Concise Access to Pyrimidine-Annulated Azepine and Azocine Derivatives by Ruthenium-Catalyzed Ring-Closing Metathesis

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Abstract: Synthetic approaches to five- and six-membered-ring systems are commonly undertaken through cyclization and cycloaddition reactions, but the formation of seven- and eight-membered-ring systems are not as abundant. An efficient and high-yielding method for the synthesis of seven- and eight-membered-ring nitrogen-containing heterocycles by ring-closing metathesis is reported.

Keywords: uracil, azepine, azocine, ring-closing metathesis

Due to the rich chemistry and biology of nitrogen-containing compounds, the synthesis of N-heterocycles has been a central and important theme in organic chemistry.[1] Medium-sized N-containing fused-ring systems, in particular seven-membered rings (azepines) and eight-membered rings (azocines), are key structures occurring in many natural products (Figure 1).[2–7] Despite their bioactivity,[8] azepine- and azocine-fused ring systems have not been much investigated. One barrier to their study is the unsatisfactory synthetic procedures available.[9]

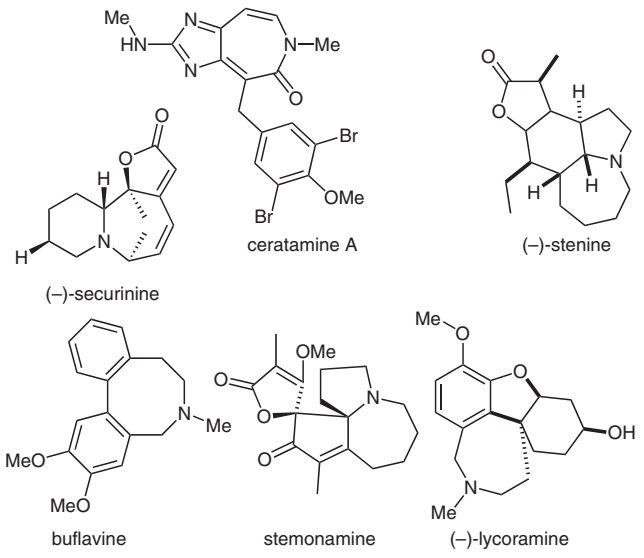

Figure 1 Azepine- and azocine-containing alkaloids

Recently, however, palladium-catalyzed intramolecular Heck coupling has been explored for the synthesis of azepine and azocine derivatives. There are two main drawbacks. The first is that palladium-catalyzed cyclization by the application of intramolecular Heck reactions require harsh reaction conditions where a nitrogen-containing compound is used as the starting material.[10] The second problem is that the two available modes of cyclization, *endo*-trig and *exo*-trig, often compete with each other. Consequently, there is always a tendency for a mixture of products to be obtained. For example, Hii et al. reported[11] the competitive formation of 7-*exo*-trig cyclized product benzazepine and 8-*endo*-trig cyclized product benzazocine, as an inseparable mixture of products in the pallladium-catalyzed intramolecular Heck reaction; however, they did demonstrate the importance of temperature and ligand effects on the regioselectivity of the reaction. These findings prompted us to undertake a study on the synthesis of biologically interesting azepine and azocine derivatives in which the major drawbacks can be overcome. In a continuation of our work on ring-closing metathesis[12] and the synthesis of bio-active heterocycles,[13] we have utilized the ring-closing metathesis protocol for the synthesis of pyrimidine-annulated azepine and azocine derivatives. Here we report our results.

For the synthesis of pyrimido-azepine and azocine derivatives, compounds **4a–c**, which are common starting materials, were prepared according to our recently published procedure.[14,15] 5-Bromouracil derivatives **1a–c** were subjected to allylamine in ethanol to give the 5-allylaminouracil derivatives **2a–c** followed by $BF_3{\cdot}Et_2O$ catalyzed Claisen rearrangement to give the 5-amino-6-allyluracil derivatives **3a–c** in excellent yields. Treatment of compounds **3a–c** with *p*-TsCl in pyridine gave the corresponding tosyl derivatives **4a–c**, which were used as the starting materials for the present study. The route for the preparation of these starting materials **4a–c** are shown in Scheme 1.

The required precursors **5a–c** for the synthesis of pyrimido-azepine derivatives, and **5d–f** for the synthesis of pyrimido-azocine derivatives, were prepared in 90–94% yields by the reaction of **4a–c** with either allyl bromide or homoallyl bromide, in the presence of anhydrous potassium carbonate in refluxing acetone for 4–5 hours (Scheme 2).

Finally, for the synthesis of the target pyrimidine-fused azepine and azocine derivatives from the substrates **5a–f**, the ring-closing metathesis strategy was adopted. Among the available metathesis catalysts (Figure 2), we used catalyst A (Grubbs 1st generation) for the present work.

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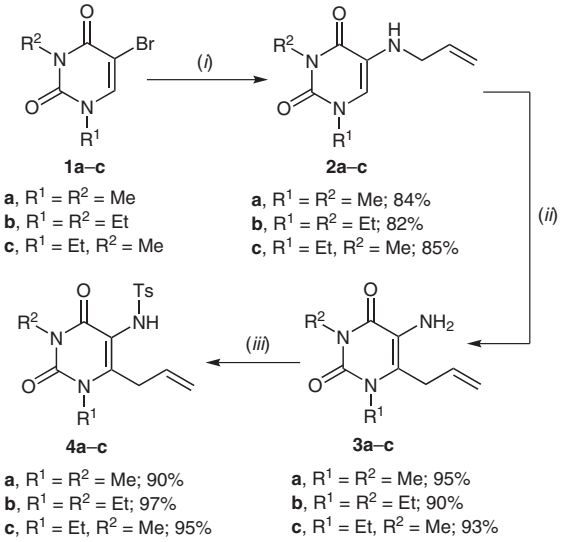
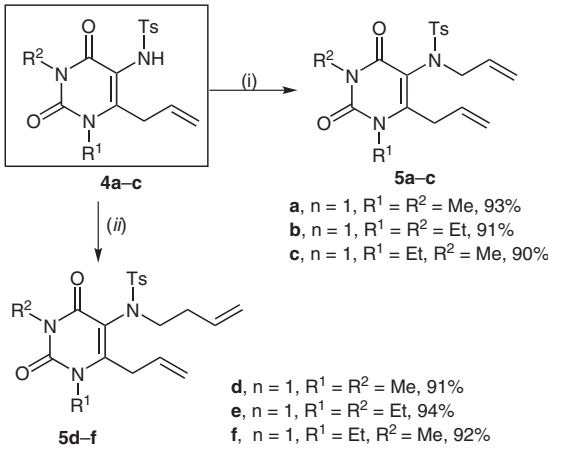


Scheme 1 Synthesis of starting materials **4a–c**. *Reagents and conditions*: (i) allyl amine, EtOH, reflux, 5–6 h; (ii) $BF_3{\cdot}OEt_2$, xylene, 120 °C, 4–5 h; (iii) TsCl, Py, 80 °C, 1–2 h.



Scheme 2 Synthesis of precursors **5a–f**. *Reagents and conditions*: (i) allyl bromide, K_2CO_3, acetone, reflux, 4–5 h; (ii) homoallyl bromide, K_2CO_3, acetone, reflux, 4–5 h.

When a dichloromethane solution of the substrate **5a** and ruthenium carbene complex **A** (5 mol%) was stirred at room temperature for ten hours under a nitrogen atmosphere, ring-closing metathesis proceeded smoothly to afford the azepine derivative **6a** in 90% yield (Scheme 3).

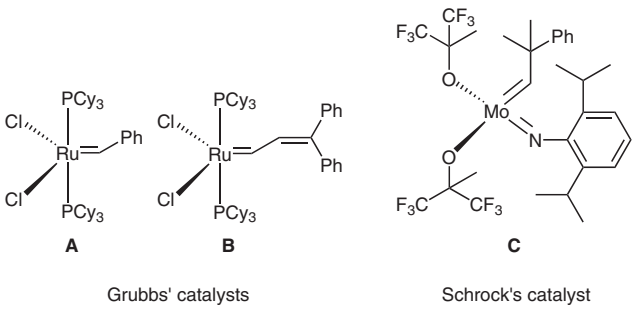
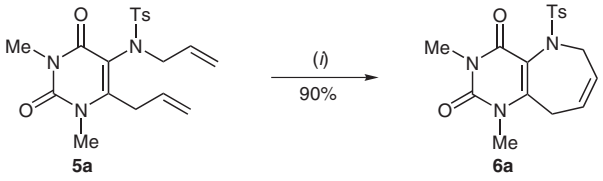


Figure 2



Scheme 3 Synthesis of azepine derivative **6a**. *Reagents and conditions*: (i) anhydrous CH_2Cl_2, Grubbs catalyst **A**, r.t., 10 h.

Encouraged by this result, further substrates **5b–f** were similarly treated with the catalyst **A** in dichloromethane to afford the corresponding azepine derivatives **6b** and **6c**, and azocine derivatives **6d–f** in 85–89% yields. The results are summarized in Table 1.

Table 1 Synthesis of Pyrimidine-Containing Azepine and Azocine Derivatives **6a–f**

Entry	Starting material **5**	Product **6**	Yield (%)
1	**5a**	**6a**	90
2	**5b**	**6b**	88
3	**5c**	**6c**	87
4	**5d**	**6d**	89
5	**5e**	**6e**	87
6	**5f**	**6f**	85

In conclusion, based on combined aza-Claisen rearrangement and ring-closing metathesis, we have developed a general and straightforward methodology for the synthesis of pyrimido-azepine and azocine derivatives in excellent yields. It is important to note that pyrimidine

derivatives and its fused heterocycles such as purines, pyrrolopyrimidines, pyrazolopyrimidine, etc., constitute the backbone of several biologically active compounds. For example, 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones have been used as anticancer agents[16] and HIV-integrase inhibitors,[17] and pteridines are potent antitumor agents.[18] For this reason, novel methodologies for the synthesis of pyrimidine scaffolds are of particular interest in medicinal chemistry. This sequence affords a very short synthesis of those derivatives and provides easy access to libraries for medicinal and pharmaceutical applications.

Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded with KBr discs with a Perkin–Elmer 120–000A apparatus. ^{1}H NMR spectra were determined as solutions in $CDCl_3$ with TMS as internal standard on a Bruker DPX-400 instrument. ^{13}C NMR spectra were determined as solutions in $CDCl_3$ on a Bruker DPX-400 instrument. MS were recorded with a Qtof Micro YA263 instrument. CHN analyses were recorded on a 2400 series II CHN analyzer (Perkin–Elmer) in the Chemistry Department of Kalyani University. Silica gel (60–120 mesh) was used for chromatographic separation. Silica gel-G [E-Mark (India)] was used for TLC. Petroleum ether (PE) refers to the fraction boiling between 60 and 80 °C.

_N_-Allyl-_N_-(6-allyl-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-4-methylbenzenesulfonamide (5a); Typical Procedure

A mixture of compound **4a** (0.50 g, 1.43 mmol), allyl bromide (0.35 g, 2.86 mmol) and anhydrous K_2CO_3 (1.0 g) was stirred for 4 h in refluxing acetone (50 mL). The reaction mixture was cooled, filtered and the solvent was removed. The residual mass was extracted with chloroform (3 × 20 mL), washed with H_2O (2 × 10 mL) and brine (5 mL) and dried (Na_2SO_4). Removal of the chloroform gave the crude product, which was purified by chromatography over silica gel (60–120 mesh; PE–EtOAc, 9:1) to give compound **5a**.

Yield: 93%; white solid; mp 94–96 °C.

IR (KBr): 1701, 1654, 1343 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.42 (s, 3 H), 3.22 (s, 3 H), 3.45 (s, 3 H), 3.50 (dd, *J* = 16.6, 5.3 Hz, 1 H), 3.85 (q, *J* = 9.0 Hz, 1 H), 3.92 (dd, *J* = 16.6, 5.2 Hz, 1 H), 4.24 (dd, *J* = 13.9, 5.1 Hz, 1 H), 5.04 (d, *J* = 10.6 Hz, 2 H), 5.17 (d, *J* = 17.4 Hz, 1 H), 5.30 (d, *J* = 10.3 Hz, 1 H), 5.70–5.84 (m, 1 H), 5.85–5.90 (m, 1 H), 7.28 (d, *J* = 8.0 Hz, 2 H), 7.71 (d, *J* = 8.0 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.3, 28.4, 32.5, 34.2, 45.4, 111.8, 119.2, 119.9, 128.2, 129.2, 132.6, 133.1, 135.9, 143.8, 151.5, 156.8, 159.7.

MS: *m*/*z* = 389 [M$^+$].

Anal. Calcd for $C_{19}H_{23}N_3O_4S$: C, 58.59; H, 5.95; N, 10.79. Found: C, 58.71; H, 5.92; N, 10.87.

_N_-Allyl-_N_-(6-allyl-1,3-diethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-4-methylbenzenesulfonamide (5b)

Yield: 91%; white solid; mp 116–118 °C.

IR (KBr): 1705, 1651, 1340 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.07 (t, *J* = 7.0 Hz, 3 H), 1.27 (t, *J* = 7.0 Hz, 3 H), 2.40 (s, 3 H), 3.49 (dd, *J* = 16.6, 5.3 Hz, 1 H), 3.85 (q, *J* = 6.9 Hz, 4 H), 3.90 (dd, *J* = 16.6, 5.2 Hz, 1 H), 4.25 (dd, *J* = 13.9, 5.1 Hz, 2 H), 5.04 (d, *J* = 10.6 Hz, 2 H), 5.17 (d, *J* = 17.4 Hz, 1 H), 5.27 (d, *J* = 10.3 Hz, 1 H), 5.73–5.87 (m, 1 H), 5.88–5.93 (m, 1 H), 7.26 (d, *J* = 8.0 Hz, 2 H), 7.67 (d, *J* = 8.0 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.6, 14.3, 21.6, 33.2, 36.8, 41.2, 51.9, 111.9, 118.8, 119.8, 128.2, 129.3, 132.6, 133.1, 136.0, 143.7, 150.6, 156.5, 159.3.

MS: *m*/*z* = 417 [M$^+$].

Anal. Calcd for $C_{21}H_{27}N_3O_4S$: C, 60.41; H, 6.52; N, 10.06. Found: C, 60.34; H, 6.59; N, 10.16.

_N_-Allyl-_N_-(6-allyl-1-ethyl-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-4-methylbenzenesulfonamide (5c)

Yield: 90%; white solid; mp 110–112 °C.

IR (KBr): 1707, 1660, 1344 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.28 (t, *J* = 7.2 Hz, 3 H), 2.42 (s, 3 H), 3.22 (s, 3 H), 3.50 (dd, *J* = 16.6, 5.3 Hz, 1 H), 3.85 (q, *J* = 7.6 Hz, 2 H), 4.07 (dd, *J* = 16.6, 5.2 Hz, 2 H), 4.22 (dd, *J* = 13.9, 5.1 Hz, 1 H), 5.04 (d, *J* = 10.0 Hz, 2 H), 5.17 (d, *J* = 17.3 Hz, 1 H), 5.27 (d, *J* = 10.3 Hz, 1 H), 5.73–5.75 (m, 1 H), 5.90–5.92 (m, 1 H), 7.28 (d, *J* = 8.0 Hz, 2 H), 7.72 (d, *J* = 7.6 Hz, 2 H).

MS: *m*/*z* = 403 [M$^+$].

Anal. Calcd for $C_{20}H_{25}N_3O_4S$: C, 59.53; H, 6.25; N, 10.41. Found: C, 59.69; H, 6.29; N, 10.32.

_N_-(6-Allyl-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-_N_-(but-3-enyl)-4-methylbenzenesulfonamide (5d)

Reaction performed according to the typical procedure described above using homoallyl bromide in place of allyl bromide.

Yield: 91%; white solid; mp 102–104 °C.

IR (KBr): 1700, 1654, 1345 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.01 (m, 1 H), 2.13–2.22 (m, 1 H), 2.42 (s, 3 H), 3.22 (s, 3 H), 3.42 (s, 3 H), 3.44–3.46 (m, 1 H), 3.60 (m, 1 H), 4.04 (m, 1 H), 4.92 (m, 1 H), 5.04 (d, *J* = 10.6 Hz, 2 H), 5.19 (d, *J* = 17.5 Hz, 1 H), 5.32 (d, *J* = 10.4 Hz, 1 H), 5.57–5.64 (m, 1 H), 5.85–5.90 (m, 1 H), 7.27 (d, *J* = 8.2 Hz, 2 H), 7.71 (d, *J* = 8.2 Hz, 2 H).

MS: *m*/*z* = 403 [M$^+$].

Anal. Calcd for $C_{20}H_{25}N_3O_4S$: C, 59.53; H, 6.25; N, 10.41. Found: C, 59.61; H, 6.30; N, 10.32.

_N_-(6-Allyl-1,3-diethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-_N_-(but-3-enyl)-4-methylbenzenesulfonamide (5e)

Yield: 94%; white solid; mp 106–108 °C.

IR (KBr): 1703, 1651, 1340 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.13 (t, *J* = 6.9 Hz, 3 H), 1.30 (t, *J* = 7.0 Hz, 3 H), 2.34–2.38 (m, 2 H), 2.42 (s, 3 H), 3.68–3.72 (m, 1 H), 3.83–3.92 (m, 1 H), 3.93–4.07 (m, 4 H), 4.08–4.15 (m, 2 H), 4.97–5.06 (m, 2 H), 5.19 (d, *J* = 17.6 Hz, 1 H), 5.31 (d, *J* = 10.4 Hz, 1 H), 5.66–5.70 (m, 1 H), 5.79–5.86 (m, 1 H), 7.28 (d, *J* = 8.4 Hz, 2 H), 7.72 (d, *J* = 8.4 Hz, 2 H).

MS: *m*/*z* = 431 [M$^+$].

Anal. Calcd for $C_{22}H_{29}N_3O_4S$: C, 61.23; H, 6.77; N, 9.74. Found: C, 61.33; H, 6.86; N, 9.82.

_N_-(6-Allyl-1-ethyl-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-_N_-(but-3-enyl)-4-methylbenzenesulfonamide (5f)

Yield: 92%; white solid; mp 126–128 °C.

IR (KBr): 1699, 1652, 1346 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.30 (t, *J* = 7.2 Hz, 3 H), 2.08–2.17 (m, 1 H), 2.23–2.31 (m, 1 H), 2.42 (s, 3 H), 3.24 (s, 3 H), 3.28–3.31 (m, 1 H), 3.58–3.66 (m, 2 H), 3.89–3.99 (m, 2 H), 4.07–4.14 (m, 1 H), 4.99–5.03 (m, 2 H), 5.19 (d, *J* = 17.6 Hz, 1 H), 5.31 (d, *J* = 10.4 Hz, 1 H), 5.60–5.71 (m, 1 H), 5.93–6.01 (m, 1 H), 7.28 (d, *J* = 8.4 Hz, 2 H), 7.72 (d, *J* = 8.4 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.3, 21.6, 28.3, 33.1, 33.2, 41.4, 48.5, 112.2, 116.9, 118.7, 128.3, 129.2, 132.6, 134.6, 135.9, 143.7, 150.9, 156.2, 159.9.

MS: *m*/*z* = 417 [M$^+$].

Anal. Calcd for $C_{21}H_{27}N_3O_4S$: C, 60.41; H, 6.52; N, 10.06. Found: C, 60.48; H, 6.56; N, 10.01.

(*Z*)-1,3-Dimethyl-5-tosyl-5,6-dihydro-1*H*-pyrimido[5,4-*b*]azepine-2,4(3*H*,9*H*)-dione (6a); Typical Procedure

5a (100 mg, 0.26 mmol) was taken in anhydrous CH_2Cl_2 (7 mL) in a small flask and degassed for 10 min with anhydrous N_2 gas. Grubbs' catalyst **A** (11 mg, 5 mol%) was dissolved in anhydrous CH_2Cl_2 and also degassed for 10 min. The catalyst solution was injected into the solution of compound **5a** and the solution was stirred at 25 °C for 10 h. The solvent was removed under reduced pressure to give a dark mass, which was purified by column chromatography over silica gel (PE–EtOAc, 8:2) to give the product **6a**.

Yield: 90%; white solid; mp 182–184 °C.

IR (KBr): 1710, 1654, 1328 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.42 (s, 3 H), 3.13 (q, *J* = 8.7 Hz, 1 H), 3.35 (s, 3 H), 3.52 (s, 3 H), 3.62 (d, *J* = 18.4 Hz, 1 H), 4.25 (t, *J* = 18.3 Hz, 2 H), 5.55–5.58 (m, 1 H), 5.73–5.77 (m, 1 H), 7.32 (d, *J* = 8.0 Hz, 2 H), 8.06 (d, *J* = 8.1 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.6, 26.6, 29.0, 33.2, 46.6, 112.7, 119.7, 128.4, 129.1, 129.3, 136.8, 143.8, 151.5, 157.9, 160.4.

MS: *m*/*z* = 361 [M$^+$].

Anal. Calcd for $C_{17}H_{19}N_3O_4S$: C, 56.50; H, 5.30; N, 11.63. Found: C, 56.64; H, 5.37; N, 11.68.

(*Z*)-1,3-Diethyl-5-tosyl-5,6-dihydro-1*H*-pyrimido[5,4-*b*]azepine-2,4(3*H*,9*H*)-dione (6b)

Yield: 88%; white solid; mp 136–138 °C.

IR (KBr): 1705, 1656, 1332 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.21 (t, *J* = 6.9 Hz, 3 H), 1.28 (t, *J* = 7.0 Hz, 3 H), 2.42 (s, 3 H), 3.03 (q, *J* = 8.9 Hz, 1 H), 3.61 (d, *J* = 18.6 Hz, 1 H), 3.94–4.10 (m, 4 H), 4.26 (t, *J* = 16.0 Hz, 2 H), 5.56–5.59 (m, 1 H), 5.75–5.79 (m, 1 H), 7.32 (d, *J* = 7.9 Hz, 2 H), 8.05 (d, *J* = 8.0 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.7, 14.6, 21.5, 26.2, 37.2, 40.9, 46.5, 112.8, 120.1, 128.3, 129.2, 129.3, 136.8, 143.7, 150.7, 157.6, 159.9.

MS: *m*/*z* = 389 [M$^+$].

Anal. Calcd for $C_{19}H_{23}N_3O_4S$: C, 58.59; H, 5.95; N, 10.79. Found: C, 58.70; H, 6.02; N, 10.86.

(*Z*)-1-Ethyl-3-methyl-5-tosyl-5,6-dihydro-1*H*-pyrimido[5,4-*b*]azepine-2,4(3*H*,9*H*)-dione (6c)

Yield: 87%; white solid; mp 160–162 °C.

IR (KBr): 1703, 1654, 1330 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.21 (t, *J* = 6.9 Hz, 3 H), 2.42 (s, 3 H), 3.06 (q, *J* = 8.8 Hz, 1 H), 3.34 (s, 3 H), 3.60 (d, *J* = 18.5 Hz, 1 H), 3.98–4.11 (m, 2 H), 4.26 (t, *J* = 18.0 Hz, 2 H), 5.56–5.59 (m, 1 H), 5.75–5.79 (m, 1 H), 7.32 (d, *J* = 7.6 Hz, 2 H), 8.06 (d, *J* = 7.6 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.7, 21.6, 26.3, 28.6, 41.1, 46.6, 112.8, 120.1, 128.4, 129.3, 129.5, 136.8, 143.8, 151.2, 157.7, 160.5.

MS: *m*/*z* = 375 [M$^+$].

Anal. Calcd for $C_{18}H_{21}N_3O_4S$: C, 57.58; H, 5.64; N, 11.19. Found: C, 57.69; H, 5.71; N, 11.11.

(*Z*)-1,3-Dimethyl-5-tosyl-5,6,7,10-tetrahydropyrimido[5,4-*b*]azocine-2,4(1*H*,3*H*)-dione (6d)

Yield: 89%; white solid; mp 178–180 °C.

IR (KBr): 1712, 1651, 1340 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.26 (q, *J* = 7.6 Hz, 1 H), 2.42 (s, 3 H), 2.64 (t, *J* = 11.4 Hz, 1 H), 2.96–3.08 (m, 2 H), 3.29 (s, 3 H), 3.56 (s, 3 H), 3.81 (dd, *J* = 14.8, 3.0 Hz, 1 H), 4.10 (q, *J* = 8.2 Hz, 1 H), 5.87–5.93 (m, 2 H), 7.31 (d, *J* = 7.8 Hz, 2 H), 8.06 (d, *J* = 7.9 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.6, 28.6, 29.1, 29.5, 33.1, 48.7, 112.8, 127.6, 128.8, 129.3, 133.6, 136.2, 143.8, 151.4, 160.2.

MS: *m*/*z* = 375 [M$^+$].

Anal. Calcd for $C_{18}H_{21}N_3O_4S$: C, 57.58; H, 5.64; N, 11.19. Found: C, 57.68; H, 5.59; N, 11.23.

(*Z*)-1,3-Diethyl-5-tosyl-5,6,7,10-tetrahydropyrimido[5,4-*b*]azocine-2,4(1*H*,3*H*)-dione (6e)

Yield: 87%; white solid; mp 132–134 °C.

IR (KBr): 1703, 1655, 1331 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.14 (t, *J* = 6.9 Hz, 3 H), 1.35 (t, *J* = 7.0 Hz, 3 H), 2.26 (q, *J* = 7.4 Hz, 1 H), 2.41 (s, 3 H), 2.66 (t, *J* = 11.1 Hz, 1 H), 2.96–3.00 (m, 2 H), 3.69 (q, *J* = 6.9 Hz, 2 H), 3.90 (q, *J* = 6.9 Hz, 2 H), 4.08–4.12 (m, 1 H), 4.26–4.29 (m, 1 H), 5.87–5.93 (m, 2 H), 7.29 (d, *J* = 6.8 Hz, 2 H), 7.91 (d, *J* = 7.4 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.8, 14.5, 21.6, 28.9, 29.1, 37.1, 42.0, 48.8, 112.8, 128.2, 128.7, 129.2, 133.1, 136.3, 143.7, 150.5, 159.9, 160.2.

MS: *m*/*z* = 403 [M$^+$].

Anal. Calcd for $C_{20}H_{25}N_3O_4S$: C, 59.53; H, 6.25; N, 10.41. Found: C, 59.41; H, 6.19; N, 10.48.

(*Z*)-1-Ethyl-3-methyl-5-tosyl-5,6,7,10-tetrahydropyrimido[5,4-*b*]azocine-2,4(1*H*,3*H*)-dione (6f)

Yield: 85%; white solid; mp 188–190 °C.

IR (KBr): 1709, 1651, 1325 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.14 (t, *J* = 7.2 Hz, 3 H), 2.26–2.32 (m, 1 H), 2.46 (s, 3 H), 2.67–2.72 (m, 1 H), 2.96–3.07 (m, 2 H), 3.32 (s, 3 H), 3.71–3.80 (m, 1 H), 3.82–3.88 (m, 1 H), 4.12–4.17 (m, 1 H), 4.32–4.37 (m, 1 H), 5.87–5.97 (m, 2 H), 7.34 (d, *J* = 8.4 Hz, 2 H), 7.99 (d, *J* = 8.4 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.6, 21.6, 28.5, 28.9, 29.0, 42.1, 48.8, 112.9, 128.2, 128.8, 129.3, 133.2, 136.2, 143.8, 150.9, 159.8, 160.7.

MS: *m*/*z* = 389 [M$^+$].

Anal. Calcd for $C_{19}H_{23}N_3O_4S$: C, 58.59; H, 5.95; N, 10.79. Found: C, 58.68; H, 5.99; N, 10.73.

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