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

Masato Hoshino, Hisao Matsuzaki, and Reiko Fujita*

Tohoku Pharmaceutical University; 4–4–1 Komatsushima, Aoba-ku, Sendai 981–8558, Japan.
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Diels–Alder reactions between N-phenylmaleimide, acting as the dienophile, and 2(1H)-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(1H)-pyridone; chloro-2(1H)-pyridone; N-phenylmaleimide; molecular orbital calculation

Preparation of isoquinuclidines via Diels–Alder (DA) reaction between a diene and 2(1H)-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(1H)-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(1H)-pyridones and Michael addition reactions of 1-unsubstituted 2(1H)-pyridones were determined using molecular orbital (MO) calculations.

DA Reactions between 2(1H)-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 1H-NMR spectra. For isoquinuclidine derivatives, the coupling constant between the bridge-head protons and H_{endo} is generally 3.5—4.5 Hz, and for H_{exo}, 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>
<thead>
<tr>
<th>Entry</th>
<th>Pyridone</th>
<th>R</th>
<th>R¹</th>
<th>R²</th>
<th>R³</th>
<th>Temp. (°C)</th>
<th>Time (d)</th>
<th>Adduct</th>
<th>Yield (%)</th>
<th>Adduct</th>
<th>Yield (%)</th>
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<tr>
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<td>Me</td>
<td>OMe</td>
<td>H</td>
<td>H</td>
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<td>4a</td>
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<td>6a</td>
<td>23</td>
</tr>
<tr>
<td>2</td>
<td>1b</td>
<td>Me</td>
<td>H</td>
<td>OMe</td>
<td>H</td>
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<td>5c</td>
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* To whom correspondence should be addressed. e-mail: refujita@tohoku-pharm.ac.jp © 2008 Pharmaceutical Society of Japan
adducts were carried out for the DA reaction of pyridones under HP conditions, the HP DA reactions did not exhibit adducts produced under AP conditions and those formed with was the sole product, which implies that was carried out under 10 kbar at 90 °C for 2 d in CH2Cl2. In the case of 2a and 2b, Michael-adduct 5d was the sole product, which implies that endo–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. 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).

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(1H)-pyridine in these cases, the Michael addition reaction occurs between 3 and presumably the enol tautomer of 2(1H)-pyridine. 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. 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(1H)-pyridones bearing a methoxy or a chloro group were
successively 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, Perkin Elmer FT-IR 1725X spectrophotometer; NMR spectra, JEOL JNM-EX270 (1H-NMR, 270 MHz; 13C-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 solution of 1a (56 mg, 0.4 mmol) and 3 (138 mg, 0.8 mmol) in CH2Cl2 (1 ml) in a Teflon tube, was placed in a high-pressure reactor and pressurized to 10bar, followed by heating to 90 °C. After 2d, 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 4b, 5a, c, 6a—c, 7a—c, 8, 11a—d, 12a—d, 13a—d, 14a—d, and 15, respectively, as summarized in Table 3.

**4-Methoxy-2-phenyl-N-phenylmaleimide (PMS Method)**

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<th>Entry</th>
<th>NR</th>
<th>Pyridone</th>
<th>Adduct (yield) (%)</th>
<th>Ea (kcal/mol)</th>
<th>Adduct (yield) (%)</th>
<th>Ea (kcal/mol)</th>
<th>Adduct (yield) (%)</th>
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<td>NH</td>
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**Table 4. Calculated Activation Energies (Ea) and Experimental Yields of Adducts for DA Reaction of 2-Pyridones with N-Phenylmaleimide (PMS Method)**

<table>
<thead>
<tr>
<th>Pyridone</th>
<th>Ea (kcal/mol)</th>
<th>Pyridone</th>
<th>Ea (kcal/mol)</th>
<th>Pyridone</th>
<th>Ea (kcal/mol)</th>
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</thead>
<tbody>
<tr>
<td>3-Ome</td>
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<td>3-Cl</td>
<td>37.34</td>
<td>3-Cl</td>
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<tr>
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<td>4-Cl</td>
<td>36.54</td>
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</tr>
<tr>
<td>5-Ome</td>
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<td>5-Cl</td>
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<td>6-Ome</td>
<td>41.66</td>
<td>6-Cl</td>
<td>45.72</td>
<td>6-Cl</td>
<td>45.72</td>
</tr>
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</table>

**Table 5. Calculated Activation Energies (Ea) for Michael Addition of 2- Pyridones with N-Phenylmaleimide Calculated at HF/6-31(d) Level**
4.53 (1H, dd, 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), 7.51 (1H, s, NMe), 7.58 (3H, s, NMe), 3.50—3.57 (2H, m, H-5), 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).

1H-NMR (DMSO-d6) δ: 33.4 (3H, s, OMe), 4.85 (1H, d, J = 1.7, 7.8 Hz, H-3'), 4.60 (1H, d, J = 2.5, 6.8 Hz, H-4'), 7.15—7.18 (2H, m, H-aromatic), 7.43—7.47 (3H, m, H-aromatic).

13C-NMR (DMSO-d6) δ: 33.41, 43.79, 44.78, 53.80, 64.16, 126.48 (C2), 127.77, 127.29, 132.93 (C2), 131.12, 136.89, 167.66, 170.73, 173.51. LMS m/z: 318 (M+2)², 316 (M+2), 259, 259, 173, 119. HR-MS m/z: Calcd for C16H14N2O4: 298.0912, Found: 298.0912.

4-Chloro-2-methyl-N-phenyl-3-oxo-2-azabicyclo[2.2.2]oct-7-ene-5,6-dicarboximide (13b) Colorless needles (acetone), mp 245—246 °C. IR (KBr) cm−1: 1780, 1710, 1596, 742. 1H-NMR (CDCl3) δ: 2.90 (3H, s, NMe), 3.33 (1H, dd, J = 2.7, 8.5 Hz, H-5), 3.46 (1H, dd, J = 1.7, 2.8, 8.5 Hz, H-6), 4.04 (1H, dd, J = 3.5, 6.8 Hz, H-4), 4.62 (1H, dd, J = 2.5, 2.8, 8.5 Hz, H-5), 4.65 (1H, d, J = 2.7, 6.1 Hz, H-7), 7.15—7.19 (2H, m, H-aromatic), 7.40—7.50 (3H, m, H-aromatic).

13C-NMR (CDCl3) δ: 33.34, 43.79, 44.78, 53.80, 64.16, 126.48 (C2), 127.77, 127.29, 132.93 (C2), 131.12, 136.89, 167.66, 170.73, 173.51. LMS m/z: 318 (M+2)², 316 (M+2), 259, 259, 173, 119. HR-MS m/z: Calcd for C16H14N2O4: 298.0912, Found: 298.0912.

3-[(2H)-pyridin-1-yl]-N-phenylmaleimide (50) Colorless needles (acetone), mp 237—240 °C. IR (KBr) cm−1: 1775, 1650, 1569. 1H-NMR (CDCl3) δ: 3.22 (2H, d, J = 7.3, 7.3 Hz, CH), 3.77 (3H, s, OMe), 4.68 (1H, dd, J = 7.3, 7.3 Hz, CH), 5.77 (1H, d, J = 2.8, 19.8 Hz, H-3'), 5.99 (1H, dd, J = 2.8, 7.6 Hz, H-5), 7.16 (1H, d, J = 7.6, 7.6 Hz, H-6), 7.32—7.65 (5H, m, H-aromatic).

13C-NMR (CDCl3) 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 C16H12N2O3: 290.0954. 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 intended final state. The activation energy was calculated using the semi-empirical molecular orbital PM5 method. 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 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 M1 and M2 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.26

References