HIGH PRESSURE DIELS-ALDER REACTION OF 1-METHYL-2(1*H*)-PYRIDONES HAVING A PHENYL GROUP WITH *N*-PHENYLMALEIMIDE

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Abstract — Diels-Alder reaction of 1-methyl-2(1*H*)-pyridones (**Ia-d**) having a phenyl group at 3,4,5, and 6 position with *N*-phenylmaleimide (**II**) under 10 kbar at 110 °C for 72 h gave a mixture of the *endo* and *exo* adducts (**IIIa-d** and **IVa-d**) in good yields, some of which were unobtainable under atmospheric pressure conditions.

Isoquinuclidine derivatives prepared by Diels-Alder reaction of 1-substituted 2(1*H*)-pyridones with dienophiles are interesting as possible intermediates for iboga alkaloides.[1] We have developed a synthetic route toward this heterocyclic ring system having various substituents.[2] We now wish to report the reaction of 1-methyl-2(1*H*)-pyridones(**Ia-d**)[3] having a phenyl group at 3,4,5, and 6 position with *N*-phenylmaleimide(**II**) under atmospheric and high pressure conditions. Isoquinuclidine derivatives having a phenyl group linked to quaternary carbon derived from **Ia,d** and **II** are expected to possess the interesting pharmacological activities.[4] 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 reaction, an application of the technique in Diels-Alder reaction of 2(1*H*)-pyridones has been reported only by Matsumoto and his co-workers.[5]

First, we examined Diels-Alder reaction of **Ia-d** with **II**(1.2 equiv.) under atmospheric pressure at 110 °C for 72 h in toluene (Table I). The reactions of **Ib,c** with **II** gave only the *endo*

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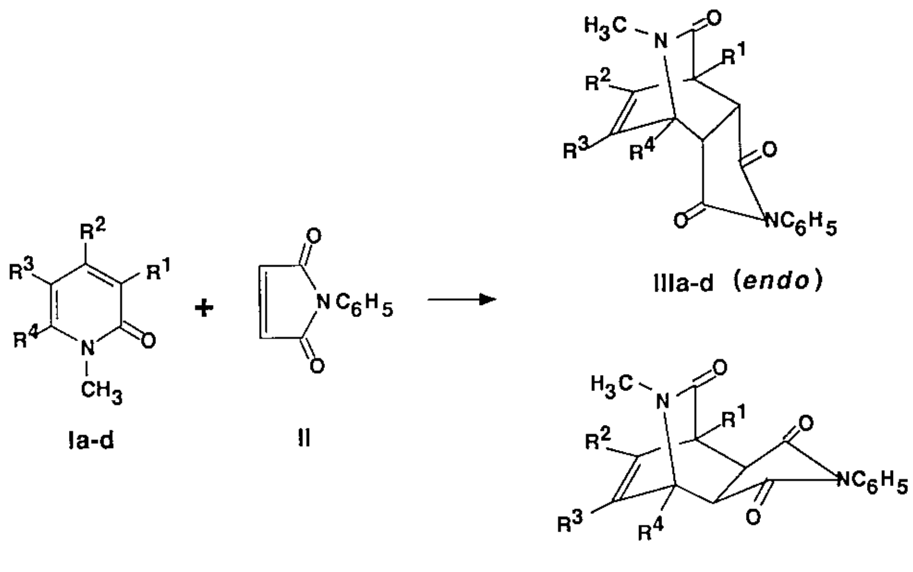
Table I. Diels-Alder Reaction of **Ia-d** with **II** under Atmospheric and High Pressure Conditions



Ia-d **II** **IIIa-d** ***(endo)*** **IVa-d** ***(exo)***

Substrate	R^1	R^2	R^3	R^4	Pressure (kbar)	Yield (%) of Products [Yield (%) of **III** and **IV**]
Ia	C_6H_5	H	H	H	atmospheric	0
					10	76 [**IIIa** (26), **IVa** (50)]
Ib	H	C_6H_5	H	H	atmospheric	50 [**IIIb** (50)]
					10	13 [**IIIb** (11), **IVb** (2)]
Ic	H	H	C_6H_5	H	atmospheric	90 [**IIIc** (90)]
					10	96 [**IIIc** (78), **IVc** (18)]
Id	H	H	H	C_6H_5	atmospheric	0
					10	84 [**IIId** (76), **IVd** (8)]

adducts(**IIIb,c**)[6] in 50% and 90% yields , however, those of **Ia,d** with **II** did not yield the Diels-Alder adducts (Table I). Next, we carried out high pressure Diels-Alder reaction of **Ia-d** with **II**(1.2 *equiv.) under 10 kbar at 110 °C for 72 h in toluene (Table I).* The reactions of **Ia,d** with **II** afforded a mixture of the *endo* and *exo* adducts in 76%(**IIIa** and **IVa**)[6] and 84%(**IIId** and **IVd**)[6] yields, respectively, which were not obtained under atmospheric pressure conditions (Table I). Furthermore, the reactions of **Ib,c** with **II** also proceeded to give a mixture of the *endo* and *exo* adducts in 13% (**IIIb** and **IVb**)[6] and 96%(**IIIc** and **IVc**)[6] yields, respectively (Table I). The structures of **IIIa-d** and **IVa-d** were confirmed by their spectral analyses. The configuration of two substituents at 5- and 6- positions in **IIIa-d** ($J_{1,6}$=$J_{4,5}$=4Hz) and **IVa-d** ($J_{1,6}$=2−2.57Hz, $J_{4,5}$=2-3.3Hz) was determind to be *endo* and *exo* from the coupling constant value in their ^{1}H-nmr spectra, respectively.

Thus, we found that, by using high pressure technique, Diels-Alder reaction of some 1-methyl-2(1*H*)-pyridones having a phenyl group was accelerated, and also gave the *exo* adducts which were not obtained under atmospheric pressure conditions.

Further investigation for the extention of these reactions is now in progress.

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6. All new compounds (**IIIa-d** and **IVa-d**) gave satisfactory spectral and analytical data. ^{1}H-Nmr spectra were recorded on JEOL PMX-60(60 MHz) (**IIIa-d** and **IVa,d**) or JNM-GSX-400 (400 MHz)(**IVb,c**) spectrometers. Selected data are as follows:

IIIa : 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, 8 Hz), 3.90 (1H, d, J=8 Hz), 4.63 (1H, m), 6.67 (1H, dd, J=6, 8 Hz), 6.90 (1H, dd, J=2, 8Hz), 7.03-7.73 (10H, m); ms m/z 358 (M+).

IIIb : 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, 8Hz), 3.77 (1H, dd, J=4, 8Hz), 4.57 (1H, m), 4.73 (1H, dd, J=4, 6Hz), 6.70 (1H, dd, J=2, 6 Hz), 6.80-7.70 (10H, m); ms m/z 358 (M+).

IIIc : 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, 8Hz), 3.77 (1H, dd, J=4, 8Hz), 4.15 (1H, dd, J=3, 6Hz), 5.10 (1H, dd, J=2, 4Hz), 6.65 (1H, dd, J=2, 6 Hz), 6.78-7.65 (10H, m); ms m/z 358 (M+).

IIId : 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, 8 Hz), 4.13 (1H, m), 4.20 (1H, d, J=8 Hz), 6.60 (1H, dd, J=6, 8 Hz), 6.85 (1H, dd, J=2, 8Hz), 7.00-7.90 (10H, m); ms m/z 358 (M+).

IVa : 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, 8 Hz), 3.77 (1H, d, J=8 Hz), 4.73 (1H, m), 6.32 (1H, dd, J=2, 8 Hz), 6.70 (1H, dd, J=6, 8Hz), 6.97-7.97 (10H, m); ms m/z 359 (M++1).

IVb : mp 279-282 °C (CH_2Cl_2-ether); ir (Nujol): 1710, 1670 cm^{-1}; ^{1}H-nmr ($CDCl_3$): δ 2.94 (3H, s), 3.32 (1H, dd, J=3.30, 8.43 Hz), 3.36 (1H, dd, J=2.57, 8.43 Hz), 4.54 (1H, m), 4.82 (1H, dd, J=2.57, 5.86 Hz),6.78 (1H, dd, J=1.83, 5.86 Hz), 7.21-7.26 (2H, m), 7.37-7.53 (8H, m); ms m/z 358 (M+).

IVc : mp 195-197 °C (CH_2Cl_2-ether); ir (Nujol): 1710, 1675 cm^{-1}; ^{1}H-nmr ($CDCl_3$): δ 2.97 (3H, s), 3.32 (1H, dd, J=3.30, 8.43 Hz), 3.36 (1H, dd, J=2.57, 8.43 Hz), 4.14 (1H, dd, J=3.30, 6.23 Hz), 5.17 (1H, m), 6.75 (1H, dd, J=2.20, 6.60 Hz), 7.21-7.26 (2H, m), 7.37-7.50 (8H, m); ms m/z 358 (M+).

IVd : 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, 8 Hz), 4.02 (1H, d, J=8 Hz), 4.20 (1H, m), 6.30 (1H, dd, J=2, 8 Hz), 6.70 (1H, dd, J=6, 8Hz), 7.03-8.03 (10H, m); ms m/z 358 (M+).

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