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Isoquinolin-1(2*H*)-ones and 1,6-naphthyridin-5(6*H*)-ones by an *N*-acylation-S_NAr sequence

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ABSTRACT

A new synthesis of 2,3-dialkyl-4-carbomethoxyisoquinolin-1(2*H*)-ones and 6,7-dialkyl-8-carbomethoxy-1,6-naphthyridin-5(6*H*)-ones is reported. The process involves treatment of a β-enaminoester with 2-fluoro-5-nitrobenzoyl chloride, 2-fluorobenzoyl chloride or 2-chloronicotinoyl chloride followed by heating in the presence of base. The conversion, which proceeds by an *N*-acylation-S_NAr reaction sequence, affords 50–86% yields when R^1 is *n*-alkyl but ≤30% yields when R^1 is α-branched.

1. Introduction

Recent efforts in our group have been focused on the development of methodology for the efficient synthesis of a variety of heterocyclic scaffolds. These have included approaches to the synthesis of 1,2,3,4-tetrahydroquinolines,[1] 1,2,3,9-tetrahydro-4*H*-carbazol-4-ones,[2] 2,3-dihydro-4(1*H*)-quinolinones,[3] 2,3-dihydro-4(1*H*)-quinazolinones[4] and 1,4- and 2,3-dihydronaphthyridinones.[5] The current study was undertaken with the goal of providing an expeditious route to 2,3-dialkyl-4-methoxycarbonylisoquinolin-1(2*H*)-ones and 6,7-dialkyl-8-methoxycarbonyl-1,6-naphthyridin-5(6*H*)-ones. Several 4-methoxycarbonylisoquinolin-1(2*H*)-ones have previously been prepared from homophthalic acid[6] and 2-bromobenzoic acid derivatives.[7] While the syntheses described were reasonably short (2–3 steps), the yields were often quite low (35–50%). These compounds are known to have significant potential for the treatment of ulcers,[8] inflammation-based diseases[9] and CNS disorders.[10] In contrast, 6,7-dialkyl-8-methoxycarbonyl-1,6-naphthyridin-5(6*H*)-ones have been reported only once in 40–50% yields by a route that differs from the current work,[11] and to the best of our knowledge, have not been evaluated for biological activity.

Our synthetic approach is based upon earlier investigations by two groups. Horii and co-workers were the first to demonstrate the use of a tandem enamination-cyclization procedure between ethyl piperidineacetate and cyclohexanone to produce 1,2,3,4,4a,5,7,8,9,10-decahydro-6*H*-benzo[*c*]quinolizin-6-one as a possible azasteroid precursor.[12] Later, the Stille group disclosed a related aza-annulation sequence and applied it to the synthesis of several alkaloid targets.[13] This process involved *N*-acylation of a conjugated enaminoester with acryloyl chloride followed by intramolecular Michael addition of the enamine to the resulting acrylamide. In the current study, we have modified this process to utilize an electron-poor fluoroaromatic moiety to serve as the acceptor for the second stage of this process. This has led to an efficient synthesis of 2,3-dialkyl-4-methoxycarbonylisoquinolin- 1(2*H*)-ones and 6,7-dialkyl-8-methoxy carbonyl-1,6-naphthyridin-5(6*H*)-ones. Based on the medicinal properties of previously reported derivatives in the isoquinoline series, this method could lead to new structures worthy of further development.

2. Results and discussion

Appropriate cyclization substrates were readily obtained from commercial sources or by standard synthetic procedures (Scheme 1). β-Ketoesters **1a**–**g**[14] were converted to β-enaminoesters **2a**–**g** by *p*-TsOH-catalyzed condensation with benzylamine in refluxing benzene with Dean–Stark removal of water. *N*-Methyl-β-enamino-ester **2h** was prepared by a literature procedure.[15] Acids **3** and **6** were converted to acid chlorides **4** and **7**, respectively, using thionyl chloride in boiling benzene, while 2-fluorobenzoyl chloride (**5**) was commercially available.

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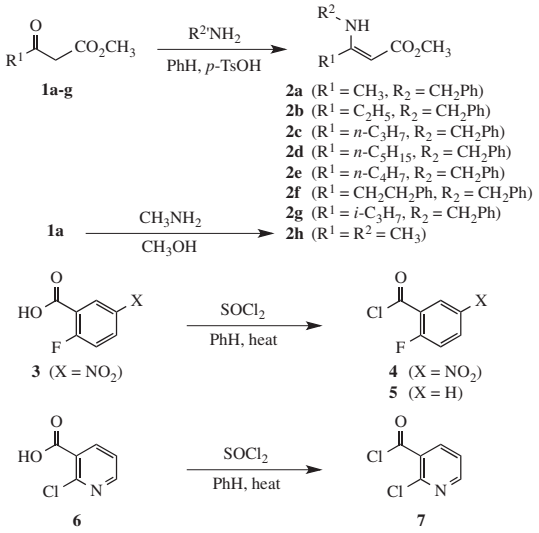
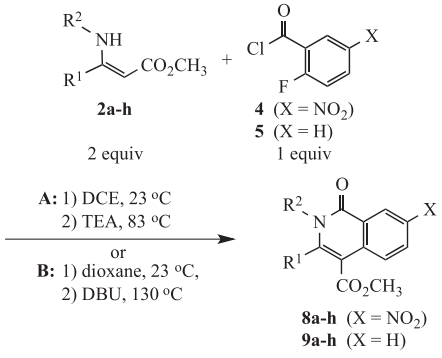


Scheme 1. Synthesis of the reaction substrates.

Our cyclization results are summarized in Tables 1 and 2. The reactions were performed by stirring enaminoesters **2a**–**h** (2 equiv) with acid chloride **4** (1 equiv) in purified 1,2-dichloroethane (DCE)[16] at 23 °C for 3 h, followed by addition of triethylamine (TEA, 2 equiv) and heating at reflux for 12–18 h. Our experiments revealed that *N*-acylation of the enaminoester proceeded best at room temperature, while the final S_NAr ring closure required heating. For substrates having a monoactivated aromatic acceptor, such as **5**, reactions were performed similarly in purified 1,4-dioxane[16] using a pressure tube with 1,8-diazabicyclo[5.4.0] undec-7-ene (DBU) as the base (2 equiv, 130 °C, 3 h) for the cyclization. Finally, reactions involving 2-chloronicotinoyl chloride **7** were achieved using the enaminoester (3 equiv, see below) in DCE with TEA as the base (2, equiv, 130 °C, 8 h). The use of anhydrous, purified solvents was essential, as the enaminoesters were both water and acid sensitive. Failure to remove these impurities from DCE and dioxane, resulted in hydrolysis of the enamine to give benzylamine, which readily added to the S_NAr acceptor ring, pre-empting the ring closure. The reaction was facilitated by the use of excess enamine. While TEA or DBU were found to be the best reagents for promoting the final cyclization, the use of these bases (or elevated temperatures) for the initial acylation had a negative impact on the overall yields. Upon completion, the crude reaction mixtures were added to aqueous NaCl and subjected to an extractive work-up. Purification was accomplished by chromatography followed by recrystallization.

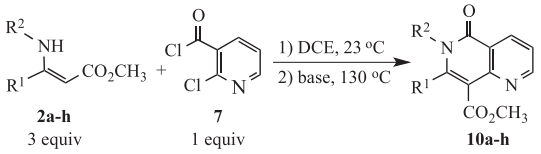
Table 1
Cyclization results for 2,3-dialkyl-4-methoxycarbonylisoquinolin-(2*H*)-ones



Entry	R^1	R^2	X	Conds	Pdt	Yield (%)
a	CH_3	CH_2Ph	NO_2	**A**	**8a**	86
b	C_2H_5	CH_2Ph	NO_2	**A**	**8b**	85
c	n-C_3H_7	CH_2Ph	NO_2	**A**	**8c**	77
d	n-C_5H_{11}	CH_2Ph	NO_2	**A**	**8d**	74
e	n-C_4H_7[a]	CH_2Ph	NO_2	**A**	**8e**	68
f	CH_2CH_2Ph	CH_2Ph	NO_2	**A**	**8f**	81
g	i-C_3H_7	CH_2Ph	NO_2	**A**	**8g**	30
h	CH_3	CH_3	NO_2	**A**	**8h**	85
a	CH_3	CH_2Ph	H	**B**	**9a**	57
b	C_2H_5	CH_2Ph	H	**B**	**9b**	52
c	n-C_3H_7	CH_2Ph	H	**B**	**9c**	58
d	n-C_5H_{11}	CH_2Ph	H	**B**	**9d**	50
e	n-C_4H_7[a]	CH_2Ph	H	**B**	**9e**	60
f	CH_2CH_2Ph	CH_2Ph	H	**B**	**9f**	73
g	i-C_3H_7	CH_2Ph	H	**B**	**9g**	30
h	CH_3	CH_3	H	**B**	**9h**	53

[a] n-C_4H_7 = 3-butenyl

Table 2
Cyclization results for 6,7-dialkyl-8-methoxycarbonyl-1,6-naphthyridin-5(6*H*)-ones



Entry	R^1	R^2	Pdt	Base: TEA Yield (%)	Base: DBU Yield (%)
a	CH_3	CH_2Ph	**10a**	70	59
b	C_2H_5	CH_2Ph	**10b**	74	62
c	n-C_3H_7	CH_2Ph	**10c**	76	68
d	n-C_5H_{11}	CH_2Ph	**10d**	70	52
e	n-C_4H_7[a]	CH_2Ph	**10e**	70	61
f	CH_2CH_2Ph	CH_2Ph	**10f**	72	60
g	i-C_3H_7	CH_2Ph	**10g**	0	0
h	CH_3	CH_3	**10h**	84	78

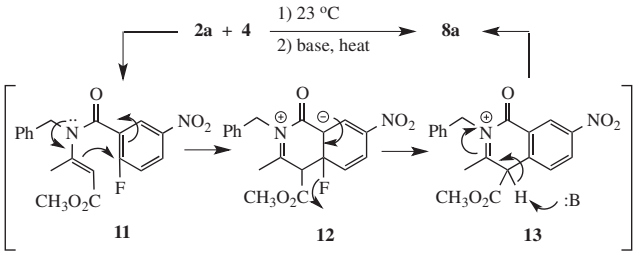
[a] n-C_4H_7 = 3-butenyl

Some further discussion is warranted regarding the use of excess enaminoester **2** for these transformations. In heterocyclizations involving **4** and **5**, 2 equiv of this reactant were necessary, with the second equivalent neutralizing the HCl produced during the acylation step. For reactions of 2-chloronicotinoyl chloride (**7**), however, it was found that 3 equiv of **2** were required for optimum conversion rather than two. This stems from the fact that **7** incorporates an extra equivalent of HCl due to the basic nitrogen of the pyridine, and this acid could sabotage the reaction sequence at several stages. Protonation at nitrogen significantly increases the C2 reactivity of 2-chloropyridines toward nucleophiles,[17] and thus, attack at this site could compete with the acylation process. Additionally, the 2-chloropyridinium cation could serve as a proton source [$pK_a \sim 0.48$ (H_2O), 2.96 (acetone)][18] to deactivate the enaminoester nitrogen or protonate the enamide double bond. Hence, it was important to neutralize this salt in addition to the HCl produced during enamide formation to decrease the probability of side reactions. This was most effectively accomplished by addition of **7** to a cooled solution containing 3 equiv of **2**. The alternative use of bases, such as TEA or DBU during the acylation stage was found to lower the overall product yields, and inorganic bases were not explored since reaction of these with HCl would produce water, which could degrade both reactants. The delocalized

enaminoesters have base properties intermediate between 2-chloropyridine and TEA, and scavenge the acid without introducing additional contaminants. They are easily prepared from inexpensive commercial chemicals and do not require purification prior to reaction. Moreover, in applications where the precursor ketoester is costly or demands independent synthesis, the required use of surplus **2** is mitigated by the fact that much of this material can be recovered, as the ketoester, and recycled.

As expected, cyclizations on aromatic acceptors with two electron-withdrawing groups or a 2-chloropyridine generally proceeded in higher yields and under milder conditions.[19] Mono-activated substrates required a stronger base and more robust thermal conditions. The sequence proved limited with respect to the steric environment adjacent to the nucleophilic enamine carbon. For example, branching at the α carbon of R^1, as in **2g**, reduced the yields from mono- and diactivated substrates and completely suppressed cyclization for heteroaromatic systems. In these cases, degradation of the acylated enamine, presumably through elimination of the halogen from the acceptor ring, competed with cyclization. Substrates having straight-chain alkyl groups at R^1, however, cyclized in good to excellent yields for all aromatic acceptors investigated, making this a viable approach to these highly functionalized heterocycles. Though most of our work was done using the *N*-benzyl-β-enaminoesters (e.g., R^2=benzyl), two reactions with the *N*-methyl derivative **2h** were equally successful. Thus, variation of both R^1 and R^2 can be used to introduce substituent diversity to these systems.

A possible mechanism is illustrated in Scheme 2 for the reaction of **2a** with **4**. In the initial step, the enaminoester **2a** is *N*-acylated by acid chloride **4** to give **11**. This would be followed by attack of the *N*-acyl-β-enaminoester on the aromatic acceptor to generate the fused-ring system **12**. Rearomatization, with loss of fluoride, would then give the 2,3-dialkyl-4-methoxycarbonyl-7-nitroisoquinolinium-1(4*H*)-one intermediate **13**. In the final step, base (TEA or DBU) would remove the acidic proton from the ester-substituted benzylic carbon to convert **13** to the final product **8a**.



Scheme 2. Possible mechanism to form a 2,3-dialkyl-4-methoxycarbonylisoquinolin-1(2*H*)-one.

3. Conclusion

In conclusion, we have developed a practical and efficient approach for the synthesis of 2,3-dialkyl-4-methoxycarbonyliso quinoline-1(2*H*)-one and 6,7-dialkyl-8-methoxycarbonyl-1,6-naphthyridin-5(6*H*)-ones using a sequential *N*-acylation-S_NAr process. The method involved room temperature *N*-acylation of readily available enaminoesters **2a**–**h** with 2-fluoro-5-nitrobenzoyl chloride, 2-fluorobenzoyl chloride, and 2-chloronicotinoyl chloride followed by heating to promote the final S_NAr ring closure. Yields were generally in the 52–86% range. The reaction proceeded smoothly for mono- and diactivated aromatic acceptor rings as well as 2-chloropyridine systems but manifested steric limitations in the ring-forming step when α-branched alkyl groups were positioned adjacent to the nucleophilic enamine carbon.

4. Experimental section

4.1. General methods

All reactions were run under dry nitrogen in oven-dried glassware. Reactions were monitored by thin layer chromatography on silica gel GF plates (Analtech, No. 21521). Preparative separations were performed by one of the following methods: (1) preparative thin layer chromatography (PTLC) on 20-cm×20-cm silica gel GF plates (Analtech, No. 02015) or (2) column chromatography on silica gel (grade 62, 60–200 mesh) containing UV-active phosphor (Sorbent Technologies, No. UV-05) packed into quartz columns. Band elution for all chromatographic methods was monitored using a hand-held UV lamp. Melting points were uncorrected. FTIR spectra were run as thin films on NaCl disks. Unless otherwise indicated, ^{1}H and ^{13}C NMR spectra were measured in $CDCl_3$ using $(CH_3)_4Si$ as the internal standard; coupling constants (*J*) are given in Hertz. Low-resolution mass spectra (electron impact/direct probe) were obtained at 70 eV.

4.2. Representative synthesis of β-enaminoesters 2

A solution of β-ketoester **1** (10 mmol) [14] in 50 mL of benzene was treated with benzylamine (10.5 mmol) and one crystal of *p*-TsOH. The solution was refluxed for 8 h with Dean–Stark removal of H_2O. The reaction was cooled and concentrated under vacuum to give the β-enaminoester as a yellow oil. The *Z* isomer was strongly favored due to intramolecular hydrogen bonding. The product was nearly pure by ^{1}H NMR, but sensitive toward chromatography. It was, therefore, used without further purification.

*4.2.1. Methyl (Z)-3-(benzylamino)-2-butenoate (**2a**).* IR: 3292, 1653, 1607 cm^{-1}; ^{1}H NMR (300 MHz): δ 8.94 (br s, 1H), 7.36–7.19 (complex m, 5H), 4.54 (s, 1H), 4.42 (d, *J*=6.6 Hz, 2H), 3.63 (s, 3H), 1.90 (s, 3H); ^{13}C NMR (75 MHz): δ 170.8, 161.9, 138.6, 128.7, 127.3, 126.6, 82.7, 49.9, 46.7, 19.3; ms: *m*/*z* 114 ($M^+-C_7H_7$).

*4.2.2. Methyl (Z)-3-(benzylamino)-2-pentenoate (**2b**).* IR: 3287, 1653, 1606 cm^{-1}; ^{1}H NMR (300 MHz): δ 8.96 (br s, 1H), 7.38–7.18 (complex m, 5H), 4.57 (s, 1H), 4.43 (d, *J*=6.6 Hz, 2H), 3.64 (s, 3H), 2.23 (q, *J*=7.1 Hz, 2H), 1.12 (q, *J*=7.1 Hz, 3H); ^{13}C NMR (75 MHz): δ 171.2, 167.0, 138.7, 128.7, 127.3, 126.7, 80.7, 50.0, 46.3, 25.1, 12.1; ms: *m*/*z* 128 ($M^+-C_7H_7$).

*4.2.3. Methyl (Z)-3-(benzylamino)-2-hexenoate (**2c**).* IR: 3287, 1655, 1606 cm^{-1}; ^{1}H NMR (300 MHz): δ 8.94 (br s, 1H), 7.37–7.21 (complex m, 5H), 4.55 (s, 1H), 4.42 (d, *J*=6.6 Hz, 2H), 3.63 (s, 3H), 2.20 (t, *J*=7.7 Hz, 2H), 1.55 (sextet, *J*=7.7 Hz, 2H), 0.95 (t, *J*=7.7 Hz, 3H); ^{13}C NMR (75 MHz): δ 171.1, 165.6, 138.7, 128.7, 127.3, 126.7, 81.8, 49.9, 46.4, 34.2, 21.2, 13.8; ms: *m*/*z* 142 ($M^+-C_7H_7$).

*4.2.4. Methyl (Z)-3-(benzylamino)-2-octenoate (**2d**).* IR: 3285, 1657, 1606 cm^{-1}; ^{1}H NMR (300 MHz): δ 8.94 (br s, 1H), 7.38–7.22 (complex m, 5H), 4.55 (s, 1H), 4.42 (d, *J*=6.6 Hz, 2H), 3.63 (s, 3H), 2.18 (t, *J*=7.1 Hz, 2H), 1.52 (quintet, *J*=7.1 Hz, 2H), 1.30 (m, 4H), 0.87 (t, *J*=6.6 Hz, 3H); ^{13}C NMR (75 MHz): δ 171.1, 165.9, 138.7, 128.7, 127.3, 126.7, 81.7, 49.9, 46.4, 32.2, 31.4, 27.7, 22.3, 13.7; ms: *m*/*z* 170 ($M^+-C_7H_7$).

*4.2.5. Methyl (Z)-3-(benzylamino)-5-phenyl-2-pentenoate (**2e**).* IR: 3285, 1653, 1606 cm^{-1}; ^{1}H NMR (300 MHz): δ 8.97 (br s, 1H), 7.38–7.20 (complex m, 8H), 7.13 (d, *J*=6.6 Hz, 2H), 4.62 (s, 1H), 4.37 (d, *J*=6.6 Hz, 2H), 3.64 (s, 3H), 2.81 (t, *J*=7.7 Hz, 2H), 2.48 (t, *J*=7.7 Hz, 2H); ^{13}C NMR (75 MHz): δ 171.1, 164.8, 140.4, 138.5, 128.8, 128.5, 128.2, 127.4, 126.7, 126.3, 82.0, 50.0, 46.4, 34.5, 34.0; ms: *m*/*z* 204 ($M^+-C_7H_7$).

*4.2.6. Methyl (Z)-3-(benzylamino)-2,6-heptadienoate (**2f**).* IR: 3286, 1655, 1610 cm^{-1}; ^{1}H NMR (300 MHz): δ 8.95 (br s, 1H), 7.39–7.21

(complex m, 5H), 5.79 (ddt, J=17.0, 9.3, 4.9 Hz, 1H), 5.02 (d, J=17.0 Hz, 1H), 5.00 (d, J=9.3 Hz, 1H), 4.56 (s, 1H), 4.43 (d, J=6.6 Hz, 2H), 3.64 (s, 3H), 2.28 (m, 4H); ^{13}C NMR (75 MHz): δ 171.0, 164.8, 138.6, 136.6, 128.8, 127.4, 126.7, 115.6, 82.0, 50.0, 46.5, 32.0, 31.5; ms: m/z 154 ($M^+-C_7H_7$).

*4.2.7. Methyl (Z)-3-(benzylamino)-4-methyl-2-pentenoate (**2g**).* IR: 3281, 1653, 1606 cm^{-1}; ^{1}H NMR (300 MHz): δ 9.07 (br s, 1H), 7.38–7.21 (complex m, 5H), 4.61 (s, 1H), 4.45 (d, J=6.0 Hz, 2H), 3.64 (s, 3H), 2.66 (septet, J=6.6 Hz, 1H), 1.10 (d, J=6.6 Hz, 6H); ^{13}C NMR (75 MHz): δ 171.8, 171.6, 138.8, 128.7, 127.2, 126.2, 78.1, 50.0, 46.0, 28.5, 21.5; ms: m/z 142 ($M^+-C_7H_7$).

*4.2.8. Methyl (Z)-3-(methylamino)-2-butenoate (**2h**).* This compound was prepared in 84% yield by a literature procedure,[16] mp 64–66 °C (lit[16] mp 65–67 °C). IR 3310, 1652, 1604 cm^{-1}; ^{1}H NMR (300 MHz): δ 8.46 (br s, 1H), 4.47 (s, 1H), 3.61 (s, 3H), 2.91 (d, J=4.9 Hz, 3H), 1.92 (s, 3H); ^{13}C NMR (75 MHz): δ 170.9, 162.8, 81.4, 49.8, 29.5, 19.1; ms: m/z 129 (M^+).

4.3. 2-Fluoro-5-nitrobenzoyl chloride (4)

This compound was prepared by refluxing acid **3** (10 mmol) with thionyl chloride (12 mmol) in benzene for 8 h. Removal of the solvent gave a tan solid, mp 59–60 °C. This material was spectroscopically pure and was used without further purification. IR: 1793, 1770, 1626, 1538, 1352 cm^{-1}; ^{1}H NMR (300 MHz): δ 9.02 (dd, J=6.0, 3.0 Hz, 1H), 8.57 (dt, J=8.8, 3.0 Hz, 1H), 7.44 (t, J=9.3 Hz, 1H); ^{13}C NMR (75 MHz): δ 164.2 (d, J=276.8 Hz), 161.3 (d, J=4.9 Hz), 143.9, 131.5 (d, J=11.5 Hz), 129.5, 123.0 (d, J=9.8 Hz), 118.9 (d, J=23.8 Hz).

4.4. 2-Chloronicotinoyl chloride (7)

This compound was prepared by refluxing acid **6** (10 mmol) with thionyl chloride (12 mmol) in benzene for 8 h. Removal of the solvent gave a tan solid, mp 39–42 °C (lit. [20] mp 39–42 °C). The ^{1}H NMR and ^{13}C NMR spectra matched those reported previously[20] and was used without further purification.

4.5. General cyclization procedure for systems with diactivated aromatic acceptor rings

A solution of enaminoester **2** (0.98 mmol) in 3 mL of purified 1,2-dichloroethane (DCE)[16] was cooled to 10 °C and a solution of **5** (100 mg, 0.49 mmol) in 3 mL of DCE was added. The solution was stirred at 23 °C for 3 h, then cooled to 10 °C and TEA (0.98 mmol, 99 mg, 0.136 mL) in 2 mL of DCE was added. The reaction was heated at reflux until complete (12–18 h). The reaction was cooled and added to aqueous NaCl. The organic layer was separated and the aqueous phase was washed with dichloromethane. The combined organic extracts were washed with aqueous NaCl, dried ($MgSO_4$), filtered, and concentrated under vacuum. The crude product was purified by PTLC eluted with 1:1 ethyl acetate/hexanes containing 1% TEA. The following compounds were prepared:

*4.5.1. 2-Benzyl-4-methoxycarbonyl-3-methyl-7-nitroisoquinolin-1(2H)-one (**8a**).* Yield: 146 mg (0.42 mmol, 85%) as a tan solid, mp 192–194 °C; IR: 1733, 1632, 1614, 1523, 1342 cm^{-1}; ^{1}H NMR (300 MHz): δ 9.13 (d, J=2.7 Hz, 1H), 8.27 (dd, J=9.9, 2.7 Hz, 1H), 7.44–7.31 (complex m, 4H), 7.07 (d, J=6.6 Hz, 2H), 5.50 (s, 2H), 3.96 (s, 3H), 2.51 (s, 3H); ^{13}C NMR (75 MHz): δ 173.1, 167.0, 151.2, 144.2, 143.4, 133.6, 129.6, 128.4, 126.7, 125.8, 125.0, 122.9, 119.6, 118.1, 52.7, 51.4, 18.8; ms: m/z 261 ($M^+-C_7H_7$). Anal. Calcd for $C_{19}H_{16}N_2O_5$: C, 64.77; H, 4.55; N, 7.95. Found: C, 64.90; H, 4.58; N, 7.74.

*4.5.2. 2-Benzyl-3-ethyl-4-methoxycarbonyl-7-nitroisoquinolin-1(2H)-one (**8b**).* Yield: 154 mg (0.42 mmol, 86%) as a tan solid, mp 128–130 °C; IR: 1730, 1630, 1613, 1523, 1354 cm^{-1}; ^{1}H NMR (300 MHz): δ 9.22 (d, J=2.7 Hz, 1H), 8.28 (dd, J=9.3, 2.7 Hz, 1H), 7.48–7.30 (complex m, 4H), 7.07 (d, J=6.0 Hz, 2H), 5.52 (s, 2H), 3.97 (s, 3H), 2.78 (q, J=7.7 Hz, 2H), 1.40 (t, J=7.7 Hz, 3H); ^{13}C NMR (75 MHz): δ 173.6, 167.0, 155.5, 144.2, 143.5, 134.0, 129.6, 128.5, 126.7, 126.3, 125.1, 123.3, 119.4, 118.2, 52.7, 50.7, 25.5, 13.7; ms: m/z 275 ($M^+-C_7H_7$). Anal. Calcd for $C_{20}H_{18}N_2O_5$: C, 65.57; H, 4.92; N, 7.65. Found: C, 65.68; H, 4.90; N, 7.53.

*4.5.3. 2-Benzyl-4-methoxycarbonyl-7-nitro-3-propylisoquinolin-1(2H)-one (**8c**).* Yield: 152 mg (0.40 mmol, 82%) as a tan solid, mp 120–121 °C; IR: 1730, 1628, 1614, 1525, 1353 cm^{-1}; ^{1}H NMR (300 MHz): δ 9.22 (d, J=2.7 Hz, 1H), 8.27 (dd, J=9.3, 2.7 Hz, 1H), 7.45 (d, J=9.3 Hz, 1H), 7.44–7.32 (complex m, 3H), 7.07 (d, J=6.6 Hz, 2H), 5.50 (s, 2H), 3.97 (s, 3H), 2.72 (t, J=7.7 Hz, 2H), 1.80 (sextet, J=7.7 Hz, 2H), 1.04 (t, J=7.7 Hz, 3H); ^{13}C NMR (75 MHz): δ 173.5, 167.1, 154.5, 144.2, 143.5, 134.0, 129.6, 128.5, 126.7, 126.3, 125.1, 123.2, 119.6, 118.3, 52.7, 50.8, 34.0, 23.0, 14.3; ms: m/z 289 ($M^+-C_7H_7$). Anal. Calcd for $C_{21}H_{20}N_2O_5$: C, 66.32; H, 5.26; N, 7.37. Found: C, 66.52; H, 5.59; N, 7.19.

*4.5.4. 2-Benzyl-4-methoxycarbonyl-7-nitro-3-pentylisoquinolin-1(2H)-one (**8d**).* Yield: 148 mg (0.36 mmol, 74%) as a tan solid, mp 122–123 °C; IR: 1733, 1628, 1613, 1523, 1343 cm^{-1}; ^{1}H NMR (300 MHz): δ 9.18 (d, J=2.7 Hz, 1H), 8.26 (dd, J=9.3, 2.7 Hz, 1H), 7.49 (d, J=9.3 Hz, 1H), 7.41–7.30 (complex m, 3H), 7.08 (d, J=6.6 Hz, 2H), 5.54 (s, 2H), 3.95 (s, 3H), 2.73 (t, J=7.7 Hz, 2H), 1.77 (quintet, J=7.7 Hz, 2H), 1.34 (m, 4H), 0.88 (t, J=6.6 Hz, 3H); ^{13}C NMR (75 MHz): δ 173.4, 167.0, 154.7, 144.1, 143.3, 134.0, 129.4, 128.3, 126.5, 126.1, 125.0, 123.0, 119.4, 118.4, 52.5, 50.7, 31.9, 31.6, 28.9, 21.8, 13.6; ms: m/z 317 ($M^+-C_7H_7$). Anal. Calcd for $C_{23}H_{24}N_2O_5$: C, 67.65; H, 5.88; N, 6.86. Found: C, 67.91; H, 5.93; N, 6.51.

*4.5.5. 2-Benzyl-3-(3-butenyl)-4-methoxycarbonyl-7-nitroisoquinolin-1(2H)-one (**8e**).* Yield: 130 mg (0.33 mmol, 68%) as a yellow solid, mp 114–116 °C; IR: 1730, 1633, 1614, 1524, 1344 cm^{-1}; ^{1}H NMR (300 MHz): δ 9.23 (d, J=2.7 Hz, 1H), 8.29 (dd, J=9.3, 2.7 1H), 7.45 (d, J=9.3 Hz, 1H), 7.44–7.31 (complex m, 3H), 7.07 (d, J=6.6 Hz, 2H), 5.82 (ddt, J=17.0, 9.9, 6.6 Hz, 1H), 5.50 (s, 2H), 5.07 (d, J=17.0 Hz, 1H), 5.06 (d, J=9.9 Hz, 1H), 3.96 (s, 3H), 2.86 (t, J=7.7 Hz, 2H), 2.50 (q, J=7.7 Hz, 2H); ^{13}C NMR (75 MHz): δ 173.4, 166.9, 153.9, 144.2, 143.5, 135.1, 133.9, 129.5, 128.5, 126.7, 126.2, 125.1, 123.2, 119.7, 118.4, 116.7, 52.7, 50.9, 33.0, 31.3; ms: m/z 301 ($M^+-C_7H_7$). Anal. Calcd for $C_{22}H_{20}N_2O_5$: C, 67.35; H, 5.10; N, 7.14. Found: C, 67.46; H, 5.12; N, 7.07.

*4.5.6. 2-Benzyl-4-methoxycarbonyl-7-nitro-3-(2-phenylethyl)isoquinolin-1(2H)-one (**8f**).* Yield: 175 mg (0.40 mmol, 81%) as a tan solid, mp 188–189 °C; IR: 1729, 1628, 1613, 1522, 1343 cm^{-1}; ^{1}H NMR (300 MHz): δ 9.28 (d, J=2.7 Hz, 1H), 8.32 (dd, J=9.3, 2.7 Hz, 1H), 7.43 (d, J=9.3 Hz, 1H), 7.42–7.23 (complex m, 6H), 7.12 (d, J=6.0 Hz, 2H), 7.05 (d, J=6.0 Hz, 2H), 5.40 (s, 2H), 4.00 (s, 3H), 3.05 (s, 4H); ^{13}C NMR (75 MHz): δ 173.6, 167.1, 153.7, 144.2, 143.8, 139.1, 133.9, 129.7, 128.9, 128.7, 128.1, 127.1, 126.9, 126.5, 125.1, 123.5, 119.8, 118.2, 52.9, 50.9, 35.6, 33.9; ms: m/z 351 ($M^+-C_7H_7$). Anal. Calcd for $C_{26}H_{22}N_2O_5$: C, 70.59; H, 4.98; N, 6.33. Found: C, 70.66; H, 5.01; N, 6.25.

*4.5.7. 2-Benzyl-3-isopropyl-4-methoxycarbonyl-7-nitroisoquinolin-1(2H)-one (**8g**).* Yield: 56 mg (0.15 mmol, 30%) as a tan solid, mp 170–172 °C; IR: 1730, 1625, 1610, 1524, 1344 cm^{-1}; ^{1}H NMR (300 MHz): δ 9.22 (d, J=2.7 Hz, 1H), 8.27 (dd, J=9.3, 2.7 Hz, 1H), 7.45–7.31 (complex m, 4H), 7.10 (d, J=6.6 Hz, 2H), 5.52 (s, 2H), 3.96

(s, 3H), 3.20 (septet, J=7.1 Hz, 1H), 1.42 (d, J=7.1 Hz, 6H); ^{13}C NMR (75 MHz): δ 174.6, 167.3, 158.1, 144.8, 143.4, 134.3, 129.6, 128.46, 128.43, 126.6, 125.6, 124.9, 123.0, 118.5, 52.6, 51.6, 31.8, 29.6, 20.6; ms: m/z 289 ($M^+-C_7H_7$). Anal. Calcd for $C_{21}H_{20}N_2O_5$: C, 66.32; H, 5.26; N, 7.37. Found: C, 66.45; H, 5.30; N, 7.23.

*4.5.8. 2,3-Dimethyl-4-methoxycarbonyl-7-nitroisoquinolin-1(2H)-one (**8h**).* Yield: 115 mg (0.42 mmol, 85%) as a yellow solid, mp 298–300 °C (darkens); IR: 1725, 1626, 1611, 1523, 1340 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.85 (d, J=2.7 Hz, 1H), 8.49 (dd, J=9.3, 2.7 Hz, 1H), 8.08 (d, J=9.3 Hz, 1H), 3.83 (s, 3H), 3.82 (s, 3H), 2.50 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 172.0, 167.0, 151.9, 144.6, 142.8, 126.4, 124.8, 121.4, 119.3, 118.7, 52.3, 35.7, 19.3; ms: m/z 276 (M^+). Anal. Calcd for $C_{13}H_{12}N_2O_5$: C, 56.52; H, 4.35; N, 10.14. Found: C, 56.57; H, 4.35; N, 10.08.

4.6. General cyclization procedure for systems with mono-activated aromatic acceptor rings

A 15-mL, screw-top, pressure vessel (ChemGlass No. CG-1880-01) was charged with enaminoester **2** (2.52 mmol) and 2 mL of purified 1,4-dioxane.[16] The solution was cooled to 15 °C and a solution of 2-fluorobenzoyl chloride (**6**) (200 mg, 1.26 mmol) in 2 mL of dioxane was added. The reaction was stirred at 23 °C for 3 h, then cooled to 15 °C and DBU (2.52 mmol, 383 mg, 0.376 mL) in 1 mL of dioxane was added. The reaction was sealed under nitrogen, and heated to 130 °C for 3 h. The reaction was cooled and concentrated under vacuum. The residue was dissolved in dichloromethane, washed with water and aqueous NaCl, dried ($MgSO_4$), filtered, and concentrated under vacuum. The resulting product was purified on a 20 cm×2 cm silica gel column eluted with increasing concentrations of ethyl acetate in hexanes. The following compounds were prepared:

*4.6.1. 2-Benzyl-4-methoxycarbonyl-3-methylisoquinolin-1(2H)-one (**9a**).* Yield: 220 mg (0.72 mmol, 57%) as a white solid, mp 113–115 °C; IR: 1727, 1618, 1602 cm^{-1}; ^{1}H NMR (300 MHz): δ 8.46 (dd, J=8.2, 1.6 Hz, 1H), 7.53 (td, J=7.1, 1.6 Hz, 1H), 7.42–7.24 (complex m, 5H), 7.08 (d, J=6.6 Hz, 2H), 5.44 (s, 2H), 3.96 (s, 3H), 2.43 (s, 3H); ^{13}C NMR (75 MHz): δ 174.2, 168.2, 149.8, 140.8, 134.6, 132.7, 129.2, 127.9, 126.7, 126.3, 125.1, 124.0, 118.2, 116.2, 52.4, 50.6, 18.6; ms: m/z 216 ($M^+-C_7H_7$). Anal. Calcd for $C_{19}H_{17}NO_3$: C, 74.27; H, 5.54; N, 4.56. Found: C, 74.19; H, 5.55; N, 4.51.

*4.6.2. 2-Benzyl-3-ethyl-4-methoxycarbonylisoquinolin-1(2H)-one (**9b**).* Yield: 210 mg (0.66 mmol, 52%) as a white solid, mp 108–109 °C; IR: 1727, 1618, 1600 cm^{-1}; ^{1}H NMR (300 MHz): δ 8.46 (d, J=8.2 Hz, 1H), 7.51 (t, J=7.1 Hz, 1H), 7.40–7.25 (complex m, 5H), 7.07 (d, J=7.1 Hz, 2H), 5.46 (s, 2H), 3.96 (s, 3H), 2.76 (q, J=7.1 Hz, 2H), 1.37 (t, J=7.1 Hz, 3H); ^{13}C NMR (75 MHz): δ 174.7, 168.2, 154.3, 140.8, 135.1, 132.7, 129.3, 128.0, 126.9, 126.6, 125.2, 124.0, 117.9, 116.5, 52.5, 50.0, 25.3, 13.8; ms: m/z 230 ($M^+-C_7H_7$). Anal. Calcd for $C_{20}H_{19}NO_3$: C, 74.77; H, 5.92; N, 4.36. Found: C, 74.91; H, 5.94; N, 4.27.

*4.6.3. 2-Benzyl-4-methoxycarbonyl-3-propylisoquinolin-1(2H)-one (**9c**).* Yield: 245 mg (0.73 mmol, 58%) as a white solid, mp 168–169 °C; IR: 1727, 1619, 1600 cm^{-1}; ^{1}H NMR (300 MHz): δ 8.46 (d, J=8.2 Hz, 1H), 7.51 (t, J=6.6 Hz, 1H), 7.40–7.25 (complex m, 5H), 7.07 (d, J=7.1 Hz, 2H), 5.44 (s, 2H), 3.96 (s, 3H), 2.69 (t, J=7.7 Hz, 2H), 1.79 (sextet, J=7.7 Hz, 2H), 1.01 (t, J=7.1 Hz, 3H); ^{13}C NMR (75 MHz): δ 174.6, 168.2, 153.3, 140.8, 135.1, 132.7, 129.3, 128.1, 127.0, 126.7, 125.3, 124.1, 118.2, 116.5, 52.5, 50.2, 33.9, 23.1, 14.3; ms: m/z 244 ($M^+-C_7H_7$). Anal. Calcd for $C_{21}H_{21}NO_3$: C, 75.22; H, 6.27; N, 4.18. Found: C, 75.31; H, 6.30; N, 4.05.

*4.6.4. 2-Benzyl-4-methoxycarbonyl-3-pentylisoquinolin-1(2H)-one (**9d**).* Yield: 229 mg (0.63 mmol, 50%) as a white solid, mp 92–93 °C; IR: 1727, 1619, 1600 cm^{-1}; ^{1}H NMR (300 MHz): δ 8.47 (d, J=7.7 Hz, 1H), 7.52 (t, J=7.1 Hz, 1H), 7.41–7.27 (complex m, 5H), 7.07 (d, J=6.6 Hz, 2H), 5.44 (s, 2H), 3.96 (s, 3H), 2.69 (t, J=7.7 Hz, 2H), 1.75 (quintet, J=7.1 Hz, 2H), 1.60 (m, 4H), 0.88 (t, J=7.1 Hz, 3H); ^{13}C NMR (75 MHz): δ 174.6, 168.2, 153.5, 140.8, 135.1, 132.7, 129.3, 128.1, 127.0, 126.7, 125.3, 124.1, 118.2, 116.5, 52.5, 50.2, 31.9, 31.8, 29.2, 22.1, 13.8; ms: m/z 272 ($M^+-C_7H_7$). Anal. Calcd for $C_{23}H_{25}NO_3$: C, 76.03; H, 6.89; N, 3.86. Found: C, 75.97; H, 6.93; N, 3.69.

*4.6.5. 2-Benzyl-3-(3-butenyl)-4-methoxycarbonylisoquinolin-1(2H)-one (**9e**).* Yield: 262 mg (0.76 mmol, 60%) as a white solid, mp 106–107 °C; IR: 1726, 1618, 1601 cm^{-1}; ^{1}H NMR (300 MHz): δ 8.48 (dd, J=6.6, 1.6 Hz, 1H), 7.53 (t, J=7.1 Hz, 1H), 7.40–7.28 (complex m, 5H), 7.07 (d, J=6.6 Hz, 2H), 5.82 (ddt, J=17.0, 10.4, 6.6 Hz, 1H), 5.42 (s, 2H), 5.06 (d, J=17.0 Hz, 1H), 5.05 (d, J=10.4 Hz, 1H), 3.96 (s, 3H), 2.83 (t, J=6.6 Hz, 2H), 2.49 (q, J=6.6 Hz, 2H); ^{13}C NMR (75 MHz): δ 174.6, 168.1, 152.6, 140.8, 135.7, 135.0, 132.8, 129.4, 128.1, 127.0, 126.7, 125.3, 124.2, 118.2, 116.5, 116.4, 52.5, 50.3, 33.3, 31.2; ms: m/z 256 (M^+). Anal. Calcd for $C_{22}H_{21}NO_3$: C, 76.08; H, 6.05; N, 4.03. Found: C, 76.01; H, 6.08; N, 3.98.

*4.6.6. 2-Benzyl-4-methoxycarbonyl-3-(2-phenylethyl)isoquinolin-1(2H)-one (**9f**).* Yield: 365 mg (0.92 mmol, 73%) as a white solid, mp 154–156 °C; IR: 1724, 1616, 1600 cm^{-1}; ^{1}H NMR (300 MHz): δ 8.48 (dd, J=6.6, 1.1 Hz, 1H), 7.53 (t, J=8.2 Hz, 1H), 7.40–7.19 (complex m, 9H), 7.12 (d, J=6.6 Hz, 2H), 7.06 (d, J=6.6 Hz, 2H), 5.40 (s, 2H), 3.98 (s, 3H), 3.03 (s, 3H); ^{13}C NMR (75 MHz): δ 174.6, 168.2, 152.5, 140.9, 138.5, 135.0, 132.8, 129.4, 128.8, 128.1, 127.0, 126.8, 126.7, 125.3, 124.2, 118.3, 116.5, 52.6, 50.2, 35.6, 33.9 (one aromatic C was unresolved); ms: m/z 306 ($M^+-C_7H_7$). Anal. Calcd for $C_{26}H_{23}NO_3$: C, 78.59; H, 5.79; N, 3.53. Found: C, 78.55; H, 5.80; N, 3.49.

*4.6.7. 2-Benzyl-3-isopropyl-4-methoxycarbonylisoquinolin-1(2H)-one (**9g**).* Yield: 126 mg (0.38 mmol, 30%) as a white solid, mp 145–147 °C; IR: 1729, 1616, 1602 cm^{-1}; ^{1}H NMR (300 MHz): δ 8.43 (dd, J=7.7, 1.1 Hz, 1H), 7.52 (td, J=7.7, 1.1 Hz, 1H), 7.42–7.23 (complex m, 5H), 7.10 (d, J=6.6 Hz, 2H), 5.47 (s, 2H), 3.95 (s, 3H), 3.19 (septet, J=6.6 Hz, 1H), 1.40 (d, J=6.6 Hz, 6H); ^{13}C NMR (75 MHz): δ 175.6, 168.5, 156.7, 141.4, 135.5, 132.7, 129.3, 128.0, 126.7, 126.1, 125.1, 123.9, 116.7, 52.4, 51.0, 31.7, 20.7 (1 aromatic C unresolved); ms: m/z 244 (M^+). Anal. Calcd for $C_{21}H_{21}NO_3$: C, 75.22; H, 6.27; N, 4.18. Found: C, 75.28; H, 6.24; N, 4.16.

*4.6.8. 2,3-Dimethyl-4-methoxycarbonylisoquinolin-1(2H)-one (**9h**).* Yield: 154 mg (0.66 mmol, 53%) as a white solid, mp 156–157 °C; IR: 1721, 1610, 1601 cm^{-1}; ^{1}H NMR (300 MHz): δ 8.41 (dd, J=8.2, 1.6 Hz, 1H), 7.64 (td, J=8.2, 1.6 Hz, 1H), 7.47 (d, J=8.8 Hz, 1H), 7.36 (t, J=7.1 Hz, 1H), 3.94 (s, 3H), 3.74 (s, 3H), 2.50 (s, 3H); ^{13}C NMR (75 MHz): δ 174.2, 168.4, 149.6, 141.1, 132.6, 126.9, 126.3, 124.0, 118.1, 115.3, 52.5, 34.7, 19.4; ms: m/z 231 (M^+). Anal. Calcd for $C_{13}H_{13}NO_3$: C, 67.53; H, 5.63; N, 6.06. Found: C, 67.66; H, 5.65; N, 5.99.

4.7. General cyclization procedure for systems with 2-chloropyridine systems

These reactions were run as above using enaminoester **2** (3.42 mmol) and **7** (200 mg, 1.14 mmol) in purified DCE.[16] The cyclization was completed by adding TEA (2.28 mmol, 230 mg, 0.317 mL) and heating at 130 °C for 8 h in a pressure tube. In each case, work-up and purification by PTLC, eluted with 1:1 ethyl acetate/hexanes containing 1% TEA, afforded the final product. [*Note*: DBU (2.28 mmol) was also used in the cyclization step, but the yields were lower.] The following compounds were prepared:

*4.7.1. 6-Benzyl-8-methoxycarbonyl-7-methyl-1,6-naphthyridin-5(6H)-one (**10a**).* Yield: 246 mg (0.80 mmol, 70%) as a tan solid, mp 143–145 °C; IR: 1727, 1617, 1600 cm^{-1}; ^1H NMR (400 MHz): δ 8.76 (dd, J=8.0, 2.0 Hz, 1H), 8.70 (dd, J=4.5, 2.0 Hz, 1H), 7.38 (dd, J=7.8, 4.5 Hz, 1H), 7.35–7.24 (complex m, 3H), 7.04 (d, J=6.6 Hz, 2H), 5.89 (br s, 2H), 3.94 (s, 3H), 2.47 (s, 3H); ^{13}C NMR (100 MHz): δ 174.5, 167.7, 152.6, 151.4, 150.4, 136.2, 136.1, 129.0, 127.6, 125.8, 120.8, 120.4, 119.1, 52.6, 48.0, 18.7; ms: m/z 217 ($M^+-C_7H_7$). Anal. Calcd for $C_{18}H_{16}N_2O_3$: C, 70.13; H, 5.19; N, 9.09. Found: C, 70.18; H, 5.20; N, 9.04.

*4.7.2. 6-Benzyl-7-ethyl-8-methoxycarbonyl-1,6-naphthyridin-5(6H)-one (**10b**).* Yield: 272 mg (0.84 mmol, 74%) as a tan solid, mp 156–158 °C; IR: 1727, 1617, 1600 cm^{-1}; ^1H NMR (400 MHz): δ 8.74 (dd, J=7.8, 2.0 Hz, 1H), 8.67 (dd, J=4.5, 2.0 Hz, 1H), 7.35 (dd, J=8.0, 4.5 Hz, 1H), 7.32–7.22 (complex m, 3H), 7.01 (d, J=6.8 Hz, 2H), 5.79 (br s, 2H), 3.94 (s, 3H), 2.77 (q, J=7.6 Hz, 2H), 1.34 (t, J=7.6 Hz, 3H); ^{13}C NMR (100 MHz): δ 174.7, 167.5, 156.0, 152.5, 150.3, 136.6, 136.0, 128.9, 127.5, 125.5, 120.8, 120.3, 118.7, 52.5, 47.4, 25.1, 13.8; ms: m/z 231 ($M^+-C_7H_7$). Anal. Calcd for $C_{19}H_{18}N_2O_3$: C, 70.81; H, 5.59; N, 8.70. Found: C, 70.88; H, 5.61; N, 8.57.

*4.7.3. 6-Benzyl-8-methoxycarbonyl-7-propyl-1,6-naphthyridin-5(6H)-one (**10c**).* Yield: 291 mg (0.87 mmol, 76%) as a tan solid, mp 162–163 °C; IR: 1727, 1617, 1600 cm^{-1}; ^1H NMR (400 MHz): δ 8.74 (dd, J=8.0, 2.0 Hz, 1H), 8.67 (dd, J=4.5, 2.0 Hz, 1H), 7.35 (dd, J=7.8, 4.5 Hz, 1H), 7.36–7.26 (complex m, 3H), 7.02 (d, J=6.8 Hz, 2H), 5.87 (br s, 2H), 3.94 (s, 3H), 2.70 (t, J=8.2 Hz, 2H), 1.74 (sextet, J=7.4 Hz, 2H), 1.01 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz): δ 174.7, 167.6, 154.9, 152.5, 150.3, 136.7, 136.1, 128.9, 127.6, 125.7, 120.9, 120.3, 118.9, 52.5, 47.6, 33.7, 23.2, 14.4; ms: m/z 245 ($M^+-C_7H_7$). Anal. Calcd for $C_{20}H_{20}N_2O_3$: C, 71.43; H, 5.95; N, 8.33. Found: C, 71.39; H, 5.92; N, 8.29.

*4.7.4. 6-Benzyl-8-methoxycarbonyl-7-pentyl-1,6-naphthyridin-5(6H)-one (**10d**).* Yield: 290 mg (0.80 mmol, 70%) as a tan solid, mp 165–166 °C; IR: 1728, 1619, 1605 cm^{-1}; ^1H NMR (400 MHz): δ 8.74 (dd, J=8.0, 4.5 Hz, 1H), 8.67 (dd, J=4.5, 2.0 Hz, 1H), 7.35 (dd, J=8.0, 4.5 Hz, 1H), 7.33–7.23 (complex m, 3H), 7.02 (d, J=6.8 Hz, 2H), 5.88 (br s, 2H), 3.93 (s, 3H), 2.71 (t, J=8.2 Hz, 2H), 1.71 (quintet, J=7.4 Hz, 2H), 1.38 (m, 4H), 0.89 (t, J=7.0 Hz, 3H); ^{13}C NMR (100 MHz): δ 174.6, 167.6, 155.1, 152.5, 150.3, 136.6, 136.0, 128.9, 127.5, 125.6, 120.8, 120.3, 118.8, 52.4, 47.6, 31.8, 31.6 29.2, 22.0, 13.8; ms: m/z 273 ($M^+-C_7H_7$). Anal. Calcd for $C_{22}H_{24}N_2O_3$: C, 72.53; H, 6.59; N, 7.69. Found: C, 72.61; H, 6.59; N, 7.63.

*4.7.5. 6-Benzyl-7-(3-butenyl)-8-methoxycarbonyl-1,6-naphthyridin-5(6H)-one (**10e**).* Yield: 278 mg (0.80 mmol, 70%) as a tan solid, mp 135–136 °C; IR: 1727, 1617, 1600 cm^{-1}; ^1H NMR (400 MHz): δ 8.75 (d, J=7.8 Hz, 1H), 8.69 (d, J=4.3 Hz, 1H), 7.37 (dd, J=7.8, 4.5 Hz, 1H), 7.34–7.23 (complex m, 3H), 7.02 (d, J=6.8 Hz, 2H), 5.89 (br s, 2H), 5.81 (ddt, J=16.8, 10.1, 6.4 Hz, 1H), 5.06 (d, J=16.6 Hz, 1H), 5.05 (d, J=10.3 Hz, 1H), 3.94 (s, 3H), 2.84 (t, J=8.0 Hz, 2H), 2.44 (q, J=7.6 Hz, 2H); ^{13}C NMR (100 MHz): δ 174.7, 167.5, 154.3, 152.6, 150.4, 136.6, 136.2, 135.7, 129.0, 127.6, 125.7, 120.9, 120.4, 119.1, 116.3, 52.5, 47.7, 33.3, 31.0; ms: m/z 257 ($M^+-C_7H_7$). Anal. Calcd for $C_{21}H_{20}N_2O_3$: C, 72.41; H, 5.75; N, 8.05. Found: C, 72.29; H, 5.77; N, 7.99.

*4.7.6. 6-Benzyl-8-methoxycarbonyl-7-(2-phenylethyl)-1,6-naphthyridin-5(6H)-one (**10f**).* Yield: 327 mg (0.82 mmol, 72%) as a tan solid, mp 141–142 °C; IR: 1726, 1620, 1601 cm^{-1}; ^1H NMR (400 MHz): δ 8.77 (d, J=7.8 Hz, 1H), 8.70 (d, J=4.5 Hz, 1H), 7.39 (dd, J=7.8, 4.5 Hz, 1H), 7.34–7.21 (complex m, 6H), 7.12 (d, J=7.2 Hz, 2H), 7.01 (d, J=7.0 Hz, 2H), 5.87 (br s, 2H), 3.96 (s, 3H), 3.04 (m, 2H), 2.97 (m, 2H); ^{13}C NMR (100 MHz): δ 174.8, 167.6, 154.2, 152.6, 150.4, 139.6, 136.6, 136.2, 129.0, 128.8, 128.1, 127.7, 126.8, 125.7, 121.0, 120.5, 119.1, 52.6, 47.7, 35.7, 33.8; ms: m/z 307 ($M^+-C_7H_7$). Anal. Calcd for $C_{25}H_{22}N_2O_3$: C, 75.38; H, 5.53; N, 7.04. Found: C, 75.41; H, 5.50; N, 6.97.

*4.7.7. 6-Benzyl-7-isopropyl-8-methoxycarbonyl-1,6-naphthyridin-5(6H)-one (**10g**).* No naphthyridinone product was formed in this reaction.

*4.7.8. 6,7-Dimethyl-8-methoxycarbonyl-1,6-naphthyridin-5(6H)-one (**10h**).* Yield: 222 mg (0.96 mmol, 84%) as a tan solid, mp 189–191 °C; IR: 1727, 1617, 1600 cm^{-1}; ^1H NMR (400 MHz): δ 8.71 (dd, J=4.5, 2.1 Hz, 1H), 8.68 (dd, J=8.0, 2.1 Hz, 1H), 7.33 (dd, J=7.8, 4.5 Hz, 1H), 3.92 (s, 3H), 3.94 (s, 3H), 2.57 (s, 3H); ^{13}C NMR (100 MHz): δ 174.2, 167.8, 152.1, 151.4, 150.2, 136.0, 120.9, 120.0, 118.5, 52.5, 32.4, 19.2; ms: m/z 232 (M^+). Anal. Calcd for $C_{12}H_{12}N_2O_3$: C, 62.07; H, 5.17; N, 12.07. Found: C, 62.21; H, 5.21; N, 11.94.

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Supplementary data

Supplementary data (experimental details, ^1H- and ^{13}C NMR spectra, and analytical data for **8a**–**h**, **9a**–**h** and **10a**–**f** and **10h**) can be found, in the online version, at http://dx.doi.org/10.1016/j.tet.2013.12.033.

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