Concise Synthesis of Pyrimido-azocine Derivatives via Aza-Claisen Rearrangement and Intramolecular Heck Reaction

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Abstract: An expedient approach involving $BF_3{\cdot}OEt_2$-catalyzed aza-Claisen rearrangement and palladium-catalyzed intramolecular Heck reaction for the synthesis of pyrimidine-fused azocine derivatives is described. The mechanistic interpretation of the plausible mode of cyclization is also described.

Key words: uracil, aza-Claisen rearrangement, azocine, Heck reaction

As a result of rich chemistry and biology of nitrogen-containing compounds, N-heterocycles, in particular eight-membered azocines, are key structures in many natural products. For example, the alkaloid manzamine A (**1**), isolated from the sea sponges *Haliclona sp*.,[1] *Xestopongia sp*.,[2] and *Pellina sp*.,[3] found in the waters of the Okinawa Sea, exhibits significant antileukemic and antimicrobial activity.[4] The okaramine A (**2**) and okaramine N (**3**) are biologically active alkaloids[5] isolated from the fungus *Penicillium simplicissum*[6] (ATCC 90288) (Figure 1).

Moreover pyrimidine derivatives and pyrimidine-fused heterocycles, such as purines, pyrrolopyrimidines, pyrazolopyrimidines etc., constitute the backbone of several biologically active compounds. 4*H*-Pyrido[1,2-*a*]pyrimidin-4-ones have been used as anticancer agents,[7] and HIV-integrase inhibitors.[8] Pteridines are potent antitumor agents.[9] Therefore, novel methodologies for the synthesis of pyrimidine-fused azocine derivatives are of particular interest in medicinal chemistry. Despite their bioactivity, azocine-fused ring systems have not been sufficiently investigated. One barrier to this, generally, may be due to unsatisfactory synthetic procedures.[10] Cyclization strategies to azocine rings are often inhibited due to entropic factors and transannular interactions.[11]

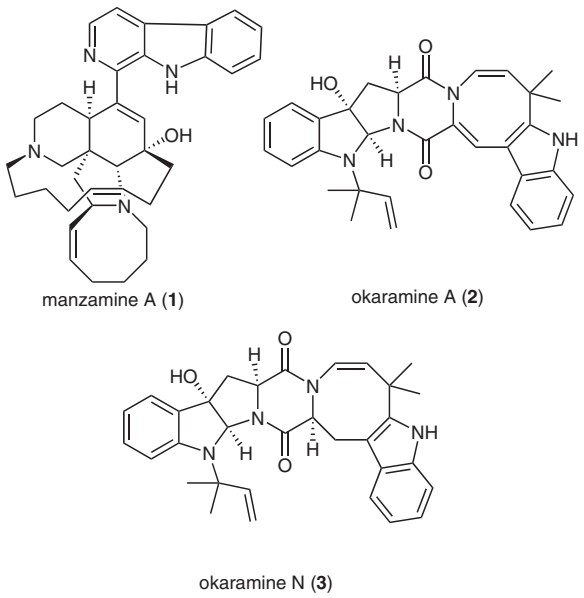
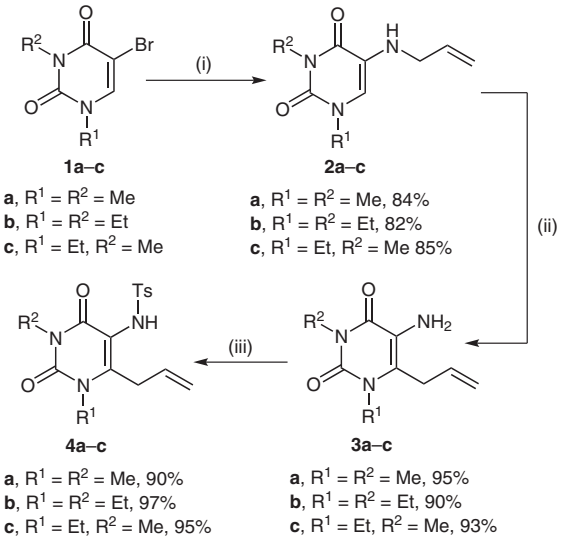


Figure 1 Examples of azocine-containing alkaloids

We recently reported pyrimidine-fused azocine derivatives by a thiophenol-mediated radical cyclization strategy.[12] In continuation of our work in palladium chemistry,[13] we undertook an initiative to synthesize pyrimido-azocine derivatives by palladium-catalyzed intramolecular Heck reaction. Here we disclose our results.

For the synthesis of pyrimidine-fused azocine derivatives, the starting materials **4a–c** were prepared according to our recently published procedure.[12,14] 5-Bromouracil derivatives **1a–c** were subjected to allylamine in ethanol to give 5-(allylamino)uracil derivatives **2a–c**, this was followed by boron trifluoride–diethyl ether complex catalyzed Claisen rearrangement to give the 6-allyl-5-aminouracil derivatives **3a–c** in excellent yields. Treatment of compounds **3a–c** with tosyl chloride in pyridine gave the corresponding tosyl derivatives **4a–c**, which are the starting



Scheme 1 Synthesis of starting materials **4a–c**. *Reagents and conditions:* (i) allylamine, 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.

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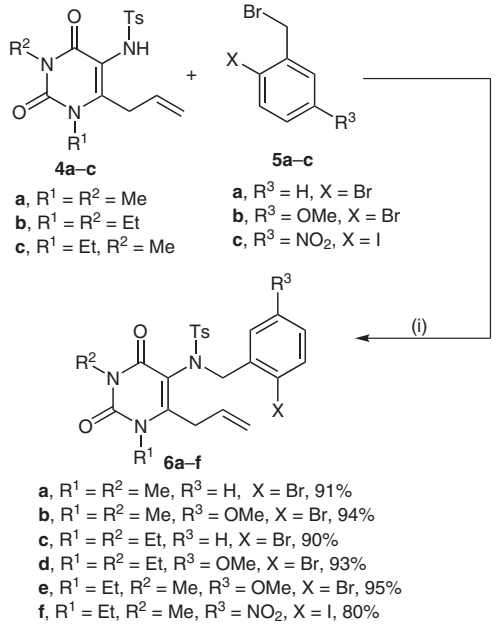
materials for the present study. The schematic route for the preparation of these starting materials **4a–c** is shown in Scheme 1.

The required Heck precursors **6a–f** for our present study were synthesized in 80–95% yields by refluxing 6-allyl-5-(tosylamino)uracil derivatives **4a–c** with benzyl bromides **5a–c** in anhydrous acetone in the presence of anhydrous potassium carbonate for four to five hours (Scheme 2).

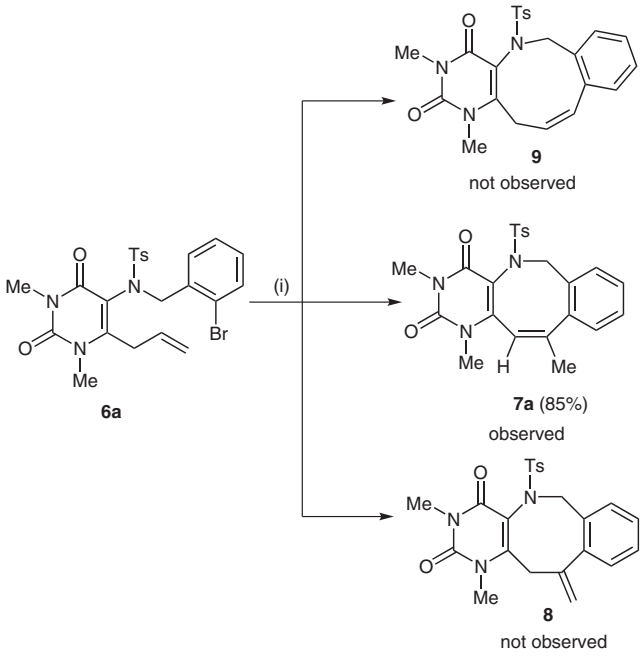
For the synthesis of our target azocine derivatives by the implementation of the Heck reaction, we initiated our investigation with substrate **6a**. When the compound **6a** was heated at 90 °C in anhydrous *N*,*N*-dimethylformamide using potassium acetate (2.75 equiv) as a base, tetrabutylammonium bromide (1.2 equiv) as a promoter, and palladium(II) acetate (10 mol%) as the catalyst under a nitrogen atmosphere, the reaction proceeded smoothly and was complete within one hour affording the pyrimido-azocine derivative **7a** in 85% yield. Among the different possibilities only one product was obtained showing complete regioselectivity (Scheme 3).

Then we performed Heck reactions of other substrates **6b–e** under the same condition to give the azocine derivatives **7b–e** in 80–85% yields. However, substrate **6f** containing the 5-nitro-2-iodobenzyl moiety afforded an intractable complex mixture. Subsequently we changed the catalyst [$Pd(PPh_3)_4$, $Pd_2(dba)_3$], base (Et_3N, Ag_2CO_3), and solvent (DMA, MeCN) and we also tried different ligands [Ph_3P, (o-Tol)$_3$P], but in all cases only complex mixtures of products were obtained. The results are summarized in Table 1.

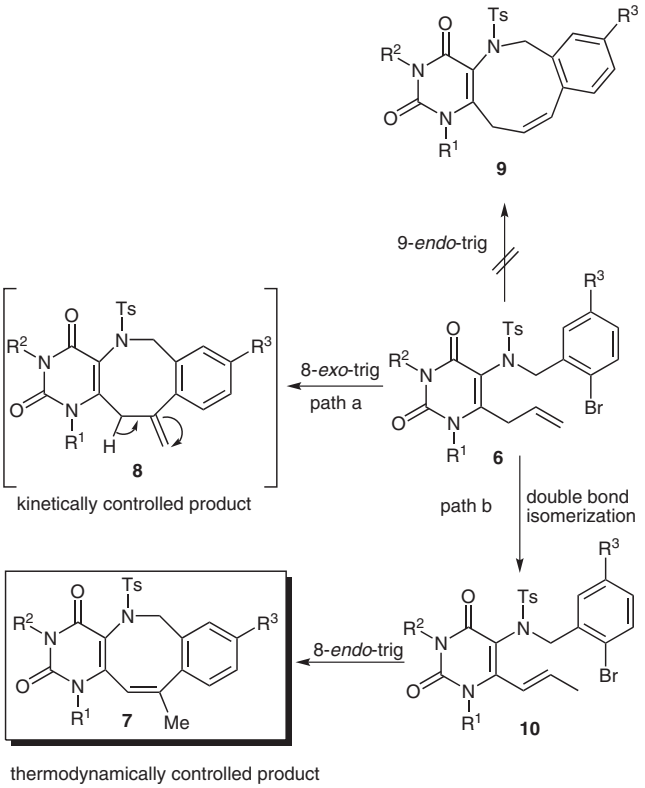
The formation of the endocyclic products **7a–e** may be rationalized via two possible pathways, i.e. either through an 8-*exo* mode (path a) of cyclization to give the kinetically controlled products **8**, which by double bond isomerization may give the thermodynamically stable products **7**. The other possibility is that a double bond isomerization (path b) prior to the Heck reaction may occur followed by 8-*endo* Heck cyclization to give the products **7** (Scheme 4).



Scheme 2 Synthesis of Heck precursors **6a–f**. *Reagents and conditions:* (i) K_2CO_3, acetone, reflux, 4–5 h.

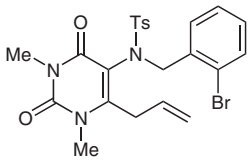
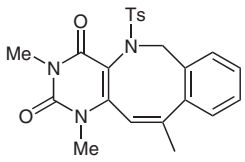
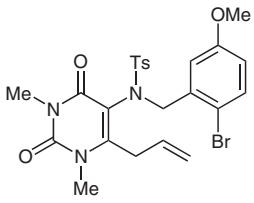
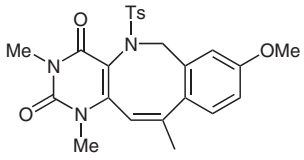
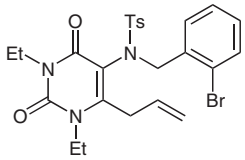
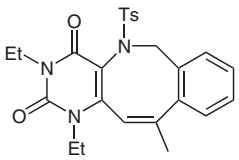
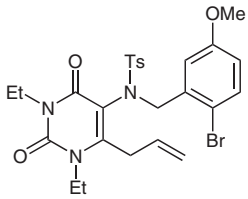
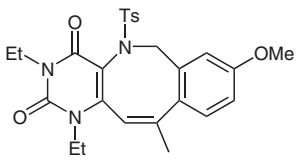
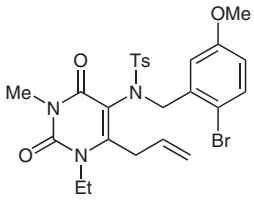
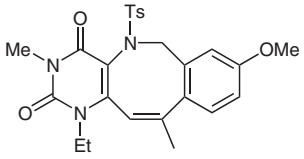
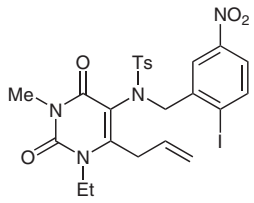


Scheme 3 Synthesis of pyrimido-azocine derivative **7a**. *Reagents and conditions:* (i) $Pd(OAc)_2$ (10 mol%), KOAc (2.75 equiv), TBAB (1.2 equiv), DMF, 90 °C, 1 h.



Scheme 4 Possible mechanistic pathway of Heck cyclization

Table 1 Synthesis of Pyrimido-azocine Derivatives via Heck Reactions

Entry	Heck precursors	Azocine derivatives	Time (h)	Yield[a] (%)
1	 **6a**	 **7a**	1	85
2	 **6b**	 **7b**	1	83
3	 **6c**	 **7c**	1.5	80
4	 **6d**	 **7d**	1.5	81
5	 **6e**	 **7e**	1	85
6	 **6f**	–[b]	1.5	–

[a] Isolated yield.
[b] Complex mixture.

In conclusion, we have developed an efficient method for the construction of pyrimido-azocine derivatives by palladium-catalyzed, ligand-free Heck coupling reaction. Here it is important to note that recently Hii et al. reported[15] the synthesis of benzazocine derivatives by a palladium-catalyzed Heck cyclization strategy using a phosphine ligand and harsh reaction conditions (140 °C) with a long reaction time required for completion (22 h). Additionally, they obtained an inseparable mixture of 7-*exo*-trig and 8-*endo*-trig cyclized products; they have studied the temperature and ligand effect on the regioselectivity. Our method is relatively simple, straightforward, and regioselective and the reaction was complete within 1–1.5 hours.

Melting points were determined in open capillaries and are uncorrected. IR spectra (KBr discs) were determined on a Perkin Elmer 120-000A spectrophotometer. ^{1}H NMR ($CDCl_3$ soln, TMS as internal standard) were determined on a Bruker DPX-400. ^{13}C NMR ($CDCl_3$ soln) were determined on a Bruker DPX-400. MS were re-

corded on a Qtof Micro YA263 instrument. CHN was recorded on a Perkin Elmer 2400 series II CHN analyzer. Silica gel (60–120 mesh) was used for chromatographic separation. Silica gel G [E. Merck (India)] was used for TLC. Petroleum ether (PE) refers to the fraction with bp 60–80 °C.

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

A mixture of **4a** (0.50 g, 1.43 mmol), 2-bromobenzyl bromide (**5a**, 0.43 g, 1.71 mmol), and dry K_2CO_3 (1.0 g) in acetone (50 mL) was stirred and refluxed for 4 h. The mixture was cooled and filtered and the solvent was removed. The residual mass was extracted with $CHCl_3$ (3 × 20 mL), washed with H_2O (2 × 10 mL) and brine (5 mL) and dried (Na_2SO_4). Removal of $CHCl_3$ gave a crude product that was chromatographed (silica gel, 60–120 mesh, PE–EtOAc, 9:1) to give **6a** as a white solid; yield: 91%; mp 184–186 °C.

IR (KBr): 1708, 1656, 1342 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.43 (s, 3 H), 3.15 (dd, *J* = 16.7, 5.1 Hz, 1 H), 3.22 (s, 3 H), 3.30 (s, 3 H), 3.55 (dd, *J* = 16.6, 4.8 Hz, 1 H), 4.68 (d, *J* = 17.4 Hz, 1 H), 4.73 (d, *J* = 13.4 Hz, 1 H), 4.87 (d, *J* = 10.2 Hz, 1 H), 4.96 (d, *J* = 13.3 Hz, 1 H), 5.00–5.03 (m, 1 H), 7.10 (t, *J* = 7.4 Hz, 1 H), 7.20–7.25 (m, 1 H), 7.29 (d, *J* = 7.8 Hz, 2 H), 7.44 (t, *J* = 7.8 Hz, 2 H), 7.72 (d, *J* = 8.0 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.9, 28.5, 33.3, 33.6, 51.5, 111.2, 118.5, 125.5, 128.1, 128.4, 129.6, 130.0, 131.4, 132.8, 132.9, 133.0, 133.3, 135.4, 136.4, 144.1, 151.7, 157.5, 159.9.

MS: *m*/*z* = 517 [M^+], 519 [M + 2]$^+$.

Anal. Calcd for $C_{23}H_{24}BrN_3O_4S$: C, 53.29; H, 4.67; N, 8.11. Found: C, 53.38; H, 4.71; N, 8.01.

_N_-(6-Allyl-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-_N_-(2-bromo-5-methoxybenzyl)-4-methylbenzenesulfonamide (6b)

White solid; yield: 94%; mp 142–144 °C.

IR (KBr): 1699, 1651, 1341 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.42 (s, 3 H), 3.20 (dd, *J* = 16.7, 5.1 Hz, 2 H), 3.30 (s, 6 H), 3.70 (s, 3 H), 4.52 (d, *J* = 13.8 Hz, 1 H), 4.73 (d, *J* = 12.4 Hz, 2 H), 4.89 (d, *J* = 11.8 Hz, 1 H), 5.62–5.75 (m, 1 H), 6.65 (d, *J* = 6.4 Hz, 1 H), 7.02–7.09 (m, 1 H), 7.24–7.28 (m, 3 H), 7.71 (d, *J* = 6.9 Hz, 1 H), 7.79 (d, *J* = 6.9 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.6, 28.3, 33.1, 33.4, 51.5, 55.4, 111.0, 118.3, 120.0, 128.1, 128.3, 129.4, 131.2, 132.9, 133.2, 133.5, 135.8, 135.9, 136.1, 136.6, 143.9, 151.5, 157.3, 159.7.

MS: *m*/*z* = 547 [M^+], 549 [M + 2]$^+$.

Anal. Calcd for $C_{24}H_{26}BrN_3O_5S$: C, 52.56; H, 4.78; N, 7.66. Found: C, 52.67; H, 4.72; N, 7.71.

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

White solid; yield: 90%; mp 154–156 °C.

IR (KBr): 1704, 1658, 1339 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.11 (t, *J* = 7.2 Hz, 6 H), 2.43 (s, 3 H), 3.16 (dd, *J* = 16.2, 4.8 Hz, 1 H), 3.26 (dd, *J* = 16.1, 4.3 Hz, 1 H), 3.77–3.88 (m, 4 H), 4.71 (d, *J* = 13.6 Hz, 1 H), 4.77 (d, *J* = 17.4 Hz, 1 H), 4.90 (d, *J* = 10.1 Hz, 1 H), 4.96 (d, *J* = 13.6 Hz, 1 H), 5.15–5.22 (m, 1 H), 7.10 (t, *J* = 7.3 Hz, 1 H), 7.23 (t, *J* = 7.5 Hz, 1 H), 7.29 (d, *J* = 7.7 Hz, 2 H), 7.43 (d, *J* = 7.8 Hz, 1 H), 7.48 (d, *J* = 7.5 Hz, 1 H), 7.74 (d, *J* = 7.8 Hz, 2 H).

MS: *m*/*z* = 545 [M^+], 547 [M + 2]$^+$.

Anal. Calcd for $C_{25}H_{28}BrN_3O_4S$: C, 54.95; H, 5.16; N, 7.69. Found: C, 55.07; H, 5.22; N, 7.58.

_N_-(6-Allyl-1,3-diethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-_N_-(2-bromo-5-methoxybenzyl)-4-methylbenzenesulfonamide (6d)

White solid; yield: 93%; mp 110–112 °C.

IR (KBr): 1699, 1652, 1342 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.11 (t, *J* = 7.2 Hz, 3 H), 1.16 (t, *J* = 7.2 Hz, 3 H), 2.45 (s, 3 H), 3.83 (s, 3 H), 3.85–3.91 (m, 6 H), 4.68 (d, *J* = 13.6 Hz, 1 H), 4.82 (d, *J* = 17.2 Hz, 1 H), 4.90–4.95 (m, 2 H), 5.15–5.19 (m, 1 H), 6.69 (dd, *J* = 8.8, 3.2 Hz, 1 H), 7.04 (d, *J* = 3.2 Hz, 1 H), 7.31 (d, *J* = 8.4 Hz, 3 H), 7.75 (d, *J* = 8.0 Hz, 2 H).

MS: *m*/*z* = 575 [M^+], 577 [M + 2]$^+$.

Anal. Calcd for $C_{26}H_{30}BrN_3O_5S$: C, 54.17; H, 5.25; N, 7.29. Found: C, 54.05; H, 5.13; N, 7.35.

_N_-(6-Allyl-1-ethyl-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-_N_-(2-bromo-5-methoxybenzyl)-4-methylbenzenesulfonamide (6e)

White solid; yield: 95%; mp 130–132 °C.

IR (KBr): 1700, 1652, 1343 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.13 (t, *J* = 6.9 Hz, 3 H), 2.43 (s, 3 H), 3.19–3.40 (m, 5 H), 3.71 (s, 3 H), 3.78–3.93 (m, 2 H), 4.63 (d, *J* = 13.6 Hz, 1 H), 4.71–4.96 (m, 3 H), 5.19–5.25 (m, 1 H), 6.67 (dd, *J* = 8.8, 3.0 Hz, 1 H), 7.01 (d, *J* = 3.0 Hz, 1 H), 7.26–7.31 (m, 3 H), 7.01 (d, *J* = 8.2 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.2, 21.7, 28.2, 32.7, 41.0, 51.7, 55.5, 111.4, 115.5, 116.6, 117.0, 118.0, 128.1, 128.3, 129.4, 132.1, 133.2, 133.5, 136.0, 136.3, 143.9, 151.0, 156.8, 159.2, 159.9.

MS: *m*/*z* = 561 [M^+], 563 [M + 2]$^+$.

Anal. Calcd for $C_{25}H_{28}BrN_3O_5S$: C, 53.38; H, 5.02; N, 7.47. Found: C, 53.45; H, 5.09; N, 7.42.

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

White solid; yield: 80%; mp 208–210 °C.

IR (KBr): 1680, 1622, 1520, 1349 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.19 (t, *J* = 7.1 Hz, 3 H), 2.44 (s, 3 H), 3.13 (dd, *J* = 17.2, 5.3 Hz, 1 H), 3.22 (s, 3 H), 3.52 (dd, *J* = 17.3, 5.0 Hz, 1 H), 3.72 (q, *J* = 7.2 Hz, 1 H), 3.97 (q, *J* = 7.0 Hz, 1 H), 4.65 (d, *J* = 17.4 Hz, 1 H), 4.75 (d, *J* = 14.4 Hz, 1 H), 4.82 (d, *J* = 10.4 Hz, 1 H), 5.00 (d, *J* = 14.6 Hz, 1 H), 5.27–5.31 (m, 1 H), 7.31 (d, *J* = 8.0 Hz, 2 H), 7.71 (d, *J* = 8.1 Hz, 2 H), 7.82 (d, *J* = 8.4 Hz, 1 H), 8.13 (dd, *J* = 8.6, 1.6 Hz, 1 H), 8.54 (d, *J* = 1.4 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.4, 21.7, 28.4, 32.5, 41.4, 55.7, 99.5, 111.3, 117.7, 123.4, 128.3, 129.5, 131.5, 132.0, 134.3, 135.6, 144.4, 146.1, 147.5, 150.8, 156.7, 159.7.

MS: *m*/*z* = 624 [M^+].

Anal. Calcd for $C_{24}H_{25}IN_4O_6S$: C, 46.16; H, 4.04; N, 8.97. Found: C, 46.27; H, 3.98; N, 9.08.

(_Z_)-1,3,11-Trimethyl-5-tosyl-5,6-dihydrobenzo[*f*]pyrimido[5,4-*b*]azocine-2,4(1*H*,3*H*)-dione (7a) by Heck reaction; Typical Procedure

A mixture of **6a** (150 mg, 0.29 mmol), TBAB (112 mg, 0.35 mmol), and fused KOAc (78 mg, 0.80 mmol) was taken up in anhyd DMF (10 mL) and N_2 was bubbled through the mixture. $Pd(OAc)_2$ (6.5 mg, 10 mol%) was added and the mixture was stirred at 90 °C for 1 h. The mixture was cooled, H_2O (20 mL) was added, and it was extracted with EtOAc (3 × 20 mL). The combined EtOAc extracts were washed with H_2O (4 × 10 mL) and brine (10 mL), and dried (Na_2SO_4). The solvent was distilled off to furnish a viscous mass that was purified by column chromatography (silica gel, 30%

EtOAc–hexane) to give **7a** as a white solid; yield: 85%; mp 250–252 °C.

IR (KBr): 1704, 1658, 1345 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.18 (s, 3 H), 2.44 (s, 3 H), 3.22 (s, 6 H), 3.29 (d, *J* = 13.0 Hz, 1 H), 4.85 (d, *J* = 12.9 Hz, 1 H), 5.90 (s, 1 H), 7.05 (d, *J* = 7.4 Hz, 2 H), 7.16 (t, *J* = 7.3 Hz, 1 H), 7.23 (t, *J* = 7.8 Hz, 1 H), 7.33 (d, *J* = 7.7 Hz, 2 H), 7.90 (d, *J* = 7.7 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.6, 25.7, 28.4, 33.2, 52.6, 111.2, 117.6, 127.7, 127.9, 128.1, 128.2, 129.5, 129.6, 131.3, 136.7, 140.1, 143.6, 146.1, 151.1, 154.2, 161.0.

MS: *m*/*z* = 437 [M^+].

Anal. Calcd for $C_{23}H_{23}N_3O_4S$: C, 63.14; H, 5.30; N, 9.60. Found: C, 63.02; H, 5.24; N, 9.65.

(*Z*)-8-Methoxy-1,3,11-trimethyl-5-tosyl-5,6-dihydrobenzo[*f*]pyrimido[5,4-*b*]azocine-2,4(1*H*,3*H*)-dione (7b)
White solid; yield: 83%; mp 230–232 °C.

IR (KBr): 1706, 1668, 1335 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.18 (s, 3 H), 2.44 (s, 3 H), 3.24 (s, 6 H), 3.71 (s, 3 H), 4.24 (d, *J* = 13.4 Hz, 1 H), 4.86 (d, *J* = 13.2 Hz, 1 H), 5.92 (s, 1 H), 6.57 (s, 1 H), 6.76 (d, *J* = 8.4 Hz, 1 H), 6.98 (d, *J* = 8.2 Hz, 1 H), 7.33 (d, *J* = 7.6 Hz, 2 H), 7.90 (d, *J* = 7.7 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.6, 26.0, 28.4, 33.2, 52.8, 55.2, 111.3, 113.6, 114.3, 117.3, 128.1, 129.2, 129.4, 129.5, 132.0, 132.9, 136.9, 143.5, 146.0, 151.2, 154.5, 159.0, 161.0.

MS: *m*/*z* = 467 [M^+].

Anal. Calcd for $C_{24}H_{25}N_3O_5S$: C, 61.65; H, 5.39; N, 8.99. Found: C, 61.56; H, 5.42; N, 9.04.

(*Z*)-1,3-Diethyl-11-methyl-5-tosyl-5,6-dihydrobenzo[*f*]pyrimido[5,4-*b*]azocine-2,4(1*H*,3*H*)-dione (7c)
White solid; yield: 80%; mp 192–194 °C.

IR (KBr): 1704, 1659, 1339 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.10 (t, *J* = 6.9 Hz, 6 H), 2.22 (s, 3 H), 2.44 (s, 3 H), 3.68 (q, *J* = 6.9 Hz, 1 H), 3.79–3.88 (m, 3 H), 4.28 (d, *J* = 13.3 Hz, 1 H), 4.90 (d, *J* = 13.2 Hz, 1 H), 5.99 (s, 1 H), 7.05 (dd, *J* = 6.9, 3.0 Hz, 2 H), 7.16 (t, *J* = 7.1 Hz, 1 H), 7.22 (d, *J* = 7.5 Hz, 1 H), 7.33 (d, *J* = 8.1 Hz, 2 H), 7.89 (d, *J* = 8.0 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.7, 13.9, 21.6, 25.9, 37.0, 41.7, 52.6, 111.3, 117.0, 127.8, 127.9, 128.1, 128.2, 129.5, 131.6, 136.9, 140.0, 143.5, 146.2, 150.3, 154.1, 160.6.

MS: *m*/*z* = 465 [M^+].

Anal. Calcd for $C_{25}H_{27}N_3O_4S$: C, 64.50; H, 5.85; N, 9.03. Found: C, 64.63; H, 5.91; N, 8.98.

(*Z*)-1,3-Diethyl-8-methoxy-11-methyl-5-tosyl-5,6-dihydrobenzo[*f*]pyrimido[5,4-*b*]azocine-2,4(1*H*,3*H*)-dione (7d)
White solid; yield: 81%; mp 222–224 °C.

IR (KBr): 1706, 1659, 1336 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.10 (t, *J* = 6.9 Hz, 6 H), 2.07 (s, 3 H), 2.43 (s, 3 H), 3.71 (s, 3 H), 3.84 (q, *J* = 6.9 Hz, 4 H), 4.24 (d, *J* = 13.5 Hz, 1 H), 4.91 (d, *J* = 13.5 Hz, 1 H), 5.97 (s, 1 H), 6.57 (s, 1 H), 6.75 (d, *J* = 6.6 Hz, 1 H), 6.99 (d, *J* = 8.4 Hz, 1 H), 7.32 (d, *J* = 7.8 Hz, 2 H), 7.87 (d, *J* = 7.9 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.7, 13.9, 21.6, 26.3, 37.0, 41.7, 52.8, 55.2, 111.3, 113.5, 114.1, 116.6, 128.1, 129.3, 129.4, 131.9, 133.1, 137.0, 143.5, 146.0, 150.2, 154.4, 158.9, 160.6.

MS: *m*/*z* = 495 [M^+].

Anal. Calcd for $C_{26}H_{29}N_3O_5S$: C, 63.01; H, 5.90; N, 8.48. Found: C, 63.12; H, 5.97; N, 8.42.

(*Z*)-1-Ethyl-8-methoxy-3,11-dimethyl-5-tosyl-5,6-dihydrobenzo[*f*]pyrimido[5,4-*b*]azocine-2,4(1*H*,3*H*)-dione (7e)
White solid; yield: 85%; mp 206–208 °C.

IR (KBr): 1703, 1659, 1338 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.11 (t, *J* = 6.9 Hz, 3 H), 2.15 (s, 3 H), 2.43 (s, 3 H), 3.22 (s, 3 H), 3.67 (q, *J* = 6.9 Hz, 1 H), 3.71 (s, 3 H), 3.85 (q, *J* = 6.9 Hz, 1 H), 4.24 (d, *J* = 13.2 Hz, 1 H), 4.85 (d, *J* = 13.3 Hz, 1 H), 5.91 (s, 1 H), 6.57 (s, 1 H), 6.75 (d, *J* = 8.4 Hz, 1 H), 6.97 (d, *J* = 8.4 Hz, 1 H), 7.33 (d, *J* = 7.8 Hz, 2 H), 7.88 (d, *J* = 7.7 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.8, 21.6, 26.1, 28.3, 41.7, 52.8, 55.2, 111.2, 113.5, 114.3, 116.7, 128.1, 129.2, 129.4, 131.9, 133.0, 136.9, 143.5, 146.1, 150.6, 154.1, 158.9, 161.0.

MS: *m*/*z* = 481 [M^+].

Anal. Calcd for $C_{25}H_{27}N_3O_5S$: C, 62.35; H, 5.65; N, 8.73. Found: C, 62.22; H, 5.59; N, 8.78.

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