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Cycloaddition reactions of 4-sulfur-substituted dihydro-2-pyridones and 2-pyridones with conjugated dienes

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Abstract

Cycloaddition reactions of sulfoxide- and sulfone-substituted dihydro-2-pyridones and 2-pyridones with electron-rich dienes gave new bicyclic and tricyclic products in good to fair yields. The reactivity, regioselectivity, and stereoselectivity of these reactions were compared with semi-empirical theoretical calculations. Evidence is provided for rather unusual two parallel reaction pathways for the cross-Diels–Alder reaction of a sulfone-substituted 2-pyridone with cyclopentadiene.

Keywords: Cycloaddition reactions; 2-Pyridones; Dihydro-2-pyridones; Conjugated dienes

1. Introduction

2-Pyridones are often used as dienes in the Diels–Alder reaction.[1] The isoquinuclidine products are valuable intermediates in the synthesis of alkaloids[2–4] and in medicinal chemistry.[5] In contrast, the use of 2-pyridones as dienophiles is less common. Only 2-pyridones (**1**) with electron-withdrawing group(s) attached to the ring can react as dienophiles with electron-rich dienes to give isoquinolone derivatives,[6–14] which can be used for the synthesis of isoquinoline alkaloids.[15–17] The electron-withdrawing groups that have been studied include CN, CO_2Me, COR, and NO_2, and the substituent on the nitrogen can be methyl, hydrogen, or arylsulfonyl. High temperature and long reaction time, or extra-high pressure is usually required. Often times the reaction yields are low, and the cycloaddition products are sometimes further decomposed. In contrast to the many studies directed toward 2-pyridones, the corresponding cycloaddition reactions of electron-deficient 5,6-dihydro-2-pyridones (**2**) with electron-rich dienes have been little studied.[18,19] Only alkyl and ester substituents at C-3 of compounds **2** have been reported for such reactions.

The synthesis of 2-pyridone ring is an area of continuing interest[20] because many compounds of this structure (such as camptothecin, Fredericamycin A, pyridoxatin, huperzine A, etc.) posses important biological activities.[21–26] We recently reported the first aza-Diels–Alder reactions of thio-substituted 1,3-butadienes with arylsulfonyl isocyanates to give 4-thio-substituted 2-pyridones,[27,28] and have studied some of their synthetic applications.[29–32] In this paper we describe the synthesis of several sulfoxide- or sulfone-substituted dihydro-2-pyridones and 2-pyridones, as well as their cycloaddition reactions with some electron-rich dienes. Unlike previous derivatives as shown in **1** and **2**, the sulfoxide and sulfone substituents can be more easily eliminated from the initial cycloaddition products. In the present study we have synthesized several interesting new isoquinolone derivatives, and have identified two parallel reaction pathways for the cross-Diels–Alder reaction of a sulfone-substituted 2-pyridone with cyclopentadiene. The reactivity, regioselectivity, and stereoselectivity of these reactions are also compared with semi-empirical theoretical calculations.

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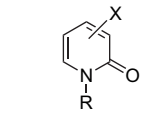
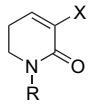


1

X = CN, CO_2Me, COR, NO_2

R = Me, H, $ArSO_2$



2

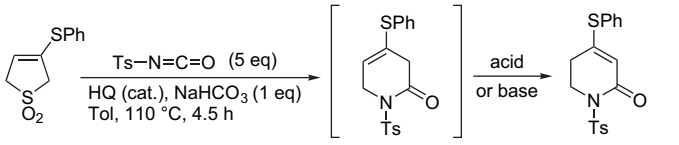
X = alkyl, CO_2Me

R = CO_2Me, $ArSO_2$

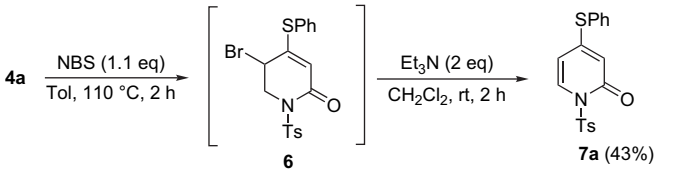
2. Results and discussion

2.1. Preparation of sulfur-substituted dihydro-2-pyridones and 2-pyridones

Reaction of 3-(phenylthio)-3-sulfolene (**3**)[33,34] with *p*-toluenesulfonyl isocyanate (PTSI) in toluene at 110 °C in the presence of 1 equiv of sodium bicarbonate and a catalytic amount of hydroquinone (HQ) gave the cyclization product **4a**, which upon treatment with acid or base yielded the conjugated dihydro-2-pyridone **5a** (Eq. 1).[28] If **4a** was directly treated with *N*-bromosuccinimide (NBS), the bromo intermediate **6** upon further reaction with triethylamine or pyrrolidine resulted in the formation of 2-pyridone **7a** (Eq. 2).[31] Oxidation of sulfides **4a**, **5a**, and **7a** with suitable equivalents of *m*-CPBA (Table 1) gave the corresponding sulfoxide **5c** and sulfones **4b**, **5b**,[28] and **7b**[31] in fair to excellent yields.



(1)



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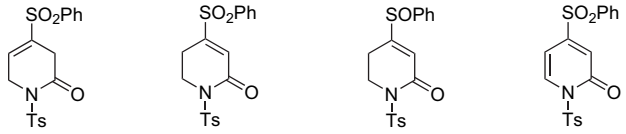
2.2. Cycloaddition reactions of sulfur-substituted dihydro-2-pyridones and 2-pyridones

We have studied the cycloaddition reactions of dihydro-2-pyridones **4b**, **5b**, **5c**, and 2-pyridone **7b** with some electron-rich dienes **8**, which include 1-methoxy-3-trimethylsilyloxy-1,3-butadiene (**8a**), 2,3-dimethyl-1,3-butadiene (**8b**), and cyclopentadiene (**8c**). Most of the cycloaddition reactions were carried out in a sealed tube using toluene as the solvent, and the results are shown in Table 2. After a few trials of reaction conditions, it was found that thermolysis of vinyl sulfone **4b** with Danishefsky's diene (**8a**) proceeded well at 160 °C for 48 h (entry 1) to give a separable mixture of cycloaddition products **9** and **10**. The X-ray structures of **9** and **10**

Table 1
Oxidation of sulfides **4a**, **5a**, and **7a**[a]

Entry	Reactant	*m*-CPBA (equiv)	Product (yield, %)
1	**4a**	3	**4b** (99)
2	**5a**	1.1	**5b** (24), **5c** (58)
3	**5a**	3	**5b** (99)
4	**7a**	3	**7b** (97)

[a] All reactions were carried out in CH_2Cl_2 at room temperature for 2 h.



4b **5b** **5c** **7b**

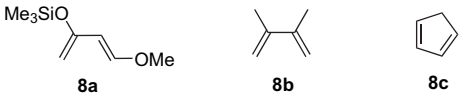
are shown in Figures 1 and 2.[35] We suspected that the minor product **10** might have derived from the reaction of **8a** with **5b**, which was isomerized from **4b** in the reaction process. We then subjected compound **4b** to the same thermolysis condition without diene **8a**. Indeed, we obtained a mixture of **4b** and **5b** in a ratio of 93:7 (Eq. 3). We also carried out a similar thermolysis of **5b**, and found that the mixture of **4b** and **5b** was obtained in 23:77 (Eq. 4). It is interesting to note that heating **5b** with **8a** at 140 °C for 24 h (entry 2) gave only product **10** in good yield. Judging from the reaction temperatures needed for the thermolysis, it is apparent that compound **5b** is more reactive than **4b**, probably because the C=C double bond of **5b** is activated by two electron-withdrawing groups whereas that of **4b** is activated by only one group. In agreement with this observation, although only a small amount of **5b** was generated from **4b** (Eq. 3), the ratio of product **10** to **9** (0.65) far exceeded that of **5b** to **4b** (0.08). On the other hand, despite the fact that during the thermolysis of **5b** with diene **8a** a significant amount of **4b** was also generated

Table 2
Cycloaddition reactions of 2-pyridones **4b**, **5b**, **5c**, and **7b** with dienes **8**

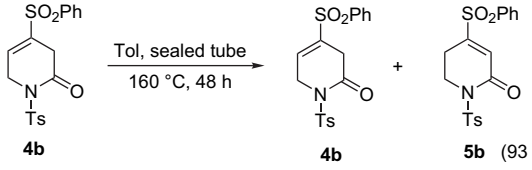
Entry	Pyridone	Diene[a]	Conditions[b]	Product (yield %)
1	**4b**	**8a**	160 °C, 48 h	**9** (40), **10** (26)
2	**5b**	**8a**	140 °C, 24 h	**10** (78)
3	**5b**	**8a**	140 °C, 24 h[c]	**10** (75)
4	**5b**	**8b**	160 °C, 48 h	**11** (75)
5	**5b**	**8c**	140 °C, 24 h	**12** (80)
6	**5c**	**8a**	140 °C, 24 h	**10** (83)
7	**5c**	**8a**	140 °C, 24 h[c]	**10** (82)
8	**7b**	**8a**	140 °C, 24 h	**13** (70)
9	**7b**	**8a**	140 °C, 24 h[c]	**13** (68)
10	**7b**	**8b**	160 °C, 48 h	**14** (71)
11	**7b**	**8c**	140 °C, 24 h	**15a** (36), **15b** (37)
12	**7b**	**8c**	80 °C, 48 h	**15a** (30), **15b** (32)[d]
13	**7b**	**8c**	50 °C, 96 h	**15a** (19), **15b** (22), **16** (29)
14	**7b**	**8c**	rt, 1 week[e]	N.R.

[a] Diene **8a** was used in 3 equiv, and dienes **8b–c** were used in large excess.
[b] All reactions were carried out in a sealed tube, using toluene as the solvent unless stated otherwise.
[c] After thermolysis, the reaction mixture was also treated with camphorsulfonic acid (CSA, 0.1 equiv) in THF at 80 °C for 4.5 h.
[d] Compound **7b** (15%) was also recovered.
[e] Neat **8c** was used.

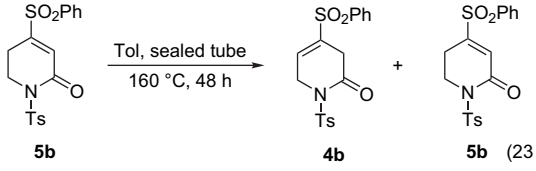
(Eq. 4), the higher reactivity of **5b** together with lower reaction temperature (140 °C in entry 2 instead of 160 °C in entry 1) led only to the formation of cycloaddition product **10** (entry 2). It is also worthwhile mentioning that cycloaddition reactions of Danishefsky's diene (**8a**) with dienophiles usually require an acidic treatment (for example, camphorsulfonic acid) to obtain the final product. However, in our studies we found that this treatment was not necessary (compare entries 2 with 3, 6 with 7, and 8 with 9 in Table 2). To explain this rather unusual result, using **5b** as an example, we propose that the initial cycloaddition product **A** could eliminate benzenesulfinic acid under thermolysis condition to form an intermediate **B**. The sulfinic acid generated could further catalyze the formation of intermediate **C**, which is then tautomerized to product **10** (Scheme 1).



8a **8b** **8c**



4b **4b** **5b** (93 : 7) (3)



5b **4b** **5b** (23 : 77) (4)

The reaction of dihydro-2-pyridone **5b** with dienes **8b** and **8c** (entries 4 and 5) gave the cycloaddition products **11** and **12**, respectively, in good yields. The X-ray structures of compounds **11** and **12** are provided in Supplementary data.[35] It is interesting to note that product **11** retains the cis relationship

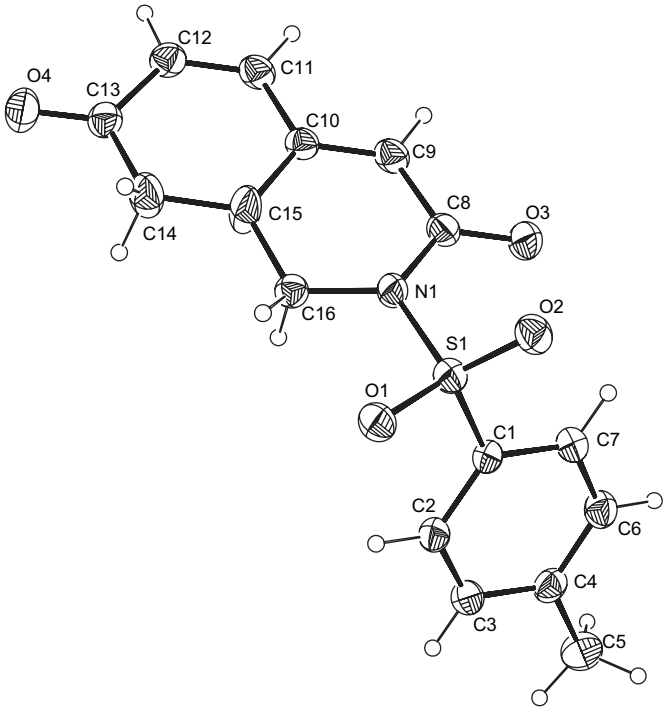
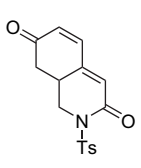
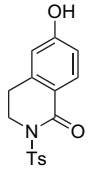


Figure 1. X-ray structure of **9**.

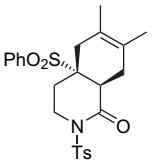
of the phenylsulfonyl group with the C-3 hydrogen, and did not eliminate benzenesulfinic acid during the thermolysis. Product **12** has the C=C double bond *endo* to the C=O group. Vinyl sulfoxide **5c** underwent the cycloaddition reaction with Danishefsky's diene (**8a**) under condition (entries 6 and 7) similar to sulfone **5b**, and gave the same product **10** even in slightly higher yields. Apparently, in this reaction benzenesulfinic acid was eliminated, which probably also catalyzed the hydrolysis of cycloaddition intermediates to the product **10** (similar to Scheme 1). Reactions of sulfone-substituted 2-pyridone **7b** with dienes **8a** and **8b** gave the cycloaddition products **13** and **14**, respectively, in good yields (entries 8–10). The X-ray structures of compounds **13** and **14** are provided in Supplementary data.[35] It is apparent that in these two reactions 2-pyridone **7b**, though bearing a diene moiety, acted as a dienophile with the electron-rich dienes



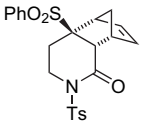
9



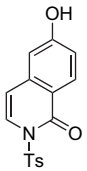
10



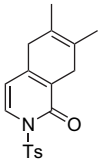
11



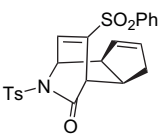
12



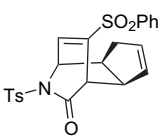
13



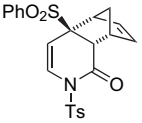
14



15a



15b



16

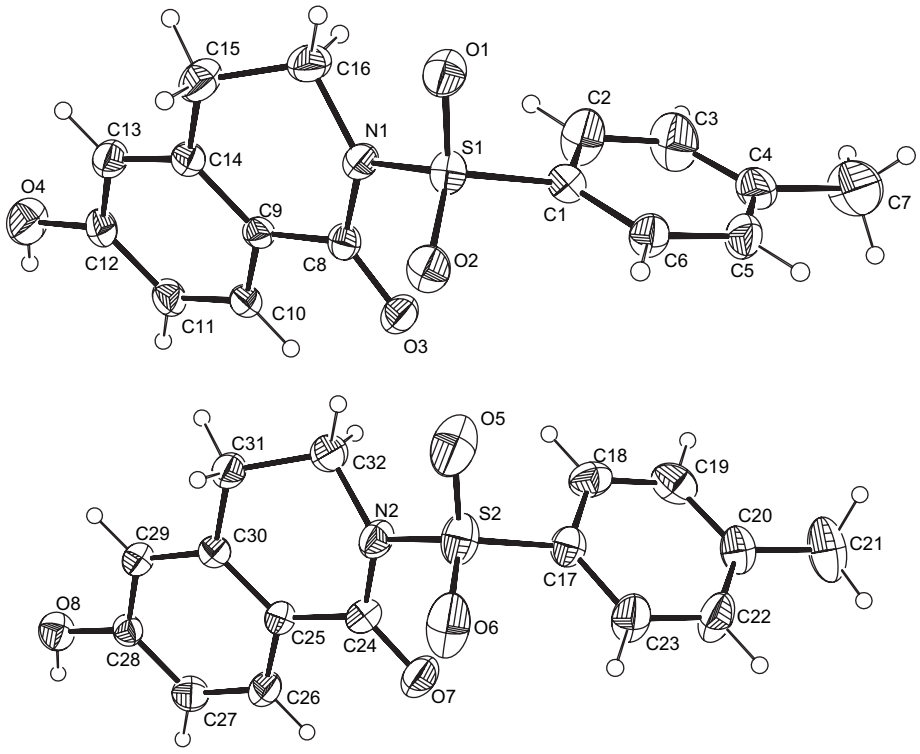
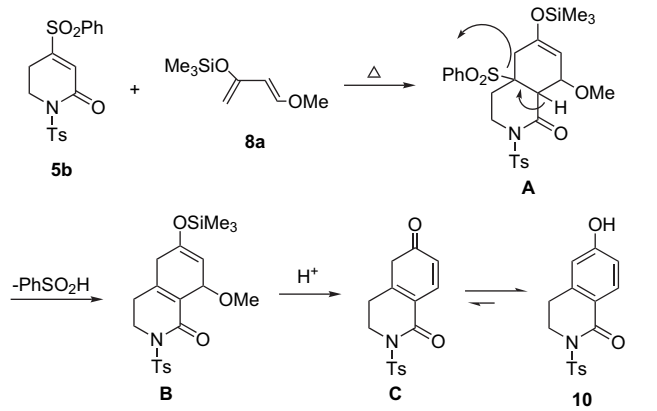


Figure 2. X-ray structure of **10**.



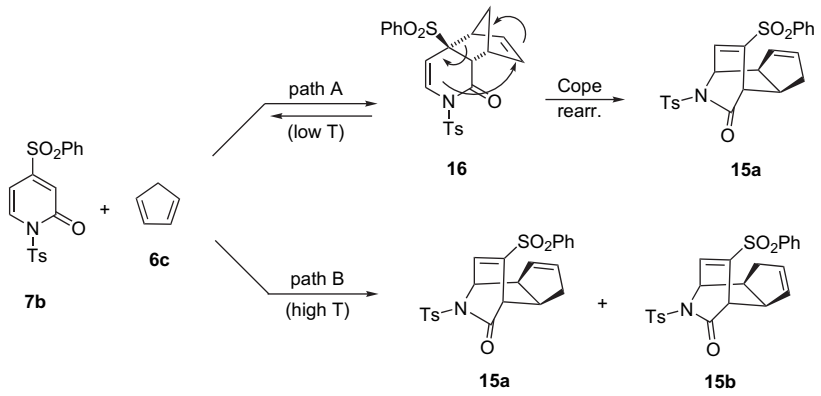
Scheme 1. Proposed mechanism for the formation of compound **10** from **5b**.

8a and **8b**. The reaction of **7b** with cyclopentadiene (**6c**) at 140 °C for 24 h (entry 11) gave a mixture of two regioisomeric cycloaddition products **15a** and **15b**, which could be separated by column chromatography. Carrying out the reaction of **7b** with **6c** at 80 °C for 48 h (entry 12) again led to the mixture of **15a** and **15b**, together with some unreacted starting material **7b**. However, if the reaction of **7b** with **6c** was performed at 50 °C for 96 h (entry 13), a new product **16** was obtained besides **15a** and **15b**. The X-ray structures of compounds **15a**, **15b**, and **16** are provided in Supplementary data.[35] Both **15a** and **15b** have the C=C double bond *endo* to the vinyl sulfone, but they differ in regiochemistry. If **7b** was stirred with neat cyclopentadiene at room temperature for 1 week (entry 14), no reaction was observed.

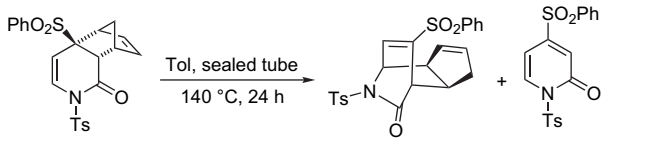
The formation of **15a** and **15b** was quite surprising, because we had expected that cyclopentadiene would react as a diene. However, there are a few reports in the literature that cyclopentadiene reacts as a dienophile with other dienes.[14,36–38] The separated **15a** and **15b**, upon subjecting to the reaction condition shown in entry 11, did not interconvert or decompose. This means that compounds **15a** and **15b** were stable, kinetic products. We also found that heating compound **16** in toluene at 140 °C for 24 h gave a quantitative conversion to a mixture of **15a** and **7b** (Eq. 5). Apparently, under this reaction condition, compound **16** underwent a Cope rearrangement to give compound **15a**, as well as a cycloreversion to give 2-pyridone **7b**. The fact that compound **15b** was not obtained from Eq. 5 indicates that compound **7b** did not react with the small amount of cyclopentadiene generated from the reaction (only 1 equiv, as opposed to large excess used in entry 11). Thus we propose the pathways for the reaction of compound **7b** with cyclopentadiene as shown in Scheme 2. At low reaction temperature such as 50 °C, cyclopentadiene can react as a diene (path A) to form the cycloaddition product **16**, which can undergo a Cope rearrangement at higher temperature to give product **15a** (not **15b**), or revert back to the starting material **7b**. However, at higher reaction temperature, cyclopentadiene preferentially reacts as a dienophile (path B) to generate products **15a** and **15b** directly.

2.3. Semi-empirical calculations

In order to explain the reactivity of dienophiles **4b**, **5b**, **5c**, and **7b** as well as the regioselectivity and stereoselectivity of the cycloaddition reactions, we have used a semi-empirical



Scheme 2. Proposed pathways for the reaction of **7b** with **6c**.



(5)

PM3 method of HyperChem to calculate the HOMO–LUMO energy differences and coefficients. As expected, the more favorable interaction is between HOMO of the diene and LUMO of the dienophile. The $HOMO_{diene}$–$LUMO_{dienophile}$ energy difference ΔE for different pairs of dienes and dienophiles is listed in Table 3. From the calculated ΔE values, the reactivity order of dienophiles is predicted: **7b**>**5b**>**4b**, **5c**; the reactivity order of dienes would be: **8a**>**8b**, **8c**. Experimentally, we found that compound **4b** was significantly less reactive than the other three dienophiles, and also that diene **8b** was less reactive than **8a** and **8c**. To explain the regioselectivity of the cycloaddition reaction, the LUMO-coefficients of dienophiles **4b**, **5b**, **5c**, and **7b** and HOMO-coefficients of dienes **8a** and **8c** are calculated (Table 4). It can be seen that the HOMO-coefficient of diene **8a** at C-4 is much larger than that at C-1. The LUMO-coefficients of compounds **5b**, **5c**, and **7b** at C-4 are larger than those at C-3. This indicates that the electron-withdrawing ability of the (TsN)C=O group attached to C-3 is greater than that of the sulfur-substituent at C-4. Experimentally, the regiospecific formation of cycloadducts **10** and **13** agrees with the theoretical calculation. For compound **4b**, the LUMO-coefficient at C-5 is much larger than that at C-4, and the structure of cycloaddition product **9** is also in agreement with this prediction. For the direct formation of cycloaddition products **15a** and **15b** from compound **7b** and cyclopentadiene (path B in Scheme 2), the more favorable

Table 3
Favorable $HOMO_{diene}$–$LUMO_{dienophile}$ energy difference ΔE calculated by HyperChem PM3 method

Entry	Diene	Dienophile	ΔE (eV)
1	**8a**	**4b**	7.40
2	**8a**	**5b**	7.33
3	**8a**	**5c**	7.40
4	**8a**	**7b**	7.23
5	**8b**	**5b**	8.23
6	**8b**	**7b**	8.13
7	**8c**	**5b**	8.23
8	**8c**	**7b**	8.14

Table 4
LUMO-coefficients of dienophiles **4b**, **5b**, **5c**, and **7b** and HOMO-coefficients of dienes **8a** and **8c**

Dienophile	LUMO-coefficients			
	C-3	C-4	C-5	C-6
4b		0.0096	0.0243	
5b	0.1524	0.1886		
5c	0.2004	0.2271		
7b	0.1869	0.1889		0.1261
Diene	HOMO-coefficients			
	C-1	C-2	C-4	
8a	0.3825		0.6454	
8c	0.1913	0.1372	0.1913	

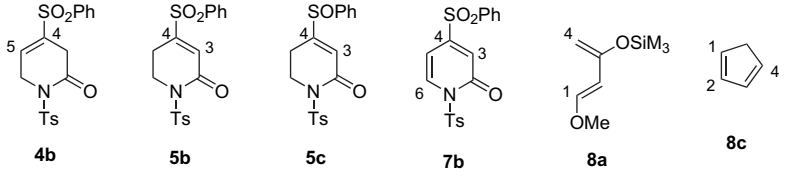


Table 5
Calculated heat of formation (ΔH_f) for cycloaddition products **12**, **15a**, **15b**, and **16**

Compound	ΔH_f (kcal/mol)
endo-**12**	−67.895
exo-**12**	−60.181
endo-**15a**	−74.366
exo-**15a**	−73.859
endo-**15b**	−74.430
exo-**15b**	−74.021
endo-**16**	−46.222
exo-**16**	−38.982

interaction of the HOMO of cyclopentadiene at C-1 with the LUMO of compound **7b** at C-3 predicts that the major regioisomer would be **15a**. However, the amounts of **15a** and **15b** obtained experimentally (entries 11–13 in Table 2) were about equal. We have also calculated the coefficients for LUMO of cyclopentadiene and HOMO of **7b** (not shown in Table 4), which would again favor the formation of product **15a**.

We have also calculated the heat of formation (ΔH_f) for cycloaddition products **12**, **15a**, **15b**, and **16** (Table 5) in order to compare the relative stability of the *endo* and *exo* stereoisomers. It can be seen that the *endo* isomers are all more stable than the *exo* isomers. Experimentally, we have only obtained the *endo* isomer for products **12**, **15a**, **15b**, and **16**. This means that these *endo* isomers are either thermodynamic products or formed faster.

3. Conclusion

We have synthesized sulfoxide- and sulfone-substituted dihydro-2-pyridones **4b**, **5b**, **5c**, and 2-pyridone **7b**, and have studied their cycloaddition reactions with electron-rich dienes **8**. Several new bicyclic and tricyclic products **9–16** have been obtained in good to fair yields. The sulfoxide or sulfone substituent not only increases the reactivity of the dienophiles, but can also be readily eliminated when reacting with Danishefsky's diene. Rather unusual two parallel reaction pathways have been established for the cycloaddition reaction of 2-pyridone **7b** with cyclopentadiene: cyclopentadiene reacts as a diene at low temperature, but as a dienophile at high temperature. The reactivity, regioselectivity, and stereoselectivity of these cycloaddition reactions agree quite well with semi-empirical theoretical calculations.

4. Experimental

4.1. General

Melting points were determined with a SMP3 melting apparatus. Infrared spectra were recorded with a Perkin Elmer 1600 FTIR spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 300 spectrometer operating at 300 and 75 MHz, respectively. Chemical shifts (δ) are reported in parts per million (ppm) and the coupling constants (J) are given in hertz. High resolution mass spectra (HRMS) were measured with a mass spectrometer Finnigan/Thermo Quest MAT 95XL. X-ray crystal structures were obtained with an Enraf-Nonius FR-590 diffractometer (CAD4, Kappa CCD). Elemental analyses were carried out with Heraeus Vario III-NCSH, Heraeus CHN-O-S-Rapid Analyzer or Elementar Vario EL III. Flash column chromatographic purifications were performed using Merck 60H silica gel.

4.2. General procedure for the oxidation of sulfides *4a* and *5a*

To a solution of sulfide **4a** or **5a** (1.4 mmol) in CH_2Cl_2 (10 mL) in an ice bath was added slowly another solution of *m*-CPBA (50%, 1.5 mmol for the preparation of **5c**, or 5.2 mmol for the preparation of **4b**) in CH_2Cl_2 (10 mL). The mixture was then stirred at room temperature for 1.5 h, and was washed sequentially with 5% $Na_2S_2O_3$ and 5% $NaHCO_3$, dried ($MgSO_4$), and evaporated. The crude product was purified by flash chromatography using ethyl acetate/hexane (1:2) as eluent to give purified product **4b** and **5c**. Sufones **5b**[28] and **7b**[31] were prepared similarly.

4.2.1. 3,6-Dihydro-4-(phenylsulfonyl)-1-tosylpyridin-2(1H)-one (*4b*)

White solid (CH_2Cl_2/hexane), mp 186–188 °C; IR (film) 3055, 2920, 2855, 1702, 1447, 1355, 1308, 1283, 1253, 1169, 1146, 1089, 812, 724, 705, 686, 654 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.90 (2H, d, J=8.3 Hz), 7.84 (2H, d, J=7.4 Hz), 7.69–7.54 (3H, m), 7.31 (2H, d, J=8.3 Hz), 7.07–7.05 (1H, m), 4.73–4.70 (2H, m), 3.14–3.11 (2H, m), 2.42 (3H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 164.2, 145.7, 137.2, 135.4, 134.8, 134.3, 129.6, 129.4, 129.0, 128.8, 128.3, 47.2, 31.7, 21.6; FABMS (relative intensity) *m/z* 392 (M^++H, 58), 155 (76), 102 (95), 91 (100), 83 (28), 81 (31), 77 (34), 71 (31), 69 (49), 67 (34), 57 (64), 55 (73), 43 (63), 41 (53); FABHRMS *m/z* 392.0658 (M^++H, calcd for $C_{18}H_{18}NO_5S_2$: 392.0626).

4.2.2. 5,6-Dihydro-4-(phenylsulfinyl)-1-tosylpyridin-2(1H)-one (*5c*)

White solid (EtOAc/hexane), mp 175–176 °C; IR (film) 3063, 2915, 2878, 1683, 1366, 1292, 1163, 1082, 688 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.90 (2H, d, J=8.2 Hz), 7.64–7.55 (5H, m), 7.33 (2H, d, J=8.2 Hz), 6.54 (1H, s), 4.09–3.99 (2H, m), 2.44–2.38 (5H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 162.0, 160.9, 145.1, 140.2, 135.1, 132.3, 129.8, 129.4, 128.4, 125.1, 122.2, 44.0, 22.1, 21.5; EIMS (relative intensity) *m/z* 375 (M^+, 0.1), 311 (51), 294 (16), 186 (30), 155 (31), 125 (12), 120 (30), 91 (100), 77 (13), 67 (18), 65 (19); HRMS *m/z* 375.0604 (calcd for $C_{18}H_{17}NO_4S_2$: 375.0599). Anal. Calcd for $C_{18}H_{17}NO_4S_2$: C, 57.58; H, 4.56; N, 3.73; S, 17.08. Found: C, 57.26; H, 4.57; N, 3.88; S, 17.02.

4.3. General procedure for the cycloaddition reaction

To a mixture of 2-pyridone **4b**, **5b**, **5c**, or **7b** (0.26 mmol) in dried toluene (3 mL) was added diene **8a** (0.78 mmol), **8b**, or

8c (1 mL). The mixture was heated in a sealed tube (see Table 2 for the reaction condition). After cooling to room temperature, the solvent was removed under vacuum and the crude product was purified by flash chromatography using ethyl acetate/hexane as eluent.

*4.3.1. 8,8a-Dihydro-2-tosylisoquinoline-3,7(1H,2H)-dione (**9**)*

Yellow solid (EtOAc), mp 192–194 °C; IR (film) 3055, 2923, 2886, 1679, 1351, 1325, 1171, 1134, 905, 710, 665 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.95 (2H, d, J=8.2 Hz), 7.34 (2H, d, J=8.2 Hz), 7.13 (1H, d, J=9.8 Hz), 6.29 (1H, d, J=9.8 Hz), 6.02 (1H, s), 4.67 (1H, dd, J=11.4, 4.8 Hz), 3.42–3.28 (2H, m), 2.81 (1H, dd, J=16.0, 5.7 Hz), 2.44 (3H, s), 2.28 (1H, dd, J=16.0, 12.6 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 195.2, 162.6, 148.1, 145.2, 141.6, 135.3, 133.3, 129.5, 128.6, 124.5, 48.6, 39.3, 32.9, 21.6; FABMS (relative intensity) *m/z* 318 (M^++H, 100), 307 (101), 154 (55), 107 (24), 91 (56), 77 (31), 57 (25); FABHRMS *m/z* 318.0800 (M^++H, calcd for $C_{16}H_{16}NO_4S$: 318.0800).

*4.3.2. 3,4-Dihydro-6-hydroxy-2-tosylisoquinolin-1(2H)-one (**10**)*

Yellow solid (CH_2Cl_2/EtOAc), mp 160–162 °C; IR (film) 3439, 1661, 1609, 1340, 1281, 1244, 1163, 1119, 1086, 706, 662 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.95 (2H, d, J=8.4 Hz), 7.84 (1H, d, J=8.7 Hz), 7.31 (2H, d, J=8.4 Hz), 6.72 (1H, dd, J=8.7, 2.1 Hz), 6.66 (1H, s), 6.22 (1H, br s), 4.19 (2H, t, J=6.3 Hz), 3.04 (2H, t, J=6.3 Hz), 2.41 (3H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 163.7, 161.0, 144.8, 142.0, 136.2, 131.7, 129.4, 128.4, 120.3, 115.1, 113.8, 44.8, 29.0, 21.6; FABMS (relative intensity) *m/z* 318 (M^++H, 100), 307 (66), 289 (42), 253 (35), 219 (19), 186 (17), 154 (100), 136 (99), 107 (63), 91 (72), 89 (52), 77 (57), 57 (31); FABHRMS *m/z* 318.0796 (M^++H) (calcd for $C_{16}H_{16}NO_4S$: 318.0800). Anal. Calcd for $C_{16}H_{15}NO_4S$: C, 60.55; H, 4.76; N, 4.41; S, 10.10. Found: C, 60.60; H, 4.85; N, 4.43; S, 10.11.

*4.3.3. 3,4,4a,5,8,8a-Hexahydro-6,7-dimethyl-4a-(phenylsulfonyl)-2-tosylisoquinolin-1(2H)-one (**11**)*

White solid (EtOAc/hexane), mp 137–138 °C; IR (film) 3115, 3032, 1702, 1549, 1422, 1265, 896, 734 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.94 (2H, d, J=8.3 Hz), 7.76 (2H, d, J=8.4 Hz), 7.67–7.63 (1H, m), 7.54 (2H, t, J=7.8 Hz), 7.32 (2H, d, J=8.3 Hz), 4.21–4.13 (2H, m), 2.84 (1H, t, J=7.5 Hz), 2.45 (3H, s), 2.48–2.25 (5H, m), 1.94 (1H, d, J=16.8 Hz), 1.52 (3H, s), 1.47 (3H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.9, 144.6, 135.4, 134.6, 134.3, 130.3, 129.1, 129.0, 128.6, 122.9, 121.2, 64.0, 43.6, 42.0, 35.9, 33.2, 24.9, 21.6, 18.7, 18.0; FABMS (relative intensity) *m/z* 474 (M^++H, 51), 332 (100), 176 (32), 155 (25), 133 (45), 91 (54), 77 (20); FABHRMS *m/z* 474.1399 (M^++H) (calcd for $C_{24}H_{28}NO_5S_2$: 474.1409). Anal. Calcd for $C_{24}H_{27}NO_5S_2$: C, 60.86; H, 5.75; N, 2.96; S, 13.54. Found: C, 60.75; H, 5.48; N, 2.95; S, 13.25.

*4.3.4. endo-4-Aza-7-benzensulfonyl-4-tosyl-tricyclo-[6.2.1.0^{2,7}]undec-9-en-3-one (**12**)*

White solid (EtOAc/hexane), mp 154–156 °C; IR (film) 3062, 2988, 2915, 1687, 1594, 1480, 1447, 1354, 1285, 1218, 1171, 1145, 901, 817, 728 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.93–7.90 (2H, m), 7.80 (2H, d, J=8.2 Hz), 7.78–7.61 (3H, m), 7.32 (2H, d, J=8.2 Hz), 6.28 (1H, dd, J=5.2, 3.0 Hz), 6.11 (1H, dd, J=5.2, 3.3 Hz), 4.19 (1H, ddd, J=13.2, 4.5, 3.0 Hz), 3.97 (1H, td, J=12.6, 2.7 Hz), 3.63 (1H, d, J=3.9 Hz), 3.50 (1H, br s), 2.97 (1H, d, J=1.5 Hz), 2.45–2.35 (5H, m), 1.73 (1H, ddd, J=16.8, 12.3, 4.8 Hz), 1.43 (1H, d, J=6.2 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.4, 145.0, 140.6, 137.1, 136.1, 135.6, 134.4, 130.0, 129.5, 129.4, 128.5, 73.1, 51.1, 48.0, 47.3, 46.2, 43.3, 29.4, 21.7; EIMS (relative intensity) *m/z* 457 (M^+, 0.1), 393 (81), 327 (44), 316 (63), 252 (94), 185 (58), 155 (61), 133 (49), 105 (44), 91 (100), 77 (62), 66 (60); HRMS *m/z* 457.1023 (calcd for $C_{23}H_{23}NO_5S_2$ *m/z* 457.1018). Anal. Calcd for $C_{23}H_{23}NO_5S_2$: C, 60.37; H, 5.07; N, 3.06. Found: C, 60.28; H, 5.04; N, 2.90.

*4.3.5. 6-Hydroxy-2-tosylisoquinolin-1(2H)-one (**13**)*

White solid (CH_2Cl_2/EtOAc), mp 222–224 °C; IR (film) 3446, 1646, 1359, 1171, 673 cm^{-1}; ^1H NMR (acetone-d_6, 300 MHz) δ 9.12 (1H, s), 8.02 (2H, d, J=8.2 Hz), 7.80 (1H, d, J=8.1 Hz), 7.59 (1H, d, J=2.7 Hz), 7.56 (1H, d, J=8.1 Hz), 7.46 (2H, d, J=8.2 Hz), 7.29 (1H, dd, J=8.7, 2.7 Hz), 6.69 (1H, d, J=8.1 Hz), 2.44 (3H, s); ^{13}C NMR (acetone-d_6, 75 MHz) δ 160.5, 158.4, 146.8, 135.8, 130.5, 130.4, 130.3, 129.4, 128.8, 124.3, 123.5, 112.5, 108.0, 21.6; FABMS (relative intensity) *m/z* 316 (M^++H, 100), 307 (18), 251 (59), 161 (48), 154 (82), 136 (76), 107 (30), 91 (53), 77 (34), 57 (20); HRMS *m/z* 316.0652 (M^++H) (calcd for $C_{16}H_{14}NO_4S$: 316.0644). Anal. Calcd for $C_{16}H_{13}NO_4S$: C, 60.94; H, 4.16; N, 4.44; S, 10.17. Found: C, 61.14; H, 4.04; N, 4.36; S, 9.81.

*4.3.6. 5,8-Dihydro-6,7-dimethyl-2-tosylisoquinolin-1(2H)-one (**14**)*

White solid (EtOAc/hexane), mp 210–211 °C; IR (film) 3054, 2987, 1664, 1422, 1366, 1256, 1176, 896 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.98 (2H, d, J=8.2 Hz), 7.91 (1H, d, J=7.8 Hz), 7.33 (2H, d, J=8.2 Hz), 6.04 (1H, d, J=7.8 Hz), 3.08 (2H, t, J=6.3 Hz), 2.93 (2H, t, J=6.3 Hz), 2.43 (3H, s), 1.67 (6H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 159.6, 146.6, 145.7, 133.9, 129.7, 129.4, 127.6, 126.9, 123.5, 120.6, 107.7, 36.6, 30.9, 21.7, 18.2, 17.9; FABMS (relative intensity) *m/z* 330 (M^++H, 100), 264 (25), 174 (55), 154 (63), 136 (58), 107 (30), 91 (50), 69 (49), 55 (42); FABHRMS *m/z* 330.1158 (M^++H) (calcd for $C_{18}H_{20}NO_3S$: 330.1164).

*4.3.7. endo-8-Aza-10-benzenesulfonyl-8-tosyl-tricyclo-[5.2.2.0^{2,6}]undec-4,10-dien-9-one (**15a**)*

White solid (CH_2Cl_2/EtOAc), mp 200–202 °C; IR (film) 3063, 2930, 2856, 1731, 1594, 1451, 1362, 1351, 1317, 1307, 1171, 1156, 1093, 747, 673 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.74 (2H, d, J=8.1 Hz), 7.62–7.57 (3H, m), 7.41 (2H, t, J=7.8 Hz), 7.27 (2H, d, J=8.1 Hz), 7.21 (1H, dd, J=6.3, 2.1 Hz), 5.53 (1H, dd, J=6.0, 3.6 Hz), 5.45 (1H,

dd, J=5.4, 2.1 Hz), 3.62–3.59 (2H, m), 2.90–2.81 (1H, m), 2.58–2.46 (4H, m), 2.16–2.10 (1H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 167.8, 145.1, 142.9, 139.9, 138.1, 136.7, 135.2, 134.0, 129.6, 129.4, 127.9, 127.8, 127.1, 55.8, 54.4, 50.7, 36.8, 35.3, 21.7; FABMS (relative intensity) *m/z* 456 (M^++H, 46), 447 (23), 391 (18), 327 (17), 299 (38), 289 (25), 265 (24), 207 (23), 154 (94), 149 (100), 105 (58), 57 (84); FABHRMS *m/z* 456.0941 (M^++H) (calcd for $C_{23}H_{22}NO_5S_2$: 456.0939). Anal. Calcd for $C_{23}H_{21}NO_5S_2$: C, 60.64; H, 4.65; N, 3.07; S, 14.08. Found: C, 60.69; H, 4.44; N, 2.88; S, 14.28.

*4.3.8. endo-8-Aza-10-benzenesulfonyl-8-tosyl-tricyclo-[5.2.2.0^{2,6}]undec-3,10-dien-9-one (**15b**)*

White solid (CH_2Cl_2/EtOAc), mp 186–187 °C; IR (film) 3063, 2923, 2849, 1727, 1359, 1322, 1171, 1156, 1089, 909, 735, 669 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.77 (2H, d, J=8.4 Hz), 7.67–7.58 (3H, m), 7.44 (2H, dt, J=7.8, 1.5 Hz), 7.27 (2H, d, J=8.4 Hz), 7.22 (1H, dd, J=6.0, 2.4 Hz), 5.54–5.49 (2H, m), 5.10 (1H, dd, J=5.5, 2.2 Hz), 3.66 (1H, dd, J=2.7, 2.4 Hz), 3.33–3.29 (1H, m), 3.16–3.08 (1H, m), 2.57–2.46 (4H, m), 1.93–1.84 (1H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 167.9, 145.9, 145.2, 138.1, 136.9, 135.3, 134.0, 133.0, 129.6, 129.3, 129.1, 128.2, 127.9, 56.2, 49.5, 48.2, 42.0, 35.5, 21.7; FABMS (relative intensity) *m/z* 456 (M^++H, 82), 447 (34), 425 (22), 390 (92), 383 (25), 327 (34), 307 (69), 299 (66), 289 (62), 265 (29), 219 (35), 205 (28), 183 (46), 165 (64), 154 (100), 149 (100), 137 (100); FABHRMS *m/z* 456.0947 (M^++H) (calcd for $C_{23}H_{22}NO_5S_2$: 456.0939).

*4.3.9. endo-4-Aza-7-benzensulfonyl-4-tosyl-tricyclo-[6.2.1.0^{2,7}]undec-5,9-dien-3-one (**16**)*

White solid (CH_2Cl_2/EtOAc), mp 145–146 °C; IR (film) 3070, 2952, 1705, 1362, 1285, 1174, 1148, 1085, 735, 665 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.76–7.73 (2H, m), 7.57–7.38 (3H, m), 7.41 (2H, t, J=7.8 Hz), 7.27 (2H, d, J=8.4 Hz), 6.72 (1H, d, J=8.7 Hz), 6.20 (1H, dd, J=5.5, 3.3 Hz), 6.08 (1H, dd, J=5.5, 2.7 Hz), 5.20 (1H, d, J=8.7 Hz), 3.77 (1H, d, J=1.5 Hz), 3.55 (1H, d, J=3.3 Hz), 3.49 (1H, br s), 2.46 (3H, s), 2.39 (1H, d, J=9.3 Hz), 1.87 (1H, d, J=9.3 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.5, 145.4, 138.8, 137.1, 136.7, 134.5, 133.8, 129.5, 129.4, 128.8, 128.4, 125.6, 104.4, 73.6, 51.2, 50.5, 49.5, 46.1, 21.7; FABMS (relative intensity) *m/z* 456 (M^++H, 82), 390 (37), 314 (100), 155 (29), 91 (28), 77 (11); FABHRMS *m/z* 456.0931 (M^++H) (calcd for $C_{23}H_{22}NO_5S_2$: 456.0939).

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Supplementary data

A PDF file containing the X-ray crystal structures of compounds **11–16** is provided. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2007.11.090.

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