

## DIELS-ALDER CYCLOADDITION USING PHENYL-2(1H)-PYRIDONES AS DIENES<sup>1</sup>

Hiroto Nakano, Takaaki Kato, Hiroshi Tomisawa, and Hiroshi Hongo\*

Tohoku College of Pharmacy, 4-4-1 Komatsushima, Aoba-ku, Sendai 981, Japan

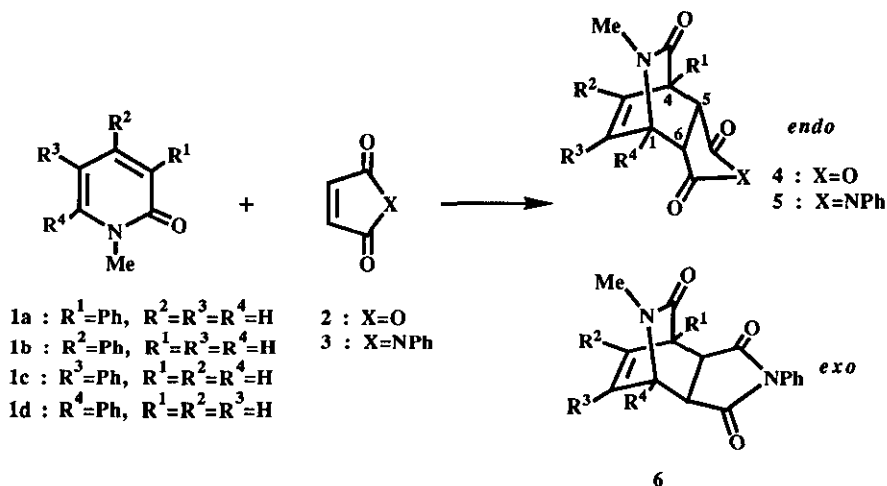
**Abstract** — Diels-Alder cycloadditions of 1-methyl-2(1H)-pyridones (**1a-d**) having a phenyl group in the ring with maleic anhydride (**2**) or *N*-phenylmaleimide (**3**) under atmospheric pressure conditions and with **3** under high pressure conditions were carried out. The reactions of **1a-d** 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(1H)-Pyridones are classified as aromatic heterocycles, and generally do not undergo efficient Diels-Alder cycloaddition.<sup>2</sup> Nevertheless, the Diels-Alder adducts from the reactions of 2(1H)-pyridones with dienophiles have an isoquinuclidine skeleton, which is commonly found in many iboga alkaloids, and therefore the adducts have potential as synthetic interemediates.<sup>3f</sup> Previously, we have developed a synthetic route toward this heterocyclic ring system having various substituents by using Diels-Alder cycloadditions of 2(1H)-pyridones with dienophiles. In the present paper, we wish to report the reactions of 1-methyl-2(1H)-pyridones (**1a-d**)<sup>4</sup> 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.<sup>5</sup> 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<sup>2,6</sup> relating to an application of the technique in Diels-Alder cycloaddition of 2(1H)-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
<b>1a</b>	atmospheric	0	0	0
	10	---	26	50
<b>1b</b>	atmospheric	55	50	0
	10	---	11	2
<b>1c</b>	atmospheric	44	90	0
	10	---	78	18
<b>1d</b>	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. <sup>1</sup>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 <sup>3g,h,i,7</sup> and 3.5-4.5 Hz, <sup>3g,h,i,7</sup> 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. <sup>1</sup>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<sup>-1</sup>; <sup>1</sup>H-nmr ( CDCl<sub>3</sub> ) : 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<sub>16</sub>H<sub>13</sub>NO<sub>4</sub> ( M<sup>+</sup> ) : 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<sup>-1</sup>; <sup>1</sup>H-nmr ( CF<sub>3</sub>COOH ) : 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<sub>16</sub>H<sub>13</sub>NO<sub>4</sub> ( M<sup>+</sup> ) : 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  $\text{cm}^{-1}$ ;  $^1\text{H}$ -nmr (  $\text{CDCl}_3$  ) :  $\delta$  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  $\text{C}_{22}\text{H}_{18}\text{N}_2\text{O}_3$  (  $\text{M}^+$  ) : 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  $\text{cm}^{-1}$ ;  $^1\text{H}$ -nmr (  $\text{CDCl}_3$  ) :  $\delta$  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 (  $\text{M}^+$  ). Anal. Calcd for  $\text{C}_{22}\text{H}_{18}\text{N}_2\text{O}_3$ : 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  $\text{CHCl}_3$  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  $\text{cm}^{-1}$ ;  $^1\text{H}$ -nmr (  $\text{CDCl}_3$  ) :  $\delta$  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  $\text{C}_{22}\text{H}_{18}\text{N}_2\text{O}_3$  (  $\text{M}^+$  ) : 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  $\text{cm}^{-1}$ ;  $^1\text{H}$ -nmr (  $\text{CDCl}_3$  ) :  $\delta$  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  $\text{C}_{22}\text{H}_{18}\text{N}_2\text{O}_3$  (  $\text{M}^+$  ) : 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  $\text{cm}^{-1}$ ;  $^1\text{H}$ -nmr (  $\text{CDCl}_3$  ) :  $\delta$  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<sub>2</sub>Cl<sub>2</sub>-ether); ir (Nujol): 1710, 1670 cm<sup>-1</sup>; <sup>1</sup>H-nmr (CDCl<sub>3</sub>) (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<sub>2</sub>Cl<sub>2</sub>-ether); ir (Nujol): 1710, 1675 cm<sup>-1</sup>; <sup>1</sup>H-nmr (CDCl<sub>3</sub>) (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<sup>-1</sup>; <sup>1</sup>H-nmr (CDCl<sub>3</sub>): 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.

## REFERENCES AND NOTES

1. A part of this work was preliminarily reported in *Heterocycles*, 1990, **30**, 359.
2. Review for Diels-Alder cycloadditions of 2(1*H*)-pyridones: K. Afarinkia, V. Vinader, T. D. Nelson, and G. H. Posner, *Tetrahedron*, 1992, **48**, 9111.
3. a) H. Tomisawa and H. Hongo, *Tetrahedron Lett.*, 1969, 2465; b) H. Tomisawa, R. Fujita, K. Noguchi, and H. Hongo, *Chem. Pharm. Bull.*, 1970, **18**, 941; c) H. Hongo, *ibid.*, 1972, **20**, 226; d) H. Tomisawa, H. Hongo, H. Kato, R. Fujita, and A. Sato, *ibid.*, 1978, **26**, 2312; e) H. Tomisawa, H. Hongo, H. Kato, T. Naraki, and R. Fujita, *ibid.*, 1979, **27**, 670; f) H. Tomisawa, H. Hongo, H. Kato, K. Sato, and R. Fujita, *Heterocycles*, 1981, **16**, 1947; g) H. Nakano, H. Tomisawa, and H. Hongo,

- J. Chem. Soc., Chem. Commun.*, **1990**, 1775; h) H. Nakano, Y. Saito, and H. Hongo, *Chem. Pharm. Bull.*, 1992, **40**, 2876; i) H. Nakano and H. Hongo, *Heterocycles*, 1993, **35**, 37.
4. **1a**: L. Bauer, C. L. Bell, and G. E. Wright, *J. Heterocycl. Chem.*, 1966, **3**, 393; **1b**: G. P. Gisby, S. E. Royall, and P. G. Sammes, *J. Chem. Soc., Perkin Trans. 1*, **1982**, 169; **1c**: S. Sugasawa and M. Kirisawa, *Pharm. Bull.*, 1955, **3**, 187; **1d**: H. Weber, *Arch. Pharmaz.*, 1975, **308**, 331.
5. M. Takeda, H. Inoue, K. Noguchi, Y. Honma, M. Kawamori, G. Tsukamoto, and S. Saito, *Chem. Pharm. Bull.*, 1976, **24**, 1002.
6. a) K. Matsumoto, K. Hamada, T. Uchida, and H. Yoshida, *Heterocycles*, 1989, **29**, 21; b) G. H. Posner and C. Switzer, *J. Org. Chem.*, 1987, **52**, 1644.
7. K. Somekawa, T. Watanabe, and S. Kumamoto, *Nippon Kagaku Kaishi*, **1978**, 412.

Received, 14th March, 1994