HETEROCYCLES, Vol. 77, No. 1, 2009, pp. 263 - 272. © The Japan Institute of Heterocyclic Chemistry
Received, 8th February, 2008, Accepted, 12th March, 2008. Published online, 14th March, 2008.
DOI: 10.3987/COM-08-S(F)4

DIELS-ALDER REACTION OF 2-PYRIDONES HAVING AN ACYL OR A SULFONYL GROUP ON NITROGEN

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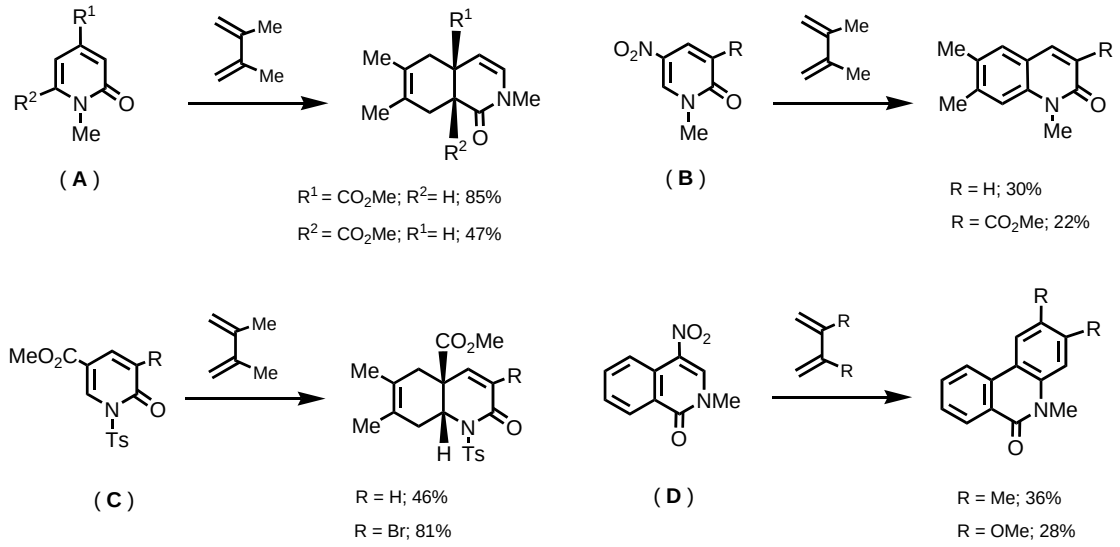
Abstract — Diels-Alder (DA) reaction of 5-methoxycarbonyl-2-pyridone, which has an electron-withdrawing acyl group at nitrogen, with 1,3-diene afforded 2-quinolone derivatives in modest yields. Further, DA reaction of 5,4-dimethoxycarbonyl-1-sulfonyl-2-pyridone gave 2-quinolone and 1-isoquinolone (1:1). DA reaction of 2-sulfonyl-1-isoquinolone afforded a functionalized phenanthridone. The site-selectivity was well correlated with the corresponding activation energies calculated using an *ab initio* molecular orbital method.

INTRODUCTION

There have been many reports describing the Diels-Alder (DA) reactions of 2(1*H*)-pyridones, which are aromatic, as dienes.[1] In contrast, we have previously reported on the DA reaction of *N*-methyl-2(1*H*)-pyridones (**A**), which have an electron-withdrawing group at the 4- or 6-position, in which **A** acts as a dienophile, giving tetrahydro-1(2*H*)-isoquinolones (Scheme 1).[2] To the best of our knowledge, there are few examples of the synthesis of tetrahydro-2(1*H*)-quinolones from the DA reaction of 2(1*H*)-pyridones. We have also reported on the DA reaction of 1-methyl-5-nitro-2(1*H*)-pyridones (**B**) to yield the aromatic 2(1*H*)-quinolone in modest yields (Scheme 1).[3] From these results, we expect that 2(1*H*)-pyridones having two electron-withdrawing groups, at the 1- and 5-positions, would have higher reactivities as dienophiles than 2(1*H*)-pyridones having a withdrawing group at the 5-position only. It is considered that the additional electron-withdrawing group at the 1-position may decrease delocalization of the unshared electrons of the nitrogen atom, thus enhancing the dienophilic character of the pyridone ring. Recently, we report a novel method of preparing

This paper is dedicated to Professor Emeritus Keiichiro Fukumoto on the occasion of his 75th birthday

tetrahydro-2(1*H*)-quinolones by DA reaction between 1-arylsulfonyl-2(1*H*)-pyridones (**C**), which have an electron-withdrawing group at the 5-position, and a diene.[4] Moreover, we described a novel DA reaction in which 2-methyl-4-nitro-1(2*H*)-isoquinolone (**D**) reacts with a diene to give aromatic 5(6*H*)-phenanthridone derivatives in modest yields (Scheme 1).[5] Herein, we wish to report DA reactions of the 1-acyl or 1-sulfonyl-2(1*H*)-pyridones, bearing a methoxy-carbonyl group at the 5-position, and 2-sulfonyl-4-methoxycarbonyl-1(2*H*)-isoquinolone. Further, site-selectivity analyses based on MO calculations of the 5-substituted 2(1*H*)-pyridones are investigated.



Scheme 1

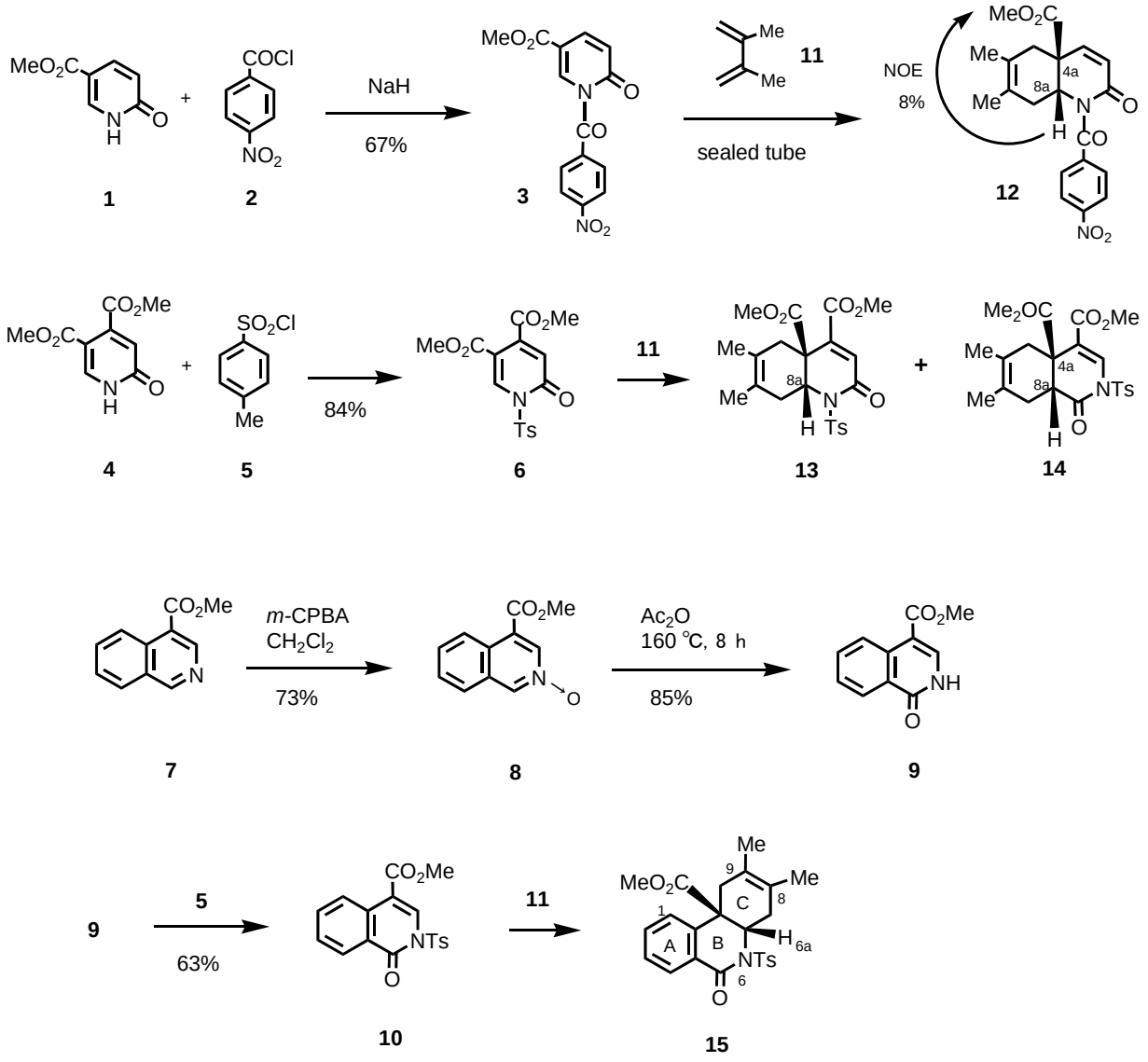
RESULTS AND DISCUSSION

1. DA reactions of 1-acyl- or 1-sulfonyl-2(1*H*)-pyridone derivatives with 1,3-butadiene

Firstly, the acylation of 2(1*H*)-pyridone **1**,[6] and sulfonylations of **4** and isoquinolone **9** were investigated (Scheme 2). Acylation of 5-methoxycarbonyl-2(1*H*)-pyridone **1**[6] with *p*-nitrobenzoyl chloride **2** (1.5 equiv.) using NaH (1.5 equiv.) as a base in THF was carried out at room temperature for 2.5 h, providing the desired 1-*p*-nitrobenzoyl-2(1*H*)-pyridone **3** in 67% yield. Acylation of **1** using Et_3N (1.5 equiv.) as a base afforded **3** in 63% yield. Under similar condition (NaH, room temperature for 6 h), the reaction of 4,5-dimethoxycarbonyl-2(1*H*)-pyridone **4**[7] with *p*-tosyl chloride **5** gave 1-*p*-tosyl-2(1*H*)-pyridone **6** in 84% yield. Also, 1(2*H*)-Isoquinolone **9** was easily prepared from isoquinoline **7** via isoquinoline-1-oxide **8** in two steps (Scheme 2). Sulfonylation of 1(2*H*)-isoquinolone **9** with **5** afforded 2-*p*-tosyl-1(2*H*)-isoquinolone **10** in 63% yield under similar conditions.

Next, as listed in Table 1 and Scheme 2, the subsequent DA reactions of 1-acyl- or 1-sulfonyl-2(1*H*)-pyridone derivatives were examined. The DA reaction of benzoylpyridone **3** with

2,3-dimethyl-1,3-butadiene **11** at 180 or 160 °C for 3 d under atmospheric pressure (Entries 1, 2) proceeded stereoselectively and the site-selectively, afford the *cis*-adduct quinolone **12** (45% and 33%), which has a benzoyl group at the 1-position. The DA reaction of **6** with **11** at 120, 140, or 180 °C (Entries 3-5) gave stereoselectively the *cis*-adduct quinolone **13** (39%, 34% and 26%) and the *cis*-adduct isoquinolone **14** (37%, 33% and 27%); the total yields were 76%, 67% and 53%, respectively. Subsequent DA reaction of **10** with **11** under atmospheric or high pressure conditions yielded the *cis*-adduct phenanthridone **15** (18%, 11% and 17%; Entries 6-8) which has electron-withdrawing groups at the 2- and 10a-positions. The DA reaction of 2(1*H*)-pyridone **3**, which has an acyl group at the 1-position afforded the *cis*-adduct quinolone the site-selectively in reasonable yield, whereas the DA reaction of 6 afforded the quinolone- and the isoquinolone-adducts in good total yield. However, the DA reaction of **10** gave the phenanthridone in low yield.

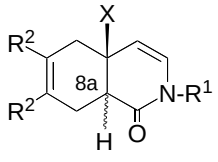


Scheme 2

Table 1. Diels-Alder reaction of **3**, **6**, **10** with **11**

Entry	Substrate	Temp. (°C)	Time (d)	Solvent	Pressure (kbar)	Adduct	Yield (%)	
1	**3**	180	3	*o*-xylene	atmospheric	**12**	45	
2	**3**	160	3	*o*-xylene	atmospheric	**12**	33	
3	**6**	120	3	*o*-xylene	atmospheric	**13** **14**	39 37	) T = 76%
4	**6**	140	3	*o*-xylene	atmospheric	**13** **14**	34 33	) T = 67%
5	**6**	180	2	*o*-xylene	atmospheric	**13** **14**	26 27	) T = 53%
6	**10**	160	6	*o*-xylene	atmospheric	**15**	18	
7	**10**	180	6	*o*-xylene	atmospheric	**15**	11	
8	**10**	90	2	CH_2Cl_2	10	**15**	17	

Assignment of the stereochemistry of the ring juncture in **12-15** were confirmed as follow. The *cis*-stereochemistry of the ring juncture in **12** was determined by NOE measurement. When H-8a (δ 5.05) was irradiated, an NOE was observed between H-8a and CH_3OOC-4a (ca. 8%) in **12**. This is consistent with a previous report, where we showed that the proton signals of the ring juncture in the *cis*-quinolone adducts appeared at δ 4.77-5.24.[8] The *cis*-stereochemistry of the ring juncture in **13** was deduced by the similarity of the ^{1}H-NMR spectra of **12** with that of **13** (H-8a, δ 5.16). The ring juncture in **15** was confirmed as *cis* from the signal at δ 5.28, which is assigned to the proton (H-6a) of the ring juncture in **15**, which possess two cyclohexane rings (B, C: quinolone type). We have previously reported that signals arising from the proton at the ring juncture of *cis*-isoquinolone adducts (δ 2.84-3.20; Figure 1) are found at lower shifts than those of the corresponding *trans*-isoquinolone adducts (δ 2.00-2.80; Figure 1).[8] The signal assigned to the proton (H-8a) of the ring juncture in **14** appeared at δ 3.12, supporting the existence *cis* stereochemistry.



X = CO_2Me, CN, COMe, CHO

R^1 = Me, H

R^2 = Me; H_{8a} = — δ2.84-2.97 R^2 = OMe; H_{8a} = — δ3.03-3.20

H_{8a} = ····· δ2.00-2.80 H_{8a} = ····· δ2.70

Figure 1. Chemical Shifts (δ) of Isoquinolones[8]

2.Site-selectivity

The DA reactions of **3** and **6** as dienophiles with **11** were theoretically studied using Gaussian 03 at B3LYP/6-31G(d) level.[9] Calculated activation energies (*Ea*) are summarized in Table 2 together with the experimental yields of the adducts. For the reaction of **3** with **11**, the calculated *Ea* value is much smaller for (5, 6) than for (3, 4) addition, supporting the formation of adduct **12** as shown experimentally. For the reaction of **6** with **11**, the difference in these *Ea* values is small, which is consistent with the fact that the experimental yields of **13** and **14** were almost the same.

Table 2. Calculted activation energies (*Ea*) and experimental yields of adducts for the Diels-Alder reaction of **3** and **6** with **11**

Entry	Substrate	Diene	Temp. (°C)	Time (d)	(3, 4)-Addition		(5, 6)-Addition	
					Ea [a)] (kcal/mol)	Yield (%)	*Ea* [a)] (kcal/mol)	Yield (%)
1	**3**	**11**	180	3	25.72	---	17.70	**12** (45)
2	**6**	**11**	120	3	19.90	**14** (37)	19.99	**13** (39)

a) The energies are calculated using Gaussian 03 at B3LYP/6-31G(d) level.

CONCLUSION

In conclusion, we have developed a synthetic methodology of preparing tetrahydro-2(1*H*)-quinolones, isoquinolone and phenanthridone through DA reaction of 2(1*H*)-pyridone derivatives, having an electron-withdrawing group at the nitrogen, in which the 2(1*H*)-pyridone acts as dienophiles. Furthermore, when studying the DA reactions of **3** and **6** working as a dienophile, the calculated *Ea* values were useful to understand the site-selectivity in these reactions.

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.

Synthesis of 5-methoxycarbonyl-1-(4-nitrobenzoyl)-2(1*H*)-pyridone (3). A solution of benzoyl chloride **2** (0.557 g, 3 mmol) in THF (10 mL) at -78 °C was added to a stirred suspension of **1**[10] (0.459 g, 3 mmol) and NaH (0.072 g, 3 mmol) in THF (20 mL) at -25 °C. After 1 h, the reaction mixture was allowed to warm to rt, and then was stirred for 2.5 h. The mixture was poured into ice water (10 mL), neutralized with 10% NaOH aqueous solution, then extracted with $CHCl_3$ (200 mL). The $CHCl_3$ extract was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography (acetone-hexane = 1:2) to give benzoylpyridone **3** (0.610 g, 67%). Colerless plates (benzene), mp 138-140 °C. IR (KBr) cm^{-1}: 1752, 1746, 1725, 1608, 1526, 859. ^{1}H-NMR ($CDCl_3$) δ:3.99 (3H, s, OCH_3), 6.45 (1H, d, *J* = 0.6, 9.6 Hz, 3-H), 8.37 (2H, dd, *J* = 2.7, 6.6 Hz, 3',5'-H), 8.42 (2H, dd, *J* = 2.7, 8.9 Hz, 2',6'-H), 8.49 (1H, dd, *J* = 2.3, 8.4 Hz, 4-H) , 9.09 (1H, dd, *J* = 0.6, 2.3 Hz, 6-H). ^{13}C-NMR ($CDCl_3$) δ: 52.5, 116.04, 123.9 (C2), 125.3, 131.6 (C2), 134.1, 141.2, 150.7, 151.2, 160.4, 162.5, 164.8. LMS *m*/*z*: 302 (M^+), 274, 150, 104. HRMS *m*/*z*: Calcd for $C_{14}H_{10}N_2O_6$, 302.0538. Found: 302.05461.

General procedures for sulfonylations of 2(1*H*)-pyridone derivatives 4, 9 with TsCl (5). A solution of sulfonyl chloride **5** (1.14 g, 6 mmol) in THF (10 mL) at -78 °C was added to a stirred suspension of **4** (0.844 g, 4 mmol) and NaH (0.144 g, 6 mmol) in THF (20 mL) at -78 °C. After 1 h, the reaction mixture was allowed to warm to rt, and then was stirred for 5 h. The mixture was poured into ice water (10 mL), neutralized with 10% NaOH aqueous solution, then extracted with $CHCl_3$ (200 mL). The $CHCl_3$ extract was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography (acetone-hexane = 1:3) to give sulfonylpyridone **6** (1.23 g, 84%). Reaction of **9** (0.305 g, 1.5 mmol) with **5** (0.475 g, 2.5 mmol) were carried out under similar condition to give **10** (0.22g, 63%).

6: Colerless plates (acetone), mp 205-206 °C. IR (KBr) cm^{-1}*:* 1740, 1724, 1687, 1616, 1532, 1311, 772, 731. ^{1}H-NMR ($CDCl_3$) δ: 2.46 (3H, s, Ph-Me), 3.88 (3H, s, OMe), 3.89 (3H, s, OMe), 6.44 (1H, d, *J* = 0.5 Hz, 3-H), 7.37 (2H, d, *J* = 8.6 Hz, 3',5'-H), 8.00 (2H, d, *J* = 8.6 Hz, 2',6'-H), 8.87 (1H, d, *J* = 0.5 Hz, 6-H). ^{13}C-NMR ($CDCl_3$) δ: 21.9, 52.7, 53.1, 108.3, 121.4, 129.6, 130.1, 131.9, 137.7, 144.7, 147.0, 158.4, 162.8, 165.4. LMS *m*/*z*: 365 (M^+), 301 (M^+-SO_2), 242, 91. HRMS *m* /*z*: Calcd for $C_{16}H_{15}NO_7S$, 365.0569. Found: 365.0601.

10: Colerless needles (acetone), mp 179-181 °C. IR (KBr) cm^{-1}: 1718, 1697, 1592, 845, 782. ^{1}H-NMR

($CDCl_3$) δ: 2.44 3.97 (3H, s, PhMe), 7.38 (2H, d, *J* = 8.6 Hz, H-benzene), 7.49 (1H, ddd, *J* = 1.0, 7.3, 8.3 Hz, H-6), 7.75 (1H, ddd, *J* = 1.5, 7.3, 8.4 Hz, H-7), 8.05 (2H, d, *J* = 8.6 Hz, H-benzene), 8.30 (1H, dd, *J* = 1.5, 8.3 Hz, H-5), 8.75 (1H, dd, *J* = 1.5, 8.3 Hz, H-8), 8.89 (1H, s, H-3). ^{13}C-NMR ($CDCl_3$) δ:21.8, 52.2, 108.6, 125.8, 126.0, 128.1, 128.5, 129.7 (C2), 129.8 (C2), 133.1, 133.5, 133.8, 134.5, 146.5, 159.9, 165.0. MS *m/z*: 357 (M^+), 293, 91. HR-MS *m/z*: Calcd for $C_{18}H_{15}NO_5S$, 357.0671. Found: 357.0698.

Synthesis of 4-methoxycarbonylisoquinoline-1-oxide (8). A suspension of **7** (3.74 g, 20 mmol) and *m*-chloroperoxybenzoic acid (4.14 g, 24 mmol) in CH_2Cl_2 (30 mL) was stirred at room temperature for 1 d, and *m*-chloroperoxybenzoic acid (4.14 g, 24 mmol) was added to the reaction mixture. After 2 d, the reaction mixture was diluted with $CHCl_3$ (200 mL), and treated with K_2CO_3 (46 g, 0.33 mol) and H_2O (15 mL). The organic layer was separated, dried over Na_2SO_4, and evaporated *in vacuo* to give **8** (2.52 g, 73%) as colorless plates (acetone), mp 102-105 °C. ^{1}H-NMR ($CDCl_3$) δ: 4.05 (3H, s, OMe), 7.58-7.78 (3H, m, aromatic –H), 7.83 (1H, dd, *J* = 1.1, 7.0 Hz, aromatic–H), 8.03 (1H, s, 3-H), 8.79 (1H, s, 1-H). ^{13}C-NMR ($CDCl_3$) δ: 53.3, 124.6, 125.6, 127.4, 127.7, 129.3, 130.1, 130.8, 137.3, 139.0, 162.2. HRMS *m/z*: Calcd for $C_{11}H_9NO_3$, 203.0582. Found: 203.0586.

Reaction of 8 with acetic anhydride. A solution of **8** (2.03 g, 10 mmol) and acetic anhydride (10 mL) was refluxed for 8 h. After concentrating the reaction mixture *in vacuo*, the residue was purified using column chromatography (EtOAc). The first fraction was evaporated to give 4-methoxy-carbonyl-1(2*H*)-isoquinolone (**9**, 3.45 g, 85%) as colorless needles (acetone), mp 154-157 °C. ^{1}H-NMR ($CDCl_3$) δ: 4.00 (3H, s, OMe), 7.38 (1H, s, 3-H), 7.60-7.77 (3H, m, aromatic–H), 8.44 (1H, d, *J* = 8 Hz, 8-H), 9.22 (1H, s, OH). ^{13}C-NMR ($CDCl_3$) δ: 53.16, 111.30, 127.68, 127.92, 128.14, 128.31, 129.39, 133.03, 135.94, 161.69, 162.20. HRMS *m/z*: Calcd for $C_{11}H_9NO_3$, 203.0582. Found: 203.0546.

General procedure for Diels-Alder reaction of 3, 6 and 10 with 11. A solution of **6** (0.365 g, 1 mmol) and **11** (0.410 g, 5 mmol) in *o*-xylene (3 mL) was heated at 120 °C for 3 d in a sealed tube. The reaction mixture was concentrated *in vacuo*, and then purified by column chromatography (acetone-hexane = 1:2). The first fraction was evaporated to give **13** (0.175 g, 39%). The second fraction was evaporated, then further purified by preparative TLC over silica gel (Et_2O-hexane = 3:1) to afford **14** (0.166 g, 37%). Reactions of **3**, **6**, **l0** (1 mmol) with **11** (5 mmol) were carried out under similar the conditions, as listed in Table 1, to afford **12-l5**, respectively. Yields of **12-l5** are summarized in Table 1.

12:Pale yellow plates (Et_2O), mp 153-155 °C. IR (KBr) cm^{-1}: 1733, 1686, 1606, 1525, 822. ^{1}H-NMR ($CDCl_3$) δ:1.63 (3H, s, 6-CH_3), 1.69 (3H, s, 7-CH_3), 2.08 (1H, m, 8-H), 2.43 (1H, d, *J* = 17.3 Hz, 5-H), 2.66 (1H, d, *J* = 17.3 Hz, 5-H), 2.77 (1H, dd, *J* = 7.1, 17.3 Hz, 8-H), 3.78 (3H, s, OCH_3), 5.10 (1H, dd,

J = 2.3, 7.1 Hz, 8a-H), 5.97 (1H, d, *J* = 9.6 Hz, 3-H), 6.68 (1H, dd, *J* = 2.3, 9.6 Hz, 4-H), 7.57 (2H, d, *J* = 8.9 Hz, 2',6'-H), 8.23 (2H, d, *J* = 8.9 Hz, 3',5'-H). ^{13}C-NMR ($CDCl_3$) δ: 18.6, 18.7, 35.0, 39.9, 47.1, 53.0, 54.5, 122.3, 124.5, 125.7, 126.0, 128.5, 142.0, 148.1, 149.0, 163.5, 171.2, 172.8. LMS *m*/*z*: 384 (M^+), 186, 159, 150. HRMS *m*/*z*: Calcd for $C_{20}H_{20}N_2O_6$, 384.1321. Found: 384.1299.

13: Coloreless oil. IR (film) cm^{-1}: 1732, 1693, 1597, 1359, 815. ^{1}H-NMR ($CDCl_3$) δ: 1.56 (3H, s, C-CH_3), 1.60 (3H, s, C-CH_3), 2.02-2.12 (1H, brm, 8-H), 2.42 (3H, s, C_6H_5-CH_3), 2.67-2.76 (2H, brm, 5,8-H), 3.18 (1H, d, *J* = 17.2 Hz, 5-H), 3.56 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 5.16 (1H, dd, *J* = 7.3, 9.8 Hz, 8a-H), 6.62 (1H, s, 3-H), 7.29-7.37 (2H, m, 3', 5'-H), 7.90-7.94 (2H, m, 2', 6'-H). ^{13}C-NMR ($CDCl_3$) δ: 18.4, 18.6, 21.7, 36.0, 38.0, 50.2, 52.6, 53.2, 57.9, 123.8, 125.6, 129.0, 129.1, 132.0, 135.7, 142.6, 145.0, 161.0, 164.5, 172.1. LMS *m*/*z:* 447 (M^+), 292 (M^+-Ts), 242. HRMS *m*/*z*: Calcd for $C_{22}H_{25}NO_7S$, 447.1352. Found: 447.1320.

14: Coloreless oil. IR (film) cm^{-1}: 1716, 1640, 1597, 1379, 815. ^{1}H-NMR ($CDCl_3$) δ: 1.52 (3H, s, C-CH_3), 1.56 (3H, s, C-CH_3), 1.80 (1H, d, *J* =18.4 Hz, 5-H), 1.86 (1H, d, *J* =16.8 Hz, 8-H), 2.45 (3H, s, C_6H_5-CH_3), 2.47 (1H, d, *J* = 16.8 Hz, 8-H), 2.63 (1H, d, *J* = 18.4 Hz, 5-H), 3.12 (1H, m, *J* = 1.0, 2.1, 4.2 Hz, 8a-H), 3.67 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 7.30-7.36 (2H, m, 3', 5'-H), 7.86-7.94 (2H, m, 2', 6'-H), 8.13 (1H, s, 3-H). ^{13}C-NMR ($CDCl_3$) δ: 18.6, 18.7, 21.7, 27.4, 35.1, 44.3, 46.4, 52.0, 52.7, 116.4, 121.5, 122.3, 128.6, 129.5, 132.8, 134.0, 145.7, 164.6, 167.7, 172.4. LMS *m*/*z:* 447 (M^+), 388, 242. HRMS *m*/*z*: Calcd for $C_{22}H_{25}NO_7S$, 447.1352. Found: 447.1388.

15: Coloreless crystalline powder (acetone), mp 240-243 °C. IR (KBr) cm^{-1}: 1720, 1697, 1660, 1624, 786. ^{1}H-NMR ($CDCl_3$) δ: 1.38 (3H, s, C-Me), 1.63 (3H, s, C-Me), 1.80-1.90 (1H, brm, CH), 2.34 (3H, s, Ph-Me), 7.75 (1H, ddd, *J* = 1.5, 7.3, 8.4 Hz, H-7), 8.05 (2H, d, *J* = 8.6 Hz, H-benzene), 8.30 (1H, dd, *J* = 1.5, 8.3 Hz, H-5), 2.53 (1H, dd, *J* = 6.6, 10.9 Hz, CH), 2.82 (2H, s, CH_2), 3.40 (3H, s, OMe), 5.28 (1H, dd, *J* = 6.6, 10.9 Hz, 6a-H), 7.19-7.33 (4H, m, aromatic-H), 7.47 (1H, ddd, *J* = 1.5, 7.8, 7.8 Hz, aromatic -H), 7.91-7.99 (3H, brm, aromatic-H). ^{13}C-NMR ($CDCl_3$) δ: 18.47, 18.7 (C2), 21.8, 37.2, 50.1 (C2), 53.0, 56.6, 121.7, 125.0, 125.6, 128.0, 128.9, 129.0 (C2), 129.0, 129.7, 133.6, 136.3, 137.0, 144.6, 162.2, 173.3. LMS *m/z*: 439 (M^+), 293, 91. HRMS *m/z*: Calcd for $C_{24}H_{25}NO_5S$, 439.1454. Found: 439.1476.

Diels-Alder reaction of 10 with 11 under High pressure. A dichloromethane solution (1 mL) of **10** (0.089 g, 0.25 mmol) and **11** (103 g, 1.25 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-EtOAc (2:1) as eluent to afford **15** (0.015 g, 17%).

Calculation of activation energies. The structures of each state were optimized using the *ab initio*

molecular orbital method Gaussian 03 at B3LYP/6-31G(d) level.[9] The reactants were assumed to be far apart at the initial state. Two types of the transition state (TS) were searched; the one making bonds at the 3 and 4 positions of **3** or **6** and the other at the 5 and 6 positions. Solvent effects were not considered. After optimizing 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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