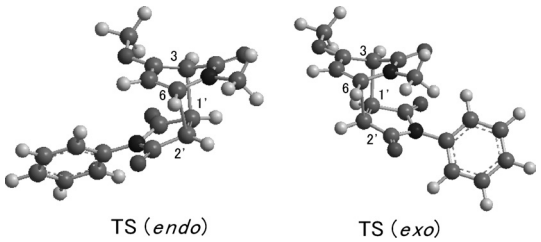


Fig. 1. Structures of *endo*- and *exo*-Type TS's for the Reaction of **1b** with **3** Optimized Using PM5 Method

Calculated interatomic distances are: C_3–$C_{1'}$=1.994 Å, C_6–$C_{2'}$=2.333 Å (left); C_3–$C_{1'}$=1.969 Å, C_6–$C_{2'}$=2.441 Å (right).

In the cases of the 4-substituted pyridones **2b** and **10b**, the sole formation of DA–Michael adducts **8** and **15** can be explained by the tautomerization of 2(1*H*)-pyridone in these cases, the Michael addition reaction occurs between **3** and presumably the enol tautomer of 2(1*H*)-pyridone. For the Michael addition reactions of **2a**—**d** and **10a**—**d** with **3**, *Ea* values were calculated using Gaussian 03 at the HF/6-31G(d) level.[20] As shown in Table 5, the lowest calculated *Ea* values correlate to the Michael reactions involving 4-substituted pyridones, which would also explain the sole formation of the DA–Michael adducts.

In summary, DA reactions between dienophile **3** and 2(1*H*)-pyridones bearing a methoxy or a chloro group were

Table 4. Calculated Activation Energies (*Ea*) and Experimental Yields of Adducts for DA Reaction of 2-Pyridones with *N*-Phenylmaleimide (PM5 Method)

Entry	NR	Pyridone	*endo*-Addition		*exo*-Addition		*Ea* (*exo*)−*Ea* (*endo*) (kcal/mol)
			Ea (kcal/mol)	Adduct (yield) (%)	*Ea* (kcal/mol)	Adduct (yield) (%)	
1	NMe	3-OMe	20.23	36	21.62	23	1.39
2	NMe	4-OMe	21.08	93	22.37	0	1.29
3	NMe	6-OMe	17.18	44	20.36	0	3.19
4	NH	3-OMe	20.85	89	22.04	0	1.19
5	NH	4-OMe	19.54[a)]	61[a)]	25.81[a)]	0	6.27[a)]
6	NH	6-OMe	19.04	0	22.21	0	3.15
7	NMe	3-Cl	23.25	73	24.93	10	1.68
8	NMe	4-Cl	22.26	77	22.77	19	0.51
9	NMe	5-Cl	22.25	88	22.87	0	0.62
10	NMe	6-Cl	22.10	0	24.52	0	2.42
11	NH	3-Cl	23.97	0	25.46	0	1.49
12	NH	4-Cl	22.09[a)]	84[a)]	28.54[a)]	0	6.45[a)]
13	NH	5-Cl	23.03	79	23.46	0	0.43
14	NH	6-Cl	23.25	0	25.50	0	2.25

a) For Michael adducts.

Table 5. Caluculated Activation Energies (*Ea*) for Michael Addition of 2-Pyridones with *N*-Phenylmaleimide Calculated at HF/6-31(d) Level

Pyridone	*Ea* (kcal/mol)	Pyridone	*Ea* (kcal/mol)
3-OMe	36.19	3-Cl	37.34
4-OMe	33.50	4-Cl	36.54
5-OMe	34.92	5-Cl	37.55
6-OMe	41.66	6-Cl	45.72

successfully carried out under the AP and HP conditions to stereoselectively afford *endo*-DA-adducts. The experimental results were supported by calculated *Ea* values of the corresponding reactions.

Experimental

The following instruments were used to obtain physical data: melting points, Yanaco micro-melting point apparatus (values are uncorrected); IR spectra, Perkin Elmer FT-IR 1725X spectrophotometer; MS spectra, JEOL JMN-DX 303/JMA-DA 5000 spectrometer; NMR spectra, JEOL JNM-GSX 400 (^{1}H-NMR, 400 MHz; ^{13}C-NMR, 100 MHz), JEOL JNM-EX270 (^{1}H-NMR, 270 MHz; ^{13}C-NMR, 67.8 MHz), and JEOL JNM-PMX 60SI spectrometers with tetramethylsilane (TMS) as an internal standard; elemental analyses, Perkin Elmer 2400 CHN Elemental Analyzer. For column chromatography, Merck Kieselgel silica gel 60 (230—400 mesh) was used.

General Procedures for Diels–Alder Reactions of 1a—c, 2a—c, 9a—d, and 10a—d with 3 a) A mixture of **1a** (0.695 g, 5 mmol) and **3** (6.92 g, 40 mmol) was heated at 110 °C for 3 d. The resulting reaction mixture was purified by column chromatography (silica gel). The first fraction, which was eluted with hexane–acetone (1 : 2), was evaporated to afford **3**. The second and third fractions were evaporated to give *exo*-DA-adduct (**6a**, 0.352 g, 23%) and *endo*-DA-adduct (**4a**, 0.560 g, 36%), respectively. b) The reactions of **1b**, **c**, **2a**—**c**, **9a**—**d**, and **10a**—**d** with **3** were carried out under the conditions listed in Tables 1 and 2, and the resulting reaction mixtures were treated in the same manner as described above to give **4b**, **c**, **5a**—**c**, **6a**—**c**, **7a**—**c**, **8**, **11a**—**d**, **12a**—**d**, **13a**—**d**, **14a**—**d**, and **15**, respectively, as summarized in Tables 1 and 2.

General Procedures for High Pressure Diels–Alder Reactions of 1a—c, 2a—c, 9a—d, and 10a—d with 3 a) A solution of **1a** (56 mg, 0.4 mmol) and **3** (138 mg, 0.8 mmol) in CH_2Cl_2 (1 ml) in a Teflon tube, was placed in a high-pressure reactor and pressurized to 10 kbar, followed by heating to 90 °C. After 2 d, the pressure was released, and the reaction mixture was purified using column chromatography (silica gel) with hexane–acetone (1 : 2) as the eluent to afford **4a** (35 mg, 31%). b) The reactions of **1b**, **c**, **2a**—**c**, **9a**—**d**, and **10a**—**d** with **3** were carried out under the conditions listed in Table 3; the reaction mixtures were treated in the same manner as described above to give **4b**, **c**, **5a**, **c**, **d**, **6a**—**c**, **7a**—**c**, **8**, **11a**—**d**, **12a**—**d**, **13a**—**d**, **14a**—**d**, and **15**, respectively, as summarized in Table 3.

4-Methoxy-2-methyl-*N*-phenyl-3-oxo-2-azabicyclo[2.2.2]oct-7-ene-5,6-*endo*-dicarboximide (4a) Colorless plates (benzene–acetone), mp 180—181 °C. IR (KBr) cm^{-1}: 1779, 1619, 736, 699. ^{1}H-NMR ($CDCl_3$) δ: 3.00 (3H, s, NMe), 3.52 (1H, dd, J=1.1, 8.3 Hz, H-5), 3.68 (1H, dd, J=4.0, 8.3 Hz, H-6), 3.85 (3H, s, OMe), 4.59 (1H, ddd, J=1.1, 4.0, 6.2 Hz, H-1), 6.50 (1H, dd, J=6.2, 8.1 Hz, H-7), 6.55 (1H, dd, J=1.1, 8.1 Hz, H-8), 6.49—7.19 (2H, m, H-aromatic), 7.36—7.47 (3H, m, H-aromatic). ^{13}C-NMR ($CDCl_3$) δ: 32.73, 41.86, 47.14, 54.62, 55.27, 82.73, 126.07 (C2), 128.85, 129.06 (C2), 129.23, 131.15, 135.16, 170.55, 171.86, 173.40. LMS *m*/*z*: 313 (M^++1), 256, 173, 139, 119. HR-MS *m*/*z*: Calcd for $C_{17}H_{17}N_2O_4$: 313.1188. Found: 313.1229.

8-Methoxy-2-methyl-*N*-phenyl-3-oxo-2-azabicyclo[2.2.2]oct-7-ene-5,6-*endo*-dicarboximide (4b) Colorless columns (acetone), mp 218—221 °C. IR (KBr) cm^{-1}: 1779, 1689, 1593, 752, 714, 693. ^{1}H-NMR ($CDCl_3$) δ: 2.97 (3H, s, NMe), 3.44 (1H, dd, J=3.7, 8.1 Hz, H-5), 3.55 (3H, s, OMe), 3.61 (1H, dd, J=4.0, 8.1 Hz, H-6), 3.90 (1H, dd, J=2.6, 3.7 Hz, H-4), 4.57 (1H, dd, J=4.0, 6.2 Hz, H-1), 5.15 (1H, dd, J=2.6, 6.2 Hz, H-7), 7.13—7.15 (2H, m, H-aromatic), 7.37—7.48 (3H, m, H-aromatic). ^{13}C-NMR ($CDCl_3$) δ: 32.04, 41.05, 47.75, 49.59, 56.32, 56.65, 93.00, 125.88, 128.90 (C2), 129.14, 131.27 (C2), 160.18, 169.96, 173.67, 173.87. LMS *m*/*z*: 312 (M^+), 173, 139, 108. HR-MS *m*/*z*: Calcd for $C_{17}H_{16}N_2O_4$: 312.1110. Found: 312.1122.

1-Methoxy-2-methyl-*N*-phenyl-3-oxo-2-azabicyclo[2.2.2]oct-7-ene-5,6-*endo*-dicarboximide (4c) Colorless plates (acetone), mp 165—166 °C. IR (KBr) cm^{-1}: 1781, 1619, 714, 699. ^{1}H-NMR ($CDCl_3$) δ: 2.93 (3H, s, NMe), 3.40 (1H, dd, J=3.6, 8.3 Hz, H-5), 3.53 (1H, d, J=8.3 Hz, H-6), 3.74 (3H, s, OMe), 4.02 (1H, ddd, J=1.6, 3.6, 5.9 Hz, H-4), 6.49 (1H, dd, J=5.9, 8.3 Hz, H-8), 6.65 (1H, dd, J=1.6, 8.3 Hz, H-7), 7.15—7.19 (2H, m, H-aromatic), 7.39—7.49 (3H, m, H-aromatic). ^{13}C-NMR ($CDCl_3$) δ: 26.15, 42.08, 45.21, 49.01, 55.11, 91.66, 126.17 (C2), 128.96, 129.17 (C2), 129.81, 131.25, 132.96, 170.87, 171.96, 174.01. LMS *m*/*z*: 312 (M^+), 297, 255, 173. HR-MS *m*/*z*: Calcd for $C_{17}H_{16}N_2O_4$: 312.1111. Found: 312.1147.

4-Methoxy-2-methyl-*N*-phenyl-3-oxo-2-azabicyclo[2.2.2]oct-7-ene-5,6-*exo*-dicarboximide (6a) Colorless plates (MeOH–acetone), mp 239—240 °C. IR (KBr) cm^{-1}: 1780, 1619, 714, 699. ^{1}H-NMR ($CDCl_3$) δ: 2.91 (3H, s, NMe), 3.32 (1H, dd, J=2.5, 8.4 Hz, H-6), 3.35 (1H, dd, J=1.1, 8.4 Hz, H-5), 3.78 (3H, s, OMe), 4.59 (1H, ddd, J=1.1, 2.5, 5.5 Hz, H-1), 6.64 (1H, dd, J=5.5, 8.0 Hz, H-7), 6.71 (1H, dd, J=1.1, 8.0 Hz, H-8), 7.15—7.19 (2H, m, H-aromatic), 7.37—7.47 (3H, m, H-aromatic). ^{13}C-NMR ($CDCl_3$) δ: 33.51, 45.78, 48.45, 54.66, 56.23, 83.39, 126.65 (C2), 129.01, 129.26 (C2), 131.34, 131.96, 135.67, 135.62, 168.64, 171.53, 173.69. LMS *m*/*z*: 313 (M^++1), 255, 173, 125, 108. HR-MS *m*/*z*: Calcd for $C_{17}H_{17}N_2O_4$: 313.1188. Found: 313.1276.

4-Methoxy-*N*-phenyl-3-oxo-2-azabicyclo[2.2.2]oct-7-ene-5,6-*endo*-dicarboximide (5a) Colorless crystalline powder ($CHCl_3$), mp 250—253 °C. IR (KBr) cm^{-1}: 1779, 1713, 1659, 753, 693. ^{1}H-NMR (DMSO-d_6) δ: 3.65 (3H, s, OMe), 3.65—3.67 (1H, br d, H-5), 3.71 (1H, d, J=4.0, 8.0 Hz, H-6),

4.53 (1H, ddd, J=1.0, 4.0, 5.3 Hz, H-1), 6.44 (1H, dd, J=1.0, 8.3 Hz, H-8), 6.56 (1H, dd, J=5.3, 8.3 Hz, H-7), 7.11—7.18 (2H, m, H-aromatic), 7.41—7.51 (3H, m, H-aromatic), 8.70 (1H, br s, NH). ^{13}C-NMR (DMSO-d_6) δ: 40.62, 47.01, 48.11, 52.93, 81.74, 126.29 (C2), 128.05, 128.44 (C2), 130.87, 131.38, 133.62, 171.97, 172.39, 173.68. LMS m/z: 298 (M^+), 255, 173. HR-MS m/z: Calcd for $C_{16}H_{14}N_2O_4$: 298.0954. Found: 298.0971.

8-Methoxy-*N*-phenyl-3-oxo-2-azabicyclo[2.2.2]oct-7-ene-5,6-*endo*-dicarboximide (8) Colorless crystalline powder (acetone), mp 160—162 °C. IR (KBr) cm^{-1}: 1780, 1619, 736, 714. ^{1}H-NMR (CDCl$_3$) δ: 2.75 (1H, dd, J=6.6, 18 Hz, H-10), 3.19 (1H, dd, J=9.4, 18 Hz, H-10), 3.57 (1H, dd, J=3.3, 8.2 Hz, H-5), 3.58 (3H, s, OMe), 3.90 (1H, dd, J=4.0, 8.2 Hz, H-6), 4.01 (1H, dd, J=2.5, 3.3 Hz, H-4), 4.30 (1H, dd, J=4.0, 6.3 Hz, H-1), 5.20 (1H, dd, J=2.6, 6.3 Hz, H-7), 5.10 (1H, dd, J=6.6, 9.4 Hz, H-9), 7.11—7.15 (2H, m, H-aromatic), 7.33—7.55 (8H, m, H-aromatic). ^{13}C-NMR (CDCl$_3$) δ: 29.71, 33.40, 40.54, 48.43, 49.63, 52.75, 53.51, 56.57, 93.44, 125.99, 126.29 (C2), 129.03, 129.10, 129.33 (C2), 129.36, 131.28, 131.31, 136.56, 160.31, 170.29, 172.15, 173.06, 173.49, 173.77. LMS m/z: 471 (M^+), 298, 205, 173. HR-MS m/z: Calcd for $C_{26}H_{21}N_3O_6$: 471.1430. Found: 471.1460.

4-Chloro-2-methyl-*N*-phenyl-3-oxo-2-azabicyclo[2.2.2]oct-7-ene-5,6-*endo*-dicarboximide (11a) Colorless columns (acetone), mp 202—203 °C. IR (KBr) cm^{-1}: 1781, 1718, 1697, 1598, 758, 689. ^{1}H-NMR (CDCl$_3$) δ: 3.07 (3H, s, NMe), 3.42 (1H, dd, J=1.0, 8.0 Hz, H-5), 3.73 (1H, dd, J=4.4, 8.0 Hz, H-6), 4.65 (1H, ddd, J=1.0, 3.3, 4.4 Hz, H-1), 6.49—6.58 (2H, m, H-7,8), 7.17—7.27 (2H, m, H-aromatic), 7.40—7.49 (3H, m, H-aromatic). ^{13}C-NMR (CDCl$_3$) δ: 33.74, 46.73, 47.80, 55.49, 68.91, 126.15 (C2), 129.13, 129.23 (C2), 130.33, 131.06, 137.23, 166.96, 171.22, 172.70. LMS m/z: 318 (M^++2), 316 (M^+), 262, 173. HR-MS m/z: Calcd for $C_{16}H_{13}ClN_2O_3$: 316.0615. Found: 316.0587.

8-Chloro-2-methyl-*N*-phenyl-3-oxo-2-azabicyclo[2.2.2]oct-7-ene-5,6-*endo*-dicarboximide (11b) Colorless needles (acetone), mp 233—235 °C. IR (KBr) cm^{-1}: 1779, 1710, 1680, 1600, 742. ^{1}H-NMR (CDCl$_3$) δ: 2.97 (3H, s, NMe), 3.50 (1H, dd, J=3.5, 8.3 Hz, H-5), 3.65 (1H, dd, J=4.1, 8.3 Hz, H-6), 4.10 (1H, dd, J=2.3, 3.5 Hz, H-4), 4.66 (1H, dd, J=4.1, 6.1 Hz, H-1), 6.45 (1H, dd, J=2.3, 6.1 Hz, H-7), 7.15—7.18 (2H, m, H-aromatic), 7.43—7.47 (3H, m, H-aromatic). ^{13}C-NMR (CDCl$_3$) δ: 33.02, 43.28, 48.12, 53.80, 58.13, 126.48 (C2), 127.77, 129.23, 129.39 (C2), 131.12, 136.89, 167.66, 173.03, 173.51. LMS m/z: 318 (M^++2), 316 (M^+), 259, 173, 119. HR-MS m/z: Calcd for $C_{16}H_{13}ClN_2O_3$: 316.0615. Found: 316.0565.

7-Chloro-2-methyl-*N*-phenyl-3-oxo-2-azabicyclo[2.2.2]oct-7-ene-5,6-*endo*-dicarboximide (11c) Colorless needles (acetone), mp 227—228 °C. IR (KBr) cm^{-1}: 1778, 1713, 1687, 1672, 1595, 752, 692. ^{1}H-NMR (CDCl$_3$) δ: 3.03 (3H, s, NMe), 3.47 (1H, dd, J=3.7, 8.0 Hz, H-5), 3.69 (1H, J=4.4, 8.0 Hz, H-6), 4.05 (1H, dd, J=3.7, 6.6 Hz, H-4), 4.61 (1H, dd, J=2.5, 4.4 Hz, H-1), 6.37 (1H, dd, J=2.5, 6.6 Hz, H-8), 7.16—7.18 (3H, m, H-aromatic), 7.36—7.50 (2H, m, H-aromatic). ^{13}C-NMR (CDCl$_3$) δ: 32.65, 41.67, 46.69, 46.83, 63.55, 125.67, 126.18 (C2), 129.09, 129.25 (C2), 131.01, 133.38, 169.83, 172.28, 173.77. LMS m/z: 318, 316 (M^+), 261, 173, 143. HR-MS m/z: Calcd for $C_{16}H_{13}ClN_2O_3$: 316.0615. Found: 316.0576.

8-Chloro-*N*-phenyl-2-(3-*N*-phenyl-2,3-dioxopyrrolyl)-3-oxo-2-azabicyclo[2.2.2]oct-7-ene-5,6-*exo*-dicarboximide (15) Colorless plates (acetone), mp 163—165 °C. IR (KBr) cm^{-1}: 1778, 1600. ^{1}H-NMR (CDCl$_3$) δ: 3.09 (1H, dd, J=6.4, 18.0 Hz, H-10), 3.20 (1H, dd, J=9.0, 18.0 Hz, H-10), 3.55 (1H, dd, J=3.5, 7.9 Hz, H-5), 4.10 (1H, dd, J=1.5, 3.5 Hz, H-4), 4.19 (1H, dd, J=4.1, 7.9 Hz, H-6), 4.30 (1H, dd, J=6.4, 9.0 Hz, H-9), 4.79 (1H, dd, J=4.1, 6.2 Hz, H-1), 6.53 (1H, dd, J=1.5, 6.2 Hz, H-7), 7.15—7.19 (2H, m, H-aromatic), 7.26—7.32 (2H, m, H-aromatic), 7.41—7.52 (6H, m, H-aromatic). ^{13}C-NMR (CDCl$_3$) δ: 34.51, 41.20, 47.30, 53.39, 57.99, 59.30, 126.23 (C2), 126.37 (C2), 126.44, 18.97, 129.13, 129.20 (C2), 129.26 (C2), 130.96, 131.38, 134.03, 169.76, 172.31, 172.47, 173.14, 173.43. LMS m/z: 477 (M^++2), 475 (M^+), 316, 318, 261, 259, 173. HR-MS m/z: Calcd for $C_{25}H_{18}ClN_3O_5$: 475.0935. Found: 475.0917.

7-Chloro-*N*-phenyl-3-oxo-2-azabicyclo[2.2.2]oct-7-ene-5,6-*endo*-dicarboximide (12c) Colorless columns (acetone), mp 290 °C. IR (KBr) cm^{-1}: 1780, 1703, 1618, 759, 694. ^{1}H-NMR (DMSO-d_6) δ: 3.57 (1H, dd, J=3.3, 7.9 Hz, H-5), 3.64 (1H, dd, J=3.3, 4.3 Hz, H-4), 3.80 (1H, dd, J=4.3, 7.9 Hz, H-6), 4.55 (1H, dd, J=2.0, 4.3 Hz, H-1), 6.60 (1H, dd, J=2.0, 4.3 Hz, H-8), 7.10—7.16 (2H, m, H-aromatic), 7.43—7.53 (3H, m, H-aromatic), 8.75 (1H, br s, NH). ^{13}C-NMR (CDCl$_3$) δ: 39.67, 40.59, 47.45, 55.49, 125.53, 126.16 (C2), 128.21, 128.60 (C2), 131.26, 133.32, 171.9, 172.87, 174.41. LMS m/z: 304 (M^++2), 302 (M^+), 259, 173, 119. HR-MS m/z: Calcd for $C_{15}H_{11}ClN_2O_3$: 302.0458. Found: 302.0453.

4-Chloro-2-methyl-*N*-phenyl-3-oxo-2-azabicyclo[2.2.2]oct-7-ene-5,6-*exo*-dicarboximide (13a) Colorless columns (acetone), mp 288—290 °C. IR (KBr) cm^{-1}: 1782, 1713, 1684, 1594, 742. ^{1}H-NMR (DMSO-d_6) δ: 3.34 (3H, s, NMe), 3.50—3.57 (2H, m, H-5,6), 4.83 (1H, ddd, J=1.7, 3.0, 5.6 Hz, H-1), 4.45 (1H, dd, J=1.7, 8.0 Hz, H-8), 6.77 (1H, dd, J=5.6, 8.0 Hz, H-7), 7.07—7.19 (2H, m, H-aromatic), 7.42—7.56 (3H, m, H-aromatic). ^{13}C-NMR (DMSO-d_6) δ: 33.23, 48.23, 48.84, 55.89, 69.04, 126.32 (C2), 128.32, 128.69 (C2), 131.18, 133.70, 137.28, 164.91, 171.22, 173.14. LMS m/z: 318 (M^++2), 316 (M^+), 261, 173, 119. HR-MS m/z: Calcd for $C_{16}H_{13}ClN_2O_3$: 316.0615. Found: 316.0633.

8-Chloro-2-methyl-*N*-phenyl-3-oxo-2-azabicyclo[2.2.2]oct-7-ene-5,6-*exo*-dicarboximide (13b) Colorless needles (acetone), mp 245—246 °C. IR (KBr) cm^{-1}: 1780, 1710, 1596, 742. ^{1}H-NMR (CDCl$_3$) δ: 2.90 (3H, s, NMe), 3.33 (1H, dd, J=2.7, 8.5 Hz, H-6), 3.46 (1H, dd, J=3.3, 8.5 Hz, H-5), 4.05 (1H, dd, J=2.3, 3.3 Hz, H-4), 4.73 (1H, dd, J=2.7, 6.1 Hz, H-1), 6.52 (1H, dd, J=2.3, 6.1 Hz, H-7), 7.13—7.23 (2H, m, H-aromatic), 7.40—7.50 (3H, m, H-aromatic). ^{13}C-NMR (DMSO-d_6) δ: 33.02, 43.28, 48.12, 53.80, 58.13, 126.48 (C2), 127.77, 129.23, 129.39 (C2), 131.12, 136.89, 17.66, 171.84, 173.03, 173.52. LMS m/z: 318 (M^++2), 316 (M^+), 259, 173, 119. HR-MS m/z: Calcd for $C_{16}H_{13}ClN_2O_3$: 316.0615. Found: 316.0669.

7-Chloro-2-methyl-*N*-phenyl-3-oxo-2-azabicyclo[2.2.2]oct-7-ene-5,6-*exo*-dicarboximide (13c) Colorless needles ($CHCl_3$), mp >300 °C. IR (KBr) cm^{-1}: 1780, 1713, 1600, 740. ^{1}H-NMR (CDCl$_3$) δ: 2.94 (3H, s, NMe), 3.30 (1H, dd, J=3.5, 8.6 Hz, H-5), 3.49 (1H, dd, J=2.8, 8.6 Hz, H-6), 4.04 (1H, dd, J=3.5, 6.8 Hz, H-4), 4.62 (1H, dd, J=2.3, 2.8 Hz, H-1), 6.45 (1H, dd, J=2.3, 6.8 Hz, H-8), 7.15—7.19 (2H, m, H-aromatic), 7.40—7.50 (3H, m, H-aromatic). ^{13}C-NMR (CDCl$_3$) δ: 33.34, 43.79, 47.12, 47.57, 64.16, 126.48 (C2), 127.11, 129.24, 129.41 (C2), 131.14, 135.94, 168.59, 173.28, 173.43. LMS m/z: 318 (M^++2), 316 (M^+), 259, 173, 119. HR-MS m/z: Calcd for $C_{16}H_{13}ClN_2O_3$: 316.0615. Found: 316.0669.

3-[4-Methoxy-2(1*H*)-pyridinyl]-*N*-phenylmaleimide (5d) Polorless needles (acetone), mp 237—240 °C. IR (KBr) cm^{-1}: 1775, 1660, 1596. ^{1}H-NMR (CDCl$_3$) δ: 3.22 (2H, d, J=7.3 Hz, CH$_2$), 3.77 (3H, s, OMe), 4.68 (1H, dd, J=7.3, 7.3 Hz, CH), 5.77 (1H, d, J=2.8 Hz, H-3), 5.99 (1H, dd, J=2.8, 7.6 Hz, H-5), 7.16 (1H, d, J=7.6 Hz, H-6), 7.32—7.65 (5H, m, H-aromatic). ^{13}C-NMR (CDCl$_3$) δ: 34.52, 55.74, 59.94, 97.29, 102.16, 126.79 (C2) 128.85, 129.23 (C2), 132.05, 137.79, 163.47, 169.14, 171.15, 172.93. LMS m/z: 298 (M^+), 178, 150. HR-MS m/z: Calcd for $C_{16}H_{14}N_2O_4$: 298.0954. Found: 298.0931.

Calculation of Activation Energy We assumed that the reactants were far apart at the initial state. The structure of each state in the reactions was optimized using the semi-empirical molecular orbital PM5 method.[19] The solvent effect was not considered. After optimizing the TS structure, the vibrational calculation was carried out to confirm that the TS had only one imaginary vibrational frequency. The intrinsic reaction coordinate calculation was also performed to ensure that the TS connected the initial and the intended final state. The activation energy Ea was calculated by the difference in energy between the TS and the initial state. The values of Ea of Michael reactions were calculated essentially in the same way as DA reaction but using *ab initio* molecular orbital Gaussian 03 method at HF/6-31G(d) level.[20]

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