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[4+2] Cycloaddition reactions of 4-sulfur-substituted 2-pyridones with electron-deficient dienophiles

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ABSTRACT

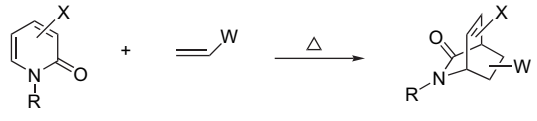
[4+2] Cycloaddition reactions of 4-(phenylthio)-1-tosyl-2-pyridone (**6a**) and 4-(phenylsulfonyl)-1-tosyl-2-pyridone (**6b**) with electron-deficient dienophiles **7** (*N*-methylmaleimide, *N*-phenylmaleimide, and methyl acrylate) gave new isoquinuclidine products **8**–**10**. The *N*-tosyl group of **6a** and **6b** was also efficiently converted to *N*-alkyl derivatives **6c**–**f**, which showed different stereoselectivity toward reactions with dienophiles **7**. Several other dienophiles **15** (dimethyl acetylenedicarboxylate, methyl vinyl ketone, ethyl vinyl ether, and methyl methacrylate) were found not to react with **6a** or **6b**, but led to the formation of tosyl migration products 4-(phenylthio)-*O*-tosyl-pyridinol (**16a**) and 4-(phenylsulfonyl)-*O*-tosyl-2-pyridinol (**16b**), respectively. The reactivity, regioselectivity, and stereoselectivity of the cycloaddition reactions were also compared with semi-empirical calculations.

1. Introduction

The synthesis of 2-pyridone ring is an area of continuing interest[1] because many compounds of this structure (such as camptothecin, Fredericamycin A, pyridoxatin, huperzine A, etc.) posses important biological activities.[2–7] 2-Pyridones can also be used as starting materials for synthesizing more complex molecules. For example, 2-pyridones (**1**) are often used as dienes in the Diels–Alder reaction.[8] The isoquinuclidine products (**2**) are valuable intermediates for the synthesis of alkaloids[9–11] and in medicinal chemistry.[12]

From literature survey of the use of 2-pyridones as dienes in the Diels–Alder reaction, we find several generalizations: (1) *N*-Unsubstituted 2-pyridones usually undergo Michael-type addition to the dienophile, instead of cycloaddition reactions.[13–15] (2) Most studies have used *N*-alkyl-substituted 2-pyridones as the diene,[16–23] and the reaction yields are in general quite low. (3) *N*-Acyl groups cannot be used for the Diels–Alder reaction because of facile acyl migration to yield 2-acyloxypyridines.[24,25] (4) Substituents on the 2-pyridone ring can affect significantly the reactivity, regioselectivity, and stereoselectivity of the cycloaddition.[23,26–34] (5) *N*-Sulfonylated 2-pyridones show greater reactivity and regiocontrol over *N*-alkyl analogues.[35–37] (6) High pressure can sometimes increase the yields of the cycloaddition reactions, but may also decrease the stereoselectivity.[38]

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,[39,40] and have studied some of their synthetic applications.[41–45] Since the only two literature reports with C-4 substituents (**1**, X=Ph, CO_2Me, COMe; R=Me)[27,30] gave good yields of cycloaddition products with dienophiles, we would also like to study the cycloaddition reactions of 4-sulfide- and sulfone-substituted 2-pyridones (**1**, X=PhS, $PhSO_2$; R=Ts, alkyl) with some electron-deficient dienophiles. The reactivity, regioselectivity, and stereoselectivity of the cycloaddition reactions will be compared with semi-empirical calculations.



1 2

2. Results and discussion

Reaction of 3-(phenylthio)-3-sulfolene (**3**)[46,47] with *p*-toluenesulfonyl isocyanate (PTSI) in tolune at 110 °C in the presence of 1 equiv of sodium bicarbonate and a catalytic amount of hydroquinone (HQ) gave the [4+2] cyclization product **4**, which was directly treated with *N*-bromosuccinimide (NBS). The bromo intermediate **5** upon further reaction with pyrrolidine in DMF resulted in the formation of 2-pyridone **6a**.[43] The overall yield of this three-step sequence was 43%. Oxidation of **6a** with *m*CPBA gave the corresponding sulfone **6b** in excellent yield.[40]

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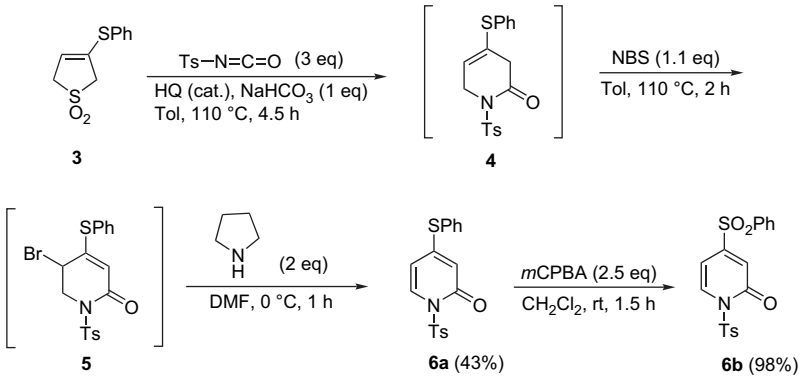
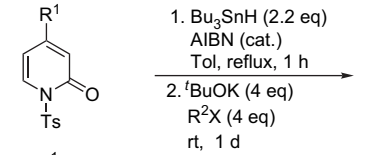


Using Parson's method of cleaving the *N*-tosyl group of amides with Bu_3SnH/AIBN,[48] followed by treatment with *t*-BuOK/RX,[40] 2-pyridones **6a** and **6b** were converted to the alkyl-substituted derivatives **6c–f** in very good yields.



6a, R^1 = SPh
6b, R^1 = SO_2Ph

6c, R^1 = SPh, R^2 = CH_3 (100%)
6d, R^1 = SPh, R^2 = Bn (89%)
6e, R^1 = SO_2Ph, R^2 = CH_3 (95%)
6f, R^1 = SO_2Ph, R^2 = Bn (100%)

Having prepared the 2-pyridones **6a–f** efficiently, we then studied their cycloaddition reactions with some electron-deficient dienophiles: *N*-methylmaleimide (**7a**), *N*-phenylmaleimide (**7b**), and methyl acrylate (**7c**). The cycloaddition reactions were carried out in sealed tubes using toluene as the solvent, and the results are shown in Table 1. After a few trials of the reaction conditions, it was found that thermolysis of sulfide-substituted 2-pyridone **6a** with dienophiles **7a** and **7b** proceeded well at 150 °C for 2 d (entries 1 and 2) to give cycloaddition products **8a** and **9a**, respectively, in good yields. The X-ray structure of **9a** (Fig. 1)[49] clearly showed that it is the *endo* addition product (C=O of the imide group cis to the C=C) and has the cis ring junction. Since compounds **8a** and **9a** have similar splitting patterns in their ^1H NMR spectra, compound **8a** is also assumed to be the *endo* addition product. The reactions of sulfone-substituted 2-pyridone **6b** with dienophiles **7a** and **7b** also proceeded at 150 °C (entries 4 and 5) to give the corresponding products **8b** and **9b**. The X-ray structure of compound **8b** (Fig. 2)[49]

Table 1
Cycloaddition reactions of 2-pyridones **6a–f** with dienophiles **7**

Entry	Pyridone	Dienophile[a]	Conditions[b]	Product (% yield)
1	**6a**	**7a**	150 °C, 2 d	**8a** (69)
2	**6a**	**7b**	150 °C, 2 d	**9a** (66)
3	**6a**	**7c**	BHT (cat.), 150 °C, 2 d	**10a** (28)
4	**6b**	**7a**	150 °C, 2 d	**8b** (50)
5	**6b**	**7b**	100 °C, 1 d; 150 °C, 1.5 d	**9b** (44)
6	**6b**	**7c**	BHT (cat.), 150 °C, 44 h	**10b** (53), **10c** (7)[c]
7	**6c**	**7b**	150 °C, 2 d	**11a** (52), **11b** (23)
8	**6d**	**7b**	150 °C, 2 d	**12a** (55), **12b** (14)
9	**6e**	**7b**	150 °C, 2 d	**13** (20)[d]
10	**6f**	**7b**	150 °C, 2 d	**14a** (21), **14b** (33)

[a] Dienophiles **7a** and **7b** were used in 10 equiv, and **7c** was used in 20 equiv.
[b] All reactions were carried out in a sealed tube, using toluene as the solvent.
[c] 4-(Phenylsulfonyl)-*O*-tosyl-2-pyridone (**16b**) was also obtained in 33%.
[d] The unreacted **6e** was also obtained in 29%.

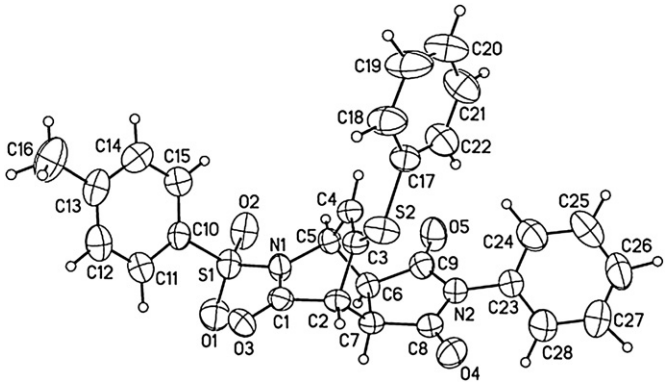


Figure 1. X-ray structure of compound **9a**.

also shows that it is the *endo* addition product. The reaction yields for **8b** and **9b** were about 20% lower than those for **8a** and **9a**. This might be due to the reactivity difference of **6a** and **6b**; the sulfide substituent in **6a** is an electron-donating group, whereas the sulfone substituent in **6b** is an electron-withdrawing group. On the other hand, the lower reactivity of **6b** may not necessarily lead to a lower yield of the cycloaddition products than **6a**, as we shall see in their reactions with methyl acrylate (**7c**).

The reaction of **6a** with **7c** in toluene at 150 °C for 2 d in the presence of a small amount of butylated hydroxytoluene (BHT) to retard the polymerization of methyl acrylate (entry 3) gave the cycloaddition product **10a** regio- and stereospecifically, albeit in low yield. Similar reaction of **6b** with **7c** (entry 6) gave a good yield of *endo* product **10b** and a small amount of *exo* product **10c**,

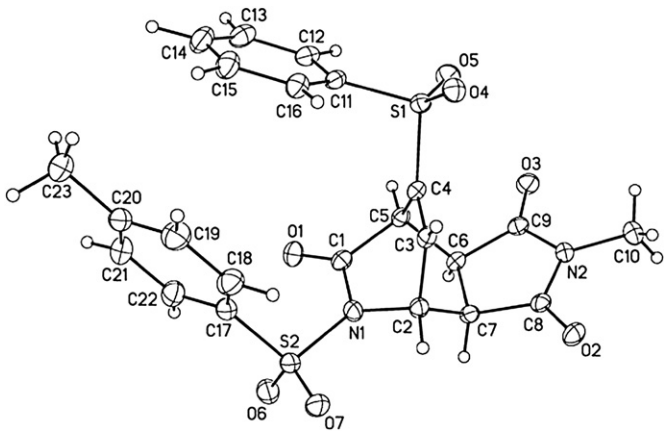


Figure 2. X-ray structure of compound **8b**.

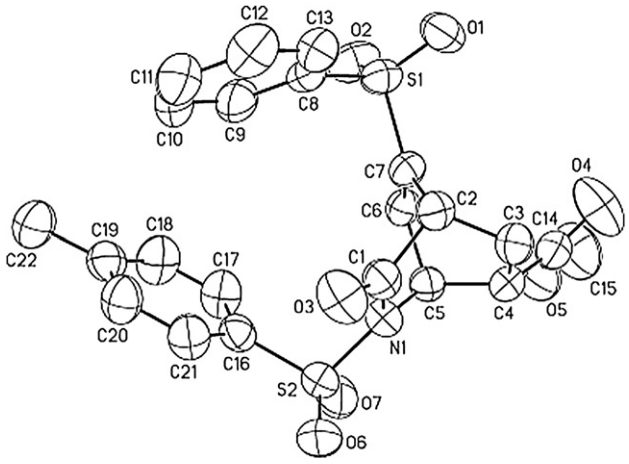
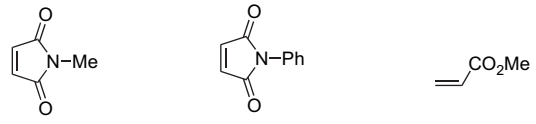


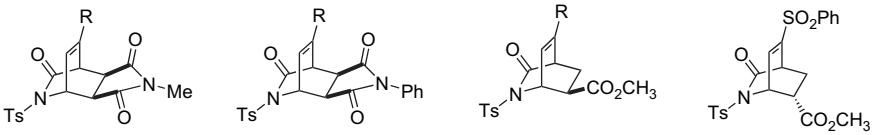
Figure 3. X-ray structure of compound **10b**.

together with some tosyl migration product **16b**. The X-ray structure of compound **10b** is shown in Figure 3,[49] which clearly shows its regiochemistry and *endo* configuration. Some important ^{1}H NMR data for compounds **10a**, **10b**, and **10c** are shown in Figure 4. Since compounds **10b** and **10c** have similar chemical shifts for H-4 and H-5, we propose that they are stereoisomers, not regioisomers. The most significant spectral difference between the *endo* and *exo* products **10b** and **10c** is the coupling constant between H-3 and H-5 ($J_{3,5}$=3.3 Hz for **10b**, $J_{3,5}$=1.8 Hz for **10c**). Compound **10a** also has $J_{3,5}$=3.3 Hz, indicating its *endo* structure. Similar observations that the *endo* isomer has larger coupling constant than the *exo* isomer have been made in the literature.[18,29] As compared to the literature results (**1**, R=Ts, X=H: 10% yield of two *endo* isomeric products, 0.6:1),[37] the presence of 4-phenylthio group in **6a** or 4-phenylsulfonyl group in **6b** significantly increases the yields and regioselectivity of the cycloaddition reaction with methyl acrylate (**7c**).

Reaction of *N*-methylated 2-pyridone **6c** with **7b** at 150 °C for 2 d (entry 7) gave good yields of the cycloaddition products **11a** and **11b**, which were separated by flash chromatography. The stereochemistry of **11a** and **11b** was established by comparing the coupling constant between H-6 and H-7 ($J_{6,7}$=4.2 Hz for **11a**, $J_{6,7}$=2.7 Hz for **11b**). Thus, in agreement with the literature observations[18,29] as well as the coupling constants for *endo* and *exo* products **10b** and **10c**, the major product **11a** was assigned the *endo* isomer, and the minor product **11b** the *exo* isomer. Reaction of *N*-benzylated 2-pyridone **6d** with **7b** at 150 °C for 2 d (entry 8) also gave a mixture of the cycloaddition products **12a** and **12b**. Stereochemical assignment is similar to that for **11a** and **11b**. The reaction of **6e** with **7b** (entry 9) gave a low yield of the *endo* product **13** together with some unreacted **6e**, whereas a similar reaction of **6f** with **7b** (entry 10) led to a mixture of the *endo* product **14a** and the *exo* product **14b**. It is rather surprising to find that the major product is **14b**. Presumably, the steric repulsion between the *N*-phenyl group with the phenylsulfonyl group in forming the *endo* product **14a** outweighs the electronic effect. From the reactions of 2-pyridones **6c–f** with **7b** (entries 7–10) it is quite obvious that substitution of the *N*-tosyl group of 2-pyridones **6a** and **6b** for an alkyl group (methyl or benzyl) led to the formation of both *endo* and *exo* cycloaddition products. This complements with the literature findings that *N*-sulfonylated 2-pyridones show greater reactivity and regiocontrol over their *N*-alkyl analogues.[35–37] We can further add that *N*-sulfonylated 2-pyridones also increase the preference for *endo* addition products over their *N*-alkyl analogues.



7a **7b** **7c**

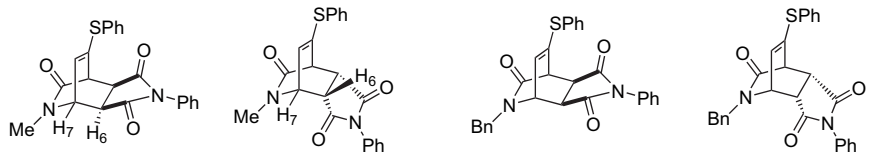


8a, R = SPh
8b, R = SO_2Ph

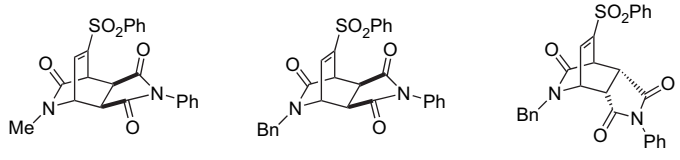
9a, R =SPh
9b, R = SO_2Ph

10a, R = SPh
10b, R = SO_2Ph

10c



11a **11b** **12a** **12b**



13 **14a** **14b**

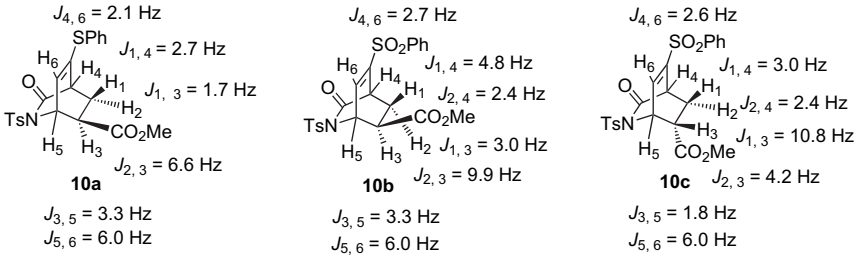
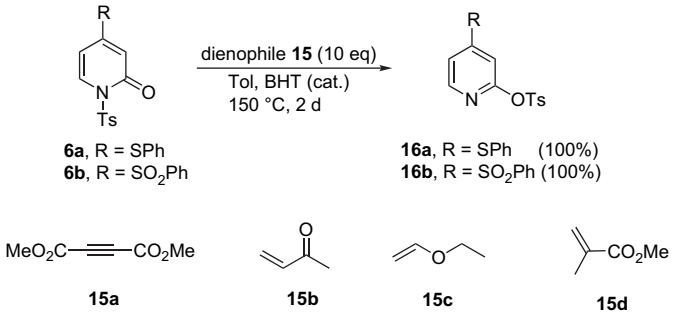


Figure 4. Some ^{1}H NMR coupling constants for compounds **10a**, **10b**, and **10c**.

We have also carried out thermolysis of 2-pyridones **6a** and **6b** with other dienophiles: dimethyl acetylenedicarboxylate (**15a**), methyl vinyl ketone (**15b**), ethyl vinyl ether (**15c**), and methyl methacrylate (**15d**), but have only obtained quantitatively the corresponding tosyl migration products **16a** and **16b**. Apparently these dienophiles **15** are less reactive (or more easily decomposed under the reaction conditions) than compounds **7**, so that the tosyl migration reaction dominates.



In order to explain the reactivity of dienes **6a–f** as well as the regioselectivity and stereoselectivity of the cycloaddition reactions, we have used a semi-empirical 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 2. Using *N*-phenylmaleimide (**7b**) as the dienophile, it is predicted from the ΔE values that the reactivity of the dienes would follow the order: **6c**, **6d**>**6a**>**6e**, **6f**>**6b**. It is quite understandable that *N*-alkyl groups in **6c** and **6d**, as compared to *N*-tosyl group in **6a**, would increase the electron density and thus the reactivity of 2-pyridones. On the other hand, 4-phenylthio group in **6a** would be a much better electron-donating group than 4-phenylsulfonyl group in **6b** so that the reactivity of **6a** would be greater than that of **6b**. The reactivity of the dienophiles would be: **7b**>**7a**>**7c**.

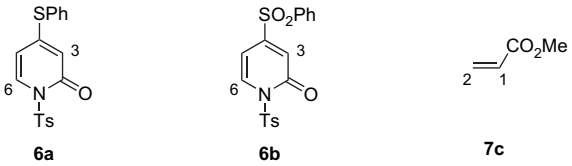
Table 2
Favorable $HOMO_{diene}$–$LUMO_{dienophile}$ energy difference ΔE calculated by HyperChem PM3 method

Entry	Diene	Dienophile	ΔE (eV)
1	**6a**	**7a**	7.66
2	**6a**	**7b**	7.53
3	**6a**	**7c**	8.76
4	**6b**	**7a**	8.27
5	**6b**	**7b**	7.92
6	**6b**	**7c**	9.36
7	**6c**	**7b**	7.37
8	**6d**	**7b**	7.38
9	**6e**	**7b**	7.78
10	**6f**	**7b**	7.84

In order to explain the regioselectivity of the cycloaddition reactions of 2-pyridones **6a** and **6b** with dienophile **7c**, we have calculated the LUMO-coefficients of dienophile **7c** and the HOMO-coefficients of dienes **6a** and **6b** (Table 3). The C-2 of methyl acrylate (**7c**) has a larger LUMO-coefficient than that at C-1, and the C-3 of **6a** and **6b** has a larger HOMO-coefficient than that at C-6. Thus, we expect that the C-2 of **7c** would be connected with the C-3 of **6a** and **6b** in the cycloaddition reaction. Indeed, the formation of **10a** from **6a**, as well as the formation of **10b** and **10c** from **6b**, agrees with this prediction.

To explain the stereoselectivity of the cycloaddition reaction, we have calculated the heat of formation (ΔH_f) for *endo* and *exo* products (Table 4). It can be seen that the *endo* products **10b**, **11a**, **12a**, and **14a** are all more stable than the corresponding *exo* products **10c**, **11b**, **12b**, and **14b**. Except for the formation of products **14**, the *endo* isomer is the major product in all the other cases. Shusherina and co-workers showed that for the reactions of 1-alkyl-3-methyl-2-pyridone with *N*-phenylmaleimide, the *endo* cycloadduct obtained at lower temperature was the kinetic product, and the *exo* cycloadduct obtained at higher temperature was the thermodynamic product.[50] It was also emphasized that the

Table 3
HOMO-coefficients of dienes **6a**, **6b**, and LUMO-coefficients of dienophile **7c**



Diene	HOMO-coefficients	
	C-3	C-6
6a	0.1913	0.0348
6b	0.1358	0.1284

Dienophile	LUMO-coefficients	
	C-1	C-2
7c	0.1657	0.2171

Table 4
Calculated heat of formation (ΔH_f) for cycloaddition products

Compound	ΔH_f (kcal/mol)
10b	−96.062
10c	−95.452
11a	−3.932
11b	−3.520
12a	17.506
12b	20.523
14a	−44.513
14b	−38.597

presence of a substituent at the ends of the conjugated system of 2-pyridone (the 3-methyl group in this case) was essential for obtaining the *exo* product. In our present studies, although there are no substituents at the ends of the conjugated system of 2-pyridones **6**, we still obtained both the *endo* and *exo* products for the reactions of *N*-phenylmaleimide with *N*-alkyl derivatives **6c**,**d**,**f**. On the other hand, only the *endo* products **9a** and **9b** were obtained from the *N*-tosyl analogues **6a** and **6b**.

3. Conclusion

We have studied the [4+2] cycloaddition reactions of 4-(phenylthio)-1-tosyl-2-pyridone (**6a**) and 4-(phenylsulfonyl)-1-tosyl-2-pyridone (**6b**) with electron-deficient dienophiles **7** (*N*-methylmaleimide, *N*-phenylmaleimide, and methyl acrylate) to give new isoquinuclidine products **8**–**10**. The yields obtained from **6a** were higher than those from **6b**, indicating the activating ability of the sulfide group as compared to the sulfone group. The *N*-tosyl group of **6a** and **6b** was also efficiently converted to the *N*-alkyl derivatives **6c**–**f**, which showed different stereoselectivity in their reactions with dienophiles **7**. Several other dienophiles **15** (dimethyl acetylenedicarboxylate, methyl vinyl ketone, ethyl vinyl ether, and methyl methacrylate) were found not to react with **6a** or **6b**, but led to the formation of tosyl migration products 4-(phenylthio)-*O*-tosyl-pyridinol (**16a**) and 4-(phenylsulfonyl)-*O*-tosyl-2-pyridinol (**16b**), respectively. The reactivity, regioselectivity, and stereoselectivity of the cycloaddition reactions were compared with semi-empirical 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, using $CDCl_3$ as solvent. 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 JEOL JMS-SX102A. Flash column chromatographic purifications were performed using Merck 60H silica gel.

4.2. General procedure for preparation of 6c–f from 6a and 6b

To a solution of compound **6a** or **6b** (0.28 mmol) and AIBN (0.06 mmol) in degassed toluene (5 mL) was added Bu_3SnH (0.17 mL, 0.62 mmol). The mixture was heated at reflux under nitrogen for 2 h. During this period another two portions of AIBN (0.06 mmol each) in toluene (5 mL) were added in 30 min interval. The reaction mixture is cooled to room temperature. Then alkyl halide (1.12 mmol) and *t*-BuOK (1.12 mmol) were added sequentially. After stirring at room temperature for 1.5 h (checked by TLC), the solvent was removed under vacuum and the crude product was purified by flash chromatography using ethyl acetate/hexane (1:2 to 1:1) with 5–10% of Et_3N as eluent to give the product **6c**–**f**.

4.2.1. *N-Methyl-4-(phenylthio)-2-pyridone (**6c**)*

Light yellow solid, mp 126–127 °C; IR (KBr) 3071, 1650, 1589, 1511, 1474, 1440, 1409, 1330, 1305, 1244, 1182, 1038, 934, 845, 752, 707, 692 cm^{-1}; ^{1}H NMR δ 3.54 (3H, s), 5.98 (1H, dd, J=1.8, 7.2 Hz), 6.03 (1H, d, J=1.8 Hz), 7.13 (1H, d, J=7.2 Hz), 7.42–7.54 (5H, m); ^{13}C NMR δ 37.0, 105.1, 113.8, 128.7, 129.88, 129.91, 135.4, 137.2, 154.2, 162.0; HRMS m/z 217.0556 (calcd for $C_{12}H_{11}NOS$: 217.0561).

4.2.2. *N-Benzyl-4-(phenylthio)-2-pyridone (**6d**)*

Light yellow liquid; IR (neat) 3061, 1652, 1592, 1513, 1495, 1474, 1455, 1440, 1360, 1305, 1244, 1160, 1118, 1073, 1047, 1025, 957, 929, 847, 750, 735, 693 cm^{-1}; ^{1}H NMR δ 5.04 (2H, s), 5.94 (1H, dd, J=2.0, 7.2 Hz), 6.06 (1H, d, J=2.0 Hz), 7.07 (1H, d, J=7.2 Hz), 7.24–7.44 (8H, m), 7.51–7.54 (2H, m); ^{13}C NMR δ 51.3, 105.3, 114.1, 128.0, 128.1, 128.6, 128.9, 129.9, 130.0, 135.6, 136.1, 136.4, 154.1, 161.5; HRMS m/z 293.0867 (calcd for $C_{18}H_{15}NOS$: 293.0874).

4.2.3. *N-Methyl-4-(phenylsulfonyl)-2-pyridone (**6e**)*

Yellow solid, mp 133–135 °C; IR (KBr) 3071, 2926, 1656, 1591, 1536, 1477, 1448, 1408, 1320, 1164, 1138, 1087, 1062, 997, 866, 782, 756, 731, 685, 647 cm^{-1}; ^{1}H NMR δ 3.53 (3H, s), 6.50 (1H, dd, J=2.1, 7.2 Hz), 7.08 (1H, d, J=2.1 Hz), 7.40 (1H, d, J=7.2 Hz), 7.56–7.66 (3H, m), 7.93–7.96 (2H, m); ^{13}C NMR δ 37.9, 101.6, 119.9, 128.3, 129.6, 134.3, 139.0, 140.4, 152.4, 161.7; HRMS m/z 249.0462 (calcd for $C_{12}H_{11}NO_3S$: 249.0460).

4.2.4. *N-Benzyl-4-(phenylsulfonyl)-2-pyridone (**6f**)*

Yellow solid, mp 155–157 °C; IR (KBr) 3070, 2930, 1661, 1593, 1536, 1446, 1323, 1163, 1085, 727, 688, 645 cm^{-1}; ^{1}H NMR δ 5.09 (2H, s), 6.47 (1H, dd, J=1.8, 7.2 Hz), 7.10 (1H, d, J=1.8 Hz), 7.25–7.35 (3H, m), 7.37 (1H, d, J=7.2 Hz), 7.53–7.66 (5H, m), 7.92–7.96 (2H, m); ^{13}C NMR δ 52.4, 101.9, 120.4, 128.36, 128.40, 128.5, 129.1, 129.6, 134.4, 135.1, 139.3, 152.2, 161.3, 170.2; HRMS m/z 325.0772 (calcd for $C_{18}H_{15}NO_3S$: 325.0773).

4.3. General procedure for cycloaddition reactions of 2-pyridones 6 with dienophiles 7 or 15

A mixture of 2-pyridone **6** (0.28 mmol) and dienophile **7** or **15** (2.8 mmol for **7a** or **7b**; 5.6 mmol for **7c** together with 20 mg of BHT; 2.8 mmol for **15** together with 20 mg of BHT) in dried toluene (5 mL) was heated in a sealed tube at an appropriate temperature for a period of time (Table 1). The solvent was then removed under vacuum, and the crude product was purified by flash chromatography using ethyl acetate/hexane as eluent to give the product.

4.3.1. *endo-4-Methyl-10-(phenylthio)-8-tosyl-4,8-diaza-tricyclo[5.2.2.0^{2,6}]undec-10-ene-3,5,9-trione (**8a**)*

White solid, mp 150–151 °C (decomp.); IR (KBr) 3072, 2947, 1782, 1732, 1705, 1597, 1435, 1359, 1280, 1244, 1171, 1092, 1023, 990, 968, 904, 813, 754, 691, 661 cm^{-1}; ^{1}H NMR δ 2.46 (3H, s), 2.95–3.00 (4H, m), 3.32 (1H, dd, J=3.3, 8.1 Hz), 3.55 (1H, dd, J=3.3, 8.1 Hz), 3.77 (1H, dd, J=0.8, 3.3 Hz), 5.62–5.65 (2H, m), 7.15 (2H, d, J=8.1 Hz), 7.31–7.40 (5H, m), 7.84 (2H, d, J=8.1 Hz); ^{13}C NMR δ 21.7, 25.1, 39.6, 47.6, 51.0, 54.3, 120.5, 128.0, 128.3, 128.5, 129.7, 129.8, 134.1, 134.9, 141.3, 145.6, 167.1, 173.4, 173.8; HRMS m/z 468.0814 (calcd for $C_{23}H_{20}N_2O_5S_2$: 468.0814).

4.3.2. *endo-4-Methyl-10-(phenylsulfonyl)-8-tosyl-4,8-diaza-tricyclo[5.2.2.0^{2,6}]undec-10-ene-3,5,9-trione (**8b**)*

White solid, mp 230–232 °C (decomp.); IR (KBr) 3065, 2906, 1783, 1704, 1596, 1440, 1383, 1308, 1156, 1089, 1017, 970, 900, 814, 733, 688, 662 cm^{-1}; ^{1}H NMR δ 2.47 (3H, s), 2.73 (3H, s), 3.30 (1H, dd, J=2.7, 8.1 Hz), 3.69 (1H, dd, J=4.5, 8.1 Hz), 4.08 (1H, dd, J=2.7, 4.8 Hz), 5.96 (1H, dd, J=4.5, 5.7 Hz), 7.30–7.80 (10H, m); ^{13}C NMR δ 21.8, 25.3, 39.2, 46.6, 46.9, 53.1, 128.2, 128.5, 129.8, 130.0, 134.5, 134.8, 137.1, 137.6, 145.2, 146.2, 165.4, 172.0, 172.8; HRMS m/z 500.0711 (calcd for $C_{23}H_{20}N_2O_7S_2$: 500.0712).

4.3.3. *endo-4-Phenyl-10-(phenylthio)-8-tosyl-4,8-diaza-tricyclo[5.2.2.0^{2,6}]undec-10-ene-3,5,9-trione (**9a**)*

White solid, mp 206–207 °C; IR (KBr) 3030, 2930, 1716, 1596, 1498, 1379, 1172, 1090, 984, 906, 752, 691, 661, 635 cm^{-1}; ^{1}H NMR δ 2.47 (3H, s), 3.43 (1H, dd, J=3.3, 8.1 Hz), 3.69 (1H, dd, J=3.9,

8.1 Hz), 3.88 (1H, dd, *J*=2.0, 3.3 Hz), 5.72–5.80 (2H, m), 7.17–7.53 (12H, m), 7.78 (2H, d, *J*=8.4 Hz); ^{13}C NMR δ 21.8, 39.6, 47.8, 51.3, 54.6, 120.4, 126.2, 128.2, 128.4, 129.2, 129.4, 129.8, 130.0, 130.1, 131.2, 134.5, 135.2, 141.7, 145.7, 167.2, 172.6, 172.8; HRMS *m*/*z* 530.0969 (calcd for $C_{28}H_{22}N_2O_5S_2$: 530.0970).

4.3.4. *endo*-4-Phenyl-10-(phenylsulfonyl)-8-tosyl-4,8-diaza-tricyclo[5.2.2.0^{2,6}]undec-10-ene-3,5,9-trione (**9b**)

White solid, mp 266–267 °C; IR (KBr) 3052, 2930, 1719, 1596, 1498, 1380, 1308, 1173, 1090, 906, 747, 688, 662, 640 cm^{-1}; ^{1}H NMR δ 2.49 (3H, s), 3.42 (1H, dd, *J*=3.0, 8.4 Hz), 3.85 (1H, dd, *J*=4.7, 8.4 Hz), 4.12 (1H, dd, *J*=2.1, 3.0 Hz), 6.05 (1H, dd, *J*=4.7, 5.7 Hz), 7.19–7.60 (13H, m), 7.80 (2H, d, *J*=8.4 Hz); ^{13}C NMR δ 21.9, 39.1, 46.6, 47.2, 53.4, 126.2, 128.2, 128.4, 129.4, 129.5, 129.8, 129.9, 130.0, 130.4, 133.9, 134.5, 134.8, 137.4, 146.2, 165.4, 171.1, 171.9; HRMS *m*/*z* 562.0863 (calcd for $C_{28}H_{22}N_2O_7S_2$: 562.0868).

4.3.5. *endo*-Methyl 3-oxo-8-(phenylthio)-2-tosyl-2-aza-bicyclo[2.2.2]oct-7-ene-6-carboxylate (**10a**)

White solid, mp 136–138 °C; IR (KBr) 3106, 2942, 2868, 2810, 1631, 1615, 1510, 1474, 1456, 1437, 1243, 1120, 1067, 1025, 988, 916, 856, 777, 748, 706, 687 cm^{-1}; ^{1}H NMR δ 2.09–2.13 (2H, m), 2.44 (3H, s), 3.25 (1H, ddd, *J*=1.7, 3.3, 6.6 Hz), 3.30 (1H, dd, *J*=2.1, 2.7 Hz), 3.70 (3H, s), 5.61 (1H, dd, *J*=3.3, 6.0 Hz), 5.93 (1H, dd, *J*=2.1, 6.0 Hz), 7.20–7.33 (7H, m), 7.85 (2H, d, *J*=8.4 Hz); ^{13}C NMR δ 21.7, 25.0, 45.6, 50.4, 52.5, 55.5, 124.0, 128.1, 129.0, 129.55, 129.63, 130.4, 133.3, 135.6, 142.3, 145.2, 169.8, 171.2; HRMS *m*/*z* 443.0855 (calcd for $C_{22}H_{21}NO_5S_2$: 443.0861).

4.3.6. *endo*-Methyl 3-oxo-8-(phenylsulfonyl)-2-tosyl-2-aza-bicyclo[2.2.2]oct-7-ene-6-carboxylate (**10b**)

White solid, mp 180–181 °C; IR (KBr) 3046, 2954, 2919, 1732, 1362, 1322, 1172, 1086, 719 cm^{-1}; ^{1}H NMR δ 1.70 (1H, ddd, *J*=3.0, 4.8, 13.5 Hz), 2.22 (1H, ddd, *J*=2.7, 9.9, 13.5 Hz), 2.46 (3H, s), 3.33 (1H, ddd, *J*=2.7, 3.3, 9.9 Hz), 3.64 (1H, dd, *J*=2.7, 4.8 Hz), 3.71 (3H, s), 5.84 (1H, dd, *J*=3.3, 6.0 Hz), 7.29–7.79 (10H, m); ^{13}C NMR δ 21.8, 25.8, 45.1, 45.3, 52.9, 54.4, 128.1, 128.2, 129.6, 129.8, 134.3, 135.0, 138.1, 138.2, 145.7, 145.9, 167.6, 170.7; HRMS *m*/*z* 475.0757 (calcd for $C_{22}H_{21}NO_5S_2$: 475.0759).

4.3.7. *exo*-Methyl 3-oxo-8-(phenylsulfonyl)-2-tosyl-2-aza-bicyclo[2.2.2]oct-7-ene-6-carboxylate (**10c**)

White solid, mp 167–169 °C; IR (KBr) 3047, 2924, 1732, 1596, 1447, 1354, 1323, 1249, 1221, 1172, 1157, 1124, 1090, 1038, 1012, 881, 854, 815, 792, 760, 741, 718, 680, 635 cm^{-1}; ^{1}H NMR δ 1.84 (1H, ddd, *J*=3.0, 10.8, 13.8 Hz), 2.46 (3H, s), 2.50 (1H, ddd, *J*=2.4, 4.2, 13.8 Hz), 2.81 (1H, ddd, *J*=1.8, 4.2, 10.8 Hz), 3.62–3.66 (1H, m), 3.77 (3H, s), 5.86 (1H, dd, *J*=1.8, 6.0 Hz), 7.28–7.65 (8H, m), 7.73 (2H, d, *J*=8.4 Hz); ^{13}C NMR δ 21.8, 25.8, 45.1, 45.3, 52.9, 54.4, 128.1, 128.18, 129.6, 129.8, 134.3, 135.0, 138.1, 138.2, 145.7, 145.9, 167.6, 170.7; HRMS *m*/*z* 475.0751 (calcd for $C_{22}H_{21}NO_5S_2$: 475.0759).

4.3.8. *endo*-8-Methyl-4-phenyl-10-(phenylthio)-4,8-diaza-tricyclo[5.2.2.0^{2,6}]undec-10-ene-3,5,9-trione (**11a**)

Yellow solid, mp 90–92 °C; IR (KBr) 3070, 2926, 1778, 1715, 1682, 1593, 1496, 1440, 1384, 1185, 1040, 998, 803, 748, 692 cm^{-1}; ^{1}H NMR δ 2.94 (3H, s), 3.45 (1H, dd, *J*=3.0, 8.1 Hz), 3.61 (1H, dd, *J*=4.2, 8.1 Hz), 3.93 (1H, dd, *J*=2.1, 3.0 Hz), 4.51 (1H, dd, *J*=4.2, 5.7 Hz), 5.81 (1H, dd, *J*=2.1, 5.7 Hz), 7.23–7.52 (10H, m); ^{13}C NMR δ 32.2, 41.2, 47.7, 51.1, 57.5, 120.3, 126.5, 129.0, 129.2, 129.4, 129.6, 129.8, 130.0, 134.4, 141.8, 170.1, 173.4, 173.9; HRMS *m*/*z* 390.1036 (calcd for $C_{22}H_{18}N_2O_3S$: 390.1038).

4.3.9. *exo*-8-Methyl-4-phenyl-10-(phenylthio)-4,8-diaza-tricyclo[5.2.2.0^{2,6}]undec-10-ene-3,5,9-trione (**11b**)

Yellow solid, mp 210–212 °C; IR (KBr) 3047, 2895, 1716, 1497, 1386, 1191, 745, 692 cm^{-1}; ^{1}H NMR δ 2.88 (3H, s), 3.26 (1H, dd, *J*=2.7, 8.4 Hz), 3.32 (1H, dd, *J*=3.0, 8.4 Hz), 3.92 (1H, dd, *J*=2.1, 3.0 Hz), 4.61 (1H, dd, *J*=2.7, 6.0 Hz), 6.04 (1H, dd, *J*=2.1, 6.0 Hz), 7.15–7.58 (10H, m); ^{13}C NMR δ 33.1, 43.6, 48.9, 51.0, 58.3, 124.8, 126.6, 129.2, 129.3, 129.4, 129.8, 130.1, 131.4, 133.6, 143.3, 168.6, 173.8, 174.0; HRMS *m*/*z* 390.1040 (calcd for $C_{22}H_{18}N_2O_3S$: 390.1038).

4.3.10. *endo*-8-Benzyl-4-phenyl-10-(phenylthio)-4,8-diaza-tricyclo[5.2.2.0^{2,6}]undec-10-ene-3,5,9-trione (**12a**)

Light yellow solid, mp 83–85 °C; IR (KBr) 3062, 2926, 1778, 1714, 1682, 1593, 1497, 1476, 1447, 1424, 1381, 1320, 1234, 1186, 1069, 1023, 965, 938, 801, 770, 750, 691 cm^{-1}; ^{1}H NMR δ 3.25 (1H, dd, *J*=4.2, 8.1 Hz), 3.38 (1H, dd, *J*=3.3, 8.1 Hz), 3.94 (1H, dd, *J*=2.1, 3.3 Hz), 4.40–4.44 (3H, m), 5.61 (1H, dd, *J*=2.1, 5.7 Hz), 7.10–7.14 (4H, m), 7.23–7.38 (11H, m); ^{13}C NMR 40.6, 47.4, 47.9, 50.0, 54.5, 121.1, 125.7, 127.6, 127.7, 128.4 (×2), 128.5, 128.6, 129.0, 129.2, 131.68, 131.74, 135.5, 140.6, 169.3, 172.8, 173.2; HRMS *m*/*z* 466.1352 (calcd for $C_{28}H_{22}N_2O_3S$: 466.1351).

4.3.11. *exo*-8-Benzyl-4-phenyl-10-(phenylthio)-4,8-diaza-tricyclo[5.2.2.0^{2,6}]undec-10-ene-3,5,9-trione (**12b**)

Light yellow solid, mp 205–207 °C; IR (KBr) 3058, 2924, 1716, 1682, 1595, 1497, 1455, 1382, 1189, 742, 691 cm^{-1}; ^{1}H NMR δ 3.15 (1H, dd, *J*=2.7, 8.7 Hz), 3.28 (1H, dd, *J*=3.0, 8.7 Hz), 3.68 (1H, d, *J*=15 Hz), 3.94 (1H, dd, *J*=2.1, 3.0 Hz), 4.47 (1H, dd, *J*=2.7, 6.0 Hz), 5.10 (1H, d, *J*=15 Hz), 5.81 (1H, dd, *J*=2.1, 6.0 Hz), 7.04–7.13 (4H, m), 7.19–7.23 (3H, m), 7.31–7.42 (8H, m); ^{13}C NMR δ 43.8, 48.6, 48.8, 51.5, 55.6, 126.7 (×2), 128.0, 128.5, 128.9, 129.2, 129.3, 129.5, 129.9, 130.7, 131.7, 133.5, 135.9, 142.5, 168.6, 173.9, 174.1; HRMS *m*/*z* 466.1351 (calcd for $C_{28}H_{22}N_2O_3S$: 466.1351).

4.3.12. *endo*-8-Methyl-4-phenyl-10-(phenylsulfonyl)-4,8-diaza-tricyclo[5.2.2.0^{2,6}]undec-10-ene-3,5,9-trione (**13**)

White solid, mp 243–244 °C; IR (KBr) 3093, 2949, 1719, 1694, 1497, 1447, 1382, 1308, 1179, 1155, 1089, 1002, 807, 749, 728, 688, 629 cm^{-1}; ^{1}H NMR δ 2.92 (3H, s), 3.40 (1H, dd, *J*=3.0, 8.4 Hz), 3.75 (1H, dd, *J*=4.5, 8.4 Hz), 4.22 (1H, dd, *J*=2.1, 3.0 Hz), 4.84 (1H, dd, *J*=4.5, 5.7 Hz), 7.20–7.23 (2H, m), 7.39–7.48 (6H, m), 7.56–7.62 (1H, m), 7.82–7.85 (2H, m); ^{13}C NMR δ 32.6, 40.7, 46.1, 46.6, 56.6, 126.4, 128.7, 129.1, 129.3, 129.8, 131.4, 134.7, 137.6, 137.9, 146.5, 168.9, 172.0, 173.0; HRMS *m*/*z* 422.0941 (calcd for $C_{22}H_{18}N_2O_5S$: 422.0936).

4.3.13. *endo*-8-Benzyl-4-phenyl-10-(phenylsulfonyl)-4,8-diaza-tricyclo[5.2.2.0^{2,6}]-undec-10-ene-3,5,9-trione (**14a**)

White solid, mp 187–188 °C; IR (KBr) 3064, 2925, 1782, 1715, 1690, 1597, 1497, 1447, 1421, 1384, 1321, 1309, 1237, 1195, 1155, 1098, 1085, 1069, 1028, 998, 961, 937, 799, 744, 730, 688, 662 cm^{-1}; ^{1}H NMR δ 3.43 (1H, dd, *J*=3.0, 8.1 Hz), 3.51 (1H, dd, *J*=4.2, 8.1 Hz), 4.26–4.32 (2H, m), 4.60 (1H, d, *J*=15 Hz), 4.78 (1H, dd, *J*=4.2, 5.7 Hz), 7.04–7.08 (2H, m), 7.17–7.20 (3H, m), 7.32–7.63 (9H, m), 7.80–7.83 (2H, m); ^{13}C NMR δ 40.6, 46.4, 46.7, 48.7, 54.1, 126.3, 128.2, 128.5, 128.6, 129.0, 129.2 (×2), 129.7, 131.2, 134.5, 135.5, 137.8, 138.4, 145.6, 168.4, 172.0, 172.9; HRMS *m*/*z* 498.1259 (calcd for $C_{28}H_{22}N_2O_5S$: 498.1249).

4.3.14. *exo*-8-Benzyl-4-phenyl-10-(phenylsulfonyl)-4,8-diaza-tricyclo[5.2.2.0^{2,6}]-undec-10-ene-3,5,9-trione (**14b**)

Light brown solid, mp 248–250 °C; IR (KBr) 3070, 2925, 1717, 1665, 1599, 1497, 1448, 1424, 1388, 1320, 1233, 1201, 1152, 1099, 1082, 947, 868, 793, 743, 722, 688, 657 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 3.12 (1H, dd, *J*=3.3, 8.4 Hz), 3.49 (1H, dd, *J*=2.4, 8.4 Hz), 3.79 (1H, d, *J*=15 Hz), 3.93 (1H, dd, *J*=1.8, 3.3 Hz), 4.77 (1H, d, *J*=15 Hz), 4.89 (1H, dd, *J*=2.4, 5.7 Hz), 6.91–6.94 (2H, m), 7.03–7.06 (2H, m), 7.27–7.29 (3H, m), 7.41–7.50 (4H, m), 7.70–7.90 (5H, m); ^{13}C NMR (DMSO-d_6) δ 43.5, 45.6, 46.4, 48.3, 55.9, 126.6, 127.48, 127.58, 127.64, 128.5, 128.7, 129.0, 130.0, 131.6, 134.6, 135.9, 138.0, 143.0, 143.9, 167.0, 173.5, 173.7; HRMS *m*/*z* 498.1244 (calcd for $C_{28}H_{22}N_2O_5S$: 498.1249).

*4.3.15. 4-(Phenylthio)-O-tosyl-pyridinol (**16a**)*

White solid, mp 164–165 °C; IR (KBr) 3047, 2923, 1625, 1123, 1033, 1009, 682 cm^{-1}; ^1H NMR δ 2.44 (3H, s), 6.62 (1H, d, J=1.5 Hz), 6.84 (1H, dd, J=1.5, 5.1 Hz), 7.31 (2H, d, J=8.1 Hz), 7.46–7.54 (5H, m), 7.85 (2H, d, J=8.1 Hz), 7.97 (1H, d, J=5.1 Hz); ^{13}C NMR δ 21.4, 109.4, 111.84, 126.0, 126.5, 129.0, 129.7, 130.5, 131.1, 134.8, 135.6, 140.9, 160.5, 163.7; HRMS m/z 357.0498 (calcd for $C_{18}H_{15}NO_3S_2$: 357.0493).

*4.3.16. 4-(Phenylsulfonyl)-O-tosyl-2-pyridinol (**16b**)*

White solid, mp 200 °C (decomp.); IR (KBr) 3070, 2680, 1823, 1643, 1527, 1495, 1448, 1360, 1333, 1315, 1246, 1216, 1159, 1131, 1105, 1074, 1031, 1007, 940, 891, 189, 804, 761, 703, 681, 636 cm^{-1}; ^1H NMR δ 2.46 (3H, s), 7.35 (2H, d, J=8.2 Hz), 7.50 (1H, s), 7.58–7.68 (4H, m), 7.89 (2H, d, J=8.2 Hz), 7.94 (2H, d, J=7.2 Hz), 8.43 (1H, d, J=5.1 Hz); ^{13}C NMR δ 21.8, 113.3, 119.4, 128.4, 128.8, 129.86, 129.90, 130.1, 133.4, 134.6, 145.9, 149.9, 154.0, 157.9; HRMS m/z 389.0388 (calcd for $C_{18}H_{15}NO_5S_2$: 389.0392).

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49. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 659438 (**9a**), 659439 (**8b**), 659440 (**10b**). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).
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