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CYCLOADDITION OF 2-PYRIDONES HAVING AN ELECTRON-WITHDRAWING GROUP

Masato Hoshino, Hisao Matsuzaki, and Reiko Fujita*

Tohoku Pharmaceutical University, 4-4-1, Komatsushima, Aoba-ku, Sendai, Miyagi 981-8558, Japan

Abstract - Cycloaddition of 1-methyl-2(1*H*)-pyridones bearing an electron-withdrawing group at 3-5 positions acting as the diene with *N*-phenylmaleimide was carried out under atmospheric and high pressure conditions to give the corresponding isoquinuclidines. Stereoselectivity of the cycloaddition of 1-methyl-2(1*H*)-pyridones was investigated using molecular orbital calculations.

INTRODUCTION

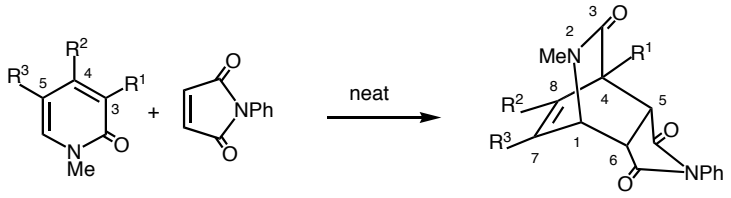
Isoquinuclidine derivatives,[1-5] which serve as useful intermediates in the synthesis of iboga alkaloids,[1-4] can be obtained via cycloadditions between 2(1*H*)-pyridones (as aromatic heterocyclic dienes) and various dienophiles.[6,7] We have previously reported the cycloaddition of 2(1*H*)-pyridones bearing a methyl, phenyl or ester substituent.[8] Herein, as an extension of our synthetic methodology, we present the cycloaddition reaction between *N*-phenylmaleimide (as the dienophile), and 1-methyl-2(1*H*)-pyridones (as the electron deficient dienes) having an electron-withdrawing substituent (COPh, or CN) at 3-5 positions. In addition to atmospheric (AP) conditions, the reactions were also performed under high pressure (HP), which has proven to be effective in surmounting the energy barriers imposed by steric and electronic effects of the cycloaddition.[9] Moreover, the stereoselectivity of the cycloaddition was investigated using molecular orbital (MO) calculations.

RESULTS AND DISCUSSION

Cycloaddition of 2(1*H*)-pyridones with *N*-phenylmaleimide.

As listed in Table 1 and Scheme 1, the cycloaddition was initially investigated using benzoylpyridones **1**-**3**[10] and *N*-phenylmaleimide **7** under AP at 110 °C for 3 d (Entries 1-3). The cycloaddition proceeded smoothly to stereoselectively afford the *endo*-adduct isoquinuclidines **8** (53%), **9** (99%), **10** (85%),

possessing a benzoyl group at the 4-, 7- or 8-position, respectively. Under similar conditions as that for **1**-**3**, the cycloaddition of cyano-2(1*H*)-pyridones **4**-**6** afforded *endo*-adducts **11** (13%, Entry 4), **12** (98%, Entry 5), **13** (59%, Entry 6), bearing a cyano group at the 4-, 7-, or 8-position, respectively. Of note, the cycloaddition of 2(1*H*)-pyridones that possess a substituent at the 4-position (**2** and **5**) resulted in quantitative yields of the corresponding isoquinuclidines.



1-6 **7** *endo* **8-13**

1 ; **8** : R^1= COPh ; R^2 = R^3 = H
2 ; **9** : R^2= COPh ; R^1 = R^3 = H
3 ; **10** : R^3= COPh ; R^1 = R^2 = H
4 ; **11** : R^1= CN ; R^2 = R^3 = H
5 ; **12** : R^2= CN ; R^1 = R^3 = H
6 ; **13** : R^3= CN ; R^1 = R^2 = H

Scheme 1

Table 1. Cycloaddition of **1-6** with **7** at 110 °C for 3 d in Sealed Tube

Entry	R^1	R^2	R^3	Pyridone	Adduct	Yield (%) *endo*
1	COPh	H	H	**1**	**8**	53
2	H	COPh	H	**2**	**9**	99
3	H	H	COPh	**3**	**10**	85
4	CN	H	H	**4**	**11**	13
5	H	CN	H	**5**	**12**	98
6	H	H	CN	**6**	**13**	59

As shown in Table 2, the cycloaddition of pyridones **1**-**6** under HP at 90 °C for 2 d (Entries 1-6) stereoselectively afforded isoquinuclidines **8** (3%), **9** (52%), **10** (30%), **11** (5%), **12** (65%), and **13** (35%), respectively. The yields of cycloaddition under HP were lower than that under AP. Especially, the lowest yields were observed for the cycloaddition of **1** and **4**, which possess a substituent at the 3-position.

The configurations of the substituents at the 5- and 6-positions of *endo*-adducts **8**-**13** 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, whereas that for H_{endo}, less than 3.5 Hz.[7]

Table 2 . Cycloaddition of **1**-**6** with **7** at 90 °C for 2 d under 10 kbar

Entry	Pyridone	Adduct	Yield (%) *endo*
1	**1**	**8**	3
2	**2**	**9**	52
3	**3**	**10**	30
4	**4**	**11**	5
5	**5**	**12**	65
6	**6**	**13**	35

Theoretical studies using MO method

Using the PM3 method,[11] theoretical calculations were carried out for the cycloaddition between **7** and 2-pyridones **1**-**6**. For each reaction, activation energies (*Ea*) were determined for the optimized transition states (TS) structures of the *endo*- and *exo*-adducts. As shown in Table 3, *Ea* values that correspond to the *endo*-adducts were lower than those of the *exo*-adducts, which is in agreement with the experimental results showing favorable yields of the *endo*-adducts. Because the experimental data in Tables 1 and 2 were obtained under identical conditions, the yields of adduct can be considered as indicators of reactivity. For both benzoyl and cyano *endo*-adducts, the *Ea* values correlate with the yields specifically, the low *Ea* values for the 4-substituted dienes correspond to the high yield and reactivity of the 2-pyridones that have a benzoyl or cyano substituent at the 4-position. As shown in Table 2, yields obtained under high pressure (10 kbar) show similar reactivity.

Table 3. Calculated Activation Energies (*Ea*) and Experimental Yields of Adducts for Cycloaddition of 2-pyridones with *N*-Phenylmaleimide (PM3 Method)

Diene (Pyridone)		*Endo* Addition		*Exo* Addition		*Ea (Exo)* - *Ea (Endo)*
		Ea (kcal/mol)	Adduct (Yield) (%)	*Ea* (kcal/mol)	Adduct (Yield) (%)	(kcal/mol)
3-COPh	**1**	38.91	53	40.62	0	1.71
4-COPh	**2**	35.09	99	35.33	0	0.24
5-COPh	**3**	35.96	85	36.99	0	0.83
3-CN	**4**	39.2.3	13	40.57	0	1.34
4-CN	**5**	36.74	98	37.55	0	0.81
5-CN	**6**	37.73	59	38.48	0	0.75

CONCLUSION

In summary, highly stereoselective cycloaddition was observed for cycloaddition between *N*-phenylmaleimide **7** and 1-methyl-2(1*H*)-pyridones **1**-**6**, which possess an electron-withdrawing group, to afford the corresponding *endo*-adducts **8**-**13**. Furthermore, our experimental results were in agreement with those of MO calculations.

EXPERIMENTAL

The following instruments were used to obtain physical data: Melting points, Yanaco micromelting point apparatus (values are uncorrected); IR spectra, Perkin Elmer FT-IR1725X 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 spectrometers (^{1}H-NMR, 270 MHz; ^{13}C-NMR, 67.8 MHz), with tetramethylsilane (TMS) as an internal standard. For column chromatography, Merck Kieselgel silica gel 60 (230-400 mesh) was used.

General Procedure for Cycloaddition of 1-6 with 7

a) A mixture of **1** (0.503 g, 2.5 mmol) and **7** (3.5 g, 20 mmol) was heated at 110 °C for 3 d. Subsequently, the reaction mixture was separated by chromatography on a column of silica gel. The solvent of the first fraction eluted with hexane-acetone (1:2) was evaporayed to afford the recovery of **7**. The solvent of second fraction was evaporayed to give *endo*-adduct (**8**, 0.510 g, 53%). b) Similarly, the reactions of **2**-**6** with **7** were carried out, under the conditions as listed in Table 1, to give **9**-**13**, respectively. The yields of **8**-**13** are summarized in Table 1.

General Procedure for High Pressure Cycloaddition of 1-6 with 7

a) A dichloromethane solution (1 mL) of **1** (85.2 mg, 0.4 mmol) and **7** (138 mg, 0.8 mmol) was placed in Teflon tube. The tube was placed in a high pressure reactor and pressurized to 10 kbar, followed by heating at 90 °C. After 2 d, the pressure was released and the reaction mixture was chlomatographed over silica gel using hexane-acetone (1:2) as eluent to afford **8** (5 mg, 3%). b) Similarly, the reaction of **2**-**6** with **7** were carried out, under the conditions listed in Table 2, to give **9**-**13**, respectively. The yields of **8**-**13** are summarized in Table 2.

4-Benzoyl-2-methyl-3-oxo-*N*-phenyl-2-azabicyclo[2.2.2]oct-7-ene-5,6-*endo*-dicarboximide (8)

Colorless needles (acetone), mp 213-214 °C. IR (KBr) cm^{-1}: 1778, 1713, 1691, 1671, 1598, 758, 689. ^{1}H-NMR ($CDCl_3$, 270 MHz) δ : 3.08 (3H, s, NMe), 3.71 (1H, dd, *J*=3.6, 8.2 Hz, H-6), 4.40 (1H, d, *J*=8.2 Hz, H-5), 4.71 (1H, dd, *J*=1.7, 3.6, 5.3 Hz, H-1), 6.60 (1H, dd, *J*=5.3, 7.9 Hz, H-7), 6.88 (1H, dd, *J*=1.7, 7.9 Hz, H-8), 7.06-7.11 (2H, m, H-aromatic), 7.31-7.91 (8H, m, H-aromatic). ^{13}C-NMR ($CDCl_3$,

67.8 MHz) δ : 32.8, 43.5, 46.8, 57.0, 62.5, 126.1, 126.5, 128.1, 128.3, 128.9, 129.0, 129.1, 129.3, 129.4, 129.8, 131.2, 132.5, 134.8, 136.5, 169.9, 173.3, 173.4, 194.9. LMS *m/z*: 386 (M^+), 329, 182. HRMS *m/z*: Calcd for $C_{23}H_{18}N_2O_4$: 386.1266. Found: 386.1238.

8-Benzoyl-2-methyl-3-oxo-*N*-phenyl-2-azabicyclo[2.2.2]oct-7-ene-5,6-*endo*-dicarboximide (9)

Colorless needles (acetone), mp 222-225 °C. IR (KBr) cm^{-1}: 1780, 1717, 1693, 1597, 751, 696. ^{1}H-NMR (DMSO-d_6, 270 MHz) δ : 2.93 (3H, s, NMe), 3.62 (1H, dd, *J*=3.3, 8.2 Hz, H-5), 4.01 (1H, dd, *J*=4.3, 8.2 Hz, H-6), 4.25 (1H, dd, *J*=2.0, 3.3 Hz, H-4), 4.97 (1H, dd, *J*=4.3, 5.6 Hz, H-1), 7.09-7.12 (2H, m, H-aromatic), 7.25 (1H, dd, *J*=2.0, 5.6 Hz, H-7), 7.40-7.67 (8H, m, H-aromatic). ^{13}C-NMR (DMSO-d_6, 67.8 MHz) δ : 31.2, 40.3, 44.4, 45.6, 55.7, 125.6, 127.9, 128.1 (C5), 128.3 (C2), 130.9, 132.4, 135.0, 139.7, 141.8, 169.0, 173.2, 173.6, 189.4. LMS *m/z*: 386 (M^+), 329, 182. HRMS *m/z*: Calcd for $C_{23}H_{18}N_2O_4$: 386.1266. Found: 386.1257.

7-Benzoyl-2-methyl-3-oxo-*N*-phenyl-2-azabicyclo[2.2.2]oct-7-ene-5,6-*endo*-dicarboximide (10)

Colorless needles (acetone), mp 237-239 °C. IR (KBr) cm^{-1}: 1779, 1718, 1685, 1599, 750, 693. ^{1}H-NMR (DMSO-d_6, 270 MHz) δ : 2.96 (3H, s, NMe), 3.68 (1H, dd, *J*=3.6, 8.2 Hz, H-5), 3.95-3.99 (2H, m, H-4, 6), 5.22 (1H, dd, *J*=2.3, 4.0 Hz, H-1), 7.07-7.19 (2H, m, H-aromatic), 7.21(1H, dd, *J*=2.3, 6.3 Hz, H-8), 7.34-7.81 (8H, m, H-H-aromatic). ^{13}C-NMR (DMSO-d_6, 67.8 MHz) δ : 32.0, 45.6, 45.9, 46.8, 55.2, 56.6, 125.8, 126.3, 128.0, 128.9, 128.2, 128.3, 128.3, 128.5, 128.7, 128.8, 131.3, 132.4, 135.4, 167.9, 174.0, 174.1, 189.4. LMS *m/z*: 386 (M^+), 329, 250, 182. HRMS *m/z*: Calcd for $C_{23}H_{18}N_2O_4$: 386.1266. Found: 386.1261.

4-Cyano-2-methyl-3-oxo- *N*-phenyl-2-azabicyclo[2.2.2]oct-7-ene-5,6-*endo*-dicarboximide (11)

Colorless plates (MeOH), mp 230-232 °C. IR (KBr) cm^{-1}: 2268, 1786, 1718, 1687, 1597, 754, 693. ^{1}H-NMR (acetone-d_6, 270 MHz) δ : 3.03 (3H, s, NMe), 3.84 (1H, d, *J*=8.3 Hz, H-5), 4.06 (1H, dd, *J*=4.3, 8.3 Hz, H-6), 4.89 (1H, dd, *J*=1.6, 4.3, 5.6 Hz, H-1), 6.67 (1H, dd, *J*=1.6, 7.9 Hz, H-8), 6.87 (1H, dd, *J*=5.6, 7.9 Hz, H-7), 7.20-7.24 (1H, m, H-aromatic), 7.42-7.51 (4H, m, H-aromatic). ^{13}C-NMR (acetone-d_6, 67.8 MHz) δ : 37.3, 44.2, 46.4, 55.7, 115.7, 115.8, 126.6 (C2), 128.5, 128.7 (C2), 130.0, 132.0, 133.4, 164.4, 172.1, 172.7. LMS *m/z:* 307 (M^+), 250, 173, 119. HRMS *m/z*: Calcd for $C_{17}H_{13}N_3O_3$: 307.0957. Found: 307.0974.

8-Cyano-2-methyl-3-oxo- *N*-phenyl-2-azabicyclo[2.2.2]oct-7-ene-5,6-*endo*-dicarboximide (12)

Colorless crystalline powder ($CHCl_3$), mp 269-270 °C. IR (KBr) cm^{-1}: 2228, 1782, 1718, 1692, 1597, 752, 698. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ : 3.21 (3H, s, NMe), 4.08 (1H, dd, *J*=3.0, 8.3 Hz, H-5), 4.22 (1H, dd, *J*=4.4, 8.3 Hz, H-6), 4.65 (1H, dd, *J*=2.0, 3.0 Hz, H-4), 5.28 (1H, dd, *J*=4.4, 5.4 Hz, H-1), 7.15-7.18 (2H, m, H-aromatic), 7.54-7.57 (3H, m, H-aromatic), 7.73 (1H, dd, *J*=2.0, 5.4 Hz, H-7).

^{13}C-NMR ($CDCl_3$, 100 MHz) δ : 32.8, 40.5, 46.3, 47.7, 56.7, 113.6, 117.1, 126.0, 126.3, 129.3, 129.4 (C2), 130.6, 144.9, 167.8, 172.3, 172.3. LMS *m/z*: 307 (M^+), 250, 173, 134, 119. HRMS *m/z*: Calcd for $C_{17}H_{13}N_3O_3$: 307.0957. Found: 307.0956.

7-Cyano-2-methyl-3-oxo- *N*-phenyl-2-azabicyclo[2.2.2]oct-7-ene-5,6-*endo*-dicarboximide (13)

Colorless needles (MeOH), mp 295-298 °C. IR (KBr) cm^{-1}: 2224, 1781, 1723, 1684, 1595, 758, 592. ^{1}H-NMR (DMSO-d_6, 400 MHz) δ : 2. 92 (3H, s, NMe), 3.64 (1H, dd, *J*=3.3, 8.0 Hz, H-5), 3.95 (1H, dd, *J*=3.3, 6.3 Hz, H-4), 3.99 (1H, dd, *J*=4.3, 8.0 Hz, H-6), 5.15 (1H, dd, *J*=1.5, 4.3 Hz, H-1), 7.12-7.17 (2H, m, H-aromatic), 7.40-7.54 (3H, m, H-aromatic), 7.70 (1H, dd, *J*=1.5, 6.3 Hz, H-8). ^{13}C-NMR (DMSO-d_6, 100 MHz) δ : 32.8, 40.8, 46.3, 46.7, 58.6, 113.5, 117.3, 126.0 (C2), 129.4 (C2), 129.5, 130.7, 146.6, 168.0, 171.9, 173.0. LMS *m/z*: 307 (M^+), 250, 173, 129. HRMS *m/z*: Calcd for $C_{17}H_{13}N_3O_3$: 307.0957. Found: 307.0952.

Calculation of Activation Energies

The structures of each state were optimized using the semi-empirical molecular orbital PM3 method.[11] The reactants were assumed to be far apart at the initial state. Solvent effects were not considered. After optimizing the TS structures, vibrational calculations were carried out to confirm that the TS had only one imaginary vibrational frequency. Intrinsic reaction coordinate calculations were also performed to ensure that the TS connected the initial and the desired final states. The *Ea* values were defined as the difference in the energies between the TS and initial states.

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