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Synthesis of sulfur-substituted quinolizidines and pyrido[1,2-*a*]azepines by ring-closing metathesis

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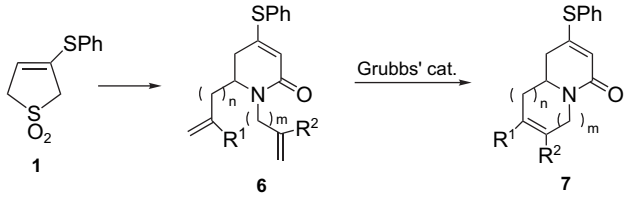
Abstract—Sulfur-substituted quinolizidines and pyrido[1,2-*a*]azepines (**7**) can be prepared by ring-closing metathesis (RCM) of 4-(phenylthio)-1,2,5,6-tetrahydropyridin-2-ones (**6**) bearing terminal alkenyl groups at both N-1 and C-6 positions, which are obtained from 3-(phenylthio)-3-sulfolene (**1**) in four steps. Some synthetic transformations of 2-(phenylthio)-1,6,9,9a-tetrahydroquinolizin-4-one (**7a**) and 2-(phenylthio)-1,6,9,10,10a-pentahydropyrido[1,2-*a*]azepin-4-one (**7d**) are also reported.

1. Introduction

The piperidine ring is among the most abundant molecular fragments in both natural and synthetic compounds with various biological activities.[1] The aza-Diels–Alder reaction is one of the most versatile routes to substituted piperidines.[2] In general, the use of strongly electron-deficient imines is a prerequisite. We have also used this method to synthesize some thio-substituted piperidine derivatives.[3]

Indolizidines and quinolizidines contain the piperidine structure, and are important framework of many natural products.[4] The less common pyridoazepines have also been found to have very strong insecticidal activity,[5] and have been studied as potential dopamine D1 receptor[6] and nicotinic acetylcholinergic receptor ligands.[7]

Ring-closing metathesis (RCM)[8] has been very useful for the synthesis of various rings, including pyridoazepines[9] and many other heterocyclic compounds.[10] We now report the synthesis of some sulfur-substituted quinolizidines and pyridoazepines by RCM (Scheme 1).



Scheme 1.

2. Results and discussion

Treatment of 3-(phenylthio)-3-sulfolene (**1**)[11] with BuLi and HMPA in THF at low temperatures, followed by reaction with allyl bromide or 4-iodobut-1-ene gave in good yield the alkylated 3-sulfolenes **2a** and **2b**,[12] respectively (Scheme 2, Table 1). However, the reaction of **1** with methallyl iodide gave an inseparable mixture of **2c** and bis-alkylation product **3** in low yield. Presumably, the steric hindrance of methallyl iodide slowed down the alkylation so that equilibration of product **2c** with unreacted 3-sulfolene anion of **1** led to bis-alkylation.

The reaction of **2** with *p*-toluenesulfonyl isocyanate (PTSI) under previously reported conditions[3c] gave the aza-Diels–Alder reaction products **4**. The inseparable mixture of **2c** and **3** was used directly for this reaction. The product **4c** was easily separated from the unreacted **3**. The yields of **4a** and **4b** were fairly good, but the yield of **4c** was only modest, probably due to some steric hindrance of the bulky side chain. Detosylation of **4** with Parsons' method (Bu_3SnH, AIBN)[13] gave amides **5** in excellent yield.

A more challenging task is the alkylation of **5** because of the low nucleophilicity of amide anion of **5** and some steric hindrance from the 6-alkyl substituent. The reaction yields varied significantly with the structure of the alkyl halides and the reaction conditions (Table 1). With optimized conditions the alkylation products **6** were obtained in fair to good yields. It should be noted that for the preparation of **6b**, the use of 1,4-diiodobutane (Method D) was much better than 4-bromobut-1-ene (Method A), which gave mostly recovered starting material **5b** due to its high propensity for elimination. The ring-closing metathesis (RCM) of **6** with the first-generation Grubbs' catalyst proceeded well in CH_2Cl_2 at room temperature except for **6e**, which required

Keywords: Aza-Diels–Alder reaction; Quinolizidines; Azepines; Ring-closing metathesis.
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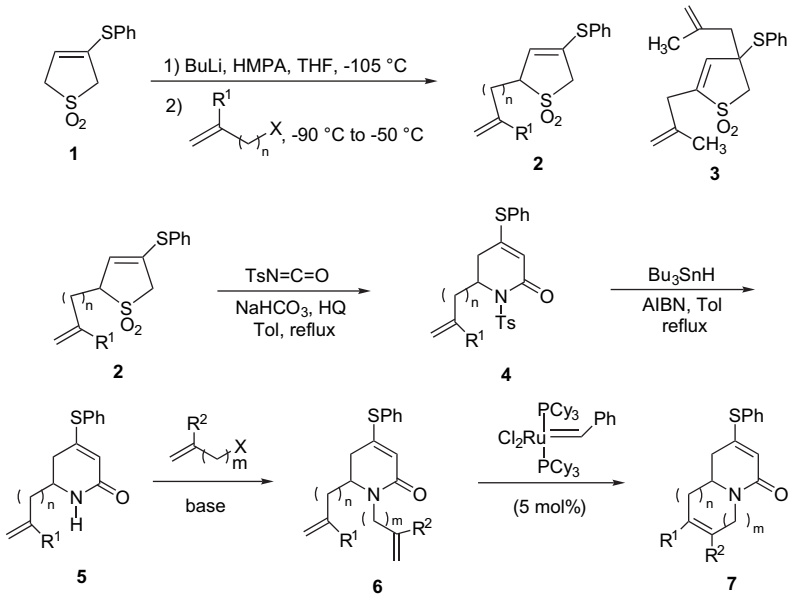


2, 4-5: **a**, n = 1, R^1 = H; **b**, n = 2, R^1 = H; **c**, n = 1, R^1 = CH_3

6-7: **a**, n = 1, m = 1, R^1 = R^2 = H; **b**, n = 1, m = 2, R^1 = R^2 = H; **c**, n = 1, m = 1, R^1 = H, R^2 = CH_3; **d**, n = 2, m = 1, R^1 = R^2 = H; **e**, n = 1, m = 1, R^1 = CH_3, R^2 = H

Scheme 2.

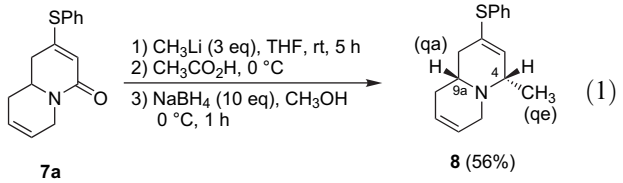
Table 1. Yields (%) of compounds **2**–**7**[a]

2a, 83	**4a**, 74	**5a**, 96	**6a**, 41 (A); 82 (B)	**7a**, 94 (E)
			6b, 14 (A); 70 (D)	**7b**, 84 (E)
			6c, 54 (B); 50 (C)	**7c**, 98 (E)
2b, 74	**4b**, 79	**5b**, 83	**6d**, 45 (A)	**7d**, 84 (E)
2c+3, 30 (9:1)	**4c**, 49	**5c**, 87	**6e**, 28 (B); 60 (C)	**7e**, 39 (F)

[a] Reaction conditions—A: NaH, THF, RX, reflux. B: BuLi, THF, −78 °C; RX, −78 °C to −50 °C. C: NaH, *t*-BuOK, RX, rt. D: NaH, $I(CH_2)_4I$, THF, reflux. E: CH_2Cl_2, rt. F: Tol, reflux.

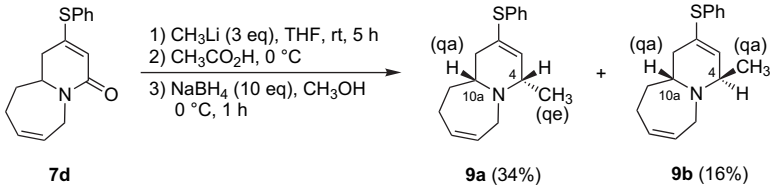
reflux in toluene. By comparing with **6c**, it appears that the methyl group in **6e** particularly hampers the RCM.

We have also briefly studied some synthetic transformations of **7a** and **7d**. Following a literature procedure,[14] **7a** was converted to *cis*-**8** (Eq. 1) and **7d** was converted to a mixture of *cis*-**9a** and *trans*-**9b** (Eq. 2). The most stable conformations of **8** and **9a** were calculated by using a PM3 method of Hyperchem, and their stereochemistry was determined by IR and NOESY techniques (Figs. 1 and 2). The IR of compound **8** shows a Bohlmann band at 2784 cm^{-1}, indicating that the lone pair electrons of nitrogen as well as H_f are at the axial position.[15] It is well known that the axial protons are more upfield than the equatorial protons in similar systems,[16] so we assign H_c as quasi-axial (qa) and H_b quasi-equatorial (qe). Since H_a at C-4 has NOE with H_c at C-6, but not with H_b, we conclude that H_a is also quasi-axial. Thus, H_a and H_f are cis to each other in compound **8**. Similarly, compound **9a** has a Bohlmann band at 2783 cm^{-1}, indicating that the lone pair electrons of nitrogen as well as H_b are at the axial position. Since H_b has NOE with both H_a and H_c, and the methyl group at C-4 has NOE with H_d at C-6, we conclude that H_a and H_b are cis to each other in compound **9a**. Compound **9b** has a Bohlmann band at 2784 cm^{-1}, and its methyl absorption in both the ^1H NMR (δ 1.14) and ^{13}C NMR (δ 15.86) spectra is more upfield than that of **9a** (δ 1.21 and 20.96, respectively). This shows that the methyl group of **9b** is at the quasi-axial position, and thus cis to the hydrogen at C-10a.



(1)

To explain the stereoselective formation of **8** and **9a**, we propose that the iminium ions **7A** and **7B** are first formed as the intermediates (Scheme 3). The hydride ion would then prefer to attack from the axial direction due to the stereoelectronic



(2)

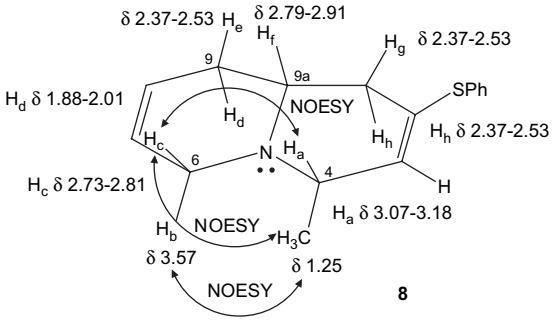


Figure 1. The most stable conformation and NOESY correlations for compound **8**.

effect.[17] In addition, approach of the hydride from the β-face leading to a chair conformation is more favorable than that from the α-face, because the latter would lead to a less stable boat conformation. However, the stereoselectivity for the reaction of **7d** is lower than that for **7a**, probably because the seven-membered ring in **7d** is more flexible and distant from the nucleophile than for the six-membered ring in **7a**.

3. Conclusion

We have synthesized sulfur-substituted quinolizidines and pyrido[1,2-*a*]azepines **7** by ring-closing metathesis of suitably substituted dihydropyridin-2-ones **6**, which are obtained from compound **1** in four steps. We have also carried out some useful functional group transformations of compounds **7a** and **7d**.

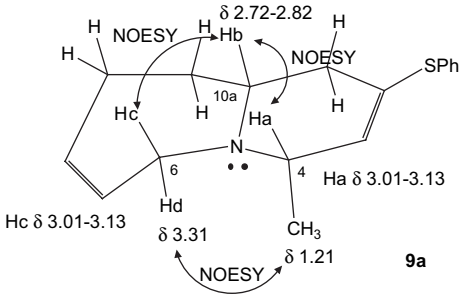


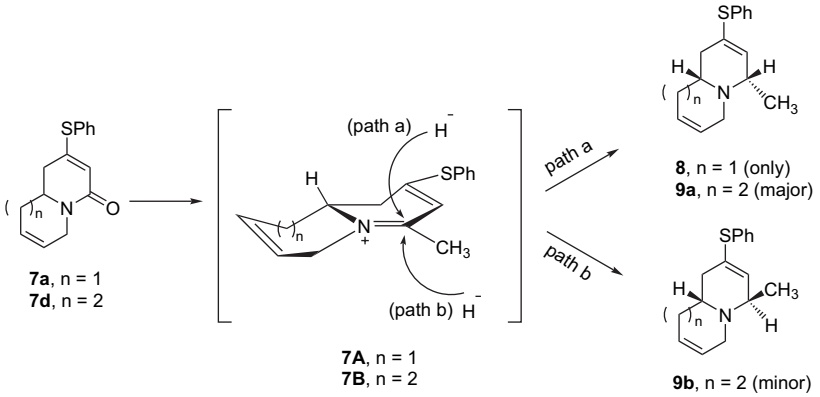
Figure 2. The most stable conformation and NOESY correlations for compound **9a**.

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 at 75 MHz, respectively. Chemical shifts (δ) are reported in parts per million (ppm) and the coupling constants (J) are given in hertz. Low resolution mass spectra (EIMS) and high resolution mass spectra (HRMS) were measured with a mass spectrometer JEOL JMS-SX102A. Flash column chromatographic purifications were performed using Merck 60 H silica gel.

4.1.1. 2-(2-Methylprop-2-enyl)-4-(phenylthio)-3-sulfolene (2c) and 2,4-bis(2-methylprop-2-enyl)-4-(phenylthio)-2-sulfolene (3). Following the general procedure for alkylation of **1**,[12] an inseparable mixture of **2c** and **3** (30% yield, 9:1 as determined by ^{1}H NMR) was obtained after flash chromatography using hexane/ethyl acetate (1:7) as eluent. The following spectral data can be discerned for **2c**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.44–7.32 (5H, m), 5.77 (1H, dd, J=2.1, 3.9 Hz), 4.87 (1H, s), 4.82 (1H, s), 4.04 (1H, br t, J=7.5 Hz), 3.78–3.65 (2H, m), 2.69–2.62 (1H, m), 2.22–2.06 (1H, m), 1.74 (3H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 139.9, 137.2, 132.7, 131.0, 129.3, 128.7, 125.4, 113.5, 64.5, 57.2, 35.9, 22.1. Since the product (**4c** and **3**) from the reaction of PTSI with the mixture of **2c** and **3** can be separated by flash chromatography, the following spectral data were obtained for pure **3**: IR (film) 3071, 2974, 1670, 1595, 1440, 1374, 1352, 1223, 1162, 1122, 1087, 909, 846, 816, 751, 705, 689 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.48–7.36 (5H, m), 6.16 (1H, t, J=1.7 Hz), 5.02 (1H, t, J=1.5 Hz), 4.93 (1H, t, J=1.5 Hz), 4.87–4.84 (2H, m), 3.62 (1H, d, J=14.9 Hz), 3.42 (1H, d, J=14.9 Hz), 2.99–2.86 (2H, m), 2.67–2.56 (2H, m), 1.78 (3H, s), 1.68 (3H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 141.8, 139.4, 138.3, 137.2 (2×), 130.0, 129.0 (2×), 117.8, 114.7, 57.6, 53.4, 47.8, 31.2, 23.9, 21.7; FABMS (relative intensity) *m/z* 335 (M^++H, 64), 279 (94), 219 (76), 161 (93), 159 (84), 151



Scheme 3.

(87), 105 (96); FAB-HRMS *m/z* 335.1064 (M^++H, calcd for $C_{18}H_{22}O_2S_2$: 334.1061).

4.2. General procedure for aza-Diels–Alder reactions of 2

To a mixture of **2** (0.50 mmol), $NaHCO_3$ (0.50 mmol) and a catalytic amount of hydroquinone in toluene (20 mL) at 110 °C under nitrogen was slowly added *p*-toluenesulfonyl isocyanate (PTSI, 2.5 mmol) with a syringe. The reaction mixture was heated at this temperature for 4.5 h. The solvent was removed under vacuum, and to the residue was carefully added 5% NaOH to decompose the unreacted PTSI. After extraction with ethyl acetate, the crude product was purified by flash chromatography using hexane/ethyl acetate with 5% Et_3N as eluent to give product **4**.

4.2.1. 6-Allyl-4-(phenylthio)-1-(4-toluenesulfonyl)-1,2,5,6-tetrahydropyridin-2-one (4a). White solid. Mp 117–118 °C; IR (film) 3072, 2977, 2921, 1672, 1595, 1475, 1441, 1382, 1348, 1224, 1167, 1088, 906, 705, 692, 662 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.92 (2H, d, *J*=8.4 Hz), 7.43–7.38 (5H, m), 7.27 (2H, d, *J*=8.4 Hz), 5.84–5.70 (1H, m), 5.18 (1H, d, *J*=2.1 Hz), 5.15–5.12 (2H, m), 4.86–4.80 (1H, m), 2.89 (1H, ddd, *J*=17.1, 6.0, 2.1 Hz), 2.57–2.44 (3H, m), 2.40 (3H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 160.9, 157.5, 144.6, 136.9, 135.4, 133.2, 130.5, 130.0, 129.23, 129.0, 127.6, 119.7, 113.8, 54.3, 37.7, 32.2, 21.7; EIMS (relative intensity) *m/z* 399 (M^+, 0.3), 358 (45), 294 (100), 295 (19), 154 (66), 91 (83), 67 (12); HRMS *m/z* 399.0968 (calcd for $C_{21}H_{21}NO_3S_2$: 399.0963).

4.2.2. 6-(But-3-enyl)-4-(phenylthio)-1-(4-toluenesulfonyl)-1,2,5,6-tetrahydropyridin-2-one (4b). White solid. Mp 126–128 °C; IR (film) 3066, 2976, 2925, 1669, 1595, 1349, 1166, 1089, 705, 691 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.91 (2H, d, *J*=8.1 Hz), 7.45–7.34 (5H, m), 7.27 (2H, d, *J*=8.1 Hz), 5.89–5.76 (1H, m), 5.17 (1H, d, *J*=2.1 Hz), 5.11–5.03 (2H, m), 4.86–4.79 (1H, m), 2.94 (1H, ddd, *J*=17.4, 5.8, 2.1 Hz), 2.48 (1H, dd, *J*=17.4, 1.2 Hz), 2.40 (3H, s), 2.18–2.11 (2H, m), 1.90–1.84 (2 H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 160.8, 157.2, 144.5, 136.8, 135.3, 135.3, 130.4, 129.94, 129.90, 129.1, 128.9, 115.8, 113.6, 54.6, 32.8, 32.0, 30.4, 21.6; EIMS (relative intensity) *m/z* 413 (M^+, 0.3), 358 (24), 294 (26), 244 (100), 245 (14), 91 (43); HRMS *m/z* 413.1121 (calcd for $C_{22}H_{23}NO_3S_2$: 413.1119).

4.2.3. 6-(2-Methylprop-2-enyl)-4-(phenylthio)-1-(4-toluenesulfonyl)-1,2,5,6-tetrahydropyridin-2-one (4c). White solid. Mp 147.4–147.9 °C; IR (film) 3062, 2959, 2942, 2919, 1665, 1593, 1440, 1337, 1265, 1164, 906, 836, 817, 752, 726, 690, 658 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.94 (2H, d, *J*=6.9 Hz), 7.47–7.37 (5H, m), 7.27 (2H, d, *J*=6.9 Hz), 5.17 (1H, d, *J*=2.1 Hz), 4.97–4.89 (2H, m), 4.80 (1H, br s), 2.89 (1H, ddd, *J*=2.1, 6.0, 17.1 Hz), 2.56 (1H, dd, *J*=1.5, 17.1 Hz), 2.49–2.42 (2H, m), 2.39 (3H, s), 1.84 (3H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 160.9, 157.7, 144.6, 141.0, 136.8, 135.4, 130.5, 130.0, 129.2, 129.0, 127.5, 115.4, 113.5, 53.1, 31.6, 41.20, 22.0, 21.6; EIMS (relative intensity) *m/z* 413 (M^+, 0.96), 360 (10), 359 (19), 358 (93), 349 (21), 294 (38), 258 (14), 155 (74), 91 (100), 67 (13); HRMS *m/z* 413.0948 (calcd for $C_{22}H_{23}NO_3S_2$: 413.1119).

4.3. General procedure for detosylation of 4

To a mixture of **4** (0.50 mmol) and AIBN (0.10 mmol) in degassed toluene (10 mL) was added Bu_3SnH (1.1 mmol). This was heated at reflux under N_2 for 2 h. During this period another two portions of AIBN (0.10 mmol each) were added in 30 min interval. The solvent was then evaporated under vacuum and the crude product was purified by flash chromatography using hexane/ethyl acetate with 5% Et_3N as eluent to give product **5**.

4.3.1. 6-Allyl-4-(phenylthio)-1,2,5,6-tetrahydropyridin-2-one (5a). White solid. Mp 144–146 °C; IR (film) 3291, 3180, 3084, 3072, 3048, 2923, 1656, 1587, 1405, 1343, 915, 839, 755 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.85–7.39 (5H, m), 5.79–5.65 (2H, m), 5.28 (1H, s), 5.21–5.15 (2H, m), 3.71–3.61 (1H, m), 2.48–2.40 (2H, m), 2.37–2.20 (2H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.9, 155.2, 135.4, 132.9, 130.1, 129.9, 128.3, 119.6, 114.3, 50.2, 39.5, 34.6; EIMS (relative intensity) *m/z* 245 (M^+, 21), 206 (100), 207 (39), 186 (14), 171 (22), 126 (27), 109 (69), 91 (12), 67 (12), 65 (20), 39 (56); HRMS *m/z* 245.0865 (calcd for $C_{14}H_{15}NO_3S_2$: 245.0874).

4.3.2. 6-(But-3-enyl)-4-(phenylthio)-1,2,5,6-tetrahydropyridin-2-one (5b). White solid. Mp 130–131 °C; IR (film) 3289, 3186, 3076, 2935, 1651, 1586, 1473, 1402, 1347, 1325, 907, 852, 753, 691 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.51–7.40 (5H, m), 6.06 (1H, br s), 5.84–5.70 (1H, m), 5.27 (1H, s), 5.09–5.00 (2H, m), 3.67–3.57 (1H, m), 2.54–2.30 (2H, m), 2.16–2.09 (2H, m), 1.78–1.56 (2H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.9, 154.7, 137.0, 135.3, 129.9, 129.8, 128.2, 115.8, 114.2, 50.4, 34.5, 33.9, 29.5; EIMS (relative intensity) *m/z* 259 (M^+, 2), 217 (19), 205 (12), 204 (100), 182 (10), 150 (20), 67 (19); HRMS *m/z* 259.1032 (calcd for $C_{15}H_{17}NOS$: 259.1031).

4.3.3. 6-(2-Methylprop-2-enyl)-4-(phenylthio)-1,2,5,6-tetrahydropyridin-2-one (5c). White solid. Mp 154.8–155.1 °C; IR (film) 3175, 3065, 2930, 2864, 1659, 1579, 1471, 1403, 1345, 1082, 1013, 896, 851, 757, 694 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.52–7.27 (5H, m), 5.60 (1H, br s), 5.28 (1H, s), 4.92 (1H, d, *J*=1.2 Hz), 4.83 (1H, s), 3.80–3.71 (1H, m), 2.43 (2H, d, *J*=7.5 Hz), 2.32–2.18 (2H, m), 1.73 (3H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.7, 155.1, 140.2, 135.3, 130.0, 129.8, 128.1, 115.0, 114.2, 48.1, 43.4, 35.0, 21.8; EIMS (relative intensity) *m/z* 259 (M^+, 4), 206 (9), 205 (29), 204 (100), 109 (13), 67 (18); HRMS *m/z* 259.1039 (calcd for $C_{15}H_{17}NOS$: 259.1031).

4.4. General procedure for alkylation of 5 (Table 1)

Method A: To a solution of **5** (0.50 mmol) in THF (6 mL) at room temperature under nitrogen was added NaH (50% dispersion, 0.75 mmol). After stirring for 30 min, the alkyl halide (3.0 mmol) was added, and the reaction mixture was refluxed for 15 h. After cooling to room temperature, the mixture was filtered and the residue was concentrated and purified by flash chromatography.

Method B: To a solution of **5** (0.50 mmol) in THF (10 mL) and HMPA (0.35 mL, 2.0 mmol) at −78 °C was added dropwise a solution of BuLi (1.6 M in hexane, 0.75 mmol). The reaction mixture was slowly warmed to −50 °C, and cooled down to −78 °C before adding the alkyl halide in one portion. The mixture was allowed to warm to room temperature and was quenched with saturated ammonium chloride. The solvent was removed under vacuum, and the residue was extracted with ethyl acetate. The crude product was purified by flash chromatography.

Method C: To a solution of **5** (0.50 mmol) in THF (6 mL) at room temperature under nitrogen were added NaH (50% dispersion, 0.75 mmol) and t-BuOK (0.75 mmol). After stirring for 30 min, alkyl halide (3.0 mmol) was added, and the reaction mixture was stirred at room temperature for 3.5 h. The solvent was evaporated and water was added. The reaction mixture was extracted with ethyl acetate, and the crude product was purified by flash chromatography.

Method D: A mixture of **5** (0.50 mmol) and NaH (50% dispersion, 10 mmol) in THF (10 mL) was heated at 80 °C for 10 min, and then 1,4-diiodobutane (2.0 mmol) in THF (5 mL) was added. The reaction mixture was heated at 80 °C for 48 h. After quenching with water and extraction with ethyl acetate, the crude product was purified by flash chromatography.

4.4.1. 1,6-Diallyl-4-(phenylthio)-1,2,5,6-tetrahydropyridin-2-one (6a). Light yellow liquid. IR (film) 3074, 2976, 2917, 1649, 1593, 1460, 1440, 1414, 1354, 1282, 1255, 921, 750, 691 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.56–7.40 (5H, m), 5.86–5.61 (2H, m), 5.38 (1H, d, J=2.4 Hz), 5.22–4.98 (4H, m), 4.66 (1H, ddt, J=1.8, 4.8, 15.6 Hz), 3.50 (1H, dq, J=6.8, 15.6 Hz), 3.40 (1H, dd, J=6.9, 15.6 Hz), 2.76 (1H, ddd, J=2.4, 6.6, 15.6 Hz), 2.39–2.31 (3H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 162.7, 150.9, 135.4, 134.0, 133.9, 129.9, 129.8, 128.6, 118.9, 117.0, 115.3. 54.1, 47.1, 35.7, 31.9; MS (relative intensity) *m/z* 285 (M^+, 6), 244 (100), 204 (10), 178 (13), 161 (9), 67(15); HRMS *m/z* 285.1182 (calcd for $C_{17}H_{19}NOS$: 285.1187).

4.4.2. 6-Allyl-1-(but-3-enyl)-4-(phenylthio)-1,2,5,6-tetrahydropyridin-2-one (6b). Light yellow liquid. IR (film) 3074, 3004, 2975, 2928, 2854, 1649, 1643, 1594, 1461, 1454, 1440, 1414, 1354, 1282, 1255, 995, 921, 851, 750, 691 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.52–7.38 (5H, m), 5.88–5.55 (2H, m), 5.38–5.33 (1H, m), 5.18–5.02 (4H, m), 4.11 (1H, td, J=6.8, 13.6 Hz), 3.45 (1H, dq, J=1.3, 6.8 Hz), 2.80–2.66 (2H, m), 2.38–2.26 (5H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 163.0, 150.9, 135.5, 133.92, 130.0, 129.9, 128.5, 119.0, 117.0, 115.2 (2×), 55.7, 45.2, 35.9, 33.23, 31.8; EIMS (relative intensity) *m/z* 299 (M^+, 4), 258 (26), 204 (10), 55 (9); HRMS *m/z* 299.1349 (calcd for $C_{18}H_{21}NOS$: 299.1344).

4.4.3. 6-Allyl-1-(2-methylprop-2-enyl)-4-(phenylthio)-1,2,5,6-tetrahydropyridin-2-one (6c). Light yellow liquid. IR (film) 3063, 2934, 2912, 1644, 1597, 1436, 1424, 1355, 1291 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.51–7.36 (5H, m), 5.71–5.62 (1H, m), 5.40 (1H, d, J=2.4 Hz), 5.15–5.05 (2H, m), 4.87–4.83 (2H, m), 4.67 (1H, d, J=15.4 Hz), 3.46–3.40 (1H, m), 3.25 (1H, d, J=15.4 Hz), 2.73 (1H, ddd, J=2.4, 6.6, 16.8 Hz), 2.35–2.30 (3H, m), 1.69 (3H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 162.7, 150.6, 141.3, 135.3, 133.9, 129.8, 129.7, 128.4, 118.7, 115.1, 112.2, 53.5, 49.6, 35.20, 31.6, 20.0; EIMS (relative intensity) *m/z* 299 (M^+,13), 259 (21), 258 (100), 55 (27); HRMS *m/z* 299.1338 (calcd for $C_{18}H_{21}NSO$: 299.1344).

4.4.4. 1-Allyl-6-(but-3-enyl)-4-(phenylthio)-1,2,5,6-tetrahydropyridin-2-one (6d). Light yellow liquid. IR (film) 3075, 2928, 1640, 1594, 1457, 1440, 1414, 1353, 1273, 1255, 992, 916, 851, 750, 692 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.53–7.35 (5H, m), 5.86–5.67 (2H, m), 5.37 (1H, d, J=2.4 Hz), 5.21–4.95 (4H, m), 4.70–4.58 (1H, m), 3.50–3.41 (1H, m), 3.33 (1H, dd, J=6.9, 15.3 Hz), 2.80 (1H, ddd, J=1.2, 5.7, 16.2 Hz), 2.29 (1H, dd, J=1.35, 17.0 Hz), 2.16–1.53 (4H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 162.5, 150.5, 137.0, 135.1, 133.8, 129.7, 129.6, 128.4, 116.8, 115.5, 115.2, 53.5, 46.8, 31.9, 30.2, 29.8; MS (relative intensity) *m/z* 299 (M^+, 18), 298 (11), 257 (11), 245 (34), 244 (100), 190 (10), 68 (10), 67 (18); HRMS *m/z* 299.1306 (calcd for $C_{18}H_{21}NOS$: 299.1344).

4.4.5. 1-Allyl-6-(2-methylprop-2-enyl)-4-(phenylthio)-1,2,5,6-tetrahydropyridin-2-one (6e). Light yellow liquid. IR (film) 3073, 2966, 2934, 2913, 2852, 1642, 1595, 1457, 1441, 1415, 1354, 1255, 1178 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.51–7.39 (5H, m), 5.84–5.73 (1H, m), 5.37 (1H, d, J=2.1 Hz), 5.22–5.15 (2H, m), 4.87 (1H, s), 4.76 (1H, s), 4.65 (1H, dd, J=2.1, 15.3 Hz), 3.61–3.55 (1H, m), 3.37 (1H, dd, J=6.6, 15.3 Hz), 2.71 (1H, ddd, J=2.1, 6.6, 16.8 Hz), 2.38–2.22 (3H, m), 1.71 (3H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 162.28, 150.71, 141.08, 135.12, 133.78, 129.63, 129.48, 128.2, 116.9, 114.6, 114.4, 52.1, 46.5, 38.7, 31.2, 22.0; EIMS (relative intensity) *m/z* 299 (M^+, 5), 245 (28), 244 (100), 53 (10), 11 (6), 10 (10); HRMS *m/z* 299.1349 (calcd for $C_{18}H_{21}NOS$: 299.1344).

4.5. General procedure for ring-closing metathesis of 6

Method E: To a solution of **6** (0.50 mmol) in CH_2Cl_2 (2 mL) was added Grubbs' catalyst (first generation, 0.025 mmol). After stirring at room temperature or under reflux for a few hours (checked by TLC), the solvent was evaporated, and the residue was then purified by flash chromatography using hexane/ethyl acetate with 5% triethylamine as eluent.

Method F: To a solution of **6** (0.50 mmol) in toluene (5 mL) was added Grubbs' catalyst (first generation, 0.025 mmol). After stirring at 120 °C under nitrogen for a few hours (checked by TLC), the solvent was evaporated, and the residue was then purified by flash chromatography using hexane/ethyl acetate with 5% triethylamine as eluent.

4.5.1. 2-(Phenylthio)-1,6,9,9a-tetrahydroquinolizin-4-one (7a). Light yellow liquid. IR (film) 3035, 2890, 2842, 1650, 1639, 1633, 1594, 1454, 1439, 1422, 1320, 1272, 1252, 751, 691, 668 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.52–7.38 (5H, m), 5.81–5.68 (2H, m), 5.35 (1H, s), 4.56 (1H, d, J=18.8 Hz), 3.82–3.71 (1H, m), 3.63–3.58 (1H, m), 2.78 (1H, dd, J=6.5, 17.0 Hz), 2.36 (2H, dt,

J=6.5, 17.0 Hz), 2.16–2.00 (1H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 164.1, 151.1, 135.3, 129.9, 129.8, 128.4, 125.1, 124.0, 115.3, 51.3, 42.5, 34.0, 31.1; EIMS (relative intensity) m/z 257 (M^+, 100), 176 (42), 148 (25), 147 (14), 67 (31); HRMS m/z 257.0869 (calcd for $C_{15}H_{15}NOS$: 257.0874).

4.5.2. 2-(Phenylthio)-1,6,7,10,10a-pentahydropyrido[1,2-*a*]azepin-4-one (7b). Light yellow liquid. IR (film) 3057, 3018, 2929, 2894, 2830, 1643, 1593, 1462, 1423, 1367, 1300, 1115, 985, 852, 752, 692 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.52–7.38 (5H, m), 5.78–5.58 (2H, m), 5.37 (1H, s), 4.16 (1H, ddd, J=4.2, 5.4, 13.8 Hz), 3.91–3.82 (1H, m), 3.26 (1H, ddd, J=3.0, 10.1, 13.8 Hz), 2.70–2.53 (2H, m), 2.51–2.20 (4H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 163.2, 151.3, 135.3, 130.4 (2×), 129.9, 128.7, 126.3, 115.7, 57.1, 43.5, 35.3, 33.5, 29.9; EIMS (relative intensity) m/z 271 (M^+, 100), 270 (85), 204 (25), 176 (20), 162 (28), 147 (14), 110 (15), 77 (15), 67 (49), 65 (17); HRMS m/z 271.1036 (calcd for $C_{16}H_{17}NOS$: 271.1031).

4.5.3. 7-Methyl-2-(phenylthio)-1,6,9,9a-tetrahydroquinolizin-4-one (7c). Light yellow liquid. IR (film) 3054, 2966, 2910, 1638, 1597, 1473, 1453, 1439, 1423, 1320, 1273, 1250, 849, 751, 691 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.52–7.38 (5H, m), 5.50–5.40 (1H, m), 5.35 (1H, s), 4.39 (1H, d, J=18.0 Hz), 3.75–3.61 (1H, m), 3.47 (1H, d, J=18.0 Hz), 2.74 (1H, dd, J=6.6, 17.1 Hz), 2.38 (1H, dd, J=6.6, 17.1 Hz), 2.33–2.23 (1H, m), 2.10–1.98 (1H, m), 1.68 (3H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 163.9, 151.0, 135.1, 131.9, 129.7, 129.6, 128.2, 118.0, 115.0, 50.9, 45.9, 33.76, 31.0, 20.3; FABMS (relative intensity) m/z 271 (M^+, 21), 270 (39), 268 (9), 204 (11), 96 (9), 94 (10); HRMS m/z 271.1111 (calcd for $C_{16}H_{17}NOS$: 271.1031).

4.5.4. 2-(Phenylthio)-1,6,9,10,10a-pentahydropyrido[1,2-*a*]azepin-4-one (7d). Dark brown liquid. IR (film) 3021, 2931, 2839, 1639, 1595, 1458, 1419, 1362, 1292, 844, 752, 692 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.51–7.37 (5H, m), 5.83–5.68 (2H, m), 5.35 (1H, dd, J=0.9, 3.6 Hz), 4.82 (1H, dd, J=4.8, 16.5 Hz), 3.85 (1H, quintet, J=6.0 Hz), 3.44–3.35 (1H, m), 2.70 (1H, ddd, J=1.5, 6.0, 16.8 Hz), 2.43–2.35 (2H, m), 2.24–2.11 (1H, m), 1.92–1.82 (2H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 163.1, 151.4, 135.2, 130.7, 129.8, 129.7, 128.6, 128.2, 115.3, 56.9, 43.0, 34.5, 31.2, 25.4; EIMS (relative intensity) m/z 271(M^+, 100), 270 (85), 204 (25), 176 (20), 162 (28), 147 (14), 110 (15), 77 (15), 67 (49), 65 (17); HRMS m/z 271.1039 (calcd for $C_{16}H_{17}NOS$: 271.1031).

4.5.5. 8-Methyl-2-(phenylthio)-1,6,9,9a-tetrahydroquinolizin-4-one (7e). Light yellow liquid. IR (film) 2927, 2856, 1632, 1592, 1457, 1437, 1417, 1328 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.54–7.38 (5H, m), 5.41 (1H, br s), 5.34 (1H, s), 4.51 (1H, d, J=18.0 Hz), 3.77–3.72 (1H, m), 3.77–3.52 (1H, m), 2.77 (1H, ddd, J=1.2, 6.6, 17.1 Hz), 2.42–2.32 (2H, m), 1.92–1.81 (1H, m), 1.69 (3H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 164.1, 151.0, 135.3, 131.5, 129.8, 129.8, 128.3, 118.6, 115.3, 51.3, 42.4, 35.8, 33.9, 22.9; EIMS (relative intensity) m/z 271 (M^+, 100), 270 (19), 256 (29), 204 (20), 176 (33), 147 (12), 94 (17), 67 (33); HRMS m/z 271.1024 (calcd for $C_{16}H_{17}NOS$: 271.1031).

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