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1-Alkyl- and (±)-1,2-Dialkyl-2,3-dihydro-1,8-naphthyridin-4(1*H*)-ones by a Tandem Michael–S_NAr Annulation Reaction

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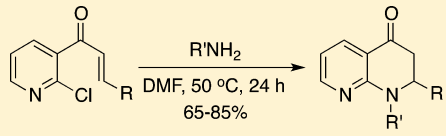
Supporting Information

ABSTRACT: A tandem Michael–S_NAr annulation reaction has been developed for the synthesis of 1-alkyl and (±)-1,2-dialkyl-2,3-dihydro-1,8-naphthyridin-4(1*H*)-ones. Treatment of 1-(2-chloropyridin-3-yl)prop-2-en-1-one (R = H) or (*E* or *Z*)-1-(2-chloropyridin-3-yl)but-2-en-1-one (R = CH_3) with R′NH_2 in DMF at 50 °C for 24 h provides 2,3-dihydro-1,8-naphthyridin-4(1*H*)-ones in 65–85% yields. Mechanistic studies suggest that the reaction sequence is initiated by Michael addition to the side chain enone.



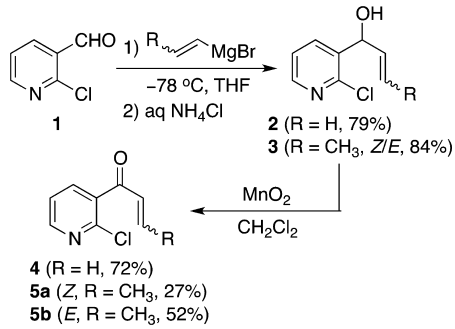
Our recent research on tandem annulation procedures involving nucleophilic aromatic substitution (S_NAr) reactions has led to the development of numerous syntheses of nitrogen heterocycles.[1,2] These earlier investigations focused primarily on sequences terminated by addition of an amine nitrogen to a fluorine-substituted aromatic ring activated by a C4 nitro group. Very few studies have examined tandem ring closures involving addition to a 2-chloropyridine in the final S_NAr reaction.[3] The current project extends the use of the 2-chloropyridine moiety as an aromatic acceptor for the tandem Michael–S_NAr reaction and reports a new synthesis of dihydronaphthyridinones.

Early investigations on the medicinal potential of dihydronaphthyridinones, and structures generated from them, demonstrated modest anaphylaxis inhibitory activity.[5] More recently, however, new derivatives have been reported as potential β-blockers for the treatment of hypertension.[6] These studies have all focused on heterocycles lacking alkyl substitution at N1. The current synthesis provides simple access to this ring system bearing alkyl groups at N1, which could permit a more thorough examination of this family of compounds.

To date, there has been only one method reported for the synthesis of 2,3-dihydro-1,8-naphthyridin-4(1*H*)-ones.[4] This synthesis involved addition of 2-aminopyridine derivatives to ethyl acrylate, hydrolysis of the ester to the acid and cyclization to give the ring-fused heterocycle using polyphosphoric acid. While this approach was scalable, the yields in the final ring-closure step were generally quite low.

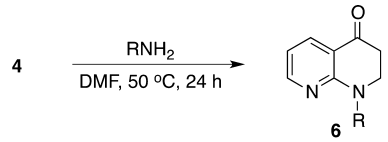
The synthesis of our annulation substrates is shown in Scheme 1. The required 3-pyridyl vinyl ketones were prepared in two steps from commercially available 2-chloro-3-pyridinecarboxaldehyde (**1**). Treatment of this aldehyde with vinylmagnesium bromide or 1-propenylmagnesium bromide in tetrahydrofuran at −78 °C gave alcohols **2** and **3**, respectively.[7] These alcohols were then oxidized to the dihydronaphthyridinone precursors **4** and **5** using manganese(IV) oxide,[8] which provided the required ketones without allylic rearrangement[9,10] or degradation of the pyridine ring.

Scheme 1. Synthesis of the Annulation Substrates



The results of our tandem Michael–S_NAr annulation reactions are summarized in Schemes 2 and 3. Since two

Scheme 2. Annulation Results from 4



	R	Product	Yield (%)
a	*c*-C_3H_5	**6a**	66
b	*c*-C_6H_{11}	**6b**	71
c	n-C_6H_{13}	**6c**	74
d	*i*-C_4H_9	**6d**	75
e	$C_6H_5CH_2CH_2$	**6e**	74
f	$C_6H_5CH_2$	**6f**	77
g	4-$ClC_6H_4CH_2$	**6g**	78
h	4-$CH_3OC_6H_4CH_2$	**6h**	76
i	4-$CF_3C_6H_4CH_2$	**6i**	72
j	*t*-C_4H_9	**6j**	17[a]

[a]This reaction was run at 100 °C for 24 h.

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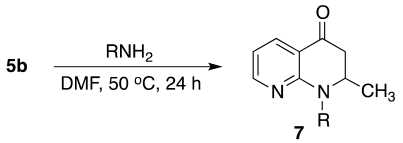
Scheme 3. Annulation Results from 5b

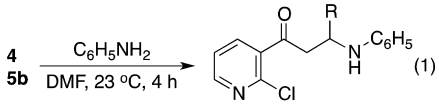


	R	Product	Yield (%)
a	*c*-C_3H_5	**7a**	72
b	*c*-C_6H_{11}	**7b**	74
c	*n*-C_6H_{13}	**7c**	85
d	*i*-C_4H_9	**7d**	85
e	$C_6H_5CH_2CH_2$	**7e**	74
f	$C_6H_5CH_2$	**7f**	83[a]
g	4-$ClC_6H_4CH_2$	**7g**	77
h	4-$CH_3OC_6H_4CH_2$	**7h**	83
i	4-$CF_3C_6H_4CH_2$	**7i**	75
j	*t*-C_4H_9	**7j**	0[b]

[a]The yield was 80% from the *Z* enone **5a**. [b]This reaction was run at 100 °C for 24 h.

bonds must be formed, the sequence requires the use of a primary amine. The reactions were performed using a 1:1.5 molar ratio of substrate to amine at 50 °C to afford the dihydronaphthyridinone products **6a**–**i** in 65–78% from **4** and **7a**–**i** in 72–85% from **5b**. The slightly higher yields from **5b** are presumably attributable to the greater stability of the β-substituted enone side-chain. The dihydronaphthyridinone products were readily purified by preparative thin layer chromatography or column chromatography (using a quartz column) where they were visualized as sky blue bands using UV detection. The products were generally isolated as yellow oils.

Further work demonstrated that reaction of both the (*Z*)-enone **5a** and the (*E*)-enone **5b** with benzylamine provided **7f** in nearly the same yield (80 vs 83%, respectively), indicating that the double bond geometry of the Michael acceptor has a minimal effect on the reaction outcome. Additionally, the annulation of **4** with *tert*-butylamine at 100 °C for 24 h gave **6j** in only 17% yield and did not produce a dihydronaphthyridinone from **5b**, illustrating the steric limitations of the process. Finally, the reaction appears to be restricted to aliphatic amines since trial reactions of **4** and **5b** with aniline gave complex mixtures at 50 °C and the Michael addition products **8a** (84%) and **8b** (87%), respectively, at 23 °C with no ring formation (see eq 1).

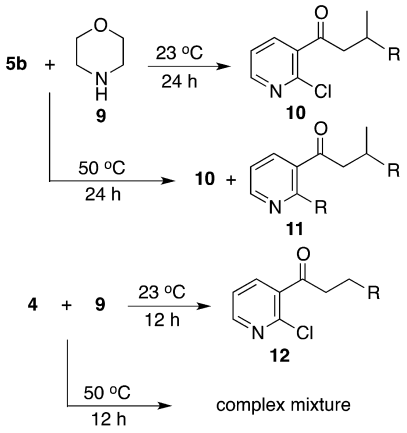


(1)

8a (R = H)
8b (R = CH_3)

Although the results using aromatic amines suggested that Michael addition to the side-chain was the initial step of the sequence, the reaction chronology using more basic aliphatic amines[11] was unclear. Thus, additional reactions with morpholine (**9**) were undertaken to elucidate this aspect of the process (see Scheme 4). As a secondary amine, **9** can undergo only one reaction of the sequence but cannot complete the ring closure. Thus, treatment of **5b** with 1.5 equivalents of **9** in DMF at 50 °C for 24 h followed by removal of excess **9** and the solvent under high vacuum at 23 °C gave 66% of a mixture of the Michael addition product **10** and the Michael–S_NAr double addition product **11**, along with 10% of recovered **5b**. This

Scheme 4. Reactions with Morpholine

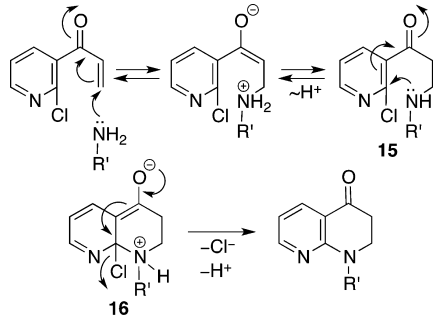


R = morpholino

mixture proved inseparable due to the instability of adducts **10** and **11** toward chromatographic separation. Additionally, the unstable nature of the products and potential reversibility of the Michael reaction[12] could alter the ratio of products observed. The reaction was, therefore, repeated at 23 °C for 24 h, and this furnished exclusively the Michael addition product **10** in 87% yield with only a trace of recovered **5b**. Similarly, reaction of **4** with **9** at 23 °C for 12 h afforded 67% of the Michael product **12**, along with 9% of recovered **4** and a trace of the double addition product. Though not unequivocal, these observations, together with the aromatic amine result, suggest that the Michael addition is the initiating step of the sequence.

The proposed mechanistic pathway is outlined in Scheme 5.[13] Following Michael addition to give **15**, the S_NAr reaction

Scheme 5. Mechanism of the Ring Closure



occurs at the chlorine-bearing carbon of the pyridine to give intermediate **16**. Rearomatization and loss of a proton, then affords the dihydronaphthyridinone. The reaction proceeds at the same temperature as substrates incorporating a fluoronitroarene acceptor,[1] but requires shorter reaction times indicating that the 2-chloropyridine ring is more reactive toward addition by nucleophiles in the S_NAr reaction.[14] The electron deficiency of the pyridine ring and the polarization of the aromatic carbon–nitrogen double bond are known to be important factors in facilitating this process.[15]

In conclusion, we have developed a new approach to the synthesis of 1-alkyl- and (±)-1,2-dialkyl-2,3-dihydro-1,8-naphthyridin-4(1*H*)-ones based on a tandem Michael addition–S_NAr reaction. The required substrates are conveniently prepared in two steps from commercial 2-chloro-3-pyridinecarboxaldehyde. The sequence gives good yields of the target

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ring system and represents a rare use of the 2-chloropyridine system as the aromatic acceptor in a tandem reaction. The reaction proceeds in high yield using primary amines that lack branching α to the nitrogen. More hindered amines and aromatic amines give reduced yields or fail to close the final ring. We are continuing to explore other variants of this potentially valuable annulation procedure.

EXPERIMENTAL SECTION

General Methods. All reactions were run using anhydrous solvents under N_2 in oven-dried glassware. Preparative separations were performed using one of the following methods: (1) flash chromatography[16] on silica gel (Davisil, grade 62, 60−200 mesh) containing 2% UV-active phosphor (Sorbent Technologies, No. UV-05) packed into quartz columns or (2) preparative thin layer chromatography (PTLC) on silica gel GF plates (Analtech, No. 02015). Band elution for both methods was monitored using a hand-held UV lamp. Melting points were uncorrected. FT-IR spectra were run as thin films on NaCl disks. ^{1}H and ^{13}C NMR spectra were measured in $CDCl_3$ at 300 and 75 MHz, respectively, using $(CH_3)_4Si$ as the internal standard. Unless otherwise indicated, low-resolution mass spectra (EI/DP) were obtained at 70 eV.

Representative Procedure for Grignard Reactions: 1-(2-Chloropyridin-3-yl)-2-propen-1-ol (2). To a −78 °C solution of 2.12 g (15.0 mmol) of 2-chloro-3-pyridinecarboxaldehyde (**1**) in 75 mL of THF was added 22.5 mL of 1.0 M vinylmagnesium bromide in THF (22.5 mmol).[7] The reaction mixture was stirred for 3.5 h at −78 °C, then quenched by addition of 50 mL of 10% NH_4Cl and extracted three times with ether. The combined ether extracts were washed with H_2O and saturated NaCl, dried over $MgSO_4$, filtered, and concentrated under vacuum to give 2.02 g (79%) of **2** as a viscous yellow oil. This product was spectroscopically pure and was used directly in the next step. IR: 3334 cm^{-1}; ^{1}H NMR: δ 8.26 (dd, J = 4.9, 2.2 Hz, 1H), 7.95 (dd, J = 7.7, 2.2 Hz 1H), 7.28 (dd, J = 7.7, 4.9 Hz, 1H), 5.98 (ddd, J = 17.2, 10.4, 5.5 Hz, 1H), 5.57 (br d, J = 5.5 Hz, 1H), 5.40 (d, J = 17.2 Hz, 1H), 5.25 (d, J = 10.4 Hz, 1H), 3.50 (br s, 1H); ^{13}C NMR: δ 149.1, 148.2, 137.5, 137.0, 136.7, 122.9, 116.3, 70.6; ms (30 eV): m/z 169, 171 (*ca* 3:1, M$^+$). Anal. Calcd for C_8H_8ClNO: C, 56.64; H, 4.72; N, 8.26. Found: C, 56.89; H, 4.79; N, 8.07.

(*Z*)- and (*E*)-1-(2-Chloropyridin-3-yl)-2-buten-1-ol (3): 2.31 g (84%) as a yellow oil; IR: 3337 cm^{-1}; ^{1}H NMR (*Z* and *E*): δ 8.26 (m, 1H), 7.98 (2 dd, J = 7.7, 2.2 Hz, 1H), 7.28 (m, 1H), 5.89−5.39 (complex m, 3H), 2.84 (br s, 0.5H), 2.76 (br s, 0.5H), 1.85 (dd, J = 6.6, 1.4 Hz, 1.5H), 1.71 (d, J = 6.6 Hz, 1.5H); ^{13}C NMR (*Z* and *E*): δ 148.9, 147.96, 147.92, 137.9, 137.7, 136.5, 130.8, 130.2, 128.7, 128.5, 122.8, 70.6, 65.7, 17.6, 13.6; ms (30 eV): m/z 183, 185 (*ca.* 3:1, M$^+$). Anal. Calcd for $C_9H_{10}ClNO$: C, 58.86; H, 5.45: N, 7.63. Found: C, 59.04; H, 5.53; N, 7.44.

Representative Procedure for Oxidation with Manganese Dioxide: 1-(2-Chloropyridin-3-yl)-2-propen-1-one (4). To a solution of 2.00 g (11.8 mmol) of **2** in 50 mL of CH_2Cl_2 was added 20.0 g of manganese(IV) oxide.[8] The reaction was stirred vigorously for 12 h at 23 °C and then filtered through a plug of Celite. The Celite was washed thoroughly with CH_2Cl_2 and the solvent was removed under vacuum to give a yellow oil. The product was purified by flash chromatography on a 30-cm × 2.5-cm silica gel column eluted with increasing concentrations of ether in hexanes to give 1.42 g (72%) of enone **4**. This compound was stored in the dark at −20 °C as a dilute solution in pentane. IR: 1671, 1609 cm^{-1}; ^{1}H NMR: δ 8.64 (dd, J = 4.9, 2.2 Hz, 1H), 7.91 (dd, J = 7.7, 2.2 Hz, 1H), 7.50 (dd, J = 7.7, 4.9 Hz, 1H), 6.94 (dd, J = 17.2, 10.4 Hz, 1H), 6.33 (d, J = 17.2 Hz, 1H), 6.25 (d, J = 10.4 Hz, 1H); ^{13}C NMR: δ 192.3, 151.1, 147.7, 138.2, 135.4, 134.4, 132.6, 122.3; ms: m/z 167, 169 (*ca.* 3:1, M$^+$). Anal. Calcd for C_8H_6ClNO: C, 57.31; H, 3.58; N, 8.36. Found: C, 57.55; H, 3.69; N, 8.13.

(*Z*)- and (*E*)-1-(2-Chloropyridin-3-yl)-2-buten-1-one (5a and 5b). *Z* isomer **5a**: 745 mg (27%) as a light-yellow solid, mp 40−42 °C; IR: 1679, 1610 cm^{-1}; ^{1}H NMR: δ 8.48 (dd, J = 4.9, 2.2 Hz, 1H), 7.84 (dd, J = 7.7, 2.2 Hz, 1H), 7.35 (dd, J = 7.7, 4.9 Hz, 1H), 6.62 (dq, J = 11.5, 1.4 Hz, 1H), 6.51 (dq, J = 11.5, 6.9 Hz, 1H), 2.20 (dd, J = 7.0, 1.4 Hz, 3H); ^{13}C NMR: δ 191.6, 150.9, 147.5, 146.5, 138.3, 136.4, 127.1, 122.5, 16.4; ms: m/z 181, 183 (*ca.* 3:1, M$^+$). Anal. Calcd for C_9H_8ClNO: C, 59.50; H, 4.41; N, 7.71. Found: C, 59.59; H, 4.47; N, 7.58.

E isomer **5b**: 1.39 g (52%) as a white solid, mp 53−55 °C; IR: 1660, 1624 cm^{-1}; ^{1}H NMR: δ 8.49 (dd, J = 4.9, 2.2 Hz, 1H), 7.72 (dd, J = 7.7, 2.2 Hz, 1H), 7.34 (dd, J = 7.7, 4.9 Hz, 1H), 6.78 (dq, J = 15.9, 6.9 Hz, 1H), 6.52 (dq, J = 15.9, 1.4 Hz, 1H), 2.00 (dd, J = 6.9, 1.4 Hz, 3H); ^{13}C NMR: δ 192.1, 150.7, 148.6, 147.5, 137.9, 135.2, 131.4, 122.2, 18.6; ms: m/z 181, 183 (*ca.* 3:1, M$^+$). Anal. Calcd for C_9H_8ClNO: C, 59.50; H, 4.41; N, 7.71. Found: C, 59.53; H, 4.41; N, 7.64.

Representative Procedure for the Tandem Michael−S_NAr Reaction: 1-Cyclopropyl-2,3-dihydro-1,8-naphthyridin-4(1*H*)-one (6a). To a solution of 67 mg (0.40 mmol) of **4** in 2 mL of DMF was added 34 mg (42 μL, 0.60 mmol) of cyclopropylamine, and the reaction was heated at 50 °C for 24 h. The reaction mixture was then cooled, added to 25 mL of saturated NaCl and extracted three times with ether. The combined ether extracts were washed with water and saturated NaCl, dried over $MgSO_4$, filtered, and concentrated under vacuum to afford a yellow oil. The product was purified on a 20-cm × 20-cm PTLC plate eluted with 4:1 hexanes:ether to give 50 mg (66%) of **6a** as a yellow oil, which crystallized on standing, mp 67−68 °C. IR: 1682 cm^{-1}; ^{1}H NMR: δ 8.43 (dd, J = 4.9, 2.2 Hz, 1H), 8.09 (dd, J = 7.7, 2.2 Hz, 1H), 6.75 (dd, J = 7.7, 4.9 Hz, 1H), 3.63 (t, J = 7.1 Hz, 2H), 2.68 (t, J = 7.1 Hz, 2H), 2.67 (m, 1H), 0.96 (m, 2H), 0.73 (m, 2H); ^{13}C NMR: δ 193.9, 161.4, 154.3, 136.1, 115.1, 114.1, 47.6, 38.2, 31.2, 8.3; ms: m/z 188 (M$^+$). Anal. Calcd for $C_{11}H_{12}N_2O$: C, 70.21; H, 6.38; N, 14.89. Found: C, 70.25; H, 6.39; N, 14.83.

1-Cyclohexyl-2,3-dihydro-1,8-naphthyridin-4(1*H*)-one (6b): 65 mg (71%) as a yellow oil; IR: 1682 cm^{-1}; ^{1}H NMR: δ 8.31 (dd, J = 4.9, 2.2 Hz, 1H), 8.07 (dd, J = 7.7, 2.2 Hz, 1H), 6.59 (dd, J = 7.7, 4.9 Hz, 1H), 4.84 (m, 1H), 3.49 (t, J = 7.1 Hz, 2H), 2.63 (t, J = 7.1 Hz, 2H), 1.86−1.68 (complex m, 5H), 1.49 (m, 4H), 1.16 (m, 1H); ^{13}C NMR: δ 193.7, 159.3, 154.4, 136.5, 114.3, 112.3, 52.8, 39.7, 37.4, 30.0, 25.9, 25.7; ms: m/z 230 (M$^+$). Anal. Calcd for $C_{14}H_{18}N_2O$: C, 73.04; H, 7.83; N, 12.17. Found: C, 73.13; H, 7.86; N, 12.05.

1-Hexyl-2,3-dihydro-1,8-naphthyridin-4(1*H*)-one (6c): 69 mg (74%) as a yellow oil; IR: 1682 cm^{-1}; ^{1}H NMR: δ 8.30 (dd, J = 4.9, 2.2 Hz, 1H), 8.04 (dd, J = 7.7, 2.2 Hz, 1H), 6.59 (dd, J = 7.7, 4.9 Hz, 1H), 3.67 (t, J = 7.7 Hz, 2H), 3.56 (t, J = 7.1 Hz, 2H), 2.69 (t, J = 7.1 Hz, 2H), 1.62 (distorted quintet, J = 7.1 Hz, 2H), 1.33 (m, 6H), 0.89 (distorted t, J = 6.8 Hz, 3H); ^{13}C NMR: δ 193.6, 159.5, 154.6, 136.2, 114.0, 112.4, 48.6, 46.0, 37.1, 31.6, 27.2, 26.7, 22.6, 14.0; ms: m/z 161 (M$^+$ − C_5H_{11}). Anal. Calcd for $C_{14}H_{20}N_2O$: C, 72.41; H, 8.62; N, 12.07. Found: C, 72.55; H, 8.64; N, 11.96.

2,3-Dihydro-1-isobutyl-1,8-naphthyridin-4(1*H*)-one (6d): 61 mg (75%) as a yellow oil; IR: 1682 cm^{-1}; ^{1}H NMR: δ 8.29 (dd, J = 4.9, 2.2 Hz, 1H), 8.05 (dd, J = 7.7, 2.2 Hz, 1H), 6.59 (dd, J = 7.7, 4.9 Hz, 1H), 3.57 (t, J = 7.1 Hz, 2H), 3.49 (d, J = 7.7 Hz, 2H), 2.69 (t, J = 7.1 Hz, 2H), 2.11 (nonet, J = 7.1 Hz, 1H), 0.97 (d, J = 7.1 Hz, 6H); ^{13}C NMR: δ 193.6, 159.7, 154.5, 136.2, 113.8, 112.4, 55.7, 46.6, 37.1, 27.3, 20.2; ms: m/z 161 (M$^+$ − C_3H_7). Anal. Calcd for $C_{12}H_{16}N_2O$: C, 70.59; H, 7.84; N, 13.73. Found: C, 70.64; H, 7.87; N, 13.62.

2,3-Dihydro-1-(2-phenylethyl)-1,8-naphthyridin-4(1*H*)-one (6e): 75 mg (74%) as a yellow solid, mp 36−37 °C; IR: 1682 cm^{-1}; ^{1}H NMR: δ 8.35 (dd, J = 4.9, 2.2 Hz, 1H) 8.05 (dd, J = 7.7, 2.2 Hz, 1H), 7.34−7.18 (m, 5H), 6.63 (dd, J = 7.7, 4.9 Hz, 1H), 3.91 (t, J = 7.1 Hz, 2H), 3.39 (t, J = 7.1 Hz, 2H), 2.95 (t, J = 7.1 Hz, 2H), 2.55 (t, J = 7.1 Hz, 2H); ^{13}C NMR: δ 193.6, 159.1, 154.6, 139.6, 136.2, 128.9, 128.4, 126.3, 114.1, 112.7, 50.9, 46.8, 37.0, 33.7; ms: m/z 161 (M$^+$ − C_7H_7). Anal. Calcd for $C_{16}H_{16}N_2O$: C, 76.19; H, 6.35; N, 11.11. Found: C, 76.12; H, 6.34; N, 11.19.

1-Benzyl-2,3-dihydro-1,8-naphthyridin-4(1*H*)-one (6f): 74 mg (77%) as a yellow oil; IR: 1682 cm^{-1}; ^{1}H NMR: δ 8.34 (dd, J = 4.4, 2.2 Hz, 1H), 8.09 (dd, J = 7.7, 2.2 Hz, 1H), 7.38−7.22 (complex m, 5H), 6.67 (dd, J = 7.7, 4.4 Hz, 1H), 4.96 (s, 2H), 3.49 (t, J = 7.1 Hz, 2H), 2.68 (t, J = 7.1 Hz, 2H); ^{13}C NMR: δ 193.4, 159.5, 154.5, 137.7, 136.4, 128.6, 127.7, 127.3, 114.2, 113.2, 51.1, 45.2, 37.1; ms: m/z 147 (M$^+$ −

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C_7H_7). Anal. Calcd for $C_{15}H_{14}N_2O$: C, 75.63; H, 5.88; N, 11.76. Found: C, 75.72; H, 5.93; N, 11.61.

1-(4-Chlorobenzyl)-2,3-dihydro-1,8-naphthyridin-4(1*H*)-one (6g): 85 mg (78%) as a yellow solid, mp 75−77 °C; IR: 1681 cm^{-1}; ^1H NMR: δ 8.33 (dd, J = 4.4, 2.2 Hz, 1H), 8.09 (dd, J = 7.7, 2.2 Hz, 1H), 7.30 (d, J = 8.8 Hz, 2H), 7.25 (d, J = 8.8 Hz, 2H), 6.69 (dd, J = 7.7, 4.4 Hz, 1H), 4.91 (s, 2H), 3.48 (t, J = 7.1 Hz, 2H), 2.69 (t, J = 7.1 Hz, 2H); ^{13}C NMR: δ 193.2, 159.4, 154.5, 136.4, 136.3, 133.1, 129.1, 128.7, 114.3, 113.4, 50.6, 45.4, 37.1; ms: m/z 147 ($M^+ - C_7H_6Cl$). Anal. Calcd for $C_{15}H_{13}ClN_2O$: C, 66.06; H, 4.77; N, 10.28. Found: C, 66.12; H, 4.79; N, 10.19.

2,3-Dihydro-1-(4-methoxybenzyl)-1,8-naphthyridin-4(1*H*)-one (6h): 82 mg (76%) as a yellow oil; IR: 2838, 1682 cm^{-1}; ^1H NMR: δ 8.34 (dd, J = 4.9, 2.2 Hz, 1H), 8.08 (dd, J = 7.7, 2.2 Hz, 1H), 7.24 (d, J = 8.8 Hz, 2H), 6.86 (d, J = 8.8 Hz, 2H), 6.66 (dd, J = 7.7, 4.9 Hz, 1H), 4.89 (s, 2H), 3.79 (s, 3H), 3.46 (t, J = 7.1 Hz, 2H), 2.68 (t, J = 7.1 Hz, 2H); ^{13}C NMR: δ 193.5, 159.5, 158.9, 154.5, 136.4, 129.6, 129.1, 114.2, 113.9, 113.1, 55.2, 50.5, 45.0, 37.1; ms: m/z 147 ($M^+ - C_8H_9O$). Anal. Calcd for $C_{16}H_{16}N_2O_2$: C, 71.64; H, 5.97; N, 10.45. Found: C, 71.73; H, 5.99; N, 10.34.

2,3-Dihydro-1-(4-trifluoromethylbenzyl)-1,8-naphthyridin-4(1*H*)-one (6i): 88 mg (72%) as a yellow solid, mp 37−39 °C; IR: 1682, 1324 cm^{-1}; ^1H NMR: δ 8.34 (dd, J = 4.9, 2.2 Hz, 1H), 8.11 (dd, J = 7.7, 2.2 Hz, 1H), 7.59 (d, J = 8.0 Hz, 2H), 7.44 (d, J = 8.0 Hz, 2H), 6.71 (dd, J = 7.7, 4.9 Hz, 1H), 5.01 (s, 2H), 3.52 (t, J = 7.1 Hz, 2H), 2.72 (t, J = 7.1 Hz, 2H); ^{13}C NMR: δ 193.1, 159.3, 154.5, 148.5, 142.0, 136.5, 127.9, 125.5 (q, J = 3.7 Hz), 124.1 (q, J = 271.6 Hz), 114.4, 113.7, 51.0, 45.7, 37.1; ms: m/z 147 ($M^+ - C_8H_6F_3$). Anal. Calcd for $C_{16}H_{13}F_3N_2O$: C, 62.75; H, 4.25; N, 9.15. Found: C, 62.91; H, 4.48; N, 9.04.

1-*tert*-Butyl-2,3-dihydro-1,8-naphthyridin-4(1*H*)-one (6j): 16 mg (17%) as a yellow solid, mp 31−32 °C; IR: 1686 cm^{-1}; ^1H NMR: δ 8.32 (dd, J = 4.9, 2.2 Hz, 1H), 8.09 (dd, J = 7.7, 2.2 Hz, 1H), 6.64 (dd, J = 7.7, 4.9 Hz, 1H), 3.60 (t, J = 6.6 Hz, 2H), 2.63 (t, J = 6.6 Hz, 2H), 1.60 (s, 9H); ^{13}C NMR: δ 194.8, 161.0, 152.7, 136.2, 115.9, 112.8, 57.6, 42.5, 38.7, 29.0; ms: m/z 189 ($M^+ - CH_3$). Anal. Calcd for $C_{12}H_{16}N_2O$: C, 70.59; H, 7.84; N, 13.73. Found: C, 70.66; H, 7.87 N, 13.57.

1-Cyclopropyl-2,3-dihydro-2-methyl-1,8-naphthyridin-4(1*H*)-one (7a): 58 mg (72%) as a yellow oil; IR: 1683 cm^{-1}; ^1H NMR: δ 8.43 (dd, J = 4.9, 2.2 Hz, 1H), 8.06 (dd, J = 7.7, 2.2 Hz, 1H), 6.71 (dd, J = 7.7, 4.9 Hz, 1H), 3.98 (quintet d, J = 6.6, 2.2 Hz, 1H), 2.88 (dd, J = 16.5, 6.0 Hz, 1H), 2.69 (m, 2H), 2.54 (dd, J = 16.5, 2.2 Hz, 1H), 1.23 (d, J = 6.6 Hz, 3H), 1.17 (m, 1H), 0.87−0.64 (m, 3H); ^{13}C NMR: δ 193.7, 159.2, 154.6, 135.4, 114.6, 113.6, 53.2, 44.3, 29.5, 15.2, 10.5, 6.2; ms: m/z 187 ($M^+ - CH_3$). Anal. Calcd for $C_{12}H_{14}N_2O$: C, 71.29; H, 6.93; N, 13.86. Found: C, 71.36; H, 6.93; N, 13.77.

1-Cyclohexyl-2,3-dihydro-2-methyl-1,8-naphthyridin-4(1*H*)-one (7b): 72 mg (74%) as a yellow oil; IR: 1682 cm^{-1}; ^1H NMR: δ 8.30 (dd, J = 4.9, 2.2 Hz, 1H), 8.03 (dd, J = 7.7, 2.2 Hz, 1H), 6.84 (dd, J = 7.7, 4.9 Hz, 1H), 4.83 (tt, J = 11.5, 3.3 Hz, 1H), 4.00 (quintet d, J = 6.6, 2.2 Hz, 1H), 2.78 (dd, J = 15.9, 5.5 Hz, 1H), 2.44 (dd, J = 15.9, 2.2 Hz, 1H), 1.94−1.67 (complex m, 6H), 1.66−1.40 (complex m, 4H), 1.20 (d, J = 6.6 Hz, 3H); ^{13}C NMR: δ 193.6, 156.9, 154.7, 135.8, 113.6, 111.6, 53.7, 45.4, 43.7, 31.6, 30.7, 26.04, 25.99, 25.7, 18.1; ms: m/z 229 ($M^+ - CH_3$). Anal. Calcd for $C_{15}H_{20}N_2O$: C, 73.77; H, 8.20; N, 11.48. Found: C, 73.83; H, 8.24; N, 11.40.

1-Hexyl-2,3-dihydro-2-methyl-1,8-naphthyridin-4(1*H*)-one (7c): 84 mg (85%) as a yellow oil; IR: 1682 cm^{-1}; ^1H NMR: δ 8.30 (dd, J = 4.9, 2.2 Hz, 1H), 8.02 (dd, J = 7.7, 2.2 Hz, 1H), 6.56 (dd, J = 7.7, 4.9 Hz, 1H), 4.22 (dt, J = 14.0, 7.1 Hz, 1H), 3.81 (quintet d, J = 6.6, 2.7 Hz, 1H), 3.00 (dt, J = 14.0, 7.1 Hz, 1H), 2.91 (dd, J = 15.9, 6.0 Hz, 1H), 2.51 (dd, J = 15.9, 2.7 Hz, 1H), 1.68 (quintet, J = 7.7 Hz, 2H), 1.44−1.28 (complex m, 6H), 1.18 (d, J = 6.6 Hz, 3H), 0.90 (distorted t, J = 7.1 Hz, 3H); ^{13}C NMR: δ 193.4, 157.5, 154.9, 135.6, 113.4, 111.9, 51.6, 46.5, 43.5, 31.7, 28.4, 26.7, 22.6, 15.9, 14.0; ms: m/z 175 ($M^+ - C_5H_{11}$). Anal. Calcd for $C_{15}H_{22}N_2O$: C, 73.17; H, 8.94; N, 11.38. Found: C, 73.21; H, 8.96; N, 11.33.

2,3-Dihydro-1-isobutyl-2-methyl-1,8-naphthyridin-4(1*H*)-one (7d): 74 mg (85%) as a yellow oil; IR: 1684 cm^{-1}; ^1H NMR: δ 8.28 (dd, J = 4.9, 2.2 Hz, 1H), 8.03 (dd, J = 7.7, 2.2 Hz, 1H), 6.75 (dd, J = 7.7, 4.9 Hz, 1H), 4.20 (dd, J = 13.2, 6.6 Hz, 1H), 3.79 (quintet d, J = 6.6, 2.2 Hz, 1H), 2.95 (dd, J = 15.9, 6.0 Hz, 1H), 2.61 (dd, J = 13.2, 7.7 Hz, 1H), 2.52 (dd, J = 15.9, 2.2 Hz, 1H), 2.11 (nonet, J = 7.1 Hz, 1H), 1.15 (d, J = 6.6 Hz, 3H), 1.02 (dd, J = 6.6 Hz, 3H), 0.97 (d, J = 6.6 Hz, 3H); ^{13}C NMR: δ 193.4, 157.7, 154.9, 135.6, 113.4, 112.0, 53.9, 52.4, 43.3, 27.5, 20.3, 20.1, 15.2; ms: m/z 175 ($M^+ - C_3H_7$). Anal. Calcd for $C_{13}H_{18}N_2O$: C, 71.56; H, 8.26; N, 12.84. Found: C, 71.68; H, 8.29; N, 12.69.

2,3-Dihydro-2-methyl-1-(2-phenylethyl)-1,8-naphthyridin-4(1*H*)-one (7e): 79 mg (74%) as a yellow oil; IR: 1680 cm^{-1}; ^1H NMR: δ 8.36 (dd, J = 4.9, 2.2 Hz, 1H), 8.03 (dd, J = 7.7, 2.2 Hz, 1H), 7.35−7.17 (complex m, 5H), 6.61 (dd, J = 7.7, 4.9 Hz, 1H), 4.49 (ddd, J = 13.2, 7.1, 5.5 Hz, 1H), 3.41 (quintet d, J = 6.6, 2.7 Hz, 1H), 3.17 (dt, J = 13.2, 7.7 Hz, 1H), 3.01 (td, J = 7.7, 2.7 Hz, 2H), 2.67 (dd, J = 15.9, 6.0 Hz, 1H), 2.32 (dd, J = 15.9, 2.7 Hz, 1H), 1.10 (d, J = 6.6 Hz, 3H); ^{13}C NMR: δ 193.4, 157.2, 155.0, 139.8, 135.6, 128.9, 128.4, 126.3, 113.5, 112.2, 52.6, 49.1, 43.2, 34.7, 16.0; ms: m/z 175 ($M^+ - C_7H_7$). Anal. Calcd for $C_{17}H_{18}N_2O$: C, 76.69; H, 6.77; N, 10.53. Found: C, 76.58; H, 6.74; N, 10.57

1-Benzyl-2,3-dihydro-2-methyl-1,8-naphthyridin-4(1*H*)-one (7f): 84 mg (83%) as a yellow oil; IR: 1682 cm^{-1}; ^1H NMR: δ 8.33 (dd, J = 4.9, 2.2 Hz, 1H), 8.08 (dd, J = 7.7, 2.2 Hz, 1H), 7.41−7.22 (complex m, 5H), 6.64 (dd, J = 7.7, 4.9 Hz, 1H), 5.72 (d, J = 15.4 Hz, 1H), 4.18 (d, J = 15.4 Hz, 1H), 3.77 (quintet d, J = 6.6, 3.3 Hz, 1H), 2.89 (dd, J = 15.9, 6.0 Hz, 1H), 2.48 (dd, J = 15.9, 3.3 Hz, 1H), 1.17 (d, J = 6.6 Hz, 3H); ^{13}C NMR: δ 193.3, 157.6, 154.9, 138.5, 135.8, 128.6, 127.4, 127.2, 113.5, 112.7, 50.4, 48.6, 43.5, 15.5; ms: m/z 237 ($M^+ - CH_3$). Anal. Calcd for $C_{16}H_{16}N_2O$: C, 76.19; H, 6.35; N, 11.11. Found: C, 76.25; H, 6.39; N, 10.98. When the *Z* isomer **5a** was used in this reaction, 81 mg (80%) of **7f** was isolated from the reaction.

1-(4-Chlorobenzyl)-2,3-dihydro-2-methyl-1,8-naphthyridin-4(1*H*)-one (7g): 88 mg (77%) as a yellow oil; IR: 1684 cm^{-1}; ^1H NMR: δ 8.32 (dd, J = 4.9, 2.2 Hz, 1H), 8.08 (dd, J = 7.7, 2.2 Hz, 1H), 7.31 (d, J = 8.0 Hz, 2H), 7.28 (d, J = 8.0 Hz, 2H), 6.66 (dd, J = 7.7, 4.9 Hz, 1H), 5.62 (d, J = 15.9 Hz, 1H), 4.19 (d, J = 15.9 Hz, 1H), 3.76 (quintet d, J = 6.6, 3.3 Hz, 1H), 2.88 (dd, J = 15.9, 6.0 Hz, 1H), 2.50 (dd, J = 15.9, 3.3 Hz, 1H), 1.17 (d, J = 6.6 Hz, 3H); ^{13}C NMR: δ 193.1, 157.5, 154.8, 137.1, 135.9, 133.0, 128.8, 128.7, 113.6, 113.0, 50.7, 48.2, 43.6, 15.6; ms: m/z 273, 271 (*ca* 3:1, $M^+ - CH_3$). Anal. Calcd for $C_{16}H_{15}ClN_2O$: C, 67.02; H, 5.24; N, 9.77. Found: C, 67.15; H, 5.26; N, 9.69.

2,3-Dihydro-1-(4-methoxybenzyl)-2-methyl-1,8-naphthyridin-4(1*H*)-one (7h): 94 mg (83%) as a yellow oil; IR: 1682 cm^{-1}; ^1H NMR: δ 8.33 (dd, J = 4.9, 2.2 Hz, 1H), 8.06 (dd, J = 7.7, 2.2 Hz, 1H), 7.28 (d, J = 8.8 Hz, 2H), 6.88 (d, J = 8.8 Hz, 2H), 6.63 (dd, J = 7.7, 4.9 Hz, 1H), 5.62 (d, J = 15.4 Hz, 1H), 4.13 (d, J = 15.4 Hz, 1H), 3.80 (s, 3H), 3.77 (quintet d, J = 6.6, 3.3 Hz, 1H), 2.85 (dd, J = 15.9, 6.0 Hz, 1H), 2.46 (dd, J = 15.9, 3.3 Hz, 1H), 1.15 (d, J = 6.6 Hz, 3H); ^{13}C NMR: δ 193.4, 158.9, 157.6, 154.9, 135.8, 130.4, 128.8, 114.0, 113.5, 112.6, 55.2, 50.2, 48.1, 43.5, 15.4; ms: m/z 267 ($M^+ - CH_3$). Anal. Calcd for $C_{17}H_{18}N_2O_2$: C, 72.34; H, 6.38; N, 9.93. Found: C, 72.49; H, 6.43; N 9.78.

2,3-Dihydro-1-(4-trifluoromethylbenzyl)-2-methyl-1,8-naphthyridin-4(1*H*)-one (7i): 96 mg (75%) as a yellow oil; IR: 1684, 1325 cm^{-1}; ^1H NMR: δ 8.32 (dd, J = 4.9, 2.2 Hz, 1H), 8.10 (dd, J = 7.7, 2.2 Hz, 1H), 7.59 (d, J = 8.2 Hz, 2H), 7.47 (d, J = 8.2 Hz, 2H), 6.68 (dd, J = 7.7, 4.9 Hz, 1H), 5.71 (d, J = 15.9 Hz, 1H), 4.29 (d, J = 15.9 Hz, 1H), 3.78 (quintet d, J = 6.6, 3.3 Hz, 1H), 2.92 (dd, J = 15.9, 6.0 Hz, 1H), 2.53 (dd, J = 15.9, 3.3 Hz, 1H), 1.20 (d, J = 6.6 Hz, 3H); ^{13}C NMR: δ 193.0, 157.5, 154.8, 142.9, 135.9, 127.6 (2C), 125.4 (q, J = 3.7 Hz), 124.1 (q, J = 272.0 Hz), 113.7, 113.2, 51.1, 48.6, 43.6, 15.7; ms: m/z 305 ($M^+ - CH_3$). Anal. Calcd for $C_{17}H_{15}F_3N_2O$: C, 63.75; H, 4.69; N, 8.75. Found: C, 63.93; H, 4.74; N, 8.53.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^1H NMR and ^{13}C NMR spectral data are provided for **2**, **3**, **4**, **5a−b**, **6a−j**, **7a−i**, **8a−b**, **10** and **12.** Experimental is also

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provided for the mechanistic experiments. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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DEDICATION

This work is dedicated to the memory of Professor Howard E. Zimmerman.

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