Diels–Alder Reactions of Nitro-2(1*H*)-pyridones with 2,3-Dimethyl-1,3-butadiene

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Diels–Alder (DA) reactions of 3- or 5-nitro-2(1*H*)-pyridones and nitro-2(1*H*)-pyridones containing a methoxycarbonyl group with 2,3-dimethyl-1,3-butadiene were examined. The DA reactions of 3-nitro-2(1*H*)-pyridones in this paper represent, to the best of our knowledge, the first report of DA reactions of 3-substituted 2(1*H*)-pyridones and consequent production of isoquinolones. Performing the same reactions with 5-nitro-2(1*H*)-pyridones yielded quinolones. DA reactions of 2(1*H*)-pyridones with nitro and methoxycarbonyl groups produced isoquinolones, quinolones and phenanthridones (the double DA adducts), aromatized or hydrogenated. The substituent effect was evaluated by calculating the activation energy, using the *ab initio* MO method.

Key words 3-nitro-2(1*H*)-pyridone; 5-nitro-2(1*H*)-pyridone; phenanthridone quinolone; isoquinolone; 4-methoxycarbonyl-5-nitro-2(1*H*)-pyridone; MO calculation

Although 2(1*H*)-pyridones are classified as aromatic heterocycles, there are many reports of Diels–Alder (DA) reactions in which 2(1*H*)-pyridones act as dienes.[1)] In our laboratory, we have developed novel DA reactions involving 2(1*H*)-pyridones which contain an electron-withdrawing group that acts as a dienophile (Chart 1).[2—4)] Thermal, uncatalyzed reactions of 1-methyl-2(1*H*)-pyridones with methoxycarbonyl, cyano, acetyl, benzoyl, and formyl groups at the 4-position produced only hydrogenated isoquinolones, in good to excellent yields.[2)] The reaction of 6-acetyl-1-methyl-2(1*H*)-pyridone yielded a phenanthridone at 11% yield,[3)] but, the DA reactions of 3- or 5-substituted 1-methyl-2(1*H*)-pyridones were unsuccessful. Recently, we reported that DA reactions of 1-sulfonyl-2(1*H*)-pyridones containing an electron-withdrawing group at the 5-position produced only hydrogenated quinolones, in moderate yields.[4)] Since the nitro group is a relatively strong electron-withdrawing group, 1-substituted 3- and/or 5-nitro-2(1*H*)-pyridones are highly electron-deficient heteroaromatic compounds. Therefore, it is to be expected that DA reactions of 3-nitropyridones would yield isoquinolones, that those of 5-nitropyridones would yield quinolones, and that reactions of 3,5-dinitropyridones with two moieties acting as dienophiles would produce double DA adducts (phenanthridones). The isoquinolone,[5)] quinolone,[6)] and phenanthridone[7)] skeletons found in many alkaloids can be expected to be potentially valuable synthetic intermediates, and to possess interesting biological properties. In the present paper, we wish to report the first synthesis of isoquinolones, quinolones, and phenanthridones using DA reactions with 1-unsubstituted and 1-substituted nitro-2(1*H*)-pyridones and nitro-2(1*H*)-pyridones containing a methoxycarbonyl group.

DA Reactions First, thermal DA reactions of 5-nitro-2(1*H*)-pyridones (**1a**, **b**,[8)] **2a**,[9)] **3**,[9)] **4**[9)]) with 2,3-dimethyl-1,3-butadiene (**5**) were examined (Chart 2, Table 1). The reactions of **1a**, **b** with **5** at 160 or 180 °C for 5 or 3 d yielded only quinolones [**6a** (30%), **6b** (26%), entries 1, 2] aromatized by release of hydrogen and nitrogen dioxide (HNO_2), followed by dehydrogenation. Performing the same reaction with 5-nitropyridone (**2a**) containing a methoxycarbonyl group at the 3-position chemoselectively yielded a functionalized quinolone [**7a** (22%), entry 3], with recovery of the starting material. DA reactions of the 3- and/or 4-substituted 5-nitropyridones (**3**, **4**), with two moieties acting as dienophiles under the conditions shown in Table 1, stereoselectively produced the same functionalized *cis*-adducts; *i.e.*, a phenanthridone [**8**, double DA adduct (27, 33%)] and a hydrogenated isoquinolone [**9** (10, 15%), entries 4, 5], respectively. Based on the fact that the reactions of **3** and **4** with **5** both yielded the same DA adducts (**8**, **9**), we hypothesized the existence of two pathways. It is well known that the nitro group functions as a leaving group and a strong electron-withdrawing group. In one pathway, **3** first arises from **4** with the release of the nitro group in **4** by heating (leaving **4** highly electron-deficient), and DA reaction of **3** then yields **8** and **9**. In the second pathway, the reaction of **4** with **5** yields **8** and **9**, as a result of elimination of the nitro group in the respective intermediates [B, C (Chart 2)]. However, A—C were not separated from the mixtures used in the reactions of **3** or **4** with **5** by column chromatography.

Next, DA reactions of 3-nitro-2(1*H*)-pyridones (**10a**, **b**,[8)] **11a**,[9)] **12a**, **b**,[8)] **13a**, **b**[9)]) with **5** were carried out under the conditions shown in Table 1. DA reactions of **10a**, **b** at 140 or 180 °C for 3 d (entries 6, 7) stereoselectively yielded a hydrogenated *cis*-isoquinolone [**14a** (20%)] and the corresponding

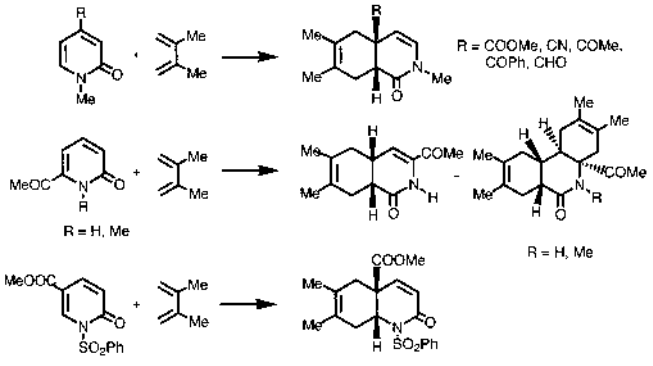

Chart 1

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Table 1. DA Reactions of 5- and 3-Nitropyridones with **5** in *o*-Xylene

Entry	Pyridone	Temp. (°C)	Time (d)	Product	Yield (%)	Product	Yield (%)	Product	Yield (%)
1	**1a**	160	5	**6a**	30				
2	**1b**	180	3	**6b**	26				
3	**2a**	160	3	**7a**	22				
4	**3**	160	3	**8**	27	**9**	10		
5	**4**	180	3	**8**	33	**9**	15		
6	**10a**	140	3	**14a**	20	**16a**	22		
7	**10b**	180	3			**16b**	15		
8	**11a**	160	3	**15a**	36				
9	**12a**	180	3	**14a**	8	**17a**	36	**19a**	33
10	**12b**	180	3			**17b**	13	**19b**	15
11	**13a**	160	3			**18a**	31	**20a**	14
12	**13b**	160	3			**18b**	13	**20b**	5

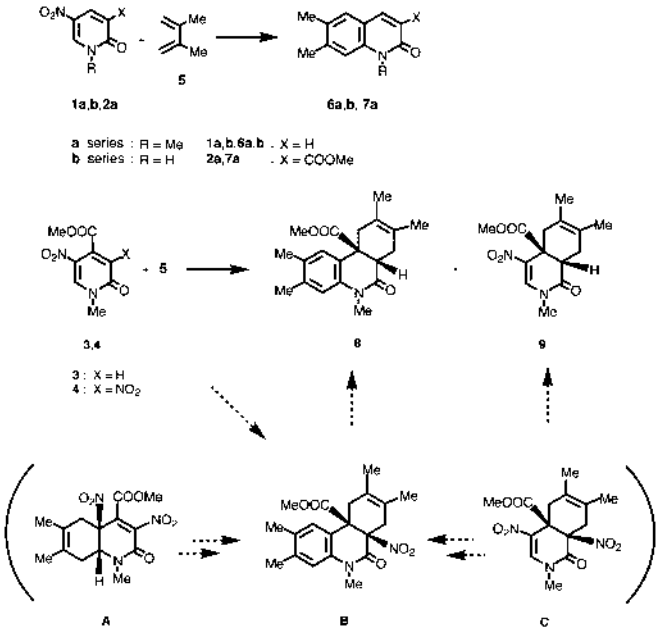


Chart 2

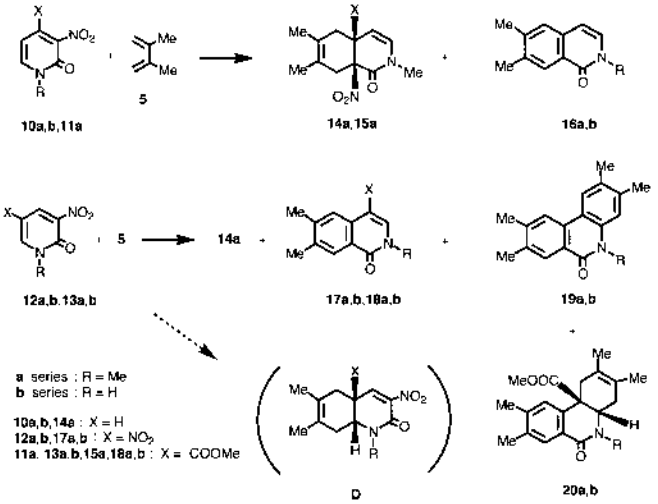


Chart 3

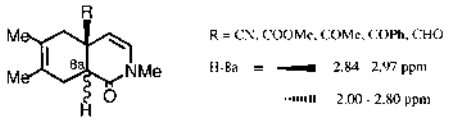
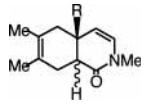


Fig. 1

aromatized isoquinolones [**16a** (22%), **16b** (15%)] (Chart 3). Performing the same reaction with **11a** yielded only the hydrogenated *cis*-isoquinolone [**15a** (36%), entry 8]. The reaction of 3,5-dinitropyridone (**12a**) at 180 °C for 3 d (entry 9) produced **14a** (8%), the aromatized 4-nitroisoquinolone [**17a** (36%)] and the phenanthridone resulting from the double DA adduct [**19a** (33%)]. Also, under the same conditions, the reaction of 1-unsubstituted 3,5-dinitropyridone (**12b**) yielded an aromatized isoquinolone [**17b** (13%)] and an aromatized phenanthridone [**19b** (15%), entry 10]. DA reactions of **13a**, **b**, with a methoxycarbonyl group at the 5-position, predominantly yielded the corresponding aromatized isoquinolones [**18a** (31%), **18b** (13%)] and, stereoselectively, the corresponding *cis*-phenanthridone adducts [double DA adducts: **20a** (14%), **20b** (5%); entries 11, 12]. The results obtained in the present study can be rationalized as follows. The aromatized **16a**, **b** result from a release of HNO_2 and dehydrogenation of DA adducts (such as **14a**). Similarly, the aromatized isoquinolones (**17a**, **b**, **18a**, **b**) are formed from DA adducts (such as **14a**). Moreover, DA reactions of **17a**, **b** with **5** lead to the formation of **19a**, **b**, followed by the elimination of HNO_2 and dehydrogenation. Additional DA reactions of **18a**, **b** yield **20a**, **b**. It was presumed that another pathway to **19a**, **b** and **20a**, **b** is the reaction of the DA adduct [D (Chart 3)] with **5**. However, D was not separated from the mixtures used in the reactions of **12a**, **b** or **13a**, **b** with **5** by column chromatography.

The stereochemistries of the ring juncture in **8**, **9**, **14a**, **15a**, and **20a**, **b** were confirmed by examination using ^{1}H-NMR, MS, and high-resolution (HR)-MS spectra. In a previous paper,[2] we reported that the signals produced by the proton of the ring juncture in the *cis*-adducts (δ 2.84—2.97) are located at a lower range than those of the corresponding *trans*-isomers (δ 2.00—2.80), owing to the deshielding effect resulting from the lactam carbonyl (Fig. 1). In that study, the signals produced by the proton of the ring juncture in the *cis*-adducts (**8**, **9**) appeared at δ 3.24 and 3.27. In another paper, we reported that the MS and HR-MS spectra of the *cis*-DA adducts produced by DA reaction of 4-substituted 2(1*H*)-pyridones with **5** mainly showed an ion peak at *m*/*z* [M−diene]$^+$, resulting from the retro-DA reaction, whereas the spectra of the *trans*-DA adducts showed ion peaks arising

Table 2. MS Spectra of *cis*- and *trans*-Adducts[10)]



R	M^+	M^+−diene (**5**)	M^+−X
cis-Adduct			
CN	216	134	82 (**5**)
COOMe	249	167	108 (167−COOMe)
trans-Adduct			
CN	216		173 (M^+−HCNO)
COOMe	249		190 (M^+−COOMe)

from the complex bond cleavage (Table 2).[10)] In that study, HRMS spectra of **8** and **9** showed the corresponding ion peaks at *m/z* 245 and *m/z* 212 $[M-C_6H_{10}]^+$ resulting from the retro-DA reaction. From these data, the stereochemistries of the ring juncture in **8** and **9** were determined to be *cis*. Similarly, in the present study, the MS and HRMS spectra of **14a**, **15a**, and **20a**, **b** predominantly showed ion peaks at *m/z* [M−diene : 155 (+1), 212, 245, 232 (+1)]$^+$ resulting from the retro-DA reaction. Based on the above data, the stereochemistries of the ring juncture in **14a**, **15a**, and **20a**, **b** were determined to be *cis*.

Activation Energy We studied theoretically the substituent effects of the dienophiles listed in Table 1 in DA reactions with **5**. We calculated the activation energy (*Ea*) of the transition state (TS), using Gaussian 98 at the RHF/3—21G level.[11)] The calculated values of *Ea* are summarized in Table 3, together with the experimentally obtained adducts and their yields. We focused our attention on whether 3,4-addition or 5,6-addition occurs in DA reactions of **5** with the dienophiles listed in Table 1. As is seen in Table 3, the calculated values of *Ea* for the 5,6-addition reactions of **1a** and **2a** containing a nitro group at 5-position of the pyridone ring are smaller than those for the respective 3,4-addition reactions (reactions 1, 2). But, the calculated values of Ea for the 3,4-addition reactions of **10a** and **13a** containing a nitro group at 3-position are smaller than those for the respective 5,6-addition reactions (reactions 4, 5). These results are consistent with the experimentally obtained compounds.

In conclusion, the DA reactions of 3-nitro-2(1*H*)-pyridones stereoselectively yielded hydrogenated or aromatized isoquinolones and double DA adducts (phenanthridones) in moderate yields. Performing the same reactions with 5-nitro-2(1*H*)-pyridones yielded only quinolones, and DA reactions of 5-nitro-2(1*H*)-pyridones bearing a methoxycarbonyl group produced chemoselectively the corresponding isoquinolones. The results indicate that the ene component of the 2(1*H*)-pyridone ring is activated by the nitro group (which acts as a dienophile). The products obtained were consistent with the activation energies calculated using the Gaussian 98 method with RHF/3—21 G.

Table 3. Calculated Activation Energies and the Experimental Yields of Adducts for the DA Reactions with **5**

Reaction	Dienophile	Activation energy (kcal/mol)		Adduct (Yield)
		(3,4)-Addition	(5,6)-Addition	
1	**1a**	37.31	35.84	**6a** (30%)
2	**2a**	33.18	32.74	**7a** (22%)
3	**3**	28.94	31.58	(**8**)+**9** (37%)[a)]
4	**10a**	33.48	39.97	**14a**+**16a** (42%)
5	**13a**	31.35	34.47	**18a**+(**20a**) (45%)[a)]

a) We hypothesize that compound **8** (**20a**) was produced from **9** (**18a**), followed by DA reaction with **5**, since the calculated value of *Ea* for production of **9** (**18a**) is considerably smaller than that for production of another intermediate compound by the 5,6-addition reaction of **3** (**13a**) with **5**, and because this intermediate compound was not experimentally obtained.

Experimental

Melting points were determined on a Yanaco melting point apparatus and are uncorrected. IR spectra were measured with a Perkin Elmer FT-IR 1725X spectrophotometer. MS were recorded on a JEOL JMS-DX303/JMS-DA5000 spectrometer. ^{1}H-NMR spectra were recorded on a JNM-GSX400, JNM-EX270 and JEOL JNM-PMX60 spectrometers with tetramethylsilane (TMS) as an internal standard. Preparative thin-layer chromatography was carried out on precoarted Silica gel 60F_{254} TLC plates (2 mm), Merck. Column chromatography was performed on Merck Kieselgel 60 (230—400 mesh).

General Procedure for DA Reactions of 1a, b and 2a with 5 A mixture of **1a** (0.9 g, 6 mmol) and **5** (2.46 g, 30 mmol) in 3 ml *o*-xylene was heated at 160 °C for 5 d in a sealed tube. The reaction mixture was chromatographed on a column of silica-gel. The solvent of the first fraction eluted with chloroform was evaporated. The residue was purified by preparative TLC over silica gel with benzene–acetone (5 : 1) to give 1,6,7-trimethyl-2(1*H*)- quinolone (**6a**). The reactions of **1b** and **2a** with **5** were performed as described above to give 6,7-dimethyl-2(1*H*)-quinolone (**6b**), and 3-methoxycarbonyl-1,6,7-trimethyl-2(1*H*)-quinolone (**7a**). The yields of **6a**, **b**, and **7a** are shown in Table 1.

6a: Colorless crystalline powder ($CHCl_3$), mp 115—117 °C. IR (KBr) cm^{-1}: 1651, 1610, 763, 722. ^{1}H-NMR ($CDCl_3$) δ: 2.33 (3H, s), 2.40 (3H, s), 3.66 (3H, s), 6.56 (1H, d, J=10.0 Hz), 7.10 (1H, s), 7.23 (1H, s), 7.56 (1H, d, J=10.0 Hz). ^{13}C-NMR ($CDCl_3$) δ: 19.08, 20.82, 29.40, 114.86, 118.73, 120.48, 128.79, 130.71, 138.29, 138.37, 140.19, 162.25. MS *m/z*: 187 (M^+), 172, 154. HR-MS *m/z*: Calcd for $C_{12}H_{13}NO$: 187.0997. Found: 187.1011.

6b: Pale brown plates (acetone), mp 235—237 °C. IR (KBr) cm^{-1}: 1652, 1606, 765, 747. ^{1}H-NMR ($CDCl_3$) δ: 2.33 (3H, s), 2.36 (3H, s), 6.26 (1H, d, J=8.0 Hz), 7.30 (2H, s), 7.59 (1H, d, J=8.0 Hz). ^{13}C-NMR ($CDCl_3$) δ: 19.31, 20.13, 116.31, 117.99, 119.90, 127.47, 131.39, 136.70, 140.36, 140.56, 164.34. MS *m/z*: 173 (M^+), 158, 144. HR-MS *m/z*: Calcd for $C_{11}H_{11}NO$: 173.0841. Found: 173.0836.

7a: Yellow plates (benzene), mp 150—152 °C. IR (KBr) cm^{-1}: 1730, 1642, 1605. ^{1}H-NMR ($CDCl_3$) δ: 2.33 (3H, s), 2.44 (3H, s), 3.71 (3H, s), 3.95 (3H, s), 7.14 (1H, s), 7.38 (1H, s), 8.31 (1H, s). ^{13}C-NMR ($CDCl_3$) δ: 19.09, 21.16, 29.72, 52.51, 114.09, 117.03, 120.98, 130.28, 131.40, 139.86, 143.47, 143.59, 158.93, 165.82. MS *m/z*: 245 (M^+), 214, 187, 154. HR-MS *m/z*: Calcd for $C_{14}H_{15}NO_3$: 245.1052. Found: 245.1035.

General Procedure for DA Reactions of 3 and 4 with 5 A mixture of **3** (1.25 g, 6 mmol) and **5** (2.46 g, 30 mmol) in 3 ml *o*-xylene was heated at 160 °C for 3 d in a sealed tube. The reaction mixture was chromatographed on a column of silica gel. The solvent of the first fraction eluted with chloroform was evaporated. The residue was purified by preparative TLC over silica gel with hexane–acetone (10 : 1) to give *cis*-4a,5,8,8a-tetrahydro-4a-methoxycarbonyl-2,6,7-trimethy1-4-nitro-1(2*H*)-isoquinolone (**9**). The solvent of the second fraction was evaporated and the residue was purified by preparative TLC over silica gel with benzene–acetone (3 : 1) to give *cis*-6a,7,10,10a-tetrahydro-10a-methoxycarbonyl-2,3,5,8,9-pentamethyl-6(5*H*)-phenanthridinone (**8**). The reaction of **4** with **5** was performed as described above to give **8** and **9**. The yields of **8** and **9** are shown in Table 1.

8: Colorless crystalline powder (acetone), mp 198—201 °C. IR (KBr) cm^{-1}: 1675, 1634, 1617, 739. ^{1}H-NMR ($CDCl_3$) δ: 1.61 (6H, s), 2.17—2.27 (2H, br m), 2.21 (3H, s), 2.51 (2H, br m, J=18.0 Hz), 2.26 (3H, s), 3.24 (1H, dd, J=5.0, 5.2 Hz), 3.35 (3H, s), 3.75 (3H, s), 6.76 (1H, s), 6.79 (1H, s). ^{13}C-NMR ($CDCl_3$) δ: 18.67, 18.94, 19.17, 19.87, 29.45, 29.88, 36.02, 41.70, 48.43, 52.61, 116.60, 122.81, 123.92, 124.81, 126.45, 131.28, 136.66, 136.94, 170.49, 174.14. MS *m/z*: 327 (M^+), 245 ($M^+-C_6H_{10}$), 174. HR-MS *m/z*: Calcd for $C_{20}H_{25}NO_3$: 327.1834. Found: 327.1828.

9: Pale yellow crystalline powder (ether), mp 187—189 °C. IR (KBr) cm^{-1}: 1749, 1704, 1600, 1535, 865. ^{1}H-NMR ($CDCl_3$) δ: 1.63 (3H, s), 1.67 (3H, s), 1.97 (2H, br d, J=15.5, 18.0 Hz), 2.69 (1H, d, J=15.5 Hz), 2.87 (1H, d, J=18.0 Hz), 3.27 (1H, dd, J=5.9, 6.5 Hz), 3.27 (3H, s), 3.73 (3H, s), 7.87 (1H, s). ^{13}C-NMR ($CDCl_3$) δ: 18.74, 18.89, 27.49, 34.61, 35.90, 42.80,

47.31, 53.19, 122.19, 122.37, 134.68, 138.63, 169.43, 171.50. MS *m/z*: 294 (M^+), 212 ($M^+-C_6H_{10}$), 166. HR-MS *m/z*: Calcd for $C_{14}H_{18}N_2O_5$: 294.1216. Found: 294.1218.

General Procedure for DA Reactions of 10a, b, and 11a with 5 A mixture of **10a** (0.9 g, 6 mmol) and **5** (2.46 g, 30 mmol) in 3 ml *o*-xylene was heated at 140 °C for 3 d in a sealed tube. The reaction mixture was chromatographed on a column of silica gel. The solvent of the first fraction eluted with chloroform was evaporated. The residue was purified by preparative TLC over silica gel with hexane–acetone (5 : 1) to give *cis*-4a,5,8,8a-tetrahydro-2,6,7-trimethy1-8a-nitro-1(2*H*)-isoquinolone (**14a**). The solvent of the second fraction was evaporated and the residue was purified by preparative TLC over silica gel with benzene–acetone (3 : 1) to give 2,6,7-trimethyl-1(2*H*)-isoquinolone (**16a**).[2a,b] The reactions of **10b** and **11a** with **5** were performed as described above to give 6,7-dimethyl-1(2*H*)-isoquinolone (**16b**), *cis*-4a,5,8,8a-tetrahydro-4a-methoxycarbonyl-2,6,7-trimethyl-8a-nitro-1(2*H*)-isoquinolone (**15a**). The yields of **14a**, **15a**, and **16a**, **b** are shown in Table 1.

14a: Colorless plates (benzene–diisopropyl ether), mp 179—180 °C. IR (KBr) cm^{-1}: 1658, 1605, 1353, 835. ^{1}H-NMR ($CDCl_3$) δ: 1.58 (3H, s), 1.63 (3H, s), 1.84—1.94 (1H, br m), 2.26 (1H, d, J=17.0 Hz), 2.45 (1H, d, J=17.0 Hz), 2.59 (1H, dd, J=7.0, 17.0 Hz), 3.05 (3H, s), 3.49 (1H, dd, J=1.7, 6.9 Hz), 5.94 (1H, d, J=9.6 Hz), 6.38 (1H, dd, J=1.7, 9.6 Hz). MS *m/z*: 237 (M^++1), 207 (M^++1−NO), 155 (M^++1−C_6H_{10}). HR-MS *m/z*: Calcd for $C_{12}H_{16}N_2O_3$: 236.1161. Found: 236.1181.

15a: Colorless columns ($CHCl_3$–ether), mp 116—118 °C. IR (KBr) cm^{-1}: 1736, 1700, 1352, 713. ^{1}H-NMR ($CDCl_3$) δ: 1.63 (3H, s), 1.64 (3H, s), 2.28 (1H, d, J=18.8 Hz), 2.60 (1H, d, J=18.8 Hz), 2.86 (1H, d, J=18.1 Hz), 3.14 (3H, s), 3.18 (1H, d, J=18.1 Hz), 3.74 (3H, s), 5.60 (1H, d, J=7.9 Hz), 6.10 (1H, d, J=7.9 Hz). ^{13}C-NMR ($CDCl_3$) δ: 18.15, 18.65, 34.41, 36.26, 36.46, 48.16, 52.96, 92.47, 111.05, 122.23, 123.04, 132.29, 163.38, 171.88. MS *m/z*: 294 (M^+), 248 (M^+-NO_2), 212 ($M^+-C_6H_{10}$), 189, 179. HR-MS *m/z*: Calcd for $C_{14}H_{18}N_2O_5$: 294.1216. Found: 294.1201.

16b: Pale yellow plates (acetone), mp 231—232 °C. IR (KBr) cm^{-1}: 1657, 1646, 1634, 782, 735. ^{1}H-NMR ($CDCl_3$) δ: 2.40 (3H, s), 2.41 (3H, s), 6.47 (1H, d, J=7.3 Hz), 7.04—7.060 (1H, br d), 7.33 (1H, s), 8.17 (1H, s), 10.36 (1H, br s). ^{13}C-NMR ($CDCl_3$) δ: 19.93, 21.99, 111.02, 121.43, 124.07, 127.08 (C2), 128.10, 131.77, 146.82, 164.33. MS *m/z*: 173 (M^+), 158. HR-MS *m/z*: Calcd for $C_{11}H_{11}NO$: 173.0841. Found: 173.0840.

General Procedure for DA Reactions of 12a, b and 13a, b with 5 A mixture of **12a** (0.9 g, 6 mmol) and **5** (2.46 g, 30 mmol) in 3 ml *o*-xylene was heated at 180 °C for 3 d in a sealed tube. The reaction mixture was chromatographed on a column of silica gel. The solvent of the first fraction eluted with chloroform was evaporated. The residue was purified by preparative TLC over silica-gel with hexane–acetone (5 : 1) to give 2,6,7-trimethyl-4-nitro-1(2*H*)-isoquinolone (**17a**). The solvent of the second fraction was evaporated and the residue was purified by preparative TLC over silica gel with benzene–acetone (3 : 1) to give 2,3,5,8,9-pentamethyl-6(5*H*)-phenanthridinone (**19a**). The reactions of **12b** and **13a**, **b** with **5** were performed as described above to give 6,7-dimethyl-4-nitro-1(2*H*)-isoquinolone (**17b**), 2,3,8,9-tetramethyl-6(5*H*)-phenanthridinone (**19b**), 4-methoxycarbonyl-2,6,7-trimethyl-1(2*H*)-isoquinolone (**18a**), *cis*-1,4,4a,10b-tetrahydro-10b-methoxycarbonyl-2,3,5,8,9-pentamethyl-6(5*H*)-phenanthridinone (**20a**), 4-methoxycarbonyl-6,7-dimethyl-1(2*H*)-isoquinolone (**18b**), *cis*-1,4,4a,10b-tetrahydro-10b-methoxycarbonyl-2,3,8,9-tetramethyl-6(5*H*)-phenanthridinone (**20b**). The yields of **17a**, **b**—**20a**, **b** are shown in Table 1.

17a: Pale red needles ($CHCl_3$), mp 224—226 °C. IR (KBr) cm^{-1}: 1654, 1602, 1346, 860, 736. ^{1}H-NMR ($CDCl_3$) δ: 2.32 (3H, s), 2.39 (3H, s), 3.79 (3H, s), 7.04 (1H, s), 7.12 (1H, s), 7.26 (1H, s). ^{13}C-NMR ($CDCl_3$) δ: 19.90, 20.89, 37.98, 122.14, 123.89, 127.05 (C2), 128.51, 137.07, 138.19 , 144.47, 161.62. MS *m/z*: 233 (M^++1), 203 (M^++1−NO), 174. HR-MS *m/z*: Calcd for $C_{12}H_{12}N_2O_3$: 232.0848. Found: 232.0870.

17b: Yellow needles (acetone), mp 265 °C (dec.). IR (KBr) cm^{-1}: 1669, 1660, 1628, 1511, 1317, 889, 788. ^{1}H-NMR ($CDCl_3$) δ: 2.45 (3H, s), 2.49 (3H, s), 8.22 (1H, s), 8.50 (1H, s), 8.51 (1H, s). ^{13}C-NMR ($CDCl_3$) δ: 19.92, 21.10, 121.33, 124.07, 127.87, 128.10, 130.33, 131.77, 139.33, 146.82, 164.31. MS *m/z*: 218 (M^+), 172. HR-MS *m/z*: Calcd for $C_{11}H_{10}N_2O_3$: 218.0691. Found: 218.0696.

18a: Colorless needles (ether–$CHCl_3$), mp 174—175 °C. IR (KBr) cm^{-1}: 1664, 1624, 1611, 794, 768, 703. ^{1}H-NMR ($CDCl_3$) δ: 2.40 (3H, s), 2.43 (3H, s), 3.65 (3H, s), 3.91 (3H, s), 8.09 (1H, s), 8.20 (1H, s), 8.56 (1H, s). ^{13}C-NMR ($CDCl_3$) δ: 19.74, 20.60, 37.44, 51.55, 105.89, 123.07, 125.26, 127.58, 132.19, 136.42, 139.64, 142.72, 162.19, 165.42. MS *m/z*: 245 (M^+), 214. HR-MS *m/z*: Calcd for $C_{14}H_{15}NO_3$: 245.1052. Found: 245.1051.

18b: Colorless needles (ether–$CHCl_3$), mp 175 °C. IR (KBr) cm^{-1}: 1725, 1624, 1611, 794, 768, 703. ^{1}H-NMR ($CDCl_3$–CF_3COOD) δ: 2.36 (3H, s), 2.46 (1H, s), 3.87 (3H, s), 8.03 (1H, s), 8.11 (1H, s), 8.60 (1H, s), 12.06 (1H, br s). ^{13}C-NMR ($CDCl_3$–CF_3COOD) δ: 19.98, 21.04, 52.24, 110.15, 121.48, 125.80, 127.30, 133.15, 136.55, 138.10, 145.77, 161.57, 165.08. MS *m/z*: 231 (M^+). HR-MS *m/z*: Calcd for $C_{13}H_{13}NO_3$: 231.0895. Found: 231.0869.

19a: Yellow plates (benzene–diisopropyl ether), mp 257—258 °C. IR (KBr) cm^{-1}: 1637.5, 1619, 736, 714, 699. ^{1}H-NMR ($CDCl_3$) δ: 2.36 (12H, s), 3.73 (3H, s), 7.10 (1H, s), 7.89 (2H, s), 8.23 (1H, s). ^{13}C-NMR ($CDCl_3$) δ: 19.48, 19.80, 20.47, 20.61, 29.86, 115.79, 117.00, 121.91, 123.21, 123.42, 128.95, 130.53, 131.40, 135.93, 136.51, 137.87, 141.69, 161.52. MS *m/z*: 265 (M^+), 250. HR-MS *m/z*: Calcd for $C_{18}H_{19}NO$: 265.1467. Found: 265.1479.

19b: Brown crystalline powder (acetone), mp 270 °C (dec.). IR (KBr) cm^{-1}: 1637.5, 1619, 736, 714, 699. ^{1}H-NMR ($CDCl_3$) δ: 2.37 (3H, s), 2.38 (3H, s), 2.44 (3H, s), 2.48 (3H, s), 7.08 (1H, s), 7.91 (1H, s), 8.00 (1H, s), 8.29 (1H, s), 10.22 (1H, br s). ^{13}C-NMR ($CDCl_3$) δ: 19.75, 19.85, 19.92, 20.96, 112.44, 116.63, 117.42, 118.19, 122.39, 122.67, 127.58, 130.61, 133.52, 134.79, 137.82, 139.86, 160.07. MS *m/z*: 251 (M^+), 236. HR-MS *m/z*: Calcd for $C_{17}H_{17}NO$: 251.1310. Found: 251.1315.

20a: Colorless columns (ether), mp 172—175 °C. IR (KBr) cm^{-1}: 1720, 1687, 788, 748. ^{1}H-NMR ($CDCl_3$) δ: 1.47 (3H, s), 1.68 (3H, s), 1.73—1.76 (1H, br m), 2.29 (3H, s), 2.31 (3H, s), 2.35—2.36 (1H, br m, J=6.2 Hz), 2.60 (1H, d, J=18.0 Hz), 2.84 (1H, d, J=18.0 Hz), 3.16 (3H, s), 3.58 (3H, s), 4.03 (1H, J=6.2, 10.3 Hz), 7.00 (1H, s), 7.82 (1H, s). ^{13}C-NMR ($CDCl_3$) δ: 18.60, 18.65, 19.41, 20.38, 32.22, 33.69, 34.29, 37.05, 49.43, 52.76, 58.96, 122.100, 124.56, 126.61, 129.38, 133.80, 136.19, 140.91, 163.68, 174.82. MS *m/z*: 327 (M^+), 245 ($M^+-C_6H_{10}$), 214. HR-MS *m/z*: Calcd for $C_{20}H_{25}NO_3$: 327.1834. Found: 327.1835.

20b: Colorless plates ($CHCl_3$–acetone), mp 250—253 °C. IR (KBr) cm^{-1}: 3435, 1658, 1621, 754, 730. ^{1}H-NMR ($CDCl_3$) δ: 1.61 (3H, s), 1.64 (3H, s), 1.90 (1H, d, J=18.1 Hz), 2.28 (6H, s), 2.29 (1H, d, J=18.1 Hz), 2.43 (1H, d, J=18.1 Hz), 2.61 (1H, J=18.1 Hz), 3.76 (3H, s), 4.35 (1H, br s), 5.88 (1H, s), 6.82 (1H, s), 7.86 (1H, s). ^{13}C-NMR ($CDCl_3$) δ: 18.75, 18.88, 19.40, 20.29, 35.59, 37.29, 50.49, 50.84, 52.63, 120.75, 124.93, 125.39, 125.60, 129.51, 136.30, 139.00, 141.84, 165.78, 173.31. MS *m/z*: 313 (M^+), 231 ($M^+-C_6H_{10}$), 200. HR-MS *m/z*: Calcd for $C_{19}H_{23}NO_3$: 313.1678. Found: 313.1671.

Calculation of Activation Energy We optimized the structures of the initial state and the TS using the restricted Hartree–Fock method with the 3—21G basis set in the Gaussian 98 program package.[11] The effect of solvent was not considered. We assumed that the diene and the dienophile were far apart at the initial state and obtained the value of the activation energy as a difference in energy between the initial state and the TS. We carried out the vibrational calculation to make sure that the TS had only one imaginary vibrational frequency. We also performed the intrinsic reaction coordinate calculation and confirmed that the TS connected the initial state and the intended product.

References and Notes

1) Review for DA cycloadditions of 2(1*H*)-pyridones; Afarinkia K., Vinader V., Nelson T. D., Posner G. H., *Tetrahedron*, **48**, 9111—9171 (1992); Tomisawa H., Fujita R., Noguchi K., Hongo H., *Chem. Pharm. Bull*., **18**, 941—946 (1970); Tomisawa H., Hongo H., *ibid*., **18**, 925—931 (1970).
2) *a*) Kato H., Fujita R., Hongo H., Tomisawa H., *Heterocycles*, **12**, 1—4 (1979); *b*) Tomisawa H., Kato H., Fujita R., Hongo H., *Chem. Pharm. Bull*., **27**, 810—812 (1979); *c*) Kato H., Fujita R., Hongo H., Tomisawa H., *Annual Report of Tohoku College of Pharmacy*, **25**, 51—55 (1978) [*Chem. Abstr*., **91**, 76252 (1991)]; *d*) Tomisawa H., Fujita R., Kato H., Hayasaka K., Kamimura T., Hongo H., *Chem. Pharm. Bull*., **36**, 1882—1885 (1988); *e*) Fujita R., Watanabe K., Masuyama T., Okuyama Y., Nakano H., Hongo H., *J. Tohoku Pharmaceutical University*, **46**, 77—81 (1999).
3) Nakano H., Date T., Okamura K., Tomisawa H., Hongo H., *Chem. Pharm. Bull*., **39**, 2471—2473 (1991).
4) Fujita R., Watanabe K., Ikeura W., Ohtake Y., Hongo H., *Heterocycles*, **53**, 2607—2610 (2000).
5) Blomquist A. T., Wasserman H., "Organic Chemistry," Vol. 25, Academic Press, London, 1972, pp. 1—594.
6) Grundon M. F., "The Alkaloids: Quinoline Alkaloids Related to Anthranic Acid," Vol. 32, Academic Press, London, 1988, pp. 341—440.
7) Mondon A., Krohn K., *Chem. Ber*., **108**, 445—468 (1975).
8) Berrie A. H., Newbold G. T., Spring F. S., *J. Chem. Soc*., **1951**, 2590—2594.

9) Fujita R., Honda R., Hongo H., *Annual Report of Tohoku College of Pharmacy*, **39**, 101—109 (1992) [*Chem. Abstr*., **121**, 82970 (1994)].
10) Fujita R., Hoshino M., Tomisawa H., *Annual Report of Tohoku College of Pharmacy*, **38**, 65—70 (1991) [*Chem. Abstr*., **118**, 168957 (1993)].
11) Gaussian 98, Revision A. 9, Frisch M. J., Trucks G. W., Schlegel H. B., Scuseria G. E., Robb M. A., Cheeseman J. R., Zakrzewski V. G., Montgomery J. A., Jr., Stratmann R. E., Burant J. C., Dapprich S., Millam J. M., Daniels A. D., Kudin K. N., Strain M. C., Farkas O., Tomasi J., Barone V., Cossi M., Cammi R., Mennucci B., Pomelli C., Adamo C., Clifford S., Ochterski J., Petersson G. A., Ayala P. Y., Cui Q., Morokuma K., Malick D. K., Rabuck A. D., Raghavachari K., Foresman J. B., Cioslowski J., Ortiz J. V., Baboul A. G., Stefanov B. B., Liu G., Liashenko A., Piskorz P., Komaromi I., Gomperts R., Martin R.L., Fox D. J., Keith T., Al-Laham M. A., Peng C. Y., Nanayakkara A., Challacombe M., Gill P. M. W., Johnson B., Chen W., Wong M. W., Andres J. L., Gonzalez C., Head-Gordon M., Replogle E.S., Pople J. A., Gaussian, Inc., Pittsburgh PA, 1998.