DIELS-ALDER CYCLOADDITION USING PHENYL-2(1*H*)-PYRIDONES AS DIENES[1]

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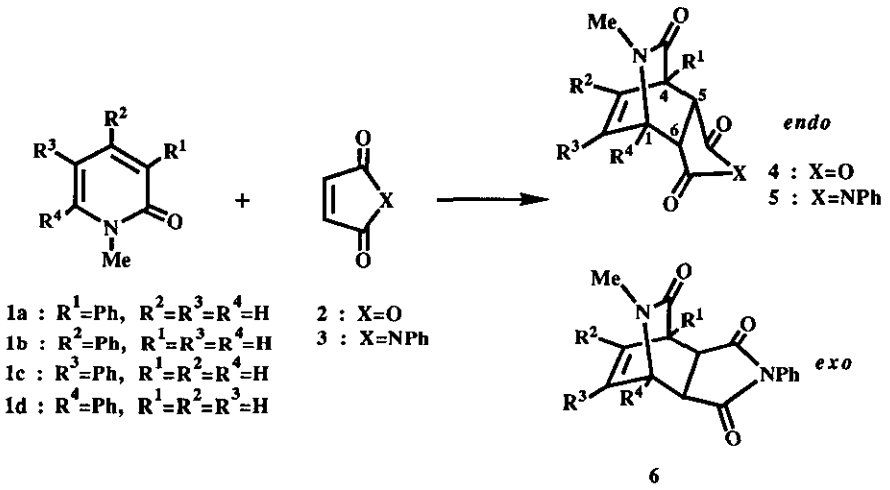
Abstract —— Diels-Alder cycloadditions of 1-methyl-2(1*H*)-pyridones (**1a-d**) having a phenyl group in the ring with maleic anhydride (**2**) or *N* -phenylmaleimide (**3**) under atmospheric pressure conditions and with **3** under high pressure conditions were carried out. The reactions of **1a-d** with **3** under 10 kbar at 110 °C for 72 h gave a mixture of the *endo* and *exo* adducts (**5** and **6**), some of which were unobtainable under atmospheric pressure conditions.

2(1*H*)-Pyridones are classified as aromatic heterocycles, and generally do not undergo efficient Diels-Alder cycloaddition.[2] Nevertheless, the Diels-Alder adducts from the reactions of 2(1*H*)-pyridones with dienophiles have an isoquinuclidine skeleton, which is commonly found in many iboga alkaloids, and therefore the adducts have potential as synthetic interemediates.[3f] Previously, we have developed a synthetic route toward this heterocyclic ring system having various substituents by using Diels-Alder cycloadditions of 2(1*H*)-pyridones with dienophiles. In the present paper, we wish to report the reactions of 1-methyl-2(1*H*)-pyridones (**1a-d**)[4] having a phenyl group in the ring with maleic anhydride (**2**) or *N*-phenylmaleimide (**3**) under atmospheric pressure conditions and with **3** under high pressure conditions. Isoquinuclidine derivatives having a phenyl group linked to quaternary carbon derived from **1a,d** with dienophiles are expected to possess the interesting pharmacological activities.[5] Although the high pressure strategy has proven extremely useful to surmount the energy barrier imposed by steric and electronic effects in cycloaddition reaction such as Diels-Alder cycloaddition, there are few publications[2,6] relating to an application of the technique in Diels-Alder cycloaddition of 2(1*H*)-pyridones. Diels-Alder cycloadditions of **1a-d** with **2** or **3** were carried out under atmospheric pressure conditions at 110 °C for 72 h in toluene. The reactions of **1b,c** with **2** or **3** gave

Dedicated to Dr. Arnord Brossi on the occasion of his 70th birthday.

stereoselectively the corresponding *endo* adducts (**4b,c** and **5b,c**), however, those of **1a,d** with **2** or **3** did not yield the adducts at all with recovering the starting materials. Next, high pressure Diels-Alder cycloadditions of **1a-d** with **3** were performed under 10 kbar at 110°C for 72 h in toluene.



Scheme 1

The reactions of **1a,d** with **3** afforded a mixture of the corresponding *endo* (**5a** and **5d**) and *exo* (**6a** and **6d**) adducts, respectively, which were not obtained under atmospheric pressure conditions. Furthermore, the reactions of **1b,c** with **3** also proceeded to give a mixture of the corresponding *endo* (**5b** and **5c**) and *exo* (**6b** and **6c**) adducts, respectively (Scheme 1 and Table I).

Table I. Diels-Alder Cycloadditions of 1a-d with 2 or 3

Substrate	Pressure (kbar)	Yield (%) of Product 4	5	6
1a	atmospheric	0	0	0
	10	---	26	50
1b	atmospheric	55	50	0
	10	---	11	2
1c	atmospheric	44	90	0
	10	---	78	18
1d	atmospheric	0	0	0
	10	---	76	8

The structures of **4b,c, 5a-d,** and **6a-d** were confirmed by their spectral analyses. It was suggested that the products (**4b,c, 5a-d,** and **6a-d**) were the corresponding 1:1 cycloadducts of 2(1*H*)-pyridones (**1a-d**) and dienophiles (**2** and **3**) from the ms data, respectively. ^{1}H-Nmr spectral data of **4b,c, 5a-d,** and **6a-d** revealed characteristic signals, respectively, due to the protons in an isoquinuclidine system, and their stereochemistries were deduced as *endo* in **4b,c** ($J_{1,6}$=$J_{4,5}$=3.0-4.3 Hz) and **5a-d** ($J_{1,6}$=$J_{4,5}$=4.0-4.3 Hz), and *exo* in **6a-d**($J_{1,6}$=2.0-2.6 Hz, $J_{4,5}$=2.0-3.3 Hz) from the coupling constants, respectively. In general, the coupling constants of *endo*-H and *exo*-H coupling with bridgehead protons are less than 3.5 Hz [3g,h,i,7] and 3.5-4.5 Hz,[3g,h,i,7] respectively, in isoquinuclidine derivatives.

Thus, it was found that, by high pressure technique, Diels-Alder cycloaddition of phenylated 1-methyl-2(1*H*)-pyridones to dienophiles was accelerated, and also gave the *exo* adducts which were not obtained under atmospheric pressure conditions.

EXPERIMENTAL

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. Ir spectra were measured with a Shimadzu IR - 300 spectrometer. ^{1}H-Nmr spectra were recorded on a JEOL JNM-PMX 60 and a JNM-GSX 400 spectrometers with tetramethylsilane as an internal standard. Ms were taken on a JEOL JNM-DX 303 spectrometer.

General procedure for the preparations of the Diels-Alder adducts (4b,c and 5b,c) :

A mixture of **1b,c** (1.85 g, 10 mmol) and **2** (1.47 g, 15 mmol) or **3** (2.6 g, 15 mmol) in toluene (20 ml) was heated at 110°C for 72 h. Then, the resulting precipitate was collected by filtration and recrystallized from benzene or acetone to give the corresponding *endo* adducts (**4b,c** and **5b,c**), respectively (Table I).

2-Methyl-8-phenyl-3-oxo-2-azabicyclo[2.2.2]oct-7-ene-5,6-*endo*-dicarboxylic anhydride (4b) : mp 187-188°C (benzene) ; ir (Nujol): 1775, 1675 cm^{-1}; ^{1}H-nmr ($CDCl_3$): δ 2.98 (3H, s), 3.73 (2H, m), 4.50 (1H, t, *J*=3.3 Hz), 4.70 (1H, dd, *J*=4.0, 6.8 Hz), 6.75 (1H, dd, *J*=3.3, 6.8 Hz), 7.38 (5H, s). High resolution ms m/z : Calcd for $C_{16}H_{13}NO_4$ (M^+) : 283.1231. Found : 283.1228.

2-Methyl-7-phenyl-3-oxo-2-azabicyclo[2.2.2]oct-7-ene-5,6-*endo*-dicarboxylic anhydride (4c) : mp 220-222°C (acetone); ir (Nujol): 1770, 1670 cm^{-1}; ^{1}H-nmr (CF_3COOH) : δ 3.23 (3H, s), 3.93 (1H, dd, *J*=4.0, 6.3 Hz), 4.20 (2H, m), 5.43 (1H, dd, *J*=3.3, 4.0 Hz), 6.77 (1H, dd, *J*=3.3, 6.3 Hz), 7.43 (5H, s). High resolution ms m/z : Calcd for $C_{16}H_{13}NO_4$ (M^+) : 283.1231. Found : 283.1227.

***N*-Phenyl-2-methyl-8-phenyl-3-oxo-2-azabicyclo[2.2.2]oct-7-ene-5,6-*endo*-dicarboximide (5b) :** mp 227-229 °C (benzene); ir (Nujol): 1710, 1670 cm^{-1}; ^{1}H-nmr ($CDCl_3$): δ 3.00 (3H, s), 3.53 (1H, dd, *J*=3.8, 8.0 Hz), 3.77 (1H, dd, *J*=4.3, 8.0 Hz), 4.57 (1H, m), 4.73 (1H, dd, *J*=4.3, 6.0 Hz), 6.70 (1H, dd, *J*=2.3, 6.0 Hz), 6.80-7.70 (10H, m). High resolution ms m/z : Calcd for $C_{22}H_{18}N_2O_3$ (M^+) : 358.1317. Found : 358.1330.

***N*-Phenyl-2-methyl-7-phenyl-3-oxo-2-azabicyclo[2.2.2]oct-7-ene-5,6-*endo*-dicarboximide (5c) :** mp 179-182 °C (benzene); ir (Nujol): 1710, 1675 cm^{-1}; ^{1}H-nmr ($CDCl_3$): δ 3.05 (3H, s), 3.55 (1H, dd, *J*=3.8, 8.3 Hz), 3.77 (1H, dd, *J*=4.3, 8.3 Hz), 4.15 (1H, dd, *J*=3.8, 6.0 Hz), 5.10 (1H, dd, *J*=2.0, 4.3 Hz), 6.65 (1H, dd, *J*=2.0, 6.0 Hz), 6.78-7.65 (10H, m). MS m/z : 358 (M^+). *Anal.*Calcd for $C_{22}H_{18}N_2O_3$: C, 73.73; H, 5.06; N, 7.82. Found: C, 73.85; H, 4.97; N, 7.59.

General procedure for high pressure Diels-Alder cycloadditions of 1a-d with 3 :

A mixture of **1a-d** (0.19 g, 1 mmol) and **3** (0.21 g, 1.2 mmol) in toluene (4.5 ml) was placed in a Teflon tube. The tube was placed in a high pressure reactor and pressurized to 10 kbar, followed by heating at 110°C. After 72 h, the pressure was released and the reaction mixture was chromatographed over silica gel using $CHCl_3$ as eluent to afford the corresponding *endo* (**5a-d**) and *exo* (**6a-d**) adducts, respectively (Table I).

***N*-Phenyl-2-methyl-4-phenyl-3-oxo-2-azabicyclo[2.2.2]oct-7-ene-5,6-*endo*-dicarboximide (5a) :** mp 170-173°C (benzene); ir (Nujol): 1710, 1670 cm^{-1}; ^{1}H-nmr ($CDCl_3$): δ 2.93 (3H, s), 3.67 (1H, dd, *J*=4.3, 8.0 Hz), 3.90 (1H, d, *J*=8.0 Hz), 4.63 (1H, m), 6.67 (1H, dd, *J*=6.3, 8.0 Hz), 6.90 (1H, dd, *J*=2.3, 8.0 Hz), 7.03-7.73 (10H, m). High resolution ms m/z : Calcd for $C_{22}H_{18}N_2O_3$ (M^+): 358.1317. Found : 358.1320.

***N*-Phenyl-2-methyl-1-phenyl-3-oxo-2-azabicyclo[2.2.2]oct-7-ene-5,6-*endo*-dicarboximide (5d) :** mp 203-205 °C (ether); ir (Nujol): 1710, 1675 cm^{-1}; ^{1}H-nmr ($CDCl_3$): δ 2.35 (3H, s), 3.53 (1H, dd, *J*=4.3, 8.0 Hz), 4.13 (1H, m), 4.20 (1H, d, *J*=8.0 Hz), 6.60 (1H, dd, *J*=6.0, 8.3 Hz), 6.85 (1H, dd, *J*=2.3, 8.3 Hz), 7.00-7.90 (10H, m). High resolution ms m/z : Calcd for $C_{22}H_{18}N_2O_3$ (M^+) : 358.1317. Found : 358.1298.

***N*-Phenyl-2-methyl-4-phenyl-3-oxo-2-azabicyclo[2.2.2]oct-7-ene-5,6-*exo*-dicarboximide (6a) :** mp 205-207 °C (ether); ir (Nujol): 1710, 1660 cm^{-1}; ^{1}H-nmr ($CDCl_3$): δ 2.97 (3H, s), 3.37 (1H, dd, *J*=2.0, 8.0 Hz), 3.77 (1H, d, *J*=8.0 Hz), 4.73 (1H, m), 6.32 (1H, dd, *J*=2.0, 8.3 Hz), 6.70 (

1H, dd, *J*=6.0, 8.3 Hz), 6.97-7.97 (10H, m). High resolution ms m/z : Calcd for $C_{22}H_{18}N_2O_3$ (M^+) : 358.1317. Found : 358.1266.

***N*-Phenyl-2-methyl-8-phenyl-3-oxo-2-azabicyclo[2.2.2]oct-7-ene-5,6-*exo*-dicarboximide (6b) :** mp 279-282 °C (CH_2Cl_2-ether); ir (Nujol): 1710, 1670 cm^{-1}; ^{1}H-nmr ($CDCl_3$) (400 MHz): δ 2.94 (3H, s), 3.32 (1H, dd, *J*=3.3, 8.4 Hz), 3.36 (1H, dd, *J*=2.6, 8.4 Hz), 4.54 (1H, m), 4.82 (1H, dd, *J*=2.6, 5.9 Hz),6.78 (1H, dd, *J*=1.8, 5.9 Hz), 7.21-7.26 (2H, m), 7.37-7.53 (8H, m). High resolution ms m/z : Calcd for $C_{22}H_{18}N_2O_3$ (M^+) : 358.1317. Found : 358.1321.

***N*-Phenyl-2-methyl-7-phenyl-3-oxo-2-azabicyclo[2.2.2]oct-7-ene-5,6-*exo*-dicarboximide (6c) :** mp 195-197 °C (CH_2Cl_2-ether); ir (Nujol): 1710, 1675 cm^{-1}; ^{1}H-nmr ($CDCl_3$) (400 Mz): δ 2.97 (3H, s), 3.32 (1H, dd, *J*=3.3, 8.4 Hz), 3.36 (1H, dd, *J*=2.6, 8.4 Hz),.4.14 (1H, dd, *J*=3.3, 6.2 Hz), 5.17 (1H, m), 6.75 (1H, dd, *J*=2.2, 6.6 Hz), 7.21-7.26 (2H, m), 7.37-7.50 (8H, m). High resolution ms m/z : Calcd for $C_{22}H_{18}N_2O_3$ (M^+) : 358.1317. Found : 358.1316.

***N*-Phenyl-2-methyl-1-phenyl-3-oxo-2-azabicyclo[2.2.2]oct-7-ene-5,6-*exo*-dicarboximide (6d) :** mp 238-241 °C (ether); ir (Nujol): 1710, 1670 cm^{-1}; ^{1}H-nmr ($CDCl_3$): δ 2.65 (3H, s), 3.40 (1H, dd, *J*=2.0, 8.3 Hz), 4.02 (1H, d, *J*=8.3 Hz), 4.20 (1H, m), 6.30 (1H, dd, *J*=2.0, 8.0 Hz), 6.70 (1H, dd, *J*=6.3, 8.0 Hz), 7.03-8.03 (10H, m). High resolution ms m/z : Calcd for $C_{22}H_{18}N_2O_3$ (M^+) : 358.1317. Found : 358.1353.

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